



CLIA Waiver Guidance

CLIAC Meeting
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Outline

- Introduction and CLIA Waiver Approval Data Update
- Recent Concerns About the Interpretation of “Accuracy” used for CLIA Waiver approvals
- Historical Definitions and Interpretations of “Accuracy” for CLIA Waivers
- Discussion of the Interpretation of “Accuracy” in the 2008 CW Guidance, and Built-in Flexibility in this Area
- Dual 510(k) and CLIA Waiver Application Pathway and Planned Dual Guidance

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

“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”

Pathways to CLIA Waived Categorization

- By Regulation – 42 CFR 493.15(c) for 9 generic tests (urinalysis dipstick, FOB, ovulation, urine pregnancy test, ESR, home use glucose, spun hematocrit, hemoglobin copper sulfate, hemoglobin single analyte)
- By FDA Clearance/Approval for home use by prescription or Over-The-Counter (OTC)
- **By meeting the statutory criteria**

Brief CLIA Waiver (CW) History

- Sept. 13, 1995 - CDC/CMS proposed rule in FR
- Jan 30, 2000 - CLIA program was transferred to FDA
- Mar 1, 2001 – FDA draft CLIA waiver guidance
- April 8, 2004 – CLIAC issues an interpretation of “accuracy” and recommendations to FDA on waiver criteria
- Sept. 7, 2005 - FDA draft CLIA waiver guidance
- Jan. 30, 2008 - FDA CLIA waiver guidance
- FDA CLIA guidance: recommendations from FDA, CLIAC, CDC, CMS, Medical Device Industry, Trade Associations (e.g., AdvaMed), Professional Associations (e.g., AACC), and Laboratorians

How does a test system meet the 2008 CLIA Waiver Guidance criteria?

- **Is the test system simple?**
 - “Simple” test characteristics
 - Labeling at 7th grade level
- **Does the test system have an insignificant risk of erroneous result?**
 - Risk Analysis and Flex Studies
 - Validated Fail-Safe and Failure Alert Mechanisms
 - **“Accuracy” Studies** - the focus of this presentation

CLIA Waivers by Application

Number Received and Status, FY10-FY14

Waiver Status	FY10	FY11	FY12	FY13	FY14
Received	5	5	6	3	15
Approved	2	3	2	2	11
Denied	3	2	4	1	0
Deleted*	0	0	0	0	1
Withdrawn	0	0	0	0	3
On Hold	0	0	0	0	0
Under Review	0	0	0	0	0

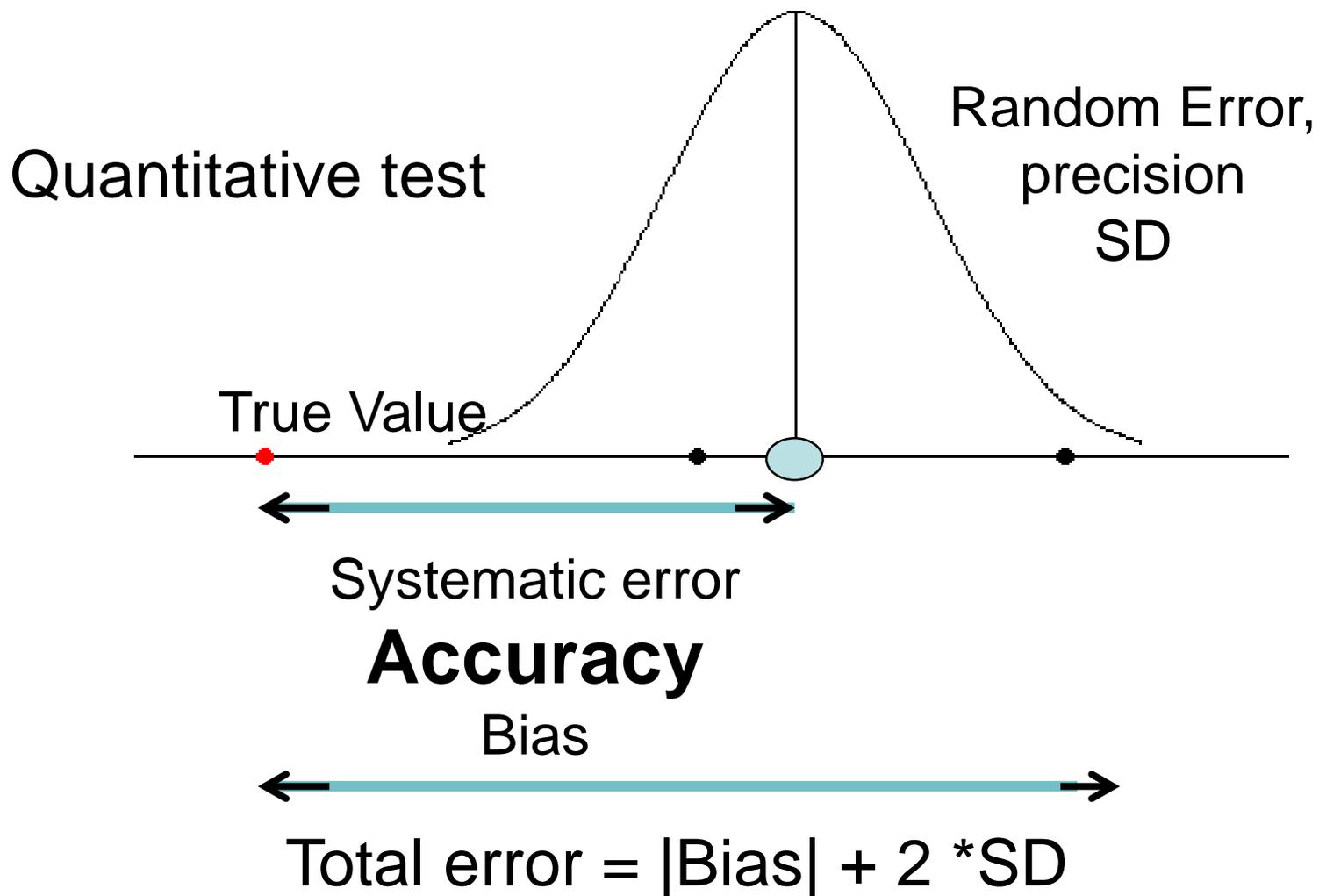
*Deleted by FDA for lack of response after being placed on hold for additional information

- Approval rates were low initially, implementation of 2008 CW guidance for qualitative tests began in FY10
- Recently FDA has gotten better at providing guidance to industry on how to demonstrate accuracy and use the flexibility in the 2008 CW guidance – culminating in increased approvals in FY14

Recent Concerns About “Accuracy” Interpretation in the 2008 CW Guidance

- Industry & others would like to demonstrate “accuracy” by comparing performance of WM in hands of waived users and WM in the hands of professional laboratory users
- Public Comments at Nov. 2014 CLIAC Meeting
 - Coalition for CLIA Waiver Reform propose return to “Accuracy” definition in FDA’s 2001 Draft Guidance.
- 21st Century Cures Proposals
 - Section 2208 – CLIA Waiver Study Design for In Vitro Diagnostics: Directs FDA to issue revised CW guidance, esp. section V. (“Accuracy”)

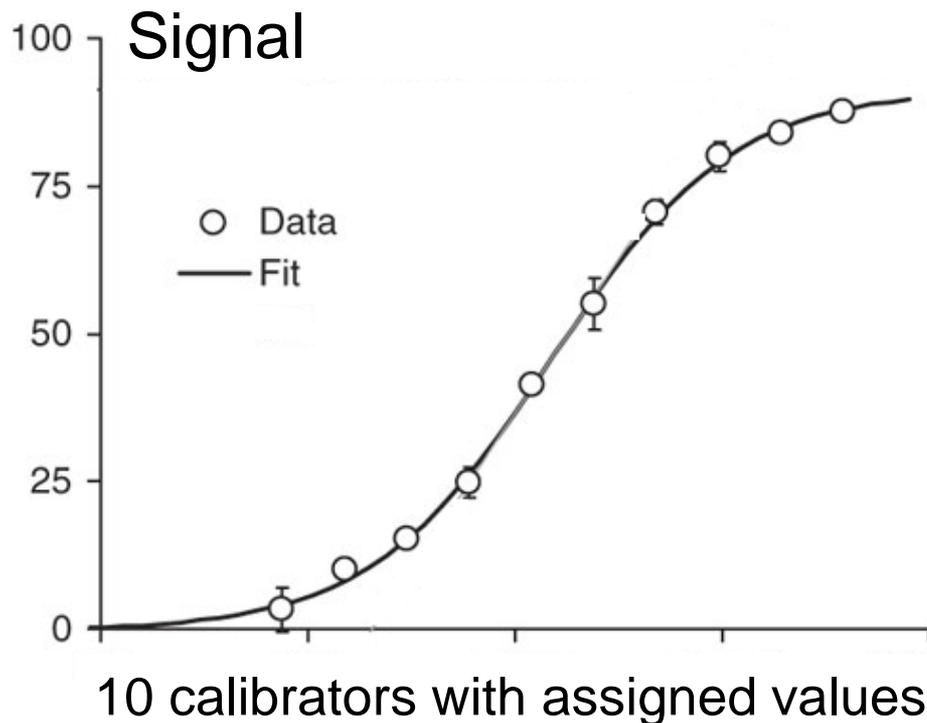
Scientific Definition of “Accurate”



Measurement Traceability is a Fundamental Issue Across Metrology

Traceable Method:

A method in which results of measurement can be related to stated references (usually national or international standards) through an unbroken chain of comparisons.



For example, In order to keep accurate time - our phones, computers, GPS systems, etc. trace back to the USNO's Master Clock

Measurement Traceability is Increasingly Recognized as an Important Aspect of Laboratory Medicine

- Providing accurate information to assist medical decision-making is an important goal of laboratory medicine, and this goal is furthered by increased traceability
- Developments in this area include:
 - EU directive on in vitro diagnostic (IVD) Devices (98/79/EC) support for ISO IVD metrological traceability standards: ISO 17511, ISO 18153
 - Establishment & development of the Joint Committee for Traceability in Laboratory Medicine (JCTLM), and International Laboratory Accreditation Cooperation (ILAC)

Demonstrating “Insignificant Risk of Erroneous Result”: “Accuracy” Studies – 2008 Guidance

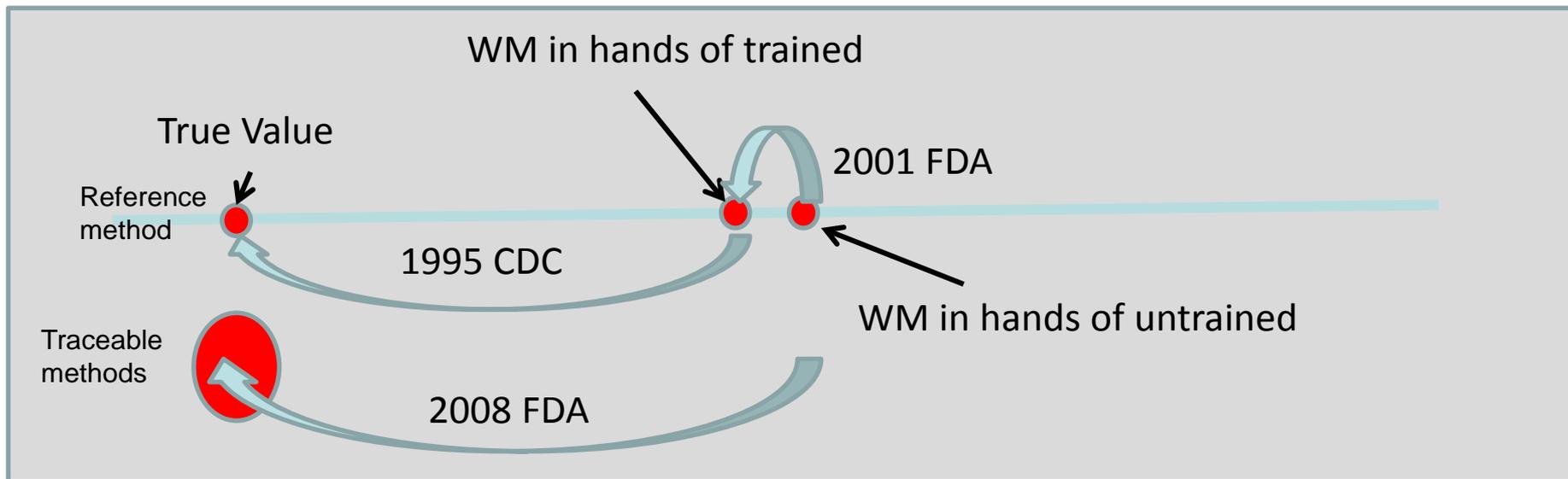
- Basic Idea:
 - Patient at a doctor’s office obtains a result from a Waived Method (WM) in the hands of intended operators
 - If instead the patient went to a lab and obtained a result from one of the best laboratory methods (Comparative Method, CM)

**If WM result for the patient is comparable (close) to
CM result for the patient**



WM is “accurate”

Comparison of “Accuracy” Interpretations for Waiver Studies



- CDC/CMS 1995 rules for CLIA Waiver considered scientific definitions of “accurate” and compared WM to a reference method
- 2001 FDA draft guidance allowed comparison of WM in hands of untrained users to WM in the hands of trained users
- 2008 FDA guidance recommends comparison of WM in the hands of untrained user to a traceable method (as recommended by CLIAC in 2004)

Demonstrating “Insignificant Risk of Erroneous Result”: “Accuracy” Studies – 2008 Guidance

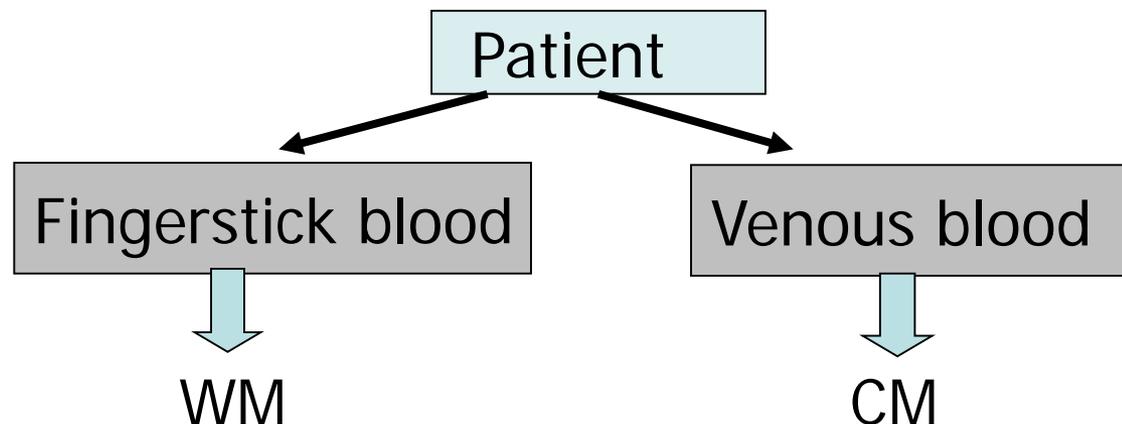
Prospective clinical study of the device proposed for waiver:

- Intended clinical sites (minimum 3)
- Intended operators (minimum 9)
- Intended sample type (most of the specimens are patient specimens)
- Testing over time, as in typical intended use setting (minimum of 2 weeks)
- User questionnaire – after study – ease of use and clear labeling

Demonstrating “Insignificant Risk of Erroneous Result”: “Accuracy” Studies

Paired Study Design

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

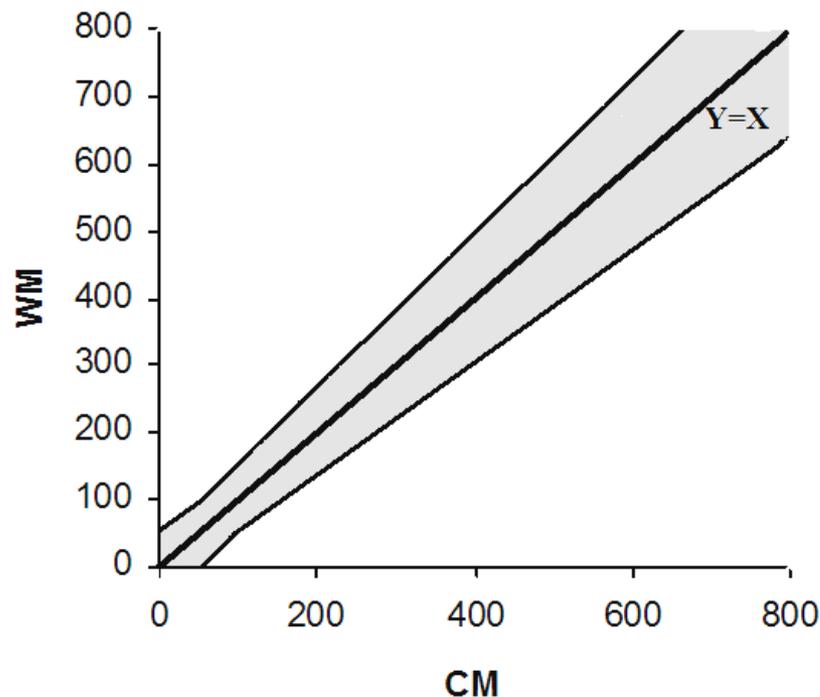


Demonstrating “Accuracy” for Quantitative Tests:

Establish Allowable Total Error (ATE) Zone:

Values of WM that fall within ATE zone are values that can be tolerated without invalidating the medical usefulness of the WM results.

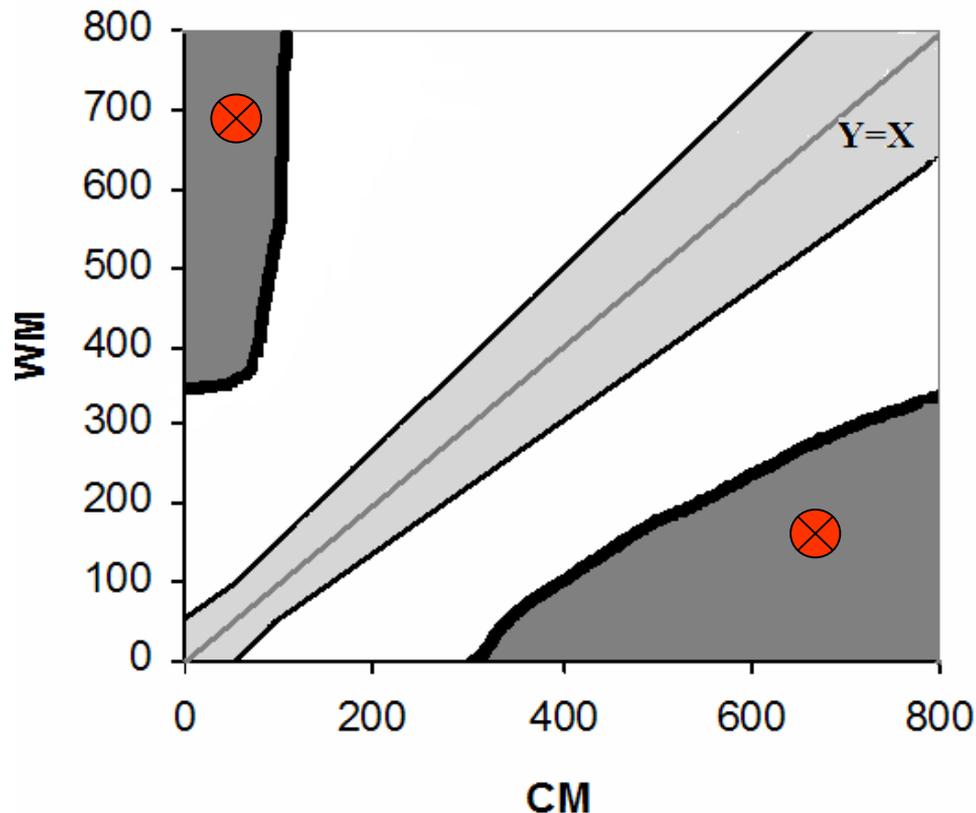
It is anticipated that no less than **95%** of sample results will fall within the ATE zone.



Demonstrating “Accuracy” for Quantitative Tests

Limits of Erroneous Results (LER) Zones:

Values of WM that fall within LER zones are values that pose a risk to a patient safety. Potential harm can occur to the patients if these WM results are utilized in medical decision-making.



It is anticipated that LER zones contain no data (360 samples) or little data (>360 samples).

Demonstrating “Accuracy” for Qualitative Tests

Part 1: Method Comparison

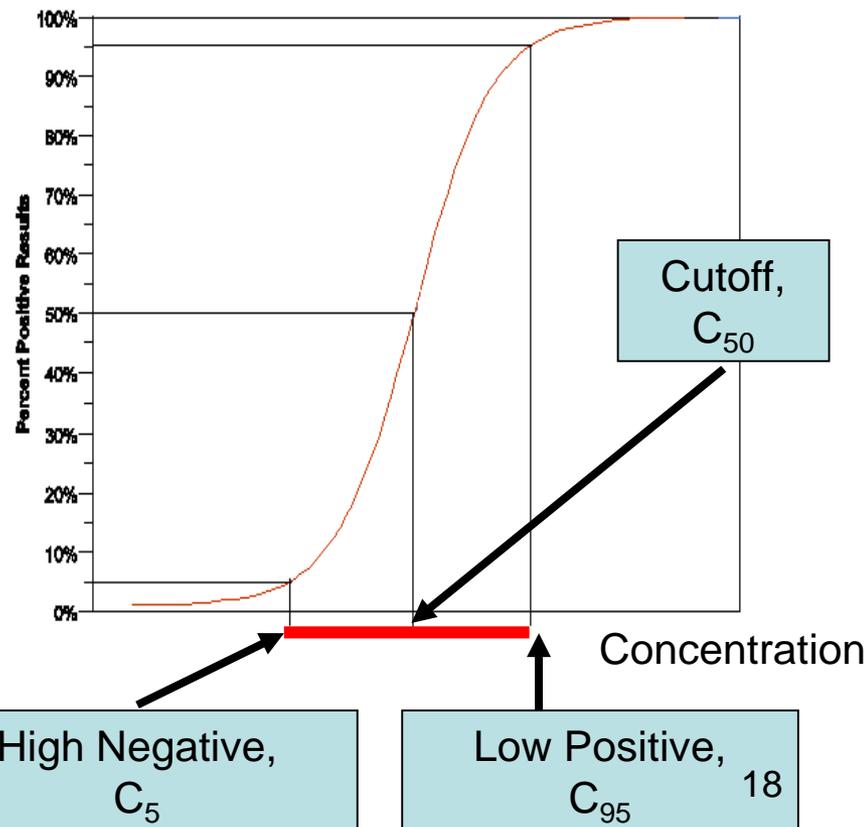
- Percent agreement (PPA and NPA) should be 95% or higher
- A lower percent may be acceptable if justified by benefit-risk analysis

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

PPA = 95.8% (115/120)

PNA = 98.3% (118/120)

Part 2: Near Cutoff Performance



Clinically Relevant Flexibility of the 2008 CLIA Waiver Guidance

- Goal is to use the best available methods
- Flexibility in Demonstrating “Accuracy” is Built-in:
 - Different types of Comparison Method (CM) may be used
 - Reference > Traceable > Well-Documented
 - Quantitative tests: Multiple approaches considered for determination of ATE and LER zones
 - Qualitative tests: Benefit/Risk justifications are considered in determination of performance criteria
- Protocol reviews with FDA are encouraged

Selection of Comparative Method (CM):

- Type A – Reference Method
- Type B – Traceable method
 - (best available traceable method); a method in which results of measurement can be related to stated references (usually national or international standards) through an unbroken chain of comparisons
- or well-documented method
 - Possible to compare test in the hands of waived intended users vs. same test in hands of laboratory professionals if higher options (reference, traceable) not available

Clinically Relevant Flexibility of the 2008 CLIA Waiver Guidance

Quantitative Tests:

- 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.

Clinically Relevant Flexibility of the 2008 CLIA Waiver Guidance

Qualitative Tests:

“The observed PPA [sensitivity] and NPA [specificity] between the test proposed for waiver and the comparative method should be 95% or greater,...

In some cases, a higher percent of agreement ... may be needed to reasonably assure that WM is “accurate”.

In some cases, a lower percent agreement .. may be medically acceptable with sufficient risk/benefit justification”.

Reopening the CLIA Waiver Guidance

- FDA has agreed to reopen the CLIA Waiver Guidance
 - We believe 2008 CW Guidance already covers Industry concerns, but this has not been communicated sufficiently to Industry and FDA staff
 - We plan to expand areas in the guidance that are not clear to better explain existing flexibility so there is no confusion

Discussion Questions for CLIAC

- Are there any issues you see with the interpretation of “Accuracy” in the 2008 CW Guidance that should be addressed in revisions?
- Are there any other aspects of the CW guidance that FDA should address in revisions?

The Dual Pathway (510(k) and CLIA Waiver by Application)

- The Dual pathway, established as part of MDUFA III, offers the opportunity for a simultaneous approval of a CLIA Waiver along with a 510(k) clearance, with potentially **significant time and cost savings due to combined study designs**
- A Pre-submission during which agreement was reached on a Dual strategy is required
- Interest in Duals is increasing...

	# of Pre-Submissions where Dual discussed	# Submitted	# Approved	# Under Review
FY13	8	0	0	0
FY14	7	1	1	0
FY15	19	3	0	3

Dual Submission Study Basic Idea

510(k) – POC, non-waived Candidate in hands of POC operators	CLIA waiver clinical study Candidate in hands of CLIA waived operators
Analytical studies as analytical sensitivity, analytical specificity, linearity, reagent stability, sample stability, and so on	Simple, Flex studies
Precision (POC sites)	
Comparison (POC sites) Candidate vs Predicate	Comparison (CLIA waived sites) Candidate vs CM
<p>Combined for Dual:</p> <p>A) 3 CLIA waived sites, 9 CLIA waived operators Comparison of Candidate vs CM</p> <p>B) Precision (CLIA waived sites)</p>	

Thank you!

- For CLIA related questions please email:

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- Special thanks to:
 - Alberto Gutierrez, Ph.D.
 - Marina V. Kondratovich, Ph.D.
 - Prakash Rath, Ph.D.

References

- CLIA Administrative Procedures Guidance

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070762.htm>

- CLIA Waiver by Application Guidance

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079632.htm>

- CLIA Public Database

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm>