CLIA Waiver

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Outline

I. Introduction

II. CLIA Waiver

III. Sequential Approach

IV. Dual Study Approach

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"

"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)
- Benefits:

  For patients – testing and results at the time of the office visit with doctor;

  Helps with the personnel shortage of trained laboratory workers
- Risks:

  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 (urine pregnancy tests, urine dipstick, …)

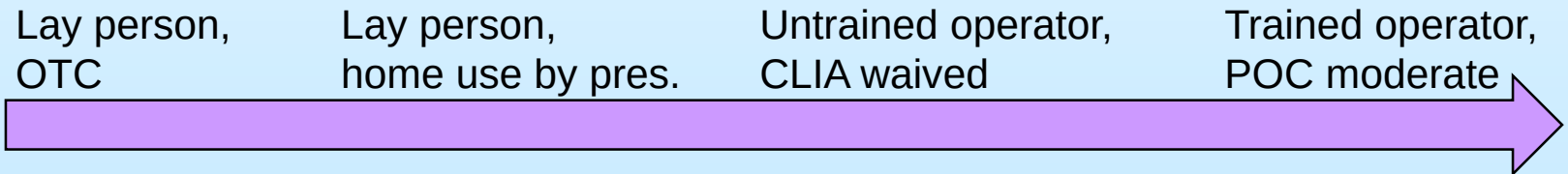
- By FDA Clearance/Approval for home use (by prescription or Over-The-Counter (OTC))

- **By meeting the statutory criteria**

  (by application)

Different Categories of Tests

Collection	Trans port	Running	Reader	Interpret ation	Action	OIR Category
Untrained operator	None	Untrained operator	Untrained operator	Physician	Physician	**CLIA Waiver**
Lay person	None	Lay person	Lay person	Lay person	Lay person	**OTC (waived)**
Lay person	None	Lay person	Lay person	Either lay person or physician	Either lay person or physician	**Home use by prescription (waived)**
Trained operator	None usually	Trained operator (POC operator)	Trained operator (POC operator)	Physician	Physician	**POC (moderate)-non-waived**
Lay person	Transp.	Trained operator (mod. or high)	Trained operator (mod. or high)	Lay person (help from physician)	Lay person, physician	**DTC**
Lay person	Transp.	Trained operator (mod. or high)	Trained operator (mod. or high)	Physician	Physician	**Collection Device**



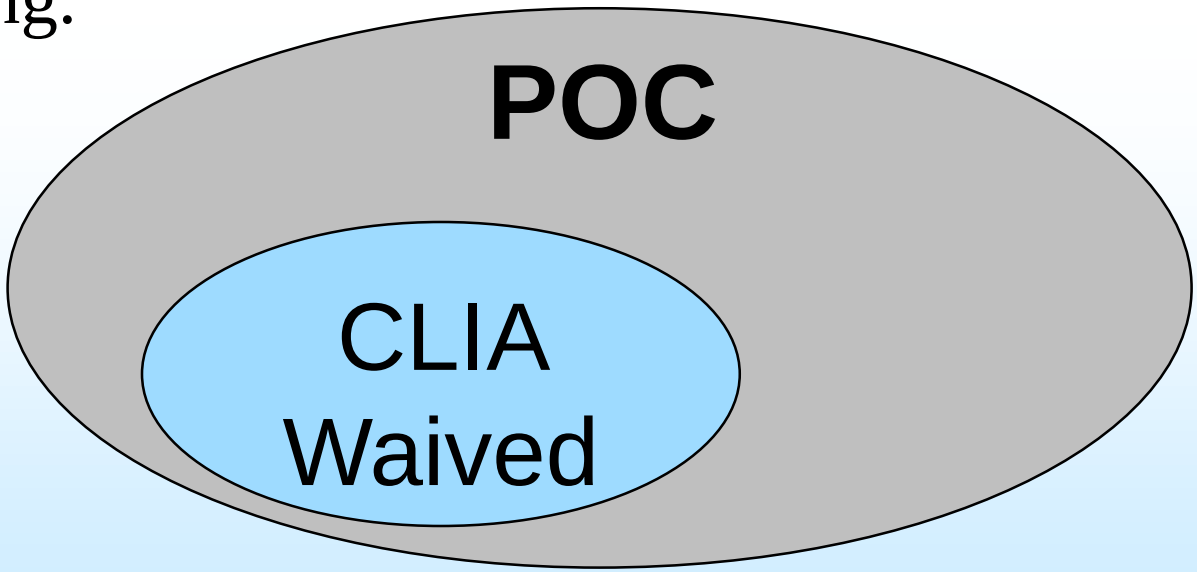
CLIA Waiver test systems are used at point of care sites

A point of care device is one that intended to be performed in an alternate site (outside a central laboratory environment), near to, or at the site of, the patient. For example,

- doctor's office
- nursing home
- emergency room
- clinic

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

- CLIA waived device is usually performed at point of care site.
- Many POC test systems are categorized as moderate complexity. They may not be “simple”; PT testing; training.



How does a test system meet CLIA waiver criteria?

A) **Is the test system simple?**

A.1 Demonstrate **"simple"**

A.2 Quick Reference Instructions (procedure steps, QC testing) at 7th grade level

B) **Does the test system have an insignificant risk of an erroneous result?**

B.1 **Risk analysis =>Flex studies**

B.2 **"Accuracy"** -valid scientific studies

- performed at 3 or more typical waived sites,
- using 9 or more "untrained" operators,
- testing real samples over time

A.1) Demonstrating "Simple"

- Fully automated instrument or unitized test system
- Uses direct unprocessed samples (e.g., fingerstick blood or venous whole blood or urine)
- No operator intervention during analysis
- No technical or specialized training – troubleshooting or complex error codes
- Easy to read test results (pos, neg, invalid, value, etc.)

A.2) "Simple": Quick Reference Instructions

- Quick Reference Instructions at 7th grade reading level
- Sometimes, User Manual (for installation of analyzer, cleaning, ..) at 7th grade reading level
- No complex error codes
- Quick Reference Instructions and User Manual should be close to the final versions

B) Demonstrating “Insignificant Risk of Erroneous Result”

B.1 Risk Analysis => Flex studies

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

- Operator error/human factors
- Specimen handling and integrity – clotted specimen, presence of interfering substance
- Reagent integrity – storage, out-dated
- Hardware, software and electronics integrity - power failures, bugs
- System stability - calibration
- Environmental factors – heat, humidity, electrical or electromagnetic interference

B) Demonstrating "Insignificant Risk of Erroneous Result"

B.1) F**lex studies**

Example

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

B.2) “Accuracy”

Different Approaches for the CLIA Waiver

Sequential Approach			**Dual Study Approach**
Clearance/Approval of **Candidate** in hands of **Trained** 510(k) De novo PMA	CLIA waiver by application **Candidate** in hands of **Untrained**		**Candidate** in hands of **Untrained**

Sequential Approach

Sequential approach

510(k) – Candidate in hands of **Trained**		CLIA waiver by Application - Candidate in hands of **Untrained**
Internal site: Analytical studies as analytical sensitivity, analytical specificity, linearity (if applicable), reagent stability, sample stability, and so on	→	Device is “Simple”, **Flex studies**
Reproducibility study: 3 sites If POC claim, 3 POC sites 2-3 POC operators per site		CLIA Waiver study Option 1 Option 2 Option 3 Option 4
Comparison study: 3 sites If POC claim, 3 POC sites 2-3 POC operators per site Candidate (Trained) vs Predicate (traceable or well-documented)		

Sequential approach

CLIA Waiver study	
Option 1	***Agreement study*** Candidate (Untrained) vs Candidate (Trained) What level of agreement is acceptable? *Quantitative test:* what systematic difference is acceptable? what change in precisions is acceptable? *Qualitative test:* What levels of PPA and NPA are acceptable? What difference in performances between untrained and trained for the samples close to the cutoff is acceptable?
Option 2	***Agreement study*** Candidate (untrained) vs Candidate (trained) with panel of samples FDA guidance “Migration Studies for IVD devices” (candidate has an internal signal)

Sequential approach

CLIA Waiver study	
Option 3	For some devices it is OK to have **only flex study** and some limited studies (e.g., performance at LoD for the qualitative tests) For example, • collection of a specimen is always performed by a professional (e.g., an endocervical swab collected by a doctor) or by a patient (e.g., a urine specimen collected by the patient), and • other pre-analytical steps are very simple (for example, placement of the entire specimen in the analyzer) Modification of devices
Option 4	**Candidate(Untrained) vs Predicate (Trained)** Predicate (traceable or well-documented)

Dual Study Approach

"Dual" Studies Approach

Basic Idea:

- Performance of the Candidate test is evaluated in the hands of untrained operators (performance of the test in the hands of trained operators is the same or better than performance of the test in the hands of untrained operators)

- These data are used to support:
  - CLIA waiver and
  - POC-non-waived test.

“Dual” Studies Approach

510(k) – POC, non-waived Candidate in hands of POC operators (trained)	**CLIA waiver Candidate in hands of CLIA waived operators (untrained)**
Analytical studies as analytical sensitivity, analytical specificity, Linearity (if applicable), reagent stability, sample stability, and so on	Simple, Flex studies
Reproducibility (POC sites)	
Comparison (POC sites)	Comparison (CLIA waived sites)

A) Reproducibility (3 CLIA waived sites)
B) Comparison (3 CLIA waived sites, 9 untrained operators)

Two pathways to submit “Dual” studies:

- Sequential pathway
- Dual submission pathway

Two pathways to submit dual studies:

- Sequential pathway

510(k) – POC, non-waived		CLIA waiver
"Simple"		

Internal site
Analytical studies such as:
• **Analytical sensitivity**
  ○ **LoQ (if Candidate test is quantitative),**
  LoD/LoB (if applicable),
• **Analytical specificity,**
• **Linearity (if Candidate device is quantitative),**
• **Precision study for lot-to-lot variability and/or other issues**
• **Reagent stability, sample stability, …**
	Later	**Internal site Flex studies**
		references

Reproducibility (3 **CLIA waiver sites**, untrained operators)		
Comparison (3 **CLIA waiver sites**, untrained operators)		
90 days		150 days

Two pathways to submit dual studies:

- **Dual submission pathway (*complete* 510(k) and CLIA waiver application in a *single* submission)**

Dual Submission
"Simple"

Internal site
Analytical studies such as:
• **Analytical sensitivity**
  ○ **LoQ (if candidate test is quantitative),**
  LoD/LoB (if applicable),
• **Analytical specificity,**
• **Linearity (if candidate device is quantitative),**
• **Precision study for lot-to-lot variability and/or other issues**
• **Reagent stability, QC stability, sample stability, …**
Flex studies

Reproducibility (3 **CLIA waiver** sites, untrained operators)
Comparison (3 **CLIA waiver sites**, untrained operators)

180 days

If the Candidate is PMA or de novo device, then only "sequential pathway",

Encourage protocol reviews through pre-Submission process

Thank you!

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