Nov 1, 2006

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

[Docket No. 2006D–0344]

Re: Comments to the Draft Guidance for Industry: Drug Interaction Studies- Study Design, Data Analysis, and Implications for Dosing and Labeling

Dear Sir/Madam:

The following comments on the draft guidance are submitted on behalf of Novartis pharmaceuticals. Novartis Pharmaceuticals corporation is an affiliate of Novartis AG (NYSE: NVS), a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group companies employ more than 78,000 people and operate in over 140 countries around the world.

Novartis Pharmaceuticals corporation researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

The publication: "**Draft Guidance for Industry: Drug Interaction Studies- Study Design, Data Analysis, and Implications for Dosing and Labeling**" is a very comprehensive document addressing many aspects of drug interaction as they relate to drug development. The document does a good job of reflecting the current view of the scientific community on the issues related to drug metabolism and drug transport. We are in agreement with the majority of the points made in the document. However, there are some areas within the draft guidance that need further clarification. Please see below our comments and suggestions (organized by major topics in the draft guidance) for your consideration.

In vitro Cytochrome P450 studies:

- **In vitro Induction assessment:**

Line 188-195:
The Draft Guidance implies that if in vitro results with either CYP1A2 or CYP3A are positive, further evaluations would be warranted with all other inducible P450 enzymes (including CYP3A and CYP1A2 again) in three additional hepatocyte preparations. It is important to note that, in many cases, if CYP3A is upregulated, CYP2Cs and CYP2B6 are not upregulated to the same extent. In such a situation, induction of these enzymes is not likely as clinically relevant as the CYP3A induction may be. Therefore, induction of

CYP3A activity does not necessarily mean clinically relevant CYP2C or CYP2B6 induction.

Line 1116-1120:
Before conducting in vitro induction studies (measured by enzymatic activities in intact cells) for a new investigational drug, it is helpful to know the CYP inhibition as well as metabolic stability of the drug in the hepatocytes. If, for some reason, at the time of the induction experiment that prior knowledge does not exist, measurements of mRNA can be helpful by eliminating false negatives when the investigational drug is also an inhibitor of the enzymes of interest. The importance of measuring mRNA is mention in Line 1172, but may be of great enough importance to mention it earlier.

Line 1143:
An EC50 alone is not sufficient for estimation of an induction potency index, but only in combination with % positive control as a second parameter. Otherwise a drug with a low EC50, but insignificant total induction potency may be regarded as inducer.

- **In vitro experiments: Identification of metabolic pathways**

Line 819-825:
Although it is mentioned later (Lines 871-873), it is helpful to emphasize that not only the **identification**, but also the **quantification** of the metabolic pathways, allows for a more informed decision making process about performing enzyme phenotyping studies and subsequent in vivo drug interaction studies.

Line 923-925:
Recombinant enzymes: The enzyme activity measured in recombinant P450s does not provide information on the relative importance of the individual pathways in human liver microsomes, *unless it is scaled to the relative abundance of that enzyme in the liver*. It is a common practice in industry to use recombinant enzymes to discern the importance a metabolic pathway. It is helpful if guidance make the extent of the validity of such approach more clear.

Line 1017-1019:
It should be noted that there are experimental limitations for including “no-solvent control”. The test compounds or control inhibitors are rarely soluble without solvents. This makes the utility of the “no-solvent control” limited.

- **In vitro evaluation of CYP Inhibition interaction studies (screen criteria for in vivo studies):**

Line 1068-1070:
The investigational drug as a Mechanism based inhibitor: There needs to be more guidance for the magnitude of MBI to substantiate a clinical DDI study in humans. Regard of potency of the inactivation (K_I and k_{inact}) as well as [I] are relevant to the

prediction of clinical DDI with MBI. Some publications provide more guidance to predictions of clinical DDI with respect to MBI and may be useful in this context:

Mayhew et al. (2000) DMD 28:10310-1037
Wang et al. (2004) DMD 32: 259-266
Ernest et al. (2005) JPET 312:583-591
Venkatakrishnan and Obach (2005) DMD 33:845-852

Line 1067-1068:
Suggested change: "For compounds containing amines…" to "For compounds containing methylenedioxy or alky and aromatic amines converted in situ to nitroso metabolites…"

General comment: In general, there is no mention of measuring microsomal protein binding in CYP inhibition studies. If there is substantial microsomal protein binding of the investigational drug, the Ki maybe over-estimated. Hence, no drug interaction may be predicted. Recommending low microsomal protein concentrations in the incubations will help obtain more accurate in vitro inhibition parameters.

In vivo (human) Cytochrome P450 studies:

Line 324:
Assessment of P450 polymorphism (genotyping or phenotyping) in the healthy volunteers or the patients can be a standard practice only if polymorphic enzymes (CYP2C9, 2C19, 2D6) have a substantial contribution (e.g. > 25%) to the clearance of the investigating drug. It would be very helpful if guidance more clearly states that phenotyping or genotyping of the subjects would not be a requirement if polymorphic enzymes contribution to the total elimination of the drug is minor.

Line 349-354:
Investigating drug as an inhibitor: The guidance states "further studies using other substrates, representing a range of substrates, based on the likelihood of co-administration, may be useful." It is helpful if guidance states the utility of the information discerned from such studies. Will it be used in the product labeling? If so, where in the label?

Line 443-444:
Investigating drug as a substrate of polymorhically expressed enzymes in PM: The guidance states: "When the above study shows significant interaction, further evaluation with weaker inhibitors may be necessary." Perhaps guidance can be more clear about the utility of the information obtained from studies with weaker inhibitors of the enzyme. If the NME is metabolized by other enzymes, it may be that in PM the contribution of other enzymes in elimination of the drug is more significant than that of EM. In such a situation, doing an inhibition study with inhibitors of those enzymes, would be more informative than doing a study with a weaker inhibitor of the polymorphicaly expressed enzyme.

Line 757: Figure 1

Please specify if the “Study other inhibitors/inducers selected based on likely co-administration” and “Study other substrates selected based on likely co-administration narrow therapeutic range” is for labeling purposes and/or suggestions for dose adjustments. Please clarify if this is a general requirement or it would be required if a certain wording was to inserted I the label.

Line 373-383:
General comment: in vivo induction ability of an NME which is a sensitive substrate of the induced enzyme can also be assessed from comparing the NME single dose vs. multiple dose PK data. If there is an indication of “auto-induction”, it is likely that the NME is an inducer of the enzyme. In such a situation in vitro induction studies may not even be necessary as there is already an in vivo evidence for induction.

Transporters: Identification of Substrates and Inhibitors

General comment: In deciding whether an in vivo transporter study should be conducted, much weight is put on the parameters discern form the in vitro transporter studies (based on the decision trees). We believe that the state of knowledge about Pgp (even less so for other transporters) is not such that we can be confident about the validity of these parameters governing the decision tree. However, decision tree is a good starting point from which guidance could evolve as the knowledge base increases. With that in mind, we have the following comments for the transporter section of the draft guidance.

Line 482-486:
Investigating drug as a substrate of Pgp: It is important to note that these studies are only definitive if the investigational drug is not a substrate for CYP3A. Since cyclosporine, ritonavir and verapamil are inhibitors of CYP3A as well as Pgp. Similarly, rifampin is inducer of both CYP3A and Pgp.

Line 1223-1231:
The use of cells which over-express specific transporters (eg. Pgp or BCRP) have been useful in determining if investigational drugs are inhibitors of these transporters using specific fluorescent probe substrates and measurements of the inhibition by flow cytometry. Potency of the inhibition is described by calculations of IC50s using the Hill equation, as well as by magnitude of the inhibition. It has been successful in our company and is a well established method. Some articles using this technique are included below. We suggest including this method in the guidance as an acceptable method to assess the transporter inhibitory properties of the investigational drug.

Choi CH, Sun KH, An CS, et al. (2002) Reversal of P-glycoprotein-mediated multidrug resistance by 5,6,7,3',4'-pentamethoxyflavone (Sinensetin). Biochem Biophys Res Commun;295(4):832-40.

Garcia-Escarp M, Martinez-Munoz V, Sales-Pardo I et al. (2004) Flow cytometry-based approach to ABCG2 function suggests that the transporter differentially handles the influx and efflux of drugs. Cytometry A;62(2):129-38.

Gupta A, Dai Y, Vethanayagam RR et al (2006) Cyclosporin A, tacrolimus and sirolimus are potent inhibitors of the human breast cancer resistance protein (ABCG2) and reverse resistance to mitoxantrone and topotecan. Cancer Chemother Pharmacol;58(3):374-83.

Gupta A, Zhang Y, Unadkat JD, Mao Q (2004) HIV protease inhibitors are inhibitors but not substrates of the human breast cancer resistance protein (BCRP/ABCG2). J Pharmacol Exp Ther;310(1):334-41.

Jekerle V, Klinkhammer W, Scollard DA, et al. (2006) In vitro and in vivo evaluation of WK-X-34, a novel inhibitor of P-glycoprotein and BCRP, using radio imaging techniques. Int J Cancer;119:414-22.

Rabindran SK, Ross DD, Doyle LA, Yang W, Greenberger LM (2000) Fumitremorgin C reverses multidrug resistance in cells transfected with the breast cancer resistance protein. Cancer Res; 60(1):47-50.

Robey RW, Honjo Y, van de Laar A et al (2001) A functional assay for detection of the mitoxantrone resistance protein, MXR (ABCG2). Biochim Biophys Acta. 2001 Jun 6;1512(2):171-82.

Shapiro AB, Ling V. (1997) Positively cooperative sites for drug transport by P-glycoprotein with distinct drug specificities. Eur J Biochem; 250:130-7.

Wang EJ, Casciano CN, Clement RP, Johnson WW. (2000) In vitro flow cytometry method to quantitatively assess inhibitors of P-glycoprotein. Drug Metab Dispos; 28:522-8.

Wang EJ, Casciano CN, Clement RP, Johnson WW. (2000) Cooperativity in the inhibition of P-glycoprotein-mediated daunorubicin transport: evidence for half-of-the-sites reactivity. Arch Biochem Biophys.; 383(1):91-8.

Wang EJ, Casciano CN, Clement RP, Johnson WW (2001) Active transport of fluorescent P-glycoprotein substrates: evaluation as markers and interaction with inhibitors. Biochem Biophys Res Commun; 289:580-5.

Line 1349-1350
Extensive repeats should only be requested for negative results if used for labeling.

Line 1411-1412
The use of 3 different filters appears excessive. Measurement of non-specific binding may provide an alternate quality control

Line 1427-1486:
The text (as it is) implies that an interaction study is warranted for every compound that we find to be a P-gp substrate, regardless of whether it is cleared via P-gp or a different mechanism like metabolism. To avoid unnecessary studies, clarification is needed to define the situations under which such in vivo studies would be required.
As mentioned earlier, the inhibitors of CYP3A4 and Pgp very often overlap. Raising the following questions: Is there a suggestion for in vivo Pgp inhibitors to use that are specific for Pgp and not CYP3A? Would some f these inhibitors be more selective for Pgp vs. CYP3A4 at a given dose?

Another area that needs consideration is the dose to be used for such studies. This is of especial concern when it comes to GI absorption where saturation of transporters occurs at high doses.

Finally, Novartis Pharmaceuticals is grateful for the opportunity to provide comments and offer suggestions and hope that the FDA will consider our response when publishing the final guidance for the use of public in the near future.

On behalf of Exploratory Development, Drug Metabolism and Pharmacokinetics department at Novartis

Sincerely,
Soraya Madani PhD
Associate Director

Drug Regulatory Affairs, FDA Liaison Office
Novartis Pharmaceutical Corp.
1700 Rockville Pike, Suite 510
Rockville, Maryland 20852