



Guidance for Industry: Role of HIV Drug Resistance Testing in Antiretroviral Drug Development.

Draft guidance issued by CDER (Division of Antiviral Drug Products) in November 2004.

Bayer Diagnostics, a division of Bayer Healthcare LLC, has welcomed the opportunity to review and comment on the above referenced draft guidance document. As a company with interests in both HIV resistance testing and antiretroviral drug development, Bayer welcomes the agency's efforts to improve clinical development of drugs, and their post approval application, by recognizing the value of diagnostic information obtained through state-of-the-art genomic technology.

Bayer Diagnostics has considered the document and is pleased to offer comments and feedback to the agency. Thank you for the opportunity to comment.

Line 117

Concern: Variable performance characteristics of commercially available assays not FDA cleared

Recommended wording:

Currently two HIV resistance assays have been cleared by FDA. In addition, several laboratory-developed 'home brew' and other investigational assays are used, for which performance characteristics of sensitivity, specificity and reproducibility have not been established or reviewed by FDA. The Division recommends the use of FDA-cleared assays where possible, to assure that assay results are easily understood and will provide accurate test results throughout the course of the drug development process, and beyond. The FDA cleared assays include the TRUGENE HIV-1 Genotyping Assay and ViroSeq HIV-1 Genotyping System¹.

Line 132

Concern: Longitudinal studying of resistance using non-standardized diagnostic tests

Recommended wording:

An efficient way to accomplish these goals is to include resistance testing in all phases of drug development with an emphasis on earlier stages of development. The Division recommends the use of FDA-cleared assays where possible, to assure that assay results are easily understood and will provide accurate test results throughout the course of the drug development process, and beyond. Where this is not possible (e.g. the genomic area of interest is not covered by a FDA-cleared device), the Division requests analytical and control data be provided that assures the assay results are reproducible over time, and if appropriate at different testing sites and operators, commensurate with the development

¹ In keeping with the 2002 CDER guidance entitled Antiretroviral Drugs Using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval, it is noted that specific FDA-approved assays are recommended. We recommend the Division treat the guidance on HIV Drug resistance testing similarly.



program.

Line 132 and 162

Concern: Longitudinal studying of resistance and variable performance characteristics of commercially available assays not FDA cleared

Recommended wording for Line 162:

We recommend that sponsors be consistent in the assay used for any particular analysis or measurement in studies. Again, the Division recommends the use of FDA-cleared assays where possible, to assure that assay results are easily understood and will provide accurate test results throughout the course of the drug development process, and beyond. Where this is not possible (e.g. the genomic area of interest is not covered by a FDA-cleared device), the Division requests analytical and control data be provided that assures the assay results are reproducible over time, and if appropriate at different testing sites and operators, commensurate with the development program.

Line 183

Concern: Variation in PBMC cell population makes it difficult to define a reference standard. Each laboratory is likely to use different sources of PBMCs to grow the strain, which will vary widely by HLA, cell type ratios etc.

Recommended change:

Bayer suggests the Division identifies in this guidance document a source or example of strain that should be used, with guidance given on how to demonstrate equivalency to this strain if a sponsor chooses to use a different one.

Line 191

Concern: To our knowledge, none of the FDA-approved or other commercial resistance assays in use claim to be applicable to HIV-2. None of the three FDA-approved HIV viral load assays (PCR, bDNA, NASBA) claim to be applicable to HIV-2. In fact, HIV-2 isolates are relatively rare. Given the lack of confirmed diagnostic assays for HIV-2 testing, it seems unreasonable to require that HIV-2 strains need to be tested.

Recommended change:

Bayer recommends the Division deletes HIV-2 from the list.

Line 268

Concern: Inconsistency in standards of review and the requirements of resistance test data between CDER and CBER.

Recommended wording:

Where the genotype assay has been FDA-cleared, the sponsor's IND should cross reference the



510(k). The data to support these performance characteristics must be submitted to the IND, if the resistance assay is not FDA-cleared. To ensure comparable standards in the oversight of these non-standardized diagnostic assays, inter-divisional review of the IND will occur, through collaboration with CBER.

Line 268

Concern: These requirements would not assure assay reliability that will be expected to fulfill the development needs described in this guidance document.

Recommended additions:

The following information must be cross referenced to a 510(k) or submitted to the sponsor's IND.

Performance characteristics must include inter-lot reliability measures, linked to an established and well characterized control as well as inter-site and operator reliability and reproducibility if the development program indicates the need.

Knowledge of the types of substances that might interfere with the assay must be documented as serial testing will occur with samples drawn at different times.

Line 274 and 287

Concern: Genotypic (and phenotypic) differences due to clade differences are difficult to establish as there are no recognized reference standards for HIV other than clade B.

Recommended change:

Bayer recommends requesting clade information of the HIV samples analyzed, but not performance characterization of the assay elaborated by clade difference. Alternatively, labeling should be clear that any base calling accuracy claims of non Clade B virus be clearly linked to the reference sequence. Guidance needs to be given as to what the Division would accept as a non-B reference sequence. Currently, a B clade reference sequence is used for all clades, B and non B.

Line 277 and 287

Concern: Neither of the two FDA-cleared HIV resistance tests has established claims for mutant/wild type ratios and data to support this is inconclusive. The Division should clarify its major area of concern or interest here, to enable sponsors to provide the relevant information to meet the needs.

Recommended wording:

Sponsors should identify if their resistance assay reliably detects emerging resistant strains of HIV. Sensitivity of detection should be established for ratios detected. The sponsor should clearly identify if detection of the emerging strains is not a characteristic of the assay, and therefore the drug development is focused on the dominant viral strain.



Line 280

Concern: It may not always be achievable or necessary to determine the entire coding sequence of the gene for the target protein.

Recommended wording:

The entire coding sequence of the gene for the target protein should be determined in the early stages of analysis of resistant variants. Where the entire sequence is not available, a justification must be provided.

Line 288

Concern: The draft guidance document referenced here has been in draft since 2001. The industry would benefit from this being issued in its final form.

Recommendation:

Bayer recommends the Division encourages CBER to finalize its guidance on HIV drug resistance genotype assays, and that this Division and CBER ensure compatibility between these two documents before they are issued. In the 2001 draft CBER proposes Class III medical device classification for HIV genotype ASRs. A HIV resistance assay is Class II. Many comments were submitted to the docket at that time, from the industry, laboratories and interest groups, rebutting this proposal which would negatively impact development in this field. This could have an impact on the Division's desire to see well characterized resistance testing as part of drug development and ultimately, patient management.

Line 365

Concern: Standardization of resistance / mutational algorithms has not been achieved in the field. Ones used commercially (whether developed in house or provided by the industry) are more up to date than the guideline provided in the 2001 CBER draft guidance document on HIV drug resistance genotype assays.

Recommended wording:

Information about the specific assays and the mutational algorithms used in protocols should be provided in the sponsor's IND or a cross reference given to the 510(k). For non-FDA cleared mutational algorithms, justification should be provided through literature support.

Line 402

Concern: Allowing a sponsor to use different assays through the development process requires very tight control on the different assay performances, and should encourage use of FDA cleared assays.

Recommended wording:

Sponsors should use FDA cleared assays where available. If this is not possible, the same assay



should be used during the drug development program, with appropriate controls in place to demonstrate assay reproducibility. If a sponsor changes assay during the course of the development, the performance characteristics of the two assays must be compared, and the data submitted to the sponsor's IND to support the change.

Line 426

Concern: This sentence is out of date and does not capture all FDA approved assays for measurement of HIV viral load.

Recommended wording:

The virologic response parameters used in these analyses are (1) proportion < 400 copies/mL (PCR, bDNA or NASBA), (2) proportion < 50 copies/mL (PCR) or <75 copies/mL (bDNA) and (3) mean change from baseline at the protocol specified time-point, using FDA-approved assays.

It is further recommended the 2002 CDER guidance entitled Antiretroviral Drugs Using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval be updated to include all three FDA approved viral load assays (i.e. add VERSANT HIV-1 RNA 3.0 Assay).

Line 460

Concern: For existing resistance profiling, the source of the mutational algorithm is relevant, as there can be differences in interpretation of the mutation patterns conferring full or partial resistance between them.

Recommended wording:

Information about the mutational algorithms used in protocols should be provided in the sponsor's IND or a cross reference given to the 510(k). For non-FDA cleared mutational algorithms, justification should be provided through literature support.

Line 650

Concern: The inclusion of resistance data in product labeling could lead to poor patient management, depending upon how it is presented, or expected to be used.

Resistance mutation patterns to specific drugs do evolve with data and expertise and the determination of partial or full resistance to a specific antiretroviral is part of the evolution of the Bayer HealthCare mutational algorithms that are cleared through FDA on a regular basis. This evolution is unlikely to be captured in the drug labeling and therefore if applied too literally, a patient's virus may exhibit some resistance mutations at their baseline sequence yet still benefit from the drug.

Where drug activity is focused on an area of the genome not included in the reverse transcriptase or protease regions, the widespread availability of FDA-cleared assays to be used in conjunction with the therapy as part of patient management is not known. The draft 2001 guidance document on HIV drug resistance genotype assays currently proposes the highest barrier for industry to develop HIV genotype Analyte Specific Reagents (ASR) to provide to laboratories, i.e. the requirement for FDA premarket approval to commercialize HIV ASR reagents.



Recommendation:

Clarify Division's expectations and objectives in requesting this information in product labeling.

Line 739

Concern: The Bayer HealthCare mutational algorithm which is FDA cleared and updated annually does not recognize E44 as a major mutation (it is a minor resistance mutation for 3TC/FTC resistance). We do recognize Q151 as a major resistance mutation which is missing from the list. This demonstrates the need to collaborate with CBER who are reviewing and clearing these mutational algorithms for the IVD industry.

Recommended change:

Bayer recommends the Division deletes E44, adds Q151 and provides some guidance on how the algorithms will be reviewed and agreed upon.

Line 903.

Concern: Lack of clarity of the definition.

Recommended wording:

The definition should include with the words "by itself". A treatment selected amino acid change that, by itself, can cause a decrease in susceptibility to one or more antiretroviral agents of the same class.

These comments are respectfully submitted to Docket 2004D-0484 on behalf of Bayer Diagnostics on February 25, 2005

Kind regards

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