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8<sup>th</sup> November, 2006

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

**Re: Draft Guidance for Industry on Drug Interaction Studies – Study Design, Data Analysis and Implications for Dosing and Labeling.** [Docket No. 2006D-0344, 71 *Federal Register*, 53696-53697, 12<sup>th</sup> September, 2006]

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc. (“Millennium”), a leading biopharmaceutical company based in Cambridge, Mass., markets VELCADE® (bortezomib) for Injection, a novel cancer product, and has a robust clinical development pipeline of product candidates. The Company's research, development and commercialization activities are focused in oncology and inflammation. By applying its knowledge of the human genome, its understanding of disease mechanisms, and its industrialized technology platform, Millennium is seeking to develop breakthrough personalized medicine products.

We commend the writers on the Draft Guidance's thoroughness and timeliness. We have the following specific comments.

1. Page 10, Section 2; page 24; page 25, 2<sup>nd</sup> para; page 26, Section 2: The following points should be clarified: (a) justification for the 25% cut-off rule that is based on *in vitro* data alone for a trigger to conduct an *in vivo* drug interaction study, and (b) calculation of 25% cytochrome P450's (CYP) contribution to total clearance. The Guidance may imply that the drug will be administered intravenously in a study conducted at some point to calculate total clearance (blood) of the investigational compound, and that a radiolabeled drug metabolism study will be conducted using oral (as an example of intended route) administration. For the calculation of the exact contribution of a CYP metabolic pathway to total clearance one needs to determine how much of that pathway is represented by

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each route of excretion. However, for compounds that show a significant excretion in feces, one cannot determine quantitatively the exact involvement of the human enzymatic pathways versus the contribution of colonic microflora unless one does bile collection studies in humans, collecting the bile quantitatively over a reasonable period of time. This is impossible to justify for most investigational compounds. As an alternative, the Guidance could specify the need for an estimated contribution of a CYP to the total plasma clearance, based on quantitation of the sum of sequential metabolites ( $\sum f_{\text{CYPn\_Seq}}$ ).

Contribution of a particular CYP to total plasma clearance,  $\text{CL}_{\text{CYPn}} = \text{CL}_p \times$  (Fraction cleared by metabolism)  $\times$  [(Fraction contribution of a particular CYP calculated by phenotypic data) or ( $\sum f_{\text{CYPn\_Seq}}$ )]

If  $[\text{CL}_{\text{CYPn}} / Q_h] + [\text{CL}_{\text{CYPn}} / Q_g] > 0.25$ , conduct clinical drug interaction study (where  $Q_h$  and  $Q_g$  are the hepatic and gut blood flow, respectively).

This should allow for the differential impact of 25% contribution of a particular CYP to low total clearance versus high total clearance compounds.

Thus, for a drug cleared 50% by metabolism and 50% by other excretion routes (biliary and urinary), and if 48% of that metabolism is by CYP3A4, the  $[\text{CL}_{\text{CYPn}} / Q_h]$  ratio would be 0.24 and that should not be cause for a clinical drug interaction study.

2. Page 24, Decision Tree: As discussed above, there should be a different treatment for low clearance versus high clearance compounds to quantify the impact of percent contribution of a CYP toward total plasma clearance. Low clearance compounds are likely to have lower impact on area under the curve (AUC) increase due to (say) 25% contribution of a particular CYP compared to an effect on high clearance compounds. The box [*NME is a substrate and contribution of pathway to elimination major or unclear*] should be changed to [*Contribution of the CYP pathway > 25% of the hepatic/intestinal blood flow*].

The box [*Presence of significant interaction?*] should be changed to [*Presence of clinically meaningful interaction?*].

3. Page 33, Section 3: The  $[I]/K_i$  approach to trigger drug interaction studies needs to be re-considered in view of the new, better approach<sup>1</sup> published by Lu et al. in which the ambiguity over, and need for,  $[I]$  determination has been removed. With this published approach one can predict AUC changes based on the *in vivo* human plasma concentration of the inhibitor and the reaction phenotyping using hepatocytes suspended in human plasma. Only those substrate and inhibitor pairs

<sup>1</sup> Lu, C.; Miwa, G.T.; Prakash, S.R.; Gan, L.-S.; Balani, S.K. (2006) A novel model for the prediction of drug-drug interactions in humans based on *in vitro* phenotypic data. *Drug Metabolism and Disposition*, published online October 4, 2006; <http://dmd.aspetjournals.org/cgi/reprint/dmd.106.011346v1>

that show clinically meaningful exposure changes (> 2-fold) need to be assessed for *in vivo* drug interactions.

4. On the issue of induction studies for drugs that have a post-marketing commitment to assess drug interactions, it would seem that there may be ethical issues involved in administering a probably potent, prototypic inducer that would render a given therapeutic less efficacious (assuming that lower drug concentrations were linked with lower efficacy) unless that combination were likely to occur clinically. We recommend that there should be some consideration of constructing an induction drug interaction study for an already approved medication (likely for a serious, life-threatening illness) related to inducers likely to be encountered clinically to see whether, and by how much, disposition (clearance) changes so that there is some specific reason for subjecting patients to this risk.
5. We note the frequent recommendation of rifampin as an inducer of CYP3A. We recommend that the use of rifampin as an inducer should include some consideration in study design of its potential to inhibit some uptake transporters, such that test drugs should be dosed the day after rifampin is stopped. This should also be the case when it is not known whether or not the test drug is a substrate for particular hepatic uptake transporters known to be inhibited by rifampin.
6. In view of the significant and increasing development of biological active substances as new therapies, the document should provide specific guidance for biologics. In our view, this is a critical omission from the current draft.
7. Provide guidance on the recently identified esterase mediated drug interactions of grapefruit juice with ester prodrugs<sup>2</sup>.

Other Key Comments/Suggestions:

1. Page 5, 2<sup>nd</sup> para. : The therapeutic concentration should be defined as “total plasma  $C_{max}$  at steady state”.
2. Page 10, Section IV.C.2: It would be helpful if "25% of the clearance pathway" were more clearly defined.
3. Page 11, Section IV.C.3: Remove the word ‘transporter’ after P-gp throughout the document.
4. Page 12, Section IV.C.4: For simultaneous inhibition of CYP3A and P-gp, ketoconazole should be permitted as an alternate to use of ritonavir, since both

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<sup>2</sup> Li, P.; Gallery, P.S.; Gan, L.L.; Balani, S.K. A new non -P-450 based inhibition attribute of grapefruit juice leading to drug-drug interactions, 14<sup>th</sup> North American ISSX meeting, Rio Grand, Puerto Rico, October 22-26, 2006. Paper#3101

compounds have similar inhibitory potency toward P-gp, and ketoconazole provides reversible as opposed to irreversible inhibition of CYP3A.

5. Page 12, Dose Selection: Ketoconazole dose could be 200 mg BID, instead of just 400 mg QD, to keep the past ketoconazole interaction studies relevant. Provide *in vivo* human doses for drugs to be used as substrates, inhibitors or inducers of other CYPs.
6. Page 28, Table 2: Add omeprazole as a preferred, and benzylnirvanol<sup>3</sup> and benzylphenobarbital<sup>4</sup> as optional, inhibitors of CYP2C19.
7. Page 36, In vitro Induction Study Design, Section (a): We recommend that concentration testing should be conducted at 10 times the proposed effective plasma concentration in order to allow for a more rational design.
8. Page 39: 2(a), (2): Recommend removal of the values for permeabilities – these will not be broadly applicable, due to inter-laboratory variability of permeability values and test criteria.
9. Page 43, C4: Add Lucifer yellow in the paracellular marker list and remove “[<sup>14</sup>C]”mannitol; i.e., change to "*Paracellular markers such as mannitol and Lucifer yellow ....*".
10. Page 43, (d)7: It is not necessary to study interday variation of investigational drugs. We recommend that sponsors should provide interday and intraday variations for prototypical efflux pump substrates and inhibitors to use as a gauge for the test system variability.
11. Page 45, Equation (3): Equation may not be reliable since efflux ratio is not a reliable number. We suggest that permeability or transport rate is used to calculate IC<sub>50</sub>.
12. Page 46, Section 3, 2<sup>nd</sup> bullet; and Page 47, Figure 1, Footnote (b): Fifty percent reduction in the efflux ratio is not a sufficient reason for conducting *in vivo* drug interaction studies. We recommend changing the text to "*significant change in the permeability or reduction in the ratio close to unity*". This is also dependent on the unknown quantitative impact of transporters on pharmacokinetics and pharmacodynamics. The system should be validated before the final guidance is published.

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<sup>3</sup> Walsky, R.L.; Obach, S.R. (2003) Verification of the selectivity of (+)N-3-benzylnirvanol as a CYP2C19 inhibitor. *Drug Metabolism and Disposition*, **31** (3), 343.

<sup>4</sup> Cai, X.; Wang, R.W.; Edom, R.W.; Evans, D.C.; Shou, M.; Rodrigues, D.A.; Liu, W.; Dean, D.C.; Baillie, T.A. (2004) Validation of (-)-N-3-Benzyl-phenobarbital as a selective inhibitor of CYP2C19 in human liver microsomes. *Drug Metabolism and Disposition*, **32** (6), 584-586.

We appreciate the opportunity to comment on this important guidance.

Sincerely,



Robert G. Pietrusko, Pharm.D.,  
Senior Vice-President, Worldwide Regulatory Affairs,  
Millennium Pharmaceuticals, Inc