



Hematology and Pathology Devices Panel Meeting

CLIA Waiver, Demonstrating “Accuracy”

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Outline

Concepts related to “accuracy”

- Traceability
- Total error
- Allowable Total Error zone
- Limits of Erroneous Results zones

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

Tests for CLIA Waiver 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.”

Demonstrating

“Insignificant Risk of Erroneous Result”

- Risk Analysis and Flex Studies
(already discussed)
- Fail-Safe and Failure Alert Mechanisms
(already discussed)
- **“Accuracy”**
(this presentation)

Demonstrating “Insignificant Risk of Erroneous Result”,
“Accuracy”

The term “accurate” tests refers to those tests that are comparable to traceable methods

(or well-documented methods).

Traceable?

Comparable?

We consider quantitative tests

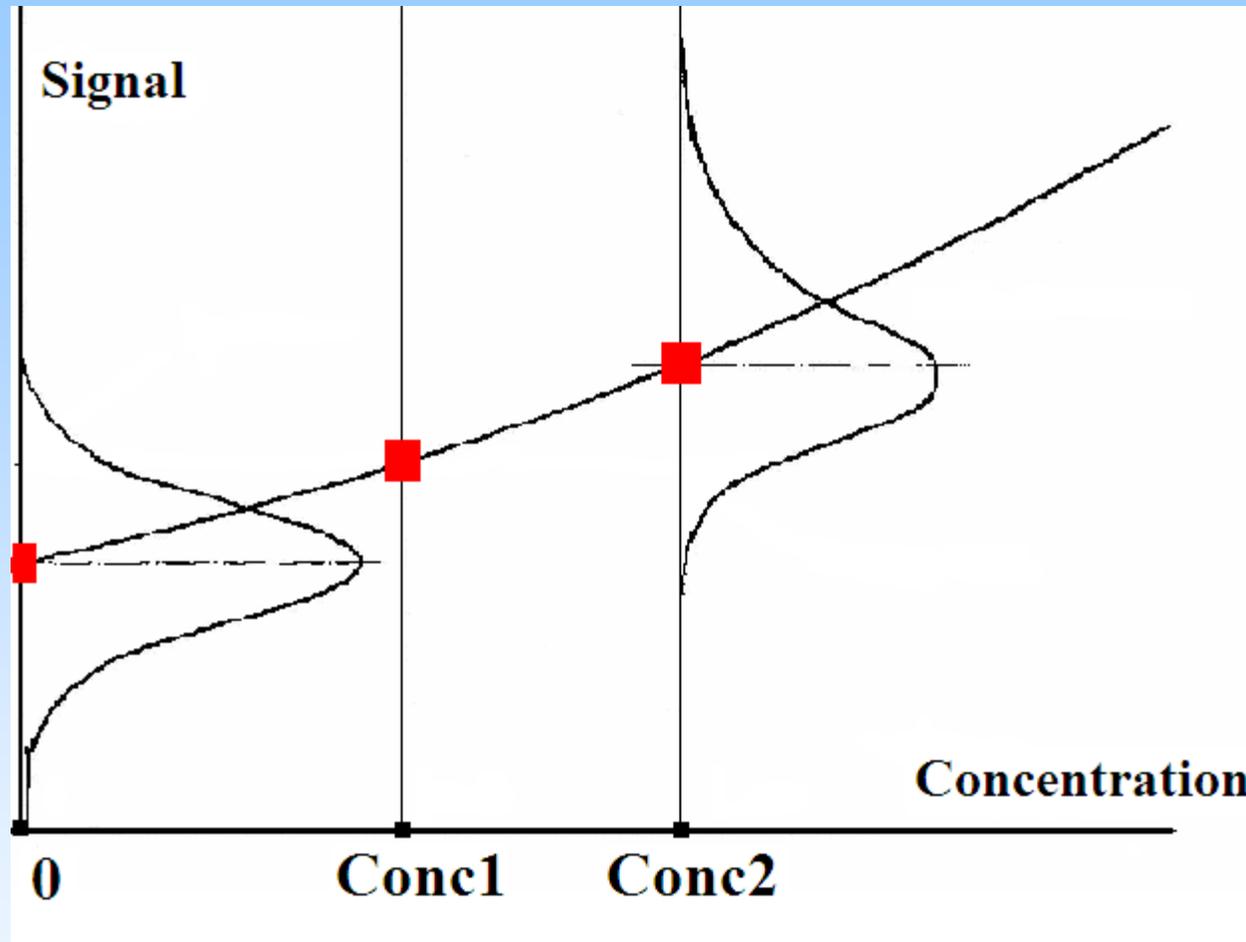
Traceability

- *Definition:*

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

- Traceability requires an established calibration hierarchy.

Traceability (basic idea)



Method is calibrated using calibrators which are related to the Reference Method or Reference Materials.

Traceability

Traceable method:

measurement values are with the same degree of trueness (systematic bias is small) as Reference Method or Reference Materials.

If traceable method has a high imprecision (large random error), then a few replicates should be performed and an average of these replicates should be considered →

Average of few measurements by traceable method
≈ True value

What is “comparable”?

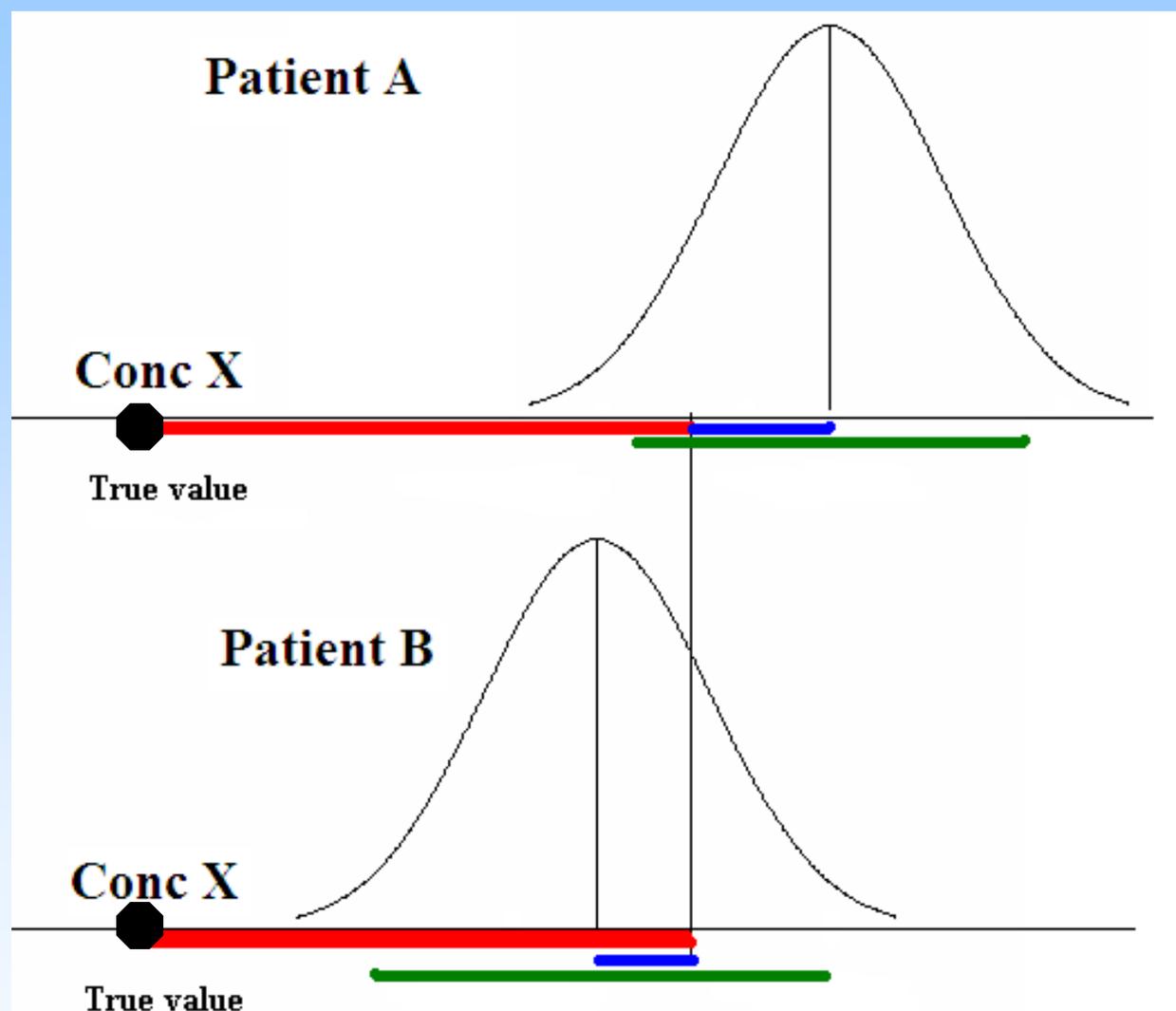
Waiver Method (WM) is comparable if the deviation of the Waiver Method result from the True Value is acceptable.

Deviation = WM Result – True Value

Deviation → Concept of Total error

Acceptable → Concept of ATE and LER zones

Total Error (General Concept)



Systematic bias

Random matrix-related interferences

Random error (imprecision)

- Same sample is tested over and over again under different conditions;
- Because the amounts of substances other than the analyte of interest vary from 10 patient to patient, the systematic bias differ from patient to patient.

Basic Error Model (General Concept)

Individual measurement of a given sample K

$$\begin{aligned} \text{WM Result} - \text{True Value} = & \\ \text{Systematic Bias} & \\ + \text{Random-Interferences} & \\ + \text{Random Error (imprecision)} & \end{aligned}$$

To evaluate a random matrix-related interference component, samples from different patients are needed.

At least 360 different samples in the CLIA Waiver study

Basic Error Model (General Concept)

Individual measurement of a given sample K

$$\begin{aligned} \text{WM Result} - \text{True Value} = \\ \text{Systematic Bias} \\ + \text{Random-Interferences} \\ + \text{Random Error (imprecision)} \end{aligned}$$

To evaluate random error component, different testing conditions are needed: sites, days, operators and so on

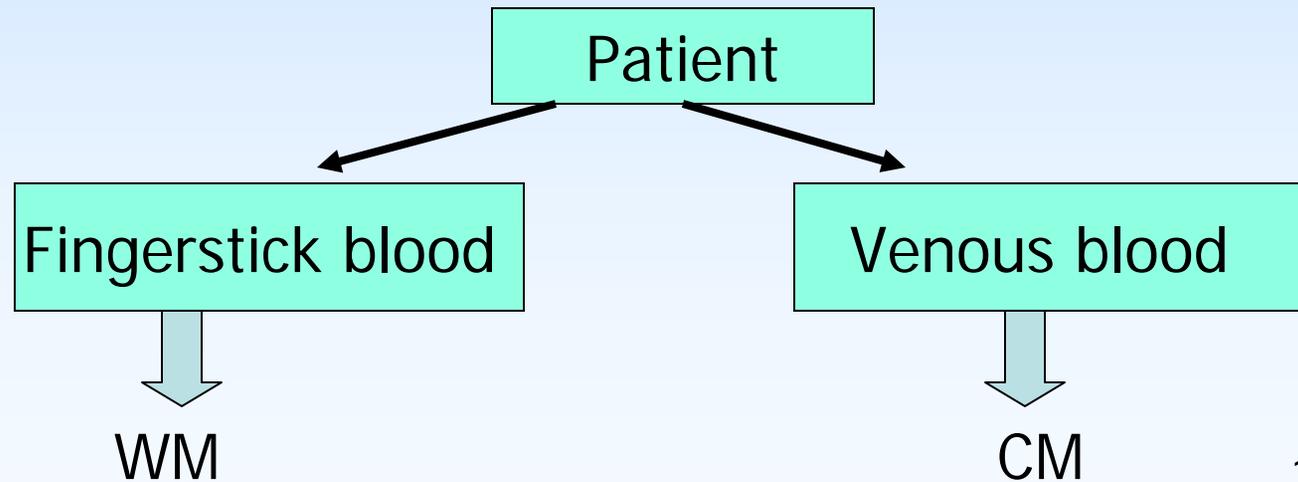
At least 3 sites,
at least 9 operators,
at least 2 weeks in
the CLIA Waiver study

Demonstrating “Accuracy”

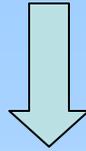
The clinical studies for evaluating “accuracy” should compare results obtained with the device proposed for CLIA Waiver (WM) to results obtained by Comparative Method (CM).

Demonstrating “Accuracy” – PAIRED study design

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



Deviation = WM Result – True Value



Selection of Comparative Method (CM):

Type A – Reference Method;

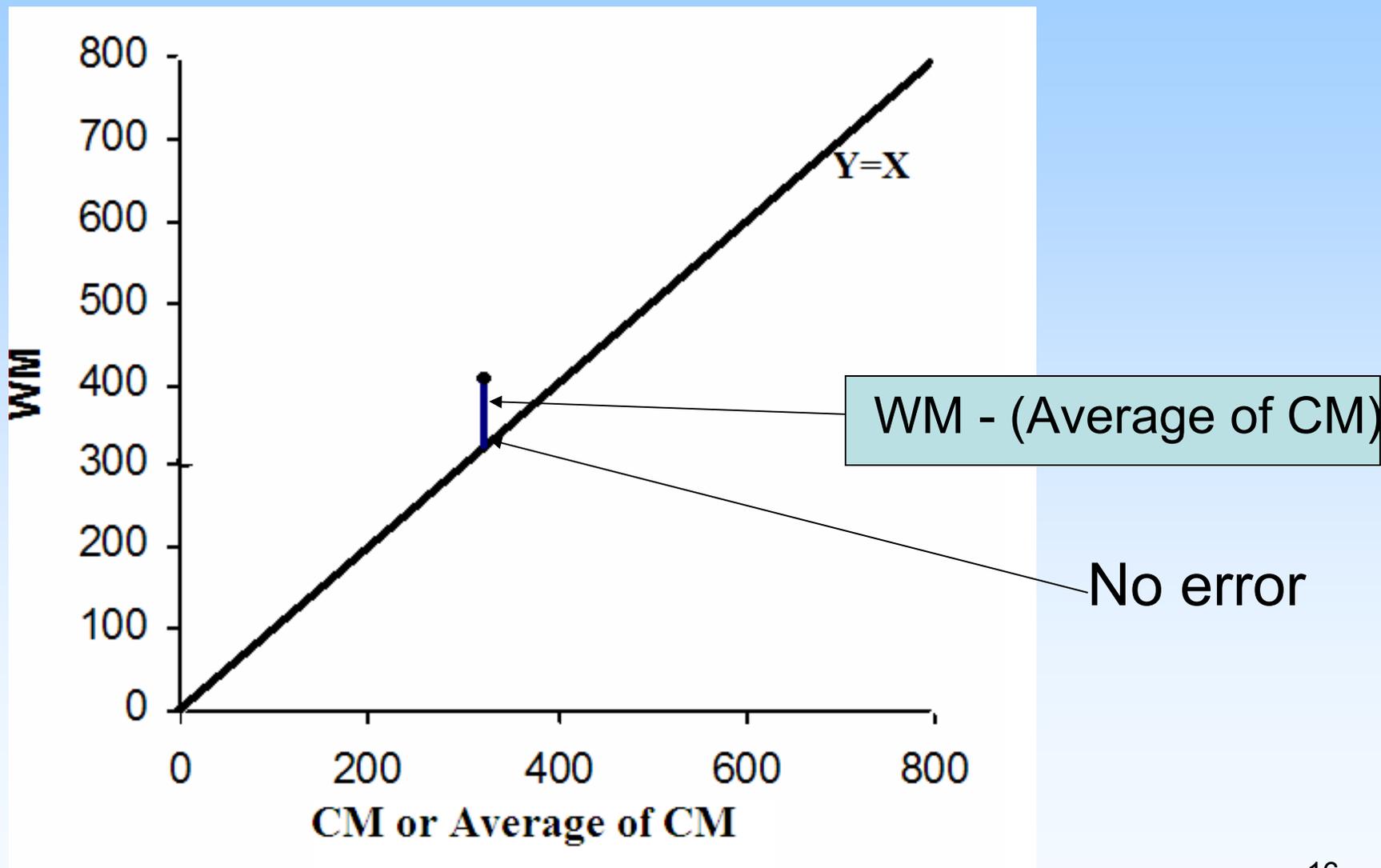
Type B – Traceable method

(best available traceable method);

or well-documented method

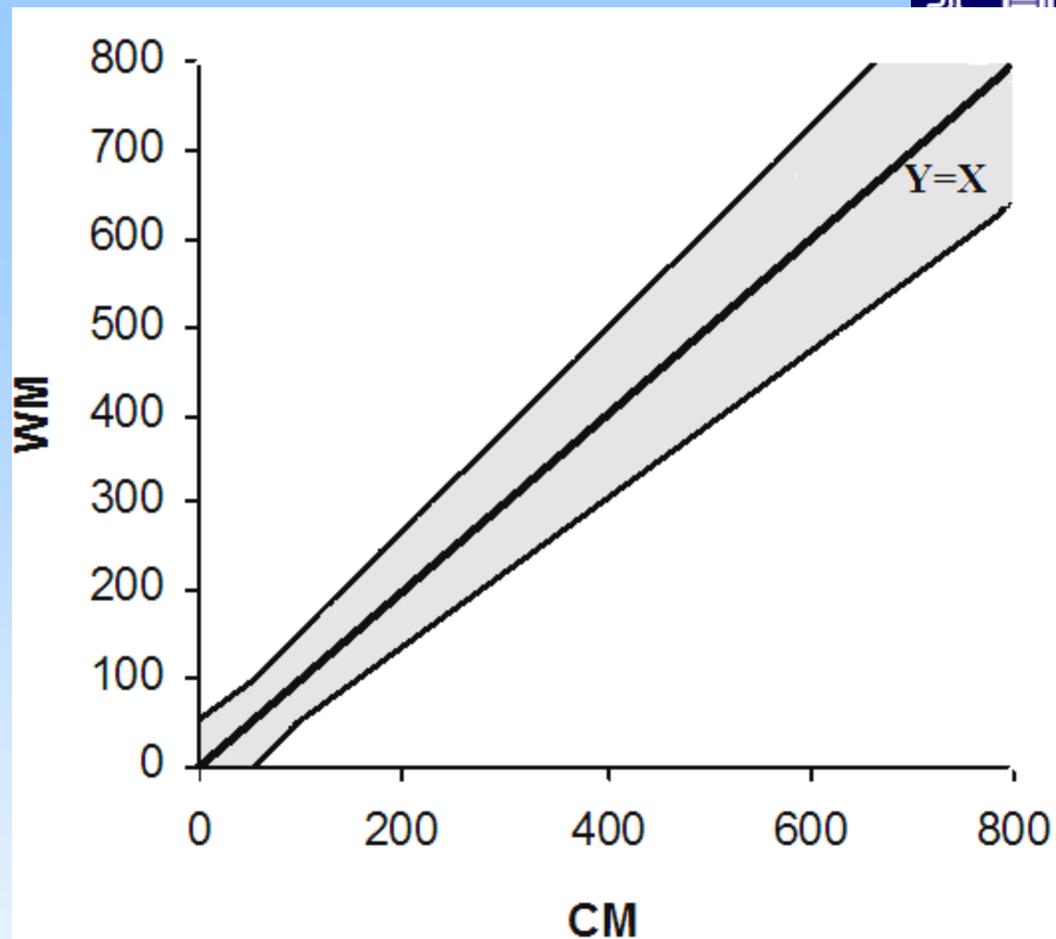
WM Result - True value

WM Result - (CM or Average of CM results)



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.

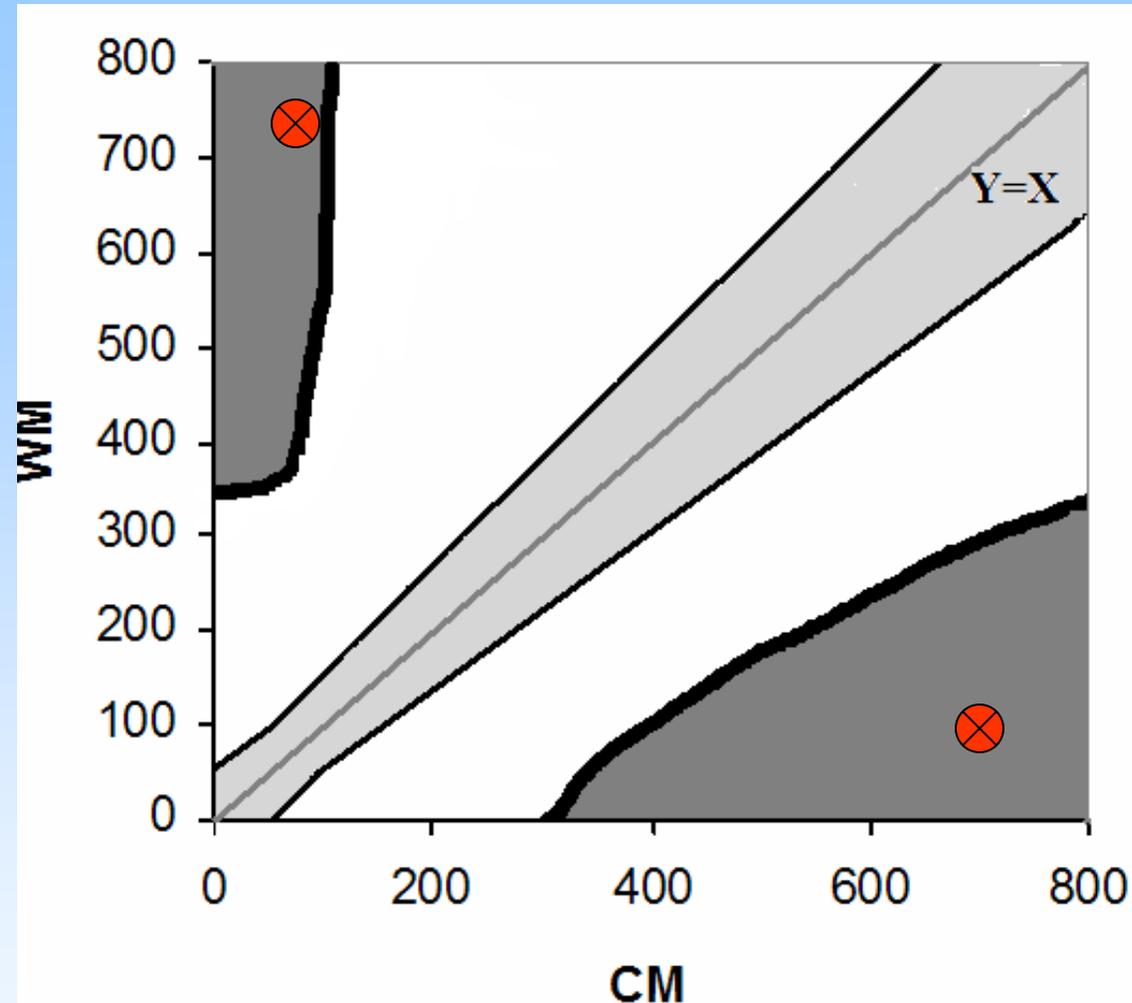


It is anticipated that no less than **95%** of sample results will fall within the ATE zone.

ATE zone is the zone around the diagonal, meaning it contains small errors including no errors.

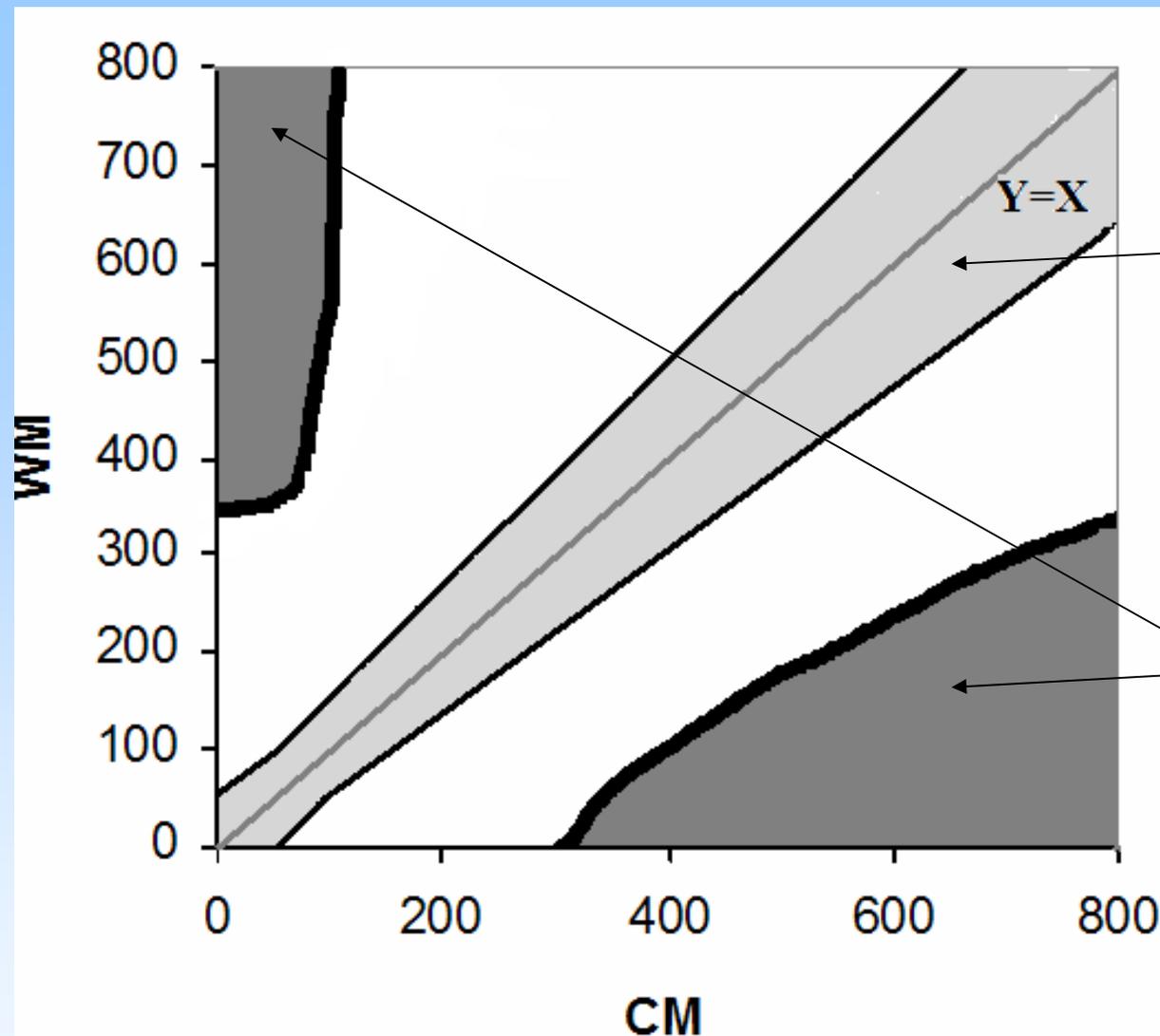
Limits of Erroneous Results (LER) Zones:

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).

LER zones are the outer zones.



Allowable Total Error Zone
($\geq 95\%$ of samples in study)

Limits of Erroneous Results Zones
(0% of samples in study for 360 samples)

ATE zone and LER zones should be established before the CLIA waiver study.

Setting Allowable Total Error Zone

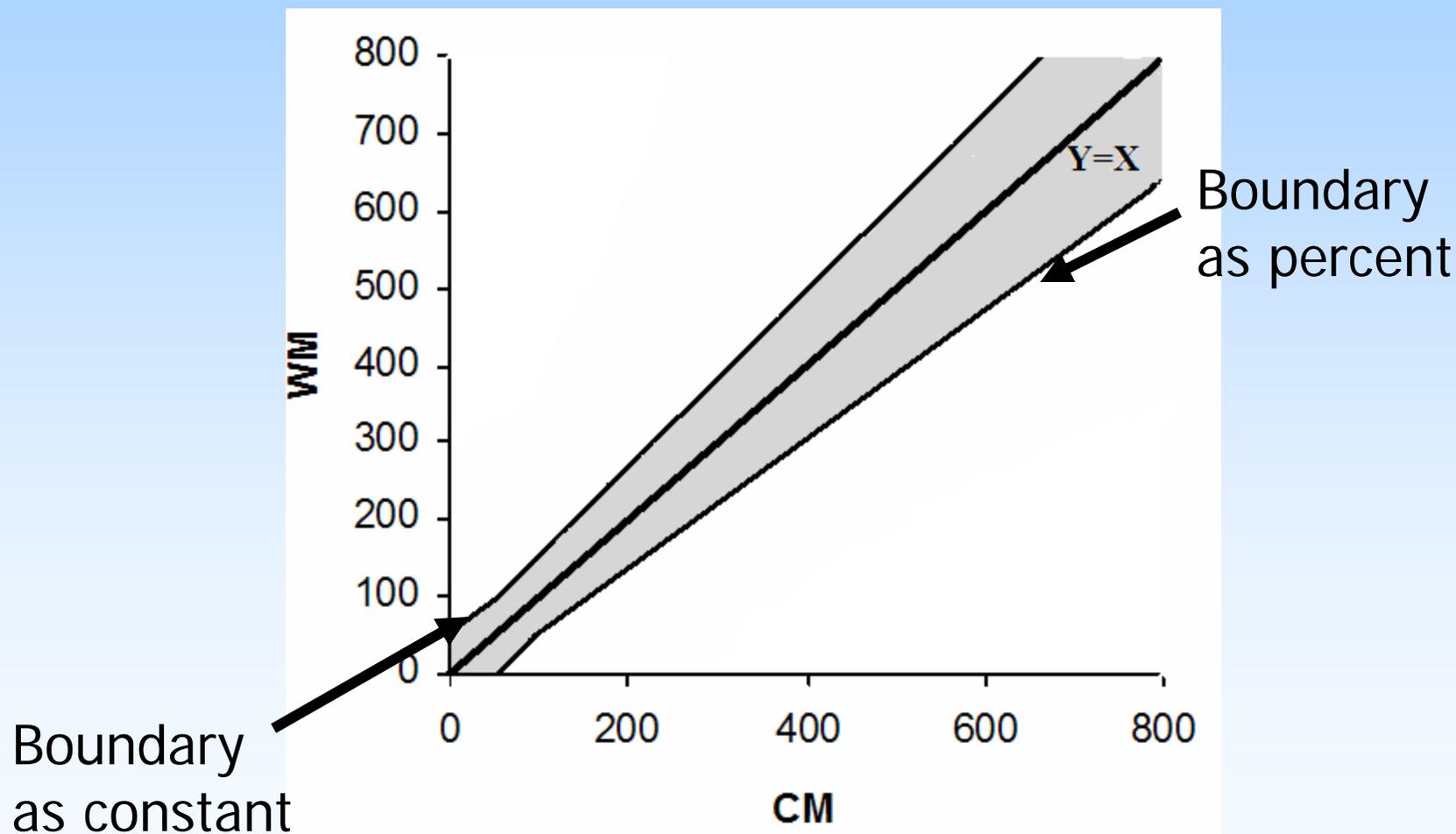
- Depend on intended use
- *Hierarchy* in CLIA waiver guidance;
 - I) Analytes listed in CLIA 88 regulation:
Performance goal for professionals in CLIA 88 regulation (CLIA, 42CFR 493.929)

For example, CLIA 88 regulation:

WBC – acceptable limits are $\pm 15\%$

Note: There can be different rules for defining the ATE zone for different ranges of CM.

Example of ATE: if $CM > 80$ units, $CM \pm 15\% * CM$;
 if $5 \leq CM \leq 80$, $CM \pm 12$ units



Setting Allowable Total Error Zone

II) For analytes not listed in the CLIA regulations, other criteria may be acceptable:

ATE zone could be based on

A) published professional recommendations from national and international expert bodies;

B) evaluation of the effect of analytical performance on clinical outcomes;

C) based on components of biological variation; other scientific approaches.

Setting Allowable Total Error Zone

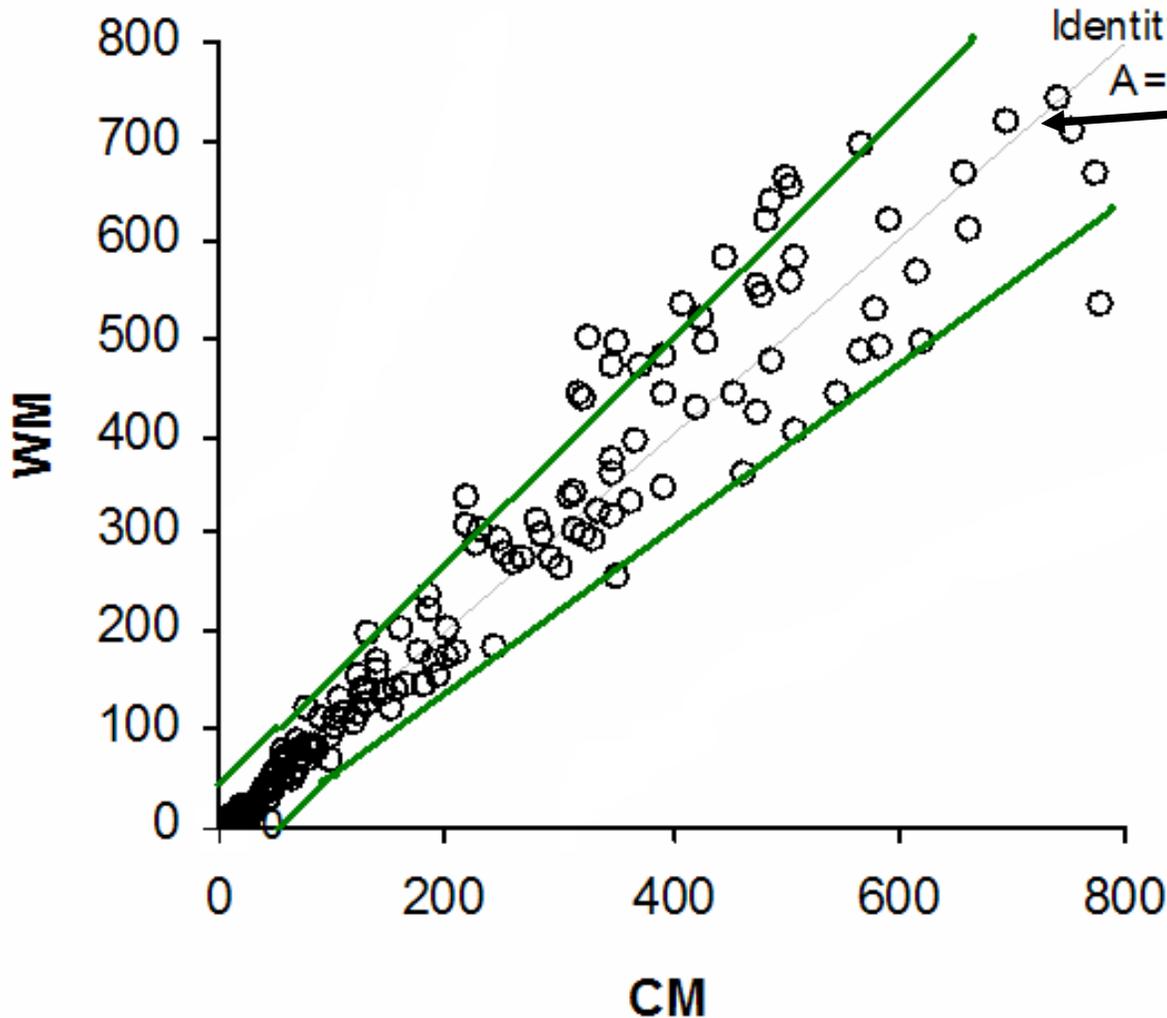
C) based on components of biological variation;

If the patient is undergoing monitoring of analyte (measuring the analyte of the patient at different time points), the variation from measurement to measurement consists of BOTH analytical and biological components (within-subject).

$$(\text{SD}_{\text{Measurement}})^2 = (\text{SD}_{\text{within-subject}})^2 + (\text{SD}_{\text{analytical}})^2$$

The larger within-subject biological variation, the larger analytical errors can be tolerated.

Allowable Total Error Zone



**Allowable
Total Error
Zone**

(at least 95% of
subjects)

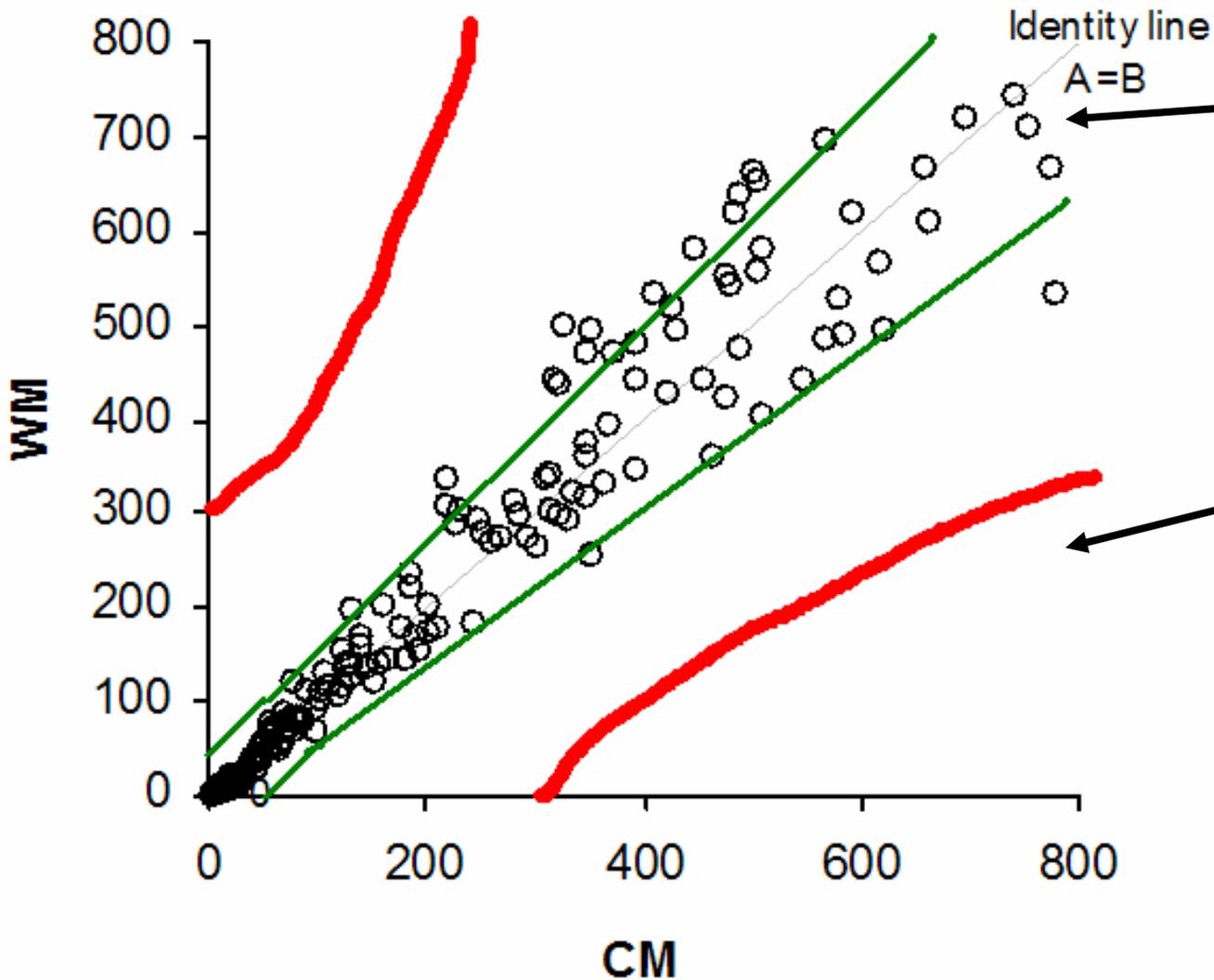
Demonstrating “Accuracy” – Performance Criteria

For ATE zone:

- 1) percentage of WM observations for the low, medium and high ranges are close to 95% for each range;
- 2) percentage of WM observations over the entire range: for 360 samples, **95%** (342/360) with lower bound of 95% CI of **92.8%**.

We are sure (95% confident) that not less than 92% of patients from the intended use populations have WM results in ATE (“clinically acceptable”).

Allowable Total Error Zone, Limits for Erroneous Results Zones



**Allowable
Total Error
Zone**

(at least 95% of subjects)

**Limits for
Erroneous
Results Zones**

(0% of subjects).

Demonstrating “Accuracy” – Performance Criteria

For LER zones:

- 1) percentage of WM observations over the entire range:
for 360 samples,
0% (0/360) with upper bound of 95% CI of **0.8%**.

We are sure (95% confident) that not more than 1% of patients from the intended use populations have WM results in LER zones (“harm for patients”).

We need your inputs on ATE and LER zones for CBC/ADCC devices.

More statistical details related to these devices will be presented by Dr. Russek-Cohen.

Thank you!