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# Guidance for Industry

## **Clinical Considerations for Accelerated and Traditional Approval of Antiretroviral Drugs Using Plasma HIV RNA Measurements**

### *Draft Guidance*

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**August 1999  
Clin**

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## **Guidance for Industry<sup>1</sup>**

# **Clinical Considerations for Accelerated and Traditional Approval of Antiretroviral Drugs Using Plasma HIV RNA Measurements**

## **I. INTRODUCTION**

This guidance is intended to assist sponsors in the clinical development of drugs for the treatment of human immunodeficiency virus (HIV) infection. Specifically, this guidance addresses the Agency's current thinking regarding designs of clinical trials that use HIV ribonucleic acid (RNA) measurements to support accelerated and traditional approvals of antiretroviral drug products. This guidance does not address specific phase-1 and -2 development issues.

The Agency believes that this guidance may be useful to pharmaceutical sponsors as they design, conduct, and analyze phase-3 clinical studies. In addition, this guidance is intended to serve as a focus for continued discussions both within the Division of Antiviral Drug Products (the Division) and among the Division and pharmaceutical sponsors, the academic community, and the public. The Agency anticipates that this guidance document will undergo future revisions as the field of HIV treatment progresses.

In addition to consulting this guidance, sponsors are encouraged to contact the Division to discuss specific issues that arise in the development of an antiretroviral drug product.

## **II. BACKGROUND**

In July 1997, the Agency convened an advisory committee meeting to consider the use of changes in HIV RNA levels as endpoints in clinical trials supporting traditional approval of antiretrovirals. Although accelerated approvals are routinely based on changes in endpoints such as CD4 cell counts and plasma HIV RNA levels, clinical endpoint trials assessing effects on mortality and/or disease progression had been a requirement for traditional approvals prior to July 1997. With the availability of potent antiretroviral drug regimens and sensitive assays for assessing plasma HIV RNA, the standards of clinical practice evolved to a paradigm emphasizing maximal and durable HIV RNA suppression. In addition, with the successes of

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<sup>1</sup>This guidance has been prepared by the Division of Antiviral Drug Products, Office of Drug Evaluation IV, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking certain aspects of on antiretroviral drug product development for accelerated and traditional approval. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statute, regulations, or both.

combination therapy and subsequent decline of HIV-related clinical illnesses, it was clear that a requirement for clinical endpoint studies for every drug approval was no longer feasible. Use of a virologic endpoint appeared to be a viable option for facilitating drug development.

To evaluate the feasibility of using HIV RNA as a study endpoint, a collaborative group of pharmaceutical, academic, and government scientists investigated relationships between treatment-induced changes in HIV RNA and clinical endpoints from ongoing and completed antiretroviral trials. In several analyses of more than 5000 patients in multiple trials, there was a clear association between initial decreases in plasma<sup>2</sup> HIV RNA, within the first 24 weeks, and a reduction in the risk of clinical progression and death. This relationship was observed across a range of patient characteristics including pretreatment CD4 counts and HIV RNA levels, prior drug experience, and treatment regimen. Based on these data, the Division of Antiviral Drug Products advisory committee concurred that favorable treatment-induced changes in HIV RNA *levels* were highly predictive of meaningful clinical benefit and that HIV RNA measurements could serve as endpoints in trials supporting both accelerated and traditional approvals. The Division proposed that accelerated approvals could be based on studies that show a drug's contribution toward shorter-term reductions in HIV RNA (e.g., 24 weeks) while traditional approvals could be based on trials that show a drug's contribution toward durability of HIV RNA suppression (e.g., at least 48 weeks). The committee agreed with this proposal and also suggested that changes in CD4 cell counts be consistent with observed HIV RNA changes when considering approval of an antiretroviral drug.

### **III. ACCELERATED APPROVAL**

Accelerated approval regulations (21 CFR 314.500) apply to drugs that “have been studied for their safety and efficacy in treating serious and or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of available therapy, or improved patient response over available therapy).” An accelerated approval may be based on a surrogate endpoint reasonably likely to predict clinical benefit (but not necessarily a fully established surrogate) or a clinical endpoint other than irreversible morbidity or mortality, where the ultimate goal of therapy is an effect on morbidity or mortality. Under accelerated approval, marketing is subject to certain conditions outlined in the regulations, principally a need to conduct further studies to establish clinical benefit.

Because continuous treatment with multiple antiretrovirals is necessary to achieve HIV suppression and because a substantial number of patients cannot tolerate or have developed virologic resistance to many of the approved drugs, new antiretrovirals are needed. Sponsors are encouraged to study patients who have limited approved treatment options due to lack of therapeutic response or intolerance. The ability to demonstrate drug activity by showing an effect on a surrogate endpoint and safety in these populations will fulfill the requirement of accelerated approval regulations. Conducting controlled, comparative studies in patients who have exhausted many treatment regimens may call for the use of innovations in study design, including the use of multiple investigational agents, factorial comparisons, and collaboration

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<sup>2</sup> Some trials measured HIV RNA in serum rather than plasma.

among two or more sponsors. Collaboration and the use of multiple investigational agents are strongly encouraged; however, phase-3 studies should be designed such that the treatment effect of each drug of interest can be isolated and the potential for drug-drug interactions can be considered.

In addition to demonstrating a drug's safety and efficacy in patients with limited options, other potential or observed therapeutic advantages of an investigational drug may be highlighted in an NDA to support accelerated approval. Examples include improved efficacy or safety profile, improved dosing schedule, novel mechanism of action, or different clinical cross-resistance profile.

## **A. Safety**

Accelerated approval regulations do not diminish the need for an adequate safety database. The majority of antiretroviral accelerated approvals to date have been supported by safety data from at least 400 to 500 patients who received the approved dose for approximately 6 months. The numbers of patients studied for antiretroviral accelerated approvals have approximated, or exceeded, the International Committee on Harmonization (ICH) guidelines for drugs intended for long-term treatment of *non-life-threatening* conditions.<sup>3</sup> The ICH guidance suggests that drug approvals be supported by safety data on at least 300 to 600 patients receiving the proposed dose for 6 months with safety data on a total of 1,500 patients, including patients exposed to the drug for a shorter term. The guidance also states that additional safety data on longer term use in a smaller cohort is advisable.

Although advanced HIV infection is life threatening, less advanced and asymptomatic HIV-infected patients also receive antiretroviral drugs for indefinite periods; therefore, the ICH guidance regarding the recommended number of patients with drug exposure of 6 months or greater is generally applicable for antiretroviral drugs. However, applicants are encouraged to discuss their proposed safety database with the Division prior to submitting an NDA. On occasion, findings in preclinical or phase 1-2 development may suggest the need for a larger database to adequately evaluate potential drug toxicity.

Controlled and comparative safety data are preferred. Safety data from uncontrolled open protocols may be useful, but often lack the degree of detailed reporting obtained in controlled clinical trials. In addition, the ability to assess causal relationships between a drug and an adverse event is more difficult when relying on uncontrolled safety data.

## **B. Efficacy**

### *1. General Issues*

Studies in a broad range of patient populations (gender, age, and race) and a range of pretreatment characteristics (e.g., advanced and early disease, heavily

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<sup>3</sup> ICH, *EIA The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions*, March 1995.

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pretreated and treatment naive) are recommended to characterize the activity of the drug. The Division recommends that NDAs include at least two adequate and well-controlled studies of a minimum of 24 weeks duration to support accelerated approval. However, given that some patients will have longer-term follow-up, submissions should include some data past 24 weeks when possible. In the setting of combination therapy, analyses at earlier time points (e.g., 16 weeks) have proven to be less discriminating for detecting important differences between treatment regimens. In addition, prior to 24 weeks, some patients may have HIV RNA levels that are still declining, especially when measured with sensitive assays.

It is important that study results clearly show the investigational drug's contribution to decreases in HIV RNA, as part of a combination regimen, in comparison to a control combination regimen.

### *2. Control Arms*

Every attempt should be made to design randomized, blinded (or partially blinded), controlled trials that provide all study patients with treatment regimens according to a standard of clinical practice while the trial is being conducted. Control regimens regarded as suboptimal or nonpreferred may be considered unethical or may jeopardize the viability of a study if there are substantial treatment discontinuations or switches. In addition, it is important that the activity of control regimens be well characterized in previous studies to support their use as active controls. Proposals for control arms that deviate from current standards of care should be supported by convincing scientific rationale and/or data and discussed with the Division before implementation. Because of the rapidly evolving nature of HIV treatment regimens and changes in accepted standards of treatment, appropriate comparison regimens can be expected to change over time.

Blinded comparisons with controls are preferred, but blinding drugs or regimens may not be feasible in all cases. When blinding is not possible, open-label protocols should have detailed procedures for treatment switches and toxicity management. Differential implementation of protocol procedures among treatment arms in open-label studies may impair interpretation of study results.

### *3. Study Design Options*

- Superiority trial designs

Phase-3 superiority trials can include *add-on* or *substitution* comparisons. In the first case, the investigational drug plus a standard combination regimen is compared to placebo plus the same standard regimen. In the second case, the investigational drug is substituted for a component of a standard regimen and compared to the standard regimen. In both cases, the regimen with the

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investigational drug must show superiority to the control regimen. In some cases, an experimental drug may be added to a background regimen of drugs that the participant or investigator chooses from a list of possibilities.

- Equivalence trial designs

Equivalence trials use substitution comparisons as described above. It is important that the contribution of the substituted drug to a regimen's overall activity be previously characterized in the population of interest. This information should be used to support an equivalency comparison and to calculate an appropriate sample size.

- Dose comparison trial designs

Dose comparison studies can support accelerated approval; the trials should be carefully designed so that treatments cover a large enough range to show a dose-response slope. However, since it would not be desirable to design a protocol using doses of antiretrovirals that are likely to be suboptimal based on preclinical or clinical data, such studies should be discussed with the Division in advance.

#### *4. Study Procedures*

Protocols should include procedures for clinical management based on changes in HIV RNA. However, to facilitate interpretation of study results, it is critical that management decisions be made in a uniform manner. This is particularly important for open-label studies. Protocol procedures that allow treatment switches for patients who never achieve HIV RNA levels below an assay limit should be applied consistently across treatment arms. For example, some protocols allow patients who have not achieved an HIV RNA reduction of 1 log<sub>10</sub> by 8 weeks to switch their antiviral regimen. These criteria may vary depending on the population studied.

#### *5. Study Endpoints*

Plasma HIV RNA measurements may be used in the primary study endpoint assessing drug efficacy. However, changes in CD4 should also be evaluated during the course of the study. It is generally recommended that sponsors use FDA approved HIV RNA assays to ensure that assay performance characteristics are understood. However, the Agency acknowledges continuing advances in the field of HIV RNA monitoring. When unapproved assays are employed, the sponsor should be prepared to provide the Division with information supporting limits and performance characteristics of the assay (see section 6).

For most studies the portion of subjects with HIV RNA levels below the assay limit at 24 weeks should be the primary endpoint for accelerated approval. Such analyses are consistent with the current goals of clinical practice. However, mean

changes in HIV RNA from baseline over time may be another useful analysis for heavily pretreated patient populations in which reduction in HIV RNA is apparent, but in which few have achieved responses below the assay limit. Analyses evaluating changes over time in CD4 cell counts should accompany the analyses of HIV RNA.

Clinical endpoint data (CDC class C events) should also be collected, analyzed, and submitted with the NDA. However, the frequency of such events is likely to be low.

#### *6. Statistical Considerations*

For equivalence comparisons, the Division has generally recommended using a delta of 10 percent for performing sample size calculations, however a smaller delta may be indicated or a larger delta may be acceptable depending on the effect size expected from the protocol's control arm in the population studied. We recommend two-sided 95 percent confidence intervals adjusted for multiple comparisons. Both equivalence and superiority can be assessed in the same study provided that the equivalence comparison and choice of delta has been specified prior to study initiation or unblinding.

Intent-to-treat analyses that include all randomized patients should be included in all NDAs. However, sensitivity analyses that use different methods of handling treatment discontinuations and missing data should also be provided in support of efficacy. At least one analysis should evaluate the effect of counting missing data or treatment discontinuations as treatment failures (above the assay limit). In general, missing HIV RNA data between study visits with values below the assay limit can be censored.

## **IV. TRADITIONAL APPROVAL**

In this guidance, the term *traditional approval* refers to approvals that are not restricted by the conditions set forth under Subpart H of the regulations (21 CFR 314.500). Traditional approval is the usual marketing clearance mechanism for the majority of drugs that have demonstrated clinical efficacy in phase-3 studies.

### **A. Safety**

As for accelerated approvals, controlled and comparative safety data are preferred. Safety data from uncontrolled compassionate use protocols may be supportive, but often lack the degree of detailed reporting obtained in controlled clinical trials. Uncontrolled safety data diminish the ability to assess causal relationships between a drug and adverse event.

## **B. Efficacy**

### *1. Study Design*

The same studies that are evaluated at 24 weeks for accelerated approval may be continued for 48 weeks and longer to support traditional approval. Traditional approval may be based on study results that show the drug's contribution toward sustained suppression of plasma HIV RNA. However, some applications may contain a combination of clinical endpoint studies and HIV RNA studies. Thus, the types of studies included may partly determine the indications granted. In addition, drugs that show a major discordance between HIV RNA and CD<sub>4</sub> cell count responses (i.e., an HIV RNA decrease with a decrease in CD<sub>4</sub> cell counts) should probably be evaluated using clinical endpoint studies.

Issues relating to choice of control arms, comparisons, and study procedures are discussed in previous sections.

### *2. Study Endpoints*

The proportion of patients with HIV RNA levels below the assay limit at 48 weeks (or longer) and time-to-loss-of-virologic-response may be considered primary endpoints for trials supporting traditional approval. The sponsor should also include supportive analyses of CD<sub>4</sub> count responses and clinical endpoints. In effect, the investigational drug should show no deleterious effect on clinical endpoints and should show favorable CD<sub>4</sub> responses. The duration of these studies should permit the last patient randomized to have passed the 48-week time point. The final study report should include all available data at the time of analysis, including that beyond 48 weeks.

- **Time-to-loss-of-virologic-response**

In superiority trials, an endpoint of time-to-loss-of-virologic-response allows participants who have lost a virologic response to switch therapy without compromising major study analyses. One definition for time-to-loss-of-virologic-response is the time between randomization (or start of treatment) and the last value below the assay limit in a patient who subsequently demonstrates two consecutive HIV RNA levels above the assay limit. Subjects who do not achieve suppression below the assay limit during the study (or within a predefined shorter time period allowing for earlier treatment switching) may then be defined as having a time to failure of zero. Analysis of the total duration below the assay limit may also be presented, usually as a secondary analysis.

Generally, subjects who experience clinical events indicating HIV disease progression, or who prematurely discontinue study treatment due to toxicity/intolerance or death, should be considered treatment failures at the time of those events. This approach may help to minimize the number of missing data

points in primary analyses. Secondary analyses based on virologic failure alone may also be performed.

Since a risk-benefit ratio is always considered in any approval, careful attention should be paid to treatment discontinuations for intolerance or toxicity. In all cases, reasons for treatment and/or study discontinuations should be clearly defined in the NDA. For example, patients who did not have a protocol-defined dose-limiting toxicity, but nonetheless had an unresolved intolerance or adverse event at the time of discontinuation, should be classified as discontinuing treatment secondary to drug intolerance and not due to *patient's choice* or *other*. Analyses should be performed, evaluating reasons for treatment discontinuations, possible baseline risks for treatment intolerance, and time until a dose-limiting adverse reaction. Such analyses are particularly crucial in studies with a substantial proportion of treatment discontinuations (greater than 20-25 percent), or in studies in which there were differential rates of discontinuations among treatment arms.

- Proportion below the assay limit

The proportion of patients with HIV RNA levels below the assay limit at 48 weeks will usually be an important secondary endpoint in superiority trials. Since statistical methods are insufficient for time-to-event analyses for equivalence comparisons, assessing proportions of patients below the assay limit is recommended for equivalence trials.

- Clinical endpoints

In the past, the Division has usually advised that two clinical endpoint trials be launched in the course of planning for a traditional approval application. Traditional approval was sometimes granted after results from a single trial were found to be sufficiently compelling. Adequate and well-controlled trials showing clinical benefit as measured by HIV-related clinical events and survival will continue to be considered necessary support for an application for traditional approval. Results of such studies may be described in the package insert, and may influence the approved indication(s). The guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 14, 1998) should be consulted for additional discussion of circumstances in which approval may be considered on the basis of a single trial.

### **C. Statistical Considerations**

The same considerations for trials supporting accelerated approval also apply to traditional approval. It should be emphasized that studies for traditional approval should be analyzed after the last patient randomized has completed 48 weeks of treatment (if still

on therapy). Therefore, many participants will have data past 48 weeks. As much extended data as possible should be included and evaluated in the NDA.

## **V. PHARMACOKINETIC CONSIDERATIONS**

Since appropriate treatment of HIV includes multiple antiretrovirals, drug-drug interaction studies are crucial in the development plans of antiretroviral drugs. Such studies should be performed based on knowledge of the metabolism of the drug and its potential effect on the pharmacokinetics of other drugs. In many cases, clinical drug interaction studies can be conducted in healthy volunteers. Generally these studies should precede phase 3-studies to aid in the selection and dosing of combination antiretroviral regimens.

In addition, drug-drug interaction studies between antiretroviral and other commonly used concomitant medications, such as oral contraceptives, drugs for PCP (pneumocystis carinii pneumonia) or MAC (mycobacterium avium complex) prophylaxis, antituberculosis treatment (esp. rifampin) and antifungals, should be conducted prior to approval and in many cases before launching phase-3 trials.

Evaluations of age, gender, and race-related differences in drug metabolism and activity should be conducted in parallel with phase-3 development. Sponsors should become familiar with two sets of regulations pertaining to pediatric patients: (1) the pediatric rule, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biologic Products in Pediatric Patients," (63 FR 66632); and (2) pediatric exclusivity, whereby submission of pediatric data fulfilling a written agreement with FDA can qualify sponsors for additional marketing exclusivity as permitted in section 505A of the Federal, Food, Drug, and Cosmetic Act (21 U.S.C. 355a).<sup>4</sup>

## **VI. REGULATORY CONSIDERATIONS WHEN USING NEW HIV RNA ASSAYS**

In this guidance a *new* assay refers to any assay that has not been approved by the FDA or to an approved assay that is being used off label. The assay that is used in the clinical trial should be identical to the assay that is used to assess the performance characteristics. Clinical studies may use HIV RNA measurements either to quantify the amount of HIV RNA in patient samples (e.g., copies/mL) or to classify a patient sample as above or below a specific value. Therefore, considerations for both quantitative and qualitative uses will be addressed in the following subsections.

It is recommended, but not required, that FDA-approved HIV RNA assays be used to support clinical trials. However, when experimental/investigational HIV RNA measurement assays are used to support clinical trials, sufficient assay performance characteristics data should be provided. This permits an independent evaluation of an assay's limitations. Review of assay performance by the Division will focus on the interpretability of data generated by the assay with

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<sup>4</sup> FDA guidance for industry pertaining to pediatric exclusivity and other pediatric-related information are available on the Internet at: <http://www.fda.gov/cder/pediatric>.

respect to the particular clinical trials in the NDA. Thus, the Division review of assay performance data does not imply that the given assay is validated or FDA-approved for patient prognosis and/or monitoring. Furthermore, this review does not imply that the given assay is automatically acceptable for future clinical trials.

Assay design rationale, essential methodology, and performance characteristics are important components of information submitted to support new assays. Assay performance characteristics studies should be conducted on specimens that are representative of the HIV target subtype (Clade/s), and from the same tissue reservoirs (serum, plasma, other) assessed in the clinical trial. Specimen stability (handling, processing, and storage protocols) data should show no significant change of HIV RNA material as measured by the assay. Generally, these data should be derived from protocol-based experiments. Protocols and quality assurance/quality control information for the assay should be submitted with the data.

#### **A. Quantitative Assays: Performance Studies**

To support clinical virology data that rely on quantitative assessments, the methodology/technology used to generate those data should be adequately described in the application. An HIV RNA quantitative assay should be able to accurately and precisely report HIV RNA copy numbers over a defined range. Assay performance characteristics should include, but are not limited to, information/data that defines the assay accuracy, precision, sample stability, and effects of certain interfering substances.

Accuracy may be assessed by calculating the mean of repeated observations of a given known sample and comparing the mean to the known input value. Assay accuracy should be determined across the proposed range of the assay. Precision may be assessed by calculating the mean square error (MSE) and converting to a percent coefficient of variation (CV). Precision should be determined across the proposed range of the assay. The quantitative limit of the assay will be determined by the lowest input value where the assay maintains its accuracy and precision. A quantitative upper limit may be similarly defined.

Ultimately, the quantitative limit should be supported by data that characterized the assay performance characteristics. Laboratory strains and unique clinical HIV test specimens should be used to derive the performance characteristics of the assay. Each of these test specimens should first be independently and adequately quantitated (i.e., by comparability to an acceptable standard) prior to being used to define the performance characteristics of the new assay.

#### **B. Qualitative Assays: Performance Studies**

Assays that are used in a qualitative manner should have the ability to distinguish between known HIV seropositive clinical specimens and known HIV seronegative specimens with 95 percent confidence. A threshold or screening cut-off value (qualitative limit), expressed in HIV RNA copy numbers per mL must be determined. An assay result would be expressed as either a  $\geq$  or  $<$  the HIV RNA copy number

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qualitative limit. However, a result that is below the screening cut-off value does not imply that the specimen is HIV negative, it implies only that the specimen has less virus material than that needed to distinguish the specimen from a known negative with 95 percent confidence. Assay performance characteristics should include, but may not be limited to, information/data that define the assay range of specificity, range of sensitivity, sample stability, and effects of certain interfering substances.

The Division recommends that the range of specificity of the assay be defined as the 95 percent confidence interval of reported observations from 500 random seronegative blood or plasma donors. The range of sensitivity of the assay may be defined as the 95 percent confidence interval of reported observations from 200 unique seropositive samples. Each of these seropositive samples should be quantified by an independent method and then diluted to the proposed qualitative limit prior to assessing the assay range of sensitivity. It is expected that the two ranges will not overlap.

Ultimately, the qualitative limit can be supported by and derived from the assay performance characteristics data. Laboratory strains and unique clinical HIV test specimens should be used to derive the performance characteristics of the assay. Each of these test specimens should first be independently and adequately quantitated (i.e., by comparability to an acceptable standard) prior to being used to define the performance characteristics of the new assay.

## **GLOSSARY OF ASSAY TERMINOLOGY**

**Quantitative Assay:** An assay that is accurate and precise over a defined range.

**Qualitative Assay:** An assay that can distinguish between a known HIV positive specimen and a HIV seronegative specimen.

**Range of Specificity:** A 95 percent confidence interval of reported observations from 500 seronegative random blood or plasma donors.

**Range of Sensitivity:** A 95 percent confidence interval of reported observations from dilution of 200 unique seropositive samples to the proposed qualitative limit, each quantified prior to dilution by an independent method.

**Quantitative Limit:** The lower boundary of the accurate and precise defined range.

**Qualitative Limit:** The lowest concentration of HIV RNA copies per mL that the assay can reliably distinguish from seronegative samples.

**Interfering Substances:** Any substance/infectious agent that may be present in a clinical sample and affect a performance characteristic of the new assay.

**Precision:** The variability in terms of the mean square error (MSE) converted to a percent CV (CV= the square root of MSE divided by the expected value x 100 percent) within the proposed range.

**Accuracy (Bias):** The mean of repeated observations of a given known sample compared to the expected value for knowns within the proposed range of the assay.

**Sample stability:** Specimen handling, processing, and storage procedures that result in no significant changes in expected HIV RNA copy numbers.