



sanofi aventis

Because health matters

Date 10-November-2006

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Via fax and UPS

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

Re: Docket No. 2006D-0344

Draft Guidance for Industry on Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling

Dear Sir/Madam:

Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, appreciate the opportunity to comment on the above-referenced draft guidance, “**Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling Unique Device Identification.**”

This intent of the guidance was to provide recommendations to sponsors of NDAs and BLAs for therapeutic biologics on carrying out in vitro or in vivo drug-drug interaction studies.

Comments:

In general, the reference documents must be clearly noted in the draft guidance.

In vivo drug interaction studies

- General

There is no mention of the use of urinary 6-hydroxycortisol to cortisol ratios to assess CYP3A induction. Consideration should be taken to include it in the guidance.

- Page 21 Appendix A Table 4

For in vivo studies, metoprolol and bupropion are considered sensitive substrates for CYP2D6 and CYP2B6, respectively, yet they are not included in the guidance or updated table. Also absent is Efavirenz, although mentioned for CYP2B6, which is reported to be an inducer, but also an inhibitor of CYP2C9, 2C19 and 3A4.

2006D-0344

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[Redacted]

- Page 22 Appendix A Table 5

Ritonavir is included in the table as a strong CYP3A inhibitor; can it be used as a test inhibitor in clinical studies with volunteers? After repeated administration, ritonavir is also reported to be a CYP inducer, which may interfere with interpretation of results. Perhaps ketoconazole (PgP and CYP3A substrate and inhibitor but not inducer) would be a more acceptable inhibitor?

- Page 22 Appendix A Table 5:

Could Atorvastatin also be considered a weak CYP3A inhibitor for clinical interaction studies?

In vitro drug interaction studies

- Page 5 Lines 199 – 200: “*Drug interactions based on CYP2B6 are emerging as important interactions. When appropriate, in vitro evaluations based on this enzyme can be conducted.*”

Can the FDA comment on when it is “appropriate” to conduct in vitro evaluations of CYP2B6. Which evaluations should be considered (e.g., inhibition, reaction phenotyping, etc)?

- Page 26 Line 844

Add as a footnote to Table 1 that 1-aminobenzotriazole is a mechanism-based inhibitor and should be pre-incubated before adding substrate (NME).

- Page 28 Table 2 (chemical inhibitors), Page 32 Table 3 (chemical substrates) and Page 35 table 5 (chemical inducers):

The tables listed above indicate that the concentrations (or ranges of concentrations) for K_m , K_i and control inducers are suggestions only, or are representative, non-exhaustive compilations from the literature. The concern is that these concentrations could be assumed to be required when conducting experiments. This point should be clarified.

- Page 32 Line 1003, “*Typical experiments for determining IC_{50} values involve incubating the substrate, if the metabolic rate is sufficient, at concentrations below its K_m to more closely relate the inhibitor IC_{50} to its K_i .*”

Sentence should read “... concentrations **at or below** its K_m ...”

- Page 33 Line 1021, “*Any solvents should be used at low concentrations (< 1% (v/v) and preferably < 0.1%). Some of the solvents inhibit or induce enzymes. The experiment can include a no solvent control and a solvent control.*”

A statement should be added regarding solvents less restrictive, e.g., “Attempts should be made to use solvents at concentrations < 1% (v/v) or preferably, 0.1%.” At times, very insoluble compounds may require more solvent and the guidance should allow that, if appropriate controls are used.

- Page 33 Line 1022, “*Any solvents should be used at low concentrations (< 1% (v/v) and preferably < 0.1%). Some of the solvents inhibit **or induce** enzymes. The experiment can include a no solvent control and a solvent control.*”

Remove “or induce” from the second sentence. Induction is not an issue in microsomes.

- Page 33 Line 1025, “ *Use of an active control (known inhibitor) is optional.*”

The use of an active control is appropriate for all experiments.

- Page 34 Lines 1065 – 1074, “*Time-dependent inhibition should be examined in standard in vitro screening protocols, because the phenomenon cannot be predicted with complete confidence from chemical structure. A 30-minute pre-incubation of a potential inhibitor before the addition of substrate is recommended. Any time-dependent and concentration-dependent loss of initial product formation rate indicates mechanism-based inhibition. For compounds containing amines, metabolic intermediate complex formation can be followed spectroscopically. Detection of time-dependent inhibition kinetics in vitro indicates follow-up with in vivo studies in humans.*”

The mechanism-based inhibitor section is not well developed. Additional content may help better explain this section.

- Page 34 Line 1071, “*Any time-dependent and concentration-dependent loss of initial product formation rate indicates mechanism-based inhibition.*”

Inhibition observed with pre-incubation may not always be due to mechanism-based inhibition. Inhibition as described in the guidance could also be due to generation of a metabolite with inhibitory properties. This should be clarified.

- Page 34 Line 1072-1074, “*For compounds containing amines, metabolic intermediate complex formation can be followed spectroscopically. **Detection of time-dependent inhibition kinetics in vitro** indicates follow-up with in vivo studies in humans.*”

Could the Agency further define “Detection of time-dependent inhibition kinetics in vitro;” As written, it may lead to unnecessary in vivo studies.

- Page 35 Line 1080, “*A drug that induces a drug-metabolizing enzyme can increase the rate of metabolic clearance of a co-administered drug that is a substrate of the induced pathway.*”

To clarify the sentence it should be changed to read “...can increase its metabolic clearance (autoinduction) or of a co-administered drug...” (modification to include autoinduction).

- Page 35 Line 1084, “*Alternatively, the induced metabolic pathway could lead to increased formation of an active compound, resulting in an adverse event.*”

To clarify the sentence it should read, “...of an active compound or toxic metabolite, resulting...” (modification to include toxic metabolites)

- Page 37 Lines 1152-1155, “*Based on our present knowledge of cellular mechanisms leading to CYP enzyme induction, if induction studies with a test drug confirm that it is not an inducer of CYP3A4 then it can be concluded that the test drug is also not an inducer of CYP2C8, CYP2C9, or CYP2C19.*”

More direction should be given regarding evaluation of in vitro induction data. If CYP3A4 induction were observed in vitro, would the FDA require in vitro data to be generated for CYP2C8, CYP2C9 or CYP2C19 induction? If in vitro and in vivo data suggests CYP3A4 induction, would the CYP2C enzymes need to be investigated in vivo if in vitro data was not available?

- Page 37 Lines 1159-1161, “*Although the most reliable method for quantifying a drug’s induction potential is measurement of enzyme activities after incubation of the drug in primary cultures of human hepatocytes, other methods are being evaluated.*”

Does the Agency agree that enzyme activities are used for the definitive assessment of CYP induction or that (modest) increases in mRNA or enzyme protein would not be interpreted as a relevant induction signal?

Transporters

- General

The transporter section (Appendix D) is much too detailed and should be made more general, as the Agency did for the CYP in vitro sections. Concern is that this will limit the ability and flexibility of individual labs to conduct experiments respective to individual issues. This is particularly true in the transporter area, which is still developing. Examples include Tables 2 and 3, with limited concentrations provided and lines 1319-1329 (Caco-2 cells should be seeded at a density of approximately $0.5-5 \times 10^5$ cells/cm² on polycarbonate microporous membrane filters and allowed to grow to confluence (typically 18-21 days); page 43 lines 1338-1357 and lines page 45 1406-1418.

Suggest the importance of characterizing the transporter cell systems within each lab with regard to reference substrates and inhibitors, for interpretation of results with test compounds. This is due to variation in the expression level of P-gp in cell systems between laboratories and thus both ratios and appropriate substrate and inhibitor concentrations can vary. The guidance might give minimum criteria for a valid cell system, for example, a digoxin ratio larger than 4 without giving an upper limit.

The wording "Net drug flux ratio" throughout the document might be misleading. The Agency may want to substitute "drug transport ratio" giving an explanation of the definition (ratio of B to A and A to B drug transport).

- Page 41 Line 1293, "*Because of the lack of inhibitor specificity, the use of multiple inhibitors is recommended to determine whether the efflux activity observed in vitro is related to P-gp.*"

Can the Agency suggest a mixture of inhibitors that would allow differentiation between transporters? What does the Agency consider to be "multiple inhibitors" (more than one)?

- Page 43 Lines 1326-1329, "*The transepithelial electrical resistance (TEER) of the polarized cells should be determined before each experiment (typical values are 100-800 Ω cm²). (4) A paracellular marker such as [¹⁴C] mannitol can be used as an additional integrity marker (typical permeability values are $< 0.2-2 \times 10^{-6}$ cm/sec).*"

Suggest that TEER *or* markers such as mannitol can be used.

- Page 43 Line 1354, "*Each experiment should be performed at least in triplicate on different days to allow for assessment of intra- and inter-day variations.*"

Disagree with the need to conduct experiments on different days. Between days variability is generally not a problem in our labs and can be controlled by use of a known Pgp substrate as a positive control.

- Page 43 Table 3 In Vitro Pgp Inhibitors

The IC₅₀ values given in this table seem to derive from one publication by Choo EF et al (2000) and are not calculated by the P_{app} Ratio R_{Ei}/R_{Ea} but from the net drug transport calculated by B>A minus A>B transport in presence and absence of inhibitor. The latter calculation is the preferred method in the literature to date (see also recommendation on Line 1425).

Are the inhibitors LY335979, GF120913 and PSC833 available and legal for use by other pharmaceutical companies?

- Page 45 Line 1425, “ $(R_{Ei}/R_{Ea}) = 1 - [(I_{max} * I_c) / (I_c + IC_{50c})]$ ”

The majority of publications refer to an IC₅₀ calculation based on the net transport (B>A minus A>B) or B>A transport (efflux) only and not on the ratio (B>A/A>B). We strongly support using the net transport calculation and that probe inhibitors and test compounds be evaluated by the same calculation method in order to interpret the data and compare with literature data.

- Page 46 Line 1449, “*A net flux ratio over 2 is considered a positive result. To further confirm whether the efflux activity observed is due to Pgp, inhibition studies with one or more potent Pgp inhibitors are needed.*”

A threshold of 2 is considered too conservative, and will result in conducting an excessive number of clinical trials. Suggested to set the threshold as a percent of verified/validated control substrate transport (e.g., 25% of control?).

- Page 47 Line 1502, “*The probe substrate concentration used should be below its apparent Km for Pgp.*”

If the cell system was validated using a number of standardized inhibitors, it is considered sufficient to include only one positive control inhibitor at one concentration in routine experiments.

- Page 49 Line 1542 Figure 1

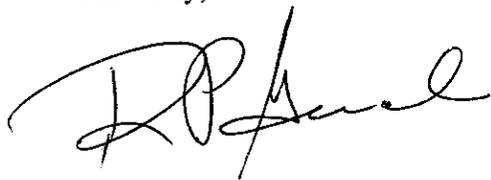
We are in agreement that no DDI study is necessary if I/IC₅₀ < 0.1. However, I/IC₅₀ > 0.1 is too conservative as a threshold for a digoxin interaction study. Suggest that IC₅₀ of test compound ≤ IC₅₀ of standard inhibitor (e.g., verapamil, IC₅₀ ~ 10-30 μM) be used as a threshold for conduct of a clinical study. In addition, should inhibition of absorption be of concern? Should “I” value calculated as dose/250 mL be evaluated, or is I total C_{max} plasma concentration for potential renal interaction?

• Examples of inconsistencies with substrate/inhibitor panels in Appendix A, table 1:

- ABCB1: loperamide and vinblastine should at least be added as drug substrates.
- ABCB11: pravastatin could be added to the list as substrate and vinblastine, statins & Bosentan are inhibitors.
- SLC22A11: OAT4 should be added as renal transporter.
- ABCC2: benzbromarone should be added as inhibitor.
- ABCG2: cyclosporine, Ko134, Ko143 and fumitremorgin C should at least be added to the list of inhibitors.
- SLCO1B3: rifampin is inhibitor
- SLCO2B1: rifamycin is inhibitor
- SLC10A1: cyclosporine is inhibitor
- SLC22A1: amantadine and desipramine are inhibitors not substrates; metformin is primarily substrate of
- OCT2 and not OCT1. Cimetidine should be added as inhibitor.
- SLC22A2: metformin should be added as substrate. Cimetidine should be added as inhibitor.
- SLC22A4: pyrilamine should be added as substrate.

On behalf of Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, we appreciate the opportunity to comment on the *Draft Guidance for Industry on Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling*.

Sincerely,



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Regulatory Development