

February 22, 2005

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



RE: Docket No. 04D-0484 Draft Guidance for Industry on the Role of Human Immunodeficiency Virus Drug Resistance Testing in Antiretroviral Drug Development

Merck & Co., Inc. is a leading worldwide human health product company. Merck's corporate strategy — to discover new medicines through breakthrough research — encourages us to spend nearly \$3 billion annually on worldwide Research and Development (R&D). Through a combination of the best science and state-of-the-art medicine, Merck's R&D pipeline has produced many of the important pharmaceutical and biological products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R&D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. In the course of developing treatments for HIV, Merck scientists regularly address issues affected by the draft guidance (hereafter referred to as the Guidance). Therefore, we are well qualified to comment on this guidance.

The Guidance is well constructed and comprehensive in covering the role of HIV resistance testing in drug development and postmarketing. It accurately reflects the topics discussed at the Nov. 2-3, 1999, Antiviral Drugs Advisory Committee meeting. However, Merck has provided below comments that may help the FDA when it finalizes the Guidance.

Lines 183-184: The Guidance indicates that for antiviral assays, the IC₅₀ value is preferred over the IC₉₀ or IC₉₅ value. We agree that the IC₅₀ value provides the most precise measure of antiviral potency in single-cycle infectivity assays, but in our experience the IC₉₅ is the most robust measure of potency in multiple-round (i.e., spreading infection) assays that detect virus production. This section also states that a reference virus for antiviral assays should be grown in Peripheral Blood Mononuclear Cells (PBMCs). However, this kind of reference is not appropriate for phenotypic assays based on recombinant viruses produced by transfection.

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Recommendation: The Guidance should indicate that the format of each antiviral assay will determine the type of reference virus that should be used and whether it is appropriate to report the IC₅₀ or IC₉₅ value.

Line 199: The specific conditions for IC₅₀ serum/AAG adjustment should be stated.

Recommendation: We suggest that 50% normal human serum is appropriate.

Lines 222-234: This section speaks to genotypic methods to identify mutations conferring a reduction in susceptibility to a drug.

Recommendation: If site-directed mutagenesis experiments within the target gene fail to recapitulate the observed resistance phenotype, then the potential effects of mutations elsewhere in the viral genome should be examined.

Lines 227-234: This section, which is listed under the heading “Genotype”, describes how to interpret genotypic findings using recombinant virus assays. This discussion is really more related to phenotypic assays rather than genotypic assays.

Recommendation: We suggest moving these sentences to the “Phenotype” section that follows (lines 238-241).

Line 270: Defining the minimum plasma viral RNA level for a genotypic assay is not straightforward unless the viral primer binding site sequences are highly conserved. This is often not the case. Genetic variability in these sites can lead to significant discordances between viral load and the ability to amplify these sequences.

Recommendation: This determination should be made with a standard isolate as a benchmark to assess PCR sensitivity under ideal conditions, with the caveat that these values may not apply to actual patient samples.

Line 281: The term “major” in the context of resistance mutations is subjective. Given the strong context-dependence of many drug resistance substitutions, (e.g. for the protease inhibitors, a mutation may be “major” in one genetic context but irrelevant in another).

Recommendation: The Guidance should avoid the use of “major,” where more select terms are available.

Line 282: It is possible to obtain the sequences of entire genes using modern amplification and sequencing technology. As was the case for the viral RT, distal regions of the protein not previously thought to be involved in resistance were implicated as the data set matured.

Recommendation: To avoid this in the future, we suggest that the entire coding sequence of each gene implicated in drug susceptibility be determined, and all observed substitutions tracked.

Line 287: Defining the number of bases that can be read successfully from sequencing primers often varies by template, and this is particularly true for HIV.

Recommendation: Incorporate general language that requires sequences to be unambiguous (e.g. by recommending Phred [or equivalent] values, requirement for

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double-strand coverage, etc.) rather than specifying that this be accomplished by certain primers.

Line 475: Because of its poor time resolution, the use of PBMC proviral DNA for sequencing should be discouraged.

Recommendation: The Guidance should specify the use of plasma or serum vRNA as the starting material for sequencing.

Lines 483-490: The terms “primary” and “secondary” mutations are often ambiguous or misleading, particularly in cases in which resistance is the consequence of the interactions of multiple substitutions whose genetic contexts are subject to change. In practice, these arbitrary terms are not particularly useful, and mutational assignments to these categories can change over time as new data are acquired (c.f. IAS Drug Resistance Panel Recommendations over the past 5 years or so).

Recommendation: We agree with the intent of this paragraph that appears to encourage following all observed genetic changes irrespective of their perceived “importance” in resistance. Therefore, it would be preferable to state it directly.

Lines 494-501: The discussion appears to refer specifically to drugs intended to be used in a salvage setting. For first-line use of a drug against “wild type” viruses, phenotypic breakpoints are less relevant and would be difficult or impossible to obtain. If natural drug susceptibilities vary across “wild type” viral populations, this would be important to capture. However, this possibility was already addressed in lines 187-194.

Recommendation: Qualify that the recommendation applies to the treatment of drug (or same class)-experienced patients.

Lines 553-556: This section speaks to conducting exposure-response analyses with regard to relevance to virologic outcome.

Recommendation: The Guidance should acknowledge that pharmacokinetic data should be obtained at steady state.

Lines 725-728: Even if the choice of a most appropriate comparator might differ for different drugs or drug targets, including the standard comparator information (perhaps in addition to another potential comparator) would make the data set internally consistent across multiple drugs.

Recommendation: It is desirable to specify what sequence is considered as a “wild type” reference. This could be either the sequence of an actual isolate, e.g. HXB2, or a clade consensus sequence.

Line 732: This list omits several polymorphic residues known to exert significant potential effects on viral PI phenotype. Even though their potential contributions are more difficult to assess because of their natural occurrence, they are nonetheless important.

Recommendation: The following should be included in the core list: L10, K20, and L63

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Lines 858-886: The term “genetic threshold” implies that resistance is an all-or-none phenomenon. While large decreases in susceptibility can occur with few mutations for some drugs, (e.g. M184V for high-level 3TC resistance), for other drugs, susceptibility is lost gradually and the judgment of what constitutes meaningful “resistance” is very subjective. In practice, this is dictated by the sensitivity limits and reproducibilities of the phenotypic assays used. It would be more accurate to refer to this as a “genetic barrier”, because the need to acquire multiple substitutions acts as a (probabilistic) barrier to the loss of drug susceptibility, but it does not imply that any particular critical threshold level is significant. In this context, the level at which “susceptibility” becomes meaningful “resistance” depends on drug potency and exposure, and this will differ for each drug.
Recommendation: Replace the word “threshold” with “barrier” in each instance from lines 858-886; substitute “resistance” with “measurable resistance” in line 862; substitute “reduced susceptibility” with “measurably reduced susceptibility” in line 863.

Lines 870-899: The only substantial difference between part A (Low genetic barrier...) and part B (High genetic barrier...) is point #1 under “in vitro evidence”—points 2 and 3 under “In vitro evidence” and points 1 and 2 under “Clinical evidence” are essentially the same in parts A and B.

Recommendation: This section could be simplified by highlighting up front the only real criteria given for distinguishing between low and high genetic barrier, i.e., whether resistance requires only one or two amino acid changes or whether multiple amino acid sequence changes are required. It should also be acknowledged that these criteria are highly subjective in nature. The remaining points in the present “In vitro evidence” and “Clinical evidence” sections could then be written once to indicate that they apply to any agent regardless of whether it has a low or a high genetic barrier.

Lines 903-908: As “key mutation” and “accessory or compensatory mutation” are defined in the Guidance, drugs that impose a high genetic barrier to resistance (particularly IDV and LPV) have no “key mutations” associated with them. No individual substitution engenders a measurable decrease in susceptibility to either of these drugs. Further, resistance results only from the accumulation of multiple “accessory or compensatory” mutations as they are defined in the Guidance.

Recommendation: The use of arbitrary and misleading terms should be avoided. Although these terms came into widespread use in an attempt to simplify the terminology, it is misleading and incorrect to take these terms literally. As was shown nearly 10 years ago (Condra et al., 1995. Nature London 374:569-571), a polymorphic residue such as L63 (which is not considered by the IAS to be either a “primary” or a “secondary” mutation) can have as large an impact on IDV resistance as V82 (which is considered by the IAS to be “primary”). The use of these terms tends to ignore the strong context sensitivities of mutational interactions, and focuses inappropriate attention on the residues that are the easiest to interpret; however, these are not necessarily the most “important.”

Lines 912-913: As used in the Guidance, “fitness” is defined by viral replication in the absence of drug, but “fitness” may change dramatically if drug is present. As an example, the recent description of a nelfinavir-dependent mutant (Matsuoka-Aizawa et al.

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2003. J Virol 77:318-27) illustrates that some mutants with apparently low “fitness” (in the absence of drug) may replicate more rapidly (become more “fit”) in the presence of drug.

Recommendation: Unless measurements of “fitness” are shown to be de-coupled from target protein activity, then they may only apply when no relevant drug(s) are present. Therefore, the biological impact of viral “fitness” is often difficult or impossible to interpret.

We welcome the opportunity to provide comments on this draft Guidance and to meet with you to discuss our comments. Please feel free to contact me at (301) 941-1402.

Sincerely,

A handwritten signature in black ink, appearing to read "Brian M. Mayhew". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Brian M. Mayhew
U.S. Regulatory Policy