How to Prepare and File for CLIA Waiver

AMDM Meeting
April 22, 2010

Carol C. Benson, M.A.
Associate Director – Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety

Overview

- Background
- Components of a CLIA waiver application
- Simple
- Risk analysis and Flex studies – Fail safe and Failure alerts
- Clinical protocol
- Comparative method, traceable or gold standard
- Clinical data including cut-off studies (for qualitative)
- Labeling and quick guide
- Quality control materials and labeling

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"

Components of CLIA Waiver Application

- Table of contents – pages numbered
- Complete description of device for simple including control materials (pictures nice)
- Results of risk analysis including the identification of potential sources of error for your device
- Results of flex studies demonstrating insensitivity of the test system to environmental and usage variations under conditions of stress

Components of CLIA Waiver Application cont.

- 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
- Complete description of the protocol and results of clinical studies
- Labeling with instructions for use at 7th grade
- Quick guide
- Educational materials

Demonstrating "Simple" - Complete description

- 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 – list 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-protocol and results

- 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 protocol and results

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 protocol and results 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

Clinical Protocol

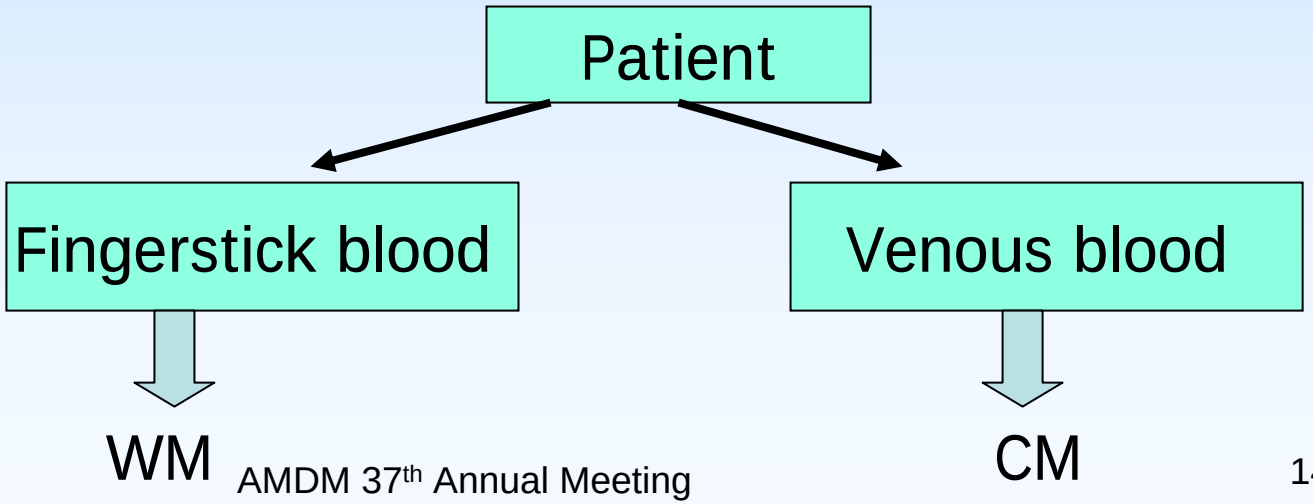
- Names of the testing sites
- Informed consent
- Financial disclosure for clin. investigator
- Inclusion and exclusion criteria
- Names, training and vocation of operators
- Operator questionnaire
- Start and end dates the study was conducted
- Quality control measures performed

Clinical Protocol – Cont.

- Identification of comparative method and traceability
- Quantitative test - ATE selected and rationale
- Quantitative test - LER selected and rationale
- Qualitative test – clinical study
- Qualitative - 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)



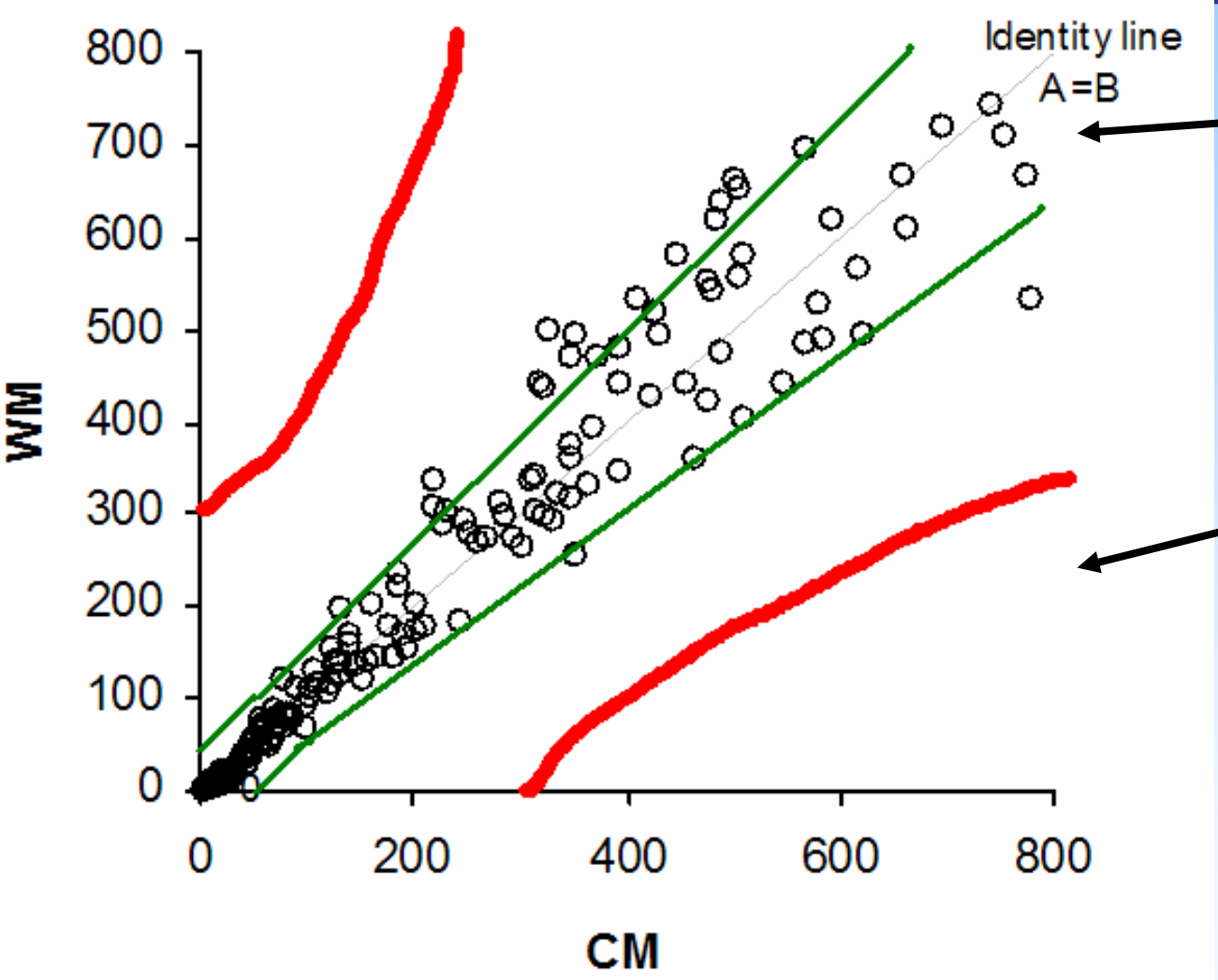
Clinical Data and Analyses

- Provide in electronic format
- Line data by site, operator, date tested
- Identify source of all samples (neat, spiked, banked, diluted, etc.)
- Identity any repeats, invalid results and discarded devices
- Do not omit any data points or call outliers

Clinical Data and Analyses – Quantitative

- Descriptive statistics
- Regression method and analysis for each site and combined
- Difference plot
- Range into low, medium, and high
- Graph of regression with ATE and LER
- Calculate percentage that fall within ATE for low, medium and high range plus overall
- Provide CI for each range and overall

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).

Clinical Data and Analyses – Qualitative

- 2 x 2 tables with positive and negative for each site and if appropriate overall
- Calculate the positive and negative percent agreement estimates with CM for each site, and if appropriate combined
- Lower two-sided 95% confidence bounds for each and if appropriate combined

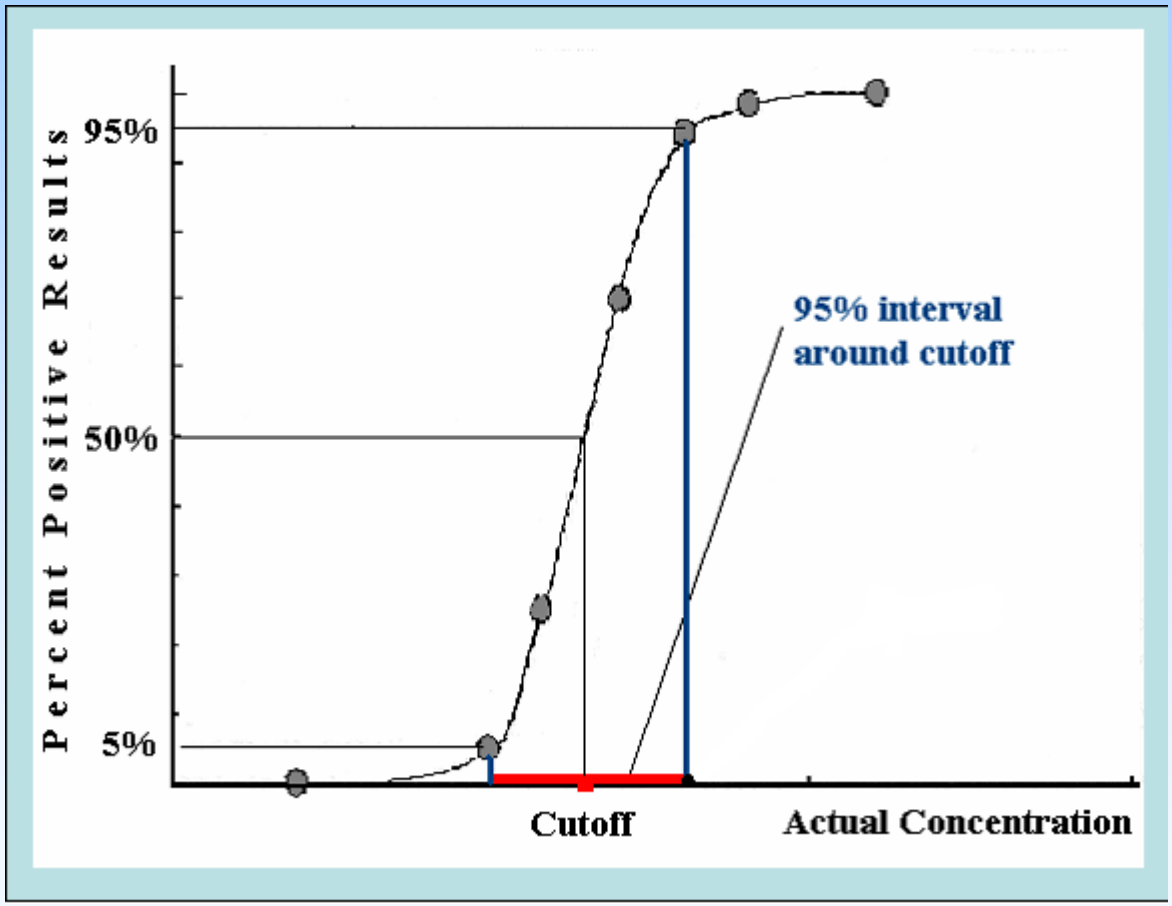
Qualitative 2x2 Chart

	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



Clinical Data and Analyses – Qualitative Cut-Off Study

- Protocol and results of cut-off study
- Calculate the percent of positive results for the weak positive sample and the percent of negative results for the weak negative sample with the two-sided 95% confidence intervals for both
- Compare the percents of positive results for the weak positive sample among the three sites (20 measurements per site) by using a Fisher-Freeman-Halton test (a generalization of Fisher's exact test

Labeling for Waived Device

- Quick reference instructions at 7th grade reading level
- PI with procedure steps at 7th grade reading level
- Educational Material

Labeling for Waived Device

- Identification of the test as CLIA waived
- Statement that a Certificate of Waiver is required to perform the test in a waived setting, and information on how users can obtain a certificate.
- Statement that laboratories with a Certificate of Waiver must follow the manufacturer's instructions for performing the test. 42 CFR 493.15(e)(1).
- Step by step instructions
- QC recommendations – frequency of testing

Labeling for Waived Device

- Action to be taken when no test result is obtained or when the result is out of the reportable range.
- Summary of CLIA waiver results
- Warnings about clinical errors that can occur even when the test result is analytically correct.
- Instructions on when and how additional testing should be done (e.g., in cases where results should be confirmed)
- Any other limitations, restrictions, and special considerations

Quality Control Material

- Intended use
- Step by step instructions (no pipetting)
- Frequency to test
- Acceptable limits
- Action to take if out of acceptable limits
- How to store

How to File for CLIA Waiver

- Reference 510(k) or PMA number
- State purpose as CLIA waiver application
- Number all pages
- Table of contents - tabs
- Include electronic copy of data - disk
- Send to:

FDA, 10903 New Hampshire Ave., Document Mail Center, WO66-G609, Silver Spring, MD 20993

Thank you!

Questions???