

CLIA Waiver

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Carol C. Benson, M.A.

Associate Director – Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety



Topics

- Introduction of CLIA waiver in general terms
- Concepts of how a test system qualifies for a CLIA waived categorization

42 U.S.C. Section 263a(d)(3)

“simple laboratory examinations and procedures that have been approved by the FDA for home use or that...are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result”

42 U.S.C. Section 263a(d)(3)

“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) ...pose no unreasonable risk of harm to the patient if performed incorrectly”

Impact of CLIA waived test systems

- Driving Technology – more simple devices
- Broadens the market for manufacturers (mod/high 17% of all CLIA labs, waived 60% of all CLIA labs)
- Benefit for patients – testing and results at the time of the office visit with doctor
- Helps with the personnel shortage of trained laboratory workers
- Waived test systems have no requirements for trained laboratory workers, no PT testing – CLIA certificate CMS and “Follow manufacturer’s instructions”

How do test systems qualify for CLIA waiver?

- By Regulation – 42 CFR 493.15(c) for 9 generic tests (FOB, u. preg., u. dipstick, OTC glucose, spun hematocrit, ovulation, hemoglobin single analyte instrument, hemoglobin copper sulfate, and ESR)
- By FDA Clearance/Approval for home use
- **By Meeting the statutory criteria**

CLIA Waiver Guidance Jan 2008 -FDA

- FDA, CLIAC, CDC, CMS, Medical Device Industry, Trade Associations (e.g., AdvaMed), Professional Associations (e.g., AACCC), and Laboratorians
- FDA interpretation law - 42 U.S.C. Section 263a(d)(3)
- Difference between guidance and law
- Law is binding/guidance is not – guidance recommends how to meet the law

CLIA Waiver Guidance -FDA

- Principles include:
 - use of “intended operators” performing waived testing under stress of multi-tasking, testing real samples over time (min. two weeks),
 - traceability requirements for comparative method on which to base “accuracy”,
 - strong risk analysis to base flex studies,
 - use of clinically based performance standards for “accuracy” (allowable total error –ATE and limits of erroneous results – LER) CLSI EP21-A

CLIA Waiver Guidance - FDA

- Scientific issues for qualitative test are addressed through controlled cut-off studies
- Ensure that the device is controlled at critical cut points
- One size may not fit all - Encourage protocol reviews with FDA through pre-IDE process

What are the similarities and differences between CLIA waived and POC devices?

Similarities –

- CLIA waived device is usually performed at point of care site.
- Both have studies demonstrating performance at POC

Differences -

- Many point of care test systems are categorized as moderate complexity.
- **They may not be simple. They have not performed CLIA waiver studies to demonstrate that they meet the CLIA waiver criteria.**

How does a test system meet CLIA waiver criteria?

- Is the test system simple?
- Does the test system have an insignificant risk of an erroneous result?

Demonstrating “Simple”

- Fully auto instrument or unitized test system
- Uses direct unprocessed samples – fingerstick blood or venous whole blood or urine
- Non technique dependent specimen or reagent manipulation
- No operator intervention during analysis
- No technical or specialized training – troubleshooting or complex error codes
- Easy to read test results (pos, neg, value, etc.)
- Clear labeling

Labeling for Waived Devices

- Quick reference instructions at 7th grade reading level
- PI with procedure steps at 7th grade reading level
- Includes QC recommendations for use of external ready to use QC materials and for frequency of testing
- Educational information

Demonstrating “Insignificant Risk of Erroneous Result”

Risk Analysis (identification of all potential sources of error and how to mitigate their risk)

Risk Analysis

- Operator error/human factors
- Specimen handling and integrity – clotted specimen, short sample, interfering sub.
- Reagent integrity – storage, out-dated
- Hardware, software and electronics integrity - power failures, bugs, p. trauma
- System stability - calibration
- Environmental factors – heat, humidity, electrical or electromagnetic interference

Demonstrating “Insignificant Risk of Erroneous Result”

- Risk Analysis (identification of all potential sources of error and how to mitigate their risk)
- Test Fail-Safe and Failure Alert Mechanisms validated through flex studies

Fail-safe and Failure alert mechanisms

Lock-out features

- No result if exp. reagents
- No result if internal electronic checks fail
- No result if QC fails

Physical features

- Strip and cartridge correct placement

Monitors of the environment

External QC materials

Internal procedural controls

Flex Studies – based on risk analysis

Potential source of error	Examples of flex studies	Examples 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, 5 & 6 drops	Studies to validate fail-safe or QC or failure alerts alert operator when < 2 drops and > 4 drops

Flex Studies – based on risk analysis

Potential source of error	Examples of flex studies	Examples of validation studies
Use of expired reagents	Study using expired reagents	Studies to validate fail-safe or QC or failure alerts
Re-use of cassette or reagent pack	Study re-using cassette or reagent pack again	alert operator when expired and re-used reagents are used

How does a test system meet CLIA waiver criteria?

- Demonstrate simple
 - Perform risk analysis – do flex studies – test fail-safe and failure alert mechanisms
 - Valid scientific studies to demonstrate “accuracy” using labeling and education materials only
- (quick ref. guide written at 7th grade level, PI or other educational materials)

Demonstrating “Insignificant Risk of Erroneous Result” - “Accuracy”

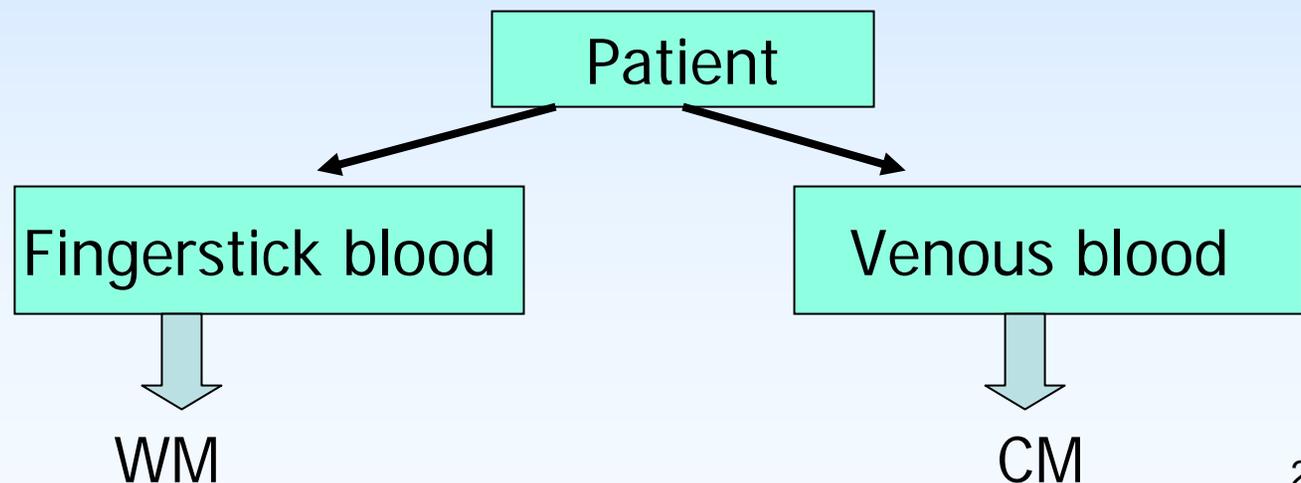


- The term “accurate” tests refers to those tests that are comparable to traceable methods (trueness).
- Prospective clinical studies of the device proposed for waiver:
 - intended clinical testing sites (min. 3)
 - intended operators (min. 9)
 - intended sample type and matrix (360)
 - testing over time, as in typical intended use setting (min. of 2 weeks)

Demonstrating “Accuracy” – Paired Study Design



- WM by intended users in CLIA waived setting
- CM by professional users in laboratory settings
- Split patient sample in 2 parts
(if impossible, second sample)

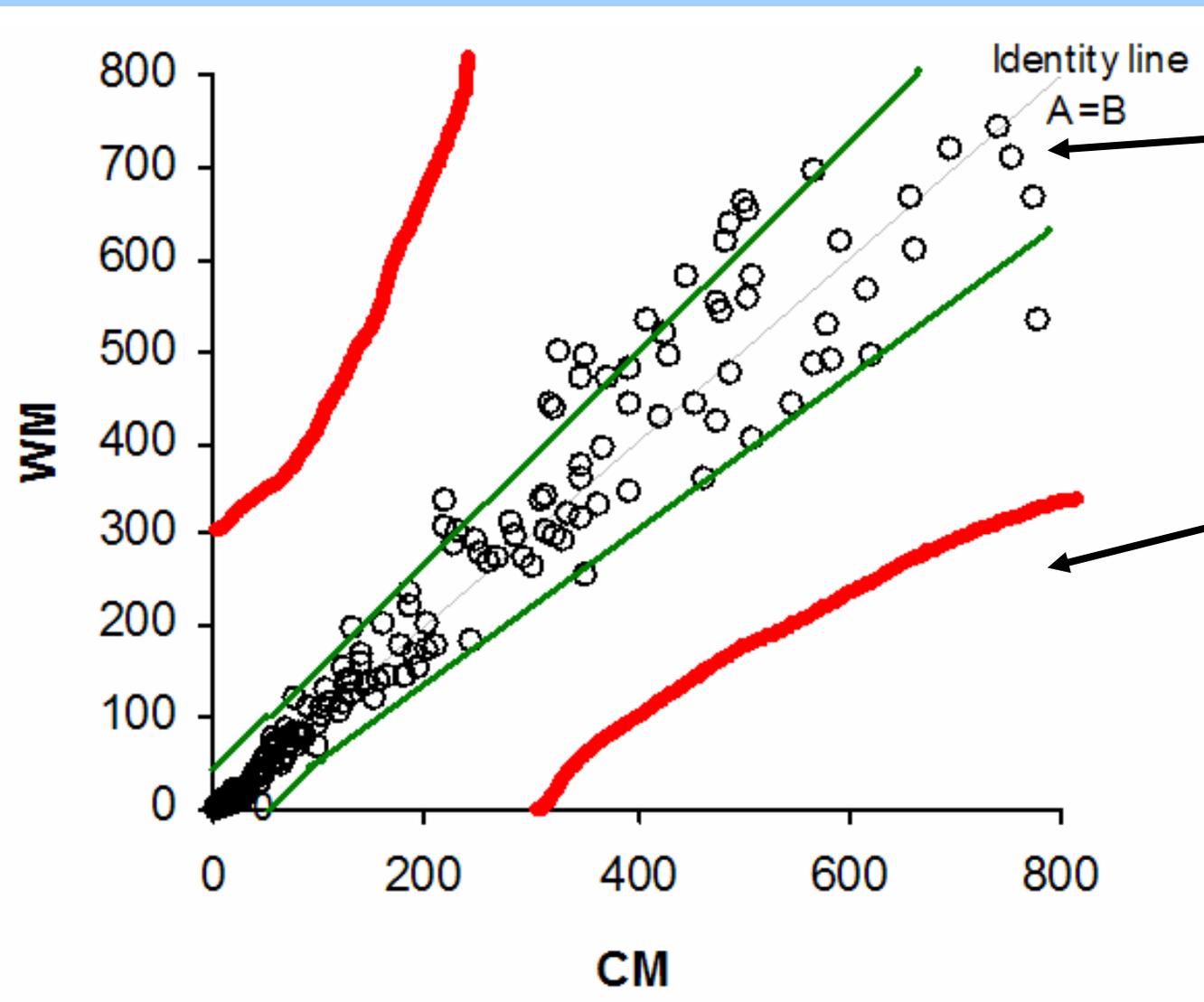


Allowable Total Error Zone, (CLSI EP21-A) Limits for Erroneous Results Zones

**Allowable
Total Error
Zone**

(at least 95% of subjects)

**Limits for
Erroneous
Results Zones**
(0% of subjects).



Demonstrating “Accuracy” – Criteria

- Some analytes have existing performance limits for professional use, these limits become the ATE (CLIA, 42CFR 493.929) for example, glucose, the limits are the target value $\pm 10\%$.
- Some analytes do not have performance limits for professional use in CLIA 42CFR 493.929 – meet the clinical needs for the analyte.

Thank you!