Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions

Guidance for Industry

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

January 2020
Clinical Pharmacology

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Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry[1]

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I. INTRODUCTION

This final guidance helps sponsors of investigational new drug applications and applicants of new drug applications evaluate drug-drug interactions (DDIs) during drug development and determine essential information to communicate in labeling.[2]

This final guidance describes 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. Specifically, this guidance provides considerations for evaluating pharmacokinetic cytochrome P450 (CYP) enzyme- or transporter-mediated interactions.

A related final January 2020 FDA guidance for industry entitled *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*[3] 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. Together, these two final guidances on DDIs describe a systematic, risk-based approach for evaluating DDIs and determining essential information to communicate in labeling.

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

[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, protein displacement, modulation of Phase II metabolic enzymes, or other mechanisms that do not involve cytochrome P450 enzymes or transporters (e.g. gastric pH change, complexation).

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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 CYP enzyme- and transporter-mediated DDIs are to:

- Determine whether the investigational drug alters the pharmacokinetics of other drugs
- Determine whether other drugs alter the pharmacokinetics of the investigational drug
- Determine the magnitude of changes in pharmacokinetic parameters
- Determine the clinical significance of the observed or expected DDIs
- Inform the appropriate management and prevention 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 assess the DDI potential 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. Regulatory decision-making generally requires prospective studies specifically designed for this purpose. Retrospective evaluation of drug concentrations from studies not designed to evaluate DDIs rarely includes sufficient precision to provide an adequate assessment (see section V.B.2 for more details).

Protocols for prospective clinical DDI studies are specifically designed to detect DDIs as a major objective, 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 appropriate OND prescription drug review division 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: Index Studies

To test whether an investigational drug is a victim of DDIs, sponsors should use index perpetrators. Index perpetrators predictably inhibit or induce drug metabolism 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 cause DDIs of the greatest magnitude when co-administered with the investigational drug (as a substrate) by altering the function of a given metabolic pathway. Results 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 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 co-administered with a known 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. Moderately sensitive index substrates are drugs whose AUC values increase 2- to <5-fold when co-administered 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 of enzymes, respectively. Moderately 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 CYP 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 DDI studies.

Evaluating the effect of an investigational drug on an endogenous substrate (e.g., 4β-hydroxycholesterol[5]) can provide information about its effect on a metabolic pathway (e.g., induction of CYP3A-mediated metabolism). However, we generally do not recommend using the endogenous substrate for the index studies because it is difficult 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

[5] Mao J, I Martin, J McLeod, G Nolan, R van Horn, M Vourvahis, and YS Lin, 2017, 4β-Hydroxycholesterol as an Emerging Biomarker of Hepatic CYP3A, Drug Metab Rev, 49(1):18-34.

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 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.[6]

Currently, substrates or perpetrators of transporters fulfilling the criteria of an index drug have not been identified (see section IV.A.2). The choice of victim or perpetrator drug for transporter studies should be based primarily on the likelihood of concomitant use 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 inhibitors on the substrates of some CYP isoforms (e.g., CYP2D6, CYP3A) as well as the impact of weak and moderate inducers on CYP3A substrates.[7,8,9] These predictions were made after prospective clinical trials showed a significant DDI between the investigational drug and strong

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

[7] 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.

[8] 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.

[9] 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.

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 January 2020 FDA guidance for industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* and the 2018 FDA guidance for industry *Physiologically Based Pharmacokinetic Analyses —Format and Content*. 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.[10] We encourage sponsors to discuss issues and considerations related to the use of in silico models with the FDA.

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

Protocol development[11] and study design can vary depending on 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-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

[10] 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.

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

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 under the intended conditions of use or as labeled.

If the substrate drug has dose-proportional pharmacokinetics, the sponsor can use any dose in the range where exposure to the drug increases in a dose-proportional manner. 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 dose-dependent pharmacokinetics of the substrate can be used to support dose selection.

3. Single or Multiple Doses

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

An inhibitor can be administered as a single dose if it is justified that single-dose administration of the inhibitor has a similar effect on the enzyme or transporter of interest to that after multiple dosing. For substrates with long half-lives it may be necessary to administer a perpetrator multiple times to cover the full time-course of the substrate exposure.

The sponsor should administer inducers as multiple doses to ensure the maximal induction of a specific pathway. It may take about 2 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., evaluation of rifampin as an inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1)), while multiple-dose administration may be appropriate in other situations (e.g., evaluation of rifampin as a CYP3A inducer).

Single-dose administration of the substrate is acceptable if the substrate does not show time-dependent pharmacokinetics (e.g., auto-inhibition or auto-induction). In those situations, 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 time-dependent 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, the route of drug administration for DDI studies should be selected based on 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

A study can use a randomized crossover (e.g., S followed by S+I, S+I followed by S, where S refers to a substrate and I designates an inhibitor or inducer), one-sequence crossover (e.g., S followed by S+I), or a parallel (e.g., S in one group of subjects and S+I in another group) design.

Crossover studies (one-sequence or randomized) are preferred over parallel study designs in order to reduce inter-subject variability. The sponsor should base the duration of the washout period on the known pharmacokinetics of the substrate and the perpetrator, the anticipated impact on the substrate's half-life, and the duration necessary for enzyme activity to return to baseline or for potential pharmacodynamic effects to return to pre-treatment levels (if pharmacodynamic effects are also assessed). Typically, the two experimental periods evaluate the substrate alone and the concomitant use 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. 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 OATP1B, and rifampin is used as an enzyme inducer, the simultaneous administration of the drug with rifampin — which is an OATP1B 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) and/or to reflect the clinically relevant conditions

(i.e., concomitant-use studies).

7. Co-Medications and Other Extrinsic Factors Affecting DDIs

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 period of time 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) or the $AUC_{0\text{-}TAU}$ (for multiple-dose studies) and the maximum concentration (C_{max}) of the substrate drug administered alone and under conditions of the anticipated interaction. Sponsors should collect data on additional pharmacokinetic parameters based upon the pharmacokinetic or pharmacological relevance for the proposed indication (e.g., the minimal concentration (C_{min}), partial AUC). 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 pharmacodynamic 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 endpoint data. The sponsor should consult with the FDA regarding pharmacodynamic endpoint evaluation.

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 co-administered 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 the time of drug discontinuation for both the investigational and co-administered drugs. If food affects the exposure of the investigational drug or co-administered drug, the sponsor should also document the time and type of food consumed. 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, 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. 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 inhibitors or inducers are available on the FDA's Web site on Drug Development and Drug Interactions.[12]

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

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 (e.g., fraction of metabolism, f_m, accounted by the enzyme $\geq$ 80 percent) 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 (see section IV.G.1). 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 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. 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 co-administered 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 sensitive substrates are listed on the FDA's Web site on Drug Development and Drug Interactions.[13, 14]

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

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

[14] CYP2B6 is not listed because we currently do not have index substrates for this enzyme. CYP2B6 is the principal enzyme involved in the formation of hydroxybupropion from bupropion which may be used as a victim drug in clinical DDI studies with measurement of hydroxybupropion concentrations to evaluate the potential inhibitory effect of an investigational drug on CYP2B6.

potential for concomitant use 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; furthermore, some of these drugs are also substrates for transporters. When conducting a DDI study, using a substrate 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 January 2020 FDA guidance for industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*, 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.[15] 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 intestinal absorption, biliary excretion, or renal active secretion is likely to be a major cause of the variability in a drug pharmacokinetics and response
- OATP1B1- and OATP1B3-mediated DDIs:
  - When hepatic/biliary elimination is a significant clearance pathway for the investigational drug, and the drug's properties (e.g., low passive membrane permeability, high hepatic concentrations relative to other tissues) support the importance of active uptake of the drug into the liver

[15] 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.

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

    - When the investigational drug undergoes significant active renal secretion (i.e., accounting for ≥ 25 percent of systemic clearance) 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 concomitant use (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 transporter-mediated DDI of the largest possible magnitude for an investigational drug that is a substrate for multiple transporters, an inhibitor of several 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 block specific transporter pathways in a relatively selective manner. For example, a single dose of rifampin inhibits the hepatic transporter OATPs, and probenecid 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 on the FDA's Web site on Drug Development and Drug Interactions.[16] Many of them not only inhibit the specified transporters but also can inhibit some other transporters and/or CYP enzymes. Thus, results from most transporter inhibition studies are not easily extrapolated to other drugs (see sections IV.A.2 and IV.A.3). Interpretation of the study results requires knowledge of the transport and metabolic pathways for the investigational drug.

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 Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*, 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.[17] When studying the investigational drug's potential to act as a perpetrator drug for a transporter, the sponsor should select a substrate whose pharmacokinetic profile is markedly altered by coadministration of known inhibitors of that transporter and is also a likely concomitant drug. Examples of transporter substrates that can be used in drug interaction studies are listed on the FDA's Web site on Drug Development and Drug Interactions. Many drugs are substrates of multiple transporters and/or enzymes. 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 concomitant drugs that are known substrates of the transporters.

The sponsor should consult with the FDA 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.

F. Cocktail Approaches

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

[17] 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.

A cocktail study includes the simultaneous administration of substrates of multiple CYP enzymes and/or transporters to study subjects. A cocktail 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. It should be noted the findings obtained with a microdose of a substrate may not always be extrapolated to a therapeutic dose of that substrate.

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 2013 FDA guidance for industry entitled *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling*).

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 (e.g., $f_m \geq 80$ percent) by a single CYP enzyme that has loss-of-function alleles (see section IV.D.1.).

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 (e.g., have not smoked in the past 6 months) 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 nicotine 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 (e.g., multiple CYP enzymes and/or transporters), 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 January 2020 FDA guidance for industry entitled *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* for more information. Sponsors are encouraged to discuss the strategies to study complex DDIs with the FDA.

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 when applicable.

The sponsor should summarize all information on pharmacodynamic endpoints. If the pharmacodynamic endpoint is a continuous response (e.g., certain blood biomarkers), 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.

When possible, 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 $AUC_{0\text{-}INF,}$ report the results with and without those subjects, and discuss the potential impact on the interpretation of the findings.

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 T_{max}. For multiple-dose studies, sponsors should also report the C_{min} and the $AUC_{0\text{-}TAU}$ at steady-state. Sponsors should report 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 relevant, population pharmacokinetic analysis should derive pharmacokinetic exposure parameters, such as $AUC_{0\text{-}INF}$, $AUC_{0\text{-}t,}$ C_{max}, and T_{max}. 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 1999 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 could be analyzed with population pharmacokinetic methods in addition to non-compartmental analysis.[18]

B. Interpreting DDI Studies

The goal of a DDI study with pharmacokinetic endpoints is to inform management and prevention 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).

[18] 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.

1. Approaches for Determining No-Effect Boundaries

There are two approaches to determining no-effect boundaries:

- Approach 1 (Preferred) — When possible, 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 2003 guidance for industry entitled *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* provides further considerations for exposure-response analysis.

  For example, 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 should be taken into consideration when determining 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 clinical management or prevention 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 clinical dose and the shortest dosing interval within its therapeutic dose range/dosing regimen.

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 substrate 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 Clinical Management and Prevention Strategies

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

In general, DDI clinical management and prevention strategies should result in drug concentrations of the victim drug that are within the no-effect boundaries. In addition, such 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 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 drug, the ability to interrupt concomitant interacting medications, and the availability of other therapeutic choices in patients with potentially clinically important interactions with the new drug.

With the above considerations, DDI management and prevention strategies may include:

- Contraindicating concomitant use
- Avoiding concomitant use
- Temporarily discontinuing one of the interacting drugs
- Modifying the dosage of the new drug
- Staggering drug administration (e.g., administer the new drug at a different time than an acid-reducing agent)
- Implementing 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 co-administered with a strong CYP3A4 index inhibitor, then one can generally assume that there is no effect when other strong, moderate, or weak CYP3A4 inhibitors are co-administered 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 co-administered. 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, it is generally challenging to extrapolate results from DDI studies evaluating transporter-mediated DDIs or transporter-metabolism interactions from one drug to other drugs (see section IV.E).

VI. LABELING RECOMMENDATIONS

The 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. The DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections of 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)). 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* (December 2016)

- *Content and Format of the Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products* (March 2010)

- *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Prescription Drug and Biological Products — Content and Format* (October 2011)

- *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2014)

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 protein
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBPK	Physiologically based pharmacokinetic
P-gp	P-glycoprotein
PLR	Physician Labeling Rule
PM	Poor metabolizers
TDI	Time-dependent inhibition
T_{max}	Time to C_{max}

VIII. DEFINITIONS

Cocktail studies	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	Clinical DDI studies that investigate DDIs between drugs likely to be used by the target population under clinically relevant scenarios.
In silico DDI studies	Simulation studies conducted with adequately validated computer models.
Index perpetrator	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	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	Drugs that decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥ 50 percent to < 80 percent.
Moderate inhibitor	Drugs that increase the AUC of sensitive index substrates of a given metabolic pathway by ≥ 2- to < 5-fold.
Moderately sensitive substrate	Drugs whose AUC values increase ≥ 2- to < 5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies, or whose AUC values increase ≥ 2- to < 5-fold in poor metabolizers for a specific enzyme compared to extensive metabolizers.
No-effect boundaries	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	Moiety that can induce or inhibit an enzyme or a transporter.
Prospective nested DDI studies	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 studies	Separate clinical trials prospectively designed to investigate a DDI as the primary endpoint.
Sensitive substrate	Drugs whose AUC values increase ≥ 5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies, or whose AUC ratio in poor metabolizers for a specific enzyme increase ≥ 5-fold compared to extensive metabolizers.

Strong inducer	Drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 80 percent.
Strong inhibitor	Drug that increase the AUC of sensitive index substrates of a given metabolic pathway ≥ 5-fold.
Substrate	Used interchangeably with *victim* (see definition for *victim*).
Retrospective DDI evaluations	Clinical evaluations that have not been prospectively and adequately designed to investigate DDIs.
Victim	Substrate whose exposure changes due to inhibition or induction of an enzyme or transporter by a perpetrating moiety.
Weak inducer	Drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 20 percent to < 50 percent.
Weak inhibitor	Drug that increases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 1.25- to < 2-fold.