CLIA Waiver Study Design and Dual Submission

2022 FDA IVD Submissions Workshop

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Outline

I. Introduction
II. POC devices (moderate) and POC devices (waived)
III. Different Approaches for CLIA waivers
IV. Dual Study Design
V. Comparison Study for
- Quantitative tests
- Qualitative tests
- Semi-quantitative tests

Definition of POC Testing
(international term “Near-Patient Testing”)

Near-Patient Testing: Testing that is performed near a patient and outside of centralized laboratory testing facilities.

NOTE 1: Users of near-patient testing can include lay or professional users.
NOTE 2: This is not intended to refer to sample collection procedures.
NOTE 3: In certain regulatory jurisdictions, this is also referred to as Point of Care Testing.

Document “Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices” by IMDRF (International Medical Device Regulators Forum), page 11.

Risk Based Regulation of IVDs

Class I - Low likelihood of harm
register & list (21CFR §807)
General Controls

Class II - Moderate likelihood of harm or risk can be mitigated
Special Controls

Class III - High or unknown likelihood of harm
Significant Risk
Pre-market Approval

Complexity of IVD devices

- Categories are based on requirements for training and experience, how difficult steps for reagents preparation, whether calibration is needed, sample preparation, controls preparation, equipment maintenance, and so on.
- From most complex to the least complex:

High complexity tests

Moderate complexity tests

Waived tests

Different Routes to CLIA Waived Test

<table>
<tr><td colspan="2">Waived by Regulation</td></tr>
<tr><td rowspan="2">Home use</td><td>OTC</td></tr>
<tr><td>By prescription</td></tr>
<tr><td colspan="2">By Application
Meet statutory criteria:
“simple”;
“insignificant risk of erroneous results”</td></tr>
</table>

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

“.. employ methodologies that are so **simple** and **accurate** as to render the likelihood of erroneous results by the user negligible, …”

CLIA Waived Test: “Simple”

- Fully automated instrument or unitized test system
- Uses direct unprocessed samples: fingerstick blood, urine, swabs, tears, …
- All steps are simple (no reagent manipulation); no operator intervention during analysis
- Operators are without laboratory training (“untrained operators”)
- Quick Reference Guide at 7th grade reading level
- Easy to read test results (pos, neg, invalid, value, etc.)

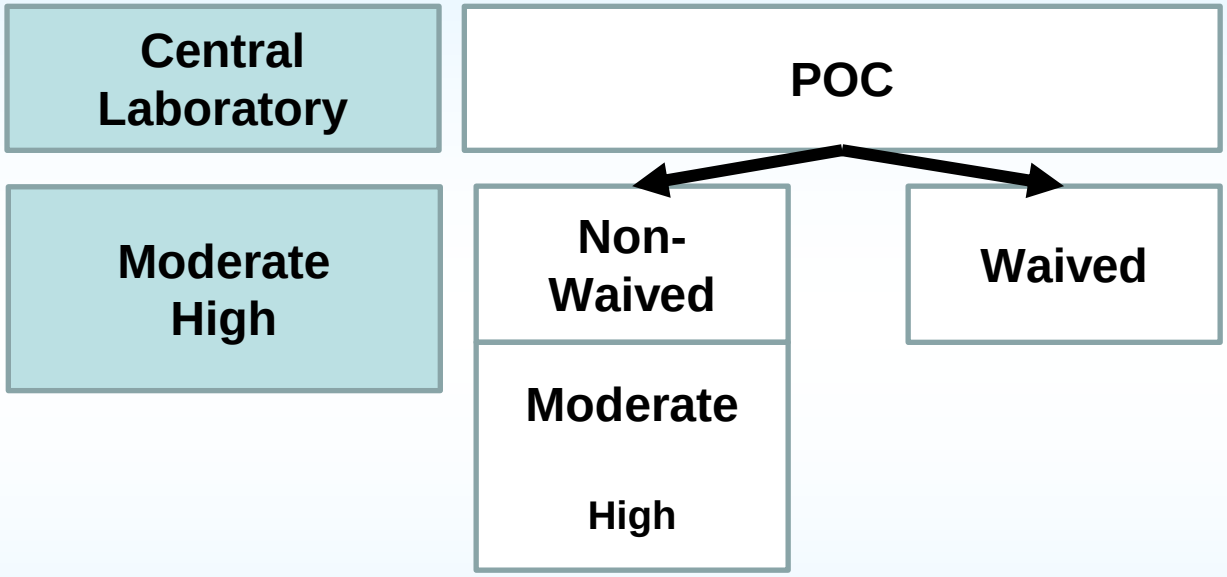
- FDA Risk Classes:
  Class I,
  Class II,
  Class III

- CLIA categories of complexity for test systems:
  -> High
  -> Moderate
  -> Waived

Examples: (Class III, moderate complexity), (Class II, high complexity)

POC is related to the location of testing relative to the patient =>
It can be PMA, de novo, 510(k);
it can be high, moderate complexity or waived

What is POC Testing ?



POC devices (moderate and waived)

- Designed for use near patient testing

  Examples of POC testing:

  POC sites (moderate):

  emergency room in a hospital,

  physicians' office laboratories,

  urgent care center,

  POC (waived): doctor's office, nursing homes

- Device is usually smaller and easier to use than laboratory analyzer

POC (non-waived), moderate complexity

- POC (non-waived), moderate complexity, **device may not be "simple"** (samples can be serum, plasma)
- **Trained operators** met moderate complexity testing qualifications
- POC lab has a Lab Director (also, POC coordinator)
- **Proficiency testing**
- POC testing requires a prescription

- Intended use – "for use at point of care sites"

POC (waived)

- Device is **“simple”** (samples as FS, saliva, ..)
- POC (waived), no any training = **“untrained operator”** use only Quick Reference Guide (7th grade)
- **No Proficiency testing**
- POC testing requires a prescription

- In the package insert –”waived”

Benefits/Risks of POC (moderate) and POC (waived)

- Benefits:
  - Reduced time until treatment onset
  - Increased access
- Risks:
  - Pre-analytic variables/signal deterioration because of specimen type, testing environment not so controlled, limited operator training (POC (moderate) or no training (POC(waived))
  - Increased risk of false results
  - Risk of infection in multiple use settings

Landscape:
Elements Impacting Device Performance

- Specimen collection
- Specimen transport
- Test execution
- Reading the test
- Test result interpretation
- Clinical action

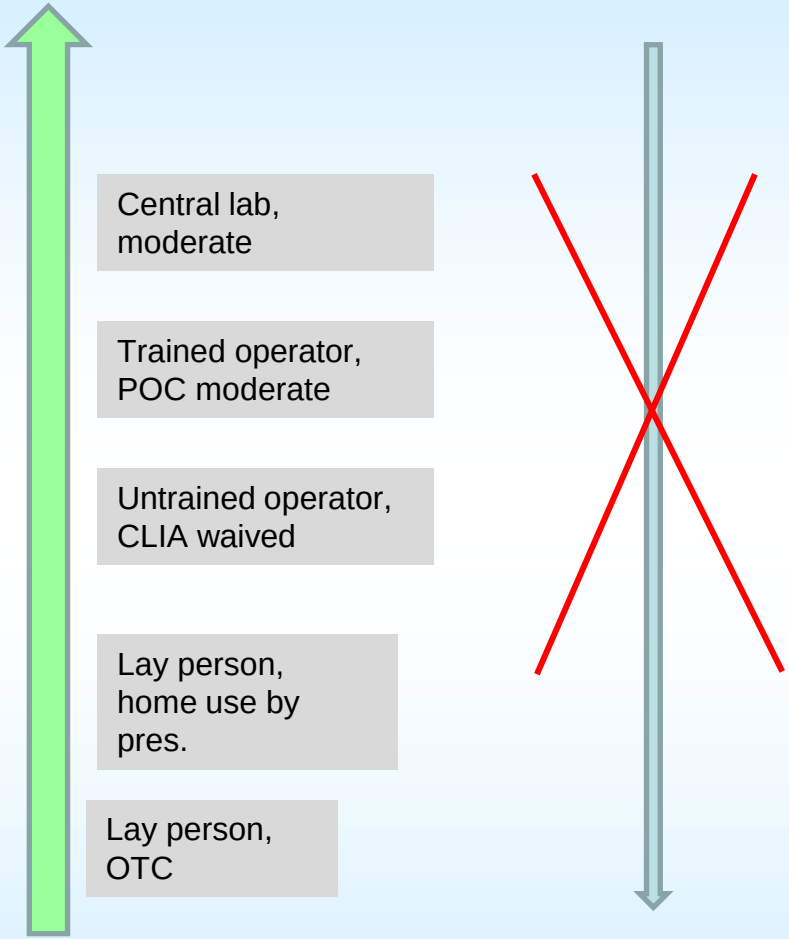
Different Personnel Involved in Testing

- Individual for collection of specimen
- Technical User (test execution)
- Clinical User (test results interpretation and clinical action)

Different Categories of Tests

Collection	Trans port	Running	Reader	Interpret ation	Action	OIR Category
Untrained operator	None	Untrained operator	Untrained operator	Physician	Physician	**CLIA Waiver**
Lay person	None	Lay person	Lay person	Lay person	Lay person	**OTC (waived)**
Lay person	None	Lay person	Lay person	Either lay person or physician	Either lay person or physician	**Home use by prescription (waived)**
Trained operator	None usually	Trained operator (POC operator)	Trained operator (POC operator)	Physician	Physician	**POC (moderate)-non-waived**
Lay person	Transp.	Trained operator (mod. or high)	Trained operator (mod. or high)	Lay person	Lay person, physician	**DTC**
Lay person	Transp.	Trained operator (mod. or high)	Trained operator (mod. or high)	Physician	Physician	**Collection Device**

CLIA waived intended user=untrained operator
POC (non-waived) intended user=trained operator



Clearance/approval based on data obtained at POC (moderate) sites does not mean that the test can be distributed to CLIA waived sites

How does a device get a POC claim?

In Vitro Clinical Test

Analytical performance—does the test measure (detect) the analyte I think it does? Correctly? How reproducibly?

Analytical accuracy
Precision
Limit of Blank,
Limit of Detection,
Limit of Quantitation,
Linearity,
……..

Clinical validation—is a patient test result associated with the expected clinical presentation of this patient?

Clinical Validation – the process through which one shows that test results are clinically meaningful, i.e., finding whether the test is able to detect or predict the disorder or target condition in the target population

Frequently, analytes for the CLIA waiver do not need to have clinical validation (it is already established) => analytical accuracy

POC Claim:

Basic Idea:

POC claim requires that the analytical accuracy study, clinical validation study (if applicable) and reproducibility study be conducted at POC settings with POC operators

- It is recommended at least **3 sites**
- For a POC claim, select sites that are diverse (e.g., emergency room, outpatient clinic, etc.)
- Selected POC sites should provide healthcare to the patients from the intended use population
- It is strongly recommended that the sponsor selects POC sites in the U.S.

  POC sites outside of the U.S. may be acceptable in some circumstances
  - Demographic differences between U.S. and foreign population do not affect test results
  - POC site operations and POC operators at foreign sites reflect the typical POC site operations and POC operators in the U.S.

POC Claim:

Basic Idea: POC claim requires that the analytical accuracy and clinical validation study (if applicable) and the reproducibility study be conducted at POC settings with POC operators

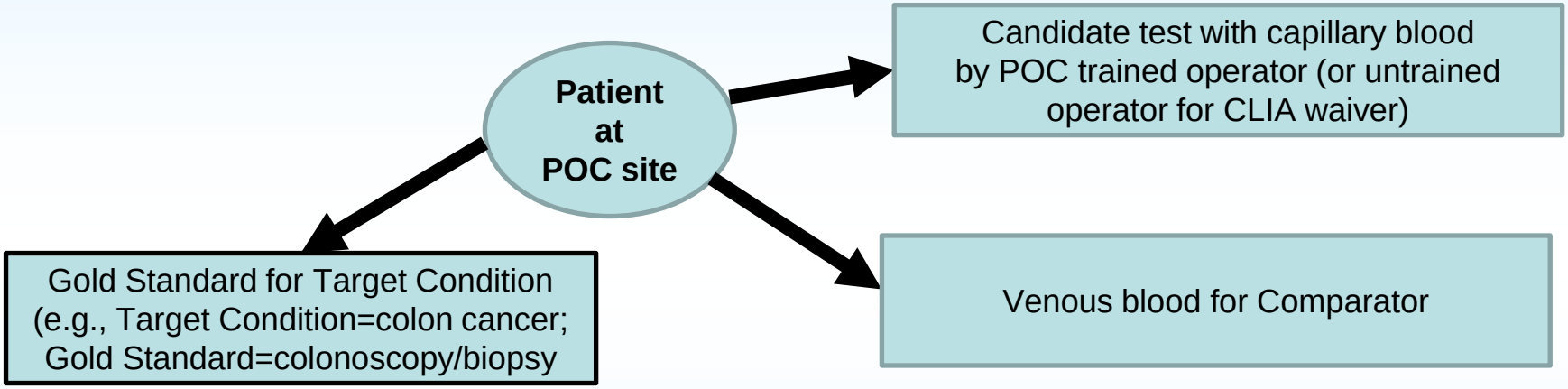
- **POC (moderate):** with **at least 2 trained operators per site (6 trained operators in total)**

- **POC (waived):** with **at least 9 untrained operators in total**

❖ example 1: 3 untrained operators per site

❖ example 2: 1 operator at site 1,
2 operators at site 2,
3 operators at site 3 and
3 operators at site 4

Evaluation Considerations for POC claim



***Analytical accuracy*:**
Candidate results vs Comparator results
(method comparison study)

Clinical performance: Candidate results vs Gold Standard for target condition

Evaluation Considerations for POC claim

- Analytical performance testing **in laboratory/internal**
  - Linearity
  - Interferences
  - Cross-reactivity
  - Sample stability
  - Reagent stability
  - LoB/LoD/LoQ
  - Evaluation of the lot-to-lot variability in order to have 1 lot in the reproducibility study
  - ……

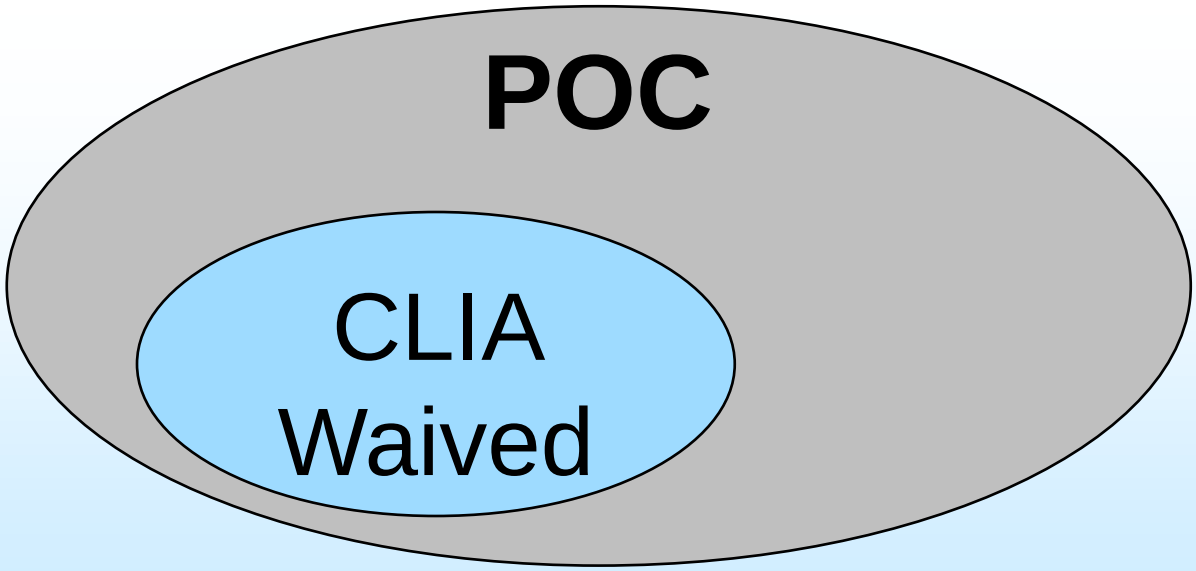
Evaluation Considerations for POC claim

- Flex study - testing in **laboratory/internal**
  - Environmental factors
    as temperature,
    humidity,
    vibration,
    tilting

  - For POC (waived), additional flex studies related to human errors

What are the similarities and differences between CLIA waived and POC (moderate) devices?

- CLIA waived device is performed at POC sites.
- Many POC test systems are categorized as moderate complexity. They may not be “simple”; PT testing; training.



How does a test meet CLIA waiver criteria?

A) **Is the test simple?**

A.1 Demonstrate **"simple"**

A.2 Quick Reference Guide (procedure steps, QC testing) and Manual (maintenance, error codes, ..) at 7th grade level

B) **Does the test have an insignificant risk of an erroneous result?**

B.1 Risk analysis **=>Flex studies**

B.2 **"Accuracy"** -valid scientific studies

- performed at 3 or more typical waived sites,
- using 9 or more "untrained" operators,
- testing real samples over time

B) Demonstrating “Insignificant Risk of Erroneous Result”

B.1 Risk Analysis **=> Flex studies**

(identification of all potential sources of error and how to mitigate their risk)

- Environmental factors – heat, humidity, electrical or electromagnetic interference
- Operator error/human factors
- Specimen handling and integrity
- Reagent integrity – storage, outdated
- System stability - calibration
- Hardware, software and electronics integrity (power failures,..)

B) Demonstrating "Insignificant Risk of Erroneous Result"

B.1) **Flex studies**

Example

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

B) Demonstrating "Insignificant Risk of Erroneous Result"

B.2 **"Accuracy"**

Basic idea:

- Patient is in a doctor's office and obtains a result from Waived Method (WM) in the hands of intended operators (untrained operators);
- If instead of this, patient went to the lab and obtained a result from one of the best laboratory methods (Comparative Method, CM) in the hands of professionals.

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

How does a device get a POC (Waived) claim by Application ?

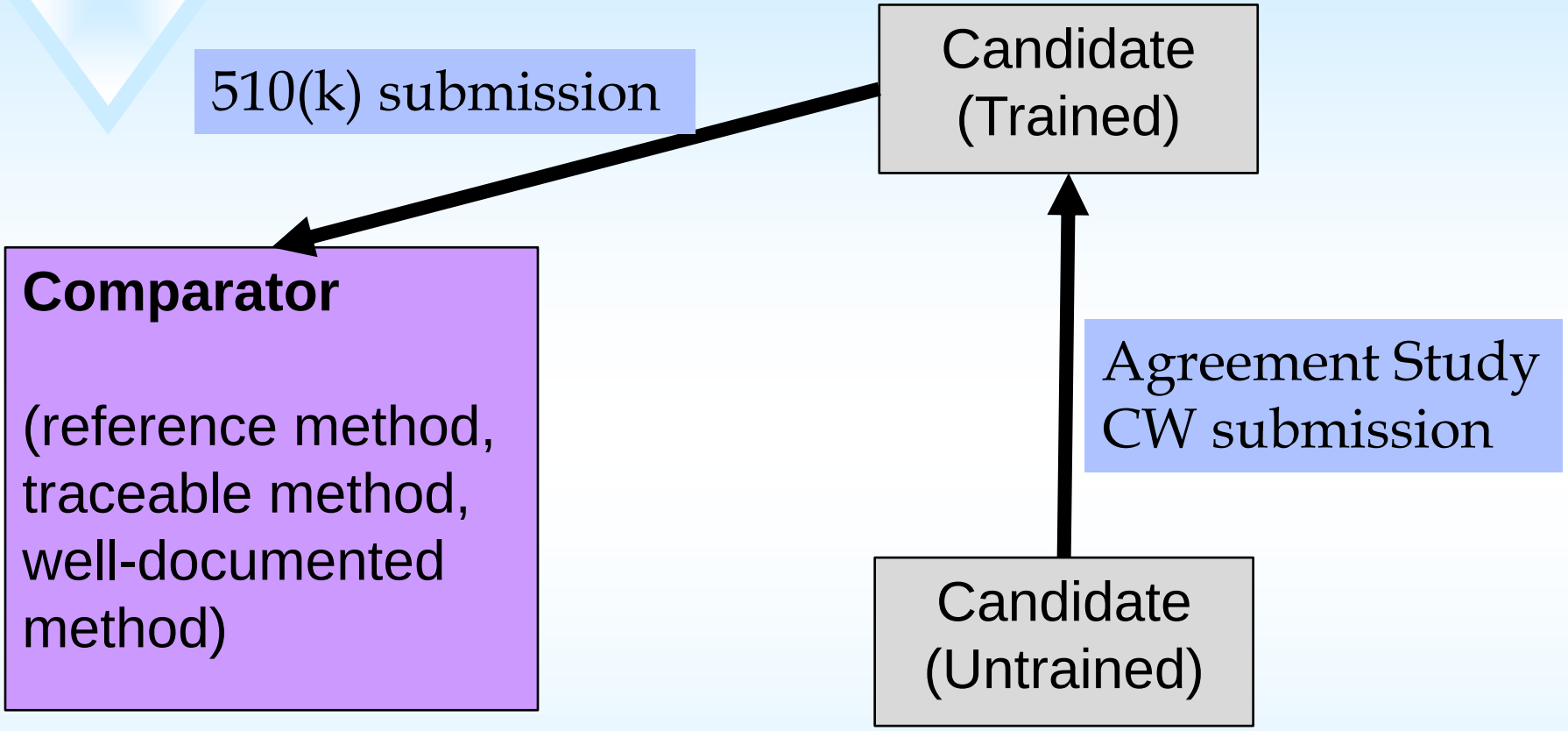
By Application

Meet statutory criteria:
"simple";
"insignificant risk of erroneous results"

There are different approaches:

- flexibility
- each approach has advantages

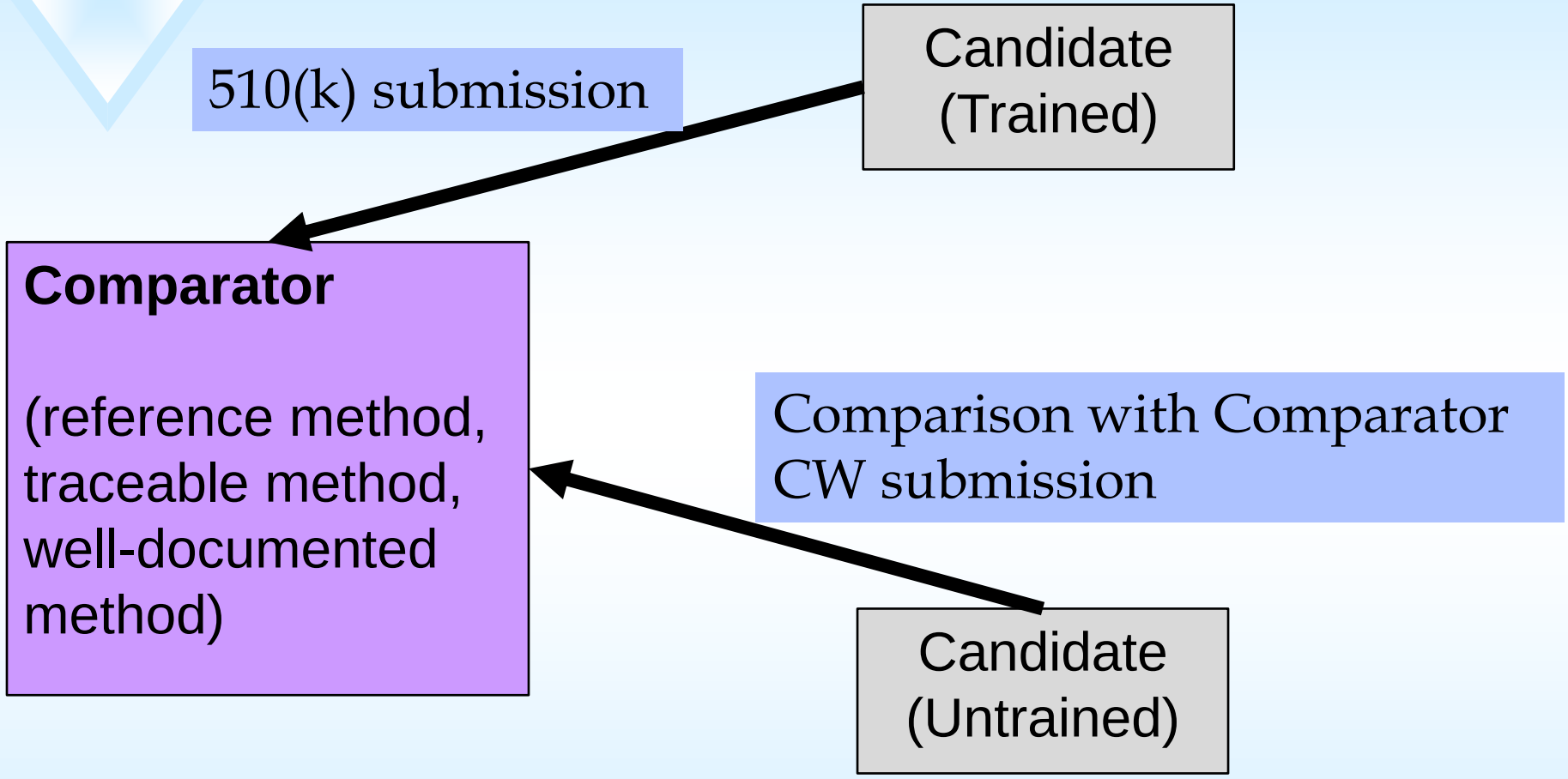
Approach 1



Pluses: after POC claim for trained operators (moderate)
agreement study can have an easy design

Minuses: accuracy of candidate (untrained) is evaluated indirectly =>
more uncertainty about “accuracy” of candidate (untrained) =>
more difficult to show acceptable performance of the candidate(untrained)

Approach 2



Pluses: after POC claim for trained operators (moderate)
direct evaluation "accuracy" of candidate (untrained) => more certainty about "accuracy" => easier to show acceptable performance of the cand.(untrained)

Minuses: comparator is in the lab (professionals)

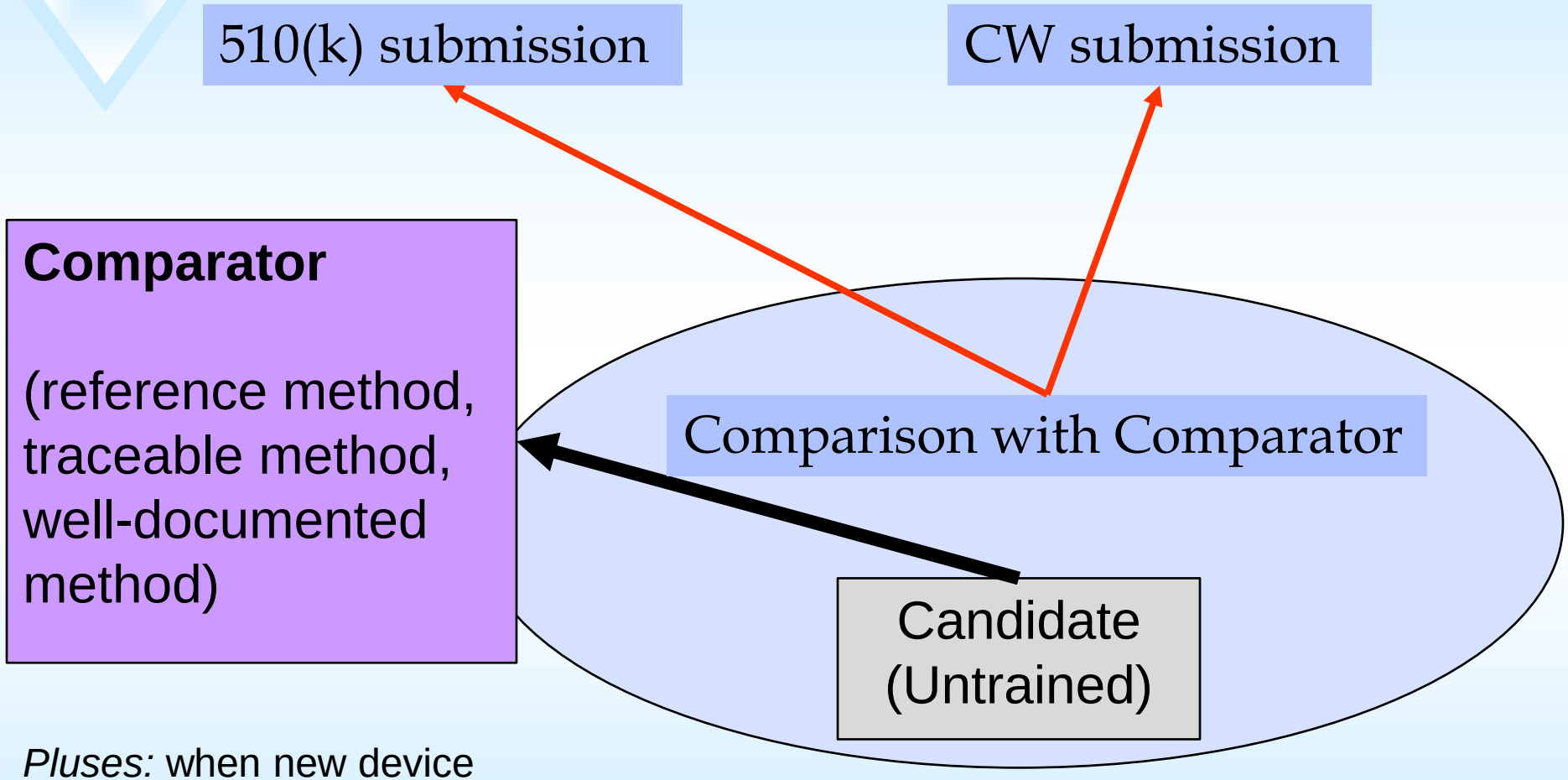
Approach 3: “Dual” Study

Basic Idea:

- Performance of the Candidate test is evaluated **only** in the hands of untrained operators (performance of the test in the hands of trained operators is the same or better than performance of the test in the hands of untrained operators)

- These data are used to support:
  - CLIA waiver and
  - POC (moderate) test.

Approach 3 ("Dual" Study)



Pluses: when new device
least burdensome approach (one study for 2 submissions)
more certainty about "accuracy" => easier to show
acceptable performance of the candidate for untrained operators

Minuses: …..

Approach 3: “Dual” Study Approach

510(k) – POC, moderate, Candidate in hands of POC operators (trained)	**CLIA waiver Candidate in hands of CLIA waived operators (untrained)**
Analytical studies as analytical sensitivity, analytical specificity, Linearity (if applicable), reagent stability, sample stability, and so on	Simple, Flex studies
Reproducibility (POC sites)	Reproducibility (CLIA waived sites)
Comparison (POC sites)	Comparison (CLIA waived sites)

A) Reproducibility (3 CLIA waived sites)
B) Comparison (3 CLIA waived sites, 9 untrained operators)

Pathways to submit for different Approaches:

Approach 1

Agreement study:

candidate (untrained) vs candidate (trained)

Approach 2

Comparison study:

Candidate (untrained) vs comparator

Approaches 1 and 2: **Sequential pathway**

510(k) – POC, moderate, device in hands of POC operators (Trained)		**CLIA waiver device in hands of CLIA waived operators (Untrained)**
Analytical studies as analytical sensitivity, analytical specificity, Linearity (if applicable), reagent stability, sample stability, and so on	**Later**	Device is “Simple”, Flex studies
Reproducibility (POC sites)		
Comparison (POC sites)		Comparison (CLIA waived sites), Reproducibility

Or Agreement study

Pathways to submit for different Approaches:

Approach 3

Dual Study:

candidate (untrained) vs comparator

Two pathways to <u>submit</u>

- ❑ Sequential pathway
- ❑ Dual submission pathway

Two pathways to submit dual studies (untrained operators):

❑ Sequential pathway

510(k) – POC, moderate		CLIA waiver
Device is "Simple"		

Internal site
Analytical studies such as:
• Analytical sensitivity
  ○ LoQ (if Candidate test is quantitative),
  LoD/LoB (if applicable),
• Analytical specificity,
• Linearity (if Candidate device is quantitative),
• Precision study for lot-to-lot variability and/or other issues
• Reagent stability, sample stability, …
• Some flex studies (environmental factors)
	Later	**Internal site Flex studies**
		references

Reproducibility (3 **CLIA waiver sites**, untrained operators)		
Comparison (3 **CLIA waiver sites**, untrained operators)		

90 days

150 days

Two pathways to submit dual studies:

- **Dual submission pathway (***complete* 510(k) and *complete* CLIA waiver application in a *single* submission)

Dual Submission
"Simple"

Internal site
Analytical studies such as:
• **Analytical sensitivity**
  ○ **LoQ (if candidate test is quantitative),**
  LoD/LoB (if applicable),
• **Analytical specificity,**
• **Linearity (if candidate device is quantitative),**
• **Precision study for lot-to-lot variability and/or other issues**
• **Reagent stability, QC stability, sample stability, …**
Flex studies

Reproducibility (3 **CLIA waiver** sites, untrained operators)
Comparison (3 **CLIA waiver sites**, untrained operators)

180 days

Dual studies: **Reproducibility**

- 3 CLIA waiver sites (that participate in the comparison study)
- 3 untrained operators per site (who participate in the comparison study)

Notes:

- Study design depends on specimen (fingerstick, venous WB)
- Lot-to-lot component of variance can be evaluated at the internal site
- Sample concentrations (dependent on type of device as quantitative, qualitative, semi-quantitative)

Dual studies:
Comparison study (Accuracy)

Dependent on type of Candidate test: quantitative, qualitative, semi-quantitative

- ❑ At least 3 CLIA waiver sites
- ❑ At least 9 untrained operators

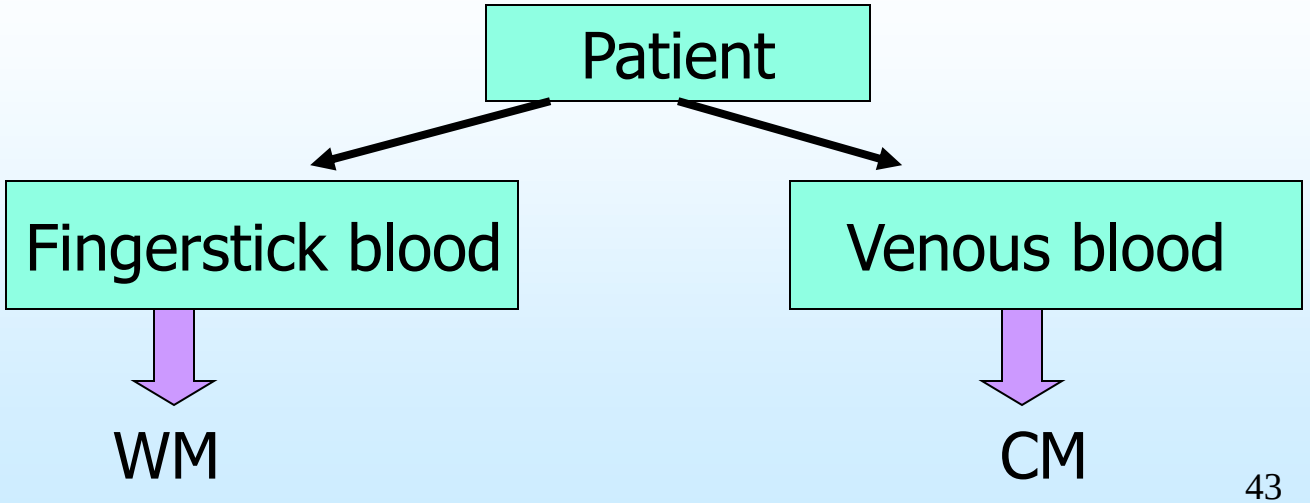
  (e.g., 1 operator at site1, 2 operators at site 2,
  3 operators at site 3 and 3 operators at site 4)
- ❑ It can be non-US sites (contact FDA)
- ❑ Duration of study at least 2 weeks (1 month is recommended)

Comparison Study: "Accuracy"

Paired Study Design

- Waiver Method (WM) by untrained operators in CLIA waived setting

- CM by professional laboratorians in laboratory settings

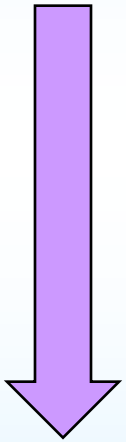


Comparison study (Accuracy)

- Patients from intended use population

Hierarchy

- Actual patient specimens
- Archived samples
- Surrogate samples
  CLSI EP39



B) Comparison Study, “Accuracy”

- Quantitative tests
- Qualitative tests
- Semi-quantitative tests

- Quantitative tests

Quantitative test

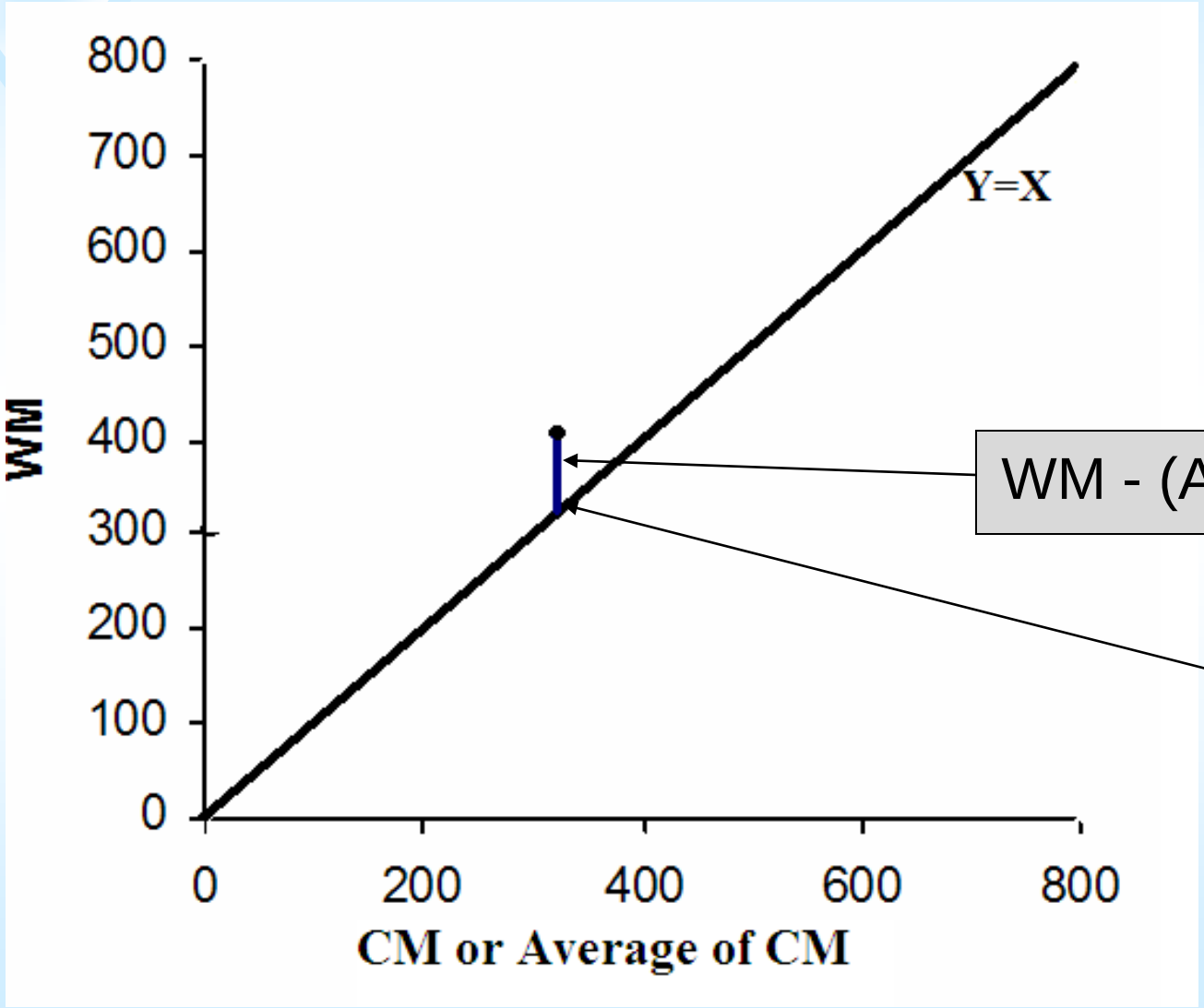
- 360 patients samples (some samples can be contrived)
- Samples should cover a measuring interval

Candidate (untrained)
vs
Comparator

Comparator:
Method in the hands of professionals

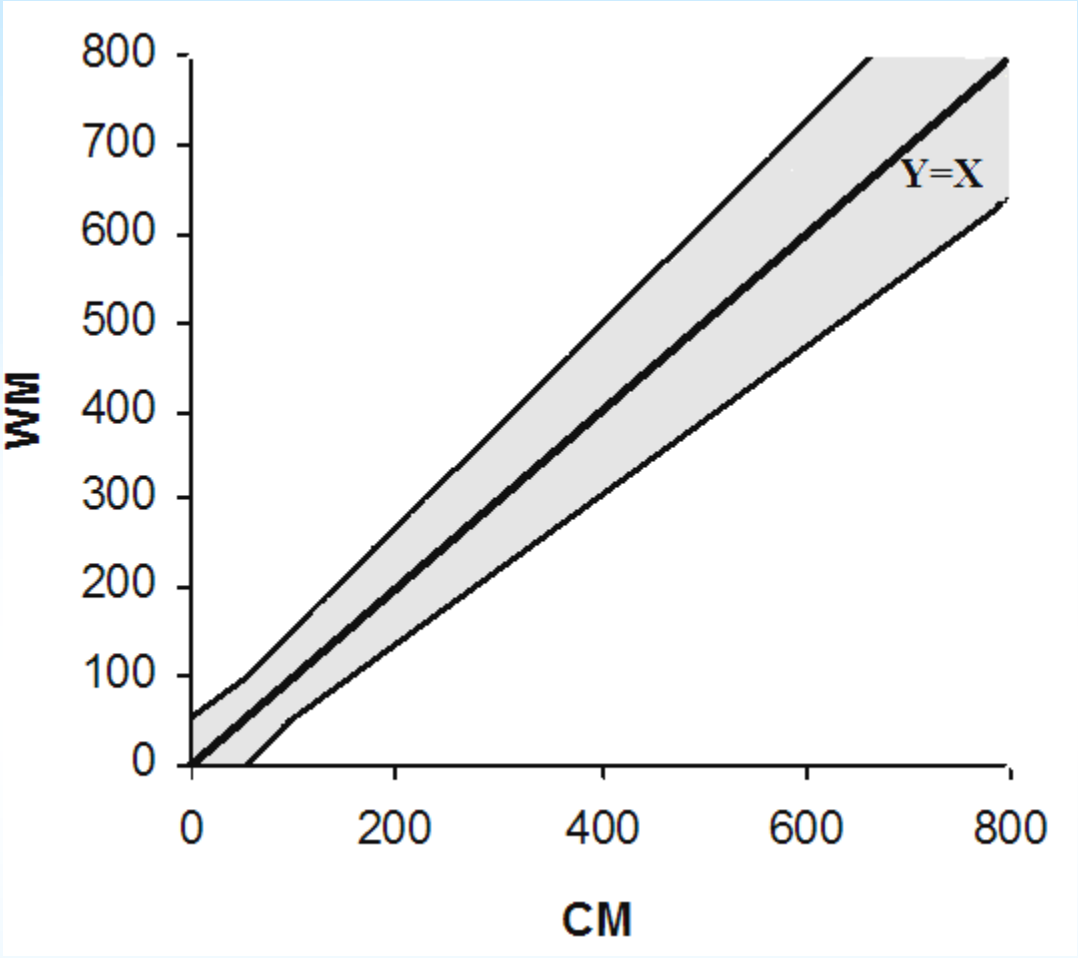
A) Reference method
B) Traceable method
C) Well-documented

Waiver Method Result - (CM or Average of CM results)



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.



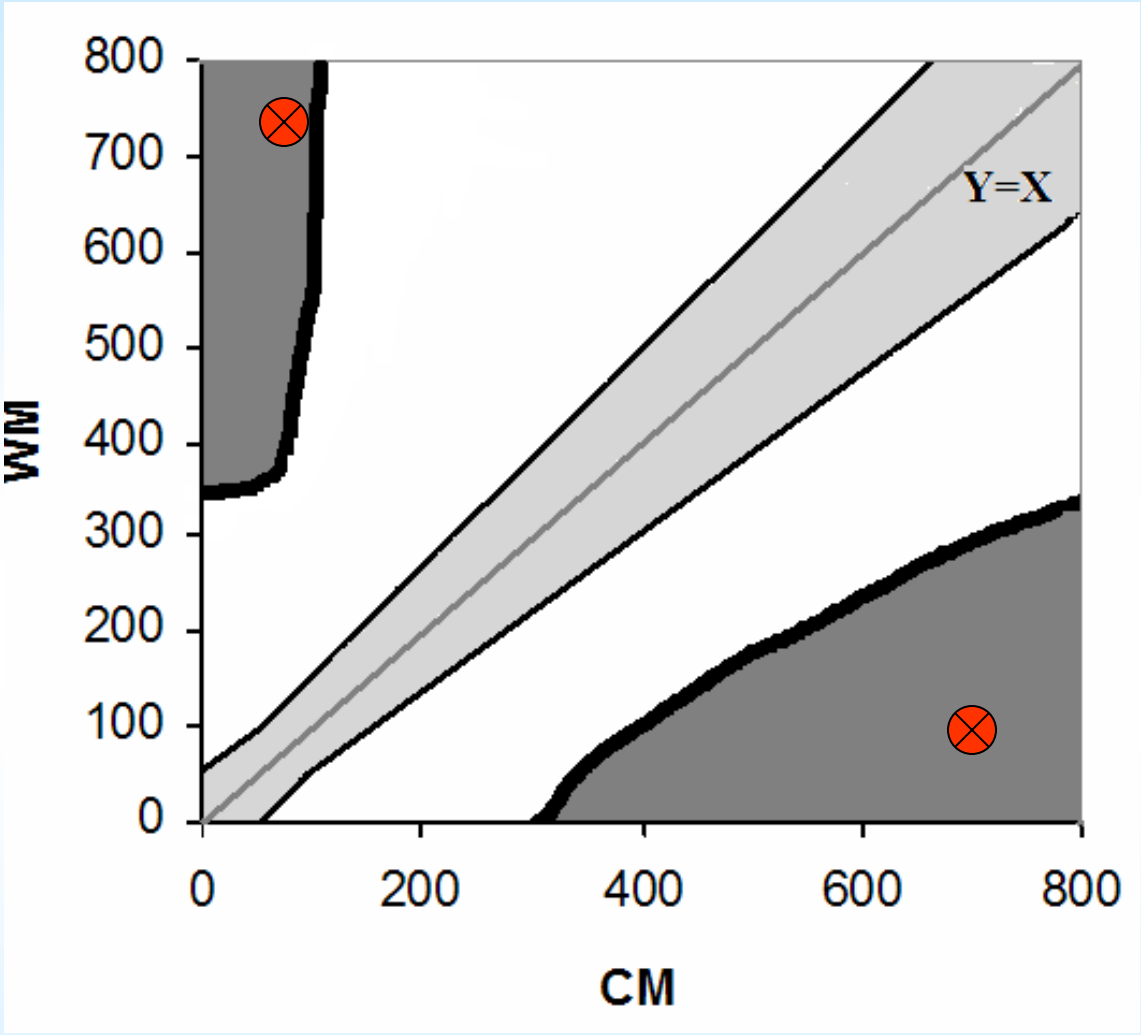
It is anticipated that no less than **95%** of sample results will fall within the ATE zone.

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.

LER zones are the outer zones.



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

Demonstrating “Accuracy” – Performance Criteria

For ATE zone:

1) Percentage of WM observations over the entire range is close to 95%:

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”).

2) Regression analysis:

Regression analysis and biases at Medical Decision Levels along with 95% CI (CLSI EP09c)

Demonstrating “Accuracy” – Performance Criteria

For LER zones:

3) 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”).

For details, see CLSI EP09c, EP21, and EP27

- Qualitative tests

Qualitative test

- At least 120 patients samples positive by Comparator (some samples can be contrived)
- Can be less than 120,

sometimes can be required more (contact OIR)

Candidate (untrained)
vs
Comparator

Comparator:
Method in the hands of professionals

As Culture,
Composite Reference method,
Another method (well-documented);
Quantitative test in lab

Demonstrating “Accuracy” – Qualitative test

		Comparator		
		Pos	Neg	
WM	Pos	115	6	121
	Neg	5	294	299
		120	300	420

- Positive percent agreement (PPA) between WM and CM (with 95% CI)
- Negative percent agreement (NPA) between WM and CM (with 95% CI)

PPA = 95.8% (115/120);
95%CI: (90.6%; 98.2%);

NPA = 98.0% (294/300);
95% CI: (95.7%; 99.1%).

PPA and NPA of 95% or higher is needed (or a lower percent may be acceptable if justified by benefit-risk analysis)

Demonstrating “Accuracy” – Qualitative test

If CM is a quantitative test or a qualitative test with available signal, calculate zones around the cutoff of the CM such that that samples having an initial CM result with an internal signal in these zones could have discordant CM results if repeated measurements by the CM were to be made on the same sample.

Detailed table of agreement

		Comparator				**Total**
		Pos		**Neg**		
		High or Moderate Pos	Low Pos (close to C95)	High Neg (close to C5)	Moderate or Low Neg	
WM (untrained)	Pos					
	Neg					
	Total					

For details, see CLSI EP12

- Semi-quantitative tests

Semi-quantitative test

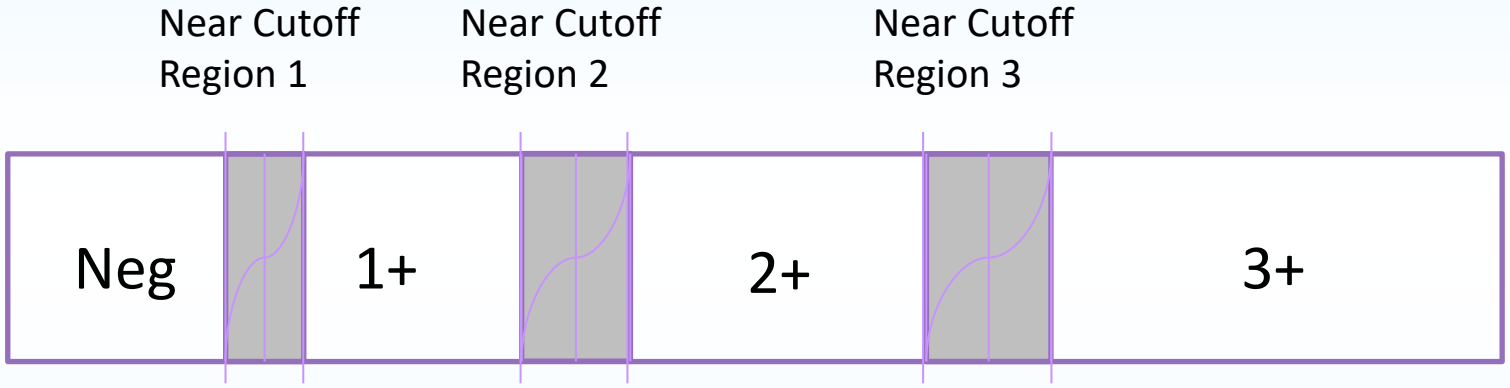
Test with ordinal outputs

Example: Neg, 1+, 2+, 3+

It is recommended to evaluate the Device vs Quantitative CM (e.g., quantitative traceable calibration method)

Why is a Quantitative CM Recommended for Semi-Quantitative Tests?

- For example, consider a semi-quantitative test for Albumin with 4 categories (bins), each covering a concentration range:



- When comparing a CM quantitative test to itself:
  - Some level of disagreement is expected for samples in the near cutoff regions
  - The extent of disagreement will increase with increased numbers of samples in the near cutoff regions

Neg: ≤19 mg/L
1+ : 20-52 mg/L
2+ : 53 -110 mg/L
3+ : ≥110 mg/L

		Comparator (quantitative)						
Range		≤17	**18-21 Near 19.5**	22-48	**49-56 Near 52.5**	57-100	**101-119 Near 109.5**	≥120
Predicted bins with at least 95% probability		Neg	Neg or 1+	1+	1+ or 2+	2+	2+ or 3+	3+
Candidate	Neg							
	1+							
	2+							
	3+							

Allowable Total Error (ATE) – green
Limits of Erroneous Results (LER) - red

Invalid Results in the CLIA Waiver Study

For each operator, provide

- ❑ Total number of performed Candidate tests;
- ❑ Number of initial Invalid results;
- ❑ Number of retested results;
- ❑ Number of final Invalid results.

- ➢ For all combined data of the clinical study, provide percent of Invalid results (initial) with 95%CI.
- ➢ **Do not consider** Invalid results as wrong results (exclude invalid from calculations (e.g., PPA and NPA))

Summary

1. What is POC testing: POC (moderate complexity) and POC (waived)

2. For a POC claim, an evaluation of the device with POC intended users in the population of patients at the POC sites (at least 3 POC sites).

3. Flex studies with regard to environmental factors, human factors and other factors

4. Analytical validation studies with specimens as capillary whole blood (FS), fresh urine, saliva, … - contact FDA for more discussions

5. Different approaches for CLIA waivers

Protocol reviews through pre-Submission (Q-sub) process

Thank you!

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