Guidance for Industry

In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Recommendations for Dosing and Labeling

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
November 1999
Clin/Pharm

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I. INTRODUCTION

This guidance provides recommendations to sponsors of new drug applications (NDAs) and biologics license applications (BLAs) for therapeutic biologics (hereafter drugs) who intend to perform in vivo drug metabolism and metabolic drug-drug interaction studies. The guidance reflects the Agency's current view that the metabolism of an investigational new drug should be defined during drug development and that its interactions with other drugs should be explored as part of an adequate assessment of its safety and effectiveness. For metabolic drug-drug interactions, the approaches considered in the guidance are offered with the understanding that whether a particular study should be performed will vary, depending on the drug in development and its intended clinical use. Furthermore, not every drug-drug interaction is metabolism-based, but may arise from changes in pharmacokinetics caused by absorption, tissue and/or plasma binding, distribution, and excretion interactions. Drug interactions related to transporters are being documented with increasing frequency and may be addressed more fully in future guidances. Although less well studied, drug-drug interactions may alter pharmacokinetic/pharmacodynamic (PK/PD) relationships. These important areas are not considered in detail in this guidance.

Previous guidance from FDA on the use of in vitro approaches to study drug metabolism and metabolic drug-drug interactions is available in a guidance document entitled *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro* (April 1997). The present guidance should be viewed as a companion to this earlier guidance. Discussion of metabolic and other types of drug-drug interactions is also provided in other guidances, including the International Conference on Harmonisation (ICH) *E8 General Considerations for Clinical Trials* (December 1997), *E7 Studies in Support of Special Populations: Geriatrics* (August 1994), and *E3 Structure and Content of Clinical Study Reports* (July 1996), and the Agency guidances *Studying Drugs Likely to be Used in the Elderly* (November 1989) and *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (July 1993).

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[1] This guidance has been prepared by the In Vivo Metabolic Drug-Drug Interaction Working Group in the Clinical Pharmacology Section of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research, with input from the Center for Biologics Evaluation and Research, at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the subject of in vivo drug metabolism and metabolic drug-drug interactions. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

II. BACKGROUND

A. Metabolism

The desirable and undesirable effects of a drug arising from its concentrations at the sites of action are usually related either to the amount administered (dose) or to the resulting blood concentrations, which are affected by its absorption, distribution, metabolism and/or excretion. Elimination of a drug or its metabolites occurs either by metabolism, usually by the liver, or by excretion, usually by the kidneys and liver. In addition, protein therapeutics may be eliminated via a specific interaction with cell surface receptors, followed by internalization and lysosomal degradation within the target cell. Hepatic elimination occurs primarily by the cytochrome P450 family of enzymes located in the hepatic endoplasmic reticulum but may also occur by non-P450 enzyme systems, such as N-acetyl and glucuronosyl transferases. P450 enzyme systems located in gut mucosa can also significantly affect the amount of drug absorbed into the systemic circulation.[2] Many factors can alter hepatic and intestinal drug metabolism, including the presence or absence of disease and/or concomitant medications. While most of these factors are usually relatively stable over time, concomitant medications can alter metabolic routes of absorption and elimination abruptly and are of particular concern. The influence of concomitant medications on hepatic and intestinal metabolism becomes more complicated when a drug, including a prodrug, is metabolized to one or more active metabolites. In this case, the safety and efficacy of the drug/prodrug are determined not only by exposure to the parent drug but by exposure to the active metabolites, which in turn is related to their formation, distribution, and elimination.

B. Metabolic Drug-Drug Interactions

Many metabolic routes of elimination, including most of those occurring via the P450 family of enzymes, can be inhibited, activated, or induced by concomitant drug treatment. Observed changes arising from metabolic drug-drug interactions can be substantial — an order of magnitude or more decrease or increase in the blood and tissue concentrations of a drug or metabolite — and can include formation of toxic metabolites or increased exposure to a toxic parent compound. Examples of substantially changed exposure associated with administration of another drug include (1) increased levels of terfenadine, cisapride, or astemizole with ketoconazole or erythromycin (inhibition of CYP3A4); (2) increased levels of simvastatin and its acid metabolite with mibefradil or itraconazole (inhibition of CYP3A4); (3) increased levels

[2] No distinction is made in this document between the effects of concomitant drugs and/or alterations in metabolism on gastrointestinal absorption and hepatic elimination, although the pharmacokinetic effects of the two may be different.

of desipramine with fluoxetine, paroxetine, or quinidine (inhibition of CYP2D6); and (4) decreased carbamazepine levels with rifampin (induction of CYP3A4). These large changes in exposure can alter the safety and efficacy profile of a drug and/or its active metabolites in important ways. This is most obvious and expected for a drug with a narrow therapeutic range (NTR), but is also possible for non-NTR drugs as well (e.g., HMG CoA reductase inhibitors). Depending on the extent and consequence of the interaction, the fact that a drug's metabolism can be significantly inhibited by other drugs and that the drug itself can inhibit the metabolism of other drugs can require important changes in either its dose or the doses of drugs with which it interacts, that is, on its labeled conditions of use. Rarely, metabolic drug-drug interactions may affect the ability of a drug to be safely marketed.

The following general concepts underlie the recommendations in this guidance:

- Adequate assessment of the safety and effectiveness of a drug includes a description of its metabolism and the contribution of metabolism to overall elimination.

- Metabolic drug-drug interaction studies should explore whether an investigational agent is likely to significantly affect the metabolic elimination of drugs already in the marketplace and, conversely, whether drugs in the marketplace are likely to affect the metabolic elimination of the investigational drug.

- Even drugs that are not substantially metabolized can have important effects on the metabolism of concomitant drugs. For this reason, metabolic drug-drug interactions should be explored, even for an investigational compound that is not eliminated significantly by metabolism.

- In some cases, metabolic drug-drug interaction studies cannot be informative unless metabolites and prodrugs have been identified and their pharmacological properties described.

- Identifying metabolic differences in patient groups based on genetic polymorphism, or on other readily identifiable factors, such as age, race, and gender, can aid in interpreting results.

- The impact of an investigational or approved interacting drug can be either to inhibit or induce metabolism.

- A specific objective of metabolic drug-drug interaction studies is to determine whether the interaction is sufficiently large to necessitate a dosage adjustment of the drug itself or the drugs it might be used with, or whether the interaction would require additional therapeutic monitoring.

- In some instances, understanding how to adjust dosage in the presence of an interacting drug, or how to avoid interactions, may allow marketing of a drug that would otherwise have been associated with an unacceptable level of toxicity. Sometimes a drug interaction may be used intentionally to increase levels or reduce elimination of another drug. Rarely, the degree of interaction caused by a drug, or the degree to which other drugs alter its metabolism, may be such that it cannot be marketed safely.

- The blood or plasma concentrations of the parent drug and/or its active metabolites (systemic exposure) may provide an important link between drug dose (exposure) and desirable and/or undesirable drug effects. For this reason, the development of sensitive and specific assays for a drug and its key metabolites is critical to the study of metabolism and drug-drug interactions.

- For drugs whose presystemic or systemic clearance occurs primarily by metabolism, differences arising from various sources, including administration of another drug, are an important source of inter-individual and intra-individual variability.

- Unlike relatively fixed influences on metabolism, such as hepatic function or genetic characteristics, metabolic drug-drug interactions can lead to abrupt changes in exposure. Depending on the nature of the drugs, these effects could potentially occur when a drug is initially administered, when it has been titrated to a stable dose, or when an interacting drug is discontinued. Interactions can occur after even a single concomitant dose of an inhibitor.

- The effects of an investigational drug on the metabolism of other drugs and the effects of other drugs on an investigational drug's metabolism should be assessed relatively early in drug development so that the clinical implications of interactions can be assessed as fully as possible in later clinical studies.

III. GENERAL STRATEGIES

To the extent possible, drug development should follow a sequence where early in vitro and in vivo investigations can either fully address a question of interest or provide information to guide further studies. Optimally, a sequence of studies should be planned, moving from in vitro studies, to early exploratory studies, to later more definitive studies, employing special study designs and methodology where necessary and appropriate. In many cases, negative findings from early in vitro and early clinical studies can eliminate the need for later clinical investigations. Early investigations should explore whether a drug is eliminated primarily by excretion or metabolism, with identification of the principal metabolic routes in the latter case. Using suitable in vitro probes and careful selection of interacting drugs for early in vivo studies, the potential for drug-drug interactions can be studied early in the development process, with further study of observed interactions assessed later in the process, as needed. In certain cases and with careful study designs and planning, these early studies may also provide information about dose, concentration, and response relationships in the general population, subpopulations, and individuals, which can be useful in interpreting the consequences of a metabolic drug-drug interaction.

A. In Vitro Studies

A complete understanding of the relationship between in vitro findings and in vivo results of metabolism/drug-drug interaction studies is still emerging. Nonetheless, in vitro studies can frequently serve as an adequate screening mechanism to rule out the importance of a metabolic pathway and drug-drug interactions that occur via this pathway so that subsequent in vivo testing is unnecessary. This opportunity should be based on appropriately validated experimental methods and rational selection of substrate/interacting drug concentrations. For example, if suitable in vitro studies indicate that CYP2D6 or 3A4 enzyme systems do not metabolize an investigational drug, then clinical studies to identify the impact of the CYP2D6 slow metabolizer phenotype or to study the effect of CYP2D6 inhibitors or CYP3A4 inhibitors/inducers on the elimination of the investigational drug will not be needed. Similarly, if in vitro studies indicate that an investigational drug does not inhibit CYP2D6 or 3A4 metabolism, then corresponding in vivo drug-drug interaction studies of the investigational drug and concomitant medications eliminated by these pathways are not needed.

In contrast, when positive findings arise in in vitro metabolic and/or drug-drug interaction studies, clinical studies are recommended because of the limited ability at present of in vitro findings to give a good quantitative estimate of the clinical importance of a metabolic pathway or interaction. Further evaluation of the utility of parameters such as the ratio between the concentration of drug and the Ki (inhibition constant) for the interaction may lead to continued improvements in the ability of in vitro studies to predict in vivo results, but the overall experience to date is not large enough to allow reliable conclusions. Although in vitro studies can assess the presence or absence of inhibition, they have limited capability to identify

induction. For this reason, in vivo studies remain the primary source of information about induction of metabolic pathways caused by concomitant medications.

B. Specific In Vivo Clinical Investigations

Appropriately designed pharmacokinetic studies, usually performed in the early phases of drug development, can provide important information about metabolic routes of elimination, their contribution to overall elimination, and metabolic drug-drug interactions. Together with information from in vitro studies, these investigations can be a primary basis of labeling statements and can often help avoid the need for further investigations. Further recommendations about these types of studies appear in section IV of this guidance.

C. Population Pharmacokinetic Screens

Population pharmacokinetic analyses of data obtained from blood samples collected infrequently (sparse sampling) in clinical studies conducted in the later phase of clinical drug development can be valuable in characterizing the clinical impact of known or newly identified interactions, and in making recommendations for dosage modifications. It may be possible that analysis or skillful examination of such data could detect unsuspected drug-drug interactions. Population pharmacokinetic data can also provide further evidence of the absence of a pharmacokinetic drug-drug interaction when this is suggested by in vitro drug-drug interaction studies. The power of a sparse sampling strategy to detect drug-drug interactions is not yet well established, however, and it is unlikely that population analysis can be used to prove the absence of an interaction that is strongly suggested by information arising from in vitro or in vivo studies specifically designed to assess a drug-drug interaction. To be optimally informative, population pharmacokinetic studies should have carefully designed study procedures and sample collections. A guidance for industry entitled *Population Pharmacokinetics* was published in February 1999.

IV. DESIGN OF IN VIVO METABOLIC DRUG-DRUG INTERACTION STUDIES

If in vitro studies and other information suggest a need for in vivo metabolic drug-drug interaction studies, the following general issues and approaches should be considered. In the following discussion, the term *substrate* (S) is used to indicate the drug studied to determine if its exposure is changed by another drug, which is termed the *interacting drug* (I). Depending on the study objectives, the substrate and the interacting drug may be the investigational agents or approved products.

A. Study Design

In vivo metabolic drug-drug interaction studies generally are designed to compare substrate levels with and without the interacting drug. Because a specific study may consider a number of questions and clinical objectives, no one correct study design for studying drug-drug interactions can be defined. A study can use a randomized crossover (e.g., S followed by S+I, S+I followed by S), a one-sequence crossover (e.g., S always followed by S+I or the reverse), or a parallel design (S in one group of subjects and S+I in another). The following possible dosing regimen combinations for a substrate and interacting drug may also be used: single dose/single dose, single dose/multiple dose, multiple dose/single dose, and multiple dose/multiple dose. The selection of one of these or another study design depends on a number of factors for both the substrate and interacting drug, including (1) acute or chronic use of the substrate and/or interacting drug; (2) safety considerations, including whether a drug is likely to be an NTR (narrow therapeutic range) or non-NTR drug; (3) pharmacokinetic and pharmacodynamic characteristics of the substrate and interacting drugs; and (4) the need to assess induction as well as inhibition. The inhibiting/inducing drugs and the substrates should be dosed so that the exposure of both drugs are relevant to their clinical use. The following considerations may be useful:

- Pharmacokinetic measures and/or parameters may be used to indicate clinically important routes of metabolism and drug-drug interactions. Subsequent interpretation of findings from these studies will be aided by a good understanding of dose/concentration and concentration/response relationships for both desirable and undesirable drug effects in the general population, in subpopulations, and within individuals. In certain instances, reliance on endpoints other than pharmacokinetic measures/parameters may be useful.

- When both substrate and interacting drug are likely to be given chronically over an extended period of time, administration of the substrate to steady state with collection of blood samples over one or more dosing intervals could be followed by multiple dose administration of the interacting drug, again with collection of blood for measurement of both the substrate and the interacting drug (as feasible) over the same intervals. This is an example of a one-sequence crossover design.

- The time at steady state before collection of endpoint observations depends on whether inhibition or induction is to be studied. Inducers can take several days or longer to exert their effects, while inhibitors generally exert their effects more rapidly. For this reason, a more extended period of time after attainment of steady state for the substrate and interacting drug may be necessary if induction is to be assessed.

- When attainment of steady state is important and either the substrate or interacting drugs and/or their metabolites exhibit long half-lives, special approaches may be useful. These include use of a loading dose to achieve steady state conditions more rapidly and

selection of a one-sequence crossover or a parallel design, rather than a randomized crossover study design.

- When a substrate and/or an interacting drug is to be studied at steady state, documentation that near steady state has been attained is important both for each drug and its metabolites of interest. This documentation can be accomplished by sampling over several days prior to the periods when samples are collected. This is important for both metabolites and the parent drug, particularly when the half-life of the metabolite is longer than the parent, and is especially important if both parent drug and metabolites are metabolic inhibitors or inducers.

- Studies can usually be open label (unblinded), unless pharmacodynamic endpoints (e.g., adverse events that are subject to bias) are part of the assessment of the interaction.

- For a rapidly reversible inhibitor, administration of the interacting drug either just before or simultaneously with the substrate on the test day might be the appropriate design to increase sensitivity.

- If the drug interaction effects are to be assessed for both agents in a combination regimen, the assessment can be done in two separate studies. If the pharmacokinetic and pharmacodynamic characteristics of the drugs make it feasible, the dual assessment can be done in a single study. Some design options are randomized three-period crossover, parallel group, and one-sequence crossover.

B. Study Population

Clinical drug-drug interaction studies may generally be performed using healthy volunteers or volunteers drawn from the general population, on the assumption that findings in this population should predict findings in the patient population for which the drug is intended. Safety considerations, however, may preclude the use of healthy subjects. In certain circumstances, subjects drawn from the general population and/or patients for whom the investigational drug is intended offer certain advantages, including the opportunity to study pharmacodynamic endpoints not present in healthy subjects and reduced reliance on extrapolation of findings from healthy subjects. In either patient or healthy/general population subject studies, performance of phenotype or genotype determinations to identify genetically determined metabolic polymorphisms is often important in evaluating effects on enzymes with polymorphisms, notably CYP2D6 and CYP2C19.

C. Choice of Substrate and Interacting Drugs

1. Substrates for an Investigational Drug

In contrast to earlier approaches that focused mainly on a specific group of approved drugs (digoxin, hydrochlorothiazide) where coadministration was likely or the clinical consequences of an interaction were of concern, improved understanding of the metabolic basis of drug-drug interactions enables more general approaches to and conclusions from specific drug-drug interaction studies. In studying an investigational drug as the interacting drug, the choice of substrates (approved drugs) for initial in vivo studies depends on the P450 enzymes affected by the interacting drug. In testing inhibition, the substrate selected should generally be one whose pharmacokinetics is markedly altered by coadministration of known specific inhibitors of the enzyme systems (i.e., a very sensitive substrate should be chosen) to assess the impact of the interacting investigational drug. Examples of substrates include, but are not limited to, (1) midazolam, buspirone, felodipine, simvastatin, or lovastatin for CYP3A4; (2) theophylline for CYP1A2; (3) S-warfarin for CYP2C9; and (4) desipramine for CYP2D6. If the initial study is positive for inhibition, further studies of other substrates may be useful, representing a range of substrates based on the likelihood of coadministration. For example, possible substrates for further study of a CYP3A4 interacting investigational drug might include dihydropyridine calcium channel blockers and triazolobenzodiazepines, or for a CYP2D6 inhibiting investigational drug might include metoprolol. If the initial study is negative with the most sensitive substrates, it can be presumed that less sensitive substrates will also be unaffected.

2. Investigational Drug as Substrate

In testing an investigational drug for the possibility that its metabolism is inhibited or induced (i.e., as a substrate), selection of the interacting drugs should be based on in vitro or other metabolism studies identifying the enzyme systems that metabolize the drug. The choice of interacting drug should then be based on known, important inhibitors of the pathway under investigation. For example, if the investigational drug is shown to be metabolized by CYP3A4 and the contribution of this enzyme to the overall elimination of this drug is substantial, the choice of inhibitor and inducer could be ketoconazole and rifampin, respectively, because of the substantial effects of these interacting drugs on CYP3A4 metabolism (i.e., they are the most sensitive in identifying an effect of interest). If the study results are negative, then absence of a clinically important drug-drug interaction for the metabolic pathway could be claimed. If the clinical study of the most potent specific inhibitor/inducer is positive and the sponsor wishes to claim lack of an interaction between the test drug and other less potent specific inhibitors, or give advice on dosage adjustment, further clinical studies would generally be recommended. Certain approved drugs are not optimal selections as the interacting drug. For example, cimetidine is not considered an optimal choice to represent drugs inhibiting a given pathway because its inhibition affects multiple metabolic pathways as well as certain drug transporters.

D. Route of Administration

The route of administration chosen for a metabolic drug-drug interaction study is important. For an investigational agent used as either an interacting drug or substrate, the route of administration should generally be the one planned for in product labeling. When multiple routes are being developed, the necessity for doing metabolic drug-drug interaction studies by all routes should be based on the expected mechanism of interaction and the similarity of corresponding concentration-time profiles for parent and metabolites. If only oral dosage forms will be marketed, studies with an intravenous formulation would not usually be needed, although information from oral and intravenous dosings may be useful in discerning the relative contributions of alterations in absorption and/or presystemic clearance to the overall effect observed for a drug interaction. Sometimes certain routes of administration can reduce the utility of information from a study. For example, an intravenous study would not reveal an interaction for any substrate that exhibits a high extraction ratio or for a low hepatic extraction drugs where intestinal CYP3A4 activity markedly alters bioavailability. For an approved agent used either as a substrate or interacting drug, the route of administration will depend on available marketed formulations, which in most instances will be oral.

E. Dose Selection

For both a substrate (investigational drug or approved drug) and interacting drug (investigational drug or approved drug), testing should maximize the possibility of finding an interaction. For this reason, the maximum planned or approved dose and shortest dosing interval of the interacting drug (as inhibitors or inducers) should be used. Doses smaller than those to be used clinically may be needed for substrates on safety grounds and may be more sensitive to the effect of the interacting drug.

F. Endpoints

1. Pharmacokinetic Endpoints

The following measures and parameters are recommended for assessment of the substrate: (1) exposure measures such as AUC, Cmax, time to Cmax (Tmax), and others as appropriate; and (2) pharmacokinetic parameters such as clearance, volumes of distribution, and half-lives. In some cases, these measures may be of interest for the inhibitor or inducer as well, notably where the study is assessing possible interactions between both study drugs. Additional measures may help in steady state studies (e.g., trough concentration (Cmin)) to demonstrate that dosing strategies were adequate to achieve near steady state before and during the interaction. In certain instances, an understanding of the relationship between dose, blood levels, and response may lead to a special interest in certain pharmacokinetic measures and/or parameters. For

example, if a clinical outcome is most closely related to peak concentration (e.g., tachycardia with sympathomimetics), Cmax or another early exposure measure might be most appropriate. Conversely, if the clinical outcome is related more to extent of absorption, AUC would be preferred. The frequency of sampling should be adequate to allow accurate determination of the relevant measures and/or parameters for the parent and metabolites. For the substrate, whether the investigational drug or approved drug, determination of the pharmacokinetics of important active metabolites is important. Because this guidance focuses on metabolic drug-drug interactions, protein binding determinations are considered unnecessary except for data interpretation.

2. Pharmacodynamic Endpoints

Pharmacokinetic measures are usually sufficient for metabolic drug-drug interaction studies, although pharmacodynamic measures can sometimes provide additional useful information. This may occur when a pharmacokinetic/pharmacodynamic relationship for the substrate endpoints of interest is not established or when pharmacodynamic changes do not result solely from pharmacokinetic interactions (e.g, additive cardiovascular effect of quinidine and tricyclic antidepressants). When an approved drug is studied as a substrate, the pharmacodynamic impact of a given change in blood level (Cmax, AUC) caused by an investigational interaction should be known from other interaction studies about the approved drug, although this may not always be the case for older drugs.

G. Sample Size and Statistical Considerations

For both investigational drugs and approved drugs, when used as substrates and/or interacting drugs in drug-drug interaction studies, the desired goal of the analysis is to determine the clinical significance of any increase or decrease in exposure to the substrate in the presence of the interacting drug. Assuming unchanged PK/PD relationships, changes may be evaluated by comparing pharmacokinetic measures of systemic exposure that are most relevant to an understanding of the relationship between dose (exposure) and therapeutic outcome.

Results of drug-drug interaction studies should be reported as 90% confidence intervals about the geometric mean ratio of the observed pharmacokinetic measures with (S+I) and without the interacting drug (S).[3] Confidence intervals provide an estimate of the distribution of the observed systemic exposure measure ratio of S+I versus S alone and convey a probability of the magnitude of the interaction. In contrast, tests of significance are not appropriate because

[3] Schuirmann, D.J., "A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Bioequivalence of Average Bioavailability," *J. Pharmacokin. and Biopharm.*, 15:657-80, 1987.

small, consistent systemic exposure differences can be statistically significant ($p < 0.05$) but not clinically relevant.

When a drug-drug interaction is clearly present (e.g., comparisons indicate twofold or greater increments in systemic exposure measures for S+I) the sponsor should be able to provide specific recommendations regarding the clinical significance of the interaction based on what is known about the dose-response and/or PK/PD relationship for either the investigational agent or the approved drugs used in the study. This information should form the basis for reporting study results and for making recommendations in the package insert with respect to either the dose, dosing regimen adjustments, precautions, warnings, or contraindications of either the investigational drug or the approved drug. FDA recognizes that dose-response and/or PK/PD information may sometimes be incomplete or unavailable, especially for an approved drug used as S.

Second, the sponsor may wish to make specific claims in the package insert that no drug-drug interaction is expected. In these instances, the sponsor should be able to recommend specific *no effect* boundaries, or clinical equivalence intervals, for a drug-drug interaction. No effect boundaries define the interval within which a change in a systemic exposure measure is considered not clinically meaningful. There are three approaches to define no effect boundaries.

Approach 1: No effect boundaries can be based on population (group) average dose and/or concentration-response relationships, PK/PD models, and other available information for the substrate drug. If the 90% confidence interval for the systemic exposure measurement in the drug-drug interaction study falls completely within the no effect boundaries, the sponsor may conclude that no clinically significant drug-drug interaction was present.

Approach 2: No effect boundaries may also be based on the concept that a drug-drug interaction study addresses the question of switchability between the substrate given in combination with an interacting drug (test) versus the substrate given alone. Based on this concept, the sponsor may wish to use an individual equivalence criterion to allow scaling of the no effect boundary and to determine other useful information as well. Sponsors who wish to use this approach are encouraged to contact the Office of Clinical Pharmacology and Biopharmaceutics to discuss approaches to study design and data analysis.

Approach 3: In the absence of no effect boundaries defined in (1) or (2) above, a sponsor may use a default no effect boundary of 80-125% for both the investigational drug and the approved drugs used in the study. When the 90% confidence intervals for systemic exposure ratios fall entirely within the equivalence range of 80-125%, standard Agency practice is to conclude that no clinically significant differences are present.

The selection of the number of subjects for a given drug-drug interaction study will depend on how small an effect is clinically important to detect, or rule out, the inter- and intrasubject variability in pharmacokinetic measurements, and possibly other factors or sources of variability not well recognized. In addition, the number of subjects will depend on how the results of the drug-drug interaction study will be used, as described above.

This guidance should not be interpreted by sponsors as generally recommending the inclusion of some number of subjects in a drug-drug interaction study such that the 90% confidence interval for the ratio of pharmacokinetic measurements falls entirely within the no effect boundaries of 80-125%. This approach, however, could be deemed appropriate by a sponsor, after considering the expected outcome of a drug-drug interaction study, the anticipated magnitude of variability in pharmacokinetic measurements, and the desired label claim that no clinically significant drug-drug interaction was present.

V. LABELING

A. Drug Metabolism

All relevant information on the metabolic pathways and metabolites and pharmacokinetic interaction should be included in the CLINICAL PHARMACOLOGY section of the labeling. The consequences of metabolism and interactions should be placed in PRECAUTIONS/WARNINGS, CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION sections, as appropriate.

B. Metabolic Drug-Drug Interaction Studies

Relevant in vitro and in vivo metabolic drug-drug interaction data describing the drug's effects on substrates and the effects of inhibitors and inducers on the drug should be presented in the DRUG-DRUG INTERACTIONS section of the labeling in the CLINICAL PHARMACOLOGY section, including both positive and important negative findings. The types of studies on which statements are based should be identified ***briefly*** in the labeling. If findings indicate a known or potential interaction of clinical significance, or lack of an important interaction that might have been expected, these should be mentioned briefly in the clinical pharmacology interactions section and described more fully in the interaction section under PRECAUTIONS, with advice on how to adjust treatment placed in WARNINGS/PRECAUTIONS, DOSAGE AND ADMINISTRATION, and CONTRAINDICATIONS, as appropriate. In certain cases, information based on clinical studies not using the labeled drug under investigation can be described with an explanation that similar results may be expected for the labeled drug. For example, a strong inhibitor of

CYP3A4 does not need to be tested with all 3A4 substrates to warn against an interaction. Examples of appropriate labeling language are provided in italics below.

DRUG-DRUG INTERACTIONS, CLINICAL PHARMACOLOGY

C In vivo metabolic drug-drug interaction studies indicate little or no pharmacokinetic effect:

Data from a drug-drug interaction study involving (drug) and (probe drug) in _____ patients/healthy individuals indicate that the PK disposition of (probe drug) is not altered when the drugs are coadministered. This indicates that (drug) does not inhibit CYP3A4 and will not alter the metabolism of drugs metabolized by this enzyme.

C In vivo metabolic drug-drug interaction studies indicate a clinically significant pharmacokinetic interaction:

The effect of (drug) on the pharmacokinetics of (probe drug) has been studied in _____ patients/healthy subjects. The Cmax, AUC, half-life and clearances of (probe drug) increased/decreased by ____% (90% Confidence Interval: ____ to ____ %) in the presence of (drug). This indicates that (drug) can inhibit the metabolism of drugs metabolized by CYP3A4 and can increase blood concentrations of such drugs. (See PRECAUTIONS, WARNINGS, DOSAGE AND ADMINISTRATION, or CONTRAINDICATIONS sections.)

Specific enzymes have been identified as metabolizing the test drug, but no in vivo or in vitro drug interaction studies have been conducted:

In vitro drug metabolism studies reveal that (drug) is a substrate of the CYP_____ enzyme. No in vitro or clinical drug interaction studies have been performed to evaluate interactions. However, based on the in vitro data, blood concentrations of (drug) are expected to increase in the presence of inhibitors of _____ such as _____,_____, or_____.

C Neither in vivo nor in vitro drug-drug interaction studies have been conducted and there is no significant metabolism of the drug:

In vivo or in vitro drug-drug interaction studies have not been conducted. The drug interaction potential resulting in changes of PK of (drug) is expected to be low because approximately 90% of the recovered dose of (drug) is excreted in the urine as unchanged drug. However, the role of other pathways of drug elimination, including drug transport systems, is not known. In addition, whether (drug) can inhibit or induce metabolic

enzymes is not known. There is potential for drug interactions mediated via modulation of various CYP enzymes.

- In vitro interaction has been studied but no in vivo studies have been conducted to confirm or refute a finding:

In vitro interaction demonstrated:

In vitro drug interaction studies reveal that the metabolism of (drug) is by CYP3A4 and can be inhibited by the CYP3A4 inhibitor ketoconazole. No clinical studies have been performed to evaluate this finding. Based on the in vitro findings, it is likely that ketoconazole, itraconazole, ritonavir, and other 3A4 inhibitors may lead to substantial increase of (drug) blood concentrations. Refer to PRECAUTIONS, as appropriate.

In vitro interaction demonstrated and the substrate drug has substantial first-pass elimination:

In vitro drug interaction studies reveal that the metabolism of (drug) is by CYP3A4 and can be inhibited by the CYP3A4 inhibitor ketoconazole. No clinical studies have been performed to evaluate this finding. Based on the in vitro findings, it is likely that ketoconazole, itraconazole, ritonavir, grapefruit juice, and other 3A4 inhibitors may lead to substantial increase of (drug) blood concentrations. Refer to PRECAUTIONS, as appropriate.

In vitro interaction not demonstrated:

In vitro drug interaction studies reveal no inhibition of the metabolism of (drug) by the CYP3A4 inhibitor ketoconazole. No clinical studies have been performed to evaluate this finding. However, based on the in vitro findings, a metabolic interaction with ketoconazole, grapefruit juice, and other 3A4 inhibitors is not anticipated. Refer to PRECAUTIONS, as appropriate.

PRECAUTIONS and/or WARNINGS

- An interacting drug causes increased concentrations of the substrate but the administration of both drugs may continue with appropriate dosage adjustment. Results of the studies are described in CLINICAL PHARMACOLOGY, DRUG-DRUG INTERACTIONS, PRECAUTIONS and/or WARNINGS and may state:

Drug_____ /class of drug causes significant increases in concentrations of _____ when coadministered, so that dose of _____ must be adjusted (see DOSAGE AND

ADMINISTRATION). If there is an important interaction, information for patients should point this out also.

- An interacting drug causes increased risk because of increased concentrations of the substrate and the interacting drug should not be used with the substrate. After describing the interaction in the CLINICAL PHARMACOLOGY section, there should be a CONTRAINDICATIONS section and possibly a boxed warning if the risk is serious.

Drug_____ /class of drug can cause significant increases in concentrations of drug_____ when coadministered. The two drugs should not be used together.

- No in vitro or in vivo drug interactions were conducted. These are described in CLINICAL PHARMACOLOGY, DRUG-DRUG INTERACTIONS, PRECAUTIONS and/or WARNINGS and may state:

There is potential for drug interactions mediated via modulation of various CYP enzymes.

DOSAGE AND ADMINISTRATION

- An interacting drug causes increased risk because of increased concentrations of the substrate, but the administration for both drugs may continue with suitable monitoring:

Drug_____/class of drug leads to significant increases in blood concentrations of _____ by _____%. The dose of _____ should be decreased by _____% when the patient is also taking _____. Patients should be closely monitored when taking both drugs.

CONTRAINDICATIONS

- An interacting drug causes increased risk because of increased concentrations of the substrate and should not be coadministered:

Drug_____ /class of drug leads to significant increases in blood concentrations of _____, with potentially serious adverse events. Administration of _____ to patients on drug_____/class of drug is contraindicated.