

Comments on Draft Guidance for Industry

**Guidance: Drug Interaction Studies – Study design, Data analysis, and
Implications for Dosing and Labeling**

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Comments on FDA, CDER, Clinical Pharmacology, Draft Guidance for Industry:
Drug Interaction Studies – Study design, Data analysis, and Implications for Dosing and Labeling, September 2006

Within Roche, a global DDI expert working group is established with the main focus on the following 2 tasks:

- to provide recommendations on judgment of pre-clinical DDI alerts that may indicate relevant clinical DDI risk;
- to generate templates for the conduct of clinical DDI studies.

The Roche expert working group brings together experts in the design of in vitro experiments; in the evaluation of animal pharmacokinetic studies; from clinical drug safety and regulatory, and from clinical pharmacology including modeling & simulation experts.

Clearly, the group is intensively watching the progress being made in the area of DDI during the last years. Please do not hesitate contact us in case any of our comments requires further clarification.

I. Introduction

General	It is suggested to mention that this guidance does not deal with considerations of pharmaceutically based DDIs like eg cation chelation, pH modifiers.
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II. Background; B. Drug-Drug Interactions; 1. Metabolism-based Drug-Drug Interactions

Page 3, line 4	Does the statement that HMG CoA reductase inhibitors are non-NTR (narrow therapeutic range) drugs reflect the general opinion of CDER?
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III. General strategies; B. Specific in vivo clinical investigations

Page 5, line 18	Although it is true that many drugs that induce CYP3A4 also induce CYP2B/C, this is not always the case: <i>Faucette Stephanie et al. The Journal of Pharmacology and Experimental Therapeutics 2006. 317. 1200-1209.</i> It is therefore suggested to confirm absence of CYP2B/C induction in vitro monitoring for respective; mRNA enzyme protein or enzyme activity, respectively.
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III. General strategies; C. Population Pharmacokinetic Screens

Page 6, Paragraph C	General comment : It would be helpful to get a decision tree (as Figure 1 page 24) describing the different scenarios: - when the PopPK approach could be used (according to in vitro or in vivo studies outcome) - for which objectives (e.g. to provide further evidence of the absence of unsuspected DDI or to detect DDI or to get statement in the label based on PopPK DDI analysis) - what is the volume of info necessary (absence or presence of concomitant the drug, daily dose info, regimen, PK concentrations, etc.) to meet such objectives.
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Page 6, line 13	FDA wrote <Simulations can provide valuable insights into optimizing the study design>. General comment, what is FDA position regarding study design based on Simulation coming from SIMCYP™.
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IV. Design of in vivo drug-drug interaction studies, C. Choice of substrate and interacting drugs; 1. Investigational drug an inhibitor or an inducer of CYP enzymes

Page 9, line 2	Several cocktail approaches claim to be validated in the sense that there are no interactions among the various P450 substrates used. It is suggested that the documents specifies which ones of the various cocktail approaches are sufficiently validated in the opinion of the Agency.
Page 9, 3 rd Paragraph	What threshold (% decrease of AUC) is used to define that an investigational drug is an inducer of CYPs?
Page 10, line 2	In case of absence of DDI as indicated by a cocktail study, the FDA may want to clarify whether the waiver of additional, dedicated DDI studies holds true in case that $[I] / K_i$ ratio is > 0.1 ?
<i>IV. Design of in vivo drug-drug interaction studies, C. Choice of substrate and interacting drugs; 2. Investigational drug as a substrate of CYP enzymes</i>	
Page 11, line 16	Appropriateness of multiple CYP inhibitor studies: Instead of giving three conditions that remain rather unclear because now thresholds are provided for (1) drug exhibits blood concentration dependent safety concerns (2) multiple CYP enzymes are responsible for the metabolic clearance, (3) the residual or non-inhibitable drug clearance is low it is suggested to state that <i>multiple CYP inhibitor studies might be considered to investigate the effect of combined inhibition of those P450 enzymes that individually contribute more than 25% to the clearance.</i>
<i>E. Dose selection</i>	
Page 12, line 6	The current text says that a dosing of the probe inhibitor ketoconazole of 400 mg qd for multiple days would be preferable to lower doses. When using rifampin as an inducer, dosing at 600 mg qd for multiple days would be preferable to lower doses. It would be helpful to specify a minimum number of days of dosing for both ketoconazole and rifampin. We suggest a pre-treatment period of 3 days for ketoconazole and of 7 days for rifampin. For rifampin, [Niemi M et al. <i>Pharmacokinetic Interactions with Rifampicin. Clinical Relevance. Clinical Pharmacokinetics</i> 2003; 42(9): 819-850] showed that near-maximum induction by rifampin was achieved after 1 week of treatment.
<i>Appendix C-2; In vitro evaluation of CYP inhibition; 3. Determining whether an NME is a reversible inhibitor</i>	
Page 33, table 4	Table 4 provides categories for the $[I] / K_i$ ratio making a relevant clinical DDI more versus less likely, respectively. It is suggested to remind the reader that likelihood of DDI depends on F_m of the victim through the metabolic pathway in question as well. Also, this table does not account for liver partitioning. It is suggested to indicate that $[I] \sim C_{max}$ may be underestimated in case of liver partitioning, in particular when the liver : plasma ratio exceeds the value predicted by physiology based modeling.
Page 34, line 5	The current text states that: If the CYP with the largest $[I] / K_i$ (or smallest K_i) shows no interaction in vivo, in vivo evaluation of the other CYPs with smaller $[I]/K_i$ (or larger K_i) will not be needed. This statement does not account for the relevance of tissue distribution of CYPs, eg a relative high K_i on CYP3A may still cause relevant DDI

	when orally co-administered with CYP3A victim due to the expression of CYP3A in the intestinal epithelium. It is suggested to add this limitation / exception.
Page 34, line 6	The current wording says that for CYP3A inhibition, two structurally unrelated substrates should be evaluated. More specification with referencing to relevant literature is warranted. Also, if the substrate being more sensitive to a CYP3A inhibitor in vitro is not midazolam, it should be clarified that in this case that substrate and not midazolam should be used as prototypical CYP3A substrate in the in vivo DDI study.
<i>Appendix C-2; In vitro evaluation of CYP inhibition; 4. Determining whether a NME is a mechanism-based inhibitor</i>	
Page 34, line 13	The description of the time-dependent inhibition assay describes a rather general protocol and does not include the assessment of reversible/irreversible inhibition (e.g. dilution from pre-incubation to enzyme assay). In the proposed assay also the formation of a metabolite with potent enzyme inhibitor activity would be positive. In addition, the observed time-dependent effect should be put into relation to the effects of positive controls run in parallel. Therefore, the formulation “Any time-dependent inhibition...” appears to be too stringent and should be changed to “Time-dependent inhibition...” as criteria to trigger follow-up in vivo studies.
<i>Appendix C-3; In vitro evaluation of CYP induction; 2. Design of in vitro drug induction studies</i>	
Page 36, line 7	Further evaluation of the immortalized liver cells is needed with a range of positive controls for various induction pathways (i.e., AhR, CAR, and PXR).
<i>Appendix C-3; In vitro evaluation of CYP induction; 3. Endpoints for subsequent prediction of enzyme induction</i>	
Page 36, (b)	When EC50 is used, Emax shall also be provided to compare the induction potency of the tested compound with the positive control.
<i>Appendix D; In vitro evaluation of P-glycoprotein (P-gp, MDR1) substrates and inhibitors; 2. Bi-directional transport assay using polarized monolayer cells</i>	
Page 40, Table 2	A range of concentrations for quinidine may be used. Suggest considering 0.05 – 10 µM.
<i>Appendix D; In vitro evaluation of P-glycoprotein (P-gp, MDR1) substrates and inhibitors; 2. Bi-directional transport assay using polarized monolayer cells; (c) Tissue culture considerations to ensure functionally polarized cells</i>	
Page 43	The description of the culture conditions is very detailed and thus restrictive. Instead, emphasis should be given for the justification of the conditions used. Various conditions could affect cell culture conditions. As various cell systems are being used, and transfectants may have to be performed individually in different laboratories, focus should be on the functional validation of the cell system used rather than on cell culture conditions.
<i>Appendix D; In vitro evaluation of P-glycoprotein (P-gp, MDR1) substrates and inhibitors; 2. Bi-directional transport assay using polarized monolayer cells; (d) design of bi-directional experiments conducted to determine whether the drug is a P-gp substrate</i>	

Page 43	The description of the experimental conditions is very detailed and thus restrictive. Instead, emphasis should be given for the justification of the conditions used.
<i>Appendix D; In vitro evaluation of P-glycoprotein (P-gp, MDR1) substrates and inhibitors; 2. Bi-directional transport assay using polarized monolayer cells; (e) Calculation of the apparent permeability of drugs through the cell monolayer</i>	
Page 43	Caution is necessary if ratio R_w of untransfected cells is deviating from unity. It is unclear how the transfection process for each individual batch of transfections may alter functional transport of endogenous transporters.
<i>Appendix D; In vitro evaluation of P-glycoprotein (P-gp, MDR1) substrates and inhibitors; 2. Bi-directional transport assay using polarized monolayer cells; (f) design of bi-directional experiments conducted to determine whether the drug is a P-gp inhibitor</i>	
Page 45	The description of the experimental conditions is very detailed and thus restrictive. Instead, emphasis should be given for the justification of the conditions used.
<i>Appendix D; In vitro evaluation of P-glycoprotein (P-gp, MDR1) substrates and inhibitors; 3. Criteria for determining whether a test drug is a substrate for P-gp, and whether an in vivo interaction study is needed</i>	
Page 46, line 14	A net flux ratio over 2 is proposed as threshold to trigger in vivo interaction studies with P-gp inhibitors. The flux ratio is typically very much dependent on the quality of the cells used, as it is outlined in the preceding paragraph. However, not only the lower end of the range of the flux ratio of a positive control substrate is important to assure sufficient quality/sensitivity of the test system, also the upper range is very much influencing the response. For digoxin we often notice flux ratios of 12-18, even up to 25 (using either LLC-PK1 or MDCK cells over-expressing MDR1), making the system much more sensitive. The flux ratio of the test compound could for example be expressed relative to the one of the positive control substrate measured in parallel in the same assay.
<i>Appendix D; In vitro evaluation of P-glycoprotein (P-gp, MDR1) substrates and inhibitors; 4. Criteria determining whether a test compound (investigational drug) is an inhibitor of P-gp, and whether an in vivo interaction study is needed</i>	
Page 48, line 8	The text sets a ratio of $[I] / IC_{50}(K_i) > 0.1$ as a threshold to recommend an in vivo DDI study with digoxin. It should be added that absence of DDI with digoxin allows concluding general absence of P-gp inhibition caused DDI.