CLIA Waiver Review Process for Quantitative Blood Lead

FDA Round Table

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Overview

- Background
- Determining simple
- Demonstrating “Insignificant Risk of an Erroneous Result – Failure Alerts and Fail-safe Mechanisms
- Demonstrating “Insignificant Risk of an Erroneous Result - Accuracy

Background

- Collaboration

  CDC – FDA - Sponsor

Demonstrating Simple

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"

Demonstrating Simple

The following information was reviewed during the CLIA waiver review process

- Device
- Type of specimen
- Procedure
- Reagent
- Operation
- Troubleshooting
- Maintenance
- Results

Demonstrating "Insignificant Risk of an Erroneous Result Failure Alerts and Fail-safe Mechanisms

Risk Analysis

The following information was reviewed during the waiver process

- Operator error/human factors
- Specimen handling and integrity – clotted specimen, short sample, interfering sub.

Failure Alerts and Fail-safe Mechanisms – cont.

- 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

Failure Alerts and Fail-safe Mechanisms-cont

Once the risk table for the device reviewed the next step is to evaluate how the risk was mitigated.

- General Recommendations
- External Control

Failure Alerts and Fail-safe Mechanisms- cont.

Lastly the flex studies/validation studies were evaluated to determine if the mitigation identified addressed the risk.

Demonstrating "Insignificant Risk of an Erroneous Result - Accuracy

The following information on accuracy is reviewed during the waiver process

- Clinical testing Sites, Participants and Testing Duration.
- Comparative Method
- Descriptive statistical analysis and total error
- Performance criteria of the working Waiver method (allowable total error and Limits of erroneous results)

Accuracy cont.

Clinical testing Sites, Participants and Testing Duration.

- Ten sites (with one additional site)
- Eleven operators
- Testing conducted over 2 months

Accuracy cont.

Comparative Method

- Graphite Furnace Atomic Absorption Spectroscopy (GFAAS)
- Reference method

Accuracy cont.

Performance criteria of the working Waiver method (allowable total error and Limits of erroneous results)

The following performance limits were set:

Allowable Total Error -ATE

- (GFAAS result ± 6 µg/dL) for GFAAS results ≤ 40 µg/dL and
- (GFAAS result ± 15%) for GFAAS results > 40

Accuracy cont.

Limits of Erroneous Results (LER)

- Zone C – 10 µg/dL (on the y-axis) extending outwards on the x-axis to a value of 70 µg/dL

Accuracy cont.

- Descriptive statistical analysis and total error
- Regression analysis
- Both ordinary least squares and Deming regression were used. The results are shown in the following table:

Method	n	intercept	95% CI (β)	Slope (β)	95% CI (β)
OLS	516	-0.46	(-0.77,-0.14)	1.04	(1.03,1.06)

Accuracy cont.

- Total error

  The term ‘total analytical error’ was used as an interval that contains a specified proportion (e.g., 95%) of the distribution of differences between the WM and CM values. Total analytical error may also be expressed in terms of relative differences.

  The data were divided into three ranges as follows:

Range of GFAAS values (µg/dL)
0 to 10
10.1 to 40
40.1to 65

Accuracy cont.

The systematic differences between Waiver Method (WM) and GFAAS results estimated by regression analysis are presented in the table below:

GFAAS µg/dL	Systematic difference between WM and GFAAS
10	-0.0 µg/dL
20	0.4 µg/dL
45	1.5 µg/dL

Accuracy cont.

Range of GFAAS values (µg/dL)	Total number of samples	Number of sample within ATE	Percent of samples within ATE
0 to 10.0	314	312	99.4%
10.1 to 40.0	138	132	95.7%
40.1 to 65.0	64	61	95.3%
0 to 65.0	516	505	97.9%

Accuracy cont.

The percentage of the samples over the entire range that fall within the ATE zone

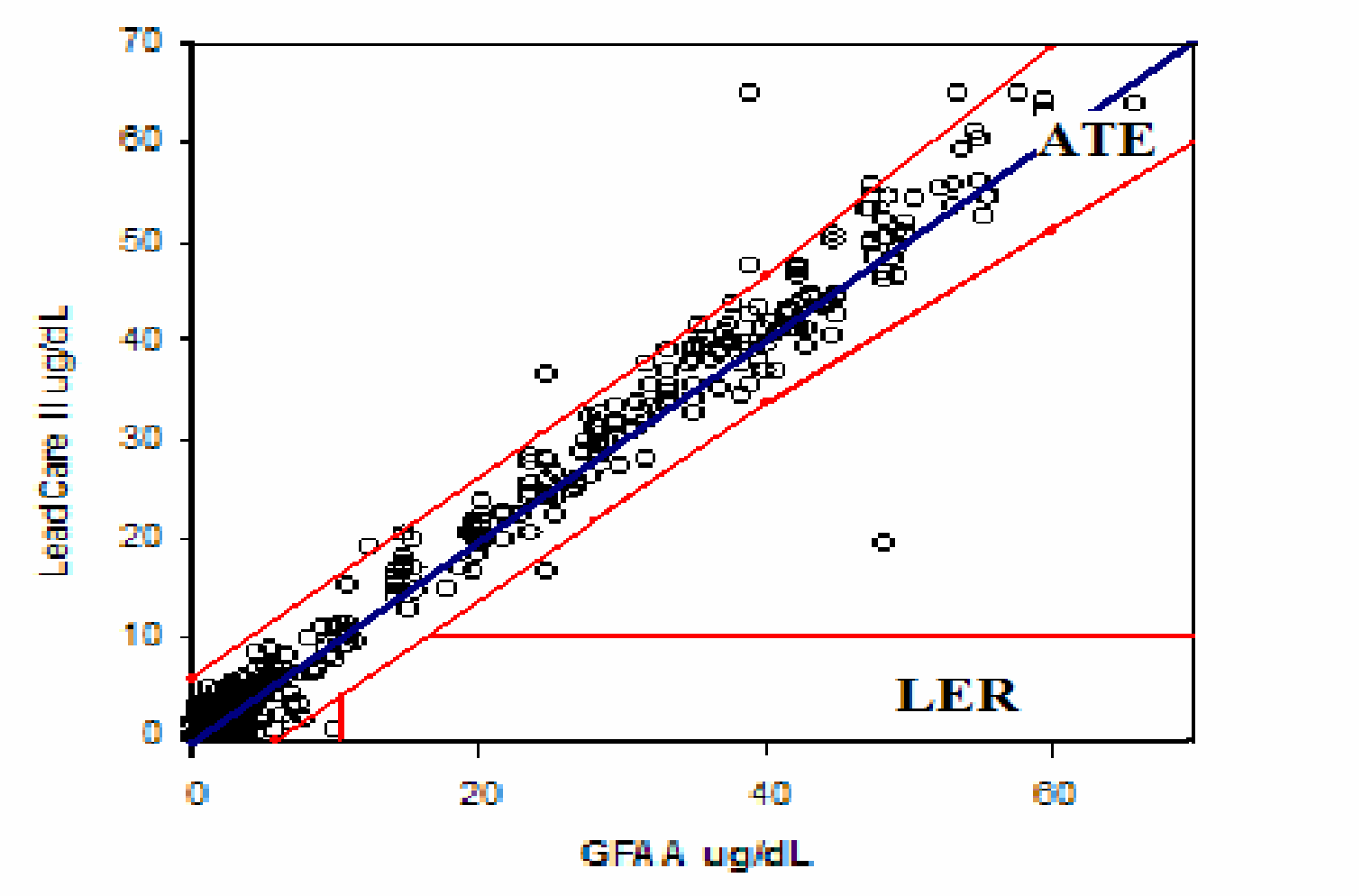
- 97.9% (505/516) with a lower bound of 95% confidence interval of 96.6%.

The LER a zone

- no samples were in the LER zone (0% with an upper bound of 95% confidence interval of 0.5%).

The scatter plot of the study results with ATE and LER zones is presented by the figure below:

Accuracy cont.



Labeling – Waiver Performance

In the Package insert the following CLIA waiver information should be added

Heading called Results of CLIA Waiver Study

- Clinical testing Sites, Participants and Testing Duration
- Type (s) of samples collected and number of samples
- Comparator method

Labeling – Waiver Performance – cont.

- ATE and LER limits
- Table showing the range of values, number within ATE and the percent of samples within ATE
- Scatter plot of results including the ATE and LER zones
- Descriptive statistics, regression and bias

Thank you!

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