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Draft Guidance for Review and Comment

**Draft Guidance for Industry
Drug Interaction Studies – Study Design, Data Analysis, and
Implications for Dosing and Labeling**

Docket No. 2006D-0344

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1/Response to Docket on Drug Interaction Studies

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The following comments are provided by Genentech, Inc. on Docket No. 2006D-0344, "Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling." We welcome FDA's efforts to provide direction on how sponsors can perform in vitro and in vivo drug metabolism, drug transport, and drug-drug interaction studies.

GENERAL COMMENTS

We have the following general comments to the draft guidance document:

1. We recommend that the final guidance document contain references, in the body of the document, to specific literature citing successful design and execution of drug-drug interaction studies, as well as values used as cutoffs for key decision making.
2. We recommend that the final guidance document address certain metabolic enzyme systems that are not included in this draft. While the information on P-glycoprotein in this draft document is very useful, it is surprising that approximately 13 of the 55 pages are devoted to this single topic. On the other hand, the document provides either cursory or no guidance on numerous other important metabolic enzyme systems (e.g., non-P450 oxygenases, Phase II metabolism enzyme systems, etc.) We believe that for the final document to be both a general and complete guidance document on drug-drug interaction studies, it must contain additional chapters, one chapter on each of these missing systems.
3. We request that the final guidance document clarify the CYP3A nomenclature used in the guidance document. For example, lines 345 and 689, Tables 3 and 5 of Appendix A, and Figure 1 of Appendix B use the term "CYP3A," whereas in Table 2 of Appendix A, Table 2 of Appendix C-1, Table 3 of Appendix C-2, and Table 5 of Appendix C-3 the terms "3A4 or 3A4/5" are used. We believe clarifying the nomenclature will reduce confusion in the guidance document about this issue.

SPECIFIC COMMENTS

We have the following specific comments in the following sections of the draft guidance document:

4. **Section III.A. In Vitro Studies (lines 167–209).** In this section on general strategies for in vitro studies, we believe that a recommendation from FDA on key parameters to be used for inhibitory analyses would be very helpful. Does FDA recommend the use of IC_{50} or K_i ?
5. **Section III.B. Specific In vivo Clinical Investigations.** In line 214, we request that FDA provide more precise guidance about when in vitro metabolism and drug-drug interaction studies need to be performed in the stages of drug development (for instance, before IND, end of Phase I, end of Phase II, etc.)
6. **Section IV.A. Study Design.** In line 312, the example of exclusion statement includes “apple or orange juice” in addition to the more commonly excluded grapefruit and grapefruit juice. While the interaction potential of grapefruit and grapefruit juice is well documented and the mechanism of this interaction is understood, to our knowledge this is not the case for apple juice. With regard to orange juice, a review of the literature suggests that interactions due to orange juice are limited primarily to orange juice products derived from Seville oranges, a close relative of grapefruit. Therefore, we recommend that the phrase “apple or orange juice” either be deleted from the example, or clarified to more precisely identify the type of orange juice. Also, we recommend that the final document clarify why “vegetables from the mustard green family” is included in the example, as well as why cranberry juice is not included.
7. **Section IV.C. Choice of Substrate and Interacting Drugs.** In lines 356–371, an inhibitor classification system is presented based on inhibitor effects on AUC. Should effects on C_{max} also be taken into account when classifying an investigational drug as a strong, moderate, or weak CYP inhibitor? We request that you clarify this point in the final version of this guidance.
8. **Section IV.C. Choice of Substrate and Interacting Drugs (lines 356–371).** Inhibitors are classified as “strong, moderate, and weak” based on fold increases in AUC of 5, 2, and 1.25. It is unclear how these cutoff values were determined. We request that FDA provide a rationale for these values in the final version of this guidance.
9. **Section IV.C. Choice of Substrate and Interacting Drugs (lines 404–408) and Appendix C-1 (lines 784–785 and 845–846).** We request that you clarify how the “>25% of the clearance pathway” was selected as the cutoff value in the final version of this guidance.

10. **Section IV.G. Sample Size and Statistical Considerations.** We agree that the default no effect boundary of 80%–125% is “a “very conservative standard” (lines 621–622). The no effect boundary of 70%–143% has already been used at several occasions for drug-drug interaction studies (e.g., Cooper 2003, Ring 2005) and could also be mentioned as a valid alternative if appropriate. We recommend that this option is mentioned in the final guidance document as a valid alternative.
11. **Appendix A – Table 1 (lines 675–683).** Line 677 states that an updated list will be provided at the noted website link. We request that the final guidance describe FDA’s plans for updating and maintaining the information at this website. In addition, we request that FDA explain why the gene names are mentioned for the transporters in this Table.
12. **Appendix A – Table 2 (lines 685–699).** We believe that glyburide is suitable as an in vivo substrate of CYP2C9 and request that the final guidance document includes this compound as suitable in Table 2.
13. **Appendix A – Table 2 (lines 685–699).** Would any of the eight listed substrates and ten listed inhibitors of 3A4/3A5 be suitable to use in in vivo clinical drug-drug interaction studies? Would some be more preferable to use? We recommend that the more preferable substrates and inhibitors of 3A4/3A5 should be mentioned in the final version of the guidance.
14. **Appendix A – Table 2 (lines 685–699).** We request that FDA include in the final guidance document a table of substrates, inhibitors, and inducers similar to Table 2 for any other important metabolic enzymes systems like for instance non-P450 oxygenases (such as flavin-containing monooxygenases) and Phase II enzymes (such as uridine diphosphoglucuronosyltransferases). (See also general comment no. 2).
15. **Appendix A – Tables 3 and 4 (lines 701–722).** We believe that Tables 3 and 4 could be merged together, and recommend a format for the merged table that would have 3 columns with the following subtitles: CYP, sensitive substrates, and substrates with narrow therapeutic range.
16. **Appendix A – Tables 5 and 6 (lines 723–752).** We also recommend that Tables 5 and 6 be merged together in the final version of this guidance.
17. **Appendix A – Table 6 (lines 740–741).** We note that CYP2C19 inhibitors, fluvoxamine and moclobemide (mentioned in Table 2, line 687), are not included in Table 6. We request that you clarify their absence from Table 6, and if the absence is in error, adjust Table 6 as appropriate.

18. **Appendix B – Figure 1 (lines 755–769).** The first box in this figure only includes six CYP isoforms and refers to “human tissues.” We request that the final guidance clarify if this decision tree is only applicable to these six CYP isoforms, as well as clarify what is meant by “human tissue.” Also, the term “major” is used in several places in the flow chart and we request that the final guidance describe what is meant by the term “major.” We note that in **line 406**, substantial metabolic pathway is define as >25%. We request that the final guidance clarify if FDA views substantial and major pathways as the same for purposes of this guidance.
19. **Appendix C-1, para.2. Studies Designed to Identify Drug Metabolizing CYP Enzymes (lines 845–846).** We believe that the first sentence under Section 2 is confusing because it seems to imply that in vivo studies investigating CYP enzyme interactions are conducted before in vitro experiments, which would not occur. We recommend that FDA clarify this sentence in the final version of this guidance.
20. **Appendix C-2, para.2. Design Considerations for In vitro CYP Inhibition Studies.**
- In **line 1004**, the guidance recommends the use of microsomal protein concentrations of less than 1 mg/mL. In our experience, protein concentrations of 1 mg/mL are still too high and need to be kept less than 0.1 mg/mL. We recommend that the final guidance be modified accordingly.
 - In **line 1006**, we request that the final guidance make specific recommendations for the buffer strength, type, and pH.
 - In **line 1017**, we request that the final guidance describe the most desirable, and the least desirable, organic solvents. We request that the final guidance contain examples, such as “Methanol and acetonitrile can be used at <1% of the total volume without substantial CYP inhibition, but dimethylsulfoxide is more potent and needs to be used at <0.1%”.
21. **Appendix C-2, para.3. Determining Whether an NME is a Reversible Inhibitor; Current recommended approach.** In **lines 1044–1045**, the following statement is made: “An estimated $[I]/K_i$ ratio of greater than 0.1 is considered positive and a follow-up in vivo evaluation is recommended.” We note that the definition of a universal cutoff value continues to be discussed in the scientific literature (e.g., Bjornsson 2003, Tucker 2001), and question how the cutoff of 0.1 was selected. We believe that a cutoff value of 0.1 may be too conservative and recommend that a higher cutoff (e.g., at least 0.5) be considered to avoid conducting unnecessary in vivo drug-drug interaction studies. We also request that the final guidance provide a rationale for the cutoff value FDA recommends.

22. **Appendix C-2, para.4 (lines 1061–1070). Determining Whether an NME is a Mechanism-Based Inhibitor.** We believe that it is more appropriate to name these compounds time-dependent inhibitors, rather than mechanism-based inhibitors. There are several criteria for a compound to be a mechanism-based inhibitor and in most cases they are not determined (for example with CYP, changes in the difference spectrum). However, time-dependent inhibitor is a criterion that most pharmaceutical companies use. In this section, there is very little description of the assay, compared with the description of CYP inhibition in Section 2. It would be helpful to describe the assay more fully, including positive controls as well as the kinetic parameters obtained (k_{inact}/K_I). We also request that the final guidance identify the criteria that should be used for designing clinical studies. For example, we request that FDA describe what k_{inact} is considered potent.
23. **Appendix C-3, para.3 (lines 1137–1138).** The draft guidance states that a drug can be considered as an enzyme inducer if it produces a change equal to or greater than 40% of the positive control. We request that the final guidance provide a rationale for this cutoff value.
24. **Appendix D-2-C (lines 1314–1316).** We note that both the seeding density and the number of days in culture are provided by the draft guidance, and request that the final guidance document discuss the appropriate range of passage number.
25. **Appendix D-2-C (lines 1315, 1318–1319, 1330, 1397).** The draft guidance indicates that “cells should be seeded [...] on polycarbonate microporous membrane filters” and that “experiments [...] are performed using polycarbonate filter inserts.” We request that the final guidance states whether polycarbonate would be the only acceptable type of filters and describe the rationale for excluding other types of appropriate material (e.g., polyester filters).
26. **Appendix D-2-C (lines 1321–1324).** With respect to the determination of TEER and permeability of paracellular markers, we request that FDA clarify whether the determinations are recommended in selected wells of the cell culture, or in all wells where bi-directional experiments are conducted. In addition, would other paracellular markers such as lucifer yellow be acceptable? If so, we recommend adding this marker in the final version of the guidance.
27. **Appendix D-2-D and F (lines 1335–1337; 1400–1402).** The draft guidance seems to indicate that the bi-directional studies should be conducted in media, rather than in buffer alone. If only media are recommended by the FDA for use, we request the final document provide guidance on binding to medium protein.

28. **Appendix D-2-D (lines 1338–1341).** We request that the final guidance describe the possible use of organic solvents to dissolve low-solubility compounds; e.g., which organic solvent could be used and what would be the maximum level acceptable.
29. **Appendix D-2-E (lines 1369–1372).** We believe that because donor compartment sampling is not mentioned in the draft guidance, C_0 should be “concentration of the test drug in the donor chamber at time 0”. In addition, we request that the final guidance discuss study design and calculation of permeability if non-specific binding is present.
30. **Appendix D-2-F.** In line 1406, we believe that although it is not clearly indicated in the sentence “after incubation of the cells for 0.5–1 hour,” this step most likely corresponds to the pre-incubation of the cells with the tested inhibitor. We request that FDA state the rationale for only pre-incubating the cells with the inhibitor and not adding the inhibitor throughout the study. We note that most P-gp inhibition studies, including those mentioned in Table 2 of the guidance document (lines 1254–1256), pre-incubate but also co-incubate the inhibitor with the probe.
31. **Appendix D-2-D, F and G (lines 1349–1350, 1356–1359, 1411–1412, 1414–1425).** The guidance recommends “determination at least in triplicate on different days to allow for assessment of intra-and inter-day variations,” confirmation of positive substrate results in the presence of at least 2–3 potent P-gp inhibitors, and determination of IC₅₀ for P-gp inhibitors. These requirements represent a high resource commitment. We request that FDA clarify at what stage of the drug discovery/development these studies need to be conducted.
32. **Appendix D-3 (line 1443).** The draft guidance states that a result is considered positive (i.e., compound identified as a P-gp substrate) when the efflux ratio is >2. We believe that this criterion is too liberal and will include too many positive results. We request that FDA describe the basis (or clinical relevance) for selecting this value as a cutoff and consider a higher value in the final version of this guidance.
33. **Appendix D-3 (lines 1451–1454).** It is not clear as to how “evaluation of available in vivo data can help determine whether an in vivo drug interaction study [...] with [...] P-gp inhibitors is recommended.” We request that the final guidance document clarify this statement.
34. **Appendix D-3 (lines 1484–1485).** We request that the final guidance document clarify and expand on the following: “An alternative is to use a % value (net flux of investigation drug relative to a probe substrate, such as digoxin.)”

35. **Appendices D-3 and D-4 (lines 1427–1549).** We request that the final guidance clarify if “in vivo interaction study” refers only to clinical studies or also to animal studies.
36. **Appendix D-4 (lines 1514–1519).** The draft guidance proposes that an investigational drug be classified as a Pg-P inhibitor based on a cutoff of 0.1 for the $[I]/IC_{50}$ ratio or K_i , but does not describe how this cutoff value was selected. We request that the final guidance provide a rationale for this cutoff value.

We appreciate the opportunity to comment on this draft guidance document and look forward to reading the revised final guidance.

REFERENCES

- TD Bjornsson et al. The conduct of in vitro and in vivo drug-drug interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. *Drug Metab Dispos.* 2003;31(7):815-32.
- KJ Cooper et al. Effect of itraconazole on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther.* 2003;73(4):322-9.
- BJ Ring et al. Effect of tadalafil on cytochrome P450 3A4-mediated clearance: studies in vitro and in vivo. *Clin Pharmacol Ther.* 2005;77(1):63-75.
- GT Tucker et al. Optimizing drug development: strategies to assess drug metabolism/transporter interaction potential-toward a consensus. *Clin Pharmacol Ther.* 2001;70(2):103-14.