
Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

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

**October 2017
Clinical Pharmacology**

Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov*

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

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

**October 2017
Clinical Pharmacology**

TABLE OF CONTENTS

I. INTRODUCTION.....	1
II. BACKGROUND	2
III. TIMING OF CLINICAL DDI STUDIES	2
IV. DESIGN AND CONDUCT OF CLINICAL DDI STUDIES	3
A. Types of DDI Studies	3
B. Study Planning and Considerations for Stand-Alone Prospective DDI Studies	6
C. Study Planning and Considerations for Prospective Nested DDI Studies.....	9
D. Specific Considerations for CYP-Mediated Interactions	10
E. Specific Considerations for Transporter-Mediated Interactions	13
F. Cocktail Approaches.....	17
G. Other Considerations.....	17
V. REPORTING AND INTERPRETING STUDY RESULTS.....	18
A. Study Results Reporting.....	18
B. Interpreting DDI Studies.....	20
VI. LABELING RECOMMENDATIONS	23
VII. ABBREVIATIONS	27
VIII. DEFINITIONS.....	28

Contains Nonbinding Recommendations

Draft – Not for Implementation

1 **Clinical Drug Interaction Studies — Study Design, Data Analysis,**
2 **and Clinical Implications**
3 **Guidance for Industry¹**
4

5
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
10 for this guidance as listed on the title page.
11

12
13
14
15 **I. INTRODUCTION**
16

17 This guidance helps sponsors of investigational new drug applications and applicants of new drug
18 applications evaluate drug-drug interactions (DDIs) during drug development and communicate
19 the results and recommendations from DDI studies.²
20

21 This guidance focuses on the conduct of clinical studies to evaluate the DDI potential of an
22 investigational drug, including: (1) the timing and design of the clinical studies; (2) the
23 interpretation of the study results; and (3) the options for managing DDIs in patients. A related
24 FDA draft guidance for industry entitled *In Vitro Drug Metabolism- and Transporter-Mediated*
25 *Drug-Drug Interaction Studies* focuses on how to assess the DDI potential of a drug in vitro and
26 how to use the results from those assessments to inform clinical DDI studies.³ Together, these
27 two guidances on DDIs describe a systematic, risk-based approach for evaluating DDIs and
28 communicating the results of DDI studies and will replace the 2012 draft guidance entitled *Drug*
29 *Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling*
30 *Recommendations*.
31

32 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
33 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
34 as recommendations, unless specific regulatory or statutory requirements are cited. The use of

¹ This guidance has been prepared by the Office of Clinical Pharmacology, Office of Translational Sciences, in the Center for Drug Evaluation and Research at the Food and Drug Administration.

² This guidance does not discuss DDIs involving therapeutic proteins.

³ When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

35 the word *should* in Agency guidances means that something is suggested or recommended, but
36 not required.

37

38

39 **II. BACKGROUND**

40

41 Patients frequently use more than one medication at a time. Unanticipated, unrecognized, or
42 mismanaged DDIs are an important cause of morbidity and mortality associated with
43 prescription drug use and have occasionally caused the withdrawal of approved drugs from the
44 market. In some instances, understanding how to safely manage a DDI may allow the FDA to
45 approve a drug that would otherwise have an unacceptable level of risk. Clinically relevant
46 DDIs between an investigational drug and other drugs should therefore be: (1) defined during
47 drug development as part of the sponsor's assessment of the investigational drug's benefits and
48 risks; (2) understood via nonclinical and clinical assessment at the time of the investigational
49 drug's approval; (3) monitored after approval; and (4) communicated in the labeling.

50

51 The goals of studies that investigate metabolism- and transporter-mediated DDIs are to
52 determine:

53

- 54 • Whether the investigational drug alters the pharmacokinetics of other drugs
- 55 • Whether other drugs alter the pharmacokinetics of the investigational drug
- 56 • The magnitude of changes in pharmacokinetic parameters
- 57 • The clinical significance of the observed or expected DDIs
- 58 • The appropriate management strategies for clinically significant DDIs

59

60

61 **III. TIMING OF CLINICAL DDI STUDIES**

62

63 After conducting in vitro drug metabolism and drug transporter studies, sponsors should
64 determine the need for and timing of clinical DDI studies with respect to other studies in their
65 clinical development program. Sponsors should evaluate DDIs before the product is
66 administered to patients who are likely to take concomitant medications that could interact with
67 the investigational drug. Furthermore, sponsors should collect enough DDI information to
68 prevent patients from being unnecessarily excluded from any clinical study because of their
69 concomitant medication use. Unnecessary restrictions on patient enrollment can result in clinical
70 study populations that are not representative of the indicated patient population. Inadequate
71 studies of DDIs can hinder the FDA's ability to determine the benefits and risks of an
72 investigational drug and could result in restrictive labeling, postmarketing requirements or
73 commitments, and/or delayed approval until sufficient information on DDIs is available.

74

75 Sponsors should summarize their DDI program at milestone meetings with the FDA. Potential
76 discussion topics at these meetings include the planning, timing, and evaluation of studies to
77 determine the DDI potential of the investigational drug.

78

79

Contains Nonbinding Recommendations

Draft – Not for Implementation

80 **IV. DESIGN AND CONDUCT OF CLINICAL DDI STUDIES**

81
82 Clinical DDI studies compare substrate concentrations in the absence and presence of a
83 perpetrator drug in vivo. For the purposes of this guidance, the terms *substrate* and *victim* are
84 used interchangeably to refer to the drug whose exposure may or may not be changed by a
85 perpetrator drug. The term *perpetrator* refers to the drug that causes an effect on the substrate
86 drug by inhibiting or inducing enzymes or transporters. *Index* perpetrators are drugs that inhibit
87 or induce a given metabolic pathway by a defined magnitude when administered with a sensitive
88 substrate and are commonly used in prospective DDI studies. See section VIII for definitions of
89 key terms used in this guidance.

90

91 **A. Types of DDI Studies**

92

93 *1. Prospective Studies and Retrospective Evaluations*

94

95 Clinical DDIs can be evaluated in prospective studies and retrospective evaluations. Proper and
96 thorough DDI evaluations that can inform regulatory decision-making generally require studies
97 specifically designed for this purpose. Retrospective evaluation of drug concentrations from
98 studies not designed to evaluate DDIs rarely include sufficient precision to provide an adequate
99 assessment of a DDI (see section V.B.2 for more details).

100

101 Prospective clinical DDI studies are specifically designed to detect DDIs. DDI assessment is a
102 major objective of the protocols for these studies, and the data analysis method and study design
103 elements (e.g., the pharmacokinetic sampling plan and the timing of concomitant medication
104 administration) are prespecified. Prospective DDI studies are often stand-alone studies.
105 However, a prespecified subgroup analysis within a larger study (e.g., a phase 3 study) may
106 qualify as a prospective DDI study if it includes certain factors common to prospective studies
107 (see section IV.C). Sponsors should contact the Office of Clinical Pharmacology in CDER
108 regarding prospective DDI studies that are nested within a larger study whose primary objective
109 is not to assess DDIs, if such a design was not previously discussed at a milestone meeting.

110

111 *2. DDI Studies With Index Perpetrators and Index Substrates*

112

113 To test whether an investigational drug is a victim of DDIs, sponsors should use index
114 perpetrators. Index perpetrators predictably inhibit or induce drug metabolism or transport by a
115 given pathway and are commonly used in prospective DDI studies. The magnitude of inhibition
116 or induction (i.e., strong or moderate) caused by index perpetrators is described in section V.B.3.
117 Strong index perpetrators are typically used to create worst-case scenarios where drug
118 metabolizing enzymes or drug transporters are inhibited or induced to the greatest extent
119 possible. Strong index perpetrators cause DDIs of the greatest magnitude when coadministered
120 with the investigational drug (as a substrate) by altering the function of a given metabolic or
121 transporter pathway. Results from index perpetrator studies provide essential information about
122 the DDI potential of an investigational drug and can inform future DDI studies.

123

124 To test whether the investigational drug is a perpetrator, sponsors should use *index* substrates,

Contains Nonbinding Recommendations

Draft – Not for Implementation

125 which have defined changes in systemic exposure when administered with a strong inhibitor or
126 inducer for a specific drug elimination pathway. *Sensitive* index substrates are drugs whose area
127 under the concentration-time curve (AUC) values increase 5-fold or more when coadministered
128 with a known strong index inhibitor for a particular pathway, or whose AUC ratio in poor
129 metabolizers for a specific enzyme is greater than or equal to 5-fold compared to extensive
130 metabolizers. *Moderate sensitive* index substrates are drugs whose AUC values increase 2- to 5-
131 fold when coadministered with a known strong index inhibitor or whose AUC values increase 2-
132 to 5-fold in individuals with certain genetic polymorphisms of a specific enzyme. Studies with
133 sensitive index substrates determine the maximum decrease or increase in substrate exposure
134 resulting from the investigational drug's induction or inhibition, respectively, of enzymes or
135 transporters. Moderate sensitive index substrates can be used if a sensitive index substrate is not
136 available for an enzyme (e.g., CYP2C9).

137
138 A list of currently recommended index drugs for specific pathways (either as substrates,
139 inhibitors, or inducers) is maintained on the FDA's Web site for Drug Development and Drug
140 Interactions.⁴ The magnitude of DDIs from studies with index inhibitors or inducers is typically
141 representative of the magnitude of the interaction for other drugs with the same level of
142 inhibition or induction (i.e., strong or moderate). Similarly, the effect of the investigational drug
143 on index substrates is representative of the effect on other sensitive substrates for that metabolic
144 pathway.

145
146 Most of the drugs listed on the FDA's Web site for Drug Development and Drug Interactions as
147 transporter substrates, inducers, or inhibitors cannot be considered as index drugs for prospective
148 DDI studies because they lack specificity for one transporter. However, clinical interaction
149 studies conducted with these drugs can provide useful information about potential DDIs with
150 concomitant drugs. See sections IV.A.3 and IV.E for considerations for transporter-mediated
151 drug interaction studies.

152
153 Evaluating the effect of an investigational drug on an endogenous substrate (e.g., 4β-
154 hydroxycholesterol) can provide information about its effect on a metabolic pathway (e.g.,
155 induction of cytochrome P450 3A- (CYP3A-) mediated metabolism). However, we do not
156 recommend using the endogenous substrate for the index studies because it is not possible to
157 consistently extrapolate the effect on an endogenous substrate to other substrates for the same
158 enzyme or transporter.

159
160 3. *DDI Studies With Expected Concomitant Drugs: Concomitant Use Studies*

161
162 Index substrates and perpetrators are not chosen based on their use in the investigational drug's
163 target population, but rather because of their well-defined interaction effects that provide
164 information about the DDI potential of the investigational drug. Therefore, the results from DDI

⁴ FDA's Web site on Drug Development and Drug Interactions can be found at
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

165 studies with index perpetrators or substrates are used to either extrapolate findings to
166 concomitant medications sharing the same DDI properties or to help design DDI studies with
167 commonly used concomitant medications in the investigational drug’s target population. In
168 contrast to DDI studies with index drugs, results from a concomitant-use study with a non-index
169 drug can be difficult to extrapolate to other drugs.

170
171 The relevant concomitant medications for study include those used to treat the same condition
172 for which the investigational drug is being studied or those used to treat common co-morbidities
173 in the patient population. Sponsors should evaluate the concomitant medications that are likely
174 to interact with the investigational drug in the clinical practice setting (e.g., add-on drug
175 therapies or treatments for common co-morbidities) using a risk-based approach that considers
176 the drug interaction mechanisms and the clinical significance of any changes in the drug’s
177 exposure. Examples and classifications of drugs for individual elimination pathways — either as
178 substrates, inhibitors, or inducers — are maintained on the FDA’s Web site for Drug
179 Development and Drug Interactions.⁵

180
181 Currently, only a few substrates or perpetrators of transporters fulfill the criteria of an index drug
182 (see section IV.A.2). The choice of victim or perpetrator drug for transporter studies should be
183 based primarily on the likelihood of coadministration of the two drugs. Results from DDI
184 studies that investigate transporter-mediated interactions are most relevant to the studied drugs;
185 extrapolation of study results to other drugs is limited. Thus, most clinical DDI studies that
186 investigate the effects of transporter interactions are considered concomitant-use studies. See
187 section IV.E for considerations when investigating transporter-mediated interactions.

188

189 4. *In Silico DDI Studies*

190

191 Physiologically based pharmacokinetic (PBPK) models can be used in lieu of some prospective
192 DDI studies. For example, PBPK models have predicted the impact of weak and moderate index
193 inhibitors on some CYP2D6 and CYP3A substrates as well as the impact of weak and moderate
194 index inducers on CYP3A substrates.^{6,7,8} These predictions were made after prospective clinical

⁵ FDA’s Web site on Drug Development and Drug Interactions can be found at
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.

⁶ Wagner C, P Zhao, Y Pan, V Hsu, J Grillo, SM Huang, and V Sinha, 2015, Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK, CPT: Pharmacometrics & Systems Pharmacology, 4(4):226-230.

⁷ Vieira, MD, MJ Kim, S Apparaju, V Sinha, I Zineh, SM Huang, P Zhao, 2014, PBPK Model Describes the Effects of Co-Medication and Genetic Polymorphism on Systemic Exposure of Drugs that Undergo Multiple Clearance Pathways, Clinical Pharmacol Ther, 95(5):550-557.

⁸ Wagner, C, Y Pan, V Hsu, JA Grillo, L Zhang, KS Reynolds, V Sinha, P Zhao, 2015, Predicting the Effect of CYP3A Inducers on the Pharmacokinetics of Substrate Drugs Using Physiologically Based Pharmacokinetic (PBPK) Modeling: An Analysis of PBPK Submissions to the US FDA, Clinical Pharmacokinetics, 54(1):117-127.

Contains Nonbinding Recommendations

Draft – Not for Implementation

195 trials showed a significant DDI between the investigational drug and strong index inhibitors or
196 inducers. Before using a PBPK modeling approach to predict the effects of moderate or weak
197 perpetrator drugs on the exposure of an investigational drug, the sponsor should verify the
198 models using human pharmacokinetic data and information from DDI studies that used strong
199 index perpetrators. Suggestions for how sponsors should conduct PBPK analyses and present
200 results for intended purposes are available in the FDA guidance for industry *In Vitro*
201 *Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies*⁹ and the FDA guidance
202 for industry *Physiologically Based Pharmacokinetic Analyses —Format and Content*.¹⁰ Because
203 of evolving science, new uses of in silico methods to predict DDIs in lieu of clinical DDI studies
204 are continuously being considered by the FDA.¹¹ We encourage sponsors to discuss with the
205 Office of Clinical Pharmacology at CDER, FDA, issues related to the use of in silico models.
206

B. Study Planning and Considerations for Stand-Alone Prospective DDI Studies

207
208
209 Protocol development¹² and study design depend on a number of factors, including:
210

- 211 • Whether the victim and/or perpetrator drugs are used acutely or chronically
212
- 213 • Whether there are exposure-related safety concerns with the substrate
214
- 215 • The pharmacokinetic and pharmacodynamic characteristics of the substrate and
216 perpetrator drugs
217
- 218 • Whether both induction and inhibition will be assessed
219
- 220 • The mechanism of the DDI (e.g., time-dependent inhibition)
221
- 222 • Whether the persistence of inhibition or induction after withdrawal of the perpetrator drug
223 will be assessed
224

225 The above factors can influence study design elements, including the number of experimental
226 allocations (e.g., two-way versus three-way cross-over), the duration of exposure to the
227 perpetrator, the substrate pharmacokinetic sampling strategy, and the study design (e.g., single-

⁹ When final, this guidance will represent the FDA’s current thinking on this topic.

¹⁰ When final, this guidance will represent the FDA’s current thinking on this topic.

¹¹ Wagner C, P Zhao, Y Pan, V Hsu, J Grillo, SM Huang, and V Sinha, 2015, Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK, CPT: Pharmacometrics & Systems Pharmacology, 4(4):226-230.

¹² Unless otherwise noted, the information below applies to both index studies and concomitant-use studies.

Contains Nonbinding Recommendations

Draft – Not for Implementation

228 dose or steady-state design). The purpose of most DDI studies is to determine the ratio of a
229 measure of substrate drug exposure (e.g., AUC ratio) in the presence and absence of a perpetrator
230 drug. The following considerations are important when designing prospective clinical DDI
231 studies to unambiguously determine this ratio.

232

233 *1. Study Population and Number of Subjects*

234

235 Most clinical DDI studies can be conducted using healthy subjects, assuming that findings in
236 healthy subjects can be used to predict findings in the intended patient population. Safety
237 considerations can prevent the use of healthy subjects in studies of certain drugs. Use of the
238 intended patient population allows the researcher to study pharmacodynamic endpoints that
239 cannot be studied in healthy subjects.

240

241 The number of subjects included in a DDI study should be sufficient to provide a reliable
242 estimate of the magnitude and variability of the interaction.

243

244 *2. Dose*

245

246 The doses of the perpetrator drug used in DDI studies should maximize the possibility of
247 identifying a DDI. Thus, the sponsor should use the maximum dose and the shortest dosing
248 interval of the perpetrator.

249

250 If the substrate drug has linear pharmacokinetics, the sponsor can use any dose in the linear
251 range. If the substrate drug has dose-dependent pharmacokinetics, the sponsor should use the
252 therapeutic dose most likely to demonstrate a DDI. When there are safety concerns in the
253 aforementioned scenarios, the sponsor can use lower doses of the substrate. A PBPK model
254 verified for the mechanism of nonlinearity of the substrate can be used to support dose selection.

255

256 *3. Single or Multiple Doses*

257

258 Single-dose administration of the perpetrator is only acceptable if the perpetrator is not a
259 potential inducer or time-dependent inhibitor.

260

261 The sponsor can administer index inhibitors as a single dose if maximal inhibition is achieved
262 and sustained following a single dose. The sponsor can administer concomitant drugs evaluated
263 as inhibitors as a single dose if clinically relevant concentrations of the concomitant drug are
264 achieved, and the degree of inhibition does not change over the dosing interval. The sponsor
265 should collect and analyze plasma samples to document that these two criteria are met.

266

267 The sponsor should administer inducers as multiple doses to ensure the maximal induction of a
268 specific pathway. It may take 2 or more weeks of daily drug administration to achieve the
269 maximum level of induction in a specific pathway. When there are multiple mechanisms of
270 interactions for a specific perpetrator, single-dose administration may be appropriate in certain
271 situations (e.g., rifampin as an inhibitor of organic anion transporting polypeptide 1B1
272 (OATP1B1)), while multiple-dose administration may be appropriate in other situations (e.g.,

Contains Nonbinding Recommendations

Draft – Not for Implementation

273 rifampin as a CYP3A inducer).

274
275 Single-dose administration of the substrate is acceptable if the substrate displays dose-
276 proportional exposure. The observed magnitude increase in exposure in single-dose studies can
277 be extrapolated to steady-state conditions. Multiple-dose administration of the substrate and a
278 perpetrator should be studied (in vivo or in silico based on in vivo single dose administration), if
279 the substrate demonstrates dose- or time-dependent nonlinear pharmacokinetics.

280

281 4. *Route of Administration*

282

283 For in vivo DDI studies, the route of administration of the investigational drug should generally
284 be the one planned for routine clinical use. When multiple routes of administration are
285 developed for clinical use, DDI studies for each route should consider the expected mechanisms
286 of the DDIs and the similarity of the corresponding concentration-time profiles for the parent
287 drug and metabolites after different routes of administration.

288

289 5. *Parallel Versus Crossover Studies*

290

291 Randomized, two-way crossover studies are preferred over parallel study designs due to reduced
292 intersubject variability. The sponsor should base the duration of the washout period on the
293 known pharmacokinetics of the substrate and the perpetrator as well as the anticipated impact on
294 the substrate's half-life. Typically, the two experimental periods evaluate the substrate alone and
295 the coadministration of the substrate and perpetrator. In some situations, a third crossover period
296 may be informative (e.g., to evaluate the time it takes for the enzyme's activity to return to
297 normal following removal of the investigational drug when it is an inducer or time-dependent
298 inhibitor, or to evaluate a pair of drugs when each drug can be the perpetrator or the substrate).

299

300 Parallel, two-arm studies can be appropriate when a crossover study design is not feasible (e.g.,
301 the drug has a long terminal half-life). Typically, parallel-design studies require larger sample
302 sizes than crossover studies.

303

304 6. *Timing of Drug Administration*

305

306 In most cases, the perpetrator and substrate drugs can be administered at the same time.
307 However, the timing of administration of the perpetrator is critical if it is both an inhibitor and an
308 inducer. For example, if the investigational drug is a substrate for CYP enzymes and OATP, and
309 rifampin is used as an enzyme inducer, the simultaneous administration of the drug with rifampin
310 — which is an OATP inhibitor — may not accurately capture the effects of enzyme induction.
311 In such cases, delayed administration of the substrate is recommended.

312

313 Sometimes multiple drug dosing schedules can be studied (in vivo or in silico) to understand
314 whether staggered dosing is a viable mitigation strategy for the DDI.

315

316 When evaluating the interaction between drugs that require different food conditions for optimal
317 absorption, the sponsor should adjust the timing of drug administration to maximize the potential

Contains Nonbinding Recommendations

Draft – Not for Implementation

318 to detect an interaction (i.e., index studies) or to reflect the clinically relevant conditions (i.e.,
319 concomitant-use studies).

320

321 7. *Baseline Condition Drug Use*

322

323 To reduce variability in the magnitude of DDIs, the sponsor should exclude and/or account for
324 the use of prescription or over-the-counter medications, dietary/nutritional supplements, tobacco,
325 alcohol, foods, and fruit juices that may affect the expression or function of enzymes and
326 transporters for a sufficient time before subject enrollment. The sponsor should exclude these
327 items for a longer time period if the DDI mechanism is induction or time-dependent inhibition.

328

329 8. *Sample and Data Collection*

330

331 Pharmacokinetic sampling times should be sufficient to characterize the AUC_{0-INF} (for single-
332 dose studies), the AUC_{0-TAU} (for multiple-dose studies), the maximum concentration (C_{max}), and
333 the minimum concentration (C_{min}) of the substrate drug administered alone and under conditions
334 of the anticipated interaction. The sampling times for single-dose studies should be planned so
335 that the mean difference between the AUC_{0-t} and the AUC_{0-INF} is less than 20 percent. Sponsors
336 should collect samples that contain the moieties needed to interpret study results; in most cases,
337 the moiety needed to interpret results will be the parent drug. The sponsor should determine
338 metabolite concentrations if the results provide information about the effect of a DDI on the
339 investigational drug's safety or efficacy, or if the data inform the mechanism of the drug
340 interaction.

341

342 All studies should collect relevant safety information based on the knowledge of existing safety
343 concerns with the administered drugs.

344

345 9. *Pharmacodynamic Endpoints*

346

347 In some situations, pharmacodynamic endpoints indicate changes in efficacy or toxicity that
348 systemic drug exposures do not predict. One possible scenario is when transporter inhibition
349 alters access of the drug to specific organs or tissues. In such scenarios, clinical consequences
350 such as altered efficacy or increased toxicity resulting from altered tissue distribution of a
351 substrate drug can be measured as pharmacodynamics endpoints, and in vitro evidence of a
352 drug's interaction potential can support data interpretation.

353

354 When in vitro data provide a plausible DDI mechanism that cannot be evaluated with systemic
355 drug exposure, sponsors can collect and analyze pharmacodynamic endpoints data.

356

357 **C. Study Planning and Considerations for Prospective Nested DDI Studies**

358

359 Prospective, nested DDI studies should be carefully designed. Stand-alone studies typically
360 include a large number of pharmacokinetic samples per subject, resulting in a rich sampling
361 strategy. In contrast, DDI studies that are part of another study (e.g., large phase 2 or phase 3
362 studies) often rely on sparse pharmacokinetic sampling with fewer samples per subject.

Contains Nonbinding Recommendations

Draft – Not for Implementation

363
364 Population pharmacokinetic analyses of data obtained from large-scale, clinical studies can help
365 characterize the clinical impact of known or newly identified interactions and determine
366 recommendations for dosage modifications when the investigational drug is a substrate. The
367 results of such analyses can be informative and sometimes conclusive when the clinical studies
368 are adequately designed to detect significant changes in drug exposure due to DDIs. Normally,
369 the exposure of coadministered drugs is not determined; therefore, it is not possible to use the
370 population pharmacokinetic method to evaluate the investigational drug as a perpetrator.
371 However, if the sponsor prospectively plans and collects the necessary data to support the
372 evaluation of targeted, concomitant drugs, population pharmacokinetic analyses can be useful for
373 evaluating the investigational drug as a perpetrator.

374
375 To be optimally informative, population pharmacokinetic analysis for prospective DDI
376 evaluation should have carefully designed study procedures and sample collection protocols.
377 The sponsor can simulate various DDI scenarios using available pharmacokinetic models (e.g.,
378 PBPK models, population pharmacokinetic models) to optimize study sampling (e.g., sampling
379 times, number of subjects) and data collection. Sponsors should document detailed information
380 on the dose given, the time of drug administration, and time of drug discontinuation for both the
381 investigational and coadministered drugs. The sponsor should also document the time of food
382 consumption if food affects the exposure of the investigational drug. Analyses should focus on
383 detecting a specific clinically meaningful change in drug exposure. The sponsor should
384 prespecify the population pharmacokinetic DDI assessment before conducting the prospective,
385 nested DDI study to increase confidence in the study's results.

386

D. Specific Considerations for CYP-Mediated Interactions

387

388

1. The Investigational Drug as a Substrate for CYP Enzymes

389

390

391 When evaluating the investigational drug as a substrate in a DDI, clinical DDI studies should
392 start with a strong index inhibitor and a strong index inducer. Moderate index inhibitors or
393 inducers are acceptable if strong index inhibitors or inducers are not available for a particular
394 enzyme. Examples of strong index inhibitors and inducers that can be used in clinical DDI
395 studies are listed below (for those enzymes that do not have strong inhibitors or inducers,
396 moderate inhibitors or inducers are listed):

397

- 398 • Strong Index Inhibitors of Cytochrome P450 (CYP) Enzymes:¹³

399

400

401

402

403

- CYP1A2: fluvoxamine
- CYP2C8: clopidogrel, gemfibrozil
- CYP2C9: fluconazole (moderate inhibitor)
- CYP2C19: fluvoxamine

¹³ CYP2B6 is not listed because we currently do not have strong or moderate index inhibitors of this enzyme.

Contains Nonbinding Recommendations

Draft – Not for Implementation

- 404 - CYP2D6: fluoxetine, paroxetine
- 405 - CYP3A: clarithromycin, itraconazole
- 406
- 407 • Strong Index Inducers of CYP Enzymes:¹⁴
- 408
- 409 - CYP2B6: rifampin (moderate inducer)
- 410 - CYP2C8: rifampin (moderate inducer)
- 411 - CYP2C9: rifampin (moderate inducer)
- 412 - CYP2C19: rifampin
- 413 - CYP3A: phenytoin, rifampin
- 414

415 These index inhibitors and inducers are preferred because there is a large body of information
416 about: (1) their defined effects on specific CYP pathways; (2) their appropriate dosing regimens;
417 (3) their safety profiles; and (4) their anticipated effects on their respective sensitive substrates.
418 Some of these inhibitors and inducers can also affect other metabolism and/or transporter
419 pathways. When selecting index inhibitors and inducers for prospective DDI studies, the
420 sponsor should consider the elimination pathways of the investigational drug as a substrate.
421 Other strong inhibitors and inducers of CYP enzymes can also be appropriate. Examples of
422 other inhibitors or inducers, information on the enzyme selectivity of these drugs, and criteria for
423 selecting index inhibitors or inducers are available on the FDA's Web site on Drug Development
424 and Drug Interactions.¹⁵

425

426 If a DDI study with a strong index inducer or inhibitor indicates that no DDI is present,
427 additional clinical studies with other inhibitors or inducers of the same enzyme are not needed.
428 If a DDI study with strong index inhibitors or inducers indicates that there is a clinically
429 significant interaction, the Agency recommends evaluating the impact of other moderate
430 inhibitors or inducers to gain a full understanding of the investigational drug's DDI potential.
431 The effect of the additional inhibitors and inducers can be evaluated in a clinical interaction
432 study or through modeling and simulation approaches, such as PBPK modeling with a verified
433 perpetrator (inhibitor or inducer) and substrate models. DDI studies with index substrates and
434 perpetrators can be used to inform potential future concomitant-use studies.

435

436 If the investigational drug is subject to significant metabolism by a genetically polymorphic
437 enzyme for which a well-defined poor metabolizer (PM) phenotype exists (e.g., for CYP2D6 and
438 CYP2C19), a comparison of the pharmacokinetic parameters of the drug in individuals with the
439 PM phenotype versus those with an extensive metabolizer (EM) phenotype can substitute for an
440 interaction study for that particular pathway. The effect of a PM phenotype is expected to be
441 similar to the effect of a strong inhibitor of that pathway. If this comparison reveals a clinically

¹⁴ CYP2D6 is not listed because the enzyme is not considered inducible, and we currently do not have index inducers for this enzyme.

¹⁵ FDA's Web site on Drug Development and Drug Interactions can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

442 significant difference in exposure between individuals with the PM and EM phenotypes, the
443 sponsor should evaluate the potential for DDIs with moderate inhibitors or inducers of the
444 enzymes as described above.

445 446 2. *The Investigational Drug as an Inhibitor or an Inducer of CYP Enzymes*

447
448 When studying an investigational drug as a potential inhibitor or inducer of a CYP enzyme, the
449 index substrate selected for the initial clinical studies should be sensitive to changes in activity or
450 amount of the CYP enzyme being evaluated. Examples of sensitive index substrates are listed
451 below:

- 452
- 453 • Sensitive Index Substrates of CYP Enzymes:¹⁶
 - 454 - CYP1A2: caffeine, tizanidine
 - 455 - CYP2C8: repaglinide (also a substrate for OATP1B1)
 - 456 - CYP2C9: warfarin, tolbutamide (both are moderate sensitive substrates)
 - 457 - CYP2C19: S-mephenytoin, omeprazole
 - 458 - CYP2D6: atomoxetine, desipramine, dextromethorphan
 - 459 - CYP3A: midazolam, triazolam
- 460

461
462 These sensitive index substrates are preferred because there is a large body of information about:
463 (1) the relative contribution of specific CYP pathways on their overall elimination; (2) their
464 appropriate dosing regimens; (3) their safety profiles; and (4) their anticipated interaction effects
465 when coadministered with strong index inhibitors and inducers. When determining which index
466 substrates to use for prospective DDI studies, the sponsor should consider the inhibition and/or
467 induction properties of the investigational drug. Other CYP enzyme substrates can also be
468 appropriate. Examples of other substrates, information on the enzyme selectivity of these drugs,
469 and criteria for selecting index substrates are available on the FDA's Web site on Drug
470 Development and Drug Interactions.¹⁷

471
472 If an initial study determines that an investigational drug either inhibits or induces the
473 metabolism of sensitive index substrates, further studies using other substrates (e.g., relevant co-
474 medications) can be useful. The sponsor should consider additional studies, depending on the
475 magnitude of the effect of the investigational drug on the sensitive index substrate and the
476 potential for coadministration with other drugs that are substrates of the same enzyme. If the
477 initial study with the most sensitive index substrates is negative, the sponsor can presume that
478 less sensitive substrates will also be unaffected.

479
480 Some substrate drugs that are typically used in DDI studies are not specific for one CYP enzyme;

¹⁶ CYP2B6 is not listed because we currently do not have index substrates for this enzyme.

¹⁷ FDA's Web site on Drug Development and Drug Interactions can be found at
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

481 furthermore, some of these drugs are also substrates for transporters. Using a substrate in a DDI
482 study that is metabolized by more than one enzyme is only appropriate if the investigational drug
483 is a selective inhibitor or inducer of the substrate’s primary CYP metabolizing enzyme. For
484 example, dextromethorphan elimination is carried out primarily by CYP2D6, with minor
485 contributions from other enzymes; therefore, dextromethorphan would be an appropriate
486 substrate for an investigational drug that is suspected to be a selective inhibitor of CYP2D6. If
487 the substrate drug is metabolized by more than one enzyme, measuring the metabolites can help
488 the sponsor interpret study results.

489
490 If the investigational drug is both an inducer and an inhibitor of an enzyme, the net effect of the
491 drug on enzyme function may be time dependent. The timing of pharmacokinetic endpoints
492 should permit an understanding of the changes in effects over time (see section IV.B.6).

493

E. Specific Considerations for Transporter-Mediated Interactions

494

1. The Investigational Drug as a Substrate of Transporters

495

496
497
498 If in vitro studies, as described in the FDA draft guidance for industry *In Vitro Drug*
499 *Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies*,¹⁸ indicate that the
500 investigational drug is a transporter substrate, the need for clinical DDI studies is determined
501 based on the drug’s putative site of action, route of elimination, likely concomitant drugs, and
502 safety considerations.¹⁹ The following general guidelines help to determine when a sponsor
503 should perform a clinical DDI study for investigational drugs that are transporter substrates in
504 vitro:

505

- P-glycoprotein (P-gp)- and breast cancer resistance protein (BCRP)-mediated DDIs:

506

- When the investigational drug must be transported into sequestered tissues (e.g.,
509 tissues in the central nervous system) to exert a pharmacological effect

510

- When the investigational drug must be kept out of sequestered tissues to avoid
512 toxicity

513

- When intestinal absorption is likely to be a major cause of the variability in drug
515 response

516

¹⁸ When final, this guidance will represent the FDA’s current thinking on this topic.

¹⁹ Giacomini KM, SM Huang, DJ Tweedie, LZ Benet, KLR Brouwer, X Chu, A Dahli, R Evers, V Fischer, KM Hillgren, KA Hoffmaster, T Ishikawa, D Keppler, RB Kim, CA Lee, M Niemi, JW Polli, Y Sugiyama, PW Swaan, JA Ware, SH Wright, SW Yee, MJ Zamek-Gliszczynski, and L Zhang, 2010, Membrane Transporters in Drug Development, *Nat Rev Drug Discov*, 9(3):215-236.

Contains Nonbinding Recommendations

Draft – Not for Implementation

- 517 • OATP1B1- and OATP1B3-mediated DDIs:
518
 - 519 - When hepatic uptake is necessary for the drug’s pharmacological effect
 - 520
 - 521 - When hepatic elimination is a significant clearance pathway for the investigational
522 drug
 - 523
- 524 • Organic anion transporter 1 and 3 (OAT1 and OAT3)-, organic cation transporter 2
525 (OCT2)-, and multidrug and toxin extrusion (MATE)-mediated DDIs:
526
 - 527 - When the investigational drug undergoes active renal secretion or there are concerns
528 about renal toxicity
 - 529

530 When testing an investigational drug as a substrate in transporter-mediated DDIs, the selected
531 perpetrator drug should be a known inhibitor of the transporter under investigation. The sponsor
532 can select perpetrators for the DDI study based on the goal of the study (e.g., if the goal of the
533 study is to gain mechanistic understanding or to conduct a clinical assessment).

534

535 Because of a general lack of index perpetrators for transporter-mediated pathways, the choice of
536 transporter perpetrators is typically based on the likelihood of coadministration (e.g., to obtain
537 clinically relevant DDI information that can inform labeling regarding the management of a
538 DDI).

539

540 A few transporter perpetrators can also be used to understand the underlying mechanisms of
541 transporter-mediated DDIs or to study the worst-case DDI scenario. For example, to understand
542 the worst possible transporter-mediated DDI for an investigational drug that is a substrate for
543 multiple transporters, an inhibitor of many transporters (e.g., cyclosporine, which inhibits
544 intestinal P-gp and BCRP and hepatic OATPs) can be used as the inhibitor in the DDI study.
545 Negative results from this kind of study can rule out the need to further evaluate the drug as a
546 substrate for any of the individual transporters. If the study result is positive, additional studies
547 with more selective inhibitors of specific transporter pathways can help determine the relative
548 contribution of each transporter to the disposition of the substrate drug. The same experimental
549 paradigm can apply to an investigational drug that is a substrate for both transporters and
550 metabolic enzymes (e.g., CYP3A and P-gp).

551

552 If the goal of the study is to determine the role of a specific pathway in the pharmacokinetics of a
553 substrate drug, then the sponsor should use a more selective inhibitor for that transporter. A few
554 inhibitors selectively block specific transporter pathways. For example, a single dose of
555 rifampin selectively inhibits the hepatic transporter OATP, and probenecid selectively inhibits
556 the renal transporters OAT1 and OAT3. Use of these inhibitors in vivo can provide a
557 mechanistic understanding of transporter-mediated DDIs. In addition, the investigational drug
558 can be a substrate of a genetically polymorphic transporter (e.g., OATP1B1 and BCRP are
559 encoded by the genetically polymorphic genes *SLCO1B1* and *ABCG2*, respectively) for which
560 phenotypes with reduced functionality exist. Similar to drugs that are substrates of CYPs
561 encoded by polymorphic genes, the relative contribution of a specific transporter to the

Contains Nonbinding Recommendations

Draft – Not for Implementation

562 disposition of the investigational drug can be evaluated in subjects with different transporter
563 genotypes (see section IV.G.1).

564
565 Examples of transporter inhibitors are listed below. Many of them not only inhibit the specified
566 transporters but also can inhibit some CYP enzymes. Interpretation of the study results using
567 such transporter inhibitors requires knowledge of the enzymatic and metabolic pathways for the
568 investigational drug. A detailed list of transporter inhibitors is maintained on the FDA's Web
569 site on Drug Development and Drug Interactions.²⁰

- 570
- 571 • Transporter Inhibitors:
 - 572 - P-gp: clarithromycin, itraconazole, quinidine, verapamil
 - 573
 - 574 - BCRP: cyclosporine (also inhibits other transporters, including P-gp, Multi-drug
575 Resistance Protein, and OATP)
 - 576
 - 577 - OATP: cyclosporine, rifampin (single dose)
 - 578
 - 579 - OCT2 or MATE1/2K: cimetidine, pyrimethamine
 - 580
 - 581 - OAT1/3: probenecid
 - 582
- 583

584 Results from most transporter inhibition studies are not easily extrapolated to other drugs,
585 because most inhibitors are not specific for a single transporter (see sections IV.A.2 and IV.A.3).

586 587 2. *The Investigational Drug as an Inhibitor or an Inducer of Transporters*

588

589 If in vitro studies, as described in the FDA guidance for industry *In Vitro Drug Metabolism- and*
590 *Transporter-Mediated Drug-Drug Interaction Studies*,²¹ indicate that the investigational drug is
591 a transporter inhibitor, the sponsor should consider a clinical drug interaction study based on
592 likely concomitant drugs and safety considerations, regardless of the investigational drug's route
593 of elimination.²²

594

²⁰ FDA's Web site on Drug Development and Drug Interactions can be found at
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.

²¹ When final, this guidance will represent the FDA's current thinking on this topic.

²² Giacomini KM, SM Huang, DJ Tweedie, LZ Benet, KLR Brouwer, X Chu, A Dahli, R Evers, V Fischer, KM Hillgren, KA Hoffmaster, T Ishikawa, D Keppler, RB Kim, CA Lee, M Niemi, JW Polli, Y Sugiyama, PW Swaan, JA Ware, SH Wright, SW Yee, MJ Zamek-Gliszczynski, and L Zhang, 2010, Membrane Transporters in Drug Development, *Nat Rev Drug Discov*, 9(3):215-236.

Contains Nonbinding Recommendations

Draft – Not for Implementation

595 When studying the investigational drug's potential to act as a perpetrator drug, the sponsor
596 should select a substrate whose pharmacokinetic profile is markedly altered by coadministration
597 of known inhibitors of the transporter and is also a likely concomitant drug. Examples of
598 transporter substrates that can be used in drug interaction studies are listed below. A detailed list
599 of substrates is maintained on the FDA's Web site on Drug Development and Drug
600 Interactions.²³ Many drugs are substrates of multiple transporters and/or enzymes. For example,
601 rosuvastatin is a substrate for BCRP, OATP1B1, and OATP1B3. The observed clinical
602 interactions can be a result of the inhibition of multiple pathways if the investigational drug is
603 also an inhibitor for the same pathways. Results from these studies are thus not easily
604 extrapolated to other drugs (see sections IV.A.2 and IV.A.3). The choice of substrates can be
605 determined by the therapeutic area of the investigational drug and the probable coadministered
606 drugs that are known substrates of the transporters. For example, digoxin, a P-gp substrate, is a
607 common probe substrate to study P-gp interactions. It is not necessarily the most sensitive P-gp
608 substrate to show P-gp interactions, but the results are clinically relevant due to its narrow
609 therapeutic index.

610

611 • **Transporter Substrates:**

612

- 613 - P-gp: digoxin, dabigatran etexilate, fexofenadine
- 614 - BCRP: rosuvastatin
- 615 - OATP1B1 or OATP1B3: pitavastatin, pravastatin, rosuvastatin
- 616 - OCT2 or MATEs: metformin
- 617 - OAT1: adefovir, ganciclovir
- 618 - OAT3: benzylpenicillin

619

620 Several drugs are substrates of more than one transporter. For example, rosuvastatin is a
621 substrate for BCRP and OATP.

622

623 The sponsor should consult with the Office of Clinical Pharmacology in CDER to determine
624 whether to evaluate the investigational drug's ability to induce transporters. Some drugs can
625 induce P-gp; however, there is no validated in vitro system to study P-gp induction. Therefore,
626 determining a drug's potential to induce P-gp should be based on clinical studies. Because of
627 similarities in the mechanisms of CYP3A and P-gp induction, results from CYP3A induction
628 studies can inform decisions about whether to investigate the induction of P-gp. If a study
629 indicates that an investigational drug does not induce CYP3A, it is not necessary to evaluate the
630 drug's potential to induce P-gp. If the clinical CYP3A induction test is positive, then the sponsor
631 should consider an additional study of the investigational drug's effect on a known P-gp
632 substrate. If the drug also inhibits P-gp, then an induction study can be combined with the
633 inhibitor study using a multiple-dose design.

634

²³ FDA's Web site on Drug Development and Drug Interactions can be found at
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

635 **F. Cocktail Approaches**

636
637 A cocktail study includes the simultaneous administration of substrates of multiple CYP
638 enzymes and/or transporters to study subjects. This approach can simultaneously evaluate a
639 drug's inhibition or induction potential for multiple CYPs and transporters as long as the study is
640 properly designed and the following conditions are satisfied: (1) the substrates are specific for
641 individual CYP enzymes or transporters; (2) there are no interactions among the substrates; and
642 (3) the study is conducted with a sufficient number of subjects. Negative results from a well-
643 conducted cocktail study can eliminate further evaluation of particular CYP enzymes or
644 transporters. Positive results from a well-conducted cocktail study that includes all elements of a
645 prospective DDI study can be interpreted and presented in labeling the same way as positive
646 results from any other well-conducted drug interaction study.

647 648 **G. Other Considerations**

649 **I. Genetics**

650
651
652 If a drug is a substrate for a polymorphic enzyme or transporter, a subject's genotype for a
653 specific enzyme or transporter affects the extent of drug induction or drug inhibition. When a
654 DDI study uses an index inhibitor or substrate (e.g., omeprazole for CYP2C19) to evaluate
655 pharmacokinetic changes, individuals who have no functional enzyme activity should typically
656 be excluded, or the study should be sufficiently powered to evaluate DDIs in subjects with
657 functional enzymes. In cases where study enrollment is not based on the genotype of a
658 polymorphic enzyme or transporter, sponsors should still routinely collect DNA from all subjects
659 for retrospective analysis of the enzymes or transporters of interest to characterize differences in
660 the magnitude of the DDI across genotype groups and to understand why some subjects have
661 unusual increases or decreases in drug concentrations (see the FDA's guidance for industry
662 entitled *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and*
663 *Recommendations for Labeling*²⁴).

664
665 The combined effects of different genotypes of polymorphic enzymes and transporters can also
666 be explored in a drug interaction study. For example, if a drug is metabolized by both CYP3A
667 and CYP2C19, examining the effect of CYP3A inhibition in CYP2C19 poor metabolizers may
668 help uncover the consequences of losing compensatory pathways. This kind of study may be
669 accomplished by prospective enrichment of poor metabolizers or through retrospective analysis,
670 provided that a sufficient number of poor metabolizers are enrolled.

671
672 In some instances, a gene-drug interaction study may substitute for a prospective DDI study and
673 vice versa. Suitable substrates for these studies have a high fraction of metabolism ($f_m > 80\%$)
674 by a single CYP enzyme that has loss-of-function alleles.

675

²⁴ We update guidances periodically. To make sure you have the most recent version of guidance, check the FDA
Drugs guidance Web page at
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

676 Comparing the pharmacokinetics of an investigational drug in subjects with different genotypes
677 of specific transporters (e.g., OATP1B1, BCRP) can help determine the importance of a specific
678 transporter in the drug's clearance pathway.

679

680 2. *Smokers*

681

682 Smoking induces CYP1A2 activity. If an investigational drug is a CYP1A2 substrate, the
683 sponsor should consider conducting a study in smokers based on the intended patient population
684 and the effect of CYP1A2 induction on the drug's exposure. The study arms for a smoking study
685 include nonsmokers (i.e., never smoked) in the control arm and current smokers in the
686 investigational arm. Data collected in the smoking study should include the number of cigarettes
687 smoked per day and, when feasible, plasma cotinine levels in both smokers and nonsmokers.
688 The sponsor should evaluate the effects of different levels of smoking if it considers the
689 information important for the patient population.

690

691 3. *Complex Drug Interactions*

692

693 When there are multiple factors that affect the absorption and disposition of an investigational
694 drug as well as multiple mechanisms of DDIs, the sponsor should evaluate the investigational
695 drug's DDI potential by integrating knowledge from multiple in vitro and clinical studies. PBPK
696 models may be useful to: (1) integrate the information from multiple studies; (2) determine
697 whether a clinical study is appropriate; and (3) inform the design of clinical studies. See the
698 FDA's draft guidance for industry entitled *In Vitro Metabolism- and Transporter-Mediated*
699 *Drug-Drug Interaction Studies*²⁵ for more information. Sponsors are encouraged to discuss the
700 strategies to study complex DDIs with the Office of Clinical Pharmacology in CDER.

701

702

703 **V. REPORTING AND INTERPRETING STUDY RESULTS**

704

705 A DDI study report should include and justify the study design and the data analysis method
706 based on what is known about the mechanism of the DDI and the pharmacokinetic properties of
707 the perpetrator and victim drugs.

708

709 **A. Study Results Reporting**

710

711 Typical pharmacokinetic endpoints for DDI studies include changes in drug exposure parameters
712 such as AUC_{0-INF} and C_{max} . Sponsors should report the pharmacokinetic results of DDI studies
713 as the geometric mean ratio of the observed pharmacokinetic exposure measures with and
714 without the perpetrator drug and include the associated 90 percent confidence interval. Sponsors
715 should also report measures of the observed variability of the interaction.

²⁵ When final, this guidance will represent the FDA's current thinking on this topic.

Contains Nonbinding Recommendations

Draft – Not for Implementation

716

717 The sponsor should summarize all information on pharmacodynamic endpoints. If the
718 pharmacodynamic endpoint is a continuous response, the sponsor can analyze the data and report
719 the results in the same manner as for pharmacokinetic endpoints. If the pharmacodynamic
720 endpoint is not a continuous response, the sponsor should consult with the FDA to determine an
721 appropriate data analysis method.

722

723 The sponsor should specify the criteria for defining outliers in the protocol and make a
724 distinction between outlying individuals versus outlying data points. In general, sponsors should
725 report results with and without suspected outliers.

726

727 The sponsor should report $AUC_{0-∞}$ values for all individuals and include the percentage of
728 extrapolation. Sponsors should highlight individuals with more than 20 percent extrapolated
729 $AUC_{0-∞}$.

730

731 1. *Non-Compartmental Analysis*

732

733 The sponsor should report substrate exposure measures for all subjects, for example, the $AUC_{0-∞}$
734 AUC_{0-t} , the percentage extrapolated $AUC_{0-∞}$, the C_{max} , and the time to C_{max} (T_{max}). For
735 multiple-dose studies, sponsors should also report the C_{min} and the AUC_{0-TAU} at steady-state.
736 Sponsors should collect data on additional pharmacokinetic parameters such as the clearance, the
737 volume of distribution, and the half-life if they help interpret the pharmacokinetic results. The
738 sponsor should also consider collecting and reporting pharmacokinetic parameters that are
739 relevant to the clinical significance of the interaction. Measuring metabolite levels can help
740 confirm the mechanism of an interaction or differentiate the effect of inhibitors or inducers on
741 pathways mediated by different CYP enzymes.

742

743 2. *Population Pharmacokinetic Analysis*

744

745 When possible, population pharmacokinetic analysis should derive pharmacokinetic exposure
746 parameters, such as $AUC_{0-∞}$, AUC_{0-t} , C_{max} , and T_{max} , in addition to the primary pharmacokinetic
747 parameters. For multiple-dose studies, sponsors should also report the C_{min} and the AUC_{0-TAU} at
748 the steady-state. Sponsors should investigate the DDI using all plausible structural elements of
749 the pharmacokinetic model (e.g., clearance (CL/F), relative bioavailability, rate of absorption).
750 Further considerations for population pharmacokinetic analysis are available in the FDA
751 guidance for industry entitled *Population Pharmacokinetics*. In certain cases, traditional
752 pharmacokinetic data analysis using non-compartmental analysis methods may not be adequate.
753 For example, it may be difficult to design a study for drugs with a long half-life that would allow
754 $AUC_{0-∞}$ to be estimated with less than 20 percent extrapolation from AUC_{0-t} . Such studies
755 should be analyzed with population pharmacokinetic methods in addition to non-compartmental
756 analysis.²⁶

²⁶ Svensson EM, C Acharya, B Clauson, KE Dooley, and MO Karlsson, 2016, Pharmacokinetic Interactions for Drugs With a Long Half-Life — Evidence for the Need of Model-Based Analysis, AAPS J, 18(1):171-179.

Contains Nonbinding Recommendations

Draft – Not for Implementation

757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800

B. Interpreting DDI Studies

The goal of a DDI study with pharmacokinetic endpoints is to inform clinical management strategies by determining whether there is a clinically significant increase or decrease in exposure to the substrate in the presence of the perpetrator. The results of a DDI study are interpreted based on the *no-effect boundaries* for the substrate drug. No-effect boundaries represent the interval within which a change in a systemic exposure measure is considered not significant enough to warrant clinical action (e.g., dose or schedule adjustment, or additional therapeutic monitoring).

1. Approaches for Determining No-Effect Boundaries

There are two approaches to determining no-effect boundaries:

- Approach 1 (Preferred) — No-effect boundaries can be based on concentration-response relationships derived from pharmacokinetic and pharmacodynamic analyses, as well as other available information for the substrate drug (e.g., the maximum-tolerated dose). A good understanding of dose-concentration and/or concentration-response relationships for desirable and undesirable drug effects, as well as knowledge of the variability of exposures in the indicated population, can facilitate data interpretation. The FDA’s guidance for industry entitled *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* provides further considerations for exposure-response analysis. The sponsor should obtain Agency agreement on the *no-effect boundaries* for the investigational drug as a substrate (victim) at milestone meetings.

If the 90 percent confidence interval for the measured changes in systemic exposures in the DDI study falls completely within these no-effect boundaries, no clinically significant DDI is present. The percentile method to determine the proportion of subjects that extend beyond the no-effect boundary can be more appropriate in some instances.

- Approach 2 (In the absence of no-effect boundaries defined in Approach 1 or when the aim of the study is to determine whether a drug is a perpetrator or not when using index substrates) — The sponsor can use a default no-effect boundary of 80 to 125 percent in these instances. When the 90 percent confidence intervals for systemic exposure ratios fall entirely within the equivalence range of 80 to 125 percent, the FDA concludes that there is no clinically significant DDI.

The 80 to 125 percent boundaries represent a very conservative standard for drugs that have wide safety margins, so Approach 1 is preferred for evaluating the impact of DDI on the safety and efficacy of the substrate drug. In the absence of a clearly defined exposure-response relationship, the totality of evidence must be taken into consideration when making a determination of the clinical impact of the DDI on the substrate drug.

Contains Nonbinding Recommendations

Draft – Not for Implementation

2. *Interpreting Results From Retrospective DDI Evaluations*

Retrospective DDI evaluations can be useful to identify DDIs that were unanticipated at the start of clinical development. Sponsors should confirm results from retrospective DDI studies that suggest risk mitigation strategies are warranted with a prospective DDI study. Negative findings from retrospective studies generally do not provide useful information to include in labeling.

3. *Classifying the Investigational Drug as an Inhibitor or Inducer*

If an investigational drug is a CYP inhibitor, it can be classified as a strong, moderate, or weak inhibitor based on its effect on an index CYP substrate. The convention is to categorize CYP inhibition in the following way:

- A strong inhibitor increases the AUC of a sensitive index CYP substrate ≥ 5 -fold.
- A moderate inhibitor increases the AUC of a sensitive index CYP substrate by ≥ 2 - to < 5 -fold.
- A weak inhibitor increases the AUC of a sensitive index CYP substrate by ≥ 1.25 - to < 2 -fold.

These categories typically describe the effect of the investigational drug when given at the highest dose and the shortest dosing interval.

If an investigational drug is a CYP inducer, it can be classified as a strong, moderate, or weak inducer based on its effect on an index CYP substrate. The convention is to categorize CYP induction in the following ways:

- A strong inducer decreases the AUC of a sensitive index CYP by ≥ 80 percent.
- A moderate inducer decreases the AUC of a sensitive index CYP substrate by ≥ 50 to < 80 percent.
- A weak inducer decreases the AUC of a sensitive index CYP substrate by ≥ 20 to < 50 percent.

This classification information helps to determine whether other drugs that have not been investigated in a DDI study have clinically significant DDIs with the investigational drug and therefore need to be mentioned in labeling. For example, if an investigational drug is a strong CYP3A inhibitor, its potential to interact with drugs that have clinically significant interactions with other strong CYP3A inhibitors should be considered, and the sponsor should add appropriate language regarding these additional interactions to the investigational drug's labeling.

Currently, there is no standardized classification system for transporter and phase II metabolizing enzyme inducers or inhibitors.

Contains Nonbinding Recommendations

Draft – Not for Implementation

846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890

4. Development of DDI Management Strategies

The FDA recommends developing DDI management strategies when a clinically significant DDI is identified. An interaction is clinically significant if coadministration of the drugs leads to safety, efficacy, or tolerability concerns greater than those present when the drugs are administered alone.

In general, DDI management strategies should result in drug concentrations of the victim drug that are within the no-effect boundaries. In addition, DDI management strategies should consider several factors, including, but not limited to:

- The exposure-response relationships for safety and efficacy
- The variability of the observed DDI data, if available
- The expected duration of concomitant drug use (e.g., acute, short-term, or chronic use of one or both of the drugs)
- The timing of the introduction of the concomitant medication (e.g., will the new drug be given to a patient already taking a concomitant medication or will the concomitant medication be given to a patient already taking the new drug)
- The mechanism of the DDI (e.g., competitive, noncompetitive or time-dependent inhibition, induction, combined inhibition and induction)
- The availability of monitoring parameters (e.g., therapeutic drug monitoring, laboratory tests)
- The medical need for the new agent, the ability to interrupt concomitant interacting medications, and the availability of other therapeutic choices in patients with potentially clinically important interactions with the new agent.

With the above considerations, DDI management and prevention strategies may include contraindicating concomitant use, avoiding concomitant use, temporary discontinuation of one of the interacting drugs, dosage modifications of the new drug or the concomitant drug, including staggered drug administration (e.g., administer the new drug at a different time than an acid reducing agent), and specific monitoring strategies (e.g., therapeutic drug monitoring, laboratory testing).

5. Extrapolating Study Results

Clinical evaluation of all possible combinations of drugs is not feasible. When possible, results from DDI studies should be extrapolated to other drugs and clinical situations. Results from DDI studies with index drugs are generally relevant to other drugs and may represent a worst-case

Contains Nonbinding Recommendations

Draft – Not for Implementation

891 scenario for other drugs (see section IV.A.2). For example, if there is no effect on the exposure
892 of an investigational drug when coadministered with a strong CYP3A4 index inhibitor, then one
893 can generally assume that there is no effect when other strong, moderate, or weak index
894 CYP3A4 inhibitors are coadministered with the investigational drug. If a strong CYP2D6 index
895 inhibitor results in a significant increase in exposure of the investigational drug, these results can
896 be directly extrapolated to other strong CYP2D6 inhibitors. Extrapolation of positive findings to
897 moderate and weak inhibitors is not always possible (see section IV.A.4). In cases where
898 extrapolation is not possible, the FDA may recommend a dedicated clinical DDI study.

899
900 Concomitant-use DDI studies can be warranted in cases when extrapolation is not feasible and
901 drugs with DDI potential are likely to be coadministered. Although concomitant-use studies
902 have limited potential for extrapolation to other drugs, they may have great relevance to
903 practitioners and patients.

904
905 Because of the lack of specific transporter substrates and inhibitors and possible interplay with
906 metabolism, results from DDI studies evaluating transporter-mediated DDIs or transporter-
907 metabolism interactions generally cannot be extrapolated to other drugs (see section IV.E).

908
909

VI. LABELING RECOMMENDATIONS

910
911

912 Prescribing information should include a summary of essential DDI information that is needed
913 for the safe and effective use of the drug by the health care provider. This information can
914 include data and results from prospective clinical DDI studies (e.g., stand-alone DDI studies,
915 nested DDI studies), population pharmacokinetic analyses, modeling and simulations,
916 postmarketing reports, or data extrapolated from other information.

917

918 DDI information in labeling should inform prescribing decisions by including clinically relevant
919 findings about the following if appropriate:

920

921 • Metabolic and transport pathways

922

923 • Metabolites

924

925 • Pharmacokinetic or pharmacodynamic interactions

926

927 • Clinical implications of clinically significant pharmacokinetic or pharmacodynamic
928 interactions

929

930 • Clinical implications of genetic polymorphisms of drug metabolizing enzymes and
931 transporters

932

933 • Recommended risk mitigation strategies (e.g., dosage adjustments or monitoring
934 recommendations)

935

Contains Nonbinding Recommendations

Draft – Not for Implementation

936 The DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections of a drug labeling
937 include the majority of the DDI information. When DDI information has direct implications for
938 the safe and effective use of the drug, this information is often included in varying levels of
939 detail in other sections of the labeling (e.g., BOXED WARNING, DOSAGE AND
940 ADMINISTRATION, CONTRAINDICATIONS, and/or WARNINGS AND PRECAUTIONS
941 sections), and must be discussed in more detail in the DRUG INTERACTIONS section (§
942 201.57(c)(8)(i)). When drug interaction information appears in multiple sections of labeling,
943 sponsors should cross-reference DDI information in accordance with the recommendations in
944 FDA guidance for industry entitled *Labeling for Human Prescription Drug and Biological*
945 *Products — Implementing the PLR Content and Format Requirements*. Regulatory requirements
946 and guidance recommendations for information on drug interactions in several sections of the
947 prescribing information are presented below. General content recommendations for different
948 labeling sections are provided below.

949

- 950 • **DRUG INTERACTIONS** — The DRUG INTERACTIONS section describes clinically
951 significant drug interactions, clinical implications, and practical instructions for
952 preventing or managing these interactions. Clinically significant interactions (predicted
953 or observed) may occur with other prescription drugs, over-the-counter drugs, classes of
954 drugs, dietary supplements, and foods or juices. An interaction is clinically significant if
955 concomitant use of the products leads to safety, efficacy, or tolerability concerns greater
956 than those present when the drugs are administered alone. The description of the
957 interaction must also include a brief discussion of the mechanisms of the interaction, if
958 known. Interactions that are described in the CONTRAINDICATIONS or WARNINGS
959 AND PRECAUTIONS sections must be discussed in more detail under this section (§
960 201.57(c)(8)(i)). The sponsor should present information in this section in the format that
961 best accommodates the breadth and complexity of the information and ensures clarity and
962 understanding (e.g., by using tables, subsections, headings/subheadings).

963

964 Results from DDI studies that indicate the absence of a DDI should generally not appear
965 in this section, unless this information is clinically relevant for the health care provider
966 (e.g., if two drugs are commonly used together, or if a drug does not have the same
967 interaction as other drugs in the same class). Details of drug interaction pharmacokinetic
968 studies that are included in the CLINICAL PHARMACOLOGY section that are pertinent
969 to clinical use of the drug must not be repeated in this section (§ 201.57(c)(8)(i)).

970

971 This section must also contain practical guidance on known interference of the drug with
972 a laboratory test — as reliance on the erroneous test result would influence clinical
973 decision making — and, if feasible, provide practical guidance on how to modify the
974 drug’s administration to allow the practitioner to conduct the laboratory test (§
975 201.57(c)(8)(ii)).

976

- 977 • **CLINICAL PHARMACOLOGY** — Drug interaction information in the
978 Pharmacokinetics subsection (subsection 12.3 of the CLINICAL PHARMACOLOGY
979 section) must be included under the “Drug Interactions Studies” heading (§
980 201.57(c)(13)(i)). This heading includes detailed information that informs the actionable

Contains Nonbinding Recommendations

Draft – Not for Implementation

981 recommendations in the DRUG INTERACTIONS section of labeling. This information
982 should include both positive and pertinent negative results from specific clinical
983 pharmacology studies, population analyses, or other modeling and simulation approaches
984 (e.g., PBPK modeling) that evaluate DDIs. Sponsors should also include study design
985 information that may inform prescribing decisions (e.g., if a clinically relevant difference
986 in exposures between patients and healthy volunteers was observed, then the sponsor
987 should define the DDI study population under this heading). Additional information
988 regarding the potential mechanisms of DDIs can also be included, unless this information
989 is self-evident from other headings or subheadings (e.g., Metabolism) in the
990 Pharmacokinetics subsection. The sponsor should present information in this section in
991 the format that best accommodates the breadth and complexity of the information and
992 ensures clarity and understanding (e.g., by using text, tables, and/or figures)

993

994 Positive and pertinent negative results from pertinent in vitro drug interaction studies not
995 further investigated in clinical studies should also be included under this heading.
996 Brevity is encouraged.

997

998 • **DOSAGE AND ADMINISTRATION** — This section must include dosage modifications
999 due to drug interactions (see 21 CFR 201.57(c)(3)(i)(H)) and should only include
1000 information that has specific implications for a drug's dosing regimen (e.g., dosage
1001 adjustments, alteration of the timing of a dose relative to dosing of another drug) or
1002 administration. This section should omit the description and mechanism of the drug
1003 interaction, clinical implications, study findings, and other practical instructions for
1004 preventing or managing the drug interaction (except for dosage or administration
1005 modification). When there is not enough information to support a dosage or
1006 administration modification, the interaction should ordinarily not be discussed in this
1007 section.

1008

1009 • **CONTRAINDICATIONS** — This section lists other drugs that should not be
1010 coadministered with the drug because the risk clearly outweighs any possible therapeutic
1011 benefit. Known hazards, not theoretical possibilities, must be listed (see § 201.57(c)(5)).

1012

1013 • **WARNINGS AND PRECAUTIONS** — This section includes a brief discussion of any
1014 known or predicted drug interactions with serious or otherwise clinically significant
1015 outcomes with a cross-reference to the DRUG INTERACTIONS section. When
1016 deciding whether a clinically significant drug interaction should appear in both the
1017 WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS sections rather than
1018 only the DRUG INTERACTIONS section, factors to consider include, but are not
1019 limited to: (1) the seriousness of the interaction; (2) whether or not the interaction can be
1020 prevented or managed; (3) the evidence of causality; and (4) the likelihood of
1021 concomitant drug use. This section also includes information on any known interference
1022 by the product with laboratory tests and references the section where the detailed
1023 information is presented (e.g., DRUG INTERACTIONS section) (see § 201.57(c)(6)).

1024

1025 • **PATIENT COUNSELING INFORMATION** — Interactions or effects from other drugs

Contains Nonbinding Recommendations

Draft – Not for Implementation

1026 or foods must be included in the PATIENT COUNSELING INFORMATION section if
1027 they concern an important risk (e.g., are mentioned in the BOXED WARNING,
1028 CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections) (§
1029 201.57(c)(18)(i)). Additionally, an interaction should be included if coadministration
1030 could be initiated by the patient (e.g., an interaction with food or an over-the-counter
1031 drug or dietary supplement). A complete listing of known drug interactions should
1032 typically not be included in the PATIENT COUNSELING INFORMATION section
1033 because the decision to coadminister two prescription drugs generally rests with the
1034 provider at the time of prescribing.

1035
1036 For more specific recommendations on content for these labeling sections, refer to the following
1037 FDA guidances for industry:

- 1038
- 1039 • *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological*
1040 *Products — Content and Format*
 - 1041
 - 1042 • *Content and Format of the Dosage and Administration Section of Labeling for Human*
1043 *Prescription Drug and Biological Products*
 - 1044
 - 1045 • *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling*
1046 *for Prescription Drug and Biological Products — Content and Format*
 - 1047
 - 1048 • *Patient Counseling Information Section of Labeling for Human Prescription Drug and*
1049 *Biological Products — Content and Format*

1050
1051 Essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or
1052 diluents (see § 201.57(c)(3)) are not considered drug interactions. This information must appear
1053 in the DOSAGE AND ADMINISTRATION section, not the DRUG INTERACTIONS section.

1054
1055

VII. ABBREVIATIONS

AUC _{0-t}	Area under the plasma concentration-time curve integrated from time of administration (0) to time of last quantifiable observation (t)
AUC _{0-INF}	Area under the plasma concentration-time curve from time of administration extrapolated to infinity from AUC _{0-t}
AUC _{0-TAU}	Area under the plasma concentration-time curve integrated across the dosing interval
BCRP	Breast cancer resistance protein
C _{max}	Maximum concentration
C _{min}	Minimum concentration
CYP	Cytochrome P450
DDI	Drug-drug interaction
EM	Extensive metabolizers
MATE	Multidrug and toxin extrusion
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBPK	Physiologically based pharmacokinetic
P-gp	P-glycoprotein
PM	Poor metabolizers
TDI	Time-dependent inhibition
T _{max}	Time to C _{max}

1056
1057

VIII. DEFINITIONS

Cocktail studies	A cocktail study evaluates an investigational drug as a potential inducer or inhibitor of multiple enzymes and/or transporters and includes the simultaneous administration of multiple substrates for multiple CYP enzymes and/or transporters to study subjects.
Concomitant-use studies	Concomitant-use studies are clinical DDI studies that investigate DDIs between drugs likely to be used by the target population under clinically relevant scenarios.
In silico DDI studies	In silico DDI studies are simulation studies conducted with adequately validated computer models.
Index perpetrator	Index perpetrators are drugs recommended for use in prospective clinical DDI studies because they have well-established potency and selectivity profiles that cause a defined degree of inhibition or induction of a given elimination pathway when administered with a sensitive and specific substrate of that pathway.
Index substrate	Index substrates are drugs recommended for use in prospective clinical DDI studies as substrates because they have well-established sensitivity and specificity profiles that demonstrate a defined degree of change in exposures when administered with a strong inhibitor or inducer for that specific elimination pathway.
Moderate inducer	Moderate inducers are drugs that decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥ 50 percent to < 80 percent.
Moderate inhibitor	Moderate inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway by ≥ 2 - to < 5 -fold.
Moderate sensitive substrate	Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 2 - to < 5 -fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.
No-effect boundaries	No-effect boundaries represent the interval within which a change in a systemic exposure measure is considered not significant enough to warrant clinical action (e.g., dose or schedule adjustment, or additional therapeutic monitoring)
Perpetrator	A perpetrator is a moiety that can induce or inhibit an enzyme or a transporter.
Prospective nested DDI studies	Prospective nested DDI studies are clinical DDI investigations that are part of trials with a primary endpoint different than investigation of DDIs. However, these trials are adequately designed to prospectively investigate DDIs and define DDIs as one of the endpoints.
Prospective stand-alone DDI	Prospective stand-alone DDI studies are separate clinical trials prospectively designed to investigate a DDI as the primary endpoint.

studies

Sensitive substrate	Sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 5 -fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.
Strong inducer	A strong inducer is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 80 percent.
Strong inhibitor	A strong inhibitor is a drug that increase the AUC of sensitive index substrates of a given metabolic pathway ≥ 5 -fold.
Substrate	The term <i>substrate</i> is used interchangeably with <i>victim</i> (see definition for <i>victim</i>).
Retrospective DDI evaluations	Retrospective DDI evaluations are clinical evaluations that have not been prospectively and adequately designed to investigate DDIs.
Victim	A victim is a substrate whose exposure changes due to inhibition or induction of an enzyme or transporter by a perpetrating moiety.
Weak inducer	A weak inducer is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 20 percent to < 50 percent.
Weak inhibitor	A weak inhibitor is a drug that increases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 1.25 - to < 2 -fold.

1058