DEPARTMENT OF HEALTH & HUMAN SERVICES

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: **October 20, 1999**

To: **Antiviral Drugs Advisory Committee Members and Consultants**

From: **HIV Drug Resistance Working Group of DAVDP**

Through: **Heidi Jolson, M.D., M.P.H.**
Director, Division of Antiviral Drug Products HJolson 10/20/99

Subject: **Background information for the open session of the Antiviral Drugs Advisory Committee of November 2-3, 1999, HIV Resistance Testing**

The purpose of this memorandum is to provide background material for the Division of Antiviral Drug Products' Advisory Committee meeting to be held on November 2 and 3, 1999. On these two days, the committee will be asked to consider the potential roles of HIV-I drug resistance testing in the development of antiretroviral drugs. Our primary goal for this meeting is to obtain committee feedback on the amount and type of resistance data that should be obtained during the course of antiretroviral drug development. We hope that the proceedings of this meeting will be instrumental in stimulating further research into HIV resistance testing for both drug development and surveillance. This meeting will also serve as a basis for a FDA guidance document on the use of resistance testing in antiretroviral drug development.

Please refer to the enclosed agenda for an outline of presentations and objectives to be addressed during the meeting on HIV-l drug resistance testing. This agenda was developed in collaboration with the HIV Resistance Collaborative Group (RCG) (Douglas Richman, M.D., chairman), composed of representatives from academia, industry, and the community. While the goal of the RCG is the formulation of recommendations on the appropriate use of resistance testing in clinical trials and clinical practice, the focus of this advisory committee meeting is the appropriate use of HIV-l drug resistance testing in the drug development process. For this reason, data from retrospective and prospective clinical trials will be presented in order to determine whether the available evidence supports the clinical utility of HIV-1 genotypic and/or phenotypic analyses in drug development; patient management issues will not be the focus of this meeting.

There is no doubt that the issues surrounding HIV-l drug resistance are complex. In order to facilitate the presentations and discussions, the meeting will be divided into four sessions, followed by an open public hearing, presentation of regulatory proposals, and committee discussion and summation.

The first Session on Day 1 will address performance characteristics and limitations of the currently available genotyping and phenotyping assays, as well as the Center for Biologics Evaluation and Research (CBER) policies on assay regulation. In the afternoon, Session 2 will summarize the information derived from the currently available prospective and retrospective clinical studies, which have used genotyping or phenotyping technology.

Session 3, on the morning of Day 2, will focus on practical considerations for the use of HIV- 1 drug resistance testing in the drug development process, including relevant patient populations, timing of samples, and confounding variables. After the mid-morning break, the potential role of resistance testing in drug development as envisioned by DAVDP will be presented along with an historical perspective on drug resistance in the context of antibacterial drug development.

Background Considerations

In addition to questions concerning available resistance testing technology, other factors may complicate the interpretation of HIV-l drug resistance testing in clinical trials. Because viral evolution is a dynamic process, resistance testing by any methodology provides information under particular virologic, immunologic, pharmacologic and clinical conditions present when the sample is obtained. Some factors that the committee should take into consideration during the course of this meeting are:

1. Drug resistance is only one of many factors that determine treatment outcome. The success or failure of antiretroviral therapy in HIV infected individuals also depends on complex host immune functions (e.g., CD4 and cytotoxic lymphocyte cell function), pharmacologic properties of a drug, and clinical issues such as drug adherence and tolerability. Pharmacologic properties that influence treatment outcome are multiple and complex including, absorption, tissue/compartmental distribution, protein binding, clearance, activation/nonactivation, and drug-drug interactions.
2. The complex nature of combination therapy may confound the relationship between baseline resistance testing and treatment outcome. In many situations, the ability to discriminate the effect of a decrease in susceptibility of one drug may be obscured by the activity of other drugs in a regimen.
3. Patient characteristics such as baseline CD4 count, HIV RNA level, prior treatment history may also confound the relationship between results from resistance testing at baseline and treatment outcome.
4. HIV-l resistance assays are in a dynamic state of development; the quality of the data generated is only as good as the validity of the methods used to generate the data.
5. Resistance testing of plasma RNA may not adequately reflect the state of viral evolution in all compartments or anatomic reservoirs (CNS, genital tract, integrated DNA in resting CD4 cells). Evaluating these sites for the presence of HIV and viral resistance may be an important part of future drug development, particularly as the transmission of resistant virus has appeared to increase.

Advisory Committee Sessions:

SESSION I:

Performance Characteristics and Limitations of Currently Avaliable Genotypic and Phenotypic Assays

The presentations in Session I will address performance characteristics and limitations of the currently available genotypic and phenotypic assays. The first speaker will be Dr. Andrew Dayton from the Center for Biologic Evaluation and Research (CBER), FDA who will review current policies on assay regulation.

In September 1999, CBER convened a Blood Products Advisory Committee Meeting to discuss the reclassification of commercial HIV genotyping assays from Class III (clinical trials demonstrating safety and effectiveness are required prior to approval), to Class II (clinical trials may not be required prior to approval). The advisory committee recommended reclassification to a Class II product with the addition of special controls to assure appropriate use of these assays. The committee suggested the development of a guidance document with recommendations for non-clinical analytic sensitivity standards, clinical and non-clinical validation of phenotypic drug sensitivity as predicted by genotype, and post-marketing clinical surveillance to evaluate whether clinical progression correlates with data derived from HIV-l genotypic resistance testing. The committee also emphasized the importance of establishing a consensus algorithm to help interpret the meaning of results obtained from genotypic assays.

Following Dr. Dayton's presentation, Douglas Richman, MD will provide an overview of the principles of resistance testing and performance characteristics of the currently available genotypic and phenotypic assays including sensitivity, specificity, precision, validation, quality control, reproducibility, interpretation, and correlation between genotype and in vitro phenotype.

The committee will then be asked to consider the following questions for Session 1:

1. What are the relative strengths and limitations of genotypic versus phenotypic assays in assessing resistance to antiretroviral drugs throughout the stages of drug development? Please comment on the potential roles of these two types of assays throughout drug development.
2. What studies are needed to further define performance characteristics of available assays in order for them to be useful in drug development?
3. What quality control data are needed to support use of these assays in clinical trials and drug development. What additional studies should be conducted with respect to reproducibility and quality control?

SESSION 2

Evaluation of Relationships between Genotype, Phenotype and Treatment Outcome

Two prospective clinical studies utilizing genotyping for treatment-experienced patients with virologic failures will be presented. Dr. Phillipe Clevenbergh will present the VIRADAPT study, a randomized study of standard of care vs. therapy guided by knowledge of genotypic mutations. After six months of treatment, the proportion of patients with HIV RNA less than 200 copies/ml was 32% in the genotype group versus 14% in the standard of care group. However, patients in the genotype arm received more diverse and individualized combinations of antiretroviral agents. The GART study (CPCRA 046), to be presented by Dr. John Baxter, employed a similar design and also showed a greater proportion of patients randomized to the genotype assay having HIV RNA below the level of detection. Further analysis of this study shows that patients in the genotype assay arm received a greater total number of medications and a greater number of medications deemed to be sensitive. Criticisms of this study focus on the expert advice provided by virologists utilizing the interpertation of the genotype assay and the absence of expert advice for those in the control arm. While the results of these studies are encouraging, the question remains whether improved outcome was solely attributable to genotyping or the result of a more aggressive approach to therapy recommended by experts.

Retrospective studies utilizing resistance technology analyzed in a standardized fashion will be presented in the remainder of this session. Dr. John Mellors will provide an overview of retrospective studies and methodologies including the development of mutational algorithms. Dr. Victor DeGruttola will describe a standardized methodology developed by the RCG, referred to as Data Analysis Plan (DAP). A copy of the Data Analysis Plan is included in the background package.

The DAP, which includes a mutational algorithm for defining resistance and statistical methodology for assessing treatment outcome, was initially developed as a tool to evaluate data from retrospective resistance substudies in a standardized fashion. The goal was to evaluate whether baseline resistance testing results could predict treatment outcome in several retrospective analyses with the hopes of establishing the clinical relevance of resistance testing. However, an equally important aspect to this exercise is an evaluation of the utility of the DAP itself as a method for analyzing actual resistance data. Therefore, we would like the committee to comment on the DAP methodology for possible use in the regulatory evaluation of resistance data.

Session 2 Questions:

1. What are some important principles for developing algorithms that classify mutational constellations as “drug resistant”? How should mutational algorithms and/or phenotypic breakpoints be developed in the future?
2. In addition to the covariates and methodology for assessing treatment response included in the DAP what additional covariates or methodologies should be considered when evaluating resistance data?

3. Do the data presented support the clinical utility of HIV genotypic testing for use in drug development?
4. Do the data presented support the clinical utility of HIV phenotypic testing for use in drug development?
5. What are the limitations of the data correlating mutational patterns with clinical outcome?
6. What additional clinical studies are needed to further define the clinical utility of resistance testing?

SESSION 3

Practical Considerations for the Use of Resistance Testing in Antiretroviral Drug Development and Use

There is no doubt that resistant viruses are becoming more prevalent, and transmission of HIV resistant to one or more antiretroviral agents has been well documented. As mentioned previously, other factors may confound interpretation of resistance data, such as the presence of naturally occurring polymorphisms, sampling issues, complexity of combination therapy, and compartmentalizion of HIV. Dr. Susan Little will provide a review of the prevalence of HIV resistance in newly infected individuals and Richard D'Aquilla will provide a review of other factors to consider in the interpretation of resistance data. This information is intended to stimulate discussion on the following questions:

Session 3 Questions

1. Please comment on the types of patient populations in which HIV resistance testing might be useful in drug development.
2. Please comment on the timing of HIV resistance testing in the setting of a clinical trial.
3. Please comment on factors that may confound the interpretation of resistance testing in the setting of clinical trials and what may be done to reduce these confounding effects.

SESSION 4

Potential Roles of Resistance Testing in Drug Development

The last session will focus on the Agency's perspective regarding genotypic and phenontypic resistance testing as it pertains to drug development. An analogy with antibacterial resistance will be presented as an historical perspective, as well as an overview of DAVDP's current thinking on the issues surrounding the use of HIV-l drug resistance testing in drug development. Our goal is to define the type of preclinical resistance data that is necessary to support a clinical program, the type of data needed to characterize a drug's ability to induce resistance and class cross-resistance, and the necessary data to support marketing claims relating to resistance.

Session 4 Questions

1. Please comment on the amount and type of preclinical resistance data sufficient to support a clinical development program.
2. What type of in vitro and clinical data should be provided by drug sponsors to characterize the clinical activity of an antiretroviral drug against "resistant" virus? In your discussion, please include details such as, methods, patient subsets, number of patients, number of isolates, duration of treatment, number of drugs, definitions for assessing treatment response, etc. Should different standards be required to support a labeled Indication (for treatment of resistant subpopulations) as compared to that to support descriptive statements in the Microbiology section?
3. What type of in vitro and clinical data should be provided by drug sponsors to characterize an antiretroviral's ability to induce resistance and cross-resistance? In your discussion, please include details such as methods, patient subsets, number of patients, number of isolates, duration of treatment, number of drugs, definitions for assessing treatment response, etc.
4. What types of post-marketing evaluations regarding drug resistance/cross resistance should be conducted?

We look forward to two days of interesting and productive discussions. It is clear that, in order to develop effective new antiretroviral agents and generate successful treatment regimens, an extensive collaboration between industry, academia, and government will be necessary. If drug resistance technology is to be used productively in the drug development process, consensus regarding standardization and interpretation of assays, and algorithms to determine clinically significant mutations will be necessary. At the end of this workshop we hope to have a clearer understanding of the currently available assays, and what further work needs to be done to enhance the potential usefulness of these technologies in the drug development process. While many challenges must be faced, there are also great opportunities to optimize the use of HIV-I resistance technology in drug development and clinical trials to improve treatment outcome.

Bibliography:

1. Hirsch MS, Conway B, D'Aquila RT, et al. Antiretroviral drug resistance testing in adults with HIV infection. JAMA 1998;279: 1984-91.
2. Wainberg MA, Friedland G. Public health implications of antiretroviral therapy and HIV drug resistance. JAMA 1998;279: 1977-83.
3. Mayers, D. Drug-resistant HIV-l, the virus strikes back. JAMA 1998;279:2000
4. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-l therapy: the VIRADAPT randomised controlled trial. Lancet 1999;353:2 195-99.
5. Baxter JD, Mayers DL, Wentworth DN, et al. Final results of CPCRA 046: a pilot study of antiretroviral management based on plasma genotypic antiretroviral resistance testing (GART) in patients failing antiretroviral therapy. Third International Workshop on HIV Drug Resistance and Treatment Strategies, San Diego 1999, abstract 61.
6. Little SJ, Darr ES, D'Aquila RT, et al. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. JAMA 1999;282: 1142-49.
7. Boden D, Jurley A, Zhang L, et al. HIV-l drug resistance in newly infected individuals. JAMA 1999;282: 1135-41.
8. Yerly S, Kaiser L, Race E, et al. Transmission of antiretroviral-drug-resistant HIV- 1 variants. Lancet 1999;354:729-33.
9. Gunthard HF, Wong JK, Ignacio CC, et al. Human immunodeficiency virus replication and genotypic resistance in blood and lymph nodes after a year of potent antiretroviral therapy. J Virol 1998;72:2422-8.
10. Roberts B, Pau C, Weinstock H, et al. Phenotypic evidence for cellular compartmentalization of AZT-resistant HIV-l. Sixth Conference on Retroviruses and Opportunistic Infections 1999, Chicago, abstract number 299.

Attachments:

1. Hirsch MS, Conway B, D' Aquila RT, et al. Antiretroviral drug resistance testing in adults with HIV infection. JAMA 1998;279: 1984-9 1.
2. Wainberg MA, Friedland G. Public health implications of antiretroviral therapy and HIV drug resistance. JAMA 1998;279: 1977-83.
3. Mayers, D. Drug-resistant HIV-l, the virus strikes back. JAMA 1998;279:2000
4. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. Lancet 1999;353:2 195-99.
5. Baxter JD, Mayers DL, Wentworth DN, et al. Final results of CPCRA 046: a pilot study of antiretroviral management based on plasma genotypic antiretroviral resistance testing (GART) in patients failing antiretroviral therapy. Third International Workshop on HIV Drug Resistance and Treatment Strategies, San Diego 1999, abstract 61.
6. HIV Resistance Collaberative Group, Data Analysis Plan for Resistance Studies
7. Little SJ, Darr ES, D'Aquila RT, et al. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. JAMA 1999;282: 1142-49.

8. Scott, J, Dix, L, Ait-Khaled, M, et al.. The predictive quality of genotype and phenotype data on virologic failure in HIV-l infected subjects who had failed a protease inhibitor regimen (CNAA2007).
9. Miller, V, Cozzi-Lepri, A, Hertogs, K, et al. Association between phenotypic drug resistance and virologic response to mega-HAART regimen in patients from the Frankfurt HIV Cohort.
10. HIV Resistance Collaborative Group Data Analysis Plan: Baseline Genotype as a Predictor of Week 24 HIV RNA ≥ 500 copies/ml in ACTG 333.