



USAID
FROM THE AMERICAN PEOPLE

HIV Rapid Test Kits USAID Approval and Technical Guidance June 17, 2013 Revision

Part 1

A. Introduction

1. This document contains the requirements for USAID evaluation and approval of HIV rapid test kits and related technical guidance. The requirements are subject to change at any time.
2. An HIV rapid test kit is an assay for diagnosis of infection with HIV-1/2 or type specific diagnosis of HIV-1 and HIV-2, from which test results can be read directly, within 30 minutes of the time the specimen is applied to the device, without calibration or calculations. Currently, USAID does not evaluate HIV rapid test kits marketed as HIV home tests or self-test kits.
3. Approved test kits are on the **USAID List of Approved HIV Test Kits (List)** (formerly USAID List of Approved HIV/AIDS Test Kits) at: http://transition.usaid.gov/our_work/global_health/aids/TechAreas/treatment/scms.html. The Supply Chain for Health Division, Office of HIV/AIDS, Bureau of Global Health (GH/OHA/SCH) maintains the List.
4. Under ADS 312, GH/OHA/SCH has “restricted commodity” approval authority to approve HIV/AIDS rapid test kits for use in PEPFAR and USAID-supported overseas global health programs.
5. The approval process is a cooperative effort between GH/OHA and the DGHA International Laboratory Branch of the Centers for Disease Control and Prevention (CDC/ILB). CDC/ILB prepares a Rapid HIV Test Evaluation Report (Attachment A), which is used in the approval process.

B. June 17, 2013 Revision

This Revision replaces the “HIV Rapid Test Kit Process for USAID Approval and Technical Guidance”, dated March 5, 2010. This Revision applies to test kits

submitted for USAID approval after [insert date above]. Test kits already approved by USAID under the March 5, 2010, guidance continue to be approved, but are subject to re-evaluation at USAID's discretion.

The major changes are the following:

1. Approval by a Stringent Regulatory Authority (SRA) other than the U.S. Food and Drug Administration (FDA) is no longer a basis for approval.
2. FDA-approval continues to be a basis for technical approval. But FDA-approved test kits must now meet the general and documentation requirements. And USAID may require additional region-specific evaluations or other documentation of performance.
2. Prequalification of a test kit by the World Health Organization (WHO) is now a basis for technical approval. But USAID reserves the right to require the test kit be evaluated by CDC/ILB. A WHO prequalified test kit must meet the general and documentation requirements.
3. USAID will publish the results of CDC/ILB technical evaluations for both "approved" and "not approved" test kits.
4. USAID reserves the right to perform or participate in site inspections of manufacturing facilities for the purpose of assessing the quality management system for approved test kits.
5. USAID reserves the right to conduct post-approval lot verifications to determine if a test kit continues to meet inter-lot consistency and other approval standards.
6. Failure to maintain performance that meets the approval standards can result in suspension or removal from the List.

C. USAID List of Approved Rapid HIV Test Kits

1. The List includes, but is not limited to, the following information:
 - Market name and product code of tests
 - Names and corporate addresses of manufacturers
 - Address(es) of manufacturing site(s)
 - CDC/ILB evaluation reports (both approved and not approved)
 - Basis for technical approval: FDA-approved, WHO prequalified or USAID/CDC evaluation
 - Dates of approval or non-approval
 - Dates of and reasons of suspension, removal and reinstatement

2. GH/OHA/SCH updates the List when:

- a new test kit is approved or not approved
- a test kit is suspended removed or reinstated
- GH/OHA/SCH has confirmed that a test kit is no longer produced or available

D. Steps for USAID Approval

1. There are three sequential steps for USAID approval:

- Step 1 General Requirements (Section E)
- Step 2 Documentation Requirements (Dossier Review) (Section F)
- Step 3 Technical Requirements (Section G)

2. There are three ways to meet the technical requirements:

- FDA Approval
- WHO Prequalification
- CDC/ILB Evaluation

3. USAID approval applies only to the specific test kit and components submitted for evaluation, and that test kit's specific manufacturing and component manufacturing sites.

4. Although operational characteristics of test kits are not used for approval, CDC/ILB also assesses the following:

- Number of steps
- Total run time
- Ease of interpretation
- Overall ease of use
- Training requirements
- Recommended storage conditions
- Shelf life
- Kit box size
- Individual test packaging
- Required accessories necessary for operation of the test kit that are not provided with the test kit (specimen collection device, buffer, and any other materials needed for test performance, etc.)
- Test kit presentation (e.g. number of tests within one box per product code, if multiple product codes available)
- Amount and type of waste generated (e.g., biohazard)

E. Step 1 – General Requirements

A test kit must meet the following general requirements:

1. The test kit must be an assay for diagnosis of infection with HIV-1/2 or type specific diagnosis of HIV-1 and HIV-2, from which test results can be read directly, within 30 minutes of the time specimen is applied to the device, without calibration or calculations.
2. The test kit must use direct, unprocessed specimens (unprocessed whole blood, urine or oral fluid).
3. All reagents necessary to conduct the test, including diluents, must be included in the test kit and ready to use in the testing procedure without any additional manipulation.
4. After initial addition of specimen and reagents, the test kit should require only minimal operator intervention or procedural steps during the analysis.
5. The test kit must not require special storage conditions (e.g. refrigeration or cold chain).
6. The test kit must not require specialized equipment to perform (for example, centrifuge, washers, spectrophotometers, etc.).

F. Step 2 - Documentation Requirements (Dossier Review)

1. The manufacturer must submit a physical copy to CDC/ILB and electronic copies to CDC/ILB and GH/OHA/SCH (see Section I below), of the following:
 - a. **Dossier.** A complete dossier explaining the technical specifications of the product including:
 - 1) The test principle and methods;
 - 2) Type(s) of specimens used (e.g., whole blood);
 - 3) Test procedure, including the time needed to run the test;
 - 4) Sensitivity, specificity (including where the studies were performed to generate these values and 95% confidence intervals);
 - 5) Reproducibility across multiple test kit lots (e.g. including number of samples, type of specimens, number of kit lots);
 - 6) Demonstration of stability throughout the shelf life of the product under recommended storage conditions;
 - 7) For FDA-approved test kits, evidence of satisfactory test performance from regions outside of the U.S.
 - b. **Product Information**, including:
 - 1) Manufacturer name and address
 - 2) Component manufacturers and addresses
 - 3) Product code
 - 4) Items included in the kit
 - 5) Number of individual tests in each kit
 - 6) Additional items required to perform the test but not included in the kit (e.g., sample collection equipment)

- 7) Shelf life
- 8) Recommended storage conditions

- c. **Product directions and information.** The test kit's product insert, instructions for use (IFU) and any other product directions and information must describe the test procedure in precise, grammatically correct, and easy to understand language.

- d. **Quality Management System.** Evidence that the main manufacturing site and any component manufacturing sites have a certified quality management system, e.g., ISO 13485:2003 or Good Manufacturing Practice (GMP) certification.

- e. **Manufacturer Standard Provisions.** A statement to the effect that the manufacturer agrees to the Manufacturer Standard Provisions in Attachment B.

NOTE: The manufacturer should mark any proprietary information

3. If the documentation is approved, CDC/ILB will provide the manufacturer instructions on meeting the technical requirements. If the documentation is not approved, CDC/ILB will notify the manufacturer of the reasons and give the manufacturer an opportunity to correct the documentation.

G. Step 3 - Technical Requirements - FDA Approved and WHO Prequalified

1. FDA-Approved

a. A test kit can meet the technical requirements by being approved or licensed by FDA. "Rest of world" test kits (for example, test kits with the same name as the FDA-approved test kit, but manufactured to different standards or in a different location than the FDA-approved test kit) are not considered to be FDA-approved and must be approved by USAID.

b. USAID reserves the right to require an additional evaluation process to determine satisfactory performance with specimens from appropriate regions outside of the U.S. as a condition of approval.

2. WHO Prequalification

A test kit can meet the technical requirement by successfully completing WHO's prequalification of diagnostics process and being included on the WHO List of Prequalified Diagnostics. However, USAID reserves to require a CDC/ILB evaluation under Section H of the test as a condition of approval.

H. Step 3 – Technical Requirements – CDC/ILB Evaluation

1. For the CDC/ILB evaluation, a test kit must meet the following technical requirements:
 - a. A sensitivity of at least 99% [false negative rate of <1%] for detection of HIV infection including HIV-1 and HIV-2.
 - b. A specificity of at least 98% [false positive rate of <2%] for detection of HIV infection including HIV-1 and HIV-2.
 - c. Invalid test results must be less than 1% of the total tested (this includes defective tests or components).
 - d. Inter-lot and inter-reader variability of additional 2 lots must be less than 10% and 5% respectively when compared to the reference lot; dilution panels will be performed and must demonstrate end-point consistency with +/- 1 dilution.
 - e. The test kit must have an internal control or other failure alert mechanism to notify the operator that sufficient volume has been applied and that the assay functions properly.
 - f. All components of the test kit, including the kit product insert, must be consistent with the approved dossier submission.
2. The manufacturer must submit at its expense to CDC/ILB (see Section I below) individual tests with accessories, in the following numbers:
 - 2,000 randomly selected individual tests from one lot
 - 200 randomly selected individual tests from a second consecutive lot
 - 200 randomly selected individual tests from a third consecutive lot
3. The manufacturer must submit the regulatory version of the test kit it intends to supply to PEPFAR and other USG supported overseas programs.
4. The manufacturer must label individual tests and kits and package individual tests into kits as they will be marketed. Manufacturers must indicate how it determines a manufacturing lot or batch.
5. For test kits detecting HIV-antibodies in plasma or serum specimens, CDC/ILB evaluates the test kit using a well-characterized panel of 1500 archived HIV-positive and HIV-negative samples obtained from diverse geographic areas and including different HIV types and subtypes.
6. CDC/ILB uses selected commercial seroconversion panels for rapid test kits that claim detection of acute infection (p24 or RNA detection).
7. CDC/ILB evaluates for lot-to-lot consistency (3 kit lots) using a set of dilution series specimens (N=100) for end-point comparisons.

8. For test kits requiring fresh, unprocessed specimens (e.g., whole blood, oral fluid); a specific collection device; or region-specific testing; CDC/ILB and USAID identifies a collaborative laboratory to evaluate the test kit against the technical requirements. This requires development and approval of a research protocol that will require a significant time investment and funding. There is no guarantee of funding for such field evaluations.

H. Post-Approval Monitoring

1. USAID conducts post-approval monitoring to assure ongoing quality, including verifications to determine if a test kit continues to meet inter-lot consistency and other approval standards.
2. USAID may perform or participate in site inspections for purposes of assessing the quality management system for approved test kits.
3. USAID may require a re-approval of an approved test kit to determine if it meets revised general, documentation or technical requirements.

I. Requests for Re-Evaluation

1. If a test kit does not meet CDC/ILB technical requirements, the manufacturer may request a second evaluation only, no sooner than 12 months from the date of completion of the first evaluation. If the test kit fails the second evaluation, a manufacturer may not submit a third request no sooner than least 12 months from the date of the completion of the second evaluation. Each request for a re-evaluation is considered a new application and will be considered in turn with other applications.
2. A manufacturer requesting a re-evaluation must document how it has corrected the technical deficiencies through changes in manufacturing, design, etc.; furnish an evaluation from an independent laboratory demonstrating acceptable performance; and assign the test a new product code.
3. If CDC/ILB determines that the manufacturer's documentation and the independent laboratory evaluation have addressed the technical deficiencies, CDC/ILB will re-evaluate the test.

J. Suspension, Removal and Reinstatement

1. USAID may suspend or remove a test kit from the List for quality issues reasons including, but not limited to: failure to notify USAID of any significant changes to the test kit, its components or manufacturing processes or site within 30 days; failure to furnish requested information; unacceptable

performance of test kits in the field (including reductions in sensitivity, specificity or high rates of invalid results (>1%)).

2. Reinstatement of a test kit suspended or removed from the List for any reason requires re-evaluation. In addition, USAID may require a site inspection, lot release evaluations or other conditions necessary to ensure on-going quality.

K. Contacts

1. CDC/ILB

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2. USAID/GH/OHA/ TLR

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3. USAID/GH/OHA/SCH

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Attachment A - RAPID HIV TEST EVALUATION REPORT

**Center for Diseases Control and Prevention
Division of Global HIV/AIDS
International Laboratory Branch
RAPID HIV TEST EVALUATION REPORT – PART A**

DOSSIER REVIEW – GENERAL INFORMATION

Date dossier received	
Name/Date of the person reviewing dossier	
Name of the test	
Name of the manufacturer	
Name/Contact information of the manufacturer (including name, address, telephone number and email)	
Review	<input type="checkbox"/> Initial Review <input type="checkbox"/> Re-submission of Dossier <input type="checkbox"/> 2 nd application

DOSSIER SPECIFICATIONS AND/OR EQUIREMENTS

Test kit insert included	<input type="checkbox"/> Yes, and reviewed <input type="checkbox"/> No
Run time indicated	<input type="checkbox"/> Yes, run time <input type="checkbox"/> No
Sensitivity and specificity reported	<input type="checkbox"/> Yes <input type="checkbox"/> No
Study Information	List of study location: No of positive: No of Negative:
Reproducibility across multiple test kit lots	<input type="checkbox"/> Yes <input type="checkbox"/> No
Test principle described	<input type="checkbox"/> Yes <input type="checkbox"/> No

Sample type	Check all that applies: <input type="checkbox"/> Whole blood <input type="checkbox"/> Serum <input type="checkbox"/> Plasma <input type="checkbox"/> Others _____
Requires special processing of samples	<input type="checkbox"/> Yes, Explain: _____ <input type="checkbox"/> No
Test kit stability (Study demonstrated)	<input type="checkbox"/> Yes <input type="checkbox"/> No
Test kit components	<input type="checkbox"/> Test device <input type="checkbox"/> Sample transfer device <input type="checkbox"/> Buffer <input type="checkbox"/> Other
Stringent Regulatory Authority (SRA) approval	<input type="checkbox"/> US FDA <input type="checkbox"/> Health Canada <input type="checkbox"/> European Medicines Agency (EMA) <input type="checkbox"/> European Free Trade Association (EFTA) <input type="checkbox"/> Japan Ministry of Health, Labour and Welfare (MHLW) <input type="checkbox"/> Other
Manufacturing process has GMP certification	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Other _____

DOSSIER APPROVAL

Dossier approved	<input type="checkbox"/> Yes <input type="checkbox"/> No Signature/Date:
Comments by the reviewer	
Date and name of the person who sent the notification to the manufacturer for test kit shipment	

**Center for Diseases Control and Prevention
Division of Global HIV/AIDS
International Laboratory Branch
RAPID HIV TEST EVALUATION REPORT – PART B**

Table 1: General Characteristics of the RT kit

	Parameters	RT Performance
1	Name of the Test/Product Code	
2	Manufacturer/City/Country/point of contact information/ phone number/ e-mail	
3	Duration in the market	
4	Approval Status (U.S. FDA, WHO, UE, etc.) a. Kit Approval b. Manufacturer Approval c. Facility Approval d. Other Regulatory Authority	
5	Number of Tests/Kit	
6	General Principle of the Test	
7	Antigen(s) Used	
8	Recommended Storage (score) (select one)	<input type="checkbox"/> 4°C = 5 points <input type="checkbox"/> RT = 10 points
9	Shelf Life (score) (select one)	< 6 months to ≥ 1 year (2 to 10) <input type="checkbox"/> 2 points <input type="checkbox"/> 4 points <input type="checkbox"/> 6 points <input type="checkbox"/> 8 points <input type="checkbox"/> 10 points
10	Kit Box Dimensions (score) (select one)	Extra-large to Extra small (2 to 10) <input type="checkbox"/> 2 points <input type="checkbox"/> 4 points <input type="checkbox"/> 6 points <input type="checkbox"/> 8 points <input type="checkbox"/> 10 points
11	Individual test packaging (score) (select one)	Poor to very good (2 to 10) <input type="checkbox"/> 2 points <input type="checkbox"/> 4 points <input type="checkbox"/> 6 points

		<input type="checkbox"/> 8 points <input checked="" type="checkbox"/> 10 points
12	Amount of Waste Generated (score) (select one)	Significant to negligible amounts (2 to 10) <input type="checkbox"/> 2 points <input type="checkbox"/> 4 points <input type="checkbox"/> 6 points <input type="checkbox"/> 8 points <input type="checkbox"/> 10 points
13	Cost/Kit and Cost/Test (USD)	
14	No. of Tests Manufactured/Year (availability)	
15	No of Lots/Year	
Subtotal score		

Table 2: Test Performance

	Parameters	RT Performance
1	Kit lot(s) used	
2	Sensitivity (> 99%)	
3	Specificity (> 98%)	
4	Positive Predictive Value	
5	Negative Predictive Value	
6	Inter-lot Variability (Acceptable if < 10%, using dilution panel)	
7	Inter-Reader (3) Variability (Acceptable if <10%, using dilution panel)	

Table 3: Detailed Operational Characteristics

	Parameters	RT Performance
1	Number of Steps (score) (select one)	1 Step to 5 Steps (10 to 2) <input type="checkbox"/> 2 points <input type="checkbox"/> 4 points <input type="checkbox"/> 6 points <input type="checkbox"/> 8 points <input type="checkbox"/> 10 points
2	Reagent Preparation	None
3	Run Time (min-max) (score) (select one)	> 30 minutes to ≤ 10 minutes (2 to 10) <input type="checkbox"/> 2 points <input type="checkbox"/> 4 points

		<input type="checkbox"/> 6 points <input type="checkbox"/> 8 points <input type="checkbox"/> 10 points
4	Stability Results	
5	Ease of Interpretation (score) (select one)	Very difficult to very easy (2 to 10) <input type="checkbox"/> 2 points <input type="checkbox"/> 4 points <input type="checkbox"/> 6 points <input type="checkbox"/> 8 points <input type="checkbox"/> 10 points
6	Run kit diluent or PBS on 2 devices: Control line Present with addition of kit diluent (select one)	<input type="checkbox"/> Yes <input type="checkbox"/> No
8	Additional Supplies/Reagents Needed	
9	Additional Equipment Needed	
10	External Controls Included	
11	No of Tests/Operator/Hour	
12	No of Invalid Tests/1500 tests	
13	Claim (HIV-1, HIV-1/2 or distinguish 1 & 2)	
14	Overall ease of Use (score) (select one)	Very difficult to very easy (2 to 10) <input type="checkbox"/> 2 points <input type="checkbox"/> 4 points <input type="checkbox"/> 6 points <input type="checkbox"/> 8 points <input type="checkbox"/> 10 points
15	Training Requirements (score) (select one)	Extensive to None (2 to 10) <input type="checkbox"/> 2 points <input type="checkbox"/> 4 points <input type="checkbox"/> 6 points <input type="checkbox"/> 8 points <input type="checkbox"/> 10 points
16	No. of Weak Reactive	
17	Additional Comments	
Subtotal score		

Table 4: Overall Recommendations

	Parameters	RT Performance
1	Qualifying Statement	
2	Lot-to-Lot consistency (Acceptable if >90%)	

3	Suitability for high- or low- volume facility (select one)	<input type="checkbox"/> High <input type="checkbox"/> Medium to High <input type="checkbox"/> Low to medium <input type="checkbox"/> Low <input type="checkbox"/> N/A
4	Suitability as a screening or confirmatory test (select one)	<input type="checkbox"/> Screening <input type="checkbox"/> Confirmatory <input type="checkbox"/> Both <input type="checkbox"/> N/A
5	Further in-country evaluation	
6	Overall Comments	
Total Points		

Attachment B

USAID Approval of HIV Rapid Test Kits Manufacturer Standard Provisions

1. The Manufacturer acknowledges that USAID makes public the results of the evaluation whether approved or not.
2. The Manufacturer acknowledges that USAID may require a re-evaluation of an approved test kit at any time.
3. The Manufacturer agrees to provide written notice to GH/OHA/SCH within 30 days and prior to supplying an approved test kit of:
 - a. Any manufacturing or design change in the test kit or components;
 - b. Any change in manufacturing or component manufacturing sites and provide evidence of GMP compliance at any new site; and
 - c. Any service bulletins, safety notices, recall notices, etc. issued by the Manufacturer or other problem that could impact performance with the approved test kit or any component.
4. The Manufacturer agrees to promptly provide GH/OHA/SCH with the results of any site inspection by a third party of the Manufacturer's test kit facilities and any component facilities at any time during the approval process or after approval.
5. The Manufacturer agrees to provide GH/OHA/SCH with any additional information that USAID determines is necessary to approve a test kit and assure ongoing quality.
6. The Manufacturer agrees that GH/OHA/SCH may inspect or participate in site inspections of the Manufacturer's facilities and any component facilities for purposes of assessing the quality management system of an approved test kit or a test kit submitted for approval. As part of any site inspection, USAID reserves the right to examine, or inspect test kits in the course of manufacture and packaging and to take samples for independent analysis and testing.
7. The Manufacturer agrees to make every effort to notify GH/OHA/SCH of any possible counterfeiting, piracy, or unauthorized sales by third parties of diluted, adulterated, impure, misbranded, mislabeled, unsafe, ineffective, inefficacious, or otherwise non-standard items of the same type and brand as the approved test kit.
8. The Manufacturer should mark any information that it regards as proprietary.