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July 25, 2005

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

Re: **Docket No. 2005D-0183: Draft Guidance for Industry on Antiviral Drug Development—Conducting Virology Studies and Submitting the Data to the Agency**

Abbott is pleased to have the opportunity to comment on the “*Draft Guidance for Industry on Antiviral Drug Development—Conducting Virology Studies and Submitting the Data to the Agency.*” We have reviewed the draft guidance and we have the following comments:

1. Section III. Nonclinical Virology Reports

Subsection A – Overview

Lines 87-90: “*We suggest that sponsors complete in vitro drug combination activity studies of the investigational drug with the approved drugs before the initiation of clinical trials that will examine the efficacy of the investigational drug in combination with approved drugs.*”

Some further discussion in the final guidance would be useful to clarify whether this refers to *in vitro* drug combination activity studies with the investigational drug and all other drugs that are to be used with it in the clinical trial program or only with those for which there may be a rational basis for interaction.

2. Section III (B) (2) Antiviral activity

a) Lines 188-191: “*When no satisfactory cell culture or animal model exists for the target human virus, it is particularly important to know whether or not a drug’s active moiety enters cells, if it has a proposed intracellular site of action, and if the intracellular concentration is consistent with biochemical studies identifying an inhibitory concentration.*”

Because the intracellular concentration includes the free drug and the protein bound drug, the intracellular inhibitory concentration may be much higher than the inhibitory concentration in biochemical studies if a given drug is highly protein bound. Therefore, line 190: it may be better to change the original sentence to” if the intracellular concentration **correlates** with biochemical studies.”

- b. Line 192, “Cell-based assays and host cell lines for studying viruses such as Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) replication may advance and improve, but at the present time are limited.”

We recommend revising this sentence as follows: “Cell-based assays and host cell lines for studying HBV and HCV **replication have advanced.**”

- c. Line 198-206, describe HBV assay but not HCV assay. We recommend the following revision after line 206 to describe HCV assay:

“Currently, assays that examine HCV replication using the HCV replicon system include, but are not limited to:

- Measuring HCV RNA polymerase or HCV serine protease activity in biochemical assays
- Measuring the level of HCV RNA in HCV replicon cells in the presence of a series dilution of the investigational drug by RT-PCR

3. Section III (B)(5) – Resistance

a. General Comment: For comments on resistance testing, please refer to the February 28, 2005 letter from PhRMA which was submitted to Docket Number 2004D-0484 in response to the “*Draft Guidance for Industry: Role of HIV Drug Resistance Testing on Antiretroviral Drug Development.*”

b. Line 337: We recommend adding the following sentences because methods of resistance selection for HIV drugs and HCV drugs are different:

Methods that select the HCV resistance using HCV replicon system include, but are not limited to:

- *In the first method, HCV replicon cells are cultured at very low density in the presence of neomycin and a fixed concentration of the investigational drug using multiple cultures to test different concentrations. Three weeks post-treatment, the cells containing resistant replicon will form colonies that are then expanded for genotypic and phenotypic characterization.*
- *In the second method, HCV replicon cells are passaged in the presence of a fixed concentration of drug, but in the absence of neomycin, using multiple cultures to test different concentrations. The HCV replicon cells from each passage are harvested and stored for phenotypic and genotypic characterization.*

4. Section III; Subsection B(5)(d) – Cross-Resistance:

a. Lines 404-406: *“Cross-resistance analyses are important in the development of treatment strategies (i.e., establishing the order in which drugs are given).”*

We recommend deletion of this sentence. It is not clearly established that sequencing based on these resistance considerations is a clinically effective and safe strategy. Studies on cross-resistance described elsewhere in this paragraph are important for other reasons and this sentence is not necessary to support the recommendations in the rest of the paragraph.

b. Line 415 - 416, *“If phenotyping is performed in cell lines, the IC₅₀ value obtained in the cell line should be validated with clinical isolates.”*

We recommend adding **“or recombinant mutant clones”** after **“clinical isolates”**.

5. Section IV—Proposal for Monitoring Resistance Development

a. Lines 465-467: *“Sponsors are strongly encouraged to collect (at a minimum) phenotype and genotype data for baseline isolates from all patients and endpoint isolates from all virologic failures and discontinuations (not suppressed).”*

If genotypic testing of an isolate reveals wild type sequence or well-characterized targets and viruses, additional phenotypic testing should not be necessary.

b. Lines 467-470: *“Virologic failures are protocol defined but for HIV-1 studies often include: 1) Rebound: confirmed (two consecutive) plasma viral load values greater than Lower Limit of Quantification (LLOQ) after achieving confirmed level below LLOQ during the treatment phase....”*

1. While the draft guidance suggests resistance testing be performed at virologic failure, the definitions include rebound or lack of suppression to below the lower limit of quantification (LLOQ), or HIV RNA <50 copies/mL using current assays. Since current commercially available HIV resistance assays are unable to reliably amplify in the 50 to 500 copy/mL range, perhaps resistance testing should be reserved for patients experiencing rebound/lack of suppression with HIV RNA >500 copies/mL.

2. If resistance testing is performed at rebound, the guidance should clarify whether the first, second, or both isolates leading to the definition of rebound should be tested.

6. Appendix 1: Template for Submitting HIV Resistance Data

[Note: for additional comments on the Template for Submitting HIV Resistance Data, please refer to pages 14 and 15 of the February 28, 2005 letter from PhRMA to Docket No. 2004D-0484, “Draft Guidance for Industry: Role of HIV Drug Resistance Testing in Antiretroviral Drug Development.”]

a. Lines 532-539: The definitions included in this section are for HBV, not HIV, which this appendix is intended to address.

We recommend deleting this section (lines 532-539).

b. Line 584: We recommend deletion of the p2/NC protease cleavage site since this site is not extremely critical for conferring resistance and, therefore, the additional resources needed to obtain these data may not be justified.

c. Lines 605-613: *“Approved/investigational anti-HIV agents (List first agents in the same class in alphabetical order followed by agents with the same target protein in alphabetical order. End with agents outside drug class in alphabetical order)”*

With respect to “investigational anti-HIV agents,” the guidance should clarify whether it is FDA’s expectation that phenotypic data for investigational agents not being developed by the sponsor should be included in the evaluation.

d. Lines 626-648: Regarding the recommendations for display of phenotype information, this section recommends columns with *“total number of PI mutations,” “total number of NRTI mutations,”* and *“total number of NNRTI mutations per patient isolate (for baseline and endpoint isolates).”*

The value of these columns is unclear since all mutations per isolate are already provided and a reviewer could analyze the data using any desired combinations rather than the specified lists which are likely to vary by drug.

7. Appendix 3: Template for Submitting HCV Resistance Data

Lines 800-807: The definitions included in this section are for HBV, not HCV, which this appendix is intended to address. This section has to be replaced with HCV – i.e., 1) Rebound: confirmed (two consecutive) plasma **HCV RNA**...increase in serum HCV RNA...nadir. 2) and 3) change **HBV DNA to HCV RNA**.

Thank you for consideration of these comments in finalizing this guidance document. Should you have any questions, please contact Mr. Thomas Hassall at (301) 255-0080 or by FAX at (301) 255-0090.

Sincerely,



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