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

Subject: **Docket No. 2006D-0344**
Draft Guidance for Industry on Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling

Dear Sir/Madam:

Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA, which strives to serve patients by transforming the promise of science and biotechnology into therapies that have the power to dramatically improve people's lives.

We are pleased to provide the attached comments on the draft guidance, *Draft Guidance for Industry on Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling*.

If you have any questions regarding our comments, or how we may assist with further development of this guidance, please contact Jenny Peters at (805)-447-8840.

Sincerely,

Jenny Peters
Amgen Global Regulatory Affairs & Safety

Key Philosophical or Strategy Issues
The guidance cites a number of informational web links, including a link for an updated list of transporters (page 18). Will the Agency be continually updating these links?
Although what is presented in the draft guidance may be considered state-of-the art today, it could become obsolete quickly. Presumably the Agency does not plan on updating the guidance very often. Thus, if the FDA considers it important to describe these methodologies, it may be best to establish a website to accomplish. It appears FDA plans on establishing a website that lists CYP probes and inhibitors as well as a list of transporters.
Addition of supporting literature references throughout the document would be useful.

Item with Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed change
L-86	minor	Any changes of safety and/or efficacy are important. In this light, the phrases of "most obvious" and "expected" are inappropriate.	1) Remove "…in important ways." 2) replace "most obvious and expected" with "especially critical"
L-87	minor	Narrow Therapeutic Index Drugs are left undefined. This ambiguity could lead to unnecessary drug drug interaction (DDI) studies or disagreements between the sponsor and the agency.	Add: "The definition of narrow therapeutic index drugs is modality dependent."
L-127	minor	The sentence beginning with "Rarely, the degree…" is written awkwardly.	Rewrite sentence for clarity. "Only rarely does either the degree of interaction caused by a drug or the degree to which other drugs alter its metabolism preclude granting a marketing authorization."
L-131	minor	This section is not adequately referenced and only clinically significant transporter DDI should be discussed.	This section should define and discuss only transporters with demonstrated clinically significant DDI (ie, not attributable to concommitant CYP interactions). The text should be anchored to clinically significant DDI with appropriate references. If data is available but not in public domain, please so state.

Item with Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed change
L-140	minor	As an inhibitor, what in vitro IC50 or [I]/IC50 should be used to trigger a concern?	Incorporate statements about the utility of in vitro data for predicting transporter DDI.
L-163	major	The discussion around making dose adjustments needs to be limited to the situation where the sponsor's drug is subject to drug interactions, not causing interactions.	Add the following statements to the end of the sentence on line 165…"where the investigational drug is subject to DDI by marketed agents."
L-173	minor	"…so that subsequent in vivo testing is unnecessary."	The authors should indicate whether the reverse is true, eg, can the in vitro determination that a compound which potently inhibits a CYP create a condition where the in vivo study is unnecessary, providing that the sponsor is prepared to include the strong inhibition language in the product label?
L-177	major	What is meant by "Therapeutic concentration"?	Authors should define the concept in terms of bound vs unbound concentration and Cmax vs Cave.
L-193	minor	The role of CYP3A4 as a universal indicator of CYP and transporter induction appears weak.	The authors should include wording around the exclusion of CYPs and transporters if CYP3A4 induction is not observed.
L-197	major	The guidance states that if in vitro induction of CYP3A is not observed, then in vivo studies may not be needed for not only CYP3A but also for CYPs 2C and 2B and P-gp. Presumably this ability to extrapolate conclusions also applies to in vivo studies. That is, if in vivo induction of CYP3A is not observed, then in vivo studies would not be needed for the other CYPs and transporter.	Add "In addition, if in vivo induction of CYP3A is not observed, then additional in vivo studies would not be needed for the other CYPs and transporter."

Item with Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed change
L-230 thru 231	minor	"Simulations can provide valuable insights into optimizing the study design." It is unclear whether this sentence is a general statement about simulation, whether it is a statement about the use of simulation to design in vivo studies to assess drug-drug interactions, or whether it is a statement about the use of simulation to design large-scale clinical studies in order to detect DDIs.	Please clarify intent of sentence.
L-245 thru 246	minor	"Consultation with FDA regarding study protocols is recommended." There are certain drug-drug interaction studies that are routine. Consultation with the FDA on these studies would unnecessarily use up FDA resources that would be best served for studies that were not as routine. It may be helpful to be more specific as to what sort of studies or situations would make consultation value added for industry and the FDA.	Replace with "Consultation with FDA regarding study protocols is recommended when there are specific issues or questions."
L-268	major	The document correctly states that a dose that results in the highest clinical concentration of interacting drug should be used. The guidance should also note that in some cases, the most sensitive assessment will involve using the **lowest** clinical dose of the substrate.	Add "In some cases, the most sensitive assessment will involve using the lowest clinical dose of the substrate."

Item with Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed change
L-268	minor	The guidance states that drug interaction studies should often be performed early in development (see *General Strategies* section of text beginning on line 144). At this stage, the final clinical doses are typically not known and thus such studies are often performed using sub-optimal doses. A question that often arises is to what extent can a clean drug interaction study be extrapolated to higher doses? For example, if an early study demonstrates that an new molecular entity at a dose of 20 mg does not affect CYP3A activity in vivo (as demonstrated by a lack of effect on midazolam exposure), would there be a need to perform an additional clinical drug interaction study if the top clinical dose ends up being 30 or 40mg?	Add "With drug interaction studies done early in development, the highest clinical dose is generally not yet known. In some cases, data extrapolations will allow conclusions to be made in support of labeling statements."
L-300 thru 303	minor	At this point it should be mentioned that if a pharmacodynamic endpoint is of interest, then a fourth arm of no drug (or matching placebo for both drugs) should be considered. Without this arm it would be difficult to determine if a pharmacodynamic interaction were synergistic or antagonistic.	Add "If a pharmacodynamic endpoint is of interest, then a fourth arm of no drug (or matching placebo for both drugs) should be considered."
L-305 thru 316	minor	Participants to be excluded should include smokers due to CYP1A induction.	Add "smokers (due to CYP1A induction)"
L-358	major	The classification system offered is somewhat arbitrary and may be open to misinterpretation, depending on the co-administered drugs in question.	Authors should consider clearly associating the classification system with pharmacokinetic endpoints and potential toxicological effects.

Item with Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed change
L-375 thru 378	major	If in vitro evaluation cannot rule out the possibility of CYP3A induction, would an in vivo evaluation with oral midazolam be needed IF urinary 6β-hydroxycortisol to cortisol ratios in multiple-dose studies did not suggest in vivo induction? Urinary 6β-hydroxycortisol to cortisol ratios have been known to be consistently increased following repeated dosing of CYP3A inducers and have been evaluated in multiple-dose studies for the assessment of CYP3A induction potential. (Reference: Galteau MM, Shamsa F. Urinary 6beta-hydroxycortisol: a validated test for evaluating drug induction or drug inhibition mediated through CYP3A in humans and in animals. *Eur J Clin Pharmacol.* 2003;59(10):713-33)	Please address if urinary 6β-hydroxycortisol to cortisol ratios can be use to support the lack of in vivo CYP3A induction if in vitro evaluation cannot rule out the possibility of CYP3A induction.
L-392 thru 393	major	If metabolic ratios from the in vivo cocktail study are used instead of AUC or Cmax (due to limited PK samplings), would a no-effect boundary of 80-125% be required to demonstrate negative results? Or would negative results be based on P values?	Please specify the criteria for "negative results" from the in vivo cocktail study.
L441 thru 445	major	Is there a preference of studying poor metabolizers versus doing a formal drug-drug interaction trial? If yes, the guidance should address as poor metabolizers are typically difficult to recruit, thus without a preference, industry will probably most often default to a drug-drug interaction trial. The guidance should clarify.	
L-479	major	The guidance does not give a clear definition of a P-gp substrate/inhibitor in the clinic.	More information around the in vitro/in vivo correlation of substrate and inhibitor for P-gp is needed.

Item with Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed change
L-487 thru 488	major	As recommended by the guidance, if an investigational drug is a substrate of both CYP3A and P-gp, an in vivo study with ritonavir can be conducted. In this case, a separate study with ketoconazole is not needed.	Add: "If ritonavir is used, a separate study with a CYP3A inhibitor (ie, ketoconazole) is not needed."
L-540	minor	Current ICH guidance on the evaluation of QT prolongation should be cited (ICH E14).	Include appropriate reference to ICH E14 to text.
L-542 thru 561 PK endpoints	major	The assessments of inhibition or induction should be based on AUC. Amgen appreciates that other PK parameters might be of relevance for the assessment of the clinical relevance for a particular interaction. Other PK parameters may be used as supportive data. As shown in Tables 5 and 6, the classification of inhibitors (ie, strong, moderate, weak) is based mainly on the changes in AUC (ie, $\geq$ 5-fold increase in AUC, etc).	Please specify primary PK parameters.
L-597	minor	"...will be to add the drug to the list of inhibitors or inducers likely already present in the labeling of the older drug." This statement seems to suggest that the FDA will continuously update the labels of older drugs as new interacting drugs are approved. Is this the intent?	
L-599	minor	These statements need to be clarified. The paragraph flips back and forth between the two scenarios of causing an interaction versus being subject to an interaction.	Restructure the paragraph to flow with perpetrator of an interaction first, followed by subject to an interaction.

Item with Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed change
L-611 thru 625	major	Two points need to be added to the guidance: 1) If the sponsor is to define its own no effect boundaries (Approach 1), then they should consult with the FDA in order to have agreement that these indeed would be considered no effect boundaries by the FDA. 2) In a study in which the goal is to rule out an entire class by using the most sensitive substrate, 80-125% is the only acceptable no effect boundaries.	Add "For Approach 1, sponsors should consult with the FDA in order to have agreement regarding no effect boundaries." Add "In a study in which the goal is to rule out an entire class by using the most sensitive substrate, 80-125% is the only acceptable no effect boundaries."
L-632	minor	It has been documented that there can be interindividual variability in the magnitude of metabolic drug interactions. Because of this, reviewers may be tempted to look at the largest individual subject's chance in exposure as a measure of the magnitude of drug interactions. This approach, however, can lead to a gross overestimation of the magnitude of interaction, depending on the magnitude of other sources of intraindividual variability. Thus, it would be beneficial if the guidance explicitly specifically stated in this section that individual subject data should not typically be used to asses the magnitude of an interaction.	Add "Individual subject data should not typically be used to asses the magnitude of an interaction."
L-675 thru 686 Appendix A	minor	These tables serve as a review of the literature and do not provide any specific guidance surrounding the conduct of drug interaction studies. As the major focus of this document is to provide guidance to the industry on the conduct on in vivo and in vitro drug interaction studies, tables that simply review the literature and will not be updated on a regular basis serve no purpose in this draft.	Remove such tables from the document but maintain access to them on the FDA website. Links provided within the document will be sufficient.

<table>
<tr><th>Item with Reference Line #</th><th>Relative Importance (major or minor)</th><th>Key Concerns with Explanation of Position</th><th>Proposed change</th></tr>
<tr><td>Line 688
Table 2</td><td>minor</td><td>It would be helpful to provide optimal dosage and duration for index inhibitors and inducers as suggested in Section E of the guidance.</td><td>Please provide optimal dosage and duration for index inhibitors and inducers, if possible.</td></tr>
<tr><td>Lines 726 thru 755
Tables 5 and 6</td><td>minor</td><td>Both of these tables use the same criteria for classification of strong, moderate, and weak CYP inhibitors. Further, Table 6 is not easy to read.</td><td>Suggest combine both of these tables into 1 and modify the format to:
<table>
<tr><th>CYP</th><th>Strong inhibitors</th><th>Moderate inhibitors</th><th>Weak inhibitors</th></tr>
<tr><td>1A2</td><td></td><td></td><td></td></tr>
<tr><td>.....</td><td></td><td></td><td></td></tr>
<tr><td>3A4</td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td>L-868</td><td>minor</td><td>There are inconsistent recommendations regarding substrate/inhibitor concentrations.</td><td>The guidance should propose a strategy if recommendation on Line 868 (eg, drug concentrations and kinetic parameters) and L-177 (e.g., therapeutic concentrations) are in conflict.</td></tr>
<tr><td>L-889
Table 2</td><td>major</td><td>Furafylline and methoxsalen are mechanism based inhibitors (as noted in the footnote) and as such should not have apparent Ki values.</td><td>Remove these Ki values.</td></tr>
<tr><td>L-889
Table 2</td><td>minor</td><td>There are relatively few reported clinical drug interactions for CYP 2A6 and thus the importance of this information in the table can be debated.</td><td>Remove this data from the table and list a reference to it on the website.</td></tr>
<tr><td>L- 918</td><td>minor</td><td>The recommended pre-incubation period of 15 to 30 minutes seems overly generic for the assessment of mechanism-based inhibition.</td><td>A note regarding pre-incubation of mechanism based inhibitors is useful; however, no specific time period should be given as this will depend on the inhibitor in question.</td></tr>
<tr><td>L-993
Table 3</td><td>minor</td><td>Rosiglitazone para-hydroxylation is noted as an acceptable metabolic pathway to monitor for inhibition of CYP2C8. Rosiglitazone N-desmethylation appears to be the more commonly used metabolic pathway of rosiglitazone when assessing CYP2C8 pharmacokinetics.</td><td>This should either be changed to rosiglitazone N-desmethylation or, at the least, both pathways listed.</td></tr>
</table>

Item with Reference Line #	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed change
L- 1011	minor	The comment "standardized assay conditions" is vague and does not add much in the way of guidance. Does this statement refer to standardized conditions within a laboratory or across the industry?	This comment should either be removed or clarified.
L-1051	minor	Should the extent of protein binding be taken into account in the proposed assessments?	
L-1061	minor	The guidance states that if the CYP with the largest [I]/Ki shows no interaction then evaluation of other CYPs is not needed. While this is generally true, it may not apply for CYP3A4, since this enzyme is contained at high levels in the gut wall and the local concentration of drug in the gut can be significantly higher than that achieved systemically.	Add "While this is generally true, it may not apply for CYP3A4, since this enzyme is contained at high levels in the gut wall and the local concentration of drug in the gut can be significantly higher than that achieved systemically."
L-1070	major	The sentence implicating that any observation of time or concentration dependent inhibition is indicative of mechanism based inhibition is incorrect. There are additional criteria (as defined by Silverman and others) that must be met to classify a compound as a mechanism based inhibitor.	This sentence should be modified to indicate that such observations only indicate time or concentration dependent inhibition and are not automatically indicative of mechanism based inhibition.
L-1191	minor	The focus on P-gp, probe molecule and method selection was valuable. This whole section should be anchored to literature references whenever possible with a focus on discerning compounds likely to cause clinically significant transporter related DDI	Authors should cite pivotal literature on techniques and their application towards characterizing drug interactions.