

Reclassification of HIV Point of Care and Laboratory-based serological and NAT diagnostic devices from Class III (PMA) to Class II 510(k)

Issue Summary

Prepared for the July 19, 2018 Meeting of the Blood Products Advisory Committee (BPAC)

UPDATES to the issue summary posted online for the March 21, 2018 Blood Products Advisory Committee meeting:

- 1) Removal of diagnostic supplemental tests from footnote of tests excluded from this proposal, with clarification that donor screening supplemental tests are still excluded (page 3)
- 2) Addition of supplemental tests to tests included in this proposal (pages 5–6)
- 3) Removal of supplemental tests from tests excluded from this proposal (page 6)
- 4) Comment that table refers to first-line diagnostic devices (page 9)
- 5) Clarification of adverse event analysis (page 10)
- 6) Addition of special controls for supplemental tests (pages 18–19)
- 7) Inclusion of table of supplemental tests affected by this proposal, appendix 1 (page 24)

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1. Introduction and purpose of the panel meeting

The Division of Emerging and Transfusion Transmitted Diseases (DETTD) in the Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA), has regulatory oversight of diagnostic tests for retroviral infectious agents including Human Immunodeficiency Virus (HIV). FDA is convening this Meeting of the Blood Products Advisory Committee (BPAC) and the Medical Devices Advisory Committee (Microbiology Devices Panel) to discuss and make recommendations regarding reclassification of HIV nucleic-acid (NAT) and serology-based Point-of-Care (PoC) and laboratory-based (lab-based) diagnostic devices¹. These devices currently are regulated as Class III devices per section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)) and FDA is proposing to reclassify these devices into Class II. FDA is seeking expert advice on the appropriate classification of these devices and the development of special controls for the proposed Class II designation. The Panel will discuss reclassification of HIV diagnostic devices on July 19, 2018.

2. Background

a. Regulation of In Vitro Diagnostic Devices

Per 21 CFR 809.3, in vitro diagnostic devices are defined as “*reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.*” FDA regulations applicable to in vitro diagnostic devices are based on the FDA classification of the device. The current approach to classification is guided by several laws, most prominently the 1976 Medical Device Amendments to the original Federal Food, Drug and Cosmetic Act (FD&C Act) (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/>). Medical devices, including in vitro diagnostic devices, are classified into three regulatory classes based on the risk and the level of control necessary to assure the safety and effectiveness of a device:

- Class I: Low risk devices for which general controls are sufficient to provide a reasonable assurance of safety and effectiveness of the device.
- Class II: Moderate risk devices that require both general and special controls to provide a reasonable assurance of safety and effectiveness of the device.
- Class III: High risk devices for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness.

1) Class I Devices

¹ Excluded from this proposal are blood donor screening tests, home-use/over the counter tests, viral load and, phenotypic drug resistance tests (see pages 6 and 7). Supplemental tests for confirming blood donor screening tests also are excluded.

Class I devices are those devices for which general controls are sufficient to provide a reasonable assurance of device safety and effectiveness. Class I devices are also devices that do not present a potential unreasonable risk of illness or injury despite insufficient evidence to conclude that general controls are sufficient. General controls are not device-specific but apply generally to all devices.

Examples of general controls may include but are not limited to:

- Registration of manufacturing facilities and listing of products;
- Good Manufacturing Practices (GMPs);
- Restrictions on sale and distribution or use; and
- Other regulatory controls, e.g., labeling, adverse event reporting, controls against misbranding, adulteration of the device.

2) Class II Devices

Class II devices are devices that cannot be classified as Class I because general controls alone are insufficient to provide reasonable assurance of device safety and effectiveness. However, sufficient information on device performance is available to establish special controls that can provide such assurance. Examples of special controls may include:

- Performance standards;
- Post-market surveillance;
- Patient registries;
- Guidelines;
- Reporting requirements;
- Other appropriate action deemed necessary for mitigating the risks of the device.

Class I reserved (non-exempt) and Class II non-exempt submissions are reviewed by FDA under the 510(k)-pre-market notification (PMN) paradigm. These devices are *cleared* for marketing if they are determined to be at least as safe and effective as a preexisting ‘predicate’ device (i.e., the device is ‘substantially equivalent’ to the predicate device). Substantial equivalence broadly encompasses the following:

- The new device has the same intended use as the predicate and the new device has the same technological characteristics as the predicate, or
- The new device has the same intended use as the predicate, but the new device has different technological characteristics and the information submitted to FDA about the device both (a) does not raise new questions of safety and effectiveness and (b) demonstrates that it is at least as safe and effective as the legally marketed device. A claim of substantial equivalence does not necessarily imply that the new and predicate devices must be identical in technology or performance. Substantial equivalence is established by a range of evidence, including intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics as applicable.

3) Class III Devices

Class III devices are high risk devices for which insufficient or inadequate information exists to determine that general and special controls can provide reasonable assurance of the safety and effectiveness of the device. Devices that are life sustaining or life supporting, of substantial importance in preventing impairment of human health, or present unreasonable risk of illness or injury can be classified as Class II if special controls can be developed to mitigate the risks, otherwise, these devices are Class III. Class III devices require pre-market approval (PMA) of submissions in which demonstration of the performance of the device requires the submission of valid scientific data independent of other similar devices on the market. FDA exerts the highest level of regulatory control over Class III devices.

b. Regulation and reclassification of HIV PoC and lab-based diagnostic devices

1) Current regulatory status of HIV PoC and lab-based diagnostic devices

Currently, HIV PoC and lab-based devices are regulated as Class III devices under 513(1)(c); therefore, new devices require approval of a PMA prior to marketing. The product code (procode) MZF is used for all HIV diagnostic devices regardless of technology or if they are indicated for PoC or laboratory use. Currently, eight PoC serological tests labeled for professional use (i.e., not home-use) and twelve lab-based tests—eleven serological tests and one NAT-based diagnostic test—are approved and commercially available (Appendix 1). All of the available PoC HIV diagnostic tests met the validation and performance measures discussed at the September 15, 2000 BPAC meeting that the lower bound of the 95% CI for sensitivity and specificity must be $\geq 98\%$ and were validated using at least the minimum recommended number of clinical samples (Table 1 in Section 3 and [1]).

Reclassification would be accomplished by administrative order under 513(f)(3) of the FD & C Act because there is no Class III device-specific regulation for these tests.

2) Devices included in this proposal

This proposal applies to HIV PoC and lab-based serological and NAT-based tests with claims as an aid in diagnosis and to devices with a stand-alone or additional claim as a supplemental test. These devices have the following general Intended Uses and exclusions (tailored to the specific device):

PoC: *“The [...] test is intended for use as a point-of-care test to aid in the diagnosis of infection with HIV-1 [and HIV-2]. It is not intended for use in screening blood, plasma, cell, or tissue donors.”*

Lab-based: *“The [...] test is intended to be used as an aid in the diagnosis of HIV-1/HIV-2 infection.... It is not intended for use in screening blood or plasma donors.”*

c. Supplemental/confirmatory devices:

“The [...] test is intended for use as an additional, more specific test for [HIV antibodies] in specimens collected from individuals of unknown risk for HIV- 1 which

are found to be repeatedly reactive by [approved diagnostic test]. It is not intended for screening or reinstating potential blood donors.”

3) Devices excluded from this proposal

- a. *Blood donor screening tests* are excluded from reclassification because they are regulated as BLAs (biological license applications) under section 351 of the Public Health Service Act and thus are not subject to classification.

Blood donor screening devices have the following general Intended Use:

“The [...] test is intended for use to screen for [HIV] in specimens from human donors, including donors of Whole Blood, blood components, Source Plasma, and other living donors. This test is not intended for use as an aid in diagnosis of infection with HIV.”

- b. *Home use/over the counter (OTC) tests* are not being considered for reclassification here. OTC use of devices raise distinct issues of safety and effectiveness and require special controls that are designed to address concerns specific to OTC devices, including the usability of the device. The performance standards and study designs being proposed here for professional-use PoC and lab-based diagnostic devices are not sufficient for OTC devices.

These home-use devices have the following general Intended Use:

The [...] test is intended as an over-the-counter (OTC) test for consumer use as an aid in the diagnosis of infection with HIV-1 and HIV-2.”

- c. *Viral-load tests* are not included in this proposal because these devices are used for patient monitoring, which raises different issues of safety and effectiveness such as how to correlate changes in viral load with clinically meaningful changes in patient management. Thus, the special controls proposed here for diagnostic tests are not sufficient and reclassification of viral load tests.

These devices have the following general Intended Use:

The [...] test is intended for use in conjunction with clinical presentation and other laboratory markers of disease progress for the clinical management of HIV-1 infected patients. The [...] test is not intended to be used as a screening test for HIV or as a diagnostic test to confirm the presence of HIV infection.”

- d. *Phenotypic drug-resistance tests* that are used to determine the susceptibility of HIV to drugs are excluded from this proposal because these tests are still in the development stage, and the performance standards and study designs necessary for approval of these devices have not yet been demonstrated.

3. Testing for HIV infection

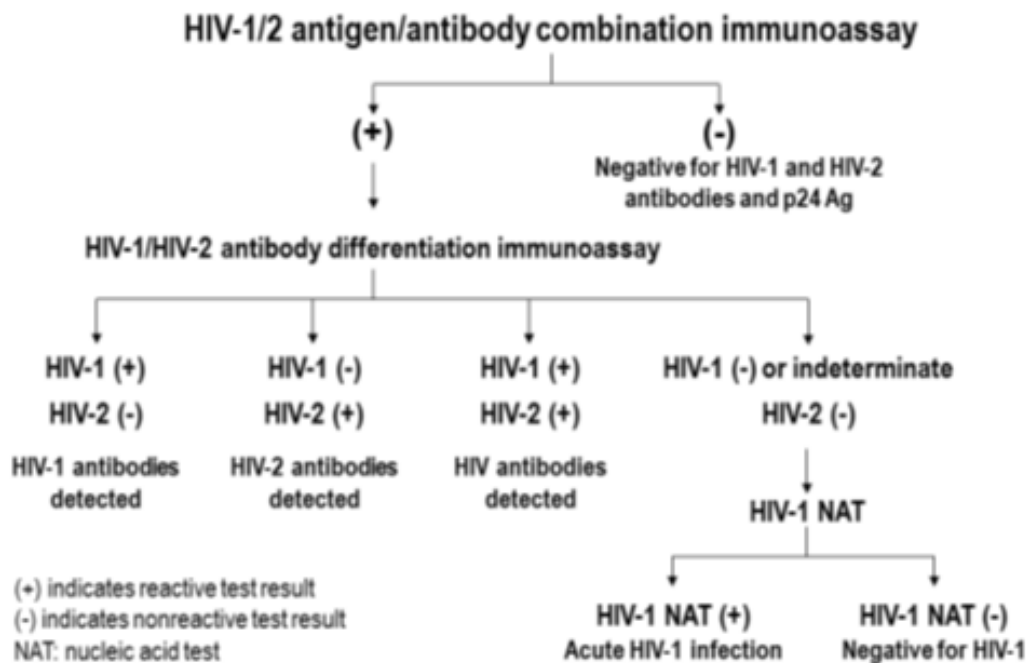
The first HIV test approved by the FDA in 1985 detected only HIV-1 IgG. The test was initially licensed to detect HIV in blood donations to protect the blood supply and not for

diagnostic use. However, this and similar tests for antibodies to HIV-1 later became available for diagnostic testing. The early generation of HIV tests had estimated window periods of 42-56 days between the time of infectivity and detection [2, 3]. Since that time, advancements in test design, including synthetic and recombinant antigens, incorporation of monoclonal antibodies to the HIV p24 antigen and development of NAT tests have improved the sensitivity and specificity of HIV diagnostic devices, enabled differentiation of some HIV-1 subgroups as well as IgG and IgM and HIV-2 and shortened the window period to possibly less than one week with NAT testing [4].

In 1989 the CDC developed an algorithm for testing for HIV infection, which recommended a sequence of tests that should be performed before a final diagnosis of HIV infection is made. In 2014 the CDC and the Association of Public Health Laboratories released an updated algorithm that reflected the changes in diagnostic tests, particularly the introduction of tests that detect HIV-2 and HIV antigen p24 (Figure 1) [3]. Recommendations on communicating the results of testing also were released [5]. Initial screening is recommended using an FDA-approved instrumented (lab-based) 4th generation combination (Antigen/antibody, or Ag/Ab) assay, followed by confirmation of reactive results with an FDA-approved assay that differentiates between HIV-1 and HIV-2. Samples that are negative or indeterminate on the differentiating assay are further tested by NAT test prior to providing a final result to the patient. The full algorithm and associated notes can be accessed at <https://stacks.cdc.gov/view/cdc/23446#>. All PoC and rapid tests include a recommendation in their labeling that initial reactive results should only be considered preliminary and should be followed up by entering the algorithm at the first step. The CDC regularly releases technical updates (<https://www.cdc.gov/hiv/dhap/new/index.html>) based on new information and device capabilities; in 2017 it issued a technical update on the use of a 4th generation PoC for discrimination of HIV-1 and HIV-2 when access to an instrumented laboratory test is not available or not feasible [6].

Advances in treatment and enhanced access to care have significantly improved the prognosis for people living with HIV infection [7]; however, Lancet HIV's editorial board recently commented that "...one essential part of the prevention armamentarium has, at times, been overlooked: accessible testing." [8]. Many recommendations encourage broad testing in the U.S. to decrease spread of HIV. According to the CDC, more than one million people in the United States are living with HIV infection and about 15% do not know that they are infected [9]. Informing people of their infection status is critical: more than 39,000 people were diagnosed with HIV infection in the U.S. in 2015, and about 40% of the infections were transmitted by people who are unaware of their status [10]. To increase the percentage of people who know their status in the U.S., the CDC's 2014 [*Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings*](#) [11] advised routine HIV screening of adults, adolescents, and pregnant women in health care settings in the United States. The US Preventative Services Task Force in 2013 issued recommendations that included screening of adolescents and adults ages 15–65 years old. It also recommended testing pregnant women, including those who present in labor whose HIV status is unknown or who lack prenatal care [12]. Thus, in the U.S., screening is recommended for adults at least once, and those with additional risk factors should be screened more often, up to every three to six months.

Figure 1. CDC’s recommended HIV screening algorithm using “fourth-generation” HIV-1/2 antigen/antibody tests



PoC HIV diagnostic devices are used in a variety of clinical settings, including testing women in labor who lack prenatal care [13, 14]. They also are critical for bringing treatment to underserved populations [15, 16] by enabling testing in non-clinical settings (NCS), including transitional housing, community fairs, or door-to-door outreach. The outsized public health benefit of rapid testing programs in NCS can be evaluated by comparing the percentage of new HIV infections that were diagnosed in NCS versus conventional clinical sites. A CDC analysis of testing in 23 different site types found that although 25% of the tests were performed in NCS, they detected twice the number of positives than detected in clinical sites [17]. Pottie, et. al. reported in a meta-analysis of several international studies that patients who elected to have rapid testing over lab-based testing had a three-fold increase of uptake of testing and a two-fold increase in their receipt of results, whether the subjects were approached in clinics or in NCS [18]. It follows that innovative approaches to PoC testing may further improve detection of new infections in these vulnerable populations.

Rationale for reclassification

The down classification of HIV diagnostic devices described above will benefit the medical device industry as well as HIV-infected patients and their physicians. This proposal, if finalized, will enable a least-burdensome approach to regulation of these devices and streamline the regulatory process for HIV PoC devices. Specifically, regulated industry will no longer be required to submit a PMA but can instead submit a 510(k) to the Agency for review prior to marketing their device. A 510(k) is a less-burdensome pathway to market, which typically results in a shorter premarket review time and provides the public timelier

access to devices. FDA anticipates that the special controls proposed below will ensure that new devices maintain the safe and effective performance demonstrated by approved HIV diagnostic devices when the new devices are reviewed under the 510(k) pathway. Inclusion of both laboratory-based diagnostic devices and PoC diagnostic tests in this proposal will provide predictability, consistency, and clarity across different settings for HIV diagnostic testing.

The performance of the eight PoC and twelve available laboratory-based HIV diagnostic devices that was the basis for approval is summarized in Appendices 3 (PoC tests) and 4 (lab-based tests). The range of point estimates and the range of the lower bounds of the 95% CI of the sensitivity and specificity for PoC and lab-based devices that were the basis for device approval are presented in Table 1. Each device met the performance criteria that are proposed in the special controls (§ 8, below): that the lower bound of the two-sided 95% confidence intervals for sensitivity and specificity must be $\geq 98\%$ for PoC and $\geq 99\%$ for lab-based devices. Numerous investigators also have evaluated the performance of these devices in different clinical settings and have found that performance when tested per the intended use is generally consistent with the manufacturer’s claims, although exceptions have occurred [3].

Table 1. Range of point estimates and lower bound of the 95% CI for approved PoC and lab-based first-line diagnostic devices

	PoC	PoC	Lab-based	Lab-based
	Range of Point estimates (%)	Range of 95% CI lower bounds (%)	Range of Point estimates (%)	Range of 95% CI lower bounds (%)
Sensitivity (Se)	98.9–100	98–99.5	100	99.4–99.84
Specificity (Sp)	98.6–100	99–99.8	99.58–100	99.1–99.88
Sample number	Se Minimum > 500 subjects Sp Maximum > 3600 subjects	Se Minimum > 500 subjects Sp Maximum > 3600 subjects	Se Minimum > 300 subjects Sp Maximum > 11 000 subjects	Se Minimum > 300 subjects Sp Maximum > 11 000 subjects

Changes in the clinical outcomes and therapeutic management of people infected with HIV can lead to changes in how devices are used and how the results are interpreted, and the effect of these changes should be considered in future device reviews and labeling. For example, it has been proposed that high compliance by individuals at high risk for infection to pre-exposure prophylaxis (PrEP) recommendations has the potential for changing the prevalence of infection [20, 21]. When the prevalence of a disease changes, the positive predictive value of a device changes. This means that if the prevalence of HIV infection decreases in a traditionally high-risk population, the likelihood that a reactive result reflects actual infection may decrease significantly. This change may have important implications for patient counseling and screening programs and therefore, emerging issues in HIV infection

need to be considered in device result interpretation guidelines and warnings and limitations in the package inserts.

Several studies in the literature describe evaluations of devices' abilities to detect acute infection in infants and children under the age of two [22, 23]. These studies describe an off-label use of these devices, but point to the persistent need for improved testing in at-risk populations. One goal is that reclassification will help to meet these needs by decreasing the regulatory burden on manufacturers interested in developing newer tests while maintaining device performance.

4. Adverse events

A search of the CDRH MAUDE database from 12/30/2000 through 1/31/2018 using the procode MZF and of Biologic Product Deviation Reports (BPDRs) for each manufacturer or device trade name was conducted. Results are presented in Table 2. Unrelated reports (e.g., blood donor screening, international reports) were removed from this list. Only events for first-line (non-supplemental) diagnostic tests reported in the U.S. are included. More than 100 million diagnostic devices were sold during this time period.

Analysis of adverse event reports

Deaths

Three deaths were reported. In one case, an ill patient arrived at the hospital and a sample was taken for testing. The test was performed but the patient died before the results could be returned. The cause of death was not determined, but was not device related. In the second case, a subject in a clinical trial of a device died while enrolled in the study, but before the test was used. This was reported as a death, non-device related. In the third case, a subject received a preliminary false positive test results but died before confirmatory test results could be received.

Injuries, malfunctions, and "other" or "no response"

Eighteen false positive events were reported as injuries. Three events related to user error or other (e.g., splash from vial, reaction to fingerprick) were also reported as injuries. No transmissions were associated with these events. One hundred thirty-four false positive and fourteen false negative results were reported as malfunctions. Twenty-six events were reported as "other" or "no response." These included false positive, false negative, out-of-specification controls, or events using proficiency samples. These also included reports from instruments or faults in manufacture, e.g., missing labels. No adverse events to patients were reported from these events.

Table 2. Adverse Event reports (MDR and BPDR) from December 30, 2000–January 31, 2018

Event Type Reported	Lab	PoC	Total
Death	1	2	3
Injury	9	12	21
False positive	8	10	18
False negative	0	0	0
Other (accident)	1	2	3
Malfunction	90	65	155
False positive	74	60	134
False negative	13	1	14
Other	3	4	7
Other	23	3	26
No response	7	0	7
Total	130	82	212

A comprehensive analysis of adverse events has not raised concerns about the general performance of this class of devices, and indicates that the performance standards under which these devices were approved are robust to provide a reasonable assurance of safety and effectiveness. It is important to note that a review of adverse event reports may raise concerns about the performance of a specific device, and the FDA has the authority to investigate and take action as warranted based on this information. This authority and the actions available to the Agency are the same regardless of device class.

5. Recalls

A search was conducted of the FDA’s Medical Device Recalls database using the produce code MZF and the time from the first approval to the present; no recalls were reported.

6. Identified risks to health and relevant mitigation measures

Risks

- Risks to health from these devices include the risk that a false positive result may lead to unnecessary treatment of an individual, leading to possible adverse effects. For example,

the clinician may initiate anti-retroviral treatment and women tested while in labor may undergo unnecessary Cesarean sections as well as exposure of herself and her neonate to antiretroviral drugs. In addition, unnecessary anxiety and stress can result from communication of a false-positive result even if later clarified.

- False negative results may lead to disease progression in the individual and the public health risk of transmitting the virus to others.
- Emerging risks or device limitations that are not included in the package inserts may lead to incorrect test interpretation and patient counseling.
- Errors in manufacturing may lead to invalid or inaccurate tests being used for diagnosing HIV infection, which may cause either false positive or false negative results with the associated impact on the patient and on public health.

Mitigation measures

- The risks to health can be mitigated by providing users a device description that contains information required by the general and special controls, clinical and analytical validation, and labeling.
- The device-specific special controls will be designed to ensure the established sensitivity and specificity is maintained in new devices, decreasing the risk of false negative and false positive results.
- The device-specific special controls will require submission of manufacturing information to ensure that the devices are manufactured properly, thereby reducing the risk of false positive and false negative results.
- The device-specific special controls will require labeling be updated as new information on risks and limitations are understood.

7. Special controls

Special controls are regulatory requirements for Class II devices and per 21 U.S.C. 360d: *“Shall include provisions to provide reasonable assurance of [the device’s] safe and effective performance”* and may include any requirements to provide reasonable assurance of safety and effectiveness of the device.

The proposed device-specific special controls for HIV PoC and lab-based serology and NAT devices will specify performance requirements, specify manufacturing information that needs to be submitted for review, require submission of complaint logs, and inform device labeling. If finalized, the special controls included in the regulation are required performance criteria that all new devices with the same Intended Use must meet in order to be cleared under the 510(k) paradigm to demonstrate substantial equivalence.

The specific wording of the special controls below should not be considered the final language that will be contained in the regulation; these are proposed controls that can be revised in response to recommendations from the panel and from public comments on the proposed order.

a. Point of Care serology and NAT

- 1) The intended use in the 21 CFR 809.10 compliant labeling must include a statement that the device is for point-of-care use.

- 2) If the device has CLIA waiver status, the mode of operation that is CLIA waived must be clearly described and other, non-CLIA-waived modes of operation must be clearly identified.
- 3) The intended use in the 21 CFR 809.10 compliant labeling must include the following restrictions:
 - That sales of the device are restricted to clinical laboratories that have an adequate quality assurance program, including planned systematic activities that provide adequate confidence that requirements for quality will be met and where there is assurance that operators will receive and use the instructional materials.
 - That the device is for use only by an agent of a clinical laboratory.
 - That test subjects must receive the “Subject Information Notice” prior to specimen collection and appropriate information when test results are provided.
- 4) The intended use in the 21 CFR 809.10 compliant labeling must state that the device is not intended for use in screening blood, plasma, cell, or tissue donors.
- 5) The 21 CFR 809.10 compliant labeling must include instructions to follow the CDC guidelines to inform the test subject of the test result and its interpretation. The instructions also should state that negative results do not exclude possible infection, and that reactive results are preliminary.
- 6) A detailed explanation of the principles of operation and procedures for assay performance must be included in the device’s 21 CFR 809.10 compliant labeling.
- 7) Warnings must be updated to reflect current clinical practice and disease presentation and management and include, at minimum, the following statements:
 - “This kit has been approved for use with [specify the matrices] only. Use of this test kit with specimen types other than those specifically approved for this device may cause inaccurate test results.
 - “This test is not intended to be used to monitor individuals who are undergoing treatment.”
- 8) Limitations must be updated to reflect current clinical practice and disease presentation and management and include, at minimum, the following limitations:
 - That a non-reactive test result does not exclude the possibility of exposure to HIV.
 - That a positive or reactive result is interpreted as Preliminary Positive for HIV-1 and/or HIV-2 and that the test is intended as an aid in the diagnosis of infection with HIV-1/2.
 - That positive or reactive test results should be confirmed by additional testing using fresh samples.
- 9) Premarket notification submissions must include detailed device description documentation, including the device components, ancillary reagents required but not

- provided, an explanation of the methodology. Additional information appropriate to the technology must be included, e.g., design of antigen(s) and capture antibodies. For devices with assay calibrators: the submission must also address the design and nature of all primary, secondary and subsequent quantitation standards used for calibration.
- 10) Premarket notification submissions must contain detailed documentation of analytical performance studies appropriate to the technology employed that include but are not limited to:
- Limit of blank, Limit of detection, cutoff determination, precision, reproducibility, drug interference, endogenous interference, cross reactivity, carry-over, seroconversion sensitivity panel testing, genotype detection panel testing, quality control, matrix equivalency (if applicable), sample stability studies, reagent stability studies, and additional studies as applicable to specimen type and intended use for the device. Samples selected for use in analytical studies or used to prepare samples for use in analytical studies must be from subjects with clinically relevant circulating genotypes in the U.S.
- 11) Analytical sensitivity of the device must be at least as sensitive as approved tests. Samples should include 200 world-wide high risk subjects, ≥ 10 seroconversion panels, ≥ 10 HIV-1 dilution series, and 1–3 low titer panels. Analytical specificity of the device must be at least as specific as approved tests. Samples should include ≥ 200 samples from patients with differential diagnoses, including HIV, HBV, HCV and other relevant conditions and ≥ 100 samples from potential interfering substances as appropriate. The effect of nucleic-acid isolation and purification procedures on detection of the correct genotype should be evaluated as appropriate.
- 12) Premarket notification submissions must include detailed documentation from a well-conducted multisite study. Performance should be analyzed relative to an FDA cleared or approved comparator. This study must be conducted using fresh patient samples, with an FDA acceptable number of HIV positive and negative samples that reflect what would be obtained in real world testing. The study designs, including the number of samples tested, must be sufficient to meet the following criteria:
- Clinical sensitivity of the device should have a lower bound of the 95% Confidence Interval of $\geq 98\%$. Clinical Specificity should have a lower bound of the 95% Confidence Interval of $\geq 98\%$.
 - Group O claim is optional but if included, this should be tested using ≥ 10 samples HIV-2 claim is optional, but if included should be tested using ≥ 200 repository/fresh HIV-2 positive samples.
- 13) For devices with assay calibrators: The calibration standard used in manufacturing this device must be FDA recognized. Further, as part of verification and validation activities performed under 21 CFR 820.30 design controls, analytical testing must be performed following the release of a standard reference lot of the material used for device clearance, or when there is a transition to a new calibration standard.

- 14) As appropriate, premarket notification submissions must include proposed risk mitigation procedures and methods for the postmarket identification of genetic mutations and/or detectability of the different genotypes (e.g., regular review of published literature, complaint file and MDR review). These procedures include monitoring of device performance in relationship to the emergence of genetic mutations and/or different genotypes. In addition, such procedures and methods must include criteria for redesign of the device.
- 15) Premarket notification submissions must include the following:
- A description of all critical reagents, including amino acid sequences for the antigen and procedures used to ensure that critical reagents are acceptable.
 - A list of manufacturing sites, including those of suppliers of critical reagents.
 - A design verification summary to establish that design outputs meet design inputs.
 - Failure Modes Effects Analysis (FMEA) and/or Hazard Analysis and Critical Control Points (HACCP).
 - Final release criteria to be used for manufactured device lots with an appropriate justification that lots released at the extremes of the specifications will meet the claimed analytical and clinical performance characteristics as well as the stability claims.
 - All stability protocols, including acceptance criteria. Stability studies must include an assessment of stability for reagents provided with the device and indicated specimen types.
 - Final release test results for three conformance lots.
 - Multisite reproducibility study that includes the testing of three independent production lots.
- 16) Premarket notification submissions must include proposed procedure(s) for addressing complaints meeting the requirements of 21 CFR section 820.198, medical device reports meeting the requirements of 21 CFR part 803, product recalls and corrections meeting the requirements of 21 CFR part 806, change management meeting the requirements of 21 CFR sections 820.30(i) and 820.70(b), and product corrective and preventive actions meeting the requirements of 21 CFR section 820.100.
- 17) Manufacturers must submit a log of all complaints containing event (e.g., false negative, false positive), lot, date, population, including if it was MDR reported. The report should be submitted annually on the anniversary of clearance.
- 18) A new premarket submission is required for any change to the intended use, critical reagents (such as but not limited to lysis buffer, reaction buffer, antigen(s), antibody(ies), primers, detection reagents, etc.), reaction conditions, final release specifications or shelf life, and manufacturing site changes as these changes could

significantly affect the safety or effectiveness of the device per the latest FDA guidance.

b. Lab-based serology and NAT

- 1) The intended use in the 21 CFR 809.10 compliant labeling must include a statement that the device is for prescription use only.
- 2) The intended use in the 21 CFR 809.10(b)(2) compliant labeling must state the following:

“It is not intended for use in screening blood, plasma, cell, or tissue donors.”
- 3) A detailed explanation of the interpretation of results must be provided in the device’s 21 CFR 809.10(b) compliant labeling, including that reactive results are considered presumptive for HIV infection.
- 4) Warnings must be updated to reflect current clinical practice and disease presentation and management.
- 5) Limitations must be updated to reflect current clinical practice and disease presentation and management and include, at a minimum, the following limitations:
 - A specimen with a final positive result should be investigated further with supplemental confirmatory HIV-specific tests per the current CDC confirmatory algorithms.
 - The interpretation of specimens with a final positive result and indeterminate by supplemental testing is not definitive; further clarification may be obtained by testing a follow-up specimen taken at least one month later.
 - Results and supplemental assay results should be interpreted in conjunction with the patient’s clinical presentation, history, and other laboratory results. If the results are inconsistent with clinical evidence, additional testing is suggested to confirm the result.
 - A test result that is nonreactive does not exclude the possibility of exposure to or infection with HIV-1 and/or HIV-2. Nonreactive results in this assay for individuals with prior exposure to HIV-1 and/or HIV-2 may be due to analyte levels that are below the limit of detection of this assay.
- 6) A detailed explanation of the principles of operation and procedures for assay performance must be included in the device’s 21 CFR 809.10(b) compliant labeling. Premarket notification submissions must include detailed device description documentation, including the device components, ancillary reagents required but not provided and an explanation of the methodology. Additional information appropriate to the technology must be included, e.g., design of primer/probe sequences, rational for the selected gene target(s). For devices with assay calibrators: the submission must also address the design and nature of all primary, secondary and subsequent quantitation standards used for calibration.

- 7) Premarket notification submissions must contain detailed documentation of analytical performance studies appropriate to the technology employed that include but are not limited to:

Limit of blank, limit of detection, cutoff determination, precision, reproducibility, drug interference, endogenous interference, cross reactivity, carry-over, seroconversion sensitivity panel testing, genotype detection panel testing, quality control, matrix equivalency (if applicable), sample stability studies, reagent stability studies, and additional studies as applicable to specimen type and intended use for the device. Samples selected for use in analytical studies or used to prepare samples for use in analytical studies must be from subjects with clinically relevant circulating genotypes in the U.S.

- 8) Analytical Sensitivity of the device must be at least as sensitive as approved tests. Samples should include 200 world-wide high risk subjects, ≥ 10 seroconversion panels, ≥ 10 HIV-1 dilution series, and 1–3 low titer panels. Analytical specificity of the device must be at least as specific as approved tests. Samples should include ≥ 200 samples from patients with differential diagnoses, including HIV, HBV, HCV and other relevant conditions and ≥ 100 samples from potential interfering substances as appropriate. The effect of nucleic-acid isolation and purification procedures on detection of the correct genotype should be evaluated as appropriate.
- 9) Premarket notification submissions must include detailed documentation from a well-conducted multisite study. Performance should be analyzed relative to an FDA cleared/approved comparator. This study must be conducted using fresh patient samples, with an FDA acceptable number of HIV positive and negative samples that reflect what would be obtained in real world testing. The study designs, including number of samples tested, must be sufficient to meet the following criteria:
- Clinical sensitivity of the device should have a lower bound of the 95% Confidence Interval of $\geq 99\%$. Clinical Specificity should have a lower bound of the 95% Confidence Interval of $\geq 99\%$.
 - A Group O detection claim is optional but if included, this should be tested using ≥ 10 samples HIV-2 claim is optional, but if included should be tested using ≥ 200 repository/fresh HIV-2 positive samples.
- 10) For devices with assay calibrators: The calibration standard used in manufacturing this device must be FDA recognized. Further, as part of verification and validation activities performed under 21 CFR 820.30 design controls, analytical testing must be performed following the release of a standard reference lot of the material used for device clearance, or when there is a transition to a new calibration standard.
- 11) As appropriate, premarket notification submissions must include proposed risk mitigation procedures and methods for the postmarket identification of genetic mutations and/or detectability of the different genotypes (e.g., regular review of published literature, complaint file and MDR review). These procedures include monitoring of device performance in relationship to the emergence of genetic

mutations and/or different genotypes. In addition, such procedures and methods must include criteria for redesign of the device.

12) Premarket notification submissions must include the following:

- A description of all critical reagents, including amino acid sequences for the antigen and procedures used to ensure that critical reagents are acceptable.
- A list of manufacturing sites, including those of suppliers of critical reagents.
- A design verification summary to establish that design outputs meet design inputs.
- Failure Modes Effects Analysis (FMEA) and/or Hazard Analysis and Critical Control Points (HACCP).
- Final release criteria to be used for manufactured device lots with an appropriate justification that lots released at the extremes of the specifications will meet the claimed analytical and clinical performance characteristics as well as the stability claims.
- All stability protocols, including acceptance criteria. Stability studies must include an assessment of stability for reagents provided with the device and indicated specimen types.
- Final release test results for three conformance lots.
- Multisite reproducibility study that includes the testing of three independent production lots.

13) Premarket notification submissions must include proposed procedure(s) for addressing complaints meeting the requirements of 21 CFR section 820.198, medical device reports meeting the requirements of 21 CFR part 803, product recalls and corrections meeting the requirements of 21 CFR part 806, change management meeting the requirements of 21 CFR sections 820.30(i) and 820.70(b), and product corrective and preventive actions meeting the requirements of 21 CFR section 820.100.

14) Manufacturers must submit a log of all complaints containing event (e.g., false negative, false positive), lot, date, population, including if it was MDR reported. The report should be submitted annually on the anniversary of clearance.

15) A new premarket submission is required for any change to the intended use, critical reagents (such as but not limited to lysis buffer, reaction buffer, antigen(s), antibody(ies), detection reagents, primers, probes, etc.), reaction conditions, final release specifications or shelf life, and manufacturing site changes as these changes could significantly affect the safety or effectiveness of the device.

c. Supplemental tests: additional intended use

If the test is intended for supplementary or confirmatory use in addition to use as an aid in diagnosis, additional special controls apply:

- 1) For the confirmatory or supplementary claim in addition to a diagnostic claim, a clinical study must be performed that includes samples that were initially reactive and repeatedly reactive on an FDA-approved diagnostic test, but were negative or indeterminate on a confirmatory test.
- 2) The Intended use must include the statement “Also intended for use as an additional, more specific test to confirm the presence of antibodies to HIV-1 and HIV-2 for specimens found to be repeatedly reactive by diagnostic screening procedures.”

d. Supplemental tests: stand-alone test

If the test is intended solely as a supplementary/confirmatory test, the applicable special controls in a. and b. above, apply. In addition, the following special controls apply:

- 1) The labeling must include a statement “intended for use as an additional, more specific test to confirm the presence of antibodies to HIV-1 and HIV-2 for specimens found to be repeatedly reactive by diagnostic screening procedures. Not for initial diagnosis” or “not intended as a first-line test”.
- 2) A clinical study must be performed that includes samples that were initially reactive and repeatedly reactive on an FDA-approved diagnostic test, but were negative or indeterminate on a confirmatory test.

e. Differentiation claim

If the test is intended to differentiate different types of HIV, the applicable special controls in a. and b. above, apply. In addition, the following special controls apply:

- 1) The labeling must include the statement that the test is intended for the confirmation and differentiation of individual antibodies to different types of Human Immunodeficiency Virus.
- 2) Analytical and clinical sensitivity and specificity for each of the HIV types and subtypes intended to be differentiated must be performed.
- 3) The results interpretation must include instructions to the user on how to interpret the results, including un-typable and co-infection results.

8. Question for the panel

The reclassification process for down-classifying a device from Class III to Class II is dependent on the extent to which the available risk mitigations, such as labeling and special controls, provide reasonable assurance of safety and effectiveness of the diagnostic device. FDA is mandated to publish special controls as part of the new regulation that outline what is necessary to develop a safe and effective new diagnostic device. In this context, please discuss the following:

Do committee members believe that special controls as described above, in addition to general controls, are necessary and sufficient to mitigate the risks to health presented by HIV serology and NAT point of care and laboratory-based diagnostic devices if reclassified to class II?

In addressing this question, please discuss additional special controls that could be recommended for down-classified HIV diagnostic tests, and specific aspects of the proposed controls that should be revised.

9. Appendix 1. Affected tests

Marketed point of Care tests included in this proposal

STN	Trade name	Manufacturer	Analyte	Specimen (WB: whole blood FS: fingerstick)	Approval Date
BP000023 /52	Reveal (G2, G3, G4) Rapid HIV-1 Antibody Test https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm545616.htm	MedMira Laboratories, Inc.	HIV-1	Serum, Plasma	4/16/2003 PoC: 10/15/2015
BP010047	OraQuick ADVANCE* Rapid HIV-1/2 Antibody Test https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091491.htm	OraSure Technologies	HIV-1, HIV-2	Oral Fluid, Plasma, WB, FS	11/7/2002* 6/22/2004
BP030025	Uni-Gold™ Recombigen® HIV-1/2 https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091636.htm	Trinity Biotech	HIV-1, HIV-2	Serum, Plasma, WB, FS	12/23/2003 PoC: 02/04/2013
BP050009	SURE CHECK HIV 1/2 ASSAY https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091240.htm	Chembio Diagnostic Systems, Inc.	HIV-1, HIV-2	FS, WB, blood, serum, plasma	5/25/2006
BP050010	HIV 1/2 STAT-PAK ASSAY https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091243.htm	Chembio Diagnostic Systems, Inc.	HIV-1, HIV-2	FS, WB, serum, plasma	5/25/2006
BP090032	INSTI™ HIV-1 Antibody Test Kit https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm235024.htm	bioLytical Laboratories Inc	HIV-1, HIV-2	Plasma, WB, FS	11/29/2010
BP120032	Chembio DPP® HIV 1/2 Assay https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm333601.htm	Chembio Diagnostic Systems, Inc.	HIV-1, HIV-2	Oral fluid, Serum, Plasma, WB, FS	12/19/2012

STN	Trade name	Manufacturer	Analyte	Specimen (WB: whole blood FS: fingerstick)	Approval Date
BP120037	Alere Determine™ HIV-1/2 Ag/Ab Combo https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm364651.htm	Alere Scarborough, Inc.	HIV-1, HIV-2, p24	Serum, Plasma, WB, FS	8/8/2013

*added claims to and changed name from OraQuick Rapid HIV-1/2 (2004) and OraQuick Rapid HIV-1 tests (2002)

Marketed lab-based tests included in this proposal

STN	Trade name	Manufacturer	Analyte	Specimen	Approval Date
BL125030	Genetic Systems HIV-1/HIV-2 PLUS O EIA https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm091151.htm	Bio-Rad Laboratories	HIV-1, HIV-2	Serum, Plasma	8/5/2003
BP040046	Multispot HIV-1/HIV-2 Rapid Test https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091222.htm	Bio-Rad Laboratories	HIV-1, HIV-2	Fresh/frozen Plasma, Serum	11/12/2004
BP050030	ADVIA Centaur HIV 1/O/2 Enhanced https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091217.htm	Siemens	HIV-1, HIV-2	Serum, plasma	5/17/2006
BP050051	VITROS Anti-HIV 1+2 https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091601.htm	Ortho Clinical Diagnostics, Inc.	HIV-1, HIV-2	Serum, plasma	3/27/2008
BL103966/5040	APTIMA HIV-1 RNA Qualitative Assay https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm149922.htm	Gen-Probe, Incorporated	HIV-1 RNA	Plasma	10/4/2006
BP090022	Avioq HIV-1 Microelisa System* https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM185273.pdf	Avioq, Inc	HIV-1	Serum, Plasma, DBS, Oral fluid	9/21/2009
BP090080	Architect HIV Ag/Ab Combo https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm216291.htm	Abbott Laboratories	HIV-1, HIV-2, p24	Serum, plasma	6/18/2010
BP100064	GS HIV Combo Ag/Ab** https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm264723.htm	Bio-Rad	HIV-1, HIV-2, p24	Serum, plasma	7/22/2011
BP140103	ADVIA Centaur Ag/Ab Combo (CHIV) https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm450386.htm	Siemens	HIV-1, HIV-2, p24	Serum, plasma	6/8/2015

STN	Trade name	Manufacturer	Analyte	Specimen	Approval Date
BP140111	BioPlex 2200 System HIV Ag-Ab https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm455818.htm	Bio-Rad	HIV-1, HIV-2, p24	Serum, plasma	7/23/2015
BP160050	Elecsys HIV combi PT https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm564192.htm	Roche	HIV-1, HIV-2, p24	Serum, plasma	6/21/2017
BP160122	VITROS Immunodiagnostic Products HIV Combo https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm588917.htm	Ortho-Clinical Diagnostics, Inc.	HIV-1, HIV-2, p24	Serum, plasma	12/13/2017

*Originally licensed as Vironostika Microelisa system (bioMerieux, 1987) and subsequent versions

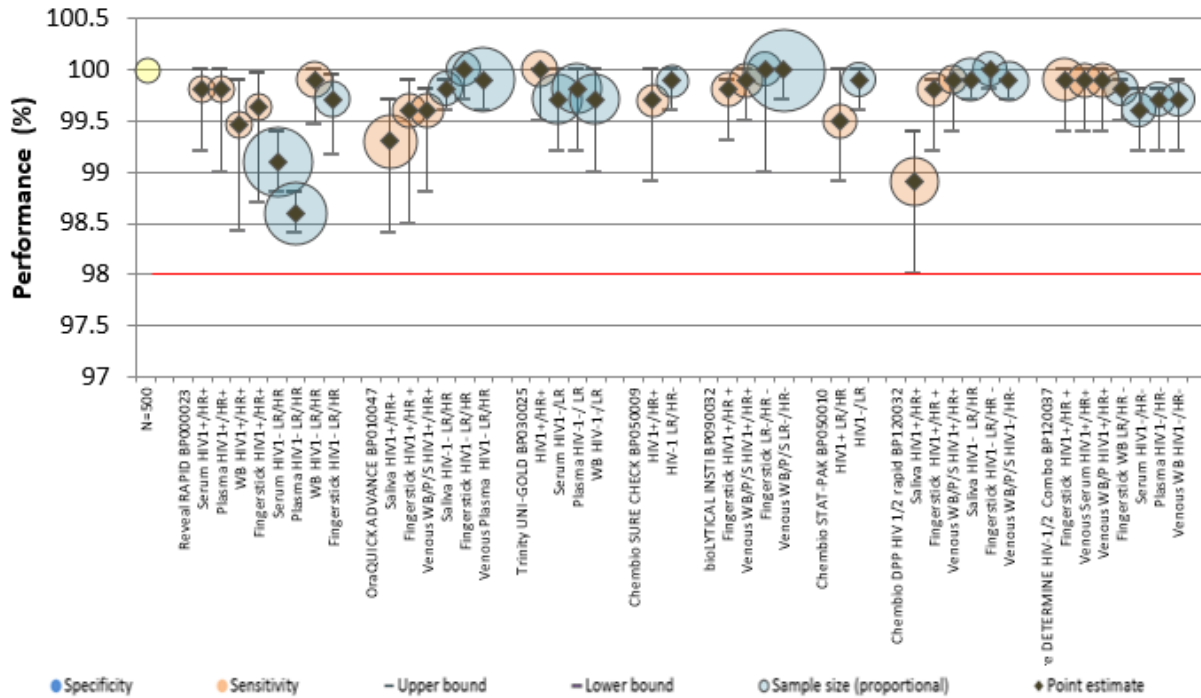
** Originally licensed as Genetic Systems rLAV EIA (1986) and subsequent versions

Supplemental tests included in this proposal

STN	Trade name	Manufacturer	Analyte	Specimen	Approval Date
BP140120	Geenius HIV 1/2 Supplemental Assay https://www.fda.gov/BiologicsBloodVaccines/BloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm420713.htm	Bio-Rad Laboratories	HIV-1, HIV-2	Plasma, serum, cadaveric	10/24/2009
BP010009	Cambridge Biotech HIV-1 Urine Western Blot https://www.fda.gov/BiologicsBloodVaccines/BloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091228.htm	Maxim Biomedical, Inc.	HIV-1	Urine	6/21/2001
BL103843	Cambridge Biotech HIV-1 Western Blot https://www.fda.gov/BiologicsBloodVaccines/BloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm093507.htm	Maxim Biomedical, Inc.	HIV-1	Serum/Plasma	5/28/1998
BL103288	Flurognost HIV-1 IFA	Sanochemia Pharmazeutika, AG	HIV-1	Serum/Plasma	2/5/1992
BP950004	OraSure HIV-1 Western Blot Kit https://www.fda.gov/BiologicsBloodVaccines/BloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm091471.htm	OraSure Technologies, Inc	HIV-1	Oral fluid	6/3/1996
BL103655	GS HIV-1 Western Blot	Bio-Rad Laboratories	HIV-1	Serum/Plasma	11/13/1998

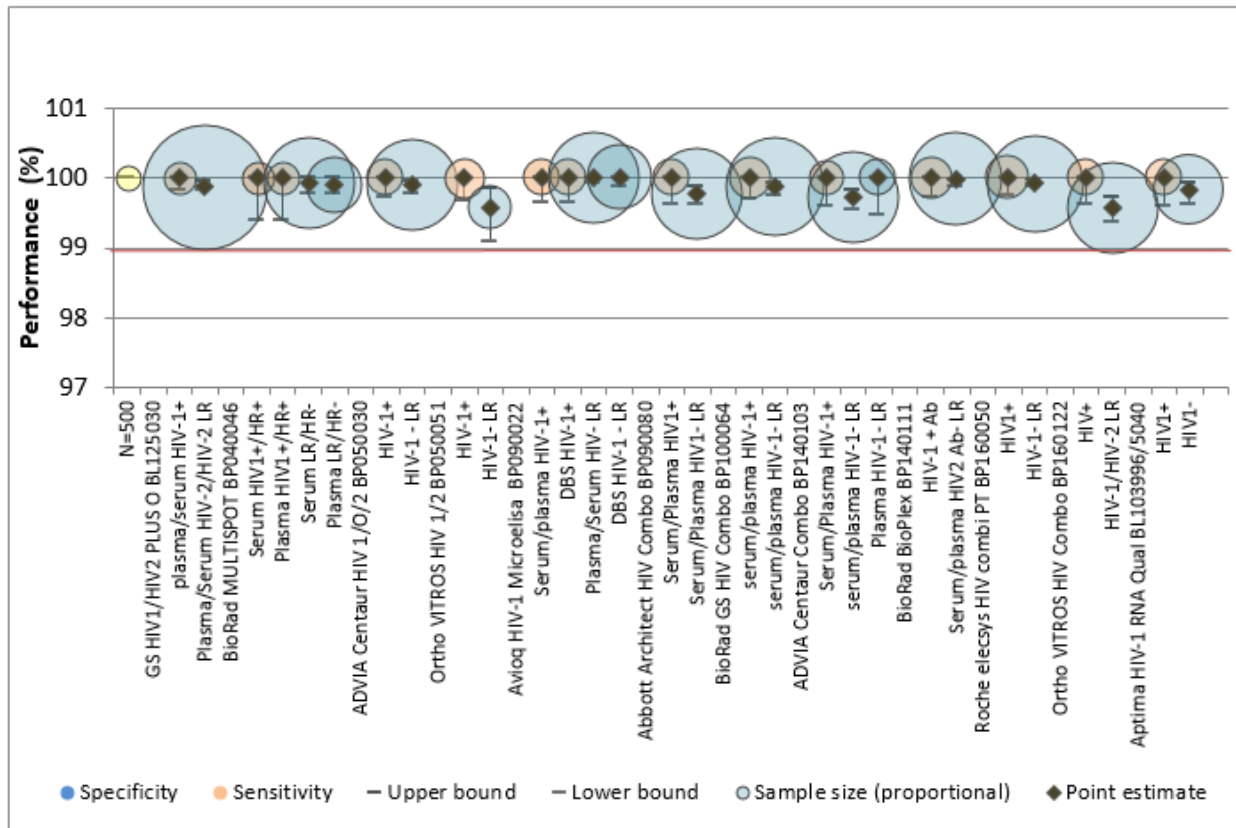
10. Appendix 2. Performance of HIV PoC diagnostic tests

The sensitivity and specificity of each device is presented by date of submission. The size of the circles is proportional to the number of samples tested in each study; N=500 is represented by the yellow circle at the far left. Error bars show the upper and lower bounds of the 95% CI and the diamonds indicate the point estimate. Sensitivity studies are represented by pink circles; specificity studies are represented by blue circles. The red line at 98% indicates the expected lower bound for both sensitivity and specificity.



11. Appendix 3. Performance of HIV lab-based diagnostic tests

The sensitivity and specificity of each device is presented by date of submission, except for the APTIMA RNA test, which is at the far right. The size of the circles is proportional to the number of samples tested in each study; N=500 samples is represented by the yellow circle at the far left. Error bars show the upper and lower bounds of the 95% CI and the diamonds indicate the point estimate. Sensitivity studies are represented by pink circles; specificity studies are represented by blue circles. The red line at 99% indicates the expected lower bound for both sensitivity and specificity.



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