

# CLIA Waiver

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# Topics

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

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

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“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)

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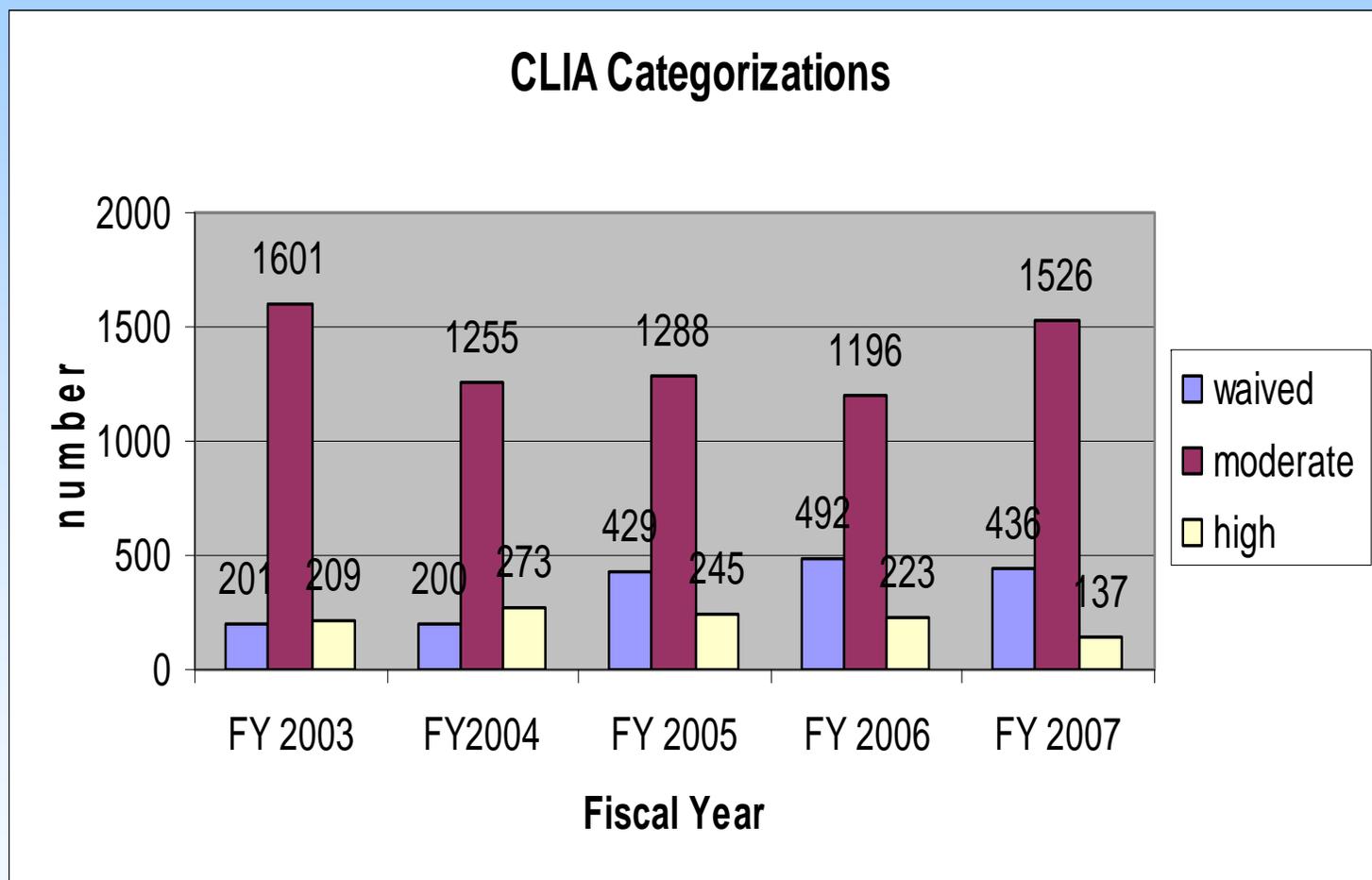
“including those that – (A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or (B) ...pose no unreasonable risk of harm to the patient if performed incorrectly”

# Impact of CLIA waived test systems

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- 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”

# CLIA Categorizations



# How do test systems qualify for CLIA waiver?

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- 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 History

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- Sept. 13, 1995 - CDC/CMS proposed rule
- Nov. 21, 1997 - FDA modernization act
- Sept. 7, 2005 – FDA draft CLIA waiver guidance
- Jan. 30, 2008 - FDA CLIA waiver guidance

# CLIA Waiver Guidance 2008 -FDA

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- 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

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- 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)

# CLIA Waiver Guidance

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- 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

# CLIA waiver test systems are used at point of care sites

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A point of care device is one that is used near the patient by health care professionals for example:

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

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

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## 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?

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

# Demonstrating “Simple”

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- 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

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- Quick reference instructions at 7<sup>th</sup> 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”

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

# Risk Analysis

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- Operator error/human factors
- Specimen handling and integrity – clotted specimen, presence of 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”

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- 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

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## 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

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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

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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

# Flex Studies – based on risk analysis

Potential source of error	Examples of flex studies	Examples of validation studies
Operational storage 2- 4 °C  What happens when stored improperly?	Study storage at 0, 2, 4, 10, 25, 37 °C  Studies show device fails at 0 & > 25 °C	Studies to validate fail-safe or QC or failure alerts  alert operator to frozen conditions or > 25 °C

# How does a test system meet CLIA waiver criteria?

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- 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 7<sup>th</sup> grade level, PI or other educational materials)

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

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- 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)
  - user questionnaire – after study – ease of use and clear labeling

# Demonstrating “accuracy” using a paired sample design

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Paired Sample design uses a sample for WM and a sample for CM

- The clinical studies compare the results obtained with the device proposed for CLIA Waiver (WM) to the results obtained by the Comparative Method (CM) that is traceable to a reference method.
- The CM for the clinical study is performed in the laboratory setting by laboratory professionals.

# Demonstrating “accuracy” – Criteria

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Quantitative - Establish Allowable Total Error (ATE) and Limits of Erroneous Results (LER) zones for the analyte in question before study begins

Qualitative – most qual. devices need 95% or better agreement between WM and CM

- Some analytes have existing performance limits for professional use, these limits become the ATE (CLIA, 42CFR 493.929) for example, leukocytes, the limits are the target value  $\pm 15\%$ .
- Some analytes do not have performance limits for professional use in CLIA 42CFR 493.929 – meet the clinical needs for the analyte.

# More about how “accuracy” is evaluated from our statistician

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Establish and evaluate  
**Allowable Total Error (ATE)**  
(for 95% of differences for WM  
and CM)

Establish and evaluate  
**Limits for Erroneous Results**  
(LER) (no observations in LER)

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Thank you!