

Friday, October 27, 2006

The FDA Commissioner  
c/o Division of Dockets Management  
5630 Fishers Lane  
Room 1061 (HFA-305)  
Rockville, MD 20852

Re: Docket No. 2006D-0344

Dear Commissioner:

This correspondence is in reference to Docket No. 2006D-0344 entitled "Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling." We would like to offer comments on this guidance. We feel qualified to do so since a large portion of our careers have been spent generating some of the information contained in this draft guidance.

We would urge FDA to use the correct term "sex" rather than "gender" to describe male/female differences. Sex is the DNA based term to differentiate men from women; gender is a sociologic classification (1). We realize some consider "gender" to be more politically acceptable, however, scientifically it is incorrect.

Section IIB1: Metabolism-based drug-drug interactions: This section suggests that metabolic drug-drug interactions should be explored even for investigational compounds that are not eliminated significantly by metabolism because of the potential for "*important effects on the metabolism of concomitant drugs.*" In addition, it notes that some such interactions can not be detected *in vitro*. One efficient way to assess such effects on the CYP450 enzymes is through the use of cocktail studies to assess potential for drug-drug interactions.

Section IIIA: *In vitro* studies: This section suggests that if *in vitro* studies indicate that an investigational drug does not induce or inhibit drug metabolizing enzymes (DMEs) or transporters then no further *in vivo* studies are needed to examine this. However, a publication from the FDA has previously reviewed published data and shown that *in vitro-in vivo* results are often discordant (2). We believe that for drugs that show no *in vitro* interaction, the use of a single cocktail study can elucidate whether or not an *in vivo* occurs. We believe that all drugs under development should be subjected to a cocktail study to elucidate whether an *in vivo* drug interaction occurs with the major CYP enzymes, regardless of *in vitro* findings.

Section IV-C-1: This section outlines initial studies for inhibitory and inducible drug interactions. One section suggests: "*If the initial study determines an investigational drug either inhibits or induces metabolism, further studies using other substrates, representing a range of substrates, based on the likelihood of co-administration, may be useful.*" This raises the question of whether specific drug-drug interaction studies should be done if probe studies reveal an interaction. These types of studies are done in an attempt to guide clinical drug dosing but unfortunately the generated data are often misleading or inaccurate.

We recently completed Monte Carlo simulations for moderate and strong inhibitors of CYP3A using midazolam (MDZ) as the isozyme substrate. The simulations were done with previously generated data. The following table shows the large range of dosage reductions for this probe drug with moderate and strong enzyme inhibitors.

**Fractional Dose Needed to Obtain Same MDZ AUC at Inhibition as Baseline AUC for Population Quantiles**

<u>Inhibitor</u>	<u>1%</u>	<u>25%</u>	<u>50%</u>	<u>75%</u>	<u>99%</u>
Moderate	0.10	0.22	0.30	0.40	0.90
Strong	0.02	0.06	0.10	0.16	0.42

As is noted, the range of dosage reduction needed during the inhibited phase is large for both moderate and strong inhibitors. While the FDA has formerly suggested specific drug-drug interaction studies to guide dosing, the findings from these studies are generally so broad that accurate dosage adjustment recommendations cannot be made. A clinical example of this is the drug interaction between warfarin and amiodarone. Warfarin is used by approximately 3 million people in the U.S. The current FDA approved label for amiodarone (a drug that inhibits the metabolism of warfarin) suggests that “prothrombin time increases 100% with the addition of amiodarone and thus, the dose of warfarin should be decreased 1/3-1/2 and INR monitored.” However, published data show that the interaction resulted in an increase in prothrombin time ranging from 22-108% (3). Thus, guidelines such as those provided in the product label are not accurate and may result in either thrombosis or hemorrhage in patients receiving warfarin plus amiodarone. While INR monitoring is recommended, the practical application of this in the clinical setting (i.e., INR measurements at adequate frequencies to avoid drug induced complications in the ambulatory setting) is questionable.

In addition, the FDA makes the following recommendation in this section of the guidance concerning the use of cocktails to discern drug interactions: *“However, positive results can indicate the need for further in vivo evaluation to provide quantitative exposure changes (such as AUC, Cmax), if the initial evaluation only assessed the changes in the urinary parent to metabolite ratios. The data generated from a cocktail study can supplement data from other in vitro and in vivo studies in assessing a drug’s potential to inhibit or induce CYP enzymes.”* Once again, we believe that the need for further specific drug-drug interaction studies is unnecessary even when the initial data were obtained using urinary metabolic ratios. One can obtain a qualitative assessment of the extent of inhibition or induction by doing cocktail studies alone.

We urge FDA to reconsider the need for specific drug-drug interaction studies. Drug label should contain information on the effect of drugs on drug metabolizing enzymes and transporters with appropriate warnings as to the consequences for drug interactions. Attempting to provide specific dose reduction recommendations is problematic for the reasons cited above.

Section IV-G: The guidance states: “*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.*” We believe that this is problematic as sponsors will often describe a drug-drug interaction as “not clinically significant” with little or no PK/PD data in support. We believe that this process needs to be scrutinized more closely by FDA.

Table 2 lists *in vivo* substrates for specific CYP enzymes. We would like to offer the following comments on these substrates:

CYP2C9: We agree that warfarin (when administered with vitamin K which we believe should be footnoted) is a useful substrate (the S isomer). Tolbutamide appears to be useful, but there is the potential for clinically significant hypoglycemia. In addition, there are data to suggest that tolbutamide is also a substrate for CYP2C19.

CYP2C19: The data validating lansoprazole and pantoprazole as CYP2C19 probes are lacking. We would suggest removing these from the list.

CYP2D6: The data validating desipramine and atomoxetine as CYP2D6 probes are lacking. Dextromethorphan and metoprolol are validated. We would suggest deleting desipramine and atomoxetine and adding metoprolol.

CYP3A4/5: Midazolam is the gold standard as a probe. Data suggest that buspirone is a weak CYP3A5 substrate and thus may only measure CYP3A4 activity (4). The drugs felodipine, lovastatin, eletriptan, sildenafil and simvastatin have either not been validated versus midazolam, are not CYP3A specific, or have been shown not to be valid CYP3A probes (5). The probe alfentanil has been compared to midazolam, has been validated, and should be added to the listing (6). Triazolam appears to be an appropriate probe.

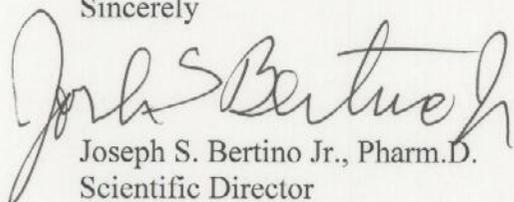
Table 5: Classification of CYP3A inhibitors: Previous data have shown that telithromycin is a moderate rather than a strong CYP3A inhibitor (7).

Appendix C-3-2, Design of *in vitro* drug induction studies: This section addresses induction but not enzyme activation. Activation, while being less dramatic than induction, tends to increase substrate clearance (for CYP3A substrates) by approximately 35% (8). We would suggest that guidance be provided to drug developers to examine the potential for heterocyclic activation *in vitro*.

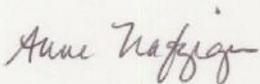
Overall, we would like to commend the FDA on its work on this guidance.

Please don't hesitate to contact us at 518-429-2000 if further clarification on these comments is needed. We would like to offer any assistance that we can.

Sincerely



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Scientific Director



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#### REFERENCES

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