Feedback on FDA Guidance for Industry: DDI Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling

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Focus: Drug Transporter Issues

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Major Comments:

Page 17 (line 679, Table 1):
ABCB1 inhibitors are listed, but not all of these are commercially available. For example, GF120918, LY335979, and PSC833 must be provided per request or synthesized internally. With this consideration, is it reasonable to suggest using these compounds?

Page 43 (lines 1356):
I would suggest adding a statement suggesting that the amount of compound (analyte) depleted from the donor compartment at each time point over the course of the transport experiment be calculated. It has been shown that, in order to ensure sink conditions and lack of "back-transport" of the compound from the receiver compartment to the donor compartment, this value should be calculated prior to interpretation of the data. A good practice, especially for compounds that are highly permeable, is to determine the slope of the amount transported only up to the point where >80% of the amount of compound added to the donor compartment still remains in the donor compartment. In this way, back-transport (and lack of linearity) of the compound is minimized due to maintenance of sink conditions. This may require taking more early time points (under 1 hr) if the experiment is designed to continue for 2-4 hours, just in case the later time points need to be ignored due to lack of sink conditions.

The comment above is also applicable for the statement made on page 44, lines 1382-1383, i.e. where it is stated that "flux through the monolayer must be linear with time."

Page 47 (line 1488-1491):
A concern is stated that flux ratios ≥ 2 may represent a "...value that is too liberal and will lead to too may positive results." Is this a consensus opinion amongst PhRMA members? In my opinion, this flow chart describing how to evaluate compounds as substrates for P-gp is quite reasonable.

Page 48 (lines 1520-1522):
Does [I] refer to plasma concentration or concentration of drug in the GI tract? Is there any concern amongst PhRMA members that, especially with respect to potential interactions with P-gp in the GI tract, this should be better defined? Additionally, it appears as though IC50 and Ki are being treated equally.....I think it may be quite difficult to generate Ki values and IC50 values would be more appropriate.

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The estimate of potential P-gp inhibition may be the most contentious issue in this document. What I would consider to be open questions are the following:

- How relevant is the [I]/Ki relationship, established for CYP450 inhibition, to transporter interactions? This area is not as well defined for transporters (even P-gp) as it is for the CYP450s.

- In the previous version of this document, there was a cutoff IC50 value of <10 μM for classification of a compound as an inhibitor of P-gp. While it could be argued that this is an arbitrary value, is an [I]/IC50 (or Ki) > 0.1 any less arbitrary, considering the statement in the first bullet point?

Minor Comments:

Page 4 (lines 131 to 141):
Generally OK, but I would recommend adding a statement emphasizing the lack of specific probe substrates for the transporters mentioned in this paragraph. Admittedly this is described later in the document, but it could be considered key background information.

Page 12 (line 488):
Ritonavir has been shown to interact with multiple transporters, primarily as an inhibitor. It may be more appropriate to suggest using a more specific inhibitor of P-gp and CYP3A in this paragraph, e.g. ketoconazole.

Page 39 (line 1222, Table 1):
In the "Tissues" column, "oocytes injected with cRNA for transporters" is listed. This heterologous expression system has the additional disadvantage of expression of transporters on a membrane type (frog egg) that is markedly different from epithelial and endothelial cells that typically express transporters endogenously. Thus, it would be a good idea to list this in the Comments section.

Page 39 (lines 1247):
Moderate passive permeability is defined as 2-30 x 10^{-6} cm/sec. From my perspective, if a compound exhibits absorptive permeability above 20 x 10^{-6} cm/sec, this is quite high.

Page 40 (line 1260, Table 2):
I would suggest listing paclitaxel (Taxol) as an acceptable P-gp substrate for use in these types of studies. Paclitaxel is a very good P-gp substrate, is available commercially, binds to a specific site on P-gp, and is only known to be metabolized by CYP2C8.

Page 41 (lines 1293):
Due to lack of inhibitor specificity, it is suggested that "the use of multiple inhibitors" be employed. It may be a good idea to clarify that this type of study would be most

successful if the various inhibitors were used either it separate experiments, or separately and then also in a "cocktail" format in order to get the most useful information.

Page 43 (line 1335-1336):
This line should read "...using polycarbonate filter inserts or side-side diffusion chambers...."

Page 45 (lines 1409-1411):
It should be noted somewhere that MDCK-WT cells express canine P-gp, and this must be considered carefully when comparing transport data using MDCK-MDR1 and MDCK-WT cell lines. Studies have shown that canine P-gp demonstrates some substrate overlap with human P-gp (example: vinblastine).