

December 1, 2006

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

To Whom It May Concern:

Absorption Systems LP, a preclinical ADME CRO located in Exton, PA, would like to submit the following comments and questions to the FDA regarding the Draft Guidance for Industry on Drug Interaction Studies, dated September 2006. Please keep in mind that these comments and questions come from the perspective of a contract research organization that is actively involved in the preclinical studies covered by this particular guidance.

Our approach to preclinical studies is, first, to validate a system extensively prior to using it to perform contract studies, as we have done with the Caco-2 cell monolayer model for BCS studies. We are in the process of validating MDR1-transfected MDCK cells in a similar way, for use in identifying and characterizing P-gp substrates and inhibitors. We propose to perform certain of the recommended studies as part of the validation study rather than performing them as part of every study with an unknown test compound. With that in mind, please consider the following:

- We understand the reason for including non-transfected MDCK cells as a control when testing for P-gp substrates, to rule out false positives that might be substrates of canine but not human P-gp (Appendix D.2.[d][6]), but why would we need to include non-transfected cells as a control when testing for P-gp inhibitors (Appendix D.2.[f][2])?
  - If we have already characterized the efflux ratio of a probe substrate in both transfected and non-transfected cells, is it necessary to include non-transfected cells as an arm in every P-gp inhibitor test? Or can we refer to a validation study as evidence that the vast majority of the P-gp protein and/or functional activity is due to the human protein, so that a test compound that reduces the efflux ratio of a probe substrate by at least 50% must be acting primarily or solely on the human protein?
  - We propose to compare the effects of a series of P-gp inhibitors in MDR1-transfected MDCK cells and non-transfected MDCK cells in a validation study but not in every study with an unknown test compound. Is that acceptable?
  - For P-gp inhibitor studies, we propose to report the efflux ratio of the probe substrate(s) in transfected and non-transfected cells (from the validation study), then do the inhibitor test in transfected cells only. Is that acceptable?

2006D-0344

C 11

- 
- The draft guidance recommends that P-gp substrate and inhibitor tests should be performed at least in triplicate on different days (Appendix D.2.[d][7] and Appendix D.2.[f][5]). We propose to test inter-day variability in a validation study only, not on an ongoing basis. If the results of our validation study demonstrate that there is no significant difference between tests performed on different days, is that sufficient to preclude the need to repeat every test with an unknown test compound on different days?

In addition to the validation-related concerns (above), we have a few other questions and comments, as follows.

- In Appendix D.2.[b], the draft guidance recommends using three proprietary compounds that are not commercially available: elacridar (GSK compound GF120918), valspodar (Novartis compound PSC833) and zosuquidar (Kanisa compound LY335979). We would very much like to use these compounds as reference inhibitors in the validation of the P-gp inhibitor assay. However, we have contacted each of the companies involved and received a polite refusal in two cases (GSK and Kanisa) and no answer in the third case (Novartis).
  - We propose that the FDA either deletes the recommendation to use these compounds from the final guidance or provides an incentive to the owners of the compounds to make them available for the recommended use.
- If we know the mean steady-state  $C_{max}$  in humans at the highest proposed clinical dose of a test compound, for the initial P-gp inhibitor assessment is it acceptable to test a 10-fold higher concentration and if inhibition is less than 50% call it negative? The rationale is that the trigger for further clinical study is  $[I]/IC_{50}$  (or  $[I]/K_i$ )  $>0.1$  (Appendix D.4.).
  - For a drug with a low  $C_{max}$ , the test concentration calculated in this way might be much lower than the initial test concentration suggested in Appendix D.4. of the draft guidance (" $>100$  uM or as high as solubility of the compound allows").
  - The criterion based on the mean steady-state  $C_{max}$  is reasonable for considering drug-drug interactions at the blood-brain barrier or hepatocyte canalicular membrane, but is irrelevant to interactions in the intestinal lumen. To address the latter situation, we propose an initial test concentration of the highest human clinical dose (if known) divided by 250 mL (as per the BCS Guidance).
  - The question remains: Which potential site of P-gp-mediated drug-drug interactions is the FDA concerned about, or should the FDA be concerned about in terms of an initial test concentration and a trigger for further study...the blood-brain barrier or the intestinal lumen?
- Given the fact that no pure P-gp inhibitors have been reported, why is the use of "at least two to three potent inhibitors" recommended to confirm that a test compound is a P-gp substrate? Pharmacologically, we don't understand the rationale that inhibition of efflux by several marginally selective inhibitors (vs. a single inhibitor) makes it more likely that the efflux activity is related to P-gp (Appendix D.2.[d][8]).
  - In the assessment of P-gp substrates, we propose using a single concentration (10  $\mu$ M) of two inhibitors, one that inhibits efflux of a known P-gp substrate by 100% and one that inhibits efflux of a known P-gp substrate by 50% to 80%, to confirm that the observed efflux of a test compound is mediated by P-gp. We

December 1, 2006

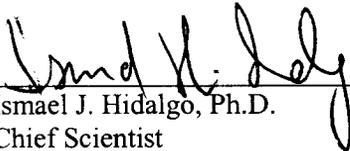
---

propose using the same inhibitors in the same manner as positive controls in the assessment of P-gp inhibitors. Is that acceptable?

- An inhibitor could be weak without being selective for another efflux transporter. So, I would suggest the use of a strong and a weak inhibitor without invoking the possible interaction of the weaker inhibitor with other transporters. Is that acceptable?

Regards,

ABSORPTION SYSTEMS LP  
By: ABSORPTION SYSTEMS GROUP LLC  
Its General Partner

  
\_\_\_\_\_  
Ismael J. Hidalgo, Ph.D.  
Chief Scientist

DCB:jlr