

Wyeth

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November 13, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Comments on Draft Guidance for Industry on Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (Docket No. 2006D-0344)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting comments on the FDA draft guidance for industry entitled, "Drug Interaction Studies -- Study Design, Data Analysis, and Implications for Dosing and Labeling." This draft guidance for industry was announced in the September 12, 2006 Federal Register (71 FR 53696-53697).

Wyeth is one of the largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer, and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications.

Wyeth appreciates the opportunity to comment on this draft guidance. In general, we recommend that the final guidance focus primarily on topics that are relatively well characterized i.e., drug metabolism and clinical drug interactions. These topics are discussed; however, the draft guidance also summarizes topics that are presently not as well understood or well characterized in the scientific community e.g., transporters other than P-glycoprotein (P-gp).

Moreover, the true clinical impact of these transporter-based drug-drug interactions is presently not well documented. Therefore, we believe that information regarding transporters other than P-gp has not been demonstrated sufficiently to support inclusion within formal written guidance at this time.

2006D-0344

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Wyeth

Additional comments are attached. We trust that the Agency will also take these comments into consideration.

Sincerely,

A handwritten signature in black ink that reads "Mark C. Baranello, Jr." The signature is written in a cursive style with a large, prominent "M" and "C".

Roy J. Baranello, Jr.
Assistant Vice President
Regulatory Policy and Operations
Global Regulatory Affairs

#	Section	Line/Table/ Figure No.	Proposed Change/Recommendation	Rationale for Revision/Supporting Commentary
1	I. Introduction	29-31	Please elaborate on the following statement, “Drug-drug interactions related to transporters are being documented with increasing frequency and are important to consider in drug development.”	Please provide more support of this general statement somewhere in the guidance and cite specific examples that demonstrate clear clinical concerns that would lead to labeling statements (e.g., >2-fold interaction in AUC or resulting in dosage recommendations) consistent with drug metabolism interactions. If examples of transporter interactions do not meet certain criteria for clinical importance, explanations for when they would still be important would be appropriate.
2	II. Background	48-141	<p>We suggest that the Agency restructure the background discussion around 3 major and independent topics.</p> <p>Change: A. Metabolism B. Drug-Drug Interactions</p> <p>To: A. Metabolism-based Drug-Drug Interactions, B. Transporter-based Drug-Drug Interactions C. Therapeutic Biologics</p>	Since the primary focus of this guidance document is in the area of metabolism-based drug-drug interactions, it is recommended that the less well-understood or well-characterized topics (transporter based interactions and therapeutic biologics) be singled out and discussed separately.
3	III. General Strategies A In Vitro Studies	199-202	Please elaborate on the following statements, “Drug interactions based on CYP2B6 are emerging as important interactions. When appropriate, in vitro evaluations based on this enzyme can be conducted. Other CYP enzymes, including CYP2A6 and CYP2E1, are less likely to be involved in clinically important drug interactions, but should be considered when appropriate.”	Under what specific circumstances will in vitro DDI studies for CYP2B6 be considered and conducted? The guidance should also describe circumstances when in vitro evaluations of 2A6 and 2E1 are advised. Presently, these three isozymes are not part of standard routine in vitro screens. General guidelines for when they should be considered would be beneficial.

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4	IV. Design of In Vivo DDI Studies	261-269	<p>With regards to the following paragraph, we suggest additional emphasis on the utility of single dose/single dose DDI studies with reversible CYP inhibition studies when feasible.</p> <p>“...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) assessment of induction as well as inhibition. The inhibiting/inducing drugs and the substrates should be dosed so that the exposures of both drugs are relevant to their clinical use, including the highest doses likely to be used. Simulations can be helpful in selecting an appropriate study design. The following considerations may be useful...”</p>	<p>The most straightforward study design feasible to address the DDI question adequately should be utilized. For many reversible substrate inhibition studies, if not the majority, a simultaneous single dose/single dose study design using maximal labeled or to be marketed doses is optimal. The guidance could benefit from emphasizing this point perhaps as an additional a bullet point.</p>
5	IV. Design of In Vivo DDI Studies	309-316	<p>The following example for dietary exclusion criteria may be restrictive, and not feasible.</p> <p>“Examples of statements in a study protocol could include ‘Participants will be excluded for the following reasons: Use of prescription or over-the-counter medications, including herbal products, or alcohol within two weeks prior to enrollment,’ ‘For at least two weeks prior to the start of the study until its conclusion, volunteers will not be allowed to eat any food or drink any beverage containing alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, brussels sprouts, mustard) and charbroiled meats.’”</p>	<p>The language is too restrictive with regards to the duration (2 weeks) of dietary exclusions, including alcohol consumption. It may not be possible to document the avoidance of all of these aspects two-weeks prior to study participation, without having subjects remain in-house for two-weeks prior. Also, there are few instances for which this specific exclusion would be necessary. In most instances, 48 hours would be an appropriate timeframe. Therefore, we recommend that exclusionary statements should be drug and protocol specific as lines 305-307 affirm, and be feasible and able to be monitored.</p>

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6	IV. Design of In Vivo DDI Studies	347-350	<p>We request that the examples provided be communicated as preferred substrates, if in fact the FDA considers them to be so.</p> <p>“Examples of substrates include (1) midazolam for CYP3A; (2) theophylline for CYP1A2; (3) repaglinide for CYP2C8; (4) warfarin for CYP2C9 (with the evaluation of S-warfarin); (5) omeprazole for CYP2C19; and (6) desipramine for CYP2D6.”</p>	<p>Are the substrates identified in the list of example substrates for use in in vivo DDI studies the “FDA preferred substrates” based on either being a most sensitive substrate (midazolam, repaglinide, omeprazole, desipramine) or one with a narrow therapeutic range (theophylline, warfarin)? If so, we recommend that the final guidance refer to them as “preferred substrates” and more readily encourage their use based on past performance.</p>
7	IV. Design of In Vivo DDI Studies	429-433	<p>We recommend that the Agency change, “If an orally administered drug is a substrate of CYP3A and has low oral bioavailability because of extensive presystemic extraction contributed by enteric CYP3A, grapefruit juice may have a significant effect on its systemic exposure. Use of the drug with grapefruit juice may call for caution, depending on the drug’s exposure-response relationship (see section V for labeling implications).”</p> <p>To:</p> <p>“If an orally administered drug is a sensitive 3A4 substrate and has low oral bioavailability because of extensive presystemic extraction contributed by enteric CYP3A, grapefruit juice may have a significant effect on its systemic exposure. Use of sensitive 3A4 substrates or 3A4 substrates with narrow therapeutic range with grapefruit juice may call for caution, depending on the drug’s exposure-response relationship (see section V for labeling implications).”</p>	<p>For labeling purposes, this statement should specifically address sensitive 3A4 substrates or 3A4 substrates with a narrow therapeutic range.</p>

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8	IV. Design of In Vivo DDI Studies	435-439	<p>We recommend that the Agency change, “If a drug is a substrate of CYP3A or P-gp and co-administration with St. John’s wort can decrease the systemic exposure and effectiveness, St John’s wort may be listed in the labeling along with other known inducers, such as rifampin, rifabutin, rifapentin, dexamethasone, phenytoin, carbamazepine, or phenobarbital, as possibly decreasing plasma levels.”</p> <p>To:</p> <p>“If a drug is a sensitive substrate of CYP3A or P-gp or substrate of 3A4 or P-gp with a narrow therapeutic range and co-administration with St. John’s wort can decrease the systemic exposure and effectiveness, St John’s wort may be listed in the labeling along with other known inducers, such as rifampin, rifabutin, rifapentin, dexamethasone, phenytoin, carbamazepine, or phenobarbital, as possibly decreasing plasma levels.”</p>	<p>For labeling purposes, this statement should specifically address sensitive 3A4 or P-gp substrates or 3A4 or P-gp substrates with a narrow therapeutic range.</p>
9	IV. Design of In Vivo DDI Studies	479-480	<p>Please provide further details regarding the statement, “In testing an investigational drug for the possibility that it may be an inhibitor/inducer of P-gp, selection of digoxin or other known substrates of P-gp may be appropriate.”</p>	<p>Considering the importance placed on P-gp-mediated DDIs throughout the guidance document, it seems that the statement provides limited utility. Please be more specific, e.g., what in vitro data drives the conduct of these in vivo studies?</p>

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10	IV. Design of In Vivo DDI Studies	484-488	<p>We recommend that the Agency change, “In testing an investigational drug for the possibility that its transport may be inhibited or induced (as a substrate of P-gp), an inhibitor of P-gp, such as ritonavir, cyclosporine, or verapamil, or an inducer, such as rifampin should be studied. In cases where the drug is also a CYP3A substrate, inhibition should be studied by using a strong inhibitor of both P-gp and CYP3A, such as ritonavir.”</p> <p>To:</p> <p>“In testing an investigational drug for the possibility that its transport may be inhibited or induced (as a substrate of P-gp), an inhibitor of P-gp, such as ketoconazole, ritonavir, cyclosporine, or verapamil, or an inducer, such as rifampin should be studied. In cases where the drug is also a CYP3A substrate, inhibition should be studied by using a strong inhibitor of both P-gp and CYP3A, such as ketoconazole or ritonavir.”</p>	<p>Ketoconazole should be identified in addition to, or instead of, ritonavir. In general there is high concordance between P-gp and 3A4 substrates; i.e., the majority of sensitive P-gp substrates are also sensitive 3A4 substrates and thus would have a ketoconazole study performed (“preferred” 3A4 inhibitor). Moreover, it appears that ketoconazole may be more potent than ritonavir as a P-gp inhibitor. (See Appendix D, Table 3.)</p>

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11	G. Sample Size and Statistical Considerations	591-603	<p>We recommend that the following paragraph be moved to a more appropriate section of the guidance e.g., Section V. “Labeling Implications” or deleted, “When a drug-drug interaction of potential importance is clearly present (e.g., comparisons indicate twofold (or lower for certain NTR drugs) or greater increments in systemic exposure measures for (S+I)), the sponsor should 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. For a new drug, the more difficult issue is the impact on the investigational drug as substrate. For inhibition or induction by the investigational drug, the main consequence of a finding will be to add the drug to the list of inhibitors or inducers likely already present in labeling of the older drug. This information can 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 the investigational drug or the approved drug. FDA recognizes that dose-response and/or PK/PD information can sometimes be incomplete or unavailable, especially for an older approved drug used as S.”</p>	<p>The paragraph does not pertain to sample size or statistical considerations.</p>

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12	G. Sample Size and Statistical Considerations	606-608	<p>We recommend that the Agency change, “In these instances, it would be helpful for the sponsor to recommend specific no effect boundaries, or clinical equivalence intervals, for a drug-drug interaction.”</p> <p>To:</p> <p>“In these instances, it is recommended that the sponsor employ the two one-sided test procedure using pre-specified no effect boundaries, or clinical equivalence intervals, to establish the claim of no drug-drug interaction.”</p>	<p>Statistically, the no effect boundaries do not have any meaning outside the context of the two one-sided test procedure. The two one-sided test procedure is not referenced anywhere within the document, however, no effect boundaries are mentioned in detail.</p>
13	Appendix A	Table 2, Page 19	<p>For consistency within the document, we recommend that guidance be provided for enzyme 2A6.</p>	<p>Table 2 includes examples beyond 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4 by including 2B6 and 2E1. To be consistent with language in line 201, guidance for 2A6 is recommended.</p>
14	Appendix A	Table 2 691-696	<p>We request that document state the scientific rationale for classifying 3A4 substrates differently for 3A4 versus other isozymes.</p> <p>“Substrates for any particular CYP enzyme listed in this table are those with plasma AUC values increased by 2-fold or higher when co-administered with inhibitors of that CYP enzyme; for CYP3A, only those with plasma AUC increased by 5-fold or higher are listed. Inhibitors listed are those that increase plasma AUC values of substrates for that CYP enzyme by 2-fold or higher. For CYP3A inhibitors, only those that increase AUC of CYP3A substrates by 5-fold or higher are listed. Inducers listed are those that decrease plasma AUC values of substrates for that CYP enzyme by 30% or higher.”</p>	<p>Providing rationale for these apparent discrepancies would be important for readers of guidance not already aware of 3A4 differences.</p>

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15	Appendix A	Tables 3 & 4	We suggest that the Agency combines these two tables.	Why is there a table for CYP3A4, as well as a table for other CYP substrates? The formats are identical.
16	Appendix A	Table 3 711-713	We recommend that examples be included in footnote 3, see bolded text below. Also we suggest that the Agency provide other examples of serious safety concerns. “CYP3A <i>substrates with narrow therapeutic range</i> refers to drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of CYP3A inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes for astemizole, cisapride and terfenadine).”	Only a few of the drugs identified as having narrow therapeutic range cause Torsades de Pointes (TdP). Providing other examples of serious safety concerns and specifying drugs associated with TdP would be beneficial.
17	Appendix A	Tables 5 & 6	We suggest that the Agency combine these two tables.	Why is there a table for CYP3A4, as well as a table for other CYP substrates? The formats are identical.

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18	Appendix A	<p>Tables 5 & 6</p> <p>729-731</p> <p>732-734</p> <p>735-737</p>	<p>Please clarify differences in dosing recommendation for strong inhibitors versus moderate and weak inhibitors. See bolded text below.</p> <p>“A strong inhibitor is one that caused a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance of CYP3A substrates (not limited to midazolam, a sensitive CYP3A substrate) in clinical evaluations.”</p> <p>“A moderate inhibitor is one that caused a > 2- but < 5-fold increase in the AUC values or 50-80% decrease in clearance of sensitive CYP3A substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations.”</p> <p>“A weak inhibitor is one that caused a > 1.25 - but < 2-fold increase in the AUC values or 20-50% decrease in clearance of sensitive CYP3A substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations.”</p>	<p>It is not clear why the following language -- “...when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations” -- for moderate and weak inhibitors is not also applicable for strong inhibitors. All studies should be performed at maximal clinical doses/exposures.</p>
19	Appendix C-1	<p>787-788</p> <p>848-849</p>	<p>We request clarification of two similar, but separate statements. See below.</p> <p>“Identification of CYP enzymes is warranted if CYP enzymes contribute > 25% of a drug’s total clearance.”</p> <p>“If human in vivo data indicate CYP enzymes contribute > 25% of a drug’s clearance, studies to identify drug metabolizing CYP enzymes in vitro should be conducted.”</p>	<p>It is often difficult during early drug development to have information available on the quantitative contribution of CYP-mediated clearance to a drug’s overall clearance in humans. Therefore, the Agency’s suggested criteria of >25% may not be readily obtainable for initiation of CYP identification studies. Can the Agency provide alternative suggestions? For example, will extrapolated clearance based on in vitro-in vivo scaling be used as a guide?</p>

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20	Appendix C-2	1002-1006	<p>We suggest the following revision. See bolded text below.</p> <p>“Typical experiments for determining IC50 values involve incubating the substrate, if the metabolic rate is sufficient, at concentrations below at its Km to more closely relate the inhibitor IC50 to its Ki. For Ki determinations, both the substrate and inhibitor concentrations should be varied to cover ranges above and below the drug’s Km and inhibitor’s Ki.”</p>	<p>For the determination of IC50 values, the probe substrate concentration should be at its Km value (not below its Km value as indicated in the draft guidance), so that the IC50 values may be related to their Ki values.</p>
21	Appendix C-3	Table 5	<p>Request consideration that rifampicin be considered as the preferred 2B6 inducer</p>	<p>Our data has shown that rifampicin (10 uM) is a more potent inducer of CYP2B6 than phenobarbital, which has to be used at concentrations as high as 1mM to get a similar effect. Hence we suggest rifampicin be recommended as the preferred inducer and phenobarbital as an acceptable inducer.</p>

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22	Appendix D	1292-1294 1361-1364 1514-1518	<p>We request that the Agency elaborate on the following statements</p> <p>“Because of the lack of inhibitor specificity, the use of multiple inhibitors is recommended to determine whether the efflux activity observed in vitro is related to P-gp.”</p> <p>“To strengthen the results from bi-directional transport studies, it is recommended that additional experiments be conducted in the presence of potent P-gp inhibitors (at least 2-3 potent P-gp inhibitors; see Table 3 for examples).”</p> <p>“If the efflux of the probe substrate is inhibited by the investigational drug, then the inhibition should be studied over a range of concentrations to determine IC50 or Ki. IC50 or Ki values may be experiment-dependent. Therefore, the obtained IC50 or Ki values should be compared to IC50 or Ki values obtained for 2-3 known potent P-gp inhibitors (positive controls).”</p>	<p>It would be useful to list the transporters that are inhibited by the indicated agents (in Table 3 on p. 42 of the draft guidance), so that the most appropriate inhibitors may be chosen to address the transporters in question. Since the inhibition of uptake (e.g. OATP) versus efflux (e.g. P-gp) transporters will have very different effects on the efflux (BA/AB) ratios in a monolayer system, and dependent on the system used, the recommended usage of at least 2-3 P-gp inhibitors may not be always necessary.</p>
23	Appendix D	1520-1522	<p>We request clarification of what “[I]” represents in the following statement, “If [I]/ IC50 (or Ki) is > 0.1, then the investigational drug is likely a P-gp inhibitor. An in vivo drug interaction study with a P-gp substrate such as digoxin should be conducted.”</p>	<p>Since P-gp is present in various tissues including intestinal enterocytes, liver and the blood-brain-barrier, what was the inhibitor concentration ([I]) that was referred to for the consideration of [I]/Ki?</p>