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Food and Drug Administration,
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Rockville, MD 20852
United States of America

**Boehringer Ingelheim
(Canada) Ltd.**

August 19, 2005

**RE: Docket No. 2005D-0183: Proposed Draft Guidance,
Guidance for Industry: Antiviral Drug Development –
Conducting Virology Studies and Submitting Data to the
Agency:**

Boehringer Ingelheim Feedback

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To Whom It May Concern:

Boehringer Ingelheim Pharmaceuticals is a worldwide healthcare company and among the medicines that we develop and distribute are those for the treatment of HIV. Therefore, we are pleased to provide comments regarding the above-referenced Draft Guidance.

Global Comments:

- The guidance document should distinguish between clinical studies in healthy volunteers and infected patients when reference is made to phase 1 clinical studies

A. Overview

2005D-0183

C3

Line 89: The guidance document should distinguish between approved agents that are permitted to be used in an individual study and those that will be excluded from use in the proposed studies

B. Recommended Components of Nonclinical Virology Reports

1. Mechanism of Action

Line 102: The guidance document should specify known human metabolites and those for which structural elucidation has yet to occur, since it is not always possible to identify all the human metabolites from non clinical in vitro and in vivo studies. This may be due to species differences in metabolism and/or low levels of metabolites formed by human enzymes/tissues in vitro. It may be helpful for guidance to distinguish between prodrugs or drugs known to require metabolic activation such as nucleoside analogues, for which characterization of the active entity is essential, and drugs which are administered as the active entity.

2. Antiviral Activity

a. Antiviral activity in vitro

Line 171: Fusion assays are more relevant to MoA determination rather than measurement of intrinsic antiviral activity.

Line 178: The guidance document should be written in a way that recognizes that other explanations for this phenomenon are available: for example 1. when the available biochemical assays do not adequately measure the biochemical process responsible for the antiviral activity (e.g. chain termination by NRTIs such as 3TC is not adequately measured by IC50 values for RT inhibition); and 2, when less than 50% inhibition of the biochemical process is required for 50% inhibition of viral replication in vitro

b. Antiviral activity in vitro in the presence of serum proteins

Line 218: Lower concentrations of AAG (1mg/mL) have typically been used. Does the agency require human serum albumin to be tested?

C. Inhibitory quotient

Line 223: The guidance document should state that the agency is open to arguments about why a plasma IQ may not be an appropriate PK measure (e.g. accumulation of the drug in the principal organ in which the virus replicates). This could be particularly relevant to hepatitis C if there is significant accumulation in hepatocytes.

4 In Vitro Combination Activity Analysis

Line 278: Three drug combination studies are extremely difficult to perform and interpret and should not be recommended.

Line 289: The guidance document should note the difficulties faced by assessment of combination studies involving agents targeting different viruses: for combination of antiviral agents active against different viruses, the weak antiviral activity of one agent may be difficult to adequately discriminate from low level cytotoxicity and may not be relevant to the clinical drug concentrations used for treatment of the co-infection.

5. Resistance

a/b. Selection of resistance virus in vitro/Genotypic analysis

Line 333: We suggest replacing the starting concentration from 'half the IC₅₀' value to an 'appropriate multiple of the IC₅₀ value'.

Line 319 and 349: Selection of resistant virus in vitro can require considerable effort both in the generation of resistant virus and the accurate characterization of the mutations observed. When selection of resistance has proven difficult, it

may be unrealistic to repeat the in vitro selection experiment several times as suggested. While it is reasonable to expect selection experiments to be attempted in different genetic backgrounds (for example, to understand resistance pathways that maybe observed in wild type versus a common mutant genetic background), it should be acknowledged that characterization of the resistance pathways can only be truly assessed in the clinic and as such the agency only expects a reasonable level of characterization to be performed. We suggest that the broader request to characterize resistance pathway in different genetic backgrounds would be better placed in section IV Proposal for monitoring resistance development.

Line 356: The guidance document should adequately discriminate between the requirements of assays used for non-clinical studies prior to the initiation of clinical studies and the studies performed during analysis of viruses from clinical studies.

IV. Proposal for Monitoring Resistance Development

Line 466: Performing phenotyping on baseline virus from all treatment naïve patients is inconsistent with Line 529. We ask the agency to consider that for clinical studies of antiretroviral drugs in treatment-naïve HIV infected patients, phenotypic data from all failure patients at baseline and time of failure is an acceptable requirement.

Line 465: The definition of virological failure is not consistent with the definition used on Line 532 (Appendix 1). In addition depending upon the LLOQ, amplification could be problematic at low viral loads, limiting the ability to perform resistance testing on the virus. We suggest that the agency consider providing guidance on how to handle failed amplification due to low viral load or amend the guidance to read “we strongly encourage sponsors to conduct genotypic and phenotypic analysis ...”. We also suggest that guidance is provided on whether the agency expects sponsor to test the first sample above the LLOQ or the confirmatory sample.

APPENDIX 1:

Template for Submitting HIV Resistance Data

Line 533, 534, 535, 536 HBV DNA should read HIV RNA. Similar inconsistencies appear in the appendix dealing with HCV resistance data

IV. Protease Cleavage Sites (for protease inhibitors only)

Line 584 : Inclusion of the p2/NC cleavage site is unusual – would it be possible for the agency to provide a rationale for genotypic analysis of the three specified cleavage sites versus other cleavage sites.

Line 584 : Please can the agency specify the number of amino acids on either side of the CS they require.

VI. Column with Total Number of PI Mutations in Patient Isolate

Line 629 : Please can the agency provide a rationale for why other significant mutations are not included on the list e.g. L10, L33, I47, F53

VII. Column with Total Number of NRTI Mutations in Patient Isolate

Line 637 : Please can the agency provide a rationale for why other significant mutations are not included on the list e.g. Q151, 219.