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25 February 2005

Food and Drug Administration  
Division of Dockets Management (HFD-240)  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20852

**RE: Comments to Docket No. 2004D-0484  
Draft Guidance for Industry on the Role of HIV Drug Testing in  
Antiretroviral Drug Development**

Sir or Madam:

Gilead Sciences, Inc. (Gilead) hereby submits comments on the Draft Guidance for Industry titled "Role of HIV Drug Resistance Testing in Antiretroviral Drug Development" (Docket No. 2004D-0484).

As indicated in the Federal Register Notice of November 29, 2004 (Volume 69, Number 228, Pages 69374-69375), two copies of the comments are included in this submission.

Please contact me at (650) 522-5093 or by facsimile at (650) 522-5489 if you have any questions or need additional information. You may also contact Pamela Danagher, Associate Director, Regulatory Affairs at (650) 522-6395. We share the same facsimile number.

Sincerely,

Christophe Beraud, Ph.D.  
Senior Associate, Regulatory Affairs

**2004D-0484**

**C 5**

**Gilead Sciences, Inc. Comments on the Draft Guidance for Industry on the Role of HIV Drug Resistance Testing in Antiretroviral Drug Development.**

Docket No. 2004D-0484, Federal Register: November 29, 2004 (Volume 69, Number 228, Pages 69374-69375)

Gilead Sciences, Inc. (Gilead) hereby submits comments on the Draft Guidance for Industry titled “*Role of HIV Drug Resistance Testing in Antiretroviral Drug Development*”.

Gilead appreciates the Food and Drug Administration’s (the Agency’s) efforts to provide the industry with clear guidance regarding the integration of HIV drug resistance testing in the clinical development program of antiretroviral drugs to treat HIV infection. While recognizing that the document prepared by the Division of Antiviral Drug Products (the Division) represents the Agency’s current thinking on the design and implementation of an HIV drug resistance testing plan during clinical development, additional considerations and clarifications should be included in the final guidance.

**1. Organization of the comments**

Comments on specific sections of the draft guidance document are provided in the order in which they appear in the document issued by FDA. Reference to the section number, page number and line number of the document is made for each comment. In addition, excerpts from the draft guidance referred to in the comments are provided in italic font.

**2. Gilead’s Comments**

*2.1. Section IV. Nonclinical studies, B. Antiviral Activity In Vitro*

Page 4  
Lines 178-184

*The in vitro antiviral activity of a compound indicates that it effectively inhibits replication and forms the basis for defining phenotypic resistance (detected by reductions in susceptibility to the investigational drug, see below). The concentration of an investigational drug required to inhibit virus replication by 50 percent (IC<sub>50</sub>) should be determined. The use of the IC<sub>50</sub> value for determining shifts in susceptibility is preferred because it can be determined with greater precision than an IC<sub>90</sub> or IC<sub>95</sub> value. A well-characterized wild-type HIV laboratory strain grown in peripheral blood mononuclear cells (PBMCs) should serve as a reference standard.*

The state-of-the-art phenotyping technologies utilize modern recombinant approaches to generate viruses to determine drug IC<sub>50</sub> values against panels of viral strains. A number of commercial assays have been developed (such as ViroLogic and Virco assays) that

have been widely and successfully used throughout the industry. These well-validated and controlled assays use a laboratory reference virus grown in immortalized cell lines which allows for reproducibility and accurate comparison of the data across independent experiments. Gilead's experience with PBMC-grown HIV strains suggests that these viruses are extremely difficult to use for analysis of large sets of samples and produce results that are highly variable and not very reproducible. Gilead would recommend that the Division consider the utilization of well-validated assays employing recombinant technologies to determine shifts in IC<sub>50</sub> values and characterize phenotypic resistance.

2.2. *Section IV. Nonclinical studies, D. Cross-Resistance*

Page 6

Lines 251-256

*HIV variants resistant to one drug in a class of antiretroviral agents may be resistant to another drug in the same class. Recombinant viruses containing drug resistance associated mutations to an investigational drug should be tested for susceptibility to approved and investigational drugs of the same class. Conversely, laboratory strains and 10-30 well-characterized clinical isolates containing resistance-associated mutations for each of the approved and investigational members of the same class should be tested for susceptibility to the investigational drug.*

It has been shown that some NRTI resistance mutations confer hypersusceptibility to NNRTIs (See Appendix 1). This suggests a theoretical potential for NRTI/NNRTI cross-resistance. Therefore, cross-resistance testing should not only involve drugs belonging to the same class but also drugs targeting the same protein. Gilead recommends that the guidance be modified to consider cross-resistance testing with drugs directed at the same molecular target.

2.3. *Section V. Clinical: Use of Resistance Testing in Clinical Phases of Drug Development, B. Data Collection*

Page 9

Lines 369-372

*To characterize drug resistance during development, sponsors are strongly encouraged to collect the following information:*

- *Baseline phenotype and genotype on all study participants.*

*The reasons for obtaining baseline samples for phenotype and genotype on all clinical trial participants are twofold. First, the prevalence and rate of transmission of drug resistant virus is increasing (Little et al., 2002), and may continue to increase, as the HIV population becomes more treatment experienced. Second, collection of baseline data provides an opportunity to examine the relationship*

*between genotype/phenotype and virologic response to drug. Use of resistance testing in study protocols may help in choosing appropriate combination regimens for treatment experienced patients (see section V.C.4 for further details).*

Gilead agrees that collecting baseline genotypic data from all study participants is necessary to determine the presence of possible baseline resistance mutations even among treatment-naïve patients.

While collecting baseline phenotypic data on all study participants might appear to be a comprehensive approach to characterize resistance during drug development, Gilead does not believe that this systematic approach is always scientifically justified for the following reasons:

- In treatment-naïve patients, phenotypic data for proven drug classes such as reverse transcriptase inhibitors or protease inhibitors does not yield a sufficient range of variability (< 3 fold) to warrant testing of all patients at baseline. In phase 3 clinical studies of treatment-naïve patients, an approach based on baseline genotyping of all patients followed by phenotyping of samples with possible resistance would provide as much valuable information in terms of characterizing the relationship between genotype/phenotype and virologic response to the drug. This approach would also address the Division's concern regarding the increasing prevalence of HIV drug resistance in treatment-naïve patients.
- For some classes of drugs such as entry inhibitors or fusion inhibitors, there is a higher variability among treatment-naïve patients. In this instance, the sample size for phenotypic analyses should be guided by statistical considerations in order to gather sufficient data to establish the efficacy of the test drug. In the case of poorly-characterized new drug classes, the sponsor should establish a plan during the drug development program to evaluate the variability of the drug response in treatment-naïve patients based on statistical approaches.
- Similarly, for treatment-experienced patients, a sufficient sample size should be determined to allow prediction of clinically relevant breakpoints for drug activity. In both cases, phenotypic data from every patient enrolled in a study may not be necessary to support robust conclusions, and therefore the size of the sample for phenotypic analyses should be determined based on statistical considerations.

As an additional note, please note that practical, logistical and other considerations do occasionally preclude the possibility of obtaining baseline resistance data for individual clinical trial subjects. The Division should clarify how these patients should be treated in the resistance analysis.

2.4. *Section V. Clinical: Use of Resistance Testing in Clinical Phases of Drug Development, C. Types of Analyses, 2. Development of HIV Mutations*

Page 12

Lines 475-490

*The Division strongly recommends that genotypic testing be performed on all patients who meet the definition of a lack or loss of virologic response, preferably while on study drug or as soon as possible after discontinuation of study drug. Studies have shown that wild-type virus may outgrow resistant HIV strains in the absence of selective drug pressure. For this reason, it can be useful to collect and store samples for resistance testing at the same timepoints that HIV RNA testing is done. These samples can provide important information on the development of resistance, especially for drugs that may have more than one possible resistance pathway.*

*The proportion of subjects who develop any NRTI (nucleoside analogue reverse transcriptase inhibitor)-, NNRTI (nonnucleoside reverse transcriptase inhibitor)-, or PI-associated mutation and the time to development of these mutations should be presented. Both primary and secondary mutations should be evaluated. For example, for subjects receiving a new PI, it is important to evaluate the development of primary and secondary PI mutations along with any other changes in the PR (protease) and RT gene, when applicable. It is also important to assess the genotypic basis of drug susceptibility changes attributable to extragenic sites, such as the protease cleavage sites.*

Gilead agrees with the Division that understanding the development of HIV mutations upon drug exposure is an important part to understanding the drug efficacy profile. The Division should provide sponsors with additional guidance regarding the circumstances in which testing of stored samples to help estimate time to mutation development should be considered.

In Gilead's experience, there are often very few samples available with adequate viral load for such mid-point analyses. Gilead proposes that an end-point analysis would be sufficient to characterize fulminate development of resistance while on study drugs and then additional mid-point analyses could be undertaken based on sample availability. Additional guidance from the Division should also be provided regarding the recommended approach to estimate the distribution of time to mutation development.

2.5. *Section V. Clinical: Use of Resistance Testing in Clinical Phases of Drug Development, C. Types of Analyses, 5. Cross-Resistance*

Page 14

Lines 540-546

*Phase 3 trials should incorporate prospective rollover designs to provide for assessment of virologic responses in study subjects administered subsequent antiretroviral regimens. When possible, the design of the rollover study should include a randomized control. Every effort should be made to capture as much information as possible from the original*

*studies. Resistance testing can be used to assess the genotype and phenotype of antiretroviral experienced patients that predict success or failure after exposure to previous therapies. This testing can involve longer follow-up of study subjects, perhaps continuing into the postmarketing period.*

The Guidance for Industry titled “*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*” offers guidance to sponsors on the evidence to be provided to demonstrate the effectiveness of a drug. Gilead believes that the inclusion of prospective rollover designs in phase 3 clinical studies to assess virologic response to subsequent treatment regimens in patients failing the study regimen goes beyond the requirements for adequate and well-controlled studies as described in 21 CFR 314.126.

While Gilead agrees that studying the virologic response to subsequent treatment regimens in patients failing the study regimen is of great clinical interest, the inclusion of the proposed prospective rollover designs in phase 3 clinical studies would prove very difficult due to the small number of patients who fail treatment due to drug resistance. Design of adequate randomized controlled trials would also not be possible for the same reason.

Gilead currently offers patients who fail the study drug regimen the option to remain in the study on a voluntary basis. Resistance data is provided to the physicians and allows them to determine the best course of action for their patients. The data generated by this approach is utilized to better our understanding of the study drug as it relates to cross-resistance evaluations. These observational data are provided to the Division as part of the virology and clinical study reports.

Gilead proposes that clinical cross-resistance investigations may be better addressed in post-marketing or in treatment strategy studies. This approach would allow the generation of the necessary clinical information without hindering the patients’ access to new therapies that have been proven to be effective according to the Agency’s regulations.

2.6. *Section V. Clinical: Use of Resistance Testing in Clinical Phases of Drug Development, D. Other Considerations, 2. Dose-Finding Trials*

Page 15  
Lines 586-593

*Sponsors should collect baseline genotype/phenotype information in HIV-infected subjects who participate in pharmacokinetic/dose finding studies. Current evidence indicates that virologic response is better when drug levels can be maintained some increment above the serum-adjusted IC50 value (see section III page 5). Study subjects with baseline resistance mutations may require higher drug concentrations of the antiretroviral drug to achieve an antiviral response similar to the response observed in patients with wild-type virus. Patients with particular genotypes/phenotypes of interest should be prospectively identified for inclusion in dose-ranging studies.*

As noted in *Section 2.3*, obtaining phenotypic data in treatment-naive patients offers minimal information for most HIV-1 drug classes beyond what is available from a genotype. If resistance mutations are observed, phenotypic data can be obtained to support an assessment of the dose-response information.

### **3. Reference List**

Whitcomb, J.M. *et al.*, *Hypersusceptibility to non-nucleoside reverse transcriptase inhibitors in HIV-1: clinical, phenotypic and genotypic correlates*, AIDS, 2002, 16: 41-47

Guidance for Industry; *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998

21 CFR 314.126 – *Adequate and well-controlled studies*, 2003

### **4. Appendices**

### **Appendix 1**

Whitcomb, J.M. *et al.*, Hypersusceptibility to non-nucleoside reverse transcriptase inhibitors in HIV-1: clinical, phenotypic and genotypic correlates, AIDS, 2002, 16: 41-47.