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Nov. 9, 2006

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

Re: Docket No. 2006D-0344, CDER 20051

Dear Sir/Madam:

We would like to submit comments to the draft guidance document entitled: Guidance for Industry on Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling.

The guidelines contain parameters to determine a properly functioning PGP-containing cell model system. We believe these should be the primary determinants in the guidance - as opposed to type of membrane used to culture the cells. For example, PC and PET are functional equivalents and there are several references in the literature to support this (see references below). However, the guidance indicates PC membranes are preferred.

Allowing multiple sources of membranes assures a more stable supply (e.g., the sole source high quality polycarbonate film which was the basis for the TC membranes was discontinued).

As this is in the interest of all parties we respectfully suggest the guidance be modified to reflect acceptance of PET membranes.

Kind regards,

Charles L Crespi, Ph.D.
David Stresser, Ph.D.
Marshall Kosovsky, Ph.D.

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References using PET membranes:

1. Lau, Y., et al. Evaluation of a Novel In Vitro Caco-2 Hepatocyte Hybrid System For Predicting In Vivo Oral Bioavailability. Drug Metab. Dispos. 32: 937 (2004).
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3. Paine, M., et al. Identification of a Novel Route of Extraction of Sirolimus in Human Small Intestine: Roles of Metabolism and Secretion. J. Pharmacol. Exp. Ther. 301:174 (2002).

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5. Furfine, E., et al. Preclinical Pharmacology and Pharmacokinetics of GW433908, a Water-Soluble Prodrug of the Human Immunodeficiency Virus Protease Inhibitor Amprenavir. *Antimicrob. Agents Chemother.* 48:791 (2004).
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7. Sasabe, H., et al. Differential Involvement of Multidrug Resistance-Associated Protein 1 and P-Glycoprotein in Tissue Distribution and Excretion of Grepafloxacin in Mice. *J. Pharmacol. Exp. Ther.* 310:648 (2004).
8. Letschert, K., et al. Vectorial Transport of the Peptide CCK-8 by Double-Transfected MDCKII Cells Stably Expressing the Organic Anion Transporter OATP1B3 (OATP8) and the Export Pump ABCC2. *J. Pharmacol. Exp. Ther.* 313:549 (2005).

References using PET or PC membranes:

1. Rösmann, S., et al. Activation of Human Meprin- in a Cell Culture Model of Colorectal Cancer Is Triggered by the Plasminogen-activating System. *J. Biol. Chem.* 277:40650 (2002).
2. Rothen-Rutishauser, B., et al. Formation of Multilayers in the Caco-2 Cell Culture Model: A Confocal Laser Scanning Microscopy Study. *Pharm. Res.* 17:460 (2000).
3. Yamashita, S., et al. New and Better Protocols for a Short-term Caco-2 Cell Culture System. *J. Pharm. Sci.* 91:669 (2002).
4. Schmiedlin-Ren, P., et al. Expression of Enzymatically Active CYP3A4 by Caco-2 Cells Grown on Extracellular Matrix-Coated Permeable Supports in the Presence of 1,25-Dihydroxyvitamin D₃. *Mol. Pharm.* 51:741 (1997).
5. Sergent-Engelen, T., et al. Improved cultivation of polarized animal cells on culture inserts with new transparent polyethylene terephthalate or polycarbonate microporous membranes. *J. Bio.Tech.* 4:89 (1990).