The FDA and the CLIA Test Categorization Process

FDA Round Table
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Overview

- What – When – Why – Where
- Waived categorizations
- FDA CLIA Waiver Guidance
- Components of CLIA waiver studies
- Future categorizations

What is categorization?

Process to assign marketed test systems into 3 categories of complexity:

→Waived

→Moderate

→High

Transferred to FDA in early 2000 from CDC

What are the criteria for mod and high?

7 criteria per CMS 42 CFR 493.17

- →Knowledge
- →Training and experience
- →Reagents and materials preparation
- →Characteristics of operational steps
- →Calibration, QC, PT materials
- →Troubleshooting and maintenance
- →Interpretation and judgment

7 criteria scored as 1, 2, or 3

- → Score of 1 = minimum
- → Score of 3 = specialized
- → Total scores of 12 or < = moderate complexity
- → 13 or > = high complexity

What is categorized for CLIA?

Test systems on materials derived from the human body

→FDA cleared or approved test systems - reagent and instrument

→Stand alone cassette type test no instrument

→510(k) exempt devices such as lipase, LDH, estradiol –given X numbers

What is not categorized for CLIA?

- Sample not taken from the body - non-invasive test
- QC materials
- Calibration materials
- Breath tests

When is a new categorization needed?

- Name of device changes
- Name of distributor changes
- *Apply cleared reagents to another marketed instrument or new family member instrument introduced
- Device modification – raise/lower complex

*FDA guidance for replacement reagents
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079185.htm

Why do categorization?

- CMS regulation 42 CFR 493.17 - categorization of specific laboratory tests by level of complexity
- Majority of the categorizations are moderate
- Default is high complexity

Where to find categorizations?

- FDA website – search CLIA database

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/Search.cfm

… also have waived categorizations

- Definition of waived test
- 3 paths to waiver
- FDA guidance on CLIA waiver

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"

How do test systems qualify for CLIA waiver?

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

FDA CLIA Waiver Guidance Jan 2008

- Emphasis on intended users testing patient specimens over time

- Emphasis on traceable comparative method
- Scientifically based flex studies

- LINK - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070890.pdf

Guidance and Law - Differences

- Law is binding
- Guidance recommends how to meet the law– guidance is not binding

- Other scientific approaches to meet the law – communicate with FDA through pre-ide process

What are the components of CLIA Waiver Study?

- Determine if device is simple

- Results of risk evaluation and control including
  (1) measures implemented to mitigate the risk of errors, and
  (2) validation and/or verification studies demonstrating the ability of failure alert, fail-safe mechanisms to mitigate the risk of errors, under conditions of stress

Components of CLIA Waiver Study? cont.

- Pre-determined acceptance criteria for accuracy
  - Quantitative
  - Qualitative

- Clinical studies – min. 3 sites, 9 intended users, 2 weeks

- Labeling with instructions for use at 7th grade
- Quick guide
- Educational materials

- Results of user questionnaire

Demonstrating “Simple”

- Automated instrument or unitized test system
- Uses direct unprocessed samples – fingerstick blood or venous whole blood or urine
- Contains failure alert mechanisms
- 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.)

Risk Analysis – all potential sources of error

- 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

Verify &Validate Fail-safe/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 con't.

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

What is the comparative method?

- Gold standard
- Traceable

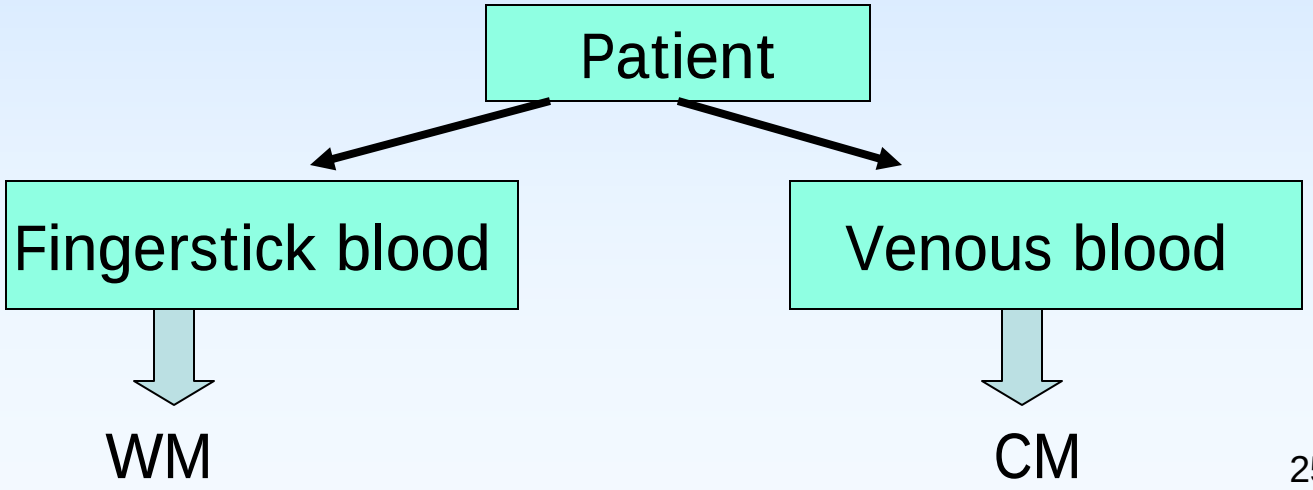
Criteria for accuracy

- Quantitative test
  - Allowable total error (ATE)- **CLSI EP21-A**
  - Limits of erroneous results (LER)

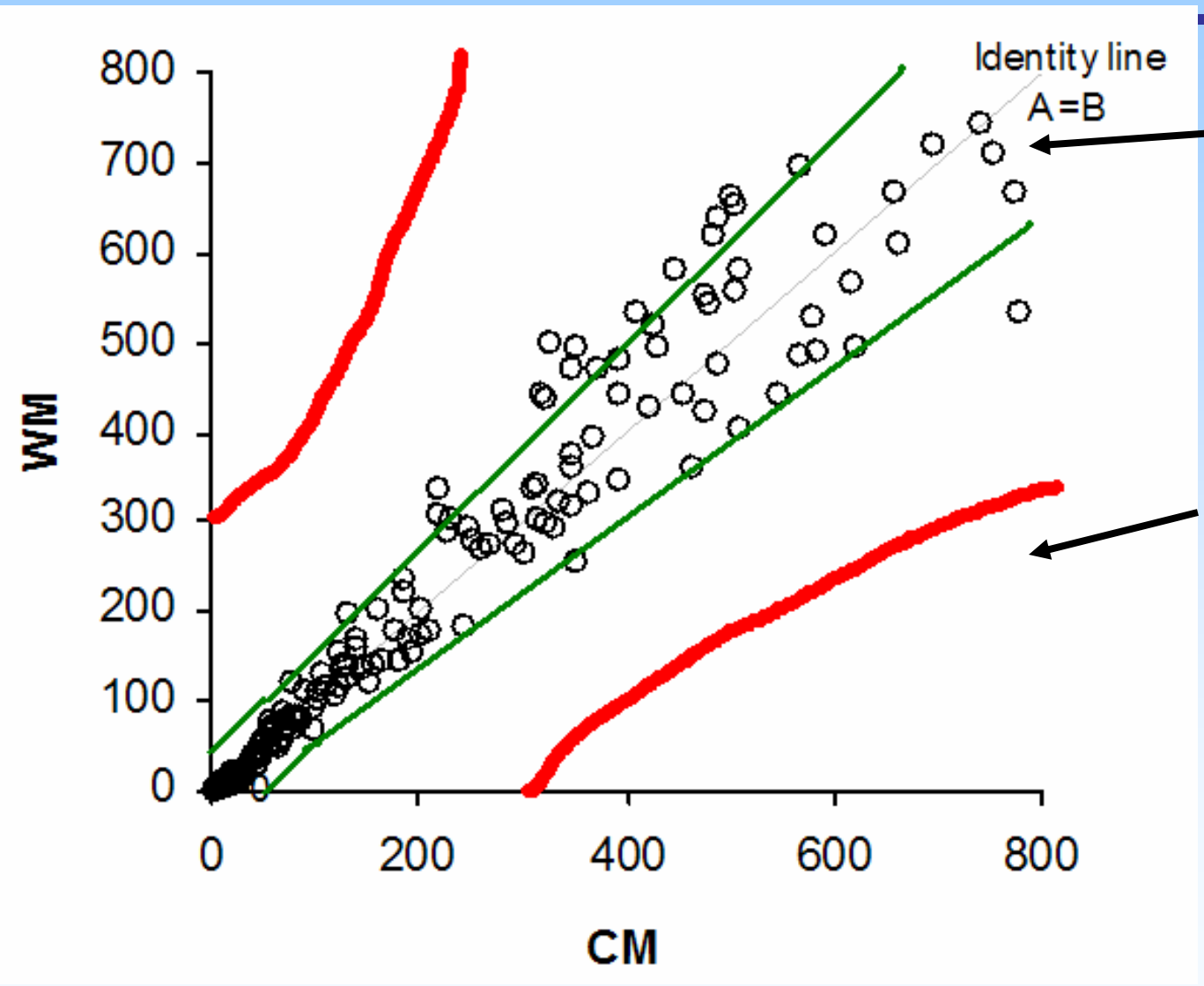
- Qualitative test
  - Percent agreement for negative
  - Percent agreement for positive
  - Performance near cut-off

Clinical Protocol – 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).

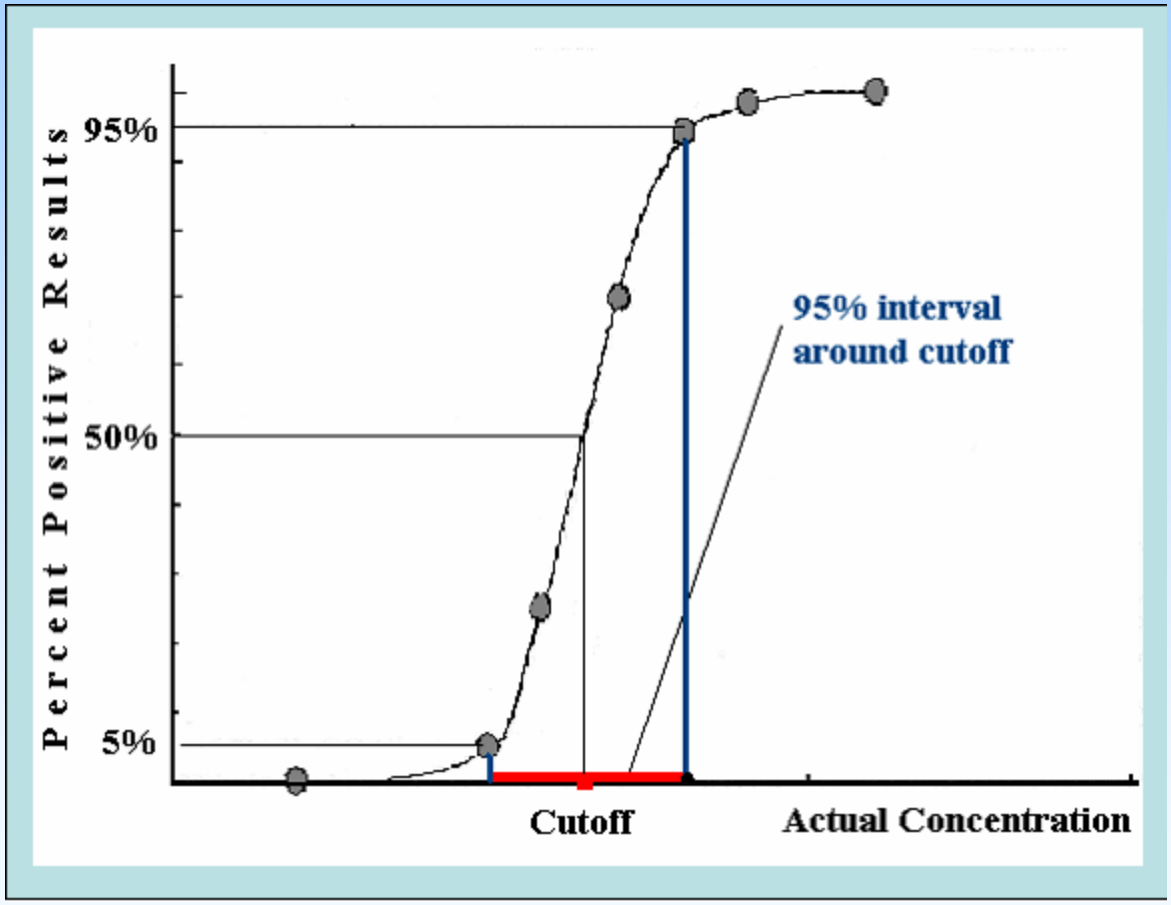
Qualitative 2x2 Chart

	CM Pos	CM Neg
WM Pos	115	2
WM Neg	5	118
	120	120

Pos. Agreement = 95.8% (115/120) with low limit of 95% two-sided CI of 90.5%;
Neg. Agreement = 98.3% (118/120) with low limit of 95% two-sided CI of 94.1%.

Positive and negative agreements between WM and CM should be not less than 95% (for some analytes, can be higher)

Cut-off study



Labeling for Waived Device

- Quick reference instructions at 7th grade reading level
- PI with procedure steps at 7th grade reading level
- Educational material
- Quality control material

Most common CLIA waived tests

- Drugs of abuse (OTC)
- Visual urine dipsticks
- Glucose monitoring systems
- Visual urine hCG

How most common are CLIA waived?

- By OTC use
  →DOA

- By regulation
  →urine dipsticks
  →visual hCG
  →glucose monitoring – (OTC)

Moderate Complexity

- General chemistries
- DOA
- Urinalysis analyzers + dipsticks (when first cleared)

Future CLIA categorizations

- Technology changes
- New analytes
- QC needs? – external vs. internal
- Continue FDA open communications – pre-ide process – workshops
- Continue collaborations (FDA, CMS, CDC)

Thank you!

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