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

Dear Sir/Madam:

On September 12, 2006, the Food and Drug Administration invited public comments on the draft Guidance for Industry titled Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling (Docket No. 2006D-0344). Clinical Pharmacology, Quintiles Inc., appreciates the opportunity to review this draft guidance and would like to make following comments.

On pages 5 – 6, lines 215 – 216:

"In addition to in vitro metabolism and drug-drug interaction studies, appropriately designed pharmacokinetic studies, usually performed in the early phases of drug development,"

It has been our experience that human mass balance/ADME studies are generally conducted after proof of concept has been established and the drug is considered to have a higher chance of success. On occasions, these studies may even be delayed into Phase IIb / III. We suggest removing the underlined section and instead indicate that these studies are encouraged to be performed in the early phases of drug development to add the most value to the drug development program,

On page 7, line 268:

"…., including the highest doses likely to be used".

There might be instances where the highest doses likely to be used may not be safe in a drug-drug interaction and a fraction of the standard clinical dose may need to be selected. We recommend acknowledging in this section that a lower dose may be acceptable, if significant drug-drug interaction is expected to ensure subject safety. A priory simulation of the predicted increase in exposure may assist in the selection of the dose.

On page 9, lines 382 – 385:

"In vivo induction evaluation has often been conducted with oral contraceptives. However, as they are not the most sensitive substrates, negative data may not exclude the possibility that the investigational drug may be an inducer of CYP3A."

Can this statement be expanded based on the clinical relevance of the extent of induction? Induction of metabolism of oral contraceptives has been a common assessment due to its clinical relevance with regard to contraceptive failure. If the new investigational entity

(NCE) proves to be a (weak) inducer using the most sensitive substrate, is this finding clinically relevant for less sensitive substrates? Specifically

1. Which substrates would need to be contraindicated in the label due to loss of clinical efficacy?
2. Would a second study be required to then rule out that NCE induces oral contraceptives?
3. Is there a classification scheme for induction similar to that of drug inhibition that can categorize induction potential - e.g., as not clinically relevant, possibly clinical relevant, definitely clinical relevant.

On pages 9-10, lines 387 – 398:

Would it be possible to provide some recommendation of appropriate cocktails. There is a lot of controversy with regard to which cocktail(s) provides an appropriate signal or clinical data that can truly discern potential drug-drug interactions.

On pages 11 – 12, line 479 – 480:

"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."

Would it be possible to propose examples for other acceptable P-gp substrates that have a better safety profile than digoxin. For example, we suggest using fexofenadine as one of the potential choices rather than digoxin to conduct this type of study. Though both fexofenadine and digoxin were reported to be substrate of P-gp, the selection of fexofenadine offers several advantages:

1. Fexofenadine is a relatively safe drug compared with digoxin, which has a narrow therapeutic index[1].
2. Fexofenadine has a shorter elimination half-life (14.4 hours)[1] than digoxin (1.5 to 2 days[1]), therefore, a drug-drug interaction study with fexofenadine as P-gp substrate can be completed in a shorter time period.
3. Fexofenadine maybe a better probe for testing intestinal P-gp activity as renal elimination is limited. Digoxin is cleared predominantly (80%) by renal elimination, including both glomerular clearance and tubular secretion clearance[2,3]. Therefore, following oral administration of digoxin, a drug interaction that changes digoxin exposure may result from altered intestinal P-gp-mediated absorption and bioavailability, and/or altered renal tubular P-gp-mediated secretion. The changes in digoxin exposure cannot be attributed exclusively to the altered intestinal P-gp activity.

On page 12, lines 520-521:

Please also see comment for page 7, line 268. Recommend qualifying the highest dose/dosing frequency that is expected to be safe.

On page 13, line 544 – 547:

"The following measures and parameters of substrate PK should be obtained in every study: (1) exposure measures such as AUC, Cmax, time to Cmax (Tmax), and others as appropriate; and (2) pharmacokinetic parameters such as clearance, volumes of distribution, and half-lives."

We recommend that secondary parameters such as clearance, volumes of distribution, and half-lives be considered optional rather than mandatory for all studies. For example, in drug-drug interaction studies at steady state in a sequential design, it may not be possible to determine half-life for both treatments (primary endpoints Css, AUCtau, Tmax). Similarly, volume of distribution following oral dosing is a function of bioavailability and may not be as meaningful as in IV interaction studies. For a single dose interaction study testing a NCE with a long half-life, a compromise might be the determination of AUC(0-t) rather than AUC(0-inf) which would preclude clearance estimates. Please clarify.

General comment:
This guidance does not mention drug-drug interaction due to protein binding / protein displacement. Is this no longer considered a clinically relevant drug-drug interaction mechanism? We recommend briefly mentioning FDA's opinion with regard to its relevance.

Thank you for your consideration of these comments. Please do not hesitate to contact us should you have any questions.

Sincerely

Clinical Pharmacology, Quintiles Inc.

References:

1. Micromedix, http://csi.micromedex.com
2. Rengelshausen J, Göggelmann C, Burhenne J, et al. Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin-clarithromycin interaction. *Br J Clin Pharmacol*. 2003;56:32-38.
3. Jalawa KM, Partanen J,Neuvonen PJ. Itraconazole decreases renal clearance of digoxin. *Ther Drug Monit*. 1997;19:609-613.