

November 1, 2006

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

**Docket Number 2006D-0344**

**Re: Draft Guidance for Industry on Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling**

Eli Lilly and Company (Lilly) appreciates the opportunity to submit comments on the Draft Guidance for Industry on Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling. Overall, the guidance was found to be a relatively well written guidance. For the drug metabolizing enzyme sections the level of detail was viewed as correct. However, Lilly believes that the transporter part of the guidance was too prescriptive for an area that is still rapidly evolving. The concern is that the guidance provided will be viewed as the expected and only acceptable set of processes and procedures in a time when the techniques are constantly changing. The transporter sections should be edited to reflect the spirit of the enzyme sections. The detail in the transport section could be published separately as an FDA opinion. Lilly likes the organization of the guidance which includes both the in vivo clinical interactions sections and in vitro sections combined in a single well organized guidance. The flow of the document with reference to the enzyme sections was very understandable.

Lilly has identified several gaps and areas where further clarification is desired. These gaps include the following.

**Gaps:**

1. **Population Pharmacokinetic Studies** (starting on Line 223). The Sponsors would benefit from greater clarity around expectations of population analyses. Points for consideration include:
  - What is the level of significance acceptable to declare an interaction (eg. MOF change along with a prespecified CL/F change)?
  - Can population predictions of exposure changes be used to qualify inhibitors as weak, moderate or strong (as conventional DDI studies)?

- Can inhibitors or inducers be grouped by class categories in evaluating these interactions? What percentage representation/sample size of each drug or agent is necessary for acceptability of an interaction analysis?
  - Is more extensive, rather than sparse sampling expected for population based drug interaction evaluations?
  - Can data obtained in population pharmacokinetic studies be included in the label?
2. **In vivo studies** (Line 241 and Line 791): The in vitro guidance indicates pathways other than the P450s are also of interest yet the in vivo section of the guidance provides no examples of non-P450 interactions. Are there in vivo substrates, inducers and inhibitors of the UGTs and other non-P450 systems of interest or importance? Are there examples of when the Agency would expect these types of studies?
  3. **Study Population** (Line 318): The guidance recommends that for drugs exhibiting polymorphic metabolic pathways, phenotypic representation in studies evaluating the extent of interactions is valuable. However, further clarity around the study design expectations would be valuable: What sample size considerations if any, should be afforded to each of the phenotypic populations within the study? Should the study report separately present interactions amongst the phenotypes in addition to the main analysis across all subjects?
  4. **Fold Increase** (starting on Line 361): The document classifies inhibitors as strong, moderate or weak based upon the fold increase in the substrate AUC. Since fold increase has different meanings to different groups of scientists, the meaning in this guidance should be defined. To some scientists a 1-fold increase is a doubling, whereas to others this would mean no change. For example, a 5-fold increase can mean a 500% increase or a 600% increase; a 1.25-fold increase could mean a 125% increase or a 25% increase depending on the definition.
  5. **Use of Cocktails** (Line 387): Examples of acceptable cocktail combinations with dosing requirements would be beneficial to Sponsors. Could the data from a study using a cocktail and demonstrating negative results be included in the label?
  6. **Pharmacodynamic Endpoints** (Line 563): In general, the document provides limited guidance with respect to pharmacodynamic interactions. Furthermore, the "Pharmacodynamic endpoints" subsection implies that pharmacodynamic endpoints are to be considered secondary or supplemental to pharmacokinetic endpoints. Consideration should be given to include criteria whereby pharmacodynamic endpoints could be acceptable as the primary or sole endpoints.
  7. **Induction** (Line 1078): There is a major gap in the induction protocols in that the Constitutive Androstane Receptor (CAR) is not addressed. Leaders in the field such as Ron Evans, Masa Negishi, and Ed LeCluyse all have found ligands or responses unique to CAR binding (Mol Pharmacol 65:292-300, 2004; Mol Endo 18:1589-1598, 2004; JBC 279:29295-29301, 2004) versus the other two major

receptors PXR and AhR which are addressed in the guidance. It is strongly suggested that a CAR response be included. Phenobarbital and phenytoin are possible positive controls and bupropion or other selective CYP2B6 substrates are possible endpoints.

8. **Pgp** (Line 1192): There is significant concern regarding the detail of experimental design outlined in this section. It is not consistent with the other parts of the guidance where broad concepts are outlined. This is of concern because the maturity of the field is just the opposite as that of the P450s; there is not yet a consensus of the most appropriate methods to do transporter experiments. Thus the authors should significantly reduce the specific methodology and focus on concepts. Specific examples of clinical consequences of interactions with Pgp would be of benefit.
9. **Tissue Cultures** (Lines 1319-1329): This section is over prescriptive, as is section d and section f. If the model is working for control substrates, it is not necessary to follow the details outlined. Specifically, TEER is not a particularly useful measure and is highly variable. The use of a paracellular marker is also unnecessary if a control compound is used and within historical values.

Lilly has identified several specific areas that are of major concern.

**Specific Major Concerns:**

Line 245: **Consultation with the FDA** regarding study protocols is recommended, but what is the response time that the Agency is willing to commit to?

Line 277: The **description of steady-state evaluations** seems too rigid for most drugs which display stationary or linear pharmacokinetics. Is historical establishment of time to steady-state (i.e., not in drug-interaction study itself) acceptable to meet the assessment of steady-state achievement? Is graphical evaluation of trough trends sufficient to declare attainment of near steady-state conditions supplemented by estimations based on known half-life? In the event, that in-study trough evaluations suggest that steady-state criteria are not met contrary to the drug's known characteristics, would study results still satisfy label-qualifications?

Line 280: The document refers to **metabolites of interest**, active metabolites and major pathways in various places. What is meant by metabolites of interest? Does this mean an active metabolite? Does major metabolite always mean  $\geq 25\%$  of clearance pathways?

Line 351-356: This section refers to Tables 2, 3 and 4 for a list of **recommended and sensitive substrates** to use in studies. Are the substrates listed in Table 3 and 4 acceptable for obtaining label language or does the sponsor need to use the list in Table 2 as the recommended substrates? The substrates in Table 3 and 4 are different from those in previous guidances.

Line 452: In the section on **multiple inhibitor studies**, point 3 states that “the residual or non-inhibitable drug clearance is low”. The concern is how does the investigator know this in advance? If not all three of the conditions are met for conducting a multiple inhibitor study, will the sponsor still be expected to conduct an in vivo study to determine the “highest” concentrations that could be reached for the selection of dose in the QTc study or will computer simulations be sufficient?

Lines 484-488: To date there is no validated **probe for P-gp**. Digoxin is not specific for P-gp. Ritonavir is a poor choice for an inhibitor of P-gp. It should be replaced with quinidine. The utility of cyclosporine as a probe substrate should be reconsidered given its poor pharmacokinetic properties that would make sample sizing and pharmacokinetic analysis inherently difficult.

Lines 542-547 (**The Pharmacokinetic Endpoints**): For some drugs such as digoxin where their long half-life preclude a reasonable determination of half-life in study designs involving sampling durations of 24 hours, the need for provision of clearance, volume and half-life for all drugs seems unnecessary and not scientifically valid. Instead, the following alternate wording is offered for consideration:

“The following measures and parameters of substrate PK should be obtained in every study: exposure measures such as AUC, C<sub>max</sub>, time to C<sub>max</sub> (T<sub>max</sub>), and others as appropriate. Additionally pharmacokinetic parameters such as clearance, volumes of distribution, and half-lives may be reported if appropriate.”

Line 577 (**Sample size**): Systems with high variability such as drugs metabolized by CYP3A4 require either a large number of subjects or relaxed goal posts. The guidance should indicate this.

Line 688 (Table 2, **CYP3A4/5, inhibitors**): Remove Ritonavir as a CYP3A inhibitor as it is known to inhibit other P450s like CYP2D6 and transporters.

#### **Specific Comments/Concerns on Appendices:**

Line 688 and line 716 (**Tables 2 and 4**): The two tables need to be cross referenced to assure everything in Table 2 is also in Table 4. For example, tolbutamide.

Line 812: The authors need to consider **non-hepatic metabolism**. The models described represent only hepatic metabolic clearance. Many drugs are metabolized by enzymes found in intestine, lung, blood and/or kidney.

Line 964: In the section on **Correlation Analyses** the authors should address the use of multivariate correlation analyses to demonstrate the role of multiple enzymes.

Line 1035: To this paragraph a discussion of the role of the **fraction of the inhibited drug** metabolized by the enzyme inhibited should be discussed (see for example: Ito et al Drug Metab Dispos 33:837-844, 2005).

Line 1067 (**Mechanism-based inhibition section**): The use of 30 min would be good only as a screen. By experience, 30 min is usually excessive and not useful for detailed kinetic analyses. For example the leader in this field, Stephen Hall, used less than 5 min pre-incubation with the HIV protease inhibitors (JPET 312:583-591, 2005) in their detailed kinetic analyses.

Line 1112 and line 1134 (**Immortalized liver cells for induction**): This is a significant departure from accepted norms. Other than one major company, the available cell lines including a recently available immortalized hepatocyte line are not routinely used to replace primary hepatocytes. The Bjornsson et al PhRMA perspective paper (Drug Metabol Dispos 31:815-832, 2003) does not endorse the use of these cells. The mechanism of induction other than PXR has not been investigated and neither has the role of transporters. During the immortalization process there is reason to be concerned that transporters in particular are not expressed as they are in normal hepatocytes. There is great concern that these cells do not reflect for all compounds what would occur in hepatocytes. These immortalized cells at best should be listed as a screening tool not a definitive tool.

Line 1192: Add **ABCB1** to list of names. Technically the protein should be referred to as ABCB1 and not P-gp or MDR1 throughout the document.

Line 1201: The phrase "**can result**" should be changed to "may result". The current language is strong considering that there is no state of the art in the field of transporter DDI's. To date there is very little clinical understanding of the implications and the probes are not even close to ideal.

Line 1221 (**Table 1**): The table is fairly confusing and adds little value. The statement: "Tends to fail to identify substrate and/or inhibitor with low permeability" should also be added to the assay type of Bi-Directional Transport. (i.e. Fexofenadine is not identified in MDCK assays as a P-gp substrate since its uptake transporter is not present).

Line 1221 (**Table 1**): A fourth assay type should be added: In-side out vesicles; The Tissues: Cell line over-expressing ABCB1; Parameters: Uptake into the vesicles; Comments: 1. Requires a radiolabel or highly sensitive analytical assay 2. Direct measure.

Lines 1224-1226: Should read "**Transport assays** (bidirectional and vesicle assays) are regarded as the definitive assays for identifying P-gp substrates and inhibitors since they measure the transport activity in a more direct manner."

Lines 1235: Add the bolded phrase as follows: "the transcellular transport **or vesicles assays** should be used..."

Line 1246: There is not a **known probe** that is selective for Pgp. Therefore this should not be stated so firmly.

Line 1247: This **criterion** is unnecessary and adds no value. The permeability values are going to vary depending on the system. If the system has been tested for activity with know substrates that will be sufficient.

Line 1285: “**Most P-gp substrates** with high affinity are also potent competitive inhibitors.” This is not true for digoxin or vinblastine.

Lines 1292-1294: If a **specific inhibitor of P-gp** is used, it is not necessary to look at multiple inhibitors or if elacridar (GF120918) and ABCG2 is not present in the cells then the use of a single inhibitor should suffice.

Line 1316: **CaCo-2** is not a preferred cell line for many reasons. The cells are highly variable from lab to lab and even over time in the same laboratory. They also express a vast array of transporters and it is difficult to interpret the data. They are a secondary choice if the lab does not have an over expressing cell line available.

Lines 1316-1317: The use of **wild type cells** as a control is not necessary and may confound data interpretation. Upon over expression of ABCB1 other transporters are also up and down regulated. The over expression of ABCB1 is also know to alter membrane composition and may alter the permeability of certain compounds. It is better to use the over-expressing cell line with inhibitor present as the control.

Lines 1319-1329 (**Tissue Culture**): This section is over prescriptive (as is section d and section f). If the model is working for control substrates it is not necessary to follow the details outlined. Specifically, TEER is not a particularly useful measure and is highly variable. The use of a paracellular marker is also unnecessary if a control compound is used and within historical values.

Lines 1338-1339 (**Bi-directional Experiments**): A **concentration range** is not necessary. If a compound is not a substrate at low concentration then the work is unnecessary at higher concentrations.

Lines 1340 (**Bi-directional Experiments**): Why **preincubate** for 30 min as 15 could suffice. Should read for “approximately” or for the “appropriate amount of time”.

Lines 1347-1350 (**Bi-directional Experiments**): The **time points** should not be listed. Time points used are normally much shorter that those listed. It should read that the permeability should be measured under initial rate kinetics. Also many labs do not use aliquots but actually remove the total volume from the receiver chamber to maintain sink conditions. The key is the maintenance of sink condition.

Lines 1352-1353 and page 44 lines 1365-1367 and lines 1393-1396, page 45 lines 1409-10: See discussion above for page 43, lines 1316-1317.

Line 1398 section f (**Bi-directional Experiments**): It should be pointed out here, as it is later in the document, that the **substrate concentration** should be at or below its Km.

Lines 1412-14 (Bi-directional Experiments): The inhibitor should also be present when the substrate is present.

Lines 1415-1416 (Bi-directional Experiments): The time course used is going to be dependent on the system and the probes. A specific time should not be outlined.

Line 1431 (Calculation): The word "effect" should be deleted.

Lines 1438-1440 (Substrate for P-gp): There is not yet significant clinical data to set the minimum flux ratio at 2. This ratio may also vary from system to system and lab to lab and should be measured with relevant probes in the system being used. However, to date there is not yet clinical data to pick what would be a poorly interacting substrate and a strong substrate.

Lines 1457-1459 (Substrate for P-gp): Please add examples of the types of data you are talking about

Lines 1462-1464 (Substrate for P-gp): This statement is not appropriate in this section. Even if other transporters were found to be involved in vitro there are not yet probes to study the interaction in vivo and confirm the in vitro data.

Lines 1491-1492 (Decision Tree): There should be clarification on the percent value reduction. Is there any clinical justification of this value?

Lines 1500-1501 (Criteria): Net flux ratios vary from lab to lab and from day to day. This is why appropriate controls should be run in all experiments.

Line 1502 (Criteria): If a specific potent inhibitor is used then it is not necessary to use 2 to 3 inhibitors.

Lines 1520-1525 (Criteria): Need to clarify that [I] is the steady state  $C_{max}$ .

Lines 1581-1582 (Evaluation): Is the clinical significance of P-gp induction known at this time? It is not yet appropriate to request a P-gp induction study for all 3A inducers

**Specific Minor Concerns:**

Line 53: Use "and/or" instead of "or".

Line 193: Add ABCB1 to list.

Line 452: Should be qualified for multiple CYP enzymes contribute significantly to the CL of the drug.

Line 523: For "multiple days" – please provide guidance on minimal timeframe.

Line 579: Should read: whether there is any **significant** increase or...

Line 679 (Table 1): Repeat the header on continuous pages.

Line 767: In the phrase “negative results from a” add appropriately powered.

Line 799: Expectation of non-P450 pathways should be discussed.

Line 897: The word “hydroxylase” is misspelled.

Line 1083: To “increased formation of an active” add “or toxic”.

Line 1379: Delete the extra “is the”.

Again Lilly very much appreciates the opportunity to comment on this draft guidance.

Sincerely,

ELI LILLY AND COMPANY

A handwritten signature in cursive script that reads "Mary Pat Knadler".

Mary Pat Knadler, PhD.  
Drug Disposition Regulatory Expert  
U.S. Regulatory Affairs