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

Guidance for Industry

DRAFT GUIDANCE

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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
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Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

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

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 A related FDA draft guidance for industry entitled *In Vitro Drug Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies* focuses on how to assess the DDI potential of a drug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risk-based approach for evaluating DDIs and communicating the results of DDI studies and will replace the 2012 draft guidance entitled *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.*

In general, FDA's guidance documents 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

[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.

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

II. BACKGROUND

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

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

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

III. TIMING OF CLINICAL DDI STUDIES

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

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

IV. DESIGN AND CONDUCT OF CLINICAL DDI STUDIES

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

A. Types of DDI Studies

1. Prospective Studies and Retrospective Evaluations

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

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

2. DDI Studies With Index Perpetrators and Index Substrates

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

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

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

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

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

3. DDI Studies With Expected Concomitant Drugs: Concomitant Use Studies

Index substrates and perpetrators are not chosen based on their use in the investigational drug's target population, but rather because of their well-defined interaction effects that provide 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.

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

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

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

4. In Silico DDI Studies

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

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[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 Pharmacokinet, 54(1):117-127.

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

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

Protocol development[12] and study design depend on a number of factors, including:

- Whether the victim and/or perpetrator drugs are used acutely or chronically
- Whether there are exposure-related safety concerns with the substrate
- The pharmacokinetic and pharmacodynamic characteristics of the substrate and perpetrator drugs
- Whether both induction and inhibition will be assessed
- The mechanism of the DDI (e.g., time-dependent inhibition)
- Whether the persistence of inhibition or induction after withdrawal of the perpetrator drug will be assessed

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

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[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.

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

1. Study Population and Number of Subjects

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

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

2. Dose

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

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

3. Single or Multiple Doses

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

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

The sponsor should administer inducers as multiple doses to ensure the maximal induction of a specific pathway. It may take 2 or more weeks of daily drug administration to achieve the maximum level of induction in a specific pathway. When there are multiple mechanisms of interactions for a specific perpetrator, single-dose administration may be appropriate in certain situations (e.g., rifampin as an inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1)), while multiple-dose administration may be appropriate in other situations (e.g., rifampin as a CYP3A inducer).

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

4. Route of Administration

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

5. Parallel Versus Crossover Studies

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

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

6. Timing of Drug Administration

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

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

When evaluating the interaction between drugs that require different food conditions for optimal absorption, the sponsor should adjust the timing of drug administration to maximize the potential to detect an interaction (i.e., index studies) or to reflect the clinically relevant conditions (i.e., concomitant-use studies).

7. Baseline Condition Drug Use

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

8. Sample and Data Collection

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

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

9. Pharmacodynamic Endpoints

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

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

C. Study Planning and Considerations for Prospective Nested DDI Studies

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

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

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

D. Specific Considerations for CYP-Mediated Interactions

1. The Investigational Drug as a Substrate for CYP Enzymes

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

- Strong Index Inhibitors of Cytochrome P450 (CYP) Enzymes:[13]

  - 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.

- CYP2D6: fluoxetine, paroxetine
- CYP3A: clarithromycin, itraconazole

- Strong Index Inducers of CYP Enzymes:[14]

  - CYP2B6: rifampin (moderate inducer)
  - CYP2C8: rifampin (moderate inducer)
  - CYP2C9: rifampin (moderate inducer)
  - CYP2C19: rifampin
  - CYP3A: phenytoin, rifampin

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

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

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

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

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

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

- Sensitive Index Substrates of CYP Enzymes:[16]

    - CYP1A2: caffeine, tizanidine
    - CYP2C8: repaglinide (also a substrate for OATP1B1)
    - CYP2C9: warfarin, tolbutamide (both are moderate sensitive substrates)
    - CYP2C19: S-mephenytoin, omeprazole
    - CYP2D6: atomoxetine, desipramine, dextromethorphan
    - CYP3A: midazolam, triazolam

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

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

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

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[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.

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

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

E. Specific Considerations for Transporter-Mediated Interactions

1. The Investigational Drug as a Substrate of Transporters

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

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

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

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

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

[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.

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- OATP1B1- and OATP1B3-mediated DDIs:

  - When hepatic uptake is necessary for the drug's pharmacological effect

  - When hepatic elimination is a significant clearance pathway for the investigational drug

- Organic anion transporter 1 and 3 (OAT1 and OAT3)-, organic cation transporter 2 (OCT2)-, and multidrug and toxin extrusion (MATE)-mediated DDIs:

  - When the investigational drug undergoes active renal secretion or there are concerns about renal toxicity

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

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

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

If the goal of the study is to determine the role of a specific pathway in the pharmacokinetics of a substrate drug, then the sponsor should use a more selective inhibitor for that transporter. A few inhibitors selectively block specific transporter pathways. For example, a single dose of rifampin selectively inhibits the hepatic transporter OATP, and probenecid selectively inhibits the renal transporters OAT1 and OAT3. Use of these inhibitors in vivo can provide a mechanistic understanding of transporter-mediated DDIs. In addition, the investigational drug can be a substrate of a genetically polymorphic transporter (e.g., OATP1B1 and BCRP are encoded by the genetically polymorphic genes *SLCO1B1* and *ABCG2*, respectively) for which phenotypes with reduced functionality exist. Similar to drugs that are substrates of CYPs encoded by polymorphic genes, the relative contribution of a specific transporter to the disposition of the investigational drug can be evaluated in subjects with different transporter genotypes (see section IV.G.1).

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

- Transporter Inhibitors:

  - P-gp: clarithromycin, itraconazole, quinidine, verapamil

  - BCRP: cyclosporine (also inhibits other transporters, including P-gp, Multi-drug Resistance Protein, and OATP)

  - OATP: cyclosporine, rifampin (single dose)

  - OCT2 or MATE1/2K: cimetidine, pyrimethamine

  - OAT1/3: probenecid

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

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

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

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[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.

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

- Transporter Substrates:

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

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

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

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[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.

F. Cocktail Approaches

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

G. Other Considerations

1. Genetics

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

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

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

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[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.

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

2. Smokers

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

3. Complex Drug Interactions

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

V. REPORTING AND INTERPRETING STUDY RESULTS

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

A. Study Results Reporting

Typical pharmacokinetic endpoints for DDI studies include changes in drug exposure parameters such as $AUC_{0\text{-}INF}$ and C_{max}. Sponsors should report the pharmacokinetic results of DDI studies as the geometric mean ratio of the observed pharmacokinetic exposure measures with and without the perpetrator drug and include the associated 90 percent confidence interval. Sponsors 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.

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

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

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

1. Non-Compartmental Analysis

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

2. Population Pharmacokinetic Analysis

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

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.

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.

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

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

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

VI. LABELING RECOMMENDATIONS

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

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

- Metabolic and transport pathways
- Metabolites
- Pharmacokinetic or pharmacodynamic interactions
- Clinical implications of clinically significant pharmacokinetic or pharmacodynamic interactions
- Clinical implications of genetic polymorphisms of drug metabolizing enzymes and transporters
- Recommended risk mitigation strategies (e.g., dosage adjustments or monitoring recommendations)

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

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

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

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

- CLINICAL PHARMACOLOGY — Drug interaction information in the Pharmacokinetics subsection (subsection 12.3 of the CLINICAL PHARMACOLOGY section) must be included under the "Drug Interactions Studies" heading (§ 201.57(c)(13)(i)). This heading includes detailed information that informs the actionable recommendations in the DRUG INTERACTIONS section of labeling. This information should include both positive and pertinent negative results from specific clinical pharmacology studies, population analyses, or other modeling and simulation approaches (e.g., PBPK modeling) that evaluate DDIs. Sponsors should also include study design information that may inform prescribing decisions (e.g., if a clinically relevant difference in exposures between patients and healthy volunteers was observed, then the sponsor should define the DDI study population under this heading). Additional information regarding the potential mechanisms of DDIs can also be included, unless this information is self-evident from other headings or subheadings (e.g., Metabolism) in the Pharmacokinetics subsection. The sponsor should present information in this section in the format that best accommodates the breadth and complexity of the information and ensures clarity and understanding (e.g., by using text, tables, and/or figures)

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

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

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

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

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

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

- *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*

- *Content and Format of the Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products*

- *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Prescription Drug and Biological Products — Content and Format*

- *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*

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

VII. ABBREVIATIONS

$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve integrated from time of administration (0) to time of last quantifiable observation (t)
$AUC_{0\text{-}INF}$	Area under the plasma concentration-time curve from time of administration extrapolated to infinity from $AUC_{0\text{-}t}$
$AUC_{0\text{-}TAU}$	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}

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 $\geq$ 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 $\geq$ 2- to < 5-fold.
Moderate sensitive substrate	Moderate sensitive substrates are drugs that demonstrate an increase in AUC of $\geq$ 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 *substrate* is used interchangeably with *victim* (see definition for *victim*).
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.