Overview of Proposed Special Controls

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Benefits/risks to reclassification

Benefits

- Facilitate submission of innovative devices
- Decrease time to market
- Expedite patient access to new devices
- Least burdensome approach: maintain safety while decreasing regulatory burdens on sponsors

Risks

- No pre-approval inspection may lead to missed manufacturing deficiencies
- Changes in the device that affect performance may not be reported

Risks to health from incorrect test result

<u>False negative result from device malfunction</u>

- Deny/delay needed treatment
- Potentially infectious person can transmit to others
- Potentially lost from care

<u>False positive result from device malfunction</u>

- Initiate unneeded treatment, e.g., anti-retroviral medication, perform unnecessary Caesarean section
- Cause patient stress

Proposed special controls for HIV diagnostic devices

Proposed special controls mitigate risks

	Currently in PMAs	Proposed special controls
Performance criteria	95% CI lower bounds: ≥ 98% PoC, 99% Lab-based	95% CI lower bounds: ≥ 98% PoC, 99% Lab-based
Clinical studies	Always require clinical studies	Require clinical studies
Pre-market Inspection	Pre-approval inspection	Summary manufacturing info submitted
CMC section	Review in submission	Summary info submitted
Changes in critical reagents	PMA supplement	Definition of critical reagents
Labeling	Approve final labeling	Include device-specific warnings and limitations

- Same in PMA and 510(k): review of analytical performance, adverse event reporting, post-market inspection, software and instrumentation

Overview: proposed special controls

Parameter	Special control
Clinical samples	• Overall Sensitivity: Number not specified, but should be from Low Risk (LR) and High Risk (HR) populations • Overall Specificity: Number not specified, from appropriate populations • Test samples from other affected populations (e.g., pediatric, women, known positive, etc.) per guidances • Supplemental: Repeat reactive/ confirmed negative and confirmed indeterminate
Clinical Performance criteria for primary study	Clinical sensitivity and specificity: • PoC: 95% CI lower bound ≥ 98% • Lab-based: 95% CI lower bound ≥ 99%
Analytical samples	• 200 world-wide/≥ 10 seroconversion panels/≥ 10 HIV-1 dilution series/1–3 low titer panels • ≥ 200 differential/≥ 100 with interfering substances
Analytical performance criteria	Analytical sensitivity and specificity: • Not less than already approved tests • Should be consistent with current technological capabilities

Overview: proposed special controls

Parameter	Special control
Manufacturing/ CMC	• Include manufacturing specifications and list of critical reagents • Include lot-release specifications and results
Reporting	• Complaint logs submitted annually
Labeling	• Appropriate IU statements and exclusions, e.g., not for donor screening • PoC-specific warnings and limitations, e.g., CLIA status (some matrices are waived), must be administered by professional, etc. • Lab-based and PoC-based warnings, e.g., patients on HAART, etc. • Labeling (limitations, warning) needs to be updated and reflect current clinical practice and scientific/disease considerations, interpretation per CDC

Overview: proposed special controls-supplemental

Parameter	Special control
Supplemental-additional claim	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.
Supplemental - stand alone	All other validation studies except performance criteria
Differentiation claim	Analytical and clinical sensitivity and specificity for each of the HIV types and subtypes intended to be differentiated must be performed. The results interpretation must include instructions to the user on how to interpret the results, including un-typable and co-infection results.

Performance criteria-Clinical

Clinical sensitivity and specificity for each specimen type claimed in the IU must meet the following minimum performance criteria:

a. Clinical Sensitivity: lower bound of the two-sided 95% CI must be:
    i. PoC: ≥ 98%
    ii. Lab-based: ≥ 99%

b. Clinical Specificity: lower bound of the two-sided 95% CI must be:
    i. PoC: ≥ 98%
    ii. Lab-based: ≥ 99%

Other claims:

a. Group O: ≥ 10 samples
b. HIV-2: ≥ 200 HIV-2+, ≥ 500 prospective HR, and ≥ 10 dilutional series
c. Supplemental: Test repeat reactive/confirmed negative, confirmed indeterminate

Performance criteria-Analytical

Analytical sensitivity and specificity study design and performance characteristics must meet the following criteria:

a. Analytical Sensitivity samples: 200 world-wide, ≥ 10 seroconversion panels, ≥ 10 HIV-1 dilution series, and 1–3 low titer panels

b. Analytical Specificity samples: ≥ 200 samples from patients with differential diagnoses, including HCV, HBV, etc., ≥ 100 interfering substances

c. Analytical sensitivity and specificity performance should be consistent with current devices and with current technological capabilities

Manufacturing/CMC

Include information on

- Critical reagents
- Device design verification summary
- Failure Modes Effects Analysis (FMEA) and/or Hazard Analysis and Critical Control Points (HACCP)
- Lot release criteria
- Final release test results for three conformance lots

Complaint reporting

Manufacturers must submit a log of all complaints including event (e.g., false negative, false positive), lot, date, population, and if the complaint was reported as an adverse event (MDR)

Note:

- The report should be submitted annually on the anniversary of clearance as a 510(k) annual report for 5 years after date of initial clearance
- This is separate from, and in addition to, the adverse event reporting that is required under 21 CFR 803
- Unlike MDR reports, complaint logs will not be publicly posted

Labeling: PoC and Lab-based

- The labeling must include:
  - Instructions to follow current guidelines for further investigation of a reactive result
  - Statement that results are preliminary
  - That a non-reactive test result does not exclude the possibility of exposure to HIV
- Limitations and warnings must be updated to reflect current clinical practice and disease presentation and management such as:
  - Possible effects of HAART/cART
  - Possible erroneous results from participants in vaccine clinical studies
  - Emerging considerations, e.g., PrEP, biotin

Labeling: PoC

- Clearly indicate which matrices/modes of operation are CLIA waived (if any)
- Include restrictions
  - Sales of the device are restricted to clinical laboratories that have appropriate controls in place
  - The device is for use only by an agent of a clinical laboratory, not for home use/OTC
  - Subjects must receive “Subject Information Notice”
  - Not intended for screening of blood donors

Labeling: Supplemental

- In addition to an aid in diagnosis claim:

  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. …..”

- For a stand-alone supplemental test:

  Include the 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”

- For a differentiation claim:

  Include the statement that the test is intended for the confirmation and differentiation of individual antibodies to different types of HIV

What input do we need from the panel?

- Discussion of the risks and benefits to health of reclassification

  Are there any additional risks we should consider?

- Discussion of special controls

  Are there any additional special controls we should include?

- Provide general recommendations

Thank you!

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https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm