Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications Final Guidances

Tamara Pinkney, MT(ASCP)
Policy Analyst
Division of Program Operations and Management
OHT7: Office of In Vitro Diagnostics and Radiological Health
Office of Product Evaluation and Quality

Center for Devices and Radiological Health

This Presentation Covers Two Complementary Final Guidances for CLIA Waiver Applications:

- Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices
  - Referred to as the “CLIA Waiver” guidance
- Recommendations for Dual 510(k) and CLIA Waiver by Application Studies
  - Referred to as the “Dual” guidance

Agenda

- Background
- Final CLIA Waiver Guidance
  - Section V. Demonstrating Insignificant Risk of an Erroneous Result – Accuracy
- Final Dual Guidance

Objectives

- Understand CLIA waiver pathway options:
  - CLIA waiver application following clearance or approval
  - Dual Submission (Combined 510(k) and CLIA waiver application following a pre-submission)
- Understand the U.S. Food and Drug Administration's (FDA) current thinking on study designs for both pathways

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Background

- CLIA waiver statutory criteria
- 21st Century Cures requirements to update the 2008 CLIA Waiver Guidance
- CLIA waiver pathways addressed by the two final guidances
- Draft guidances issued in 2017 and 2018

CLIA Statutory Criteria for Waiver

CLIA, 42 U.S.C. 263a(d)(3) Examinations and Procedures, as modified by the Food and Drug Administration Modernization Act of 1997 (FDAMA):

"The examinations and procedures [that may be performed by a laboratory with a Certificate of Waiver]… are laboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that −

A) **employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or**

B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly."

21st Century Cures Requires an Update to Sec V. of the CLIA Waiver Guidance

- Sec. 3057, CLIA Waiver Improvements, requires the FDA to publish guidance that:

  (1) revises "Section V. Demonstrating Insignificant Risk of an Erroneous Result – Accuracy" of the [2008 CLIA Waiver Guidance*]

  (2) includes the appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate accuracy

* "Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices," issued January 30, 2008

The Final Guidances Address Two CLIA Waiver Pathways

CLIA Waiver by Regulation or Clearance/Approval for Home Use

Clearance or Approval of test type listed in 42 CFR 493.15(c), or

Clearance or Approval for home use

→ CLIA Record: Waived

Stepwise CLIA Waiver by Application *(CLIA Waiver Guidance)*

Pre-Submission → **Marketing Submission (Premarket Approval [PMA], 510(k), De Novo)** → **CLIA Record: Moderate** → ***CLIA Waiver by Application***

Dual 510(k) and CLIA Waiver by Application *(Dual Guidance)*

Pre-Submission → ***Dual Submission (Combined 510(k) and CLIA Waiver)***

Draft Guidances Were Issued in 2017 and 2018

- Initial drafts of both guidances were issued in November 2017:
  - The draft CLIA Waiver guidance was entitled “Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices” and included draft revisions to Section V of the 2008 CLIA Waiver Guidance.
  - The draft Dual guidance had the same title as the current final guidance.
- Based on comments received, and multiple meetings with stakeholders, significantly revised drafts were issued in November 2018.

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Final CLIA Waiver Guidance

- Provides study design recommendations for CLIA waiver applications
  - Addresses the stepwise CLIA waiver pathway following marketing submission clearance/approval

- Significant changes were not made from the 2018 draft
  - Only limited edits to address minor technical comments and to incorporate the 2018 draft Section V into the 2008 final guidance

CLIA Waivers Focus on Two Questions

- **Is the test system simple?**
  - Simple test characteristics
  - Labeling for waived users (for example, a Quick Reference Guide at 7th grade level)
- **Does the test system have an insignificant risk of erroneous result?**
  - Risk Analysis
  - Flex Studies
  - Accuracy Studies

Test Should be Designed to be Simple to Use

Examples of "Simple" Test Characteristics:

- Automated instrument or unitized test system
- Uses direct unprocessed samples (such as, fingerstick blood, venous whole blood, nasal or throat swabs, or urine)
- Easy to read instructions (such as, a Quick Reference Guide at 7th grade level)
- No operator intervention during analysis
- No technical or specialized training – troubleshooting or complex error codes
- Easy to read test results (positive, negative, invalid, direct value, etc.)

A Systematic Risk Analysis Should be Conducted

- Recommended resource: ANSI AAMI ISO 14971, *Medical Devices - Application of Risk Management to Medical Devices* (FDA recognized standard)
- **Examples of potential sources of error to consider include:**
  - Operator error/human factors
  - Specimen handling and integrity – clotted specimen, short sample, interfering substances
  - Reagent integrity – improperly stored, outdated
  - Hardware, software and electronics integrity - power failures, bugs, physical trauma to unit
  - System stability - calibration
  - Environmental factors – temperature, humidity, atmospheric pressure, surface angle, device movement

Fail-Safe and Failure Alert Mechanisms Should be Incorporated to Mitigate Risks

Examples of Fail-safe and Failure Alert Mechanisms:

- Lock-out features
  - No result if QC fails
  - No result if reagents expired
  - No result if outside instrument temperature range
  - No result if internal electronic checks or procedural controls fail
- Physical features to ensure correct placement of components
- Monitors of the environment
  - Indicator desiccants that alert when outside storage conditions

Flex and/or Validation Studies are Conducted Based on the Risk Analysis

Potential source of error	Example of flex studies	Example of validation studies
Procedure: Add 3 drops. What happens when too many or too few drops are added?	Study adding 1, 2, 3, 4, 5, 6 drops – Observe when incorrect results occur. Device fails at 1 & 6 drops.	Studies to validate fail-safe or QC or failure alert when < 2 drops and > 5 drops.

Labeling for Waived Devices

- Test instructions intended for untrained operators should be simple and written at no higher than a 7th grade level:
  - ***Quick Reference Guide (QRG)*:** A short (usually one or two page) version of the test instructions, preferably laminated and attached to the test system. It is intended for untrained operators and contains the step by step instructions needed to perform the test with a negligible likelihood of erroneous results.
  - ***Operator's Instrument Manual*:** A short version of the instrument manual that is intended for untrained operators and includes instructions for start-up of the instrument, long term maintenance including calibration (if applicable), error codes, etc.
- **Note:** For waived test systems, the package insert should be intended for the medical professional prescribing the test and does not need to be written at a 7th grade reading level.

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The Revised Section V Focuses on Study Design Aspects Directly Related to Meeting the Statutory Criteria for CLIA Waiver

- Emphasizes validating that the accuracy of a candidate test is not meaningfully impacted by differences between non-waived and waived use, including:
  - user training and experience;
  - testing environment; or
  - patient populations.
- General information on test accuracy issues not specific to CLIA-waived tests has been replaced with references to FDA-recognized consensus standards.
  - Additionally, examples of successful CLIA waiver study designs can be found in publicly posted CLIA Waiver Decision Summaries.

Definitions

- ***Untrained Operator or Waived User**:*
  - A test operator in waived settings and with limited or no training or hands-on experience in conducting laboratory testing.

- ***Trained Operator or Moderate Complexity Laboratory User**:*
  - A test operator who meets the qualifications to perform moderate complexity testing (42 CFR 493.1423).

- **Note**: also see Section V.C.(2) *Operators* for additional recommendations.

Additional Study Design Options Provide Flexibility

- Option 1: Agreement Studies
  - Comparison study designs in which the results of the candidate test in the hands of untrained operators are compared to the results of the candidate test in the hands of trained operators
  - The FDA believes Option 1 will be appropriate for the majority of candidate tests
- Option 2: Agreement studies modeled after approaches in the FDA guidance on Assay Migration Studies for In Vitro Diagnostic Devices
- Option 3: Flex and human factors engineering studies
- Option 4: Direct Comparison to an Appropriate Comparative Method
  - Comparison study designs in which the results of the candidate test in the hands of untrained operators are directly compared to the results of an appropriate comparative method in the hands of trained operators

We’re Harmonizing Our Approach to CLIA Waiver Benefit-Risk Considerations with Other FDA Benefit-Risk Guidances

- All tests have some likelihood of erroneous results, but whether the likelihood of erroneous results in the hands of waived test users is negligible will vary from test to test depending on a number of factors, including:
  - intended use;
  - context of use (for example, patient population, use environment); and
  - probable benefit(s) and probable risk(s) or harm(s) associated with waived use of the test.
- Accordingly, the appropriate acceptance criteria for CLIA waiver accuracy studies will vary from test to test.
- For details about the FDA’s current thinking about benefit-risk considerations for medical devices, CDRH benefit-risk guidances are referenced rather than repeating similar material.

General CLIA Waiver Study Design Considerations Have Not Changed

- The FDA recommends that applicants evaluate test performance in settings designed to replicate, as closely as possible, intended:
  - CLIA-waived testing sites;
  - Patients, sample type and matrix; and
  - Untrained operators.
- Testing should be integrated into the daily workflow of the facility where the operators are often multitasking between patient care, testing, and other duties.
- Include at least 3 sites and at least 9 untrained operators (across all sites).
- Pre-Submissions are highly recommended to get feedback from the FDA on study designs before conducting the studies.

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Final Dual Guidance

- Describes an efficient single set of comparison and reproducibility study designs with untrained users for a Dual 510(k) and CLIA Waiver by Application (“Dual Submission” or Dual”)
  - The Dual study design recommendations in this guidance may also be utilized in a sequential submission approach in which a CLIA Waiver by Application follows marketing authorization (such as, PMA, De Novo)
- Significant changes were not made from the 2018 draft, only minor edits to harmonize with technical edits to the CLIA Section V guidance

Historically, Separate 510(k) and CLIA Waiver Studies Have Been Conducted in Different Clinical Settings

510(k)	**Point of Care (POC) Sites & Trained Users**
CLIA Waiver by Application	**Waived Sites & Untrained Users**

- In this two step approach, manufacturers conduct separate comparison and reproducibility studies, in different clinical settings, first to support 510(k) clearance and later to support CLIA Waiver by Application.

Process and Content of a Dual Submission

- Inform the FDA that you plan to submit a Dual Submission in a Pre-Submission prior to submitting the Dual Submission.

- A Dual Submission should contain the same information as a complete 510(k) and CLIA Waiver by Application:
  - Content related to the comparison and reproducibility studies may overlap.
    - Therefore, a single set of comparison and reproducibility studies may be used to support both 510(k) clearance and CLIA Waiver by Application.
  - All other content that would otherwise be included in separate, sequential 510(k) and CLIA Waiver by Application submissions should be included in a Dual Submission.

The Dual Approach Provides Time and Study Efficiencies

510(k) – POC

- Analytical studies as
  - analytical sensitivity,
  - analytical specificity,
  - linearity,
  - reagent stability,
  - sample stability, and so on
- ~~Comparison study (POC sites & trained users)~~
- ~~Reproducibility study (POC sites & trained users)~~

CLIA Waiver Application

- Simple,
- Flex studies
- Comparison study (CLIA waived sites and untrained users)
- Reproducibility study (CLIA waived sites and untrained users)

Comparison Study Design Recommendations

- For comparison study design and analysis we recommend you follow appropriate FDA-recognized consensus standards, such as:
  - For quantitative tests:
    - Clinical Laboratory Standards Institute (CLSI) EP21, CLSI EP27
  - For qualitative tests:
    - CLSI EP12.

- See Section V of the CLIA Waiver guidance for general study design considerations.

Reproducibility Study Design Recommendations

- For reproducibility study design and analysis, we recommend you follow appropriate FDA-recognized consensus standards (such as, CLSI EP05, CLSI EP12).
- Include a minimum of 3 of the same sites that were included in the comparison study.
- To facilitate statistical analysis, include the same number of untrained operators (likely 2 or 3) at each site.
- Include the following sources of variability: different sites, different untrained operators, different days, different runs, different lots (if applicable), and a few replicates.

Resources

- Final Guidances:
  - Administrative Procedures for CLIA Categorization
  - Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices
  - Recommendations for Dual 510(k) and CLIA Waiver by Application Studies
  - Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

- CLIA Waiver Decision Summaries

Questions?

CLIA@fda.hhs.gov

Thank You