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December 26, 2006

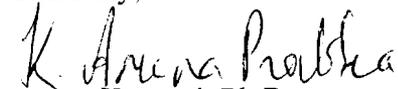
To:
The Division of Dockets Management (HFA-305)
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852

Reference: [Docket No. 2006D-0344] Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling, Draft Guidance September 2006.

Dear Sir/Madam,

This letter is to request clarification of some study designs and procedures recommended in the draft guidance referenced above. Our questions pertaining to Appendix D of the guidance ‘In Vitro Evaluation of P-glycoprotein (P-gp, MDR1) Substrates and Inhibitors’ are attached. We greatly appreciate your help in providing us with FDA’s feedback on these questions.

Sincerely,


Aruna Koganti, Ph.D
Senior Study Director
Contract Operations
In Vitro Technologies

2006D-0344

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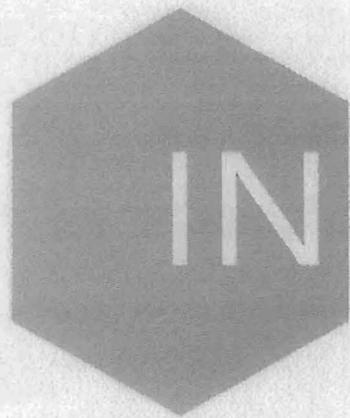
Questions Regarding Appendix D

Question 1: We use a Caco-2 cell culture system for in vitro evaluation of P-gp substrates and inhibitors. It meets most of the tissue culture considerations described in Appendix D, Line 1312, Section 2 (c), 'Tissue culture considerations to ensure functionally polarized cells', with the exception that the cells are not cultured for 18 – 21 days. We use a differentiation agent to shorten the time of culturing. The TEER values in this system may be higher than the range specified in this section (100-800 Ω cm²). However, the permeability of a group of compounds were tested to show that the rank ordering of absorption in these cultures is similar to that described in the literature for 18 – 21 day cultures. We have also demonstrated the presence of P-gp and established that the cultures are functionally polarized. ***Please confirm that the data generated from this system will be accepted by the FDA for the evaluation of P-gp substrates and inhibitors.***

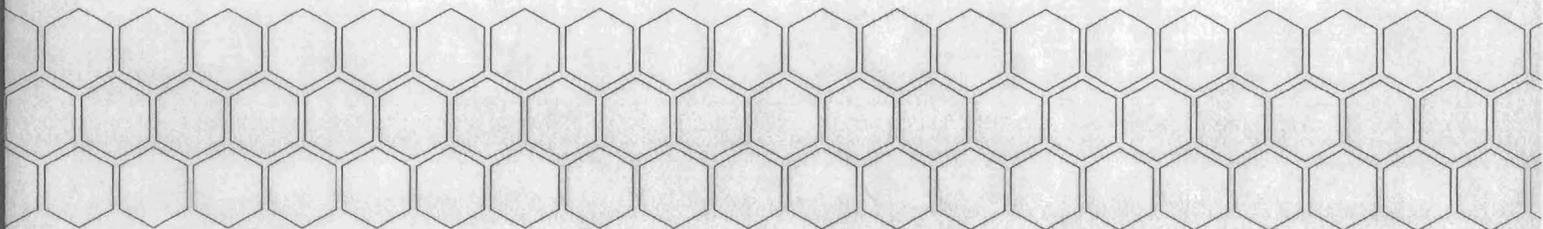
Question 2: The number of potent P-gp inhibitors recommended in evaluating the test drug as a substrate seemed inconsistent throughout the document. For example, Appendix D, Line 1363, Section 2 (d), 'Design of bi-directional experiments conducted to determine whether the drug is a P-gp substrate, states 'at least 2-3 potent P-gp inhibitors'; Appendix D, Line 1450, Section 3, 'Criteria for Determining Whether a Test Drug is a Substrate for P-gp, and Whether an In Vivo Interaction Study is Needed', states 'inhibition studies with one or more potent P-gp inhibitors are needed'; Appendix D, Line 1476, Section 3, Figure 1, states 'Is efflux significantly inhibited by 1 or more potent P-gp inhibitors?'. ***Please confirm that the data generated using one potent P-gp inhibitor will be accepted by the FDA as sufficient for the evaluation of test drugs as Pgp substrates.***

Question 3: In evaluating the test drug as an inhibitor, we generally test the permeability of a known substrate in the absence and the presence of the test drug (as an inhibitor at multiple concentrations). In our experiments, both the substrate and the test drug are present at the same time during the incubation to allow for competitive inhibition by the test drug. However, the language in the draft guidance, Appendix D, Line 1398, Section 2 (e), 'Design of bi-directional experiments conducted to determine whether the drug is a P-gp inhibitor', indicates that in step (1) (Line 1406), the test drug (as an inhibitor) is applied to the cultures and is incubated with the cultures for 0.5 – 1 hour (step (3); Line 1412). Following this the test drug is removed and replaced with medium containing the probe P-gp substrate alone in the donor chamber and incubated for an additional 1-3 hours. Could you please explain why this procedure is recommended? Our concern is that even though, the test drug is still present in the receiving chamber, the concentration of the test drug will change during the incubation if it is also not replenished in the donor chamber. ***Please confirm that the data generated will be accepted by the FDA for the evaluation of test drugs as P-gp inhibitor, if the donor chamber is replenished with both the probe substrate and the test drug at the appropriate concentration in step (3).***

Question 4: The guidance recommends that the experiments evaluating the test drug as a substrate and as an inhibitor should be repeated on different days to evaluate inter-day variability (Appendix D, Section 2 (d); Line 1354 and Section 2 (f), Line 1417). The time and cost involved are generally not palatable to most of our sponsors. *Would it be acceptable to the FDA if just the controls were repeated on multiple days and are shown to be consistent from day to day.*



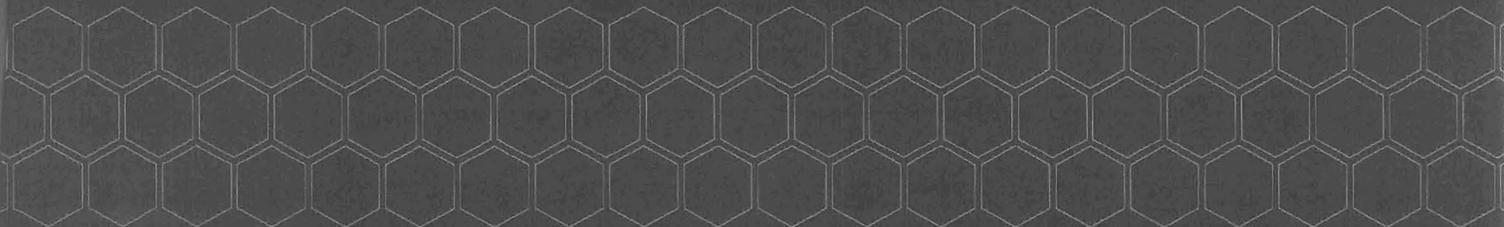
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