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# Guidance for Industry

## Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

### *DRAFT GUIDANCE*

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**February 2012  
Clinical Pharmacology**

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# **Guidance for Industry**

## **Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations**

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**February 2012  
Clinical Pharmacology**

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**Guidance for Industry<sup>1</sup>**

**Drug Interaction Studies — Study Design, Data Analysis,  
Implications for Dosing, and Labeling Recommendations**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**I. INTRODUCTION**

This guidance provides recommendations for sponsors of new drug applications (NDAs) and biologics license applications (BLAs) for therapeutic biologics regulated by CDER regarding *in vitro* and *in vivo* studies of drug metabolism, drug transport, and drug-drug or drug-therapeutic protein interactions. Drug interactions can result when one drug alters the pharmacokinetics of another drug or its metabolites. Drug interactions also can reflect the additive nature of the pharmacodynamic effect of either drug when taken with the other drug. The main focus of this guidance is pharmacokinetic drug interactions. This guidance reflects the Agency's view that the pharmacokinetic interactions between an investigational new drug and other drugs should be defined during drug development, as part of an adequate assessment of the drug's safety and effectiveness. It is important to understand the nature and magnitude of drug-drug interactions (DDI) for several reasons. Concomitant medications, dietary supplements, and some foods, such as grapefruit juice, may alter metabolism and/or drug transport abruptly in individuals who previously had been receiving and tolerating a particular dose of a drug. Such an abrupt alteration in metabolism or transport can change the known safety and efficacy of a drug.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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<sup>1</sup> This guidance has been prepared by the Drug-Drug Interaction Working Group in the Office of Clinical Pharmacology, Office of Translational Sciences, in the Center for Drug Evaluation and Research (CDER), with input from other offices in CDER.

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### **II. SUMMARY OF GUIDANCE**

The key recommendations for sponsors to consider when evaluating drug-drug interactions during drug development are listed below. The various sections of this guidance provide more details for each recommendation.

- Interactions between an investigational new drug and other drugs should be defined during drug development, as part of an adequate assessment of the drug’s safety and effectiveness. The objective of drug-drug interaction studies is to determine whether potential interactions between the investigational drug and other drugs exist and, if so, whether the potential for such interactions indicates the need for dosage adjustments, additional therapeutic monitoring, a contraindication to concomitant use, or other measures to mitigate risk.
- Development of a drug should include identification of the principal routes of elimination, quantitation of the contribution by enzymes and transporters to drug disposition, and characterization of the mechanism of drug-drug interactions.
- Sponsors who believe a complete evaluation of the potential for drug-drug interactions is not necessary for an investigational drug because of the target population and likely co-administered drugs should contact the Office of Clinical Pharmacology and the clinical division in the Office of New Drugs.
- This guidance and its appendices include numerous decision trees intended to help sponsors determine what types of drug-drug interaction studies may be needed (see Figures 2 through 7 and Appendix Figures A-1 through A-6).
- The study of drug-drug interaction for a new drug generally begins with in vitro studies to determine whether a drug is a substrate, inhibitor, or inducer of metabolizing enzymes. The results of in vitro studies will inform the nature and extent of in vivo studies that may be required to assess potential interactions. Along with clinical pharmacokinetic data, results from in vitro studies may serve as a screening mechanism to rule out the need for additional in vivo studies, or provide a mechanistic basis for proper design of clinical studies using a modeling and simulation approach.
- When testing an investigational drug for the possibility that its metabolism is inhibited or induced (i.e., as a substrate), selection of the interacting drugs should be based on in vitro or in vivo studies identifying the enzyme systems that metabolize the investigational drug. The choice of the interacting drug can then be based on known, important inhibitors and inducers of the pathway under investigation. Strong inhibitors and inducers provide the most sensitive assessment and should generally be tested first (see section V.C).
- If potential drug-drug interactions are identified based on in vitro and/or in vivo studies, sponsors should design further studies or collect information to determine (1) whether

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84 additional studies are needed to better quantify the effect and to examine the effects of  
85 weaker inhibitors (early studies usually examine strong inhibitors) on the investigational  
86 drugs as substrates and effects of investigational drugs (as inhibitors) on a range of  
87 substrates, and (2) whether dosage adjustments or other prescribing modifications (e.g.,  
88 additional safety monitoring or contraindications) are needed based on the identified  
89 interaction(s) to avoid undesired consequences.

- 90
- 91 • The potential for drug interactions with metabolites of investigational drugs (metabolites  
92 present at  $\geq 25\%$  of parent drug AUC) should be considered (see section IV.A.3).  
93
  - 94 • Metabolic drug-drug interactions should also be explored for investigational drugs that are  
95 not eliminated significantly by metabolism because such drugs can inhibit or induce a co-  
96 administered drug's metabolic pathway (see section IV.A.1).  
97
  - 98 • When evaluating a new drug as a potential cytochrome P450 (CYP) enzyme inhibitor,  
99 sponsors should consider a stepwise, model-based evaluation of metabolism-based  
100 interactions (from basic model for initial assessment to more mechanistic models including  
101 physiologically-based pharmacokinetic (PBPK) modeling) (see section IV.A.1). The criteria  
102 used for assessing “equivalence” (e.g., predicted AUC ratio of 0.8-1.25 using population-  
103 based PBPK models) may be used as an initial cutoff in deciding whether in vivo studies are  
104 needed. The criteria discussed in this guidance document are suggested values. We are open  
105 to discussion based on sponsors' interpretation.  
106
    - 107 - PBPK is a useful tool that can help sponsors (1) better design drug-drug interaction  
108 studies, including dedicated trials and population pharmacokinetic studies, and (2)  
109 quantitatively predict the magnitude of drug-drug interactions in various clinical  
110 situations. PBPK models also may offer useful alternatives to dedicated clinical  
111 studies.
    - 112
    - 113 - When submitting PBPK studies to CDER, sponsors should provide details of model  
114 assumptions, physiological and biological plausibility, the origin of the parameters,  
115 and information on uncertainty and variability.  
116
  - 117 • The evaluation of CYP enzyme induction should begin with studies of CYP1A2, CYP2B6,  
118 and CYP3A in vitro (Figure 4). If the in vitro induction results are positive according to  
119 predefined thresholds using basic models, the investigational drug is considered an enzyme  
120 inducer and further in vivo evaluation may be warranted. Alternatively, a sponsor can  
121 estimate the degree of drug-drug interactions using mechanistic models to determine the need  
122 for further in vivo evaluation (see section IV.A.1.b-3).  
123
    - 124 - It should be noted that there may be mechanisms of induction that are presently  
125 unknown. Therefore, a potential human teratogen needs to be studied in vivo for  
126 effects on contraceptive steroids if the drug is intended for use in fertile women,  
127 regardless of in vitro induction study results.

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- 128
- 129 • In addition to CYPs, other metabolizing enzymes (e.g., uridine diphosphate (UDP)-  
130 glucuronosyl transferases (UGTs)) that may be important for the drugs under evaluation  
131 should also be considered (see section IV.A.1).
- 132
- 133 • A number of transporter-based interactions have been documented in recent years (see Table  
134 1, section III.B.2).
- 135
- 136 - All investigational drugs should be evaluated in vitro to determine whether they are a  
137 potential substrate of P-glycoprotein (P-gp) or Breast Cancer Resistance Protein  
138 (BCRP) (see Figure 6, left panel, section IV.A.2). Investigational drugs should be  
139 evaluated in vitro to determine whether they are a substrate of hepatic uptake  
140 transporters Organic Anion Transporting Polypeptide 1B1(OATP1B1) or OATP1B3  
141 when their hepatic pathway is significant (see Figure 6, middle panel, section  
142 IV.A.2). Similarly, investigational drugs should be evaluated in vitro to determine  
143 whether they are a substrate of Organic Anion Transporter 1 (OAT1) or OAT3 or  
144 Organic Cation Transporter 2 (OCT2) when renal active secretion is important  
145 (Figure 6, right panel, section IV.A.2).
- 146
- 147 - Because there have been clinically significant interactions demonstrated for critical  
148 drugs that are known substrates for P-gp (e.g., digoxin), BCRP (e.g., rosuvastatin),  
149 OATP1B1/OATP1B3 (e.g., statin drugs), OAT1/OAT3 (e.g., methotrexate, tenofovir)  
150 and OCT2 (e.g., metformin), evaluation of investigational drugs as inhibitors for  
151 these transporters should be conducted (see section IV.A.2).
- 152
- 153 - The need for further in vivo drug interaction studies based on in vitro evaluation will  
154 be based on the criteria described in the decision trees in Figures A1-A6 in the  
155 Appendix.
- 156
- 157 • Because of the lack of a validated in vitro system to study transporter induction, the  
158 definitive determination of induction potential of an investigational drug on transporters is  
159 based on in vivo induction studies. The sponsor should consult with CDER about studying  
160 induction of transporters in vivo.
- 161
- 162 • Human clinical studies to assess drug-drug interactions may include simultaneous  
163 administration of a mixture of substrates of multiple CYP enzymes and transporters in one  
164 study (i.e., a “cocktail approach”) to evaluate a drug’s inhibition or induction potential (see  
165 section V.C.3). Negative results from a well-conducted cocktail study may eliminate the  
166 need for further evaluation of particular CYP enzymes and transporters. However, positive  
167 results may indicate that further in vivo evaluation should be conducted.
- 168
- 169 • The potential for interactions with drug products should be considered for certain classes of  
170 therapeutic proteins (TPs) (see Figure 7, section IV.B.2).
- 171



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- 172 - If an investigational TP is a cytokine or cytokine modulator, studies should be  
173 conducted to determine the TP's effects on CYP enzymes or transporters. The in  
174 vivo evaluations of TPs in targeted patient populations can be conducted with  
175 individual substrates for specific CYP enzymes and transporters, or studies can be  
176 conducted using a "cocktail approach" (see section V.C.3).  
177
- 178 - For TPs that will be used in combination with other drug products (small molecule or  
179 TP) as a combination therapy, studies should evaluate the effect of each product on  
180 the other. This evaluation is particularly important when the drug used in  
181 combination has a narrow therapeutic range.  
182
- 183 - When there are known mechanisms or prior experience with certain PK or PD  
184 interactions for other similar TPs, appropriate in vitro or in vivo assessments for  
185 possible interactions should be conducted.  
186
- 187 • Refer to section V for information regarding in vivo drug interaction study design. The  
188 section also contains tables on classification of in vivo inhibitors (Table 3) or inducers for  
189 CYP enzymes (Table 4), examples of sensitive in vivo CYP substrates and CYP substrates  
190 with narrow therapeutic ranges (Table 5), examples of in vivo inhibitors and inducers of  
191 selected transporters (Table 6), examples of in vivo substrates of selected transporters (Table  
192 7) and examples of in vivo CYP3A and P-gp inhibitors and their relative potency (Table 8).  
193
- 194 - Simulations (e.g., by population-based PBPK models) can provide valuable insight  
195 into optimizing the study design (see section IV.A.1).  
196
- 197 - Detailed information on the dose given and time of administration should be  
198 documented for the co-administered drugs. When relevant for the specific drug, the  
199 time of food consumption should be documented.  
200
- 201 - Population pharmacokinetic (PopPK) analyses of data obtained from large-scale  
202 clinical studies that include sparse or intensive blood sampling can help characterize  
203 the clinical impact of known or newly identified interactions and determine  
204 recommendations for dosage modifications for the investigational drug as a substrate  
205 (section V.B). DDI analyses using a population PK approach should focus on  
206 excluding a specific clinically meaningful PK change. Because exposure of co-  
207 administered drugs is not monitored in most PopPK studies, the PopPK approach may  
208 not be useful to assess the effect of the investigational drugs on other drugs.  
209
- 210 • The likelihood of drug interactions in specific populations (e.g., patients with organ  
211 impairment, and pediatric and geriatric patients) should be considered on a case-by-case  
212 basis. PBPK modeling (if well verified for intended purposes) can be helpful to guide the  
213 determination of the need to conduct population-specific studies (see "Populations" in  
214 section V.B and "Complex Drug Interactions" section V.C.4).  
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- 216 • Additional study design issues are discussed throughout the guidance (e.g., route of  
217 administration (section V.D), dose selection (section V.E), defining endpoints (section V.F),  
218 and statistical considerations (section V.G)).  
219
- 220 • Labeling recommendations with regard to drug interactions are described in section VI.  
221
- 222 - A forest plot is considered a useful tool for presenting changes in pharmacokinetic  
223 exposure measures by various intrinsic and extrinsic factors including drug  
224 interactions in the PHARMACOKINETIC subsection of the labeling (see Figure 8,  
225 section VI).  
226
- 227 - If the sponsor wishes to include a statement in the labeling that no known drug-drug  
228 interaction of clinical significance exists, the sponsor should recommend specific *no*  
229 *effect* boundaries, or clinical equivalence intervals, for a drug-drug interaction and  
230 should provide the scientific justification for the recommendations. No effect  
231 boundaries represent the interval within which a change in a systemic exposure  
232 measure is considered not clinically meaningful. These conclusions can be based on  
233 exposure-response or dose-response data.  
234
- 235 • Sponsors are encouraged to communicate with the Office of Clinical Pharmacology or the  
236 appropriate clinical review divisions within CDER regarding questions about drug  
237 interactions, in particular when  
238
- 239 - Using mechanistic or PBPK models for the prediction of drug-drug interactions  
240 including evaluation of complex drug-drug interactions  
241 - Determining the need to evaluate drug interactions with non-CYP enzymes or  
242 additional transporters that are not included in the decision trees  
243 - Determining drug-drug interaction studies involving TPs.  
244  
245  
246

### **III. BACKGROUND**

#### **A. Relevance of Drug Interactions**

251 The desirable and undesirable effects of a drug are related to its concentration at various sites of  
252 action, which is usually related to the blood or tissue concentration of the drug. The blood or  
253 tissue concentrations resulting from a dose are determined by the drug's absorption, distribution,  
254 metabolism, and excretion (ADME). Elimination of a drug or its active metabolites occurs either  
255 by metabolism to an inactive metabolite that is excreted, or by direct excretion of the drug or  
256 active metabolites. The kidneys and liver are responsible for most drug excretion. Drug  
257 interactions related to metabolism and excretion are well-recognized, but effects related to  
258 transporters are being documented with increasing frequency and are, therefore, important to  
259 consider in drug development. Therapeutic proteins may be eliminated through a specific

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260 interaction with cell surface receptors, followed by internalization and lysosomal degradation  
261 within the target cell.

262

263 The overall objective of interaction studies for a new drug is to determine:

264

265 • whether any interactions are sufficiently large to necessitate a dosage adjustment of the  
266 drug itself or of the drugs with which it might be used,

267 • whether any interactions calls for additional therapeutic monitoring, or

268 • whether there should be a contraindication to concomitant use when lesser measures  
269 cannot mitigate risk.

270

271 In some instances, understanding how to adjust a dose or dosage regimen in the presence of an  
272 interacting drug, or how to avoid drug-drug interactions, may allow marketing of a drug that  
273 would otherwise have an unacceptable level of risk. In a few cases, consequences of an  
274 interaction have led to the conclusion that the drug could not be marketed safely. In almost all of  
275 these cases, that conclusion was strengthened by the availability of alternative drugs with lower  
276 risks for interactions. Several drugs have been withdrawn from the market because of significant  
277 drug interactions that led to QT prolongation and Torsades de Pointes (TdP) arrhythmias, after  
278 warnings in drug labels did not adequately manage the risk of drug interactions. For example,  
279 terfenadine and astemizole, two early nonsedating antihistamines metabolized by CYP3A, were  
280 withdrawn after labeling failed to reduce cases of TdP sufficiently, because fexofenadine and  
281 loratadine fulfilled the need for nonsedating antihistamines that had no risk of TdP. Cisapride, a  
282 CYP3A metabolized drug, was withdrawn because its gastrointestinal benefits were not felt to  
283 outweigh its TdP risk. A fourth drug, mibefradil (a calcium channel blocker similar to verapamil  
284 and diltiazem) was a strong CYP3A inhibitor and, when used with simvastatin, caused  
285 rhabdomyolysis because of markedly increased simvastatin exposure.

286

287

#### **B. Drug Interaction Considerations for Small Molecule Drugs**

288

289 The main focus of this guidance is pharmacokinetic drug interactions. The drug development  
290 process should include evaluation of a new drug's potential to affect the metabolism or transport  
291 of other drugs and the potential for the new drug's metabolism or transport to be affected by  
292 other drugs. Use of in vitro tools to determine whether a drug is a substrate, inhibitor, or inducer  
293 of metabolizing enzymes, followed by in vivo interaction studies to assess potential interactions,  
294 has become an integral part of drug development and regulatory review. In addition to the  
295 evaluation of metabolic drug interactions, the role of transporters in drug interactions should be  
296 evaluated. This section will separately discuss drug-drug interactions at the levels of  
297 metabolizing enzymes and transporters, and also consider situations when multiple drug-drug  
298 interaction mechanisms are present.

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##### *1. Metabolism-Based Drug-Drug Interactions*

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303 Hepatic metabolism occurs primarily through the cytochrome P450 family (CYP) of  
304 enzymes located in the hepatic endoplasmic reticulum, but may also occur through non-  
305 CYP enzyme systems, such as glucuronosyl- and sulfo-transferases, which can, in  
306 general, inactivate a drug and increase its renal elimination. Some drug metabolizing  
307 enzymes are present in the gut wall and other extrahepatic tissues, in addition to the liver.  
308

309 Many metabolic routes of elimination can be inhibited or induced by concomitant drug  
310 treatment. Metabolic drug-drug interactions can cause substantial changes — an order of  
311 magnitude or more decrease or increase in the blood and tissue concentrations of a drug  
312 or metabolite — and can affect the extent to which toxic or active metabolites are  
313 formed. These large changes in exposure can alter the safety and efficacy profile of a  
314 drug and its active metabolites, regardless of whether the drug has a narrow therapeutic  
315 range (NTR). For example, certain HMG-CoA reductase inhibitors (e.g., lovastatin,  
316 simvastatin) that are extensively metabolized by CYP3A can have a 10-fold or more  
317 increase in blood levels when their metabolism is inhibited by co-administration with  
318 strong CYP3A inhibitors such as mibefradil or ketoconazole, or even moderate inhibitors  
319 such as erythromycin. Although the HMG-CoA reductase inhibitors are not NTR drugs,  
320 the blood level increases caused by interactions between HMG-CoA reductase inhibitors  
321 and CYP3A inhibitors can cause myopathy and in some cases rare and life-threatening  
322 rhabdomyolysis.  
323

324 In addition to evaluating a drug as a substrate of an enzyme that another drug may inhibit  
325 or induce, it is important to determine whether an investigational drug significantly  
326 affects the metabolic elimination of drugs already in the marketplace. Metabolic drug-  
327 drug interactions should be explored for investigational drugs that are not eliminated  
328 significantly by metabolism because such drugs can inhibit or induce a co-administered  
329 drug's metabolism pathway.  
330

331 Drug-drug interactions can differ among individuals based on genetic variation of a  
332 polymorphic enzyme. For example, a strong CYP2D6 inhibitor (e.g., fluoxetine) will  
333 increase the plasma levels of a CYP2D6 substrate (e.g., atomoxetine) in subjects who are  
334 extensive metabolizers (EM) of CYP2D6, but will have minimal effect in subjects who  
335 are poor metabolizers (PM) of CYP2D6, because these individuals have no active  
336 enzyme to inhibit. It is noted that CYP2D6 PMs will already have greatly increased  
337 levels of atomoxetine if given usual doses. There are also situations where inhibition  
338 may have a greater effect in PMs than EMs. If a drug is metabolized by a minor pathway  
339 (nonpolymorphic enzyme) and a major pathway (polymorphic enzyme), inhibition of the  
340 minor pathway will usually have minimal effect on plasma concentrations in EMs.  
341 However, the minor pathway plays a greater role in clearance of the drug in PMs of the  
342 major pathway. Thus, inhibition of the minor pathway in PMs of the major pathway can  
343 have a significant effect on drug clearance and resulting drug concentrations. Therefore  
344 studying the effect of interactions may be recommended in subjects with varied  
345 genotypes or phenotypes.  
346

#### 2. *Transporter-Based Drug-Drug Interactions*

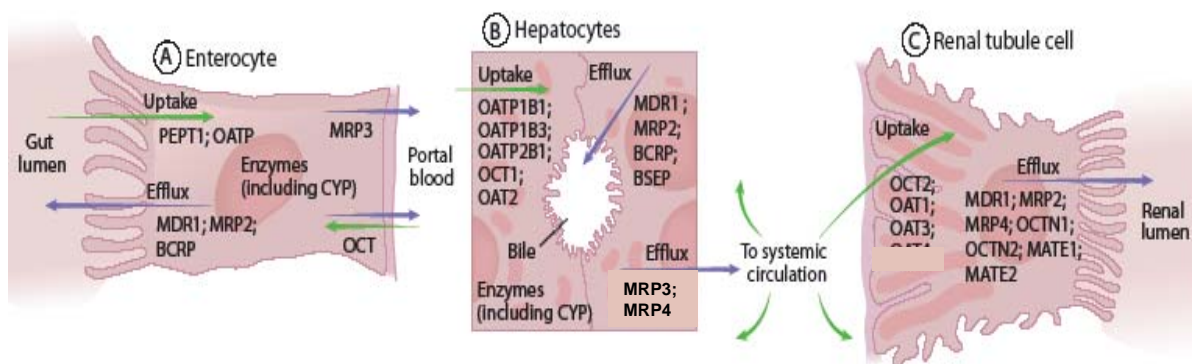
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349 Although less well-recognized than metabolizing enzymes, membrane transporters can  
350 have important effects on pharmacokinetics and drug exposure. To date, most identified  
351 transporters belong to one of two superfamilies: ATP-Binding Cassette (ABC) and  
352 Solute Carrier (SLC). Transporters govern the transport of solutes (e.g., drugs and other  
353 xenobiotics) in and out of cells. In contrast to metabolizing enzymes, which are largely  
354 concentrated in the liver and intestine, transporters are present with varying abundance in  
355 all tissues in the body and play important roles in drug distribution, tissue-specific drug  
356 targeting, drug absorption, and elimination. For example, recent research indicates an  
357 important role of transporters in the absorption, distribution, and excretion of drugs (see  
358 Figure 1 below and Table 1). Transporters can also work in concert with metabolizing  
359 enzymes and play a role in drug metabolism.

360  
361  
362 **Figure 1. Illustration of Examples of Efflux and Uptake Transporters in the Gut**  
363 **Wall (A), Liver (B), and Kidneys (C) that May Be Involved in a Drug’s Absorption,**  
364 **Distribution, Metabolism, and Excretion.**



366  
367 Abbreviations: MRP: multidrug resistance associated protein; PEPT1, peptide transporter 1; OATP:  
368 organic anion transporting polypeptide; OAT: organic anion transporter; OCT: organic cation transporter;  
369 BCRP: breast cancer resistance protein; MDR1: multidrug resistance 1(P-glycoprotein (P-gp)); MATE:  
370 multidrug and toxic compound extrusion protein (Adapted from Huang S-M, Lesko LJ, and Temple R,  
371 “Adverse Drug Reactions and Pharmacokinetic Drug Interactions,” Chapter 20, Adverse Drug Reactions  
372 and Drug Interactions in Part I (Section 4), *Pharmacology and Therapeutics: Principles to Practice*,  
373 Waldman SA and Terzic A, Eds., Elsevier, 2009).

374  
375 A number of transporter-based interactions have been documented in recent years.  
376 Analogous to drug interactions mediated by P450 enzymes, co-administration of a drug  
377 that is an inhibitor or an inducer of a drug transporter may affect the pharmacokinetics of  
378 a drug that is a substrate for that transporter. It has been shown that various drugs (e.g.,  
379 quinidine, verapamil, itraconazole) increase plasma levels of digoxin by inhibiting the  
380 efflux transporter, P-gp, at the intestinal level. Plasma levels of many HMG-CoA  
381 reductase inhibitors, including rosuvastatin, pravastatin, and pitavastatin, are increased by

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382 co-administration of inhibitors of hepatic uptake transporters (e.g., OATP1B1), such as  
383 cyclosporine and single dose rifampin. For example, co-administration of cyclosporine  
384 increases the area under the plasma concentration-time curve (AUC) of pravastatin,  
385 rosuvastatin, and pitavastatin by 10-fold, 7-fold, and 5-fold, respectively. This effect and  
386 a number of other transporter interactions are shown in Table 1 below. Because these  
387 statins are not significantly metabolized, the interactions appear to result from inhibition  
388 of transporters, including OATP1B1. Table 1 also shows a substantial effect of  
389 lopinavir/ritonavir on bosentan, which is potentially important because of bosentan's  
390 dose-related hepatotoxicity. Probenecid increases plasma concentrations of cidofovir,  
391 furosemide, and acyclovir because it inhibits their active renal tubular secretion by the  
392 transporters OAT1 and OAT3. Table 1 lists additional clinically relevant transporter-  
393 based drug-drug interactions.

394  
395 Transporters can affect the safety profile of a drug by affecting the concentration of a  
396 drug or its metabolites in various tissues. An example of transporter-mediated effects on  
397 drug toxicity involves the drug cidofovir. This antiviral drug causes nephrotoxicity;  
398 however, when administered with probenecid, an inhibitor of organic anion transport in  
399 the kidney, the uptake of cidofovir into the renal tubular cell is blocked and  
400 nephrotoxicity is reduced. Another example involves simvastatin, polymorphism of  
401 OATP1B1 was found to correlate with the prevalence of myopathy in patients receiving  
402 simvastatin. Transporter-based drug interactions and the potential effect of drug  
403 transporters on safety make it important to determine whether transporters affect the  
404 absorption and disposition of an investigational drug and whether the investigational drug  
405 can affect the absorption and disposition of other drugs through an effect on transporters.  
406

### 3. *Multiple Drug-Drug Interaction Mechanisms*

407  
408  
409 The above sections separately discuss drug-drug interactions related to effects on  
410 enzymes and transporters, but drug interactions for a specific drug may occur based on a  
411 combination of mechanisms. Such “complex drug interaction” scenarios include, but are  
412 not limited to:

- 413
- 414 • Concurrent inhibition and induction of one enzyme or concurrent inhibition of
- 415 enzyme and transporter by a drug
- 416 • Increased inhibition of drug elimination by the use of more than one inhibitor of the
- 417 same enzyme that metabolizes the drug
- 418 • Increased inhibition of drug elimination by use of inhibitors of more than one enzyme
- 419 that metabolizes the drug
- 420 • Inhibition by a drug and its metabolite or metabolites, both of which inhibit the
- 421 enzyme that metabolizes the substrate drug
- 422 • Inhibition of an enzyme other than the genetic polymorphic enzyme in poor
- 423 metabolizers taking substrate that is metabolized by both enzymes
- 424 • Use of enzyme/transporter inhibitors in subjects with varying degrees of impairment
- 425 of drug eliminating organs (e.g., liver or kidney)

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426  
427 When there are multiple factors that affect clearance and multiple mechanisms of drug–  
428 drug interactions, the prediction of in vivo interactions from results of in vitro assessment  
429 is challenging. Modeling and simulations accounting for multiple mechanisms can be  
430 helpful in the design of clinical studies to inform the potential for drug interaction or  
431 prediction of the extent of interactions (see section V.C.4).  
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**Table 1. Selected Transporter<sup>a</sup>-Mediated Clinical Significant Drug-Drug Interactions**

Gene	Aliases <sup>a</sup>	Tissue	Function	Interacting Drug	Substrate (Affected Drug)	Changes in Substrate Plasma AUC (AUC ratios)
<i>ABC Transporters of clinical importance in the absorption, disposition, and excretion of drugs</i>						
ABCB1	P-gp, MDR1	Intestinal enterocyte, kidney proximal tubule, hepatocyte (canalicular), brain endothelia	Efflux	Dronedarone	Digoxin	2.6-fold
				Quinidine	Digoxin	1.7-fold
				Ranolazine	Digoxin	1.6-fold
				Tipranavir/Ritonavir	Loperamide	0.5-fold
				Tipranavir/Ritonavir	Saquinavir/Ritonavir	0.2-fold
ABCG2	BCRP	Intestinal enterocyte, hepatocyte (canalicular), kidney proximal tubule, brain endothelia, placenta, stem cells, mammary gland (lactating)	Efflux	GF120918	Topotecan	2.4-fold
<i>SLC Transporters of clinical importance in the disposition and excretion of drugs</i>						
SLCO1B1	OATP1B1 OATP-C OATP2 LST-1	Hepatocyte (sinusoidal)	Uptake	Lopinavir/ritonavir	Bosentan	5-48 fold <sup>c</sup>
				Cyclosporine	Pravastatin	9.9-fold
				Rifampin (single dose)	Glyburide	2.3-fold
SLCO1B3	OATP1B3, OATP-8	Hepatocyte (sinusoidal)	Uptake	Cyclosporine	Rosuvastatin <sup>d, e</sup>	7.1- fold <sup>d</sup>
				Cyclosporine Lopinavir/ritonavir	Pitavastatin <sup>d</sup> Rosuvastatin <sup>d</sup>	4.6-fold 2.1-fold
SLC22A2	OCT2	Kidney proximal tubule	Uptake	Cimetidine Cimetidine Cimetidine	Dofetilide Pindolol Metformin	1.5-fold 1.5-fold 1.4-fold
SLC22A6	OAT1	Kidney proximal tubule, placenta	Uptake	Probenecid	Cephadrine	3.6-fold
				Probenecid	Cidofovir	1.5-fold
				Probenecid	Acyclovir	1.4-fold
SLC22A8	OAT3	Kidney proximal tubule, choroid plexus, brain endothelia	Uptake	Probenecid	Furosemide <sup>f</sup>	2.9-fold

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436 <sup>a</sup> Abbreviations: BCRP, breast cancer resistance protein; P-gp, p-glycoprotein; MDR, multidrug resistance; LST, liver-specific transporters; OATP, organic anion transporting  
437 polypeptide; OCT, organic cation transporter; OAT, organic anion transporter

438 <sup>b</sup> Implicated transporter refers to the likely transporter; however, because the studies are in vivo, it is not possible to assign definitively specific transporters to these interactions.

439 <sup>c</sup> Minimum predose plasma level ( $C_{\text{trough}}$ ) data from Day 4 (48-fold), Day 10 (5-fold) after co-administration.

440 <sup>d</sup> Interaction could be partly mediated by OATP1B1.

441 <sup>e</sup> Interaction could be partly mediated by BCRP.

442 <sup>f</sup> Interaction could be partly mediated by OAT1.

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### 444 **C. Drug Interaction Considerations for Therapeutic Proteins**

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446 Therapeutic proteins (TPs) typically do not undergo metabolism or transport as their  
447 clearance pathway, therefore the potential is limited for small molecule drugs (termed  
448 “drug” in this document) to affect TPs through metabolism or transport pathways.  
449 However, a drug may affect the clearance of TPs through the drug’s effect on  
450 immunogenicity (e.g., methotrexate reduces the clearance of infliximab, possibly due to  
451 methotrexate’s effect on the antibodies formed against infliximab). In addition, TPs that  
452 are cytokines or cytokine modulators may modify the metabolism of drugs that are  
453 substrates for P450 enzymes through their effects on the regulation pathways of P450  
454 enzymes. For example, cytokines such as IL-6 can produce concentration-dependent  
455 inhibition on various CYP isoforms at the transcription level or by alteration of CYP  
456 enzyme stability in patients with infection or inflammation, and increase the plasma  
457 concentrations of specific CYP substrate drugs. In contrast, cytokine modulators such as  
458 tocilizumab (anti-IL-6 receptor antibody) may reverse the apparent “inhibition” effect of  
459 the cytokines on CYP substrates, resulting in a “normalization” of CYP activities.

460

461 General points to be considered for evaluation of TP-drug interactions are discussed in  
462 section IV.B.2.

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### 465 **IV. GENERAL STRATEGIES**

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467 Development of a drug should include identification of the principal routes of  
468 elimination, quantitation of the contribution by enzymes and transporters to drug  
469 disposition, and characterization of the mechanism of drug-drug interactions. The  
470 quantitative assessment of drug-drug interaction potential for an investigational drug  
471 employs a variety of models including basic models, mechanistic static models, and more  
472 comprehensive dynamic models (e.g., physiologically-based pharmacokinetic (PBPK)  
473 models). Appropriately designed pharmacokinetic studies, usually performed in the early  
474 phases of drug development, can provide important information about metabolic and  
475 excretory routes of elimination, their contribution to overall elimination, and metabolic or  
476 transporter-mediated drug-drug interactions. Together with information from in vitro  
477 studies, these in vivo investigations can be used for PBPK model construction and  
478 refinement. Quantitative assessment of the findings from these studies helps address key  
479 regulatory questions regarding whether, when, and how to conduct further clinical drug-  
480 drug interaction studies. In many cases, negative findings from early in vitro and clinical  
481 studies eliminate the need for later clinical investigations of drug-drug interaction  
482 potential. If potential drug-drug interactions are identified based on in vitro and/or in  
483 vivo studies, sponsors should design further studies or collect information to determine  
484 (1) whether additional studies are needed to better quantify the effect and to examine the  
485 effects of weaker inhibitors (early studies usually examine strong inhibitors) on the  
486 investigational drugs as substrates and effects of investigational drugs (as inhibitors) on a  
487 range of substrates, and (2) whether dosage adjustments or other prescribing

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488 modifications (e.g., additional safety monitoring or contraindications) are needed based  
489 on the identified interaction(s) to avoid undesired consequences. Further  
490 recommendations about the types of in vivo studies that should be conducted in certain  
491 circumstances appear in section V of this guidance.

492

493 Drug interaction information is used along with information about exposure-response  
494 relationships in the general population and specific populations, to help predict the  
495 clinical consequences of drug-drug interactions.

496

#### **A. In Vitro Studies**

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499 Findings from in vitro metabolism, transport, and drug interaction studies are valuable in  
500 quantitatively assessing the drug-drug interaction potential of an investigational drug.  
501 Along with clinical pharmacokinetic data, results from in vitro studies can serve as a  
502 screening mechanism to rule out the need for additional in vivo studies, or provide a  
503 mechanistic basis for proper design of clinical studies using a modeling and simulation  
504 approach. Considerations critical for conducting in vitro studies include, but are not  
505 limited to, appropriately validated experimental methods, choice of test systems, and  
506 rational selection of substrate/interacting drug and their concentrations.

507

##### *1. In Vitro Metabolism Studies*

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510 Figure 2 below shows a decision tree that describes when in vivo metabolism-  
511 based interaction studies are indicated, based on in vitro metabolism, in vitro  
512 drug-drug interaction, and/or other appropriate pharmacokinetic data.

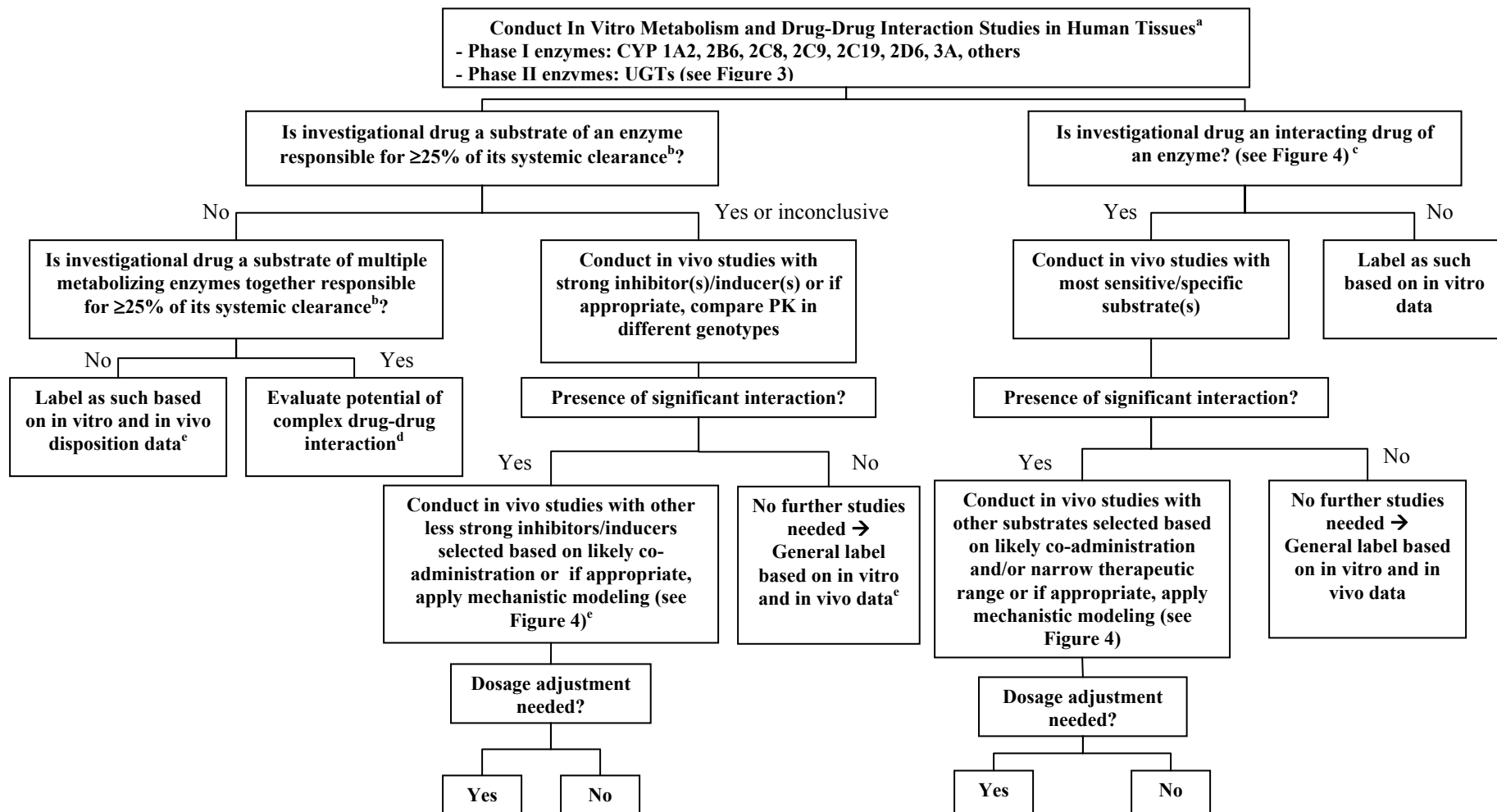
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**Figure 2. Metabolism-Based Drug-Drug Interaction Studies — Decision Tree**

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- 517       <sup>a</sup> Other Phase I enzymes (CYP and non-CYP) are discussed in section IV.A.1.a.
- 518       <sup>b</sup> Results from in vitro enzyme phenotyping experiments, human pharmacokinetic studies such as an intravenous study, a mass-balance study, and
- 519       pharmacokinetic studies in which renal/biliary clearances are determined can be evaluated together to determine the percent contribution of enzyme to
- 520       overall in vivo drug elimination in humans.
- 521       <sup>c</sup> See Figure 4 for calculation of R values and cutoff values. Sponsor may conduct an in vivo cocktail study in humans (Reference: *Clinical Pharmacology*
- 522       *and Therapeutics*, 81: 298-304, 2007). See section V.C.3.
- 523       <sup>d</sup> See section V.C.4 for evaluation of complex drug interactions.
- 524       <sup>e</sup> Additional population pharmacokinetic analysis may assist the overall evaluation of the investigational new drug as a substrate.

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a. *Drug Metabolizing Enzyme Identification — the Investigational Drug as an Enzyme Substrate*

The metabolic profile of the investigational drug should be characterized from in vitro studies. The in vitro systems include human liver tissues such as liver microsomes, microsomes expressing recombinant enzymes, or freshly isolated or cryopreserved human hepatocytes. Generally, decisions on the need for in vivo drug interaction studies with enzyme inhibitors/inducers are based on the quantitative measurement of the contribution of the enzyme to the overall systemic clearance of the substrate. We consider metabolism to be a significant pathway when it constitutes 25% or more of the drug's overall elimination. When the contribution is  $\geq 25\%$  or unknown, in vivo studies using appropriate inhibitor(s)/inducer(s) are warranted. The sequence of these in vivo studies should start with a strong inhibitor/inducer. If the results from the study with strong inhibitors/inducers indicate positive interactions, the impact of a less strong inhibitor/inducer should be evaluated. The subsequent evaluations with a less strong inhibitor/inducer can be conducted through a clinical study. Alternatively, it may be possible to conduct the evaluation through PBPK modeling (see section IV.A.1.b-3 below related to model building and strategies to evaluate drug-drug interaction using PBPK). The choice of in vivo enzyme inhibitors/inducers can be found in section V.

Minor elimination pathways mediated by a drug metabolizing enzyme may require further investigation under certain conditions. The contribution of these enzymes may become significant in specific populations (e.g., in subjects with renal impairment when the substrate drug is significantly eliminated through renal excretion, in poor metabolizers when substrate drug is predominantly metabolized by the polymorphic enzymes, or in subjects taking a strong inducer of the enzyme of minor pathway). The likelihood of metabolism-based drug interactions in these populations should be considered on a case-by-case basis (also see "Populations" in section V.B and "Complex Drug Interactions" section V.C.4).

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#### *Phase I Metabolizing Enzymes*

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Routine assessment to identify the following CYP enzymes for potential metabolism-mediated interactions is recommended: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. If an investigational drug is a substrate in vitro for a particular CYP, in vivo interaction studies with a strong inhibitor and inducer for that CYP (refer to the later sections about classification of CYP inhibitors and inducers) are recommended to determine the extent of changes in the investigational drug's pharmacokinetics. Negative results alleviate the need for further in vivo studies with less strong inhibitors or inducers, if the study is well designed and appropriate.

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If a drug is not metabolized by the major CYPs (listed above), the drug's likelihood of being a substrate for other CYP enzymes (e.g., CYP2A6, CYP2J2, CYP4F2, CYP2E1) or non-CYP Phase I enzymes should be considered. Non-CYP Phase I enzymes (enzymes involved in oxidation, reduction, hydrolysis, cyclization, and decyclization reactions) that are involved in drug metabolism include monoamine oxidase (MAO), flavin monooxygenase (FMO), xanthine oxidase (XO), and alcohol/aldehyde dehydrogenase. The potential for an investigational drug to be a substrate for these enzymes can be studied on a case-by-case basis (e.g., based on prior knowledge of the drug class).

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#### *Phase II Metabolizing Enzymes*

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Phase II enzymes (enzymes that are involved in conjugation reactions — conjugation involving, for example, glucuronic acid, sulfonates, glutathione, or amino acids) have historically attracted less attention than CYP enzymes in drug interaction evaluations, most likely because of the lack of tools to study them and a lower incidence of observed adverse drug-drug interactions.

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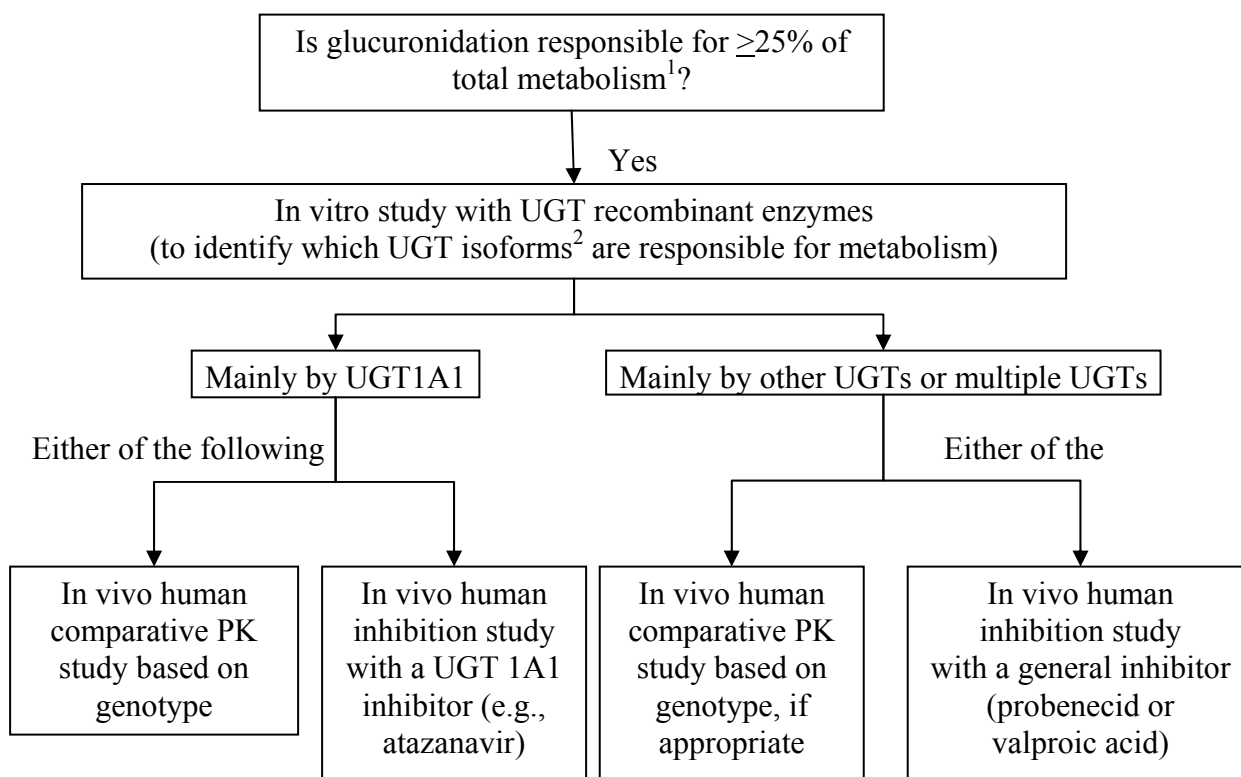
Recently, there has been an increased interest in drug-drug interactions involving UGTs (UDP glucuronosyl transferases), enzymes responsible for the biotransformation of many drugs. For example, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15 have been shown to play important roles in drug metabolism. However, determination of the contribution of each UGT isoform to the overall elimination is not as straightforward as that for CYP enzymes because of the absence of data on the abundance of these isoforms in drug eliminating organs, and the lack of specific inhibitors. For example, atazanavir has been used as a UGT1A1 inhibitor; however, it also inhibits CYP3A. Therefore, an investigation of a UGT-based drug-drug interaction may follow the decision tree outlined in Figure 3. If glucuronidation is a predominant pathway of drug elimination, in vitro studies (see Figure 3 below) to determine whether the drug is a substrate of UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, or 2B15 are recommended. These in vitro

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602 studies can be conducted using recombinant human UGTs, many of which are  
603 available from commercial sources. Results from these studies inform future in  
604 vivo drug interaction studies. In certain cases, comparative PK data in subjects  
605 with various UGT genotypes may be used to identify important UGT pathways  
606 and estimate the possible extent of interactions (e.g., comparison of PK in  
607 subjects who are poor metabolizers versus those who are extensive metabolizers).  
608 For example, UGT1A1 polymorphic variants affect the level of SN38, an active  
609 metabolite of irinotecan, which has both safety and efficacy implications. The  
610 clinical significance of interactions mediated by UGTs depends on the extent of  
611 interaction and the therapeutic range of the substrate drug.  
612

613 **Figure 3. Evaluation of Investigational Drugs as UGT Substrates**  
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615  
616 <sup>1</sup> In an in vitro system capable of informing contribution by UGT and non-UGT enzymes (e.g., hepatocytes  
617 or microsomes supplemented with appropriate co-factors).

618 <sup>2</sup> Main UGTs recommended to be studied: UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15.  
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#### *b. Evaluation of Investigational Drug as an Enzyme Inhibitor or Inducer*

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The decision to conduct an in vivo drug-drug interaction study for an investigational drug as an enzyme inhibitor and/or inducer should be based on quantitative analysis of both in vitro and clinical pharmacokinetic data. Such analysis is accomplished by a variety of algorithms and models including basic models, mechanistic static models, and more comprehensive dynamic models (e.g., physiologically-based pharmacokinetic (PBPK) models, see Figure 4).

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Basic models have been predominantly used because they are simple and practical. These models are conservative, but in some cases they eliminate the need for later clinical investigations of drug-drug interaction potential. For example, the cut-off value to decide whether further in vivo investigation of a drug as an inhibitor or an inducer is needed is generally calculated based on the ratio of intrinsic clearance values of a probe substrate for an enzymatic pathway in the absence and in the presence of the interacting drug (i.e., the R value<sup>2</sup>). Based on the estimation of an R value,<sup>2</sup> a decision can be made about whether an in vivo drug-drug interaction study is needed. Alternatively, in vitro data can be incorporated into mechanistic models to further investigate drug-drug interaction potential and determine the need to conduct a clinical drug-drug interaction study.

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Mechanistic static models incorporate more detailed drug disposition and drug interaction mechanisms for both interacting and substrate drugs (Fahmi et al. 2009). For example, these models integrate parameters such as bioavailability (in gut and liver) and fractional metabolism data (e.g., “ $f_m$ ” by a certain CYP enzyme) for substrate drugs and parameters related to all interaction mechanisms (inhibition and induction) for interacting drugs.

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A PBPK model integrates system-dependent parameters (e.g., based on human physiology) and drug-dependent parameters, which can be continuously refined. When appropriately constructed, the PBPK model offers clear advantages over static models. First, the PBPK model reflects the dynamics of drug-drug interactions, allowing the investigation of the effect of an interacting drug on the entire pharmacokinetic profile of the substrate. Second, the PBPK model can be used to evaluate concurrent mechanisms of drug-drug interactions, including the effect of inhibitory metabolites. Third, the emerging population-based PBPK models provide greater insight into the causes of uncertainty and variability when evaluating drug-drug interactions. Additionally, the inherent system-dependent

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<sup>2</sup> Ratio of estimated intrinsic clearance values in the absence and presence of an inhibitor or an inducer. For a drug that is a reversible inhibitor,  $R=1+[I]/K_i$ .  $K_i$  is the unbound inhibition constant determined in vitro. Sometimes inhibitor concentration causing 50% inhibition ( $IC_{50}$ ) is determined, and  $K_i$  can be calculated as  $IC_{50}/2$  by assuming competitive inhibition. See Figure 4 for discussion of [I] values.

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661 components make the PBPK model readily capable of investigating drug-drug  
662 interactions in the presence of multiple intrinsic and/or extrinsic factors (section  
663 V.C.4). These features make PBPK a useful option for sponsors to (1) better  
664 design drug-drug interaction studies, including dedicated trials and population  
665 pharmacokinetic studies, and (2) quantitatively predict the magnitude of drug-  
666 drug interactions in various clinical situations, including the existence of multiple  
667 patient factors such as renal impairment and/or genetic deficiency in certain  
668 metabolizing enzymes. Regardless of which prediction model is used, the  
669 sponsors should provide details of model assumptions, physiological and  
670 biological plausibility, the origin of the parameters, and information on  
671 uncertainty and variability.

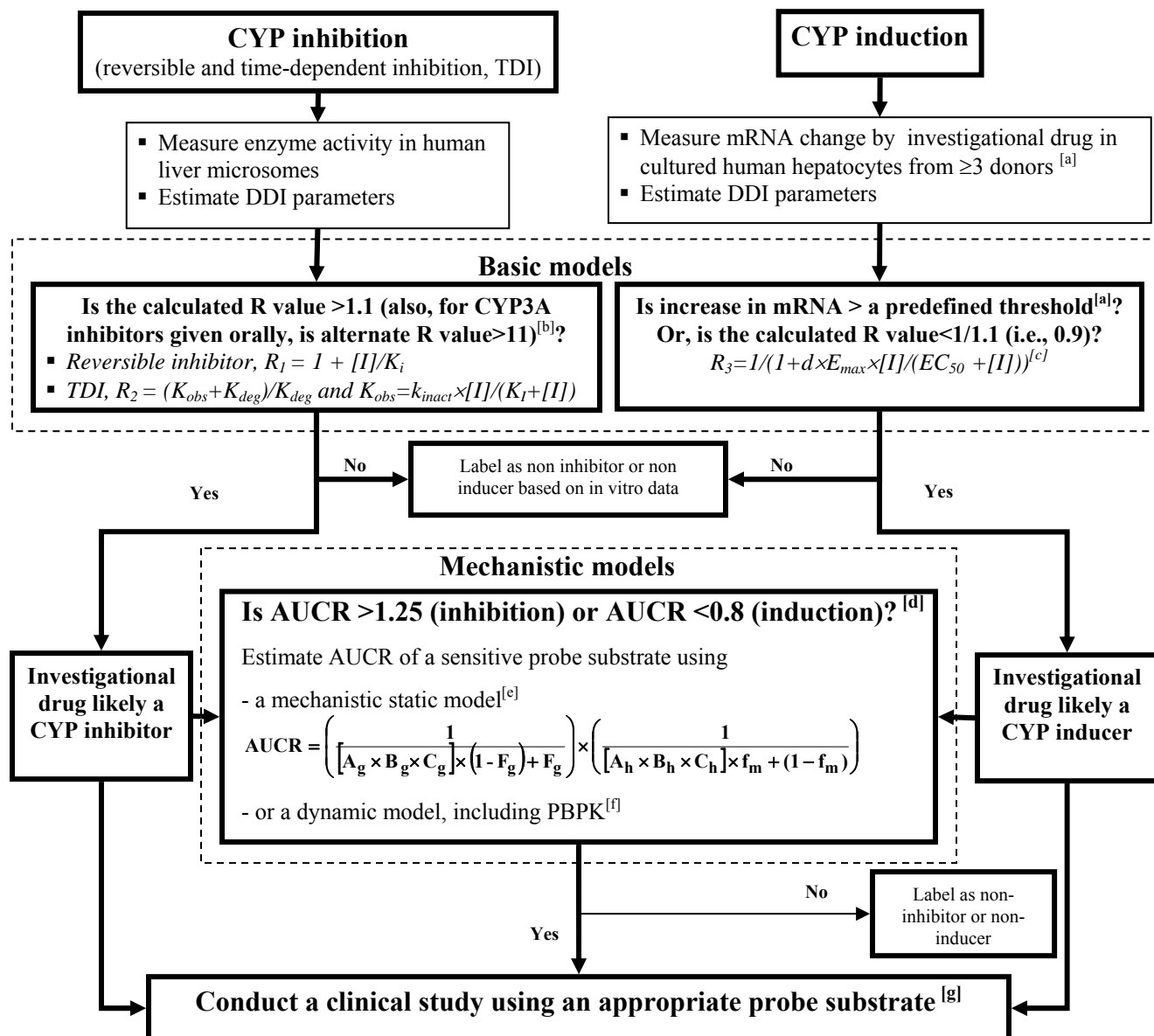
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673 The sections that follow include details on enzyme inhibitor and inducer,  
674 respectively.

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675 **Figure 4. General Scheme of Model-Based Prediction: The Investigational Drug (and**  
 676 **Metabolite Present at ≥25% of Parent Drug AUC) as an Interacting Drug of CYP Enzymes**



677 [a] An in vitro induction system may be established in cultured human hepatocytes from ≥3 donors. Use sufficient  
 678 numbers of clinical inducers and non-inducers to determine a cutoff value (e.g., as described in Fahmi, Kish et al,  
 679 2010). Note that these cutoff values may vary among different laboratories because of the variability among  
 680 hepatocyte lots.  
 681

682 [b] Equations are as described in Bjornsson et al. 2003. [I] can be estimated by the maximal total (free and bound)  
 683 systemic inhibitor concentration in plasma and the cutoff for R is 1.1. In addition, for CYP3A inhibitors that are  
 684 dosed orally, [I] should also be estimated by [I]=I<sub>gut</sub>=Molar Dose/250 mL and the cutoff for this alternate R is 11  
 685 (Zhang et al. 2008). K<sub>deg</sub> is the apparent first order degradation rate constant of the affected enzyme; K<sub>i</sub> is the  
 686 unbound reversible inhibition constant determined in vitro; k<sub>inct</sub> and K<sub>I</sub> are maximal inactivation rate constant and  
 687 apparent inactivation constant, respectively; K<sub>obs</sub> is the apparent inactivation rate constant and K<sub>obs</sub>=  
 688

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689  $k_{inact} \times [I] / (K_I + [I])$ ; and R is the ratio of intrinsic clearance by metabolizing enzyme in the absence and in the presence  
690 of inhibitor.

691  
692 <sup>[c]</sup> Equation is described in Fahmi et al. 2009.  $EC_{50}$  is the concentration causing half maximal effect;  $E_{max}$  is the  
693 maximum induction effect; and  $[I]$  is maximal total (free and bound) systemic inducer concentration in plasma; d is a  
694 scaling factor that is assumed as 1 for the basic model.

695  
696 <sup>[d]</sup> These are suggested values according to the lower and upper limit of equivalence range. However, we are open to  
697 discussion based on sponsors' interpretation. If the calculated AUCR using a mechanistic static model is outside the  
698 equivalence range, the sponsor has the option to use a dynamic model (e.g., a PBPK model) supported by available  
699 clinical pharmacokinetic data to calculate AUCR and determine whether or not there is a need to conduct clinical  
700 drug-drug interaction studies.

701  
702 <sup>[e]</sup> A mechanistic static model (or a “net effect model”) is modified from that reported by Fahmi et al. 2009.

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

703 Where  $F_g$  is the fraction available after intestinal metabolism;  $f_m$  is the fraction of systemic clearance of the substrate  
704 mediated by the CYP enzyme that is subject to inhibition/induction; subscripts “h” and “g” denote liver and gut,  
705 respectively;  $[I]_h = f_{u,b} \times ([I]_{max,b} + F_a \times K_a \times Dose / Q_h)$  (Ito et al. 2002);  $[I]_g = F_a \times K_a \times Dose / Q_{en}$  (Rostami-Hodjegan and  
706 Tucker 2004). In these equations,  $f_{u,b}$  is the unbound fraction in blood, when it is difficult to measure due to high  
707 protein binding in plasma, a value of 0.01 should be used for  $f_{u,b}$ ;  $[I]_{max,b}$  is the maximal total (free and bound)  
708 inhibitor concentration in the blood at steady state;  $F_a$  is the fraction absorbed after oral administration, a value of 1  
709 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  
710  $min^{-1}$  (Ito et al. 1998) can be used when the data is not available; and  $Q_{en}$  and  $Q_h$  are blood flow through enterocytes  
711 (e.g., 18 L/hr/70 kg, Yang et al. 2007 (a)) and hepatic blood flow (e.g., 97 L/hr/70 kg, Yang et al. 2007 (b)),  
712 respectively.

713  
714 <sup>[f]</sup> Dynamic models, including physiologically-based pharmacokinetic (PBPK) models, can be developed using both  
715 in vitro drug disposition data (e.g., protein/tissue binding, metabolism, transport, and drug-drug interaction) and  
716 physicochemical properties. The model should be refined when human pharmacokinetic data become available. The  
717 model can then be used to evaluate the drug-drug interaction potential with a sensitive substrate of the CYP enzymes  
718 of interest (Rostami-Hodjegan and Tucker 2007). The model of the substrate needs to be developed and drug  
719 interaction mechanisms should be appropriately defined by linking the models of the substrate and the interacting  
720 drug (see section IV.A.1.b-3 and Figure 5 for more details). If a metabolite is involved in a drug-drug interaction, a  
721 model for the metabolite can be established and linked to the parent drug to evaluate its inhibition/induction  
722 potential.

723  
724 <sup>[g]</sup> See Table 5 (section V.C below) and Zhang et al. 2010.

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#### *b-1. Investigational drug as an enzyme inhibitor using basic models*

The potential of an investigational drug to inhibit CYP enzymes is usually investigated in vitro using human liver tissues such as human liver microsomes or cDNA-expressed microsomes to determine the inhibition mechanisms (e.g., reversible or time-dependent inhibition) and inhibition potency (e.g.,  $K_i$ ).

The R value is dependent on the in vitro inhibition parameters and the maximum inhibitor concentration [I] that can be achieved in vivo with the highest dose. Although several algorithms to calculate [I] have been proposed, selection of [I] should justify maximum exposure of interacting drug at different tissues (Footnote [b] of Figure 4). The use of a cutoff R value of 1.1 where [I] represents maximum total (free and bound) system concentration of the inhibitor is based on an earlier FDA recommendation for reversible inhibition (Huang et al. 2007). Note an orally administered drug may inhibit CYPs that have a high expression in the intestine (e.g., CYP3A). Under such circumstances,  $I_{\text{gut}}$  (defined as molar dose/250 mL) may represent the maximum inhibitor concentrations better than the systemic concentrations. An alternate R value ( $R=1+I_{\text{gut}}/K_i$ ) of 11 should be used as a conservative criteria to avoid false negatives. This basic static model has two major uses. First, it eliminates unnecessary clinical studies when the R value is below the threshold of 11 (for orally administered drugs that may inhibit CYP3A) or 1.1. Second, it allows rank ordering of inhibition potential across different CYP enzymes (Figure 2) for the same drug so that in vivo drug-drug interaction evaluations can be prioritized. For example, an in vivo study with a sensitive substrate of the CYP with the largest R may be carried out first. If the in vivo study shows no interaction, in vivo evaluation of other CYPs with smaller R will not be needed. However, there are exceptions to this approach. For example, if a metabolite present at  $\geq 25\%$  of the parent drug AUC inhibits CYP enzymes in vitro, an R value for the metabolite should be calculated based on metabolite exposure and its inhibition potency (e.g.,  $K_i$ ) for the CYPs. The rank order of the metabolite R values should be considered when determining what in vivo studies need to be conducted.

Most inhibitory drug interactions with CYP enzymes are reversible, but in some cases the inhibitory effect increases over time and is not promptly reversible. This effect is due to irreversible covalent binding or quasi-irreversible noncovalent tight binding of a chemically reactive intermediate to the enzyme that catalyzes its formation. This class of inhibitory drug interactions is called time-dependent inhibition (TDI). Examples of TDI of CYP3A include the HIV protease inhibitors ritonavir and saquinavir, the macrolide antibiotics erythromycin and clarithromycin, and the calcium channel blockers verapamil and diltiazem. In the case of diltiazem, both parent drug diltiazem and its primary metabolite, N-desmethyldiltiazem, are time-dependent CYP3A inhibitors. An example of TDI of CYP2D6 is paroxetine, which significantly inhibits the metabolism of desipramine, tamoxifen, dextromethorphan, and bupropion. When TDI is the mode of inhibition, the inhibitory interaction will generally be greater over time following multiple dosing and be

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769 longer lasting after discontinuation of the inhibitor than in a situation when the inhibitory  
770 interaction is reversible. For example, the maximum inhibition of CYP3A in humans by  
771 erythromycin administered 200 mg three times a day appeared to occur after 4 days of  
772 dosing (the AUC values of oral midazolam, a probe substrate of CYP3A, increased 2.3-,  
773 3.4-, and 3.4- fold, respectively, on days 2, 4, and 7) (Okudaira et al. 2007). Therefore,  
774 TDI should be studied in standard in vitro screening protocols by pre-incubating the drug  
775 (a potential inhibitor) before the addition of a substrate. Any time-dependent loss of  
776 initial product formation rate may indicate time-dependent inhibition, and definitive in  
777 vitro studies to obtain TDI parameters (i.e.,  $k_{inact}$  and  $K_I$  where  $k_{inact}$  and  $K_I$  are maximal  
778 inactivation rate constant and apparent inactivation constant, respectively) are  
779 recommended. Details of this tiered approach were proposed by the PhRMA Drug  
780 Metabolism Technical Group (Grimm et al. 2009). However, prediction of TDI in vivo  
781 from in vitro inactivation parameters remains challenging because of the complexity of the  
782 mechanism as compared to reversible inhibition. Generally, TDI is evaluated under the  
783 condition when the affected enzyme level reaches a new steady state in the presence of the  
784 inhibitor, and the inhibitor does not affect de novo synthesis of the enzyme. In contrast to  
785 reversible inhibition, the R value (Figures 4) for time-dependent inhibition is dependent on  
786 the rate constant for enzyme degradation, in addition to inhibitor exposure level and the  
787 TDI parameters ( $k_{inact}$  and  $K_I$ ). Furthermore, the degradation kinetics for each CYP has  
788 not been unambiguously determined (Yang et al. 2008). If in vitro results suggest a TDI  
789 potential (e.g.,  $R > 1.1$ ), an in vivo study is recommended. Alternatively, the sponsor can  
790 estimate the degree of drug-drug interactions using mechanistic models (see Figures 4,  
791 and section IV.A.1.b-3)

#### *b-2. The investigational drug as an enzyme inducer using a basic model*

792  
793  
794  
795  
796 Several algorithms and quantitation approaches have been proposed for studying enzyme  
797 induction using in vitro data (Shou et al. 2008; Almond et al. 2009; Fahmi et al. 2009;  
798 Fahmi, Kish, et al. 2010; Fahmi and Ripp 2010). Human hepatocytes continue to be the  
799 system of choice for evaluating enzyme induction in vitro. Although freshly isolated  
800 human hepatocytes have been the gold standard, advancement in cryopreservation  
801 technology has made the cryopreserved hepatocytes available for routine use. When  
802 determining enzyme induction potential of an investigational drug using cultured human  
803 hepatocytes, the following are considered critical:

- 804  
805 • To account for inter-individual variability, hepatocyte preparations from at least three  
806 (3) donors are recommended. If the result in hepatocytes from at least one donor  
807 exceed the predefined threshold (see Figure 4, R value estimated using a basic model),  
808 the drug is considered an inducer and a follow-up evaluation is needed (e.g., see  
809 Figure 4, estimate AUCR using a mechanistic model or conduct a clinical study).
- 810 • Performance of these hepatocyte preparations in identifying enzyme induction  
811 potential of a sufficient number of clinical inducers should be demonstrated.
- 812 • The changes in the mRNA level of the target gene should be used as an endpoint

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- 813 (Fahmi, Kish, et al. 2010).
- 814 • Vehicle control, positive control (usually a known strong inducer), and negative
- 815 control (usually a known non-inducer) should be included in the experiment.
- 816 Concentrations of the positive control inducers can be found in Table 2.
- 817

818 Studies indicate that activation of the nuclear receptor, Pregnane X receptor (PXR), results

819 in co-induction of CYP3A and CYP2C. Thus, a negative in vitro result for CYP3A

820 induction eliminates the need for additional in vitro or in vivo induction studies for

821 CYP3A and CYP2C enzymes. If CYP3A induction results are positive, then induction of

822 CYP2C should be studied either in vitro or in vivo. Because CYP1A2 and CYP2B6 may

823 be induced by different nuclear receptors (e.g., aryl hydrocarbon receptor (AhR), or

824 constitutive androstane receptor (CAR)), they may not be co-induced with CYP3A.

825 Therefore, the potential for induction of CYP1A2 and CYP2B6 should be evaluated

826 regardless of the CYP3A result.

827

828 Initially, CYP1A2, CYP2B6, and CYP3A should be evaluated in vitro (Figure 4). If the

829 in vitro induction results are positive according to predefined thresholds using basic

830 models, the investigational drug is considered an enzyme inducer and therefore further in

831 vivo evaluation may be warranted. Alternatively, a sponsor can estimate the degree of

832 drug-drug interactions using mechanistic models (see Figures 4, and section IV.A.1.b-3)

833 to determine the need for further in vivo evaluation.

834

835

**Table 2. In Vitro CYP Inducers**

CYP	In Vitro Inducer * as Positive Controls	Recommended Concentration ( $\mu$ M) of the Positive Controls	Reported Fold Induction In Enzyme Activities
1A2	omeprazole lansoprazole	25-100 10	14-24 10
2B6	phenobarbital	500-1000	5-10
2C8	rifampin	10	2-4
2C9	rifampin	10	4
2C19	rifampin	10	20
2D6	none identified		
3A4	rifampin	10-50	4-31

836 \*Note that this is not an exhaustive list. For an updated list, see the following link

837 [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm)

838 [/ucm080499.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

839

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841  
842 At present, data generated from other in vitro systems are considered complementary and  
843 may be reviewed along with data generated with cultured hepatocyte systems.  
844

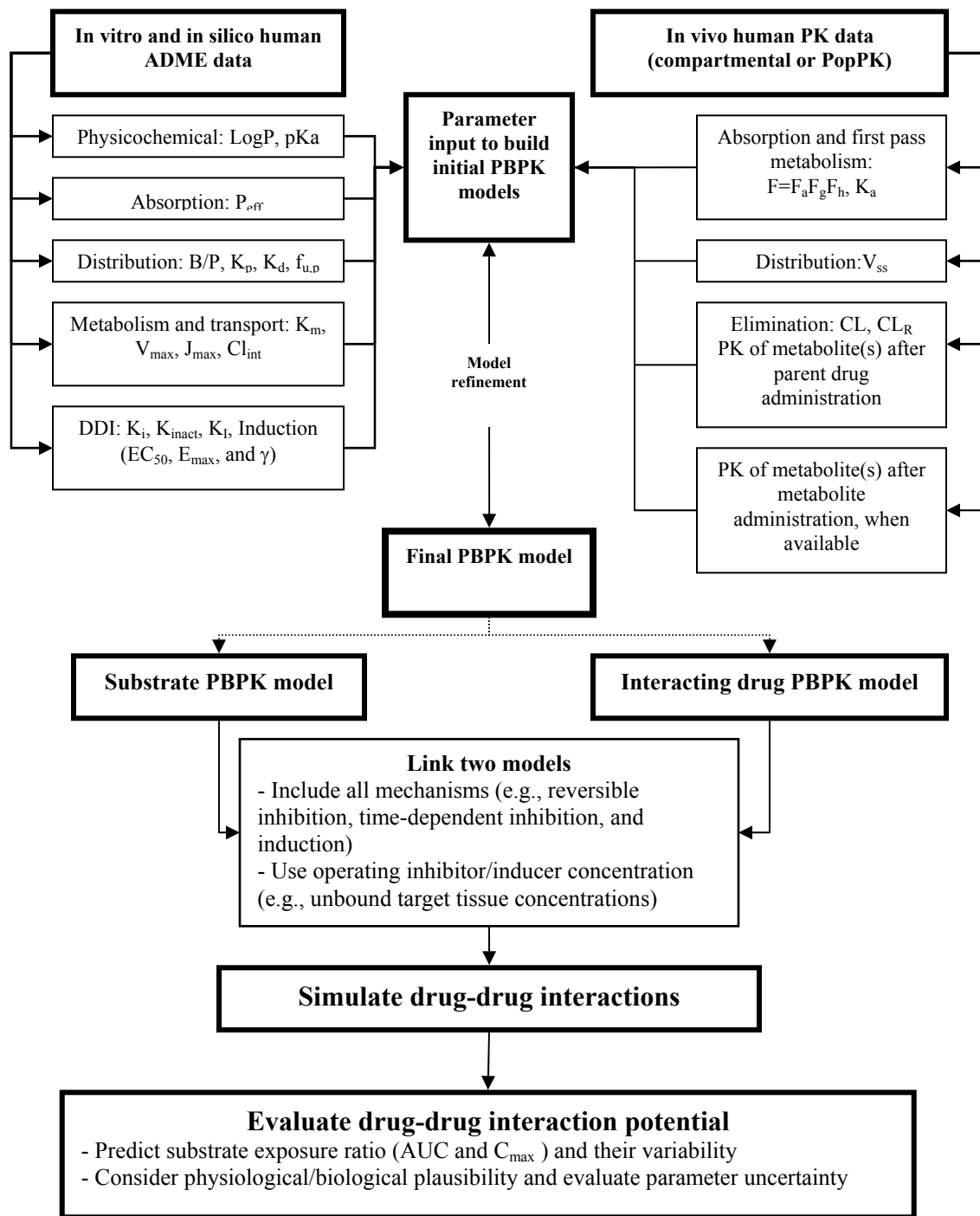
845  
846 *b-3. The investigational drug as enzyme inhibitor and/or inducer using mechanistic*  
847 *models*

848  
849 Figure 4 includes a framework for assessing drug-drug interactions using more  
850 mechanistic models, including PBPK models. Algorithms of enzyme inhibition and  
851 enzyme induction, described according to basic models in above sections (b-1 and  
852 b-2), can be incorporated into these mechanistic models. As mentioned earlier, PBPK  
853 models offer useful alternatives to dedicated clinical studies. This alternative is especially  
854 important when the sponsor would like to support the absence of meaningful clinical drug-  
855 drug interactions with an investigational drug that showed interaction potential according  
856 to a basic model. At present, the field of predicting drug-drug interactions by PBPK  
857 models is still developing and the best practices are being defined. Hence, sponsors  
858 should provide comprehensive justifications on model assumptions, physiological and  
859 biochemical plausibility, variability, and uncertainty measures. The submission  
860 containing the use of such advanced models should include a description of the structural  
861 model, source and justifications for both system- and drug-dependent parameters, type of  
862 error models, model output, data analysis, and adequate sensitivity analyses. If predefined  
863 models (structural and error) from commercially available software are employed,  
864 versions and deviations from the predefined models should be specified. Sponsors are  
865 encouraged to communicate with the FDA regarding the use of these models for the  
866 prediction of drug-drug interactions. The criteria used for assessing “equivalence” (e.g.,  
867 predicted AUC ratio of 0.8-1.25 using population-based PBPK models) may be used as an  
868 initial cutoff in deciding whether in vivo studies are needed. However, these are  
869 suggested values. We are open to discussion based on sponsors’ interpretation.  
870

871 Figure 5 shows a general scheme that uses a PBPK model to predict the degree of drug-  
872 drug interactions. PBPK models for both substrate and interacting drug (inhibitor or  
873 inducer) should be constructed separately using in vitro and in vivo disposition  
874 parameters, before they are linked through appropriate mechanisms to predict the degree  
875 of drug-drug interaction.



876 **Figure 5. Using a PBPK Model to Explore Drug-Drug Interaction Potential Between a**  
 877 **Substrate Drug and an Interacting Drug (Modified from Zhao et al. 2011).**



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879 Abbreviations: ADME, absorption, distribution, metabolism and excretion; AUC, area under the plasma  
880 concentration versus time curve; B/P, blood to plasma ratio;  $C_{max}$ , maximum concentration; CL, clearance;  $CL_r$ ,  
881 renal clearance; DDI, drug-drug interactions;  $EC_{50}$  or  $IC_{50}$ , concentration causing half maximal effect or inhibition;  
882  $E_{max}$  or  $I_{max}$ , maximum effect or inhibition; F, bioavailability;  $F_a$ , fraction absorbed;  $F_g$ , bioavailability in the gut;  $F_h$ ,  
883 bioavailability in the liver;  $f_{u,p}$ , unbound fraction in plasma;  $\gamma$ , Hill coefficient;  $J_{max}$ , maximum rate of transporter-  
884 mediated efflux/uptake;  $K_a$ , first-order absorption rate constant;  $K_d$ , dissociation constant of drug-protein complex;  
885  $K_i$ , reversible inhibition constant, concentration causing half maximal inhibition;  $K_{inact}$ , apparent inactivation constant,  
886 concentration causing half maximum inactivation;  $k_{inact}$ , apparent maximum inactivation rate constant;  $K_m$ ,  
887 Michaelis-Menten constant, substrate concentration causing half maximal reaction or transport;  $K_p$ , tissue-to-plasma  
888 partition coefficient; LogP, Logarithm of the octanol-water partition coefficient;  $P_{eff}$ , jejunum permeability; PK,  
889 pharmacokinetics; PopPK, population pharmacokinetics; V, volume of distribution;  $V_{max}$ , maximum rate of  
890 metabolite formation.

891

892

## 893 2. *In Vitro Transporter Studies*

894

### 895 a. *The Investigational Drug as a Substrate for Transporters*

896

897 Both P-gp and BCRP are expressed in the gastrointestinal tract, liver, and kidney, and  
898 have a role in limiting oral bioavailability. Therefore, all investigational drugs should be  
899 evaluated in vitro to determine whether they are a potential substrate of P-gp or BCRP  
900 (See Figure 6, left panel).

901

902 A bidirectional assay in Caco-2 cells or overexpressed cell lines is a preferred method for  
903 in vitro evaluation. If the results are positive, an in vivo evaluation in humans is  
904 recommended (see Figure A1 in the Appendix for a decision tree on when an in vivo  
905 human study is recommended based on the in vitro data).

906

907 For drugs that are highly permeable and highly soluble, the intestinal absorption is not a  
908 rate-limiting step, and, therefore, it may be appropriate to exempt such drugs from the in  
909 vivo evaluation with a P-gp or BCRP inhibitor. (For further discussion regarding the  
910 defining a drug as highly soluble and high permeable (e.g., biopharmaceutical  
911 classification class (BCS) 1 drugs), see the Guidance for Industry on *Waiver of In Vivo  
912 Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage  
913 Forms Based on a Biopharmaceutics Classification System*,  
914 [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm0  
915 70246](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246)).

916

917 Investigational drugs should be evaluated in vitro to determine whether they are a  
918 substrate of hepatic uptake transporters OATP1B1/OATP1B3 when their hepatic  
919 pathway is significant (e.g., clearance through hepatic or biliary secretion is more than or  
920 equal to 25% of the total clearance)<sup>3</sup> (Figure 6, middle panel). Similarly, investigational  
921 drugs should be evaluated in vitro to determine whether they are a substrate of OAT1/3

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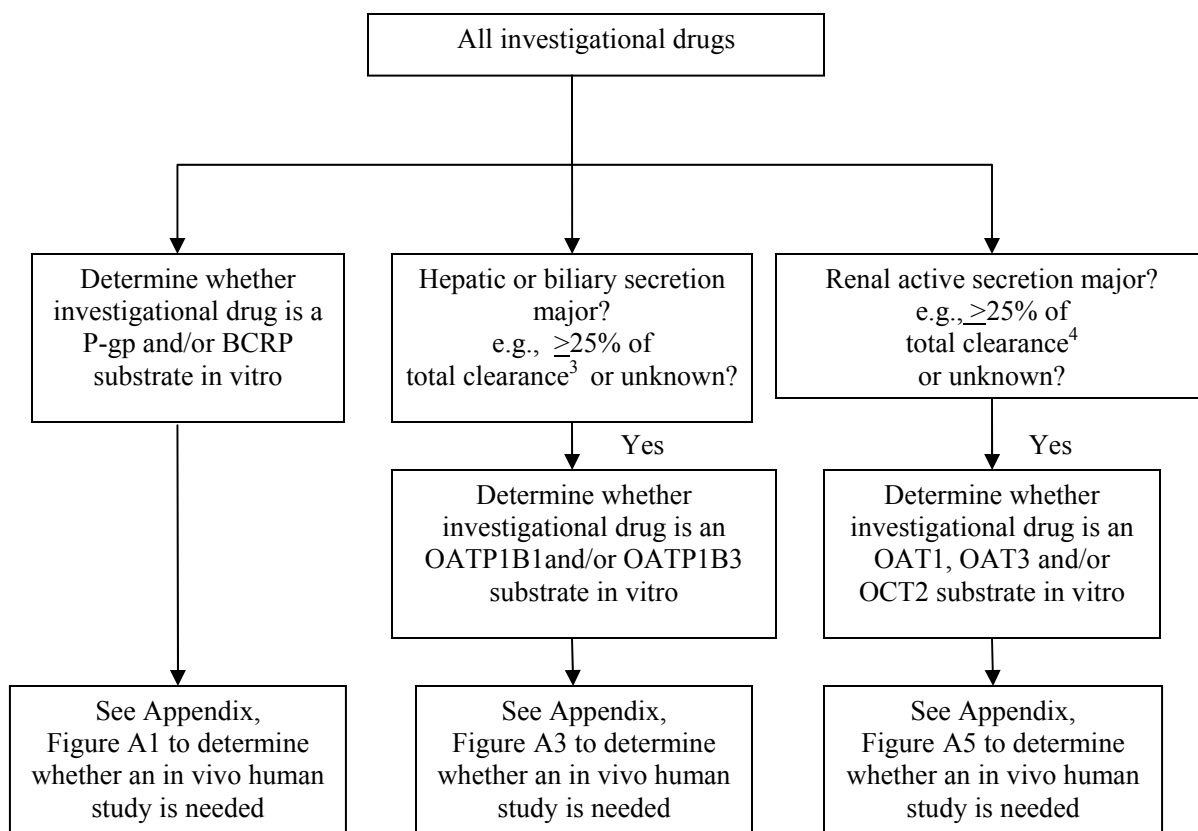
<sup>3</sup> Biliary secretion can be estimated from preclinical data, in vitro hepatocyte uptake data or radiolabeled ADME data, and nonrenal clearance data.

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922 and OCT2 when their renal active secretion is important (active secretion by kidney is  
923 more than or equal to 25% of total clearance)<sup>4</sup> (Figure 6, right panel).  
924

925 **Figure 6. Evaluation of Investigational Drugs as Substrates for P-gp, BCRP, OATP1B1,**  
926 **OATP1B3, OAT1, OAT3, and OCT2 Transporters.**



927  
928  
929 Other transporters (e.g., MRP (multidrug resistance-associated protein)) may need to be  
930 studied based on knowledge of other drugs in the same therapeutic class as the  
931 investigational new drug. Information for the other drugs may include observed drug-  
932 drug interactions that are attributed to these other transporters. New information in the  
933 literature may raise questions about additional transporters.  
934

935  
936 *b. The Investigational Drug as an Inhibitor of Transporters*  
937

<sup>4</sup> Percent (%) active renal secretion was estimated from  $(CL_r - fu * GFR) / CL_{Total}$ ; fu is the unbound fraction in plasma.

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938 Because many drugs may be used concomitantly with digoxin (a P-gp substrate) and  
939 statins (BCRP and OATP1B1/1B3 substrates), evaluation of investigational drugs as  
940 inhibitors of P-gp, BCRP, and OATP1B1/OATP1B3 should be considered. An  
941 investigational drug also should be evaluated to determine whether it inhibits OCT2,  
942 OAT1, and OAT3, because there have been clinically significant interactions  
943 demonstrated for critical drugs that are known OCT substrates (e.g., metformin) or OAT  
944 substrates (e.g., methotrexate, tenofovir, zidovudine). The need for further in vivo drug  
945 interaction studies will be based on the criteria described in the decision trees in Figures  
946 A2, A4, and A6 in the Appendix.

947  
948 The decision as to whether the investigational drug should be evaluated as an inhibitor  
949 for other transporters will be based on the therapeutic class, where unexpected drug-drug  
950 interactions may have been observed and attributed to these other transporters, and when  
951 new information becomes available in the literature.

#### 952 953 *c. The Investigational Drug as an Inducer of Transporters*

954  
955 Transporters can be induced by mechanisms similar to those for CYP enzymes (e.g., by  
956 activation of specific nuclear receptors). The expression levels of some transporters are  
957 regulated in coordination with metabolizing enzymes, and they share common nuclear  
958 factors. For example, a large number of drugs and dietary supplements (e.g., rifampin,  
959 St. John's wort) concomitantly induce the expression of CYP3A and MDR1 (P-gp),  
960 MRP2, MRP3, MRP4, and OATP1A2.

961  
962 However, methods for in vitro evaluation for transporter induction are not well  
963 understood. Cell lines are being used for in vitro P-gp induction including human colon  
964 adenocarcinoma cell line LS 180/WT, and its adriamycin-resistant (LS 180/AD 50) or  
965 vinblastine-resistant (LS 180/V) sublines. Further development is needed to validate the  
966 utility of the in vitro assays to determine the need for an in vivo induction study. Until a  
967 well-accepted system is developed, activation of nuclear receptor assays may be used as  
968 an initial evaluation of the induction potential of an investigational drug on transporters.

969  
970 The definitive determination of induction potential is based on in vivo induction studies.  
971 The sponsor should consult with FDA about studying induction of transporters in vivo.

#### 972 973 *3. Considerations of the Metabolites of Investigational Drugs*

974  
975 Metabolites formed in vivo may reach significant exposure (e.g.,  $\geq 25\%$  of the parent  
976 drug) and elicit pharmacological and/or toxicological effects. Therefore, the same  
977 considerations on further metabolism, transport, and drug interaction studies described  
978 above should be considered for relevant metabolites of the investigational drugs. The  
979 decision on which metabolite(s) should be investigated depends on multiple factors,  
980 including the knowledge in pharmacological/toxicological activities (from in vitro human  
981 cell line data and/or in vivo animal data) and the knowledge in metabolites' disposition

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982 kinetics. For example, metabolites deemed insignificant after a single dose of the parent  
983 drug may accumulate to appreciable exposure after multiple dosing if they have long  
984 half-lives. Unexpected high exposure of metabolites may be attained in subjects with  
985 decreased function of organs responsible for their elimination and in the event of drug  
986 interactions affecting the disposition of the parent drug. Appropriate assays for  
987 metabolites should be in place to monitor the metabolite levels along with the parent.  
988

989 Given the complexity of the kinetics and interaction mechanisms of formed metabolites,  
990 modeling and simulation integrating knowledge of drug disposition kinetics of both  
991 parent investigational drug and metabolites may provide a useful tool to facilitate the  
992 evaluation of drug interaction potential of metabolites (see earlier sections).  
993

#### **B. In Vivo Studies**

##### *1. In Vivo Drug-Drug Interactions*

998 For detailed discussion on recommendations of in vivo human drug-drug interaction  
999 studies, please refer to section V below  
1000

##### *2. In Vivo Drug-Therapeutic Protein (TP) Interactions*

1003 Drug-TP interactions have been observed and information about these interactions is  
1004 included in labeling. Figure 7 lists the types of studies that have been conducted during  
1005 drug development to evaluate TP and small molecule drug interactions. The following  
1006 are general considerations:  
1007

- 1008 • If an investigational TP is a cytokine or cytokine modulator, studies should be  
1009 conducted to determine the TP's effects on CYP enzymes or transporters (Huang et  
1010 al. 2010, Le Vee M et al. 2009). In vitro or animal studies have limited value in the  
1011 qualitative and quantitative projection of clinical interactions because translation of in  
1012 vitro to in vivo and animal to human results to date has been inconsistent,  
1013 necessitating in vivo drug interaction studies. The in vivo evaluations of TPs in  
1014 targeted patient populations can be conducted with individual substrates for specific  
1015 CYP enzymes and transporters, or studies can be conducted using a “cocktail  
1016 approach” (see section V.C).  
1017
- 1018 • For TPs that will be used in combination with other drug products (small molecule or  
1019 TP) as a combination therapy, studies should evaluate the effect of each product on  
1020 the other. The studies should assess effects on pharmacokinetics (PK) and, when  
1021 appropriate, pharmacodynamics (PD) of either drug. This evaluation is particularly  
1022 important when the drug used in combination has a narrow therapeutic range (e.g.,  
1023 chemotherapeutic agents).  
1024
- 1025 • When there are known mechanisms or prior experience with certain PK or PD

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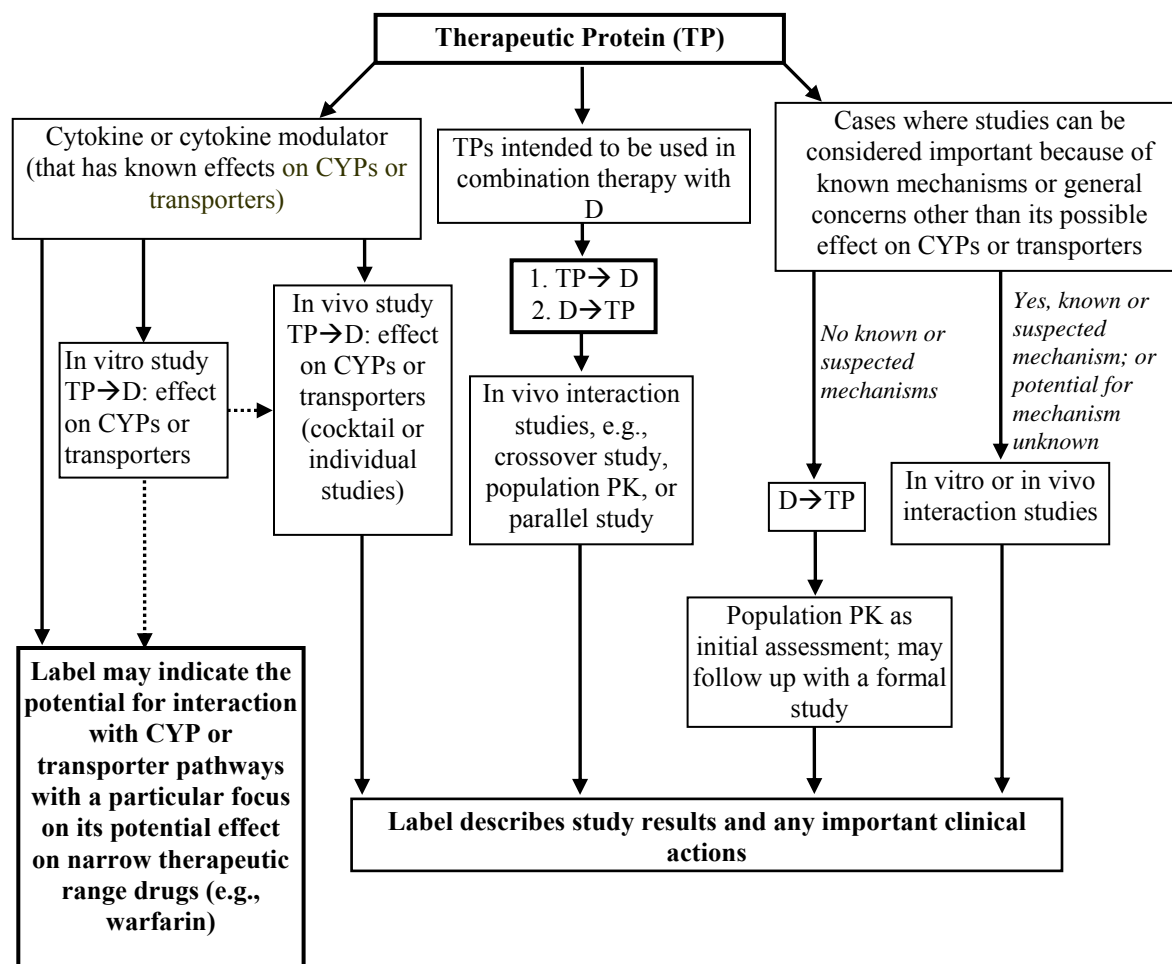
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1026 interactions, appropriate in vitro or in vivo assessments for possible interactions  
1027 should be conducted. Some interactions between drugs and TPs are based on  
1028 mechanisms other than CYP or transporter modulation. For example, methotrexate's  
1029 immunosuppressive effect may alter the clearance of concomitantly administered TPs  
1030 through the reduction of antibodies formed against TP. Other examples include  
1031 heparin's effect on palifermin (increased exposure) and paclitaxel's effect on  
1032 etanercept (increased exposure).  
1033  
1034

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1035 **Figure 7. Summary of The Types of Studies That Have Been Used During Drug**  
1036 **Development to Evaluate Therapeutic Protein (TP)–Small-Molecule Drug (D) Interactions.**  
1037 **This includes an evaluation of the effect of TP on D (TP→D) and the effect of D on TP**  
1038 **(D→TP). The broken lines suggest the limited use of in vitro studies for informing in vivo**  
1039 **study design or labeling. CYP, cytochrome P450. (Modified from Huang et al. 2010)**  
1040  
1041



1042  
1043  
1044  
1045  
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### 1047 **C. Using a Population Pharmacokinetic Approach to Assess Drug-Drug Interactions**

1048  
1049 Population pharmacokinetic (PopPK) analyses of data obtained from large-scale clinical studies  
1050 that include sparse or intensive blood sampling can help characterize the clinical impact of  
1051 known or newly identified interactions and determine recommendations for dosage  
1052 modifications for the investigational drug as a substrate. The results of such analyses can be  
1053 informative and sometimes conclusive when the clinical studies are adequately designed to  
1054 detect significant changes in drug exposure due to drug-drug interactions. PopPK evaluations  
1055 may also detect unsuspected drug-drug interactions, a particularly important possibility given the  
1056 complexity of the potential interactions (see section V.C.4), not all of which are likely to have  
1057 been anticipated and studied. PopPK evaluations can also provide further evidence of the  
1058 absence of a drug-drug interaction, when supported by prior evidence and mechanistic data. It is  
1059 unlikely, however, that population analysis will persuasively show the absence of an interaction  
1060 that is suggested by information from in vivo studies specifically designed to assess a drug-drug  
1061 interaction. To be optimally informative, PopPK studies should have carefully designed study  
1062 procedures and sample collection protocols. Simulations (e.g., by population-based PBPK  
1063 models) can provide valuable insight into optimizing the study design (see section IV.A above).  
1064 Detailed information on the dose given and time of administration should be documented for the  
1065 co-administered drugs. When relevant for the specific drug, the time of food consumption  
1066 should be documented. Population analyses should focus on excluding a specific clinically  
1067 meaningful PK change. A guidance for industry on *Population Pharmacokinetics* is available at  
1068 ([http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm)  
1069 [htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm)). Because exposure of co-administered drugs is not monitored in most PopPK studies, the  
1070 PopPK approach may not be useful to assess the effect of the investigational drugs on other  
1071 drugs.

1072

1073

### 1074 **V. DESIGN OF IN VIVO DRUG-DRUG INTERACTION STUDIES**

1075

1076 If in vitro studies and other information suggest that in vivo drug-drug interaction studies would  
1077 be helpful (e.g., based on the decision trees in Figures 2-7), the following general issues and  
1078 approaches should be considered. In the following discussion, the term *substrate* (S) is used to  
1079 indicate the drug studied to determine whether its exposure is changed by another drug. The  
1080 other drug is termed the *interacting drug* (I).

1081

#### 1082 **A. Study Design**

1083

1084 In vivo drug-drug interaction studies generally are designed to compare substrate concentrations  
1085 with and without the interacting drug. Because a specific study can address a number of  
1086 questions and clinical objectives, many study designs for investigating drug-drug interactions  
1087 can be considered. In general, crossover designs in which the same subjects receive substrate  
1088 with and without the interacting drug are more efficient. A study can use a randomized  
1089 crossover (e.g., S followed by S+I, S+I followed by S), one-sequence crossover (e.g., S followed  
1090 by S+I), or a parallel (S in one group of subjects and S+I in another group) design, and there may



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1091 be reason to have another period when the I is removed to assess effect duration. The following  
1092 possible dosing regimen combinations for a substrate and interacting drug can also be used:  
1093 single dose/single dose, single dose/multiple dose, multiple dose/single dose, and multiple  
1094 dose/multiple dose. Additional factors include consideration of the sequence of administration  
1095 and the time interval between dosing of substrate and inhibitor/inducer.

1096  
1097 The selection of a study design depends on a number of factors for both the substrate and  
1098 interacting drug, including (1) whether the substrate and/or interacting drug is used acutely or  
1099 chronically; (2) safety considerations, including whether a substrate is a narrow therapeutic  
1100 range (NTR)<sup>5</sup> or non-NTR drug; (3) pharmacokinetic and pharmacodynamic characteristics of  
1101 the substrate and interacting drugs; (4) whether there is a desire to assess induction as well as  
1102 inhibition; (5) whether the inhibition is delayed; and (6) whether there is a need to assess  
1103 persistence of inhibition or induction after withdrawal of the interacting drug. The interacting  
1104 drugs and the substrates should be dosed so that the exposures of both drugs are relevant to their  
1105 clinical use, including the highest doses likely to be used in clinical practice, and plasma levels  
1106 of both drugs should be obtained to show this. Simulations can help select an appropriate study  
1107 design (see section IV.A). The following considerations may be useful:

- 1108  
1109 • When attainment of steady state is important, and either the substrate or interacting  
1110 drug or their metabolites have long half-lives, one or both periods of a crossover  
1111 study should be long, but several other approaches can be considered, depending on  
1112 pharmacokinetic characteristics of the drug and metabolites. For example, if the  
1113 substrate has a long half-life, a loading dose could be used to reach steady state  
1114 concentrations earlier in a one-sequence crossover followed by an S+I period long  
1115 enough to allow I to reach steady state (here too, using a loading dose could shorten  
1116 that period).
- 1117  
1118 • When it is important that a substrate and/or an interacting drug be studied at steady  
1119 state for a long duration because the effect of an interacting drug is delayed, as is the  
1120 case for inducers and TDIs, documentation that near steady state has been attained for  
1121 the pertinent substrate drug and metabolites as well as the interacting drug is critical,  
1122 and both S and I should be present long enough to allow the full effect to be seen.  
1123 This documentation can be accomplished by sampling over several days prior to the  
1124 periods when test samples are collected. This information is important for  
1125 metabolites and the parent drug, particularly when the half-life of the metabolite is  
1126 longer than the parent. It is also important when the interacting drug and metabolites  
1127 are both metabolic inhibitors (or inducers). Finally, it is critical to evaluate the time it  
1128 takes for the enzyme activities to return to normal when induction or TDI is involved  
1129 so that a third crossover period in which the interacting drug (I) is removed will  
1130 generally be recommended.
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<sup>5</sup> NTR drugs are defined as those drugs for which there is little separation between therapeutic and toxic doses or the associated blood or plasma concentrations (i.e., exposures) (see page 40).

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- Studies can usually be open label (unblinded), unless pharmacodynamic endpoints (e.g., adverse events that are subject to bias) are critical to the assessment of the interaction.
  - For a rapidly reversible inhibitor, administration of the interacting drug either just before or simultaneously with the substrate on the test day might increase sensitivity by ensuring maximum exposure to the two drugs together. For a mechanism-based inhibitor (a drug that requires metabolism before it can inactivate the enzyme; an example is erythromycin), administration of the inhibitor prior to the administration of the substrate drug can maximize the effect. If the absorption of an interacting drug may be affected by other factors (e.g., the gastric pH), it may be appropriate to control the variables or confirm the absorption through plasma level measurements of the interacting drug.
  - Timing of administration may be critical in situations of concurrent inhibition and induction. For example, if the investigational drug is a substrate for both enzymes and OATP, and rifampin is used as an enzyme inducer, the simultaneous administration of the drug with rifampin (an OATP inhibitor) may underestimate enzyme induction, so delayed administration of the substrate is recommended. The optimal delayed time should be determined. In addition, it is critical to evaluate the duration of the interaction effect after the interacting drug has been removed.
  - When the effects of two drugs on one another are of interest, the potential for interactions can be evaluated in a single study or two separate studies. Some design options are randomized three-period crossover, parallel group, and one-sequence crossover.
  - To avoid variable study results because of uncontrolled use of dietary/nutritional supplements, tobacco, alcohol, juices, or other foods that may affect various metabolizing enzymes and transporters during in vivo studies, it is important to exclude, when appropriate, subjects who used prescription or over-the-counter medications, dietary/nutritional supplements, tobacco, or alcohol within 1 week prior to enrollment. In addition, investigators should explain to subjects that for at least 1 week prior to the start of the study until its conclusion, they should not eat any food or drink/beverage containing *alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family* (e.g., kale, broccoli, watercress, collard greens, kohlrabi, brussels sprouts, mustard), and *charbroiled meats*. In some instances, it is advisable to confine subjects to a study unit for the week prior to study.
  - Because interactions might differ in subgroups of different pharmacogenetic genotypes, genotyping for the enzymes and transporters involved in the interaction should be carried out when appropriate.

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### **B. Study Population**

In most situations, clinical drug-drug interaction studies can be performed using healthy volunteers, and findings in healthy volunteers will predict findings in the patient population for which the drug is intended. Safety considerations, however, may preclude the use of healthy subjects in studies of certain drugs. In addition, there are circumstances in which subjects drawn from the intended patient population offer advantages, including the opportunity to study pharmacodynamic endpoints not present in or relevant to healthy subjects.

The extent of drug interactions (inhibition or induction) may be different depending on the subjects' genotype for the specific enzyme or transporter being evaluated. For example, subjects lacking the major polymorphic clearance pathway will show reduced total metabolism or transport. However, alternative pathways can become quantitatively more important in these subjects. In such cases, the alternative pathways should be understood and studied appropriately. Thus, phenotype or genotype determinations to identify genetically determined metabolic or transporter polymorphisms are important when evaluating effects on enzymes or transporters with polymorphisms, such as CYP2D6, CYP2C19, CYP2C9, UGT1A1, and OATP1B1 (SLCO1B1). In addition, it is valuable to specify the need for stratifying the population based on genotype while conducting the DDI studies. Another alternative is to consider powering the study for the genotype status that is likely to have the highest potential for interaction.

### **C. Choice of Substrate and Interacting Drugs**

#### *1. CYP-Mediated Interactions*

##### *a. The Investigational Drug as a Substrate of CYP Enzymes — Effect of Other Drugs on Investigational Drugs*

When testing an investigational drug for the possibility that its metabolism is inhibited or induced (i.e., as a substrate), selection of the interacting drugs should be based on in vitro or in vivo studies identifying the enzyme systems that metabolize the investigational drug. The choice of the interacting drug can then be based on known, important inhibitors and inducers of the pathway under investigation. Strong inhibitors and inducers provide the most sensitive assessment and should generally be tested first. Consider, for example, an investigational drug metabolized by CYP3A with the contribution of this enzyme to the overall elimination of this drug that is either substantial ( $\geq 25\%$  of the clearance pathway) or unknown. In this case, the inhibitor and inducer can be ketoconazole and rifampin, a strong inhibitor and a strong inducer, respectively. Other strong inhibitors or inducers are acceptable. If the study results are negative, then absence of a clinically important drug-drug interaction for the metabolic pathway is demonstrated. If the clinical study of the strong inhibitor or inducer is positive, the

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1220 sponsor would generally evaluate effects through in vivo studies or mechanistic modeling  
1221 of other less potent specific inhibitors or inducers, and develop labeling advice on dosage  
1222 adjustment (the classification of CYP inhibitors and inducers is discussed in the next  
1223 section; see Table 3 for a list of CYP inhibitors and Table 4 for CYP inducers). If the  
1224 investigational drug is metabolized by CYP3A and its plasma AUC is increased 5-fold or  
1225 higher by strong CYP3A inhibitors, it is considered a *sensitive substrate* of CYP3A. The  
1226 labeling would indicate that the drug is a “sensitive CYP3A substrate” and that its use  
1227 with strong or moderate inhibitors may call for caution, depending on the drug’s  
1228 exposure-response relationship. If the investigational drug is metabolized by CYP3A and  
1229 its exposure-response relationship indicates that a two-fold increase in the exposure  
1230 levels by the concomitant use of CYP3A inhibitors may lead to serious safety concerns  
1231 (e.g., Torsades de Pointes), it is considered a “CYP3A substrate with narrow therapeutic  
1232 range” (Table 5) (see section VI for more labeling recommendations).  
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**Table 3. Classification of In Vivo Inhibitors of CYP Enzymes<sup>(1)</sup>**

<b><u>CYP Enzymes</u></b>	<b>Strong Inhibitors<sup>(2)</sup></b> ≥ 5-fold increase in AUC or > 80% decrease in CL	<b>Moderate inhibitors<sup>(3)</sup></b> ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	<b>Weak inhibitors<sup>(4)</sup></b> ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
<b>CYP1A2</b>	Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, vemurafenib, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, Daidzein, <sup>(5)</sup> disulfiram, Echinacea, <sup>(5)</sup> famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
<b>CYP2B6</b>			Clopidogrel, ticlopidine prasugrel
<b>CYP2C8</b>	Gemfibrozil <sup>(6)</sup>		Fluvoxamine, ketoconazole, trimethoprim
<b>CYP2C9</b>		Amiodarone, fluconazole, miconazole, oxandrolone	Capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast
<b>CYP2C19</b>	Fluconazole, <sup>(7)</sup> fluvoxamine, <sup>(8)</sup> ticlopidine <sup>(9)</sup>	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole	Allicin (garlic derivative), armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole, oral contraceptives <sup>(10)</sup>
<b>CYP3A</b>	Boceprevir, clarithromycin, conivaptan, grapefruit juice, <sup>(11)</sup> indinavir, itraconazole,	Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole,	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, <sup>(5)</sup>

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	ketoconazole, lopinavir/ritonavir, mibefradil, <sup>(12)</sup> nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	fosamprenavir, grapefruit juice, <sup>(11)</sup> imatinib, verapamil	goldenseal, <sup>(5)</sup> isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, zileuton
<b>CYP2D6</b>	Bupropion, fluoxetine, paroxetine, quinidine	Cinacalcet, duloxetine, terbinafine	Amiodarone, celecoxib, clobazam, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, Echinacea, <sup>(5)</sup> escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, pazopanib, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil, vemurafenib

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- (1) Please note the following: This is not an exhaustive list. For an updated list, see the following link <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.
- (2) A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.
- (3) A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
- (4) A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.
- (5) Herbal product.
- (6) Gemfibrozil also inhibits OATP1B1.
- (7) Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
- (8) Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A;
- (9) Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2.
- (10) Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
- (11) The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when

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1257 another preparation was used (e.g., low dose, single strength).

1258 (12) Withdrawn from the United States market.

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1260 **Table 4. Classification of In Vivo Inducers of CYP Enzymes<sup>(1)</sup>**

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<b>CYP Enzymes</b>	<b>Strong Inducers</b> ≥ 80% decrease in AUC	<b>Moderate Inducers</b> 50-80% decrease in AUC	<b>Weak Inducers</b> 20-50% decrease in AUC
CYP1A2		Montelukast, phenytoin, smokers versus non-smokers <sup>(2)</sup>	Moricizine, omeprazole, phenobarbital,
CYP2B6		Efavirenz, rifampin	Nevirapine
CYP2C8		Rifampin	
CYP2C9		Carbamazepine, rifampin	Aprepitant, bosentan, phenobarbital, St. John's wort <sup>(3,4)</sup>
CYP2C19		Rifampin	Artemisinin
CYP3A	Avasimibe, <sup>(5)</sup> carbamazepine, phenytoin, rifampin, St. John's wort <sup>(3)</sup>	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, clobazamechinacea, <sup>(4)</sup> pioglitazone, prednisone, rufinamide, vemurafenib
CYP2D6	None known	None known	None known

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1264 (1) Please note the following: This is not an exhaustive list. For an updated list, see the following link:  
1265 <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.

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(2) For a drug that is a substrate of CYP1A2, the evaluation of the effect of induction of CYP1A2 can be carried out by comparative PK studies in smokers vs. non-smokers.

(3) The effect of St. John's wort varies widely and is preparation-dependent.

(4) Herbal product.

(5) Not a marketed drug.

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**Table 5. Examples<sup>(1)</sup> of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range**

<b>CYP Enzymes</b>	<b>Sensitive substrates<sup>(2)</sup></b>	<b>Substrates with narrow therapeutic range<sup>(3)</sup></b>
<b>CYP1A2</b>	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
<b>CYP2B6<sup>(4)</sup></b>	Bupropion, efavirenz	
<b>CYP2C8</b>	Repaglinide <sup>(5)</sup>	Paclitaxel
<b>CYP2C9</b>	Celecoxib	Warfarin, phenytoin
<b>CYP2C19</b>	Clobazam, lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
<b>CYP3A<sup>(6)</sup></b>	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil	Alfentanil, astemizole, <sup>(7)</sup> cisapride, <sup>(7)</sup> cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine <sup>(7)</sup>
<b>CYP2D6</b>	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine, pimozide

(1) Note that this is not an exhaustive list. For an updated list, see the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.

(2) *Sensitive CYP substrates* refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor or AUC ratio in poor metabolizers vs. extensive metabolizers is greater than 5-fold.

(3) *CYP substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

(4) The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

(5) Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.

(6) Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

(7) Withdrawn from the United States market.



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1291  
1292 NTR drugs are defined as those drugs for which there is little separation between  
1293 therapeutic and toxic doses or the associated blood or plasma concentrations (i.e.,  
1294 exposures). In general, the toxicity in question is serious toxicity, not symptomatic  
1295 reversible toxicity (most drugs have adverse effects of various kinds within the  
1296 therapeutic range).

1297 Classic examples of NTR drugs include:

- 1298 • Warfarin, where a modest increase from the titrated (by international normalized  
1299 ratio, INR) concentration can cause major bleeding.
- 1300 • Drugs with concentration-related QT effects (cisapride, astemizole, dofetilide), where  
1301 a previously tolerated dose could become toxic with a doubling of serum  
1302 concentration.
- 1303 • Most cytotoxic oncologic drugs.
- 1304 • Aminoglycoside antibiotics.

1305  
1306 Although there is no well-established rule, drugs for which a doubling of serum  
1307 concentration would cause serious toxicity can be considered NTR. Note, however, that  
1308 even reasonably well-tolerated drugs can become toxic if blood levels are greatly  
1309 increased (e.g., by CYP450 inhibition). For example, lovastatin and simvastatin, used  
1310 over a substantial dose range, can cause myopathy leading to rare and life-threatening  
1311 rhabdomyolysis if taken with a strong CYP3A inhibitor (such as mibefradil, now  
1312 removed from the U.S. market), which can cause a large-fold increase in blood levels.

1313  
1314 If an orally administered drug is a substrate of CYP3A and has low oral bioavailability  
1315 because of extensive presystemic extraction by enteric CYP3A, grapefruit juice may have  
1316 a significant effect on its systemic exposure. Use of the drug with grapefruit juice may  
1317 call for caution, depending on the drug's exposure-response relationship (see section VI  
1318 for labeling recommendations).

1319  
1320 If a drug is a substrate of CYP3A or P-gp and co-administration with St. John's wort, an  
1321 inducer of this enzyme and transporter, can decrease the systemic exposure and  
1322 effectiveness, St. John's wort will be listed in the labeling along with other known  
1323 inducers, such as rifampin, rifapentin, phenytoin, carbamazepine, or phenobarbital, as  
1324 possibly decreasing plasma levels of the drug.

1325  
1326 If a drug is metabolized by a polymorphic enzyme (such as CYP2D6, CYP2C9,  
1327 CYP2C19, or UGT1A1), the comparison of pharmacokinetic parameters of this drug in  
1328 poor metabolizers and extensive metabolizers may substitute for an interaction study for  
1329 that particular pathway, as the PK in the poor metabolizers will indicate the effect of a  
1330 strong inhibitor. When the study suggests the presence of a significant interaction with

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1331 strong inhibitors or in poor metabolizers, further evaluation, including mechanistic  
1332 modeling with weaker inhibitors or intermediate metabolizers, may be recommended.

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1334 *b. The Investigational Drug as an Inhibitor or an Inducer of CYP Enzymes — Effect*  
1335 *of Investigational Drugs on Other Drugs*

1336

1337 When studying an investigational drug as the interacting drug, the choice of substrates  
1338 (approved drugs) for initial in vivo studies depends on the P450 enzymes affected by the  
1339 interacting drug. When testing inhibition, the substrate selected should generally be one  
1340 whose pharmacokinetics are markedly altered by the co-administration of known specific  
1341 inhibitors of the enzyme systems (sensitive substrates) to see the largest impact of the  
1342 interacting investigational drug. Examples of such substrates include (1) midazolam for  
1343 CYP3A; (2) theophylline for CYP1A2; (3) bupropion for CYP2B6; (4) repaglinide for  
1344 CYP2C8; (5) warfarin for CYP2C9 (with the evaluation of S-warfarin); (6) omeprazole  
1345 for CYP2C19; and (7) desipramine for CYP2D6 (see Table 5 above for additional  
1346 substrates). If the initial study determines that an investigational drug either inhibits or  
1347 induces metabolism of sensitive substrates, further studies using other substrates,  
1348 representing a range of therapeutic classes, based on the likelihood of co-administration,  
1349 may be useful. If the initial study with the most sensitive substrates is negative, it can be  
1350 presumed that less sensitive substrates also will be unaffected. It should be noted that  
1351 several of the substrates recommended for drug interaction studies are not specific  
1352 because they are substrates for more than one CYP enzyme or may be substrates for  
1353 transporters. While a given substrate may not be metabolized by a single enzyme (e.g.,  
1354 dextromethorphan elimination is carried out primarily by CYP2D6 but other enzymes  
1355 also contribute in a minor way), its use in an interaction study is appropriate if the  
1356 inhibitor (the investigational drug) to be evaluated is selective for the CYP enzyme of  
1357 interest.

1358

1359 If an investigational drug is a CYP inhibitor, it may be classified as a strong, moderate, or  
1360 weak inhibitor based on its effect on a sensitive CYP substrate. For example, CYP3A  
1361 inhibitors can be classified based on the magnitude of the change in plasma AUC of oral  
1362 midazolam or other CYP3A substrates that are similar in characteristics (e.g., fm (%  
1363 clearance contributed by CYP3A), half-life, not subject to transporter effect) as  
1364 midazolam, when the substrate is given concomitantly with the inhibitor (see Table 3  
1365 above). If the investigational drug increases the AUC of oral midazolam or other CYP3A  
1366 substrates by 5-fold or higher ( $\geq 5$ -fold), it can be considered a *strong* CYP3A inhibitor.  
1367 If the investigational drug, when given at its highest dose and shortest dosing interval (to  
1368 maximize exposure and inhibitory effect), increases the AUC of oral midazolam or other  
1369 sensitive CYP3A substrates by between 2- and 5-fold ( $\geq 2$ - and  $< 5$ -fold), it can be  
1370 considered a *moderate* CYP3A inhibitor. If the investigational drug, when given at the  
1371 highest dose and shortest dosing interval, increases the AUC of oral midazolam or other  
1372 sensitive CYP3A substrates by between 1.25- and 2-fold ( $\geq 1.25$ - and  $< 2$ -fold), it can be  
1373 considered a *weak* CYP3A inhibitor. When the investigational drug is determined to be  
1374 an inhibitor of CYP3A, its interaction with CYP3A substrates should be described in

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1375 various sections of the labeling, as appropriate (see section VI, Labeling  
1376 Recommendations).

1377  
1378 When an in vitro evaluation does not rule out the possibility that an investigational drug  
1379 is an inducer of CYP3A (see section IV.A), an in vivo evaluation can be conducted using  
1380 the most sensitive substrate (e.g., oral midazolam, see Table 5 above). When midazolam,  
1381 the most sensitive substrate, is co-administered orally following the administration of  
1382 multiple doses of the investigational drug, and there is no interaction, it can be concluded  
1383 that the investigational drug is not an inducer of CYP3A (in addition to the conclusion  
1384 that it is not an inhibitor of CYP3A). A caveat to this interpretation is that if the  
1385 investigational drug is both an inducer and inhibitor of CYP3A, such as ritonavir, the net  
1386 effect at any time it is introduced may vary. In this case, the net effect of the drug on  
1387 CYP3A function may be time-dependent.

1388  
1389 In vivo induction evaluations have often been conducted using oral contraceptives as the  
1390 substrate. However, oral contraceptives are not the most sensitive substrates for CYP3A,  
1391 so a negative result does not exclude the possibility that the investigational drug is an  
1392 inducer of CYP3A. Some compounds listed in Table 5 as sensitive substrates for the  
1393 other enzymes can also be used as substrates with the investigational drug as an inducer.  
1394 For example, omeprazole and repaglinide are CYP2C19 and CYP2C8 substrates,  
1395 respectively, but they are also metabolized by CYP3A. If omeprazole is used as a  
1396 substrate to study CYP2C19 induction, measurement of its metabolites (CYP2C19-  
1397 mediated hydroxy-omeprazole and CYP3A4-mediated omeprazole sulfone) will be  
1398 recommended for the interpretation of the study results.

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1401 *2. Transporter-Mediated Interactions*

1402  
1403 Similar to CYP enzymes, transporters may be inhibited or induced. Inhibition of  
1404 transporters by interacting drugs can lead to altered exposure of other drugs that are  
1405 substrates of transporters. Therefore, the potential for an investigational drug as a  
1406 substrate, inhibitor, or inducer for transporters should be evaluated during drug  
1407 development.

1408  
1409 Clinically significant P-gp-mediated drug interactions, mostly related to digoxin, have  
1410 been reported (Table 1). With the availability of genetic tools, our understanding of roles  
1411 of other transporters in drugs' ADME, and transporter-based interactions has improved.  
1412 A recent genome-wide association study showed that OATP1B1 polymorphism was  
1413 associated with increased incidence of myopathy in patients taking 80 mg of simvastatin  
1414 daily (Link et al. 2008). Cyclosporine increases some statin drugs' exposure 5- to 10-  
1415 fold, which appeared to be mediated by inhibition of OATP and possibly BCRP (Table  
1416 1). These data indicate that significant interactions between drugs can occur at the  
1417 transporter level.

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1419 In this guidance, BCRP, OATP, OATs, and OCTs are considered important transporters  
1420 in addition to P-gp (International Transporter Consortium 2010) and should be routinely  
1421 evaluated. Refer to Figure 6 for a possible decision tree that could be used to guide the  
1422 decision of when to study these transporters in vitro during drug development.  
1423 Additional decision trees to determine when to evaluate drug interactions in vivo are  
1424 presented in the Appendix (Figures A1-6).

1425

1426 Because the field of transporter pharmacology is rapidly evolving, other transporters  
1427 (e.g., multidrug resistance-associated proteins (MRPs), multidrug and toxin extrusion  
1428 (MATE) transporters, and bile salt export pump (BSEP) transporters) should be  
1429 considered when appropriate.

1430

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#### 1432 *a. The Investigational Drug as a Substrate of Transporters — the Effect of Other* 1433 *Drugs on an Investigational Drug*

1434

1435 When testing an investigational drug for the possibility that its transport is inhibited or  
1436 induced (i.e., as a substrate), selection of the interacting drugs should be based on in vitro  
1437 or in vivo studies identifying the transporters that are involved in the absorption and  
1438 disposition of the investigational drug (e.g., absorption and efflux in the gastrointestinal  
1439 tract, uptake and secretion in the liver, and the secretion and re-absorption in the kidney).  
1440 The choice of the interacting drug should be based on known, important inhibitors of the  
1441 pathway under investigation. Strong inhibitors provide the most sensitive assessment and  
1442 should generally be tested first. As there is overlapping selectivity in substrate and  
1443 inhibitor among transporters, negative results from a study using a broad inhibitor may  
1444 rule out the possibility for drug interaction mediated by multiple pathways. For example,  
1445 it may be appropriate to use an inhibitor of many transporters (e.g., cyclosporine, which  
1446 inhibits P-gp, OATP, and BCRP) to study its effect on a drug that may be a substrate for  
1447 these transporters. A negative result rules out the involvement of these transporters in the  
1448 drug's disposition. However, if the result is positive, it will be difficult to determine the  
1449 relative contribution of each transporter to the disposition of the substrate drug.

1450 In contrast, if the goal of the study is to determine the role of a specific pathway in the  
1451 PK of a substrate drug, then a selective and potent inhibitor for that transporter should be  
1452 used. Table 6 lists examples of inhibitors and inducers of selected transporters.

1453

1454 As an alternative, comparative PK of an investigational drug in subjects with different  
1455 genotypes of specific transporters (e.g., OATP1B1 c.521 T vs C) can be evaluated to  
1456 determine the importance of a specific transporter in the clearance pathway for the drug.  
1457 On the other hand, polymorphism data on P-gp is controversial and may not be used to  
1458 determine the role of P-gp in the disposition of investigational drugs that are substrates of  
1459 P-gp.

1460

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1461 **Table 6. Examples of In Vivo Inhibitors and Inducers of Selected Transporters<sup>(1)</sup>**

1462

<b>Transporter</b>	<b>Gene</b>	<b>Inhibitor<sup>(2)</sup></b>	<b>Inducer<sup>(3)</sup></b>
P-gp	<i>ABCB1</i>	Amiodarone, azithromycin, <sup>(4)</sup> captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, <sup>(5)</sup> felodipine, itraconazole, ketoconazole, <sup>(4)</sup> lopinavir and ritonavir, quercetin, <sup>(4)</sup> quinidine, ranolazine, ticagrelor, verapamil	Avasimibe, <sup>(6)</sup> carbamazepine, <sup>(7)</sup> phenytoin, rifampin, St John’s wort, <sup>(8)</sup> tipranavir/ritonavir
BCRP	<i>ABCG2</i>	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known
OATP1B1	<i>SLCO1B1</i>	Atazanavir, <sup>(10)</sup> cyclosporine, eltrombopag, gemfibrozil, lopinavir, <sup>(10)</sup> rifampin, <sup>(9)</sup> ritonavir, <sup>(11)</sup> saquinavir, <sup>(10)</sup> tipranavir <sup>(10)</sup>	Not known
OATP1B3	<i>SLCO1B3</i>	Atazanavir, <sup>(10)</sup> cyclosporine, lopinavir, <sup>(10)</sup> rifampin, <sup>(9)</sup> ritonavir, <sup>(11)</sup> saquinavir <sup>(10)</sup>	Not known
OCT2	<i>SLC22A2</i>	Cimetidine, quinidine	Not known
OAT1	<i>SLC22A6</i>	Probenecid	Not known
OAT3	<i>SLC22A8</i>	Probenecid cimetidine, diclofenac	Not known

- 1463 (1) Please note this is not an exhaustive list. For an updated list, see the following link  
 1464 <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.  
 1465  
 1466 (2) Inhibitors listed for P-gp are those that showed >25% increase in digoxin AUC or otherwise indicated  
 1467 if substrate is other than digoxin.  
 1468 (3) Inducers listed for P-gp are those that showed >20% decrease in digoxin AUC or otherwise indicated  
 1469 if substrate is other than digoxin.  
 1470 (4) Inhibitors listed are those that showed >25% increase in fexofenadine AUC.  
 1471 (5) Inhibitors listed are those that showed >25% increase in talinolol AUC.  
 1472 (6) Not a marketed drug.  
 1473 (7) Inducers listed are those that showed >20% decrease in fexofenadine AUC.  
 1474 (8) Herbal product.  
 1475 (9) Given as a single dose.  
 1476 (10) In vitro inhibitors for OATP. Separation of the in vivo inhibition effect from ritonavir is difficult  
 1477 because this drug is usually co-administered with ritonavir.  
 1478 (11) The in vivo inhibition effect of ritonavir cannot be easily estimated because it is usually co-  
 1479 administered with other HIV protease inhibitors that are inhibitors for OATP as well.  
 1480

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1481           ***b.     The Investigational Drug as an Inhibitor or an Inducer of Transporters — Effect***  
1482           ***of the Investigational Drugs on Other Drugs***

1483  
1484           When studying an investigational drug as the interacting drug, the choice of substrates  
1485           (approved drugs in the United States) for initial in vivo studies depends on the transport  
1486           pathway that may be affected by the interacting drug. In general, when testing inhibition,  
1487           the substrate selected should be one whose pharmacokinetics are markedly altered by co-  
1488           administration of known specific inhibitors of the transporter pathway to see the largest  
1489           impact of the interacting investigational drug. The choice of substrates can also be  
1490           determined by the therapeutic area of the investigational drug and the probable co-  
1491           administered drugs that are known substrates for transporters. Table 7 lists selected  
1492           examples of substrates for P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, and  
1493           OAT3. However, because many drugs are substrates of multiple transporters or enzymes,  
1494           specific substrates for each transporter are not available. For example, rosuvastatin is a  
1495           substrate for BCRP, OATP1B1, and OATP1B3; lapatinib is a substrate for both P-gp and  
1496           BCRP. The observed clinical interactions may be a result of inhibition of multiple  
1497           pathways if the investigational drug is also an inhibitor for the same multiple pathways.

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**Table 7. Examples of In Vivo Substrates for Selected Transporters<sup>(1)</sup>**

1500

<b>Transporter</b>	<b>Gene</b>	<b>Substrate</b>
P-gp	<i>ABCB1</i>	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	<i>ABCG2</i>	Methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan
OATP1B1	<i>SLCO1B1</i>	Atrasentan, atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, SN-38 (active metabolite of irinotecan), rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan
OATP1B3	<i>SLCO1B3</i>	Atorvastatin, rosuvastatin, pitavastatin, telmisartan, <sup>(2)</sup> valsartan, olmesartan
OCT2	<i>SLC22A2</i>	Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin
OAT1	<i>SLC22A6</i>	Adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine
OAT3	<i>SLC22A8</i>	Acyclovir, bumetanide, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, oseltamivir acid, (the active metabolite of oseltamivir), penicillin G, pravastatin, rosuvastatin, sitagliptin

1501

(1) Please note this is not an exhaustive list. For an updated list, see the following link

1502

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.

1503

(2) Selective for OATP1B3.

1504

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Because of the lack of a validated in vitro system to study transporter induction, the definitive determination of induction potential of an investigational drug on transporters is based on in vivo induction studies. The sponsor should consult with FDA about studying induction of transporters in vivo. For example, because of similarities in the mechanisms of CYP3A and P-gp induction, information from the testing of CYP3A inducibility can inform decisions about P-gp. If an investigational drug is found not to induce CYP3A in vitro, no further tests of CYP3A and P-gp induction in vivo are necessary. If a study of the investigational drug's effect on CYP3A activity in vivo is indicated from a positive in vitro screen, but the drug is shown not to induce CYP3A in vivo, then no further test of P-gp induction in vivo is necessary. However, if the in vivo CYP3A induction test is positive, then an additional study of the investigational drug's effect on a P-gp probe substrate is recommended. If the drug is also an inhibitor for P-gp, then the induction study can be conducted with the inhibitor study using a multiple-dose design.

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#### 1520 3. *Cocktail Approach*

1521  
1522 Simultaneous administration of a mixture of substrates of multiple CYP enzymes and  
1523 transporters in one study (i.e., a “cocktail approach”) in human volunteers is another way  
1524 to evaluate a drug’s inhibition or induction potential, provided that the study is designed  
1525 properly and the following factors are present: (1) the substrates are specific for  
1526 individual CYP enzymes or transporters; (2) there are no interactions among these  
1527 substrates; and (3) the study is conducted in a sufficient number of subjects (see section  
1528 V.G). Negative results from a well-conducted cocktail study can eliminate the need for  
1529 further evaluation of particular CYP enzymes. However, positive results can indicate  
1530 that further in vivo evaluation should be conducted to provide quantitative exposure  
1531 changes (such as AUC,  $C_{max}$ ), if the initial evaluation only assessed the changes in the  
1532 urinary parent to metabolite ratios. The data generated from a cocktail study can  
1533 supplement data from other in vitro and in vivo studies in assessing a drug’s potential to  
1534 inhibit or induce CYP enzymes and transporters.

#### 1535 1536 1537 4. *Complex Drug Interactions*

##### 1538 1539 a. *Multiple CYP Inhibitors*

1540  
1541 There may be situations when an evaluation of the effect of multiple CYP inhibitors on  
1542 the drug can be informative. For example, it may be appropriate to conduct an  
1543 interaction study with more than one inhibitor simultaneously if all of the following  
1544 conditions are met: (1) the drug exhibits blood concentration-dependent important safety  
1545 concerns; (2) multiple CYP enzymes are responsible for the metabolic clearance of the  
1546 drug; (3) the predicted residual or non-inhibitable drug clearance is low. Under these  
1547 conditions, the effect of multiple CYP-selective inhibitors on the investigational drug’s  
1548 blood AUC may be much greater than when the inhibitors are given individually with the  
1549 drug, and more than the product of changes in AUC observed with each individual  
1550 inhibitor. The magnitude of the combined effect will depend on the residual fractional  
1551 clearance (the smaller the fraction, the greater the concern) and the relative fractional  
1552 clearances of the inhibited pathways. Modeling and simulation approaches can help  
1553 project the magnitude of the effect based on single pair drug interaction studies.

1554  
1555 If results from a study with a single inhibitor have already triggered a major safety  
1556 concern (i.e., a contraindication), multiple inhibitor studies are unlikely to add value.

##### 1557 1558 b. *Enzyme/Transporter Interplay*

1559  
1560 There is an overlap in enzyme and transporter specificity. For example, there is  
1561 considerable overlap between CYP3A and P-gp inhibitors and inducers. Itraconazole  
1562 inhibits CYP3A and P-gp and rifampin induces CYP3A and P-gp. However, dual  
1563 inhibitors for CYP3A and P-gp do not necessarily have similar inhibition potency on



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1564 CYP3A and P-gp (Table 8). For example, the strong CYP3A inhibitor voriconazole does  
1565 not cause a large increase in exposure of a P-gp substrate, such as digoxin or  
1566 fexofenadine. In addition, some potent P-gp inhibitors such as amiodarone and quinidine  
1567 (causing  $\geq 1.5$ -fold change in digoxin or fexofenadine AUC) are weak CYP3A inhibitors.  
1568 The differential inhibition effects on CYP3A and P-gp should be considered when  
1569 inhibitors are selected for study of interactions with an investigational drug that is a  
1570 CYP3A, P-gp, or dual CYP3A and P-gp substrate (Zhang et al. 2009). To assess the  
1571 worst case scenario for a dual CYP3A and P-gp substrate, inhibition should be studied  
1572 using an inhibitor that shows strong inhibition for both P-gp and CYP3A, such as  
1573 itraconazole. However, under this condition, if the result is positive, specific attribution  
1574 of an AUC change to P-gp or CYP3A4 may not be possible. For labeling purposes,  
1575 evaluation either through in vivo interaction studies or mechanistic modeling with less  
1576 strong inhibitors for either pathways or inhibitors for one particular pathway only may be  
1577 recommended. If the goal is to determine the specific contribution of CYP3A or P-gp on  
1578 the AUC change, then a strong inhibitor for CYP3A only or a potent inhibitor for P-gp  
1579 only should be selected to discern the effect of CYP3A vs. P-gp. Table 8 lists examples  
1580 of CYP3A and P-gp inhibitors and their relative potency.  
1581

1582 **Table 8. Examples of In Vivo CYP3A and P-gp Inhibitors and Their Relative Potency**

1583

	<b>P-gp Inhibitor</b>	<b>Non-P-gp Inhibitor</b>
<b>Strong CYP3A Inhibitor</b>	Itraconazole, lopinavir/ritonavir, telaprevir, clarithromycin, ritonavir,* ketoconazole,* indinavir/ritonavir,*conivaptan	Voriconazole
<b>Moderate CYP3A Inhibitor</b>	Verapamil, erythromycin,* diltiazem, dronedarone	None identified
<b>Weak CYP3A Inhibitor</b>	Lapatinib, quinidine, ranolazine, amiodarone, felodipine, azithromycin*	Cimetidine

1584 \* Data derived with fexofenadine; all other data were derived with digoxin.

1585

1586 **Notes:**

1587 (1) The University of Washington Drug Interaction Database was used to search the data that defined the in  
1588 vivo potency of various inhibitors for CYP3A (midazolam was searched as a substrate) and P-gp (digoxin  
1589 or fexofenadine was searched as a substrate).

1590 (2) P-gp inhibitors or non-P-gp inhibitors are defined as those drugs that increase the AUC of digoxin or  
1591 fexofenadine by  $\geq 1.25$ -fold or  $<1.25$ -fold, respectively. (The asterisk indicates data derived with  
1592 fexofenadine; all other data were derived with digoxin.)

1593 (3) Strong, moderate, or weak CYP3A inhibitors are defined as those drugs that increase the AUC of oral  
1594 midazolam or other CYP3A substrates  $\geq 5$ -fold, 2-5-fold, and 1.25-2-fold, respectively.  
1595

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1596 In addition to the possibility that a drug is an inhibitor or inducer of multiple  
1597 enzymes/transporters, a drug can be an inhibitor of one enzyme/transporter and inducer  
1598 of another enzyme/transporter. For example, ritonavir is an inhibitor of CYP3A and an  
1599 inducer of UGT; tipranavir is an inhibitor of CYP3A and an inducer of P-gp. Rifampin,  
1600 an established inducer of multiple CYP enzymes and transporters, was recently found to  
1601 be an inhibitor of the uptake transporter OATP1B1 and may inhibit the uptake of an  
1602 investigational drug that is a substrate of OATP1B1. Accordingly, if a drug is a CYP  
1603 enzyme substrate and an OATP1B1 substrate, an induction study with rifampin should be  
1604 designed and interpreted carefully. The net steady state effect may vary depending on  
1605 the relative size of the individual effect on transporter and enzyme activities. Timing of  
1606 administration may become critical in situations when both enzymes and transporters can  
1607 be affected. These overlapping selectivities contribute to complex drug interactions and  
1608 make the prediction of in vivo outcome based on in vitro evaluation challenging or  
1609 impossible (Zhang et al. 2009).

1610  
1611 The implications of simultaneous inhibition of a dominant CYP enzyme(s) and an uptake  
1612 or efflux transporter that controls the availability of the drug to CYP enzymes can be just  
1613 as profound as that of multiple CYP inhibition. For example, the large effect of co-  
1614 administration of itraconazole and gemfibrozil on the systemic exposure (AUC) of  
1615 repaglinide may be attributed to collective inhibitory effects on both the enzyme  
1616 (CYP2C8) and transporters (OATP1B1) by itraconazole and gemfibrozil and their  
1617 respective metabolites.

#### 1618 1619 *c. Effect of Organ Impairment*

1620  
1621 Another type of complex drug interaction is the co-administration of substrate and  
1622 enzyme/transporter inhibitor in subjects with organ impairment. For example, if a  
1623 substrate drug is eliminated through both hepatic metabolism and renal  
1624 secretion/filtration, the use of an enzyme inhibitor in subjects with renal impairment may  
1625 cause a more than projected increase in exposure of substrate drug based on individual  
1626 effect alone.

1627  
1628 Unfortunately, current knowledge does not permit the presentation of specific guidance  
1629 for studying some of these complex drug interaction scenarios because dedicated in vivo  
1630 studies in humans may not be feasible or may raise ethical and practical considerations.  
1631 Modeling and simulation approaches integrating prior in vitro and in vivo ADME and  
1632 drug interaction data may be useful for evaluating complex drug interactions. For  
1633 example, results from dedicated single pair drug interaction studies and separate  
1634 pharmacokinetic evaluation in subjects with organ impairment may provide useful  
1635 information to strengthen the model for the evaluation of complex drug interactions.

#### 1636 1637 *d. Pediatrics and Geriatrics*

1638  
1639 Age-related changes in physiological processes governing drug disposition and drug

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1640 effect have been investigated. In some cases, disproportional alterations in binding  
1641 proteins, drug metabolizing enzymes and/or transporters, and renal filtration/secretion  
1642 caused by developmental changes have been known to result in different drug disposition  
1643 characteristics in pediatric and geriatric populations. However, dedicated drug  
1644 interaction studies in these populations may not be feasible. Simulations using system  
1645 biology approaches such as PBPK models (see section IV.A) may be helpful to predict  
1646 drug interaction potential when the model can be constructed based on sufficient in vitro  
1647 and clinical pharmacology and drug interaction data and incorporates development  
1648 changes. Population pharmacokinetic approaches with sparse sampling can be used if  
1649 properly designed (section IV.C).

1650

#### 1651 *e. Genetics*

1652

1653 When a drug-drug interaction study uses a probe drug (e.g., omeprazole for CYP2C19) to  
1654 evaluate the impact of the investigational drug on a polymorphic enzyme, individuals  
1655 who have no functional enzyme activity would not be appropriate study subjects. Drug  
1656 interaction studies that evaluate enzymes or transporters with known polymorphisms  
1657 should include collection of genotype or phenotype information to allow appropriate  
1658 interpretation of the study results. In some instances, an evaluation of the extent of drug  
1659 interactions in subjects with various genotypes may be helpful (refer to the FDA  
1660 guidance for industry on *Clinical Pharmacogenomics: Premarketing Evaluation in Early  
1661 Phase Clinical Studies*,  
1662 [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm0  
1663 64982.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm)).

1664

#### 1665 **D. Route of Administration**

1666

1667 The route of administration chosen for a metabolic drug-drug interaction study is important. For  
1668 an investigational agent, the route of administration generally should be the one planned for  
1669 clinical use. When multiple routes are being developed, the need for metabolic drug-drug  
1670 interaction studies by each route depends on the expected mechanisms of interaction and the  
1671 similarity of corresponding concentration-time profiles for parent drug and metabolites. If only  
1672 oral dosage forms will be marketed, studies with an intravenous formulation are not usually  
1673 recommended, although information from oral and intravenous dosing may be useful in  
1674 discerning the relative contributions of alterations in absorption and/or presystemic clearance to  
1675 the overall effect observed for a drug interaction. Sometimes certain routes of administration  
1676 can reduce the utility of information from a study. For example, intravenous administration of a  
1677 substrate drug may not reveal an interaction for substrate drugs where intestinal CYP3A activity  
1678 markedly alters bioavailability.

1679

#### 1680 **E. Dose Selection**

1681

1682 The doses of the substrate and interacting drug used in studies should maximize the possibility of  
1683 demonstrating an interaction. For this reason, the maximum planned or approved dose and

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1684 shortest dosing interval of the interacting drug (as inhibitors or inducers) should be used. For  
1685 example, when using ketoconazole as an inhibitor of CYP3A, the decision whether to dose at  
1686 400 mg QD or 200 mg BID for multiple days can be determined based on the pharmacokinetic  
1687 characteristics (e.g., the half-life) of the substrate drug (Zhao et al. 2009). When using rifampin  
1688 as an inducer, dosing at 600 mg QD for multiple days would be preferable to lower doses. When  
1689 there are safety concerns, doses lower than those used clinically may be recommended for  
1690 substrates. In such instances, any limitations of the sensitivity of the study to detect the drug-  
1691 drug interaction due to the use of lower doses should be discussed by the sponsor in the protocol  
1692 and study report.

1693

#### **F. Endpoints**

1694

1695  
1696 Changes in pharmacokinetic parameters generally are used to assess the clinical importance of  
1697 drug-drug interactions. Interpretation of findings (i.e., deciding whether a given effect is  
1698 clinically important) depends on a good understanding of dose/concentration and  
1699 concentration/response relationships for both desirable and undesirable drug effects in the  
1700 general population or in specific populations. The FDA guidance for industry on *Exposure-  
1701 Response Relationships — Study Design, Data Analysis, and Regulatory Applications*  
1702 ([http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.  
1703 htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm)) provides considerations in the evaluation of exposure-response relationships. In certain  
1704 instances, reliance on pharmacodynamic endpoints in addition to pharmacokinetic measures  
1705 and/or parameters may be useful. Examples include INR measurement (e.g., when studying  
1706 warfarin interactions) or QT interval measurements.

1707

##### *1. Pharmacokinetic Endpoints*

1708

1709  
1710 Substrate PK exposure measures such as AUC,  $C_{max}$ , time to  $C_{max}$  ( $T_{max}$ ), and others as  
1711 appropriate should be obtained in every study. Calculation of pharmacokinetic  
1712 parameters such as clearance, volumes of distribution, and half-lives may help in the  
1713 interpretation of the results of the trial. In some cases, obtaining these measures for the  
1714 inhibitor or inducer may be of interest as well, notably where the study is intended to  
1715 assess possible changes in the disposition of both study drugs. Additional measures may  
1716 help in steady state studies (e.g., trough concentration) to demonstrate that dosing  
1717 strategies were adequate to achieve near steady state before and during the interaction. In  
1718 certain instances, an understanding of the relationship between dose, blood  
1719 concentrations, and response may lead to a special interest in certain pharmacokinetic  
1720 measures and/or parameters. For example, if a clinical outcome is most closely related to  
1721 peak concentration (e.g., tachycardia with sympathomimetics),  $C_{max}$  or an early exposure  
1722 measure may be most appropriate for evaluation. Conversely, if the clinical outcome is  
1723 related more to extent of absorption, AUC would be preferred. The frequency of  
1724 sampling should be adequate to allow accurate determination of the relevant measures  
1725 and/or parameters for the parent molecule and metabolites. For the substrate, whether the  
1726 investigational drug or the approved drug, determination of the pharmacokinetics of  
1727 relevant metabolites is important. Also, measurement of these metabolites may be useful

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1728 to differentiate the effect of inhibitor/inducer on pathways mediated by different CYP  
1729 enzymes.

1730

#### 1731 2. *Pharmacodynamic Endpoints*

1732

1733 Pharmacokinetic measures are usually sufficient for drug-drug interaction studies,  
1734 although pharmacodynamic measures can sometimes provide additional useful  
1735 information, especially for therapeutic proteins. Pharmacodynamic measures may be  
1736 indicated when a pharmacokinetic/pharmacodynamic relationship for the substrate  
1737 endpoints of interest is not established or when pharmacodynamic changes do not result  
1738 solely from pharmacokinetic interactions (e.g., additive effect of quinidine and tricyclic  
1739 antidepressants on QT interval). In most cases, when an approved drug is studied as a  
1740 substrate, the pharmacodynamic impact of a given change in blood level ( $C_{max}$ , AUC)  
1741 caused by an investigational interacting drug should be known from other data. If a  
1742 PK/PD study is needed, it generally should include a larger population of  
1743 subjects/patients than the typical PK study (e.g., a study of QT interval effects or platelet  
1744 aggregation effects).

1745

#### 1746 **G. Statistical Considerations and Sample Size**

1747

1748 The goal of the interaction study is to determine whether there is any increase or decrease in  
1749 exposure to the substrate in the presence of the interacting drug. If there is, its implications  
1750 should be assessed by an understanding of PK/PD relations both for  $C_{max}$  and AUC.

1751

1752 Results of drug-drug interaction studies should be reported as 90% confidence intervals about  
1753 the geometric mean ratio of the observed pharmacokinetic measures with (S+I) and without the  
1754 interacting drug (S alone). Confidence intervals provide an estimate of the distribution of the  
1755 observed systemic exposure measure ratio of (S+I) versus (S alone) and convey a probability of  
1756 the magnitude of the interaction. In contrast, tests of significance are not appropriate because  
1757 small, consistent systemic exposure differences can be statistically significant ( $p < 0.05$ ), but not  
1758 clinically relevant.

1759

1760 When a drug-drug interaction of potential importance is clearly present, the sponsor should  
1761 provide specific recommendations regarding the clinical significance of the interaction based on  
1762 what is known about the dose-response and/or PK/PD relationship for the substrate drug used in  
1763 the study. This information can form the basis for reporting study results and for making  
1764 recommendations in the labeling. FDA recognizes that dose-response and/or PK/PD information  
1765 can sometimes be incomplete or unavailable, especially for an older approved drug used as a  
1766 substrate.

1767

1768 If the sponsor wishes to include a statement in the labeling that no known drug-drug interaction  
1769 of clinical significance exists, the sponsor should recommend specific *no effect* boundaries, or  
1770 clinical equivalence intervals, for a drug-drug interaction and should provide the scientific  
1771 justification for the recommendations. No effect boundaries represent the interval within which

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1772 a change in a systemic exposure measure is considered not clinically meaningful. These  
1773 conclusions can be based on dose-response data (e.g., if doses of x and 2x are known not to have  
1774 different effectiveness or toxic effects) or on PK/PD modeling (a known flat concentration-  
1775 response relationship).

1776  
1777 There are two approaches to defining no effect boundaries:

1778  
1779 *Approach 1:* No effect boundaries can be based on the population (group) average dose-related  
1780 and/or individual concentration-response relationships derived from PK/PD models, and other  
1781 available information for the substrate drug to define a degree of difference caused by the  
1782 interaction that is of no clinical consequence. If the 90% confidence interval for the systemic  
1783 exposure measurement change in the drug-drug interaction study falls completely within these  
1784 no effect boundaries, the sponsor can conclude that no clinically significant drug-drug  
1785 interaction is present.

1786  
1787 *Approach 2:* In the absence of no effect boundaries defined in Approach 1, a sponsor can use a  
1788 default no effect boundary of 80-125% for both the investigational drug and the approved drugs  
1789 used in the study. When the 90% confidence intervals for systemic exposure ratios fall entirely  
1790 within the equivalence range of 80-125%, standard Agency practice is to conclude that no  
1791 clinically significant differences are present. This is, however, a very conservative standard and  
1792 a substantial number of subjects (sample size) would need to be studied to meet it.

1793  
1794 The selection of the number of subjects for a given drug-drug interaction study will depend on  
1795 how small an effect is clinically important to detect or rule out the inter- and intra-subject  
1796 variability in pharmacokinetic measurements, and possibly other factors or sources of variability  
1797 not well recognized.

1798  
1799

## **VI. LABELING RECOMMENDATIONS**

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1801  
1802 Drug interaction information is generally included in the DRUG INTERACTIONS and  
1803 CLINICAL PHARMACOLOGY sections of labeling and presents information that is essential  
1804 for prescribers to appropriately use the drug. When drug interaction information has important  
1805 implications for the safe and effective use of the drug, it will often be included in varying levels  
1806 of detail in other sections of the labeling, such as DOSAGE AND ADMINISTRATION,  
1807 CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS. The labeling should include  
1808 clinically relevant information about metabolic and transport pathways, metabolites,  
1809 pharmacokinetic or pharmacodynamic interactions, and clinical implications of pharmacokinetic  
1810 or pharmacodynamic interactions or genetic polymorphisms of drug metabolizing enzymes and  
1811 transporters, if applicable. The description of clinical implications should include dose  
1812 adjustments or monitoring recommendations, when relevant. General content recommendations  
1813 for the appropriate labeling sections are provided below.

1814

1815 Drug interaction information in the labeling may not always result from a dedicated drug

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1816 interaction study. In certain cases, information can be extrapolated from one drug interaction  
1817 study with a set of drugs to another set of drugs, with an explanation that similar results are  
1818 expected. For example:

- 1819
- 1820 • An investigational drug that is a strong inhibitor or a strong inducer of CYP3A does  
1821 not need to be tested with all CYP3A substrates to warn about an interaction with  
1822 sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic range.  
1823 A study involving a single sensitive substrate with the investigational drug would  
1824 lead to labeling language about the use of the investigational drug with all sensitive  
1825 and NTR substrates of the affected enzyme.
  - 1826
  - 1827 • A drug that is a sensitive CYP3A substrate or a CYP3A substrate with a narrow  
1828 therapeutic range does not need to be tested with all strong or moderate inhibitors or  
1829 inducers of CYP3A to warn about an interaction with CYP3A inhibitors or inducers.  
1830 The labeling can include such a warning in the absence of a study if its metabolism is  
1831 predominantly by the CYP3A route.
  - 1832

#### 1833 **A. Drug Interactions Section of Labeling**

1834

1835 The DRUG INTERACTIONS section includes a description of the clinical implications of  
1836 clinically significant interactions with other drugs (including prescription and over-the-counter  
1837 drugs), classes of drugs, dietary supplements, and foods and practical instructions for preventing  
1838 or managing them. Recommendations for dose adjustments of co-administered drugs are  
1839 included in this section. This section also includes practical guidance on known interference  
1840 with laboratory tests. Interactions mentioned in DOSAGE AND ADMINISTRATION,  
1841 CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS must be discussed in more  
1842 detail in the DRUG INTERACTIONS section (21 CFR 201.57(c)(8)(i)). The need for dose  
1843 adjustments of co-administered drugs is summarized in this section and presented in more detail  
1844 in DOSAGE AND ADMINISTRATION. Drug interaction findings with negative results (i.e.,  
1845 no interaction was found) should generally not appear in this section unless this information is  
1846 clinically relevant for the prescriber (e.g., if two drugs are commonly used together or if a drug  
1847 does not have the same interaction as other drugs in the same class). This section may also  
1848 include a brief summary of potential mechanisms of drug interactions. (e.g., “Drug X is a strong  
1849 CYP3A inhibitor and may increase concentrations of CYP3A substrates.” or “Drug X does not  
1850 inhibit or induce CYPs 1A2, 2C9, or 2C19.”). This section does not include details of drug  
1851 interaction studies, but instead cross-references the information in the CLINICAL  
1852 PHARMACOLOGY section.

1853

1854 Drug interactions that have the most clinical relevance (e.g., result in serious or otherwise  
1855 clinically significant outcomes) should be listed first. Because the number of drug interactions  
1856 and complexity of the information in this setting varies, we recommend using the most  
1857 appropriate format to enhance communication of the information. For example, for drugs with  
1858 extensive drug interaction information, a table may be the most effective format to convey the  
1859 information. The table can list, when applicable, the co-administered drugs, potential or known

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1860 interactions (information regarding the increase or decrease in concentrations of drug, co-  
1861 administered drug, or relevant metabolites), and clinical comments (clinical concern, dose  
1862 adjustments, or advice regarding monitoring). When appropriate, the use of numbered  
1863 subsections or subheadings within a subsection are recommended to organize the information  
1864 (e.g., “Effect of Drug X on other drugs,” “Effect of other drugs on Drug X,” or subheadings for  
1865 specific drugs or drug classes). Because this section may include information about both known  
1866 and predicted drug interactions, it may be helpful to describe the data source for the information  
1867 (e.g., indicate when the information is based on a specific drug interaction study and when it is  
1868 based on a known mechanism, including simulation results, without a study).

#### 1869 **B. Clinical Pharmacology Section of Labeling**

1870  
1871  
1872 Information in the PHARMACOKINETICS subsection (12.3 Pharmacokinetics) of the  
1873 CLINICAL PHARMACOLOGY section is generally organized under descriptive subheadings  
1874 (e.g., absorption, distribution, metabolism, excretion, pharmacokinetics in specific populations,  
1875 and drug interactions). The PHARMACOKINETICS subsection should include descriptive  
1876 information related to mechanisms of drug interactions, and details of the relevant drug  
1877 interaction study results. The text should cross-reference other sections of the labeling that  
1878 describe clinical management instructions, dose adjustments, or major safety concerns related to  
1879 drug interactions (e.g., WARNINGS AND PRECAUTIONS or CONTRAINDICATIONS).

1880  
1881 If the drug is a metabolizing enzyme or transporter substrate, such information should be  
1882 included in PHARMACOKINETICS under “Metabolism,” the text should describe the  
1883 metabolic pathway(s), relevant metabolites formed, specific drug metabolizing enzymes, and  
1884 whether there is genetic variation in the drug metabolizing enzymes. If the drug is metabolized  
1885 by an enzyme subject to genetic variability, the information should be included under  
1886 “Metabolism” and cross-referenced to the fuller discussion under a PHARMACOGENOMICS  
1887 subsection of the CLINICAL PHARMACOLOGY section.

1888  
1889 Information under the “Drug Interactions” subheading includes a more detailed description of  
1890 the potential mechanisms of drug interactions than the description in the DRUG  
1891 INTERACTIONS section of labeling. The data source for the conclusions (e.g., known CYP3A  
1892 inhibitor based on in vitro and in vivo studies) should be briefly described.

1893  
1894 Under “Drug Interactions” study results may be presented in a forest plot (described below), a  
1895 table, or as text, depending on the number of studies and level of detail needed for clarity. The  
1896 information should include only those study features that are essential to understand the results.  
1897 In most cases it is not necessary to include study design, number of subjects, or population (e.g.,  
1898 healthy volunteers or patients) studied. The most relevant study design feature is likely the dose  
1899 and duration for each drug; when relevant, the information should be included. The results  
1900 should be presented as the change in relevant pharmacokinetic exposure measures (e.g., AUC  
1901 and  $C_{\max}$  and where appropriate  $C_{\min}$ ,  $T_{\max}$ ). It is important to indicate the variability of the  
1902 interaction. Results should generally be presented as geometric mean change and the 90%  
1903 confidence interval around the geometric mean change. For example, a 48% percent increase in



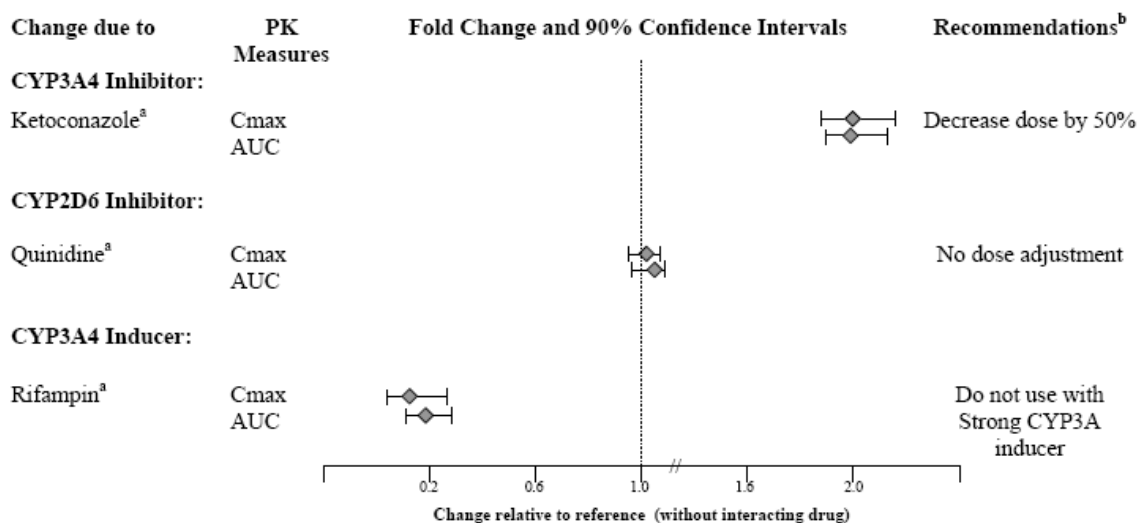
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1904 AUC could be expressed as  $\uparrow 48\%$  (90%CI:  $\uparrow 24\%$ ,  $\uparrow 76\%$ ) or as a ratio or fold change, where the  
 1905 48% percent increase would be expressed as 1.48 (90% CI: 1.24, 1.76).

1906  
 1907 In the PHARMACOKINETICS subsection, a forest plot is a useful tool for presenting changes in  
 1908 pharmacokinetic exposure measures caused by various intrinsic and extrinsic factors such as  
 1909 drug interactions, hepatic impairment, and renal impairment (see Figure 8 below). The forest  
 1910 plot should display the fold-change in key pharmacokinetic measures such as geometric mean  
 1911 AUC and geometric mean  $C_{max}$  along with the 90% confidence intervals. Such graphs should  
 1912 clearly state the reference arm (or identify it in text accompanying the figure) and can include the  
 1913 doses of studied drugs, if relevant. Separate plots can display the effect of others on the labeled  
 1914 drug, effects of the drug on other drugs, and the effects of impaired hepatic or renal function.  
 1915

1916 **Figure 8. The Effect of Various CYP Inhibitors on a Hypothetical Drug’s PK as Displayed**  
 1917 **as 90% Confidence Interval of Geometric Mean AUC and  $C_{max}$  Ratios.**



<sup>a</sup>For illustration purpose only. Assuming the interacting drugs affect CYPs only

<sup>b</sup>Recommendation will be drug dependent

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### **C. Other Labeling Sections**

As stated above, when drug interaction information has important implications for the safe and effective use of the drug, the information may be distributed among several other labeling sections (e.g., DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, or PATIENT COUNSELING INFORMATION), with a cross-reference to the DRUG INTERACTIONS or CLINICAL PHARMACOLOGY sections for more detailed information.

- **DOSAGE AND ADMINISTRATION** — This section includes information about drug interaction information that has important implications for a drug’s dosing regimen (e.g., dosage adjustments, timing of dose relative to dosing of another drug).
- **CONTRAINDICATIONS** — This section describes when other drugs should not be co-administered with the drug because the risk outweighs any potential benefit.
- **WARNINGS AND PRECAUTIONS** — This section includes a brief discussion of any known or predicted drug interactions with serious or otherwise clinically significant outcomes.
- **PATIENT COUNSELING INFORMATION** — This section includes information necessary for patients to use the drug safely and effectively, such as avoiding drinking grapefruit juice.

For more specific recommendations on labeling content for these sections of labeling, refer to the following guidances for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Prescription Drug and Biological Products – Content and Format*, and *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*. These guidances and other labeling guidances are available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065010.htm>.

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**List of Figures in the Appendix**

Figure A1. 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. .... 64

Figure A2. Decision tree to determine whether an investigational drug is an inhibitor of P-gp and when an in vivo clinical study is needed. A similar model can be applied to a BCRP inhibitor..... 66

Figure A3. Decision tree to determine whether an investigational drug is a substrate for OATP1B1 or OATP1B3 and when an in vivo clinical study is needed ..... 67

Figure A4. Decision tree to determine whether an investigational drug is an inhibitor of OATP1B1 or OATP1B3 and when an in vivo clinical study is needed ..... 68

Figure A5. 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..... 69

Figure A6. Decision tree to determine whether an investigational drug is an inhibitor of OCT2, OAT1, or OAT3 and when an in vivo clinical study is needed..... 70

1969 APPENDIX

1970

1971 **Models for Determining When In Vivo Transporter-Mediated Drug**  
 1972 **Interaction Studies Are Needed**

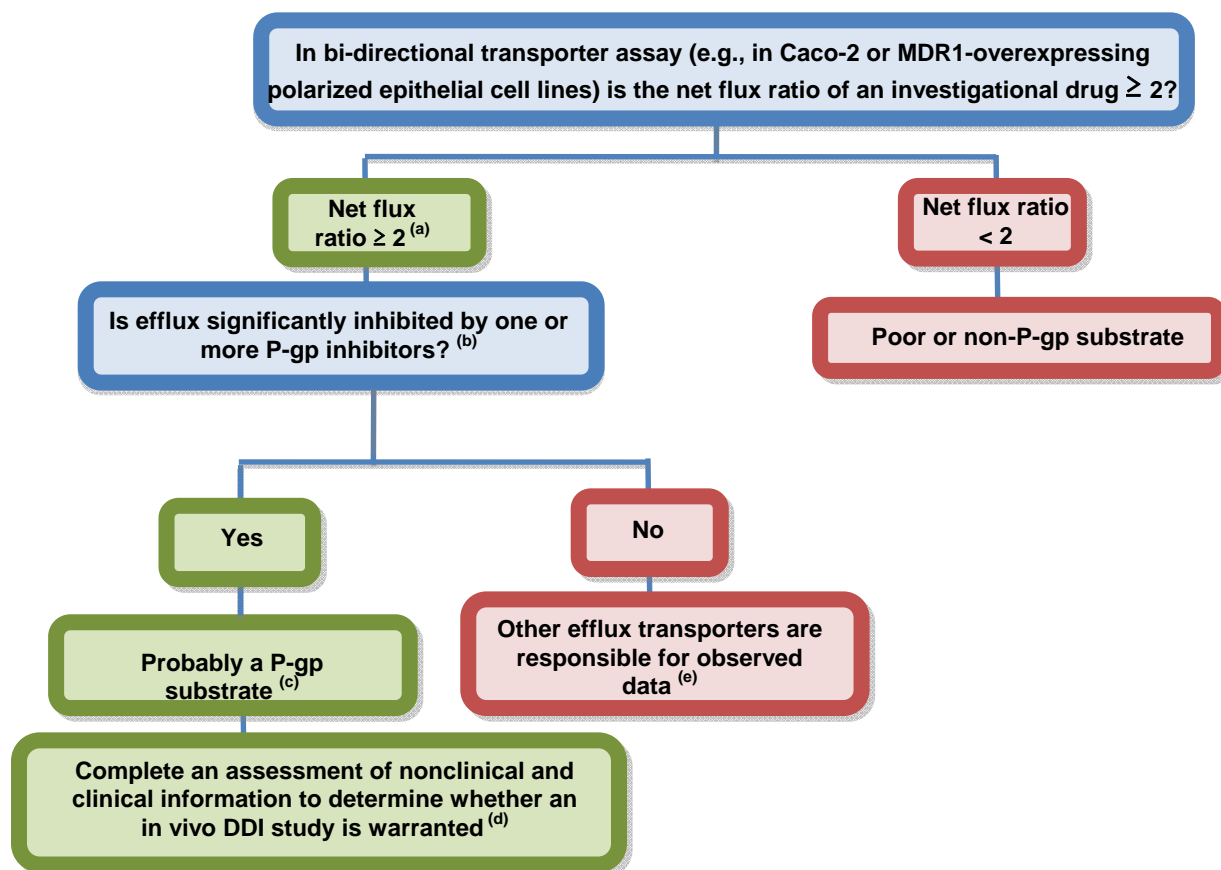
1973

1974 ***P-gp and BCRP:***

1975

1976 **Figure A1. Decision tree to determine whether an investigational drug is a substrate for P-**  
 1977 **gp and when an in vivo clinical study is needed. A similar model can be applied to a BCRP**  
 1978 **substrate — refer to IV.A.2.a, Figure 6 (Modified From Figures in Giacomini et al. 2010).**

1979



1980

1981

1982 <sup>(a)</sup> An acceptable system produces net flux ratios of probe substrates similar to the literature values. A net flux ratio  
 1983  $\geq 2$  for the investigational drug is a positive signal for further evaluation. A net flux ratio “cutoff” higher than 2 or a  
 1984 relative ratio to positive controls may be used to avoid false positives if a ratio of 2 is deemed non-discriminative as  
 1985 supported by prior experience with the cell system used.

1986 <sup>(b)</sup> Reduction of the flux ratio significantly ( $> 50\%$ ) or to unity.

1987 <sup>(c)</sup> Additional data are needed to establish clinical relevance of the in vitro data. In particular, the relative  
 1988 contribution of the transporter-mediated pathway to the overall clearance of the drug is the primary determinant of  
 1989 whether an inhibitor will have a major effect on the disposition of the investigational new drug.

1990 <sup>(d)</sup> Selection of inhibitors could be based on likelihood of co-administration and/or its inhibition potency on P-gp.

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1991 Strong P-gp inhibitors (e.g., itraconazole, verapamil) provide the most sensitive assessment and should generally be  
1992 tested first. If the drug is also a substrate for CYP3A, then inhibitors for both CYP3A and P-gp should be selected  
1993 (Table 8).

1994 <sup>(c)</sup> Based on existing knowledge of the compound class, further studies may be warranted to determine which efflux  
1995 transporters are involved. Determining whether the drug is a BCRP substrate may be explored. A similar decision  
1996 model may be used for a BCRP substrate; however, clinical studies would differ.

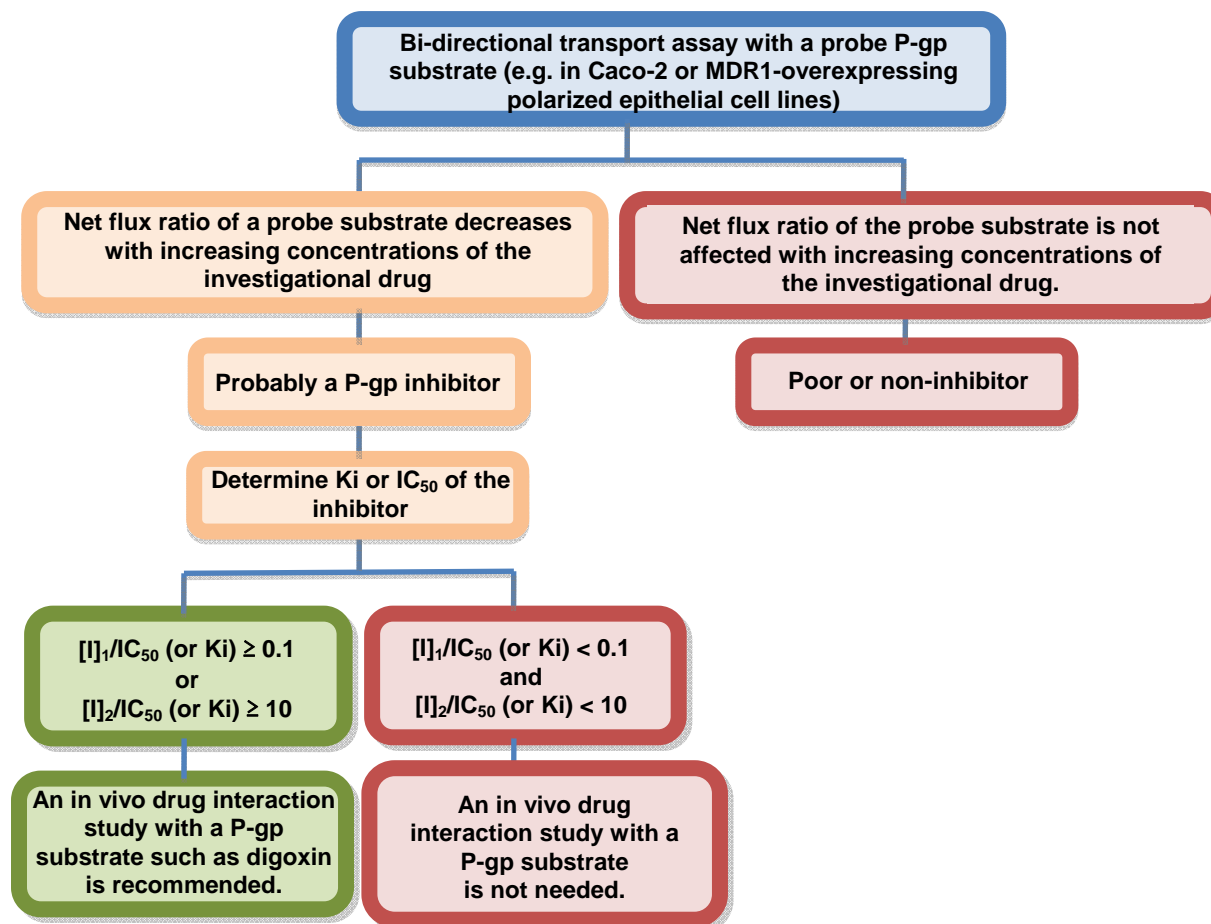
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1998 **Figure A2. Decision tree to determine whether an investigational drug is an inhibitor of P-gp**  
1999 **and when an in vivo clinical study is needed. A similar model can be applied to a BCRP**  
2000 **inhibitor) — refer to IV.A.2.b (Modified From Figures in Giacomini et al. 2010)**

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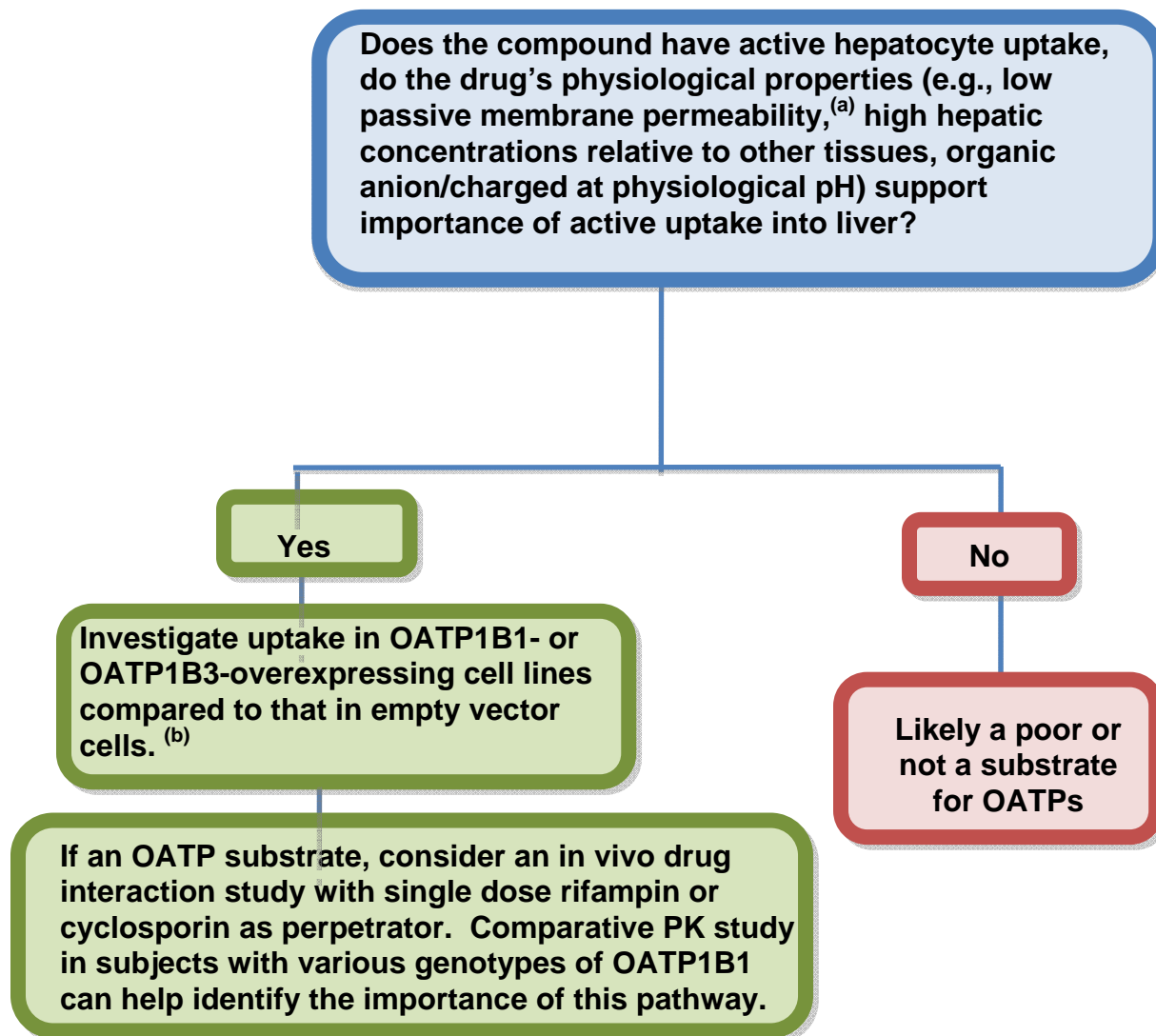
[I]<sub>1</sub> represents the mean steady-state total (free and bound) C<sub>max</sub> following administration of the highest proposed clinical dose. [I]<sub>2</sub>= Dose of inhibitor (in mol)/250 mL (if IC<sub>50</sub> is in a molar unit). For IC<sub>50</sub> determination, a unidirectional assay (e.g., B to A) based on the probe substrate can also be considered.

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2009 *OATP1B1 and OATP1B3 (Liver uptake transporters):*  
2010

2011 **Figure A3. Decision tree to determine whether an investigational drug is a substrate for**  
2012 **OATP1B1 or OATP1B3 and when an in vivo clinical study is needed— refer to IV.A.2.a,**  
2013 **Figure 6 (Modified From Figures in Giancomini et al. 2010)**



2014  
2015 <sup>(a)</sup> Low permeability needs to be defined by each lab based on standards, such as atenolol (a biopharmaceutics  
2016 classification system (BCS) reference drug). A general guide would be that  $10^{-6}$  cm/sec (10 nm/sec) or lower is  
2017 classified as "low" permeability.

2018 <sup>(b)</sup> The following criteria suggest the investigational drug is a substrate of OATP1B1 or OATP1B3: Uptake in  
2019 OATP1B1- or OATP1B3-transfected cells greater than 2-fold of that in empty vector transfected cells and is  
2020 inhibitable (e.g., >50% reduction to unity) by a known inhibitor (e.g., rifampin) at a concentration at least 10 times  
2021 of its  $K_i$ . Michaelis–Menten studies may be conducted in the transfected cells to determine the kinetic parameters of  
2022 the investigational drug. A positive control should be included. In an acceptable cell system, the positive control  
2023 should show a  $\geq 2$  fold increase in uptake compared to vector-transfected cells. An uptake ratio (transporter  
2024 transfected vs. empty vector transfected cells) other than 2 may be used if a ratio of 2 is deemed non-discriminative  
2025 as supported by prior experience with the cell system used.





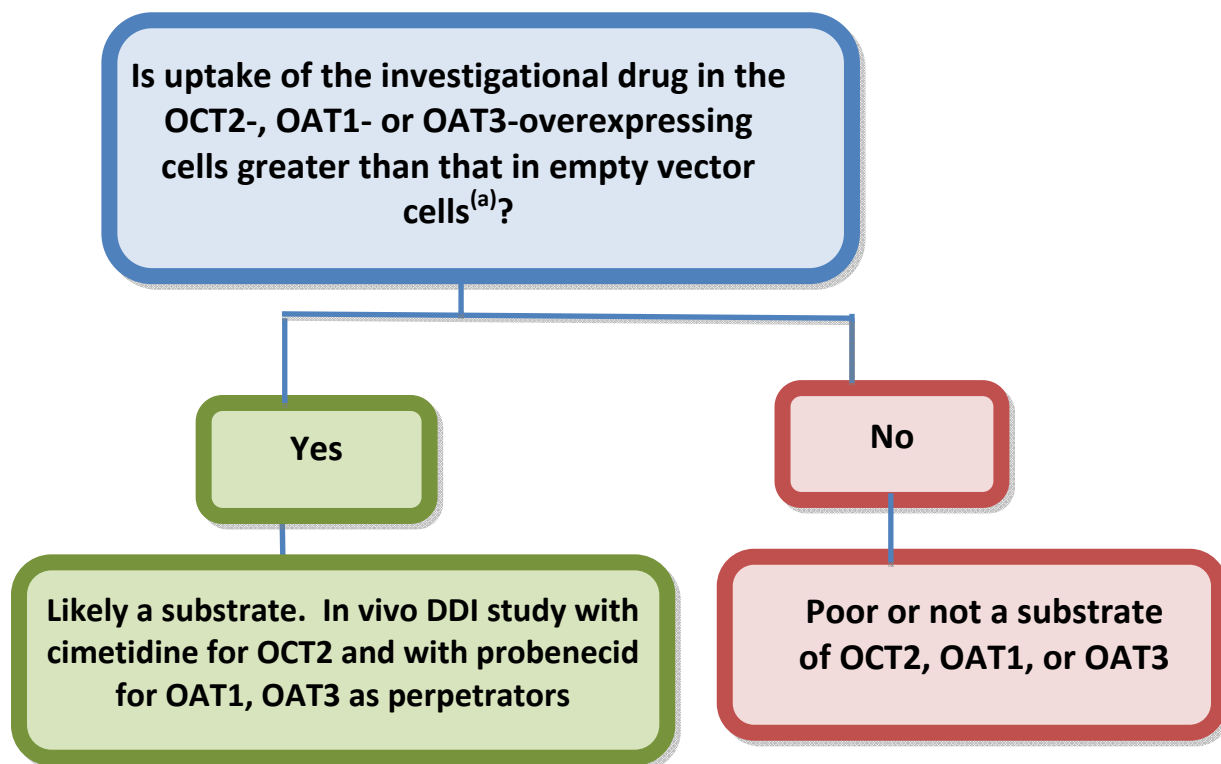
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2044 ***OCT2, OAT1, and OAT3 (renal transporters):***  
2045

2046 **Figure A5. Decision tree to determine whether an investigational drug is a substrate for**  
2047 **OCT2, OAT1, or OAT3 and when an in vivo clinical study is needed — refer to IV.A.2.a,**  
2048 **Figure 6 (Modified From Figures in Giancomini et al. 2010)**

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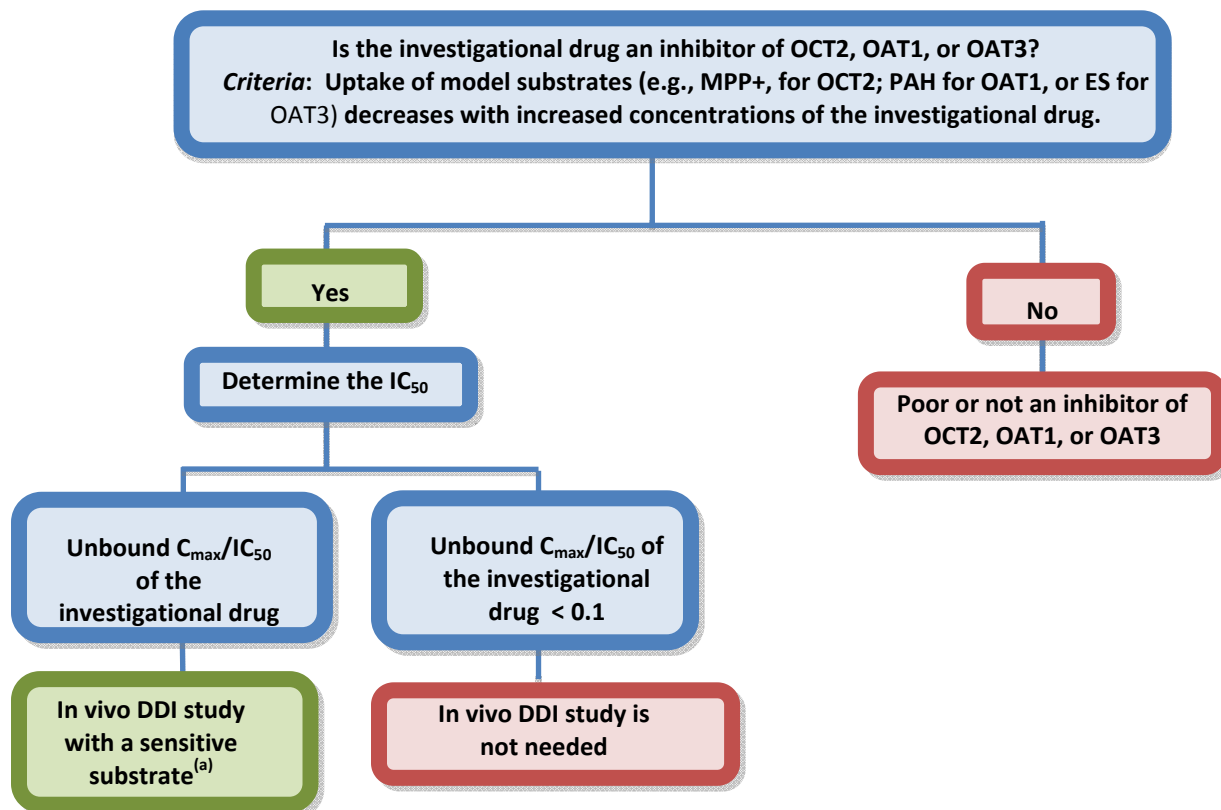
<sup>(a)</sup> The ratio of the investigational drug uptake in the cells expressing the transporter versus the control (or empty vector) cells should be greater than 2. It is important that uptake into the transfected cells be significantly greater than background in a control cell line and be inhibited 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  $\geq 2$  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.

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**Figure A6. Decision tree to determine whether an investigational drug is an inhibitor of OCT2, OAT1, or OAT3 and when an in vivo clinical study is needed — refer to IV.A.2.b (Modified From Figures in Giancomini et al. 2010)**



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MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium; PAH, *para*-aminohippuric acid; ES, estrone-3-sulfate.

<sup>(a)</sup> For the investigational drug that is an OCT2 inhibitor, metformin may be used as the substrate for the clinical drug interaction study.

For investigational drugs that are OAT1 or OAT3 inhibitors, multiple OAT1 or OAT3 substrates could be used in clinical DDI studies, including zidovudine, acyclovir, ciprofloxacin, tenofovir, or methotrexate.

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***Contains Nonbinding Recommendations***

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## *Contains Nonbinding Recommendations*

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### 2233 **ABBREVIATIONS**

2234

ABC: ATP-binding cassette  
ADME: absorption, distribution, metabolism, and/or excretion;  
AhR: aryl hydrocarbon receptor  
AUC: area under the plasma concentration-time curve  
BCRP: breast cancer resistance protein  
BCS: biopharmaceutical classification class  
BLA: biologics license application  
BSEP: bile salt export pump  
CAR: constitutive androstane receptor  
CCB: calcium channel blocker  
CYP: Cytochrome P450  
EM: extensive metabolizers  
FMO: flavin monooxygenase  
INR: international normalized ratio  
LST: liver specific transporter  
MAO: monoamine oxidase  
MATE: multidrug and toxin extrusion  
MRP: multidrug resistance-associated protein  
NDA: new drug application  
NTCP: sodium/taurocholate cotransporting polypeptide  
NTR: narrow therapeutic range  
OAT: organic anion transporter  
OATP: organic anion transporting polypeptide  
OCT: organic cation transporter  
PBPK: physiologically-based pharmacokinetic  
PD: pharmacodynamics  
P-gp: P-glycoprotein  
PK: pharmacokinetics  
PM: poor metabolizers  
PXR: pregnane X receptor  
SLC: solute carrier  
TDI: time dependent inhibition  
TdP: torsade de pointes  
TP: therapeutic protein  
UGT: uridine diphosphate (UDP)-glucuronosyl transferase  
XO: xanthine oxidase

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