Professional Practice in Clinical Chemistry

Quality Control and Proficiency Testing

Ross Molinaro, PhD, MT(ASCP), DABCC, FACB

Emory University

Atlanta, GA

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Learning Objectives

After this presentation, you should be able to:

- Define QC terms
- Provide an overview of Multi-rule QC
- Define and calculate “Sigma” as measure of process performance
- Assess Proficiency Testing
  - Requirements, Process and Function

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Important Definitions

Quality

- The totality of characteristics of a product or service that bear on its ability to satisfy stated and implied needs (customer requirements).

Quality assurance

- Planned and systematic activities to provide adequate confidence that requirements for quality will be met.

Quality management

- All activities of the overall management function that determine quality policy objectives and responsibilities; and implement them by means such as quality planning, quality control, quality assurance, and quality improvement within the quality system.

Controls and Control Charts

Routinely performance of analytical methods is monitored using stable controls.

- **Control Material -** Specimen or solution which is analyzed **solely** for monitoring performance of a method. (Never used for calibration purposes)

- **Control Charts** – Simple graphical displays in which observed values are plotted versus the time when the observations were made.

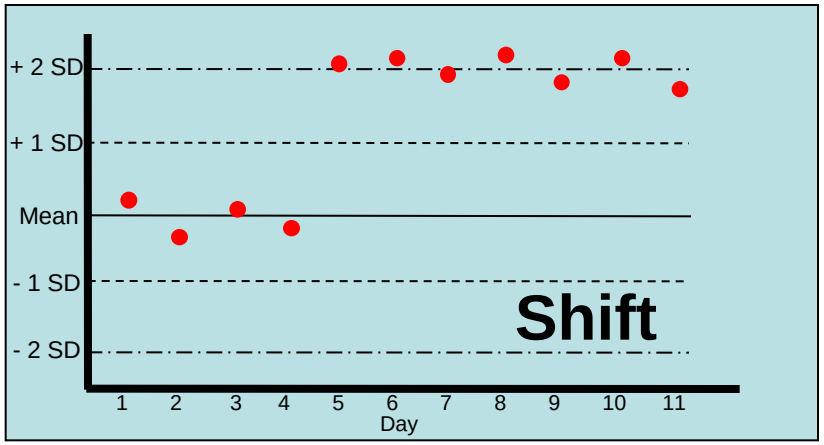
Important Definitions

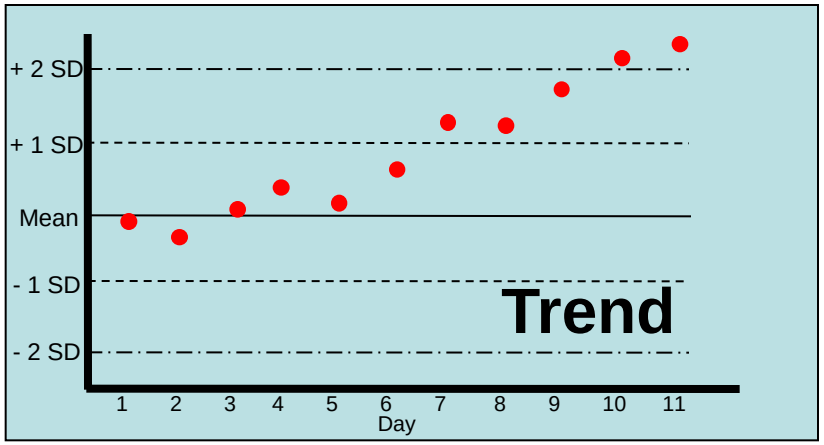
Random errors.

- Statistical fluctuations (in either direction) in the measured data due to the precision limitations of the measurement device.

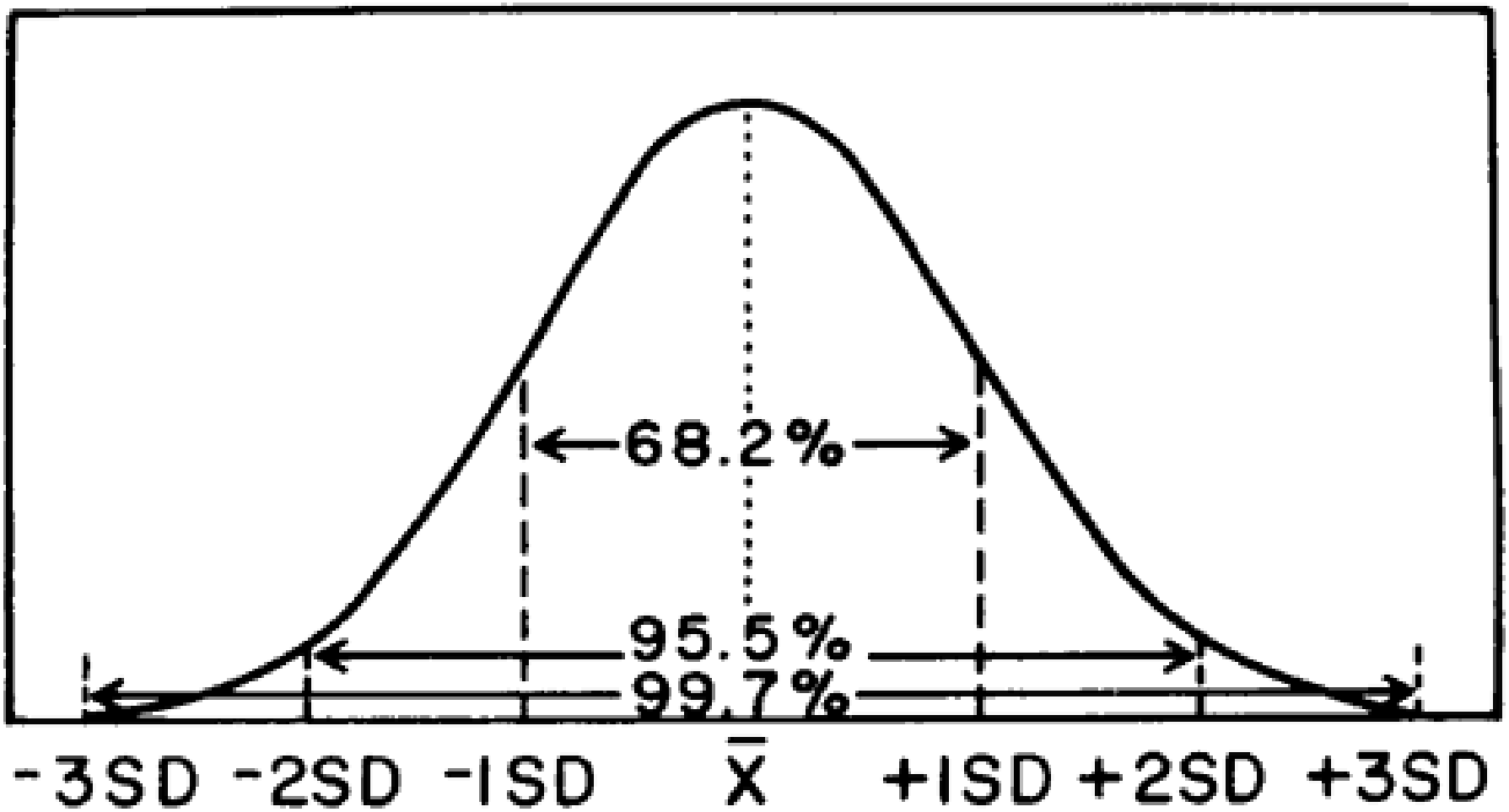
Systematic errors.

- Reproducible inaccuracies that are consistently in the same direction. Systematic errors are often due to a problem which persists throughout the entire experiment.





Levey-Jennings Chart



- N=2, 9%
- N=3, 14%
- N=4, 18%

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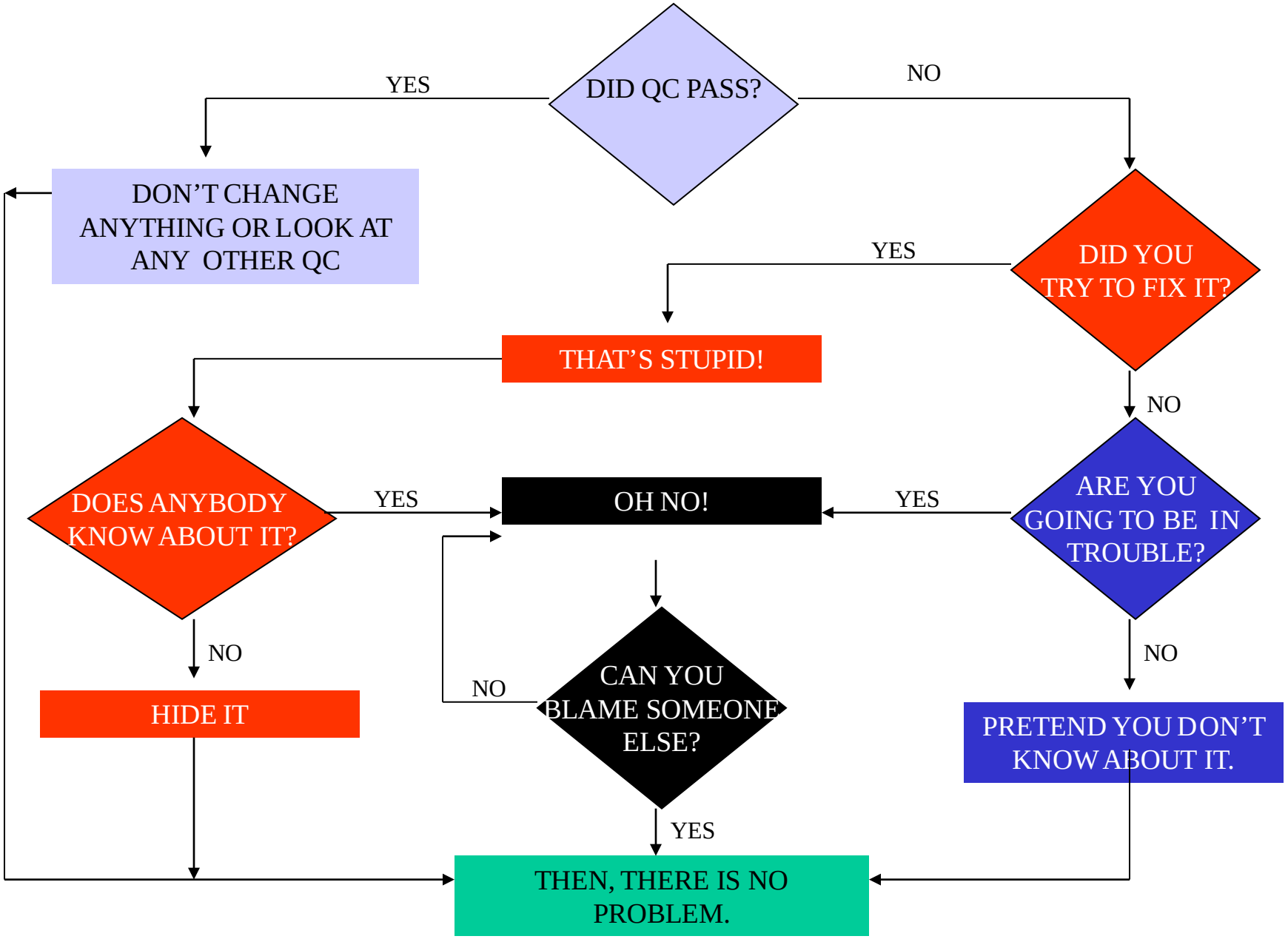
Westgard Multirule Control Charts

- This “multirule” procedure developed by Westgard and associates uses a series of control rules to interpret control data.
- The probability for false rejections is kept low by selecting only those rules whose individual probabilities for false rejection are very low (0.01).
- The probability for true error detection is improved by selecting those rules that are particularly sensitive to random and systemic errors.
- Requires a chart with lines for mean, ±1, 2, 3 sd’s.
- Works best with 2 different levels of control material at medical decision levels and/or across analytical measurement range

The *"Notsogood"* Lab QC Trouble Shooting Diagram



Westgard
Structured Rule Interpretation

- When controls fall within 2 sd's, accept the run.
- "Warning Rule" - One control ± 2 sd limit, hold patient results while inspecting control data with the 1_{3s} , 2_{2s} , R_{4s} , 4_{1s} , and 10_{x} rules. If any of these additional rules indicates that the run is "out of control", reject the run.
- When a run is "out of control" determine the type of error occurring based on the control rule violated.
- Look for sources of that type of error. Correct the problem and reanalyze the whole run including controls.

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Control rule definitions

- A_L = general symbol for a control rule
  - A is an abbreviation for a statistic, or the number of control measurements
  - L refers to the control limits, usually specified by giving the number of standard deviations from the mean; also can specify the probability for false rejection

1_{2s} = one control measurement exceeds x ± 2s limits

1_{3s} = one control measurement exceeds x ± 3s limits

2_{2s} = two consecutive control measurements exceed the same x + 2s or x - 2s limit

R_{4s} = range or difference between control measurements within a run exceeds 4s

Control rule definitions

4_{1s} =

four consecutive control measurement exceed the same x + 1s or x - 1s limit

10_{x} =

ten consecutive control measurements fall on one side of the mean

$1_{2.5s}$ =

one control measurement exceeds x ± 2.5s limits

3_{2s} =

three consecutive control measurements exceed x ± 2s limits

9_{x} =

nine consecutive control measurements fall on one side of the mean

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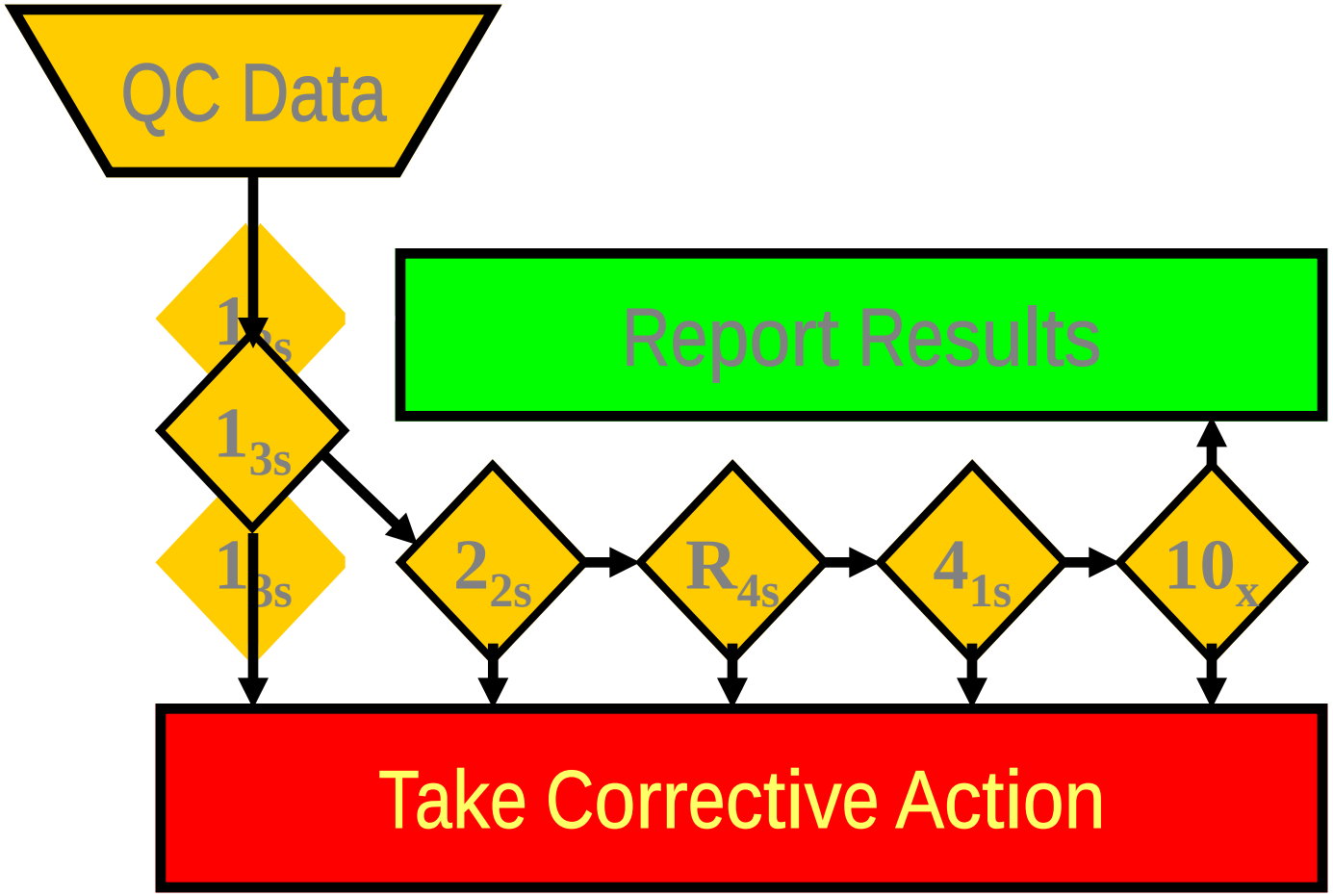
Westgard Multirules



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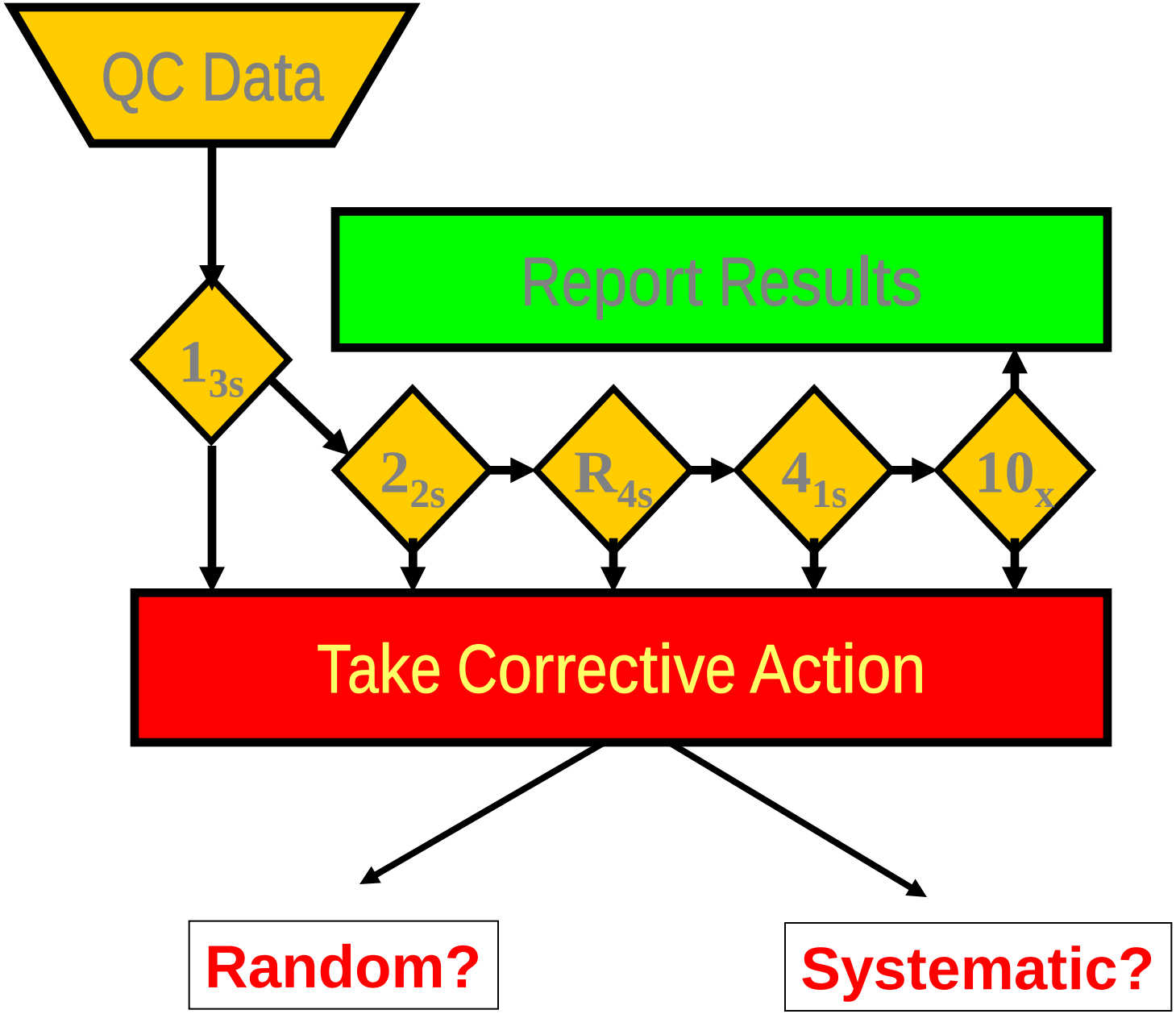

What do the Control Rules Detect?

Control Rule	Type of Error
1_{2S}	Warning
1_{3S}	Random
2_{2S}	Systematic
R_{4S}	Random
4_{1S}	Systematic
$10\,\bar{x}$	Systematic

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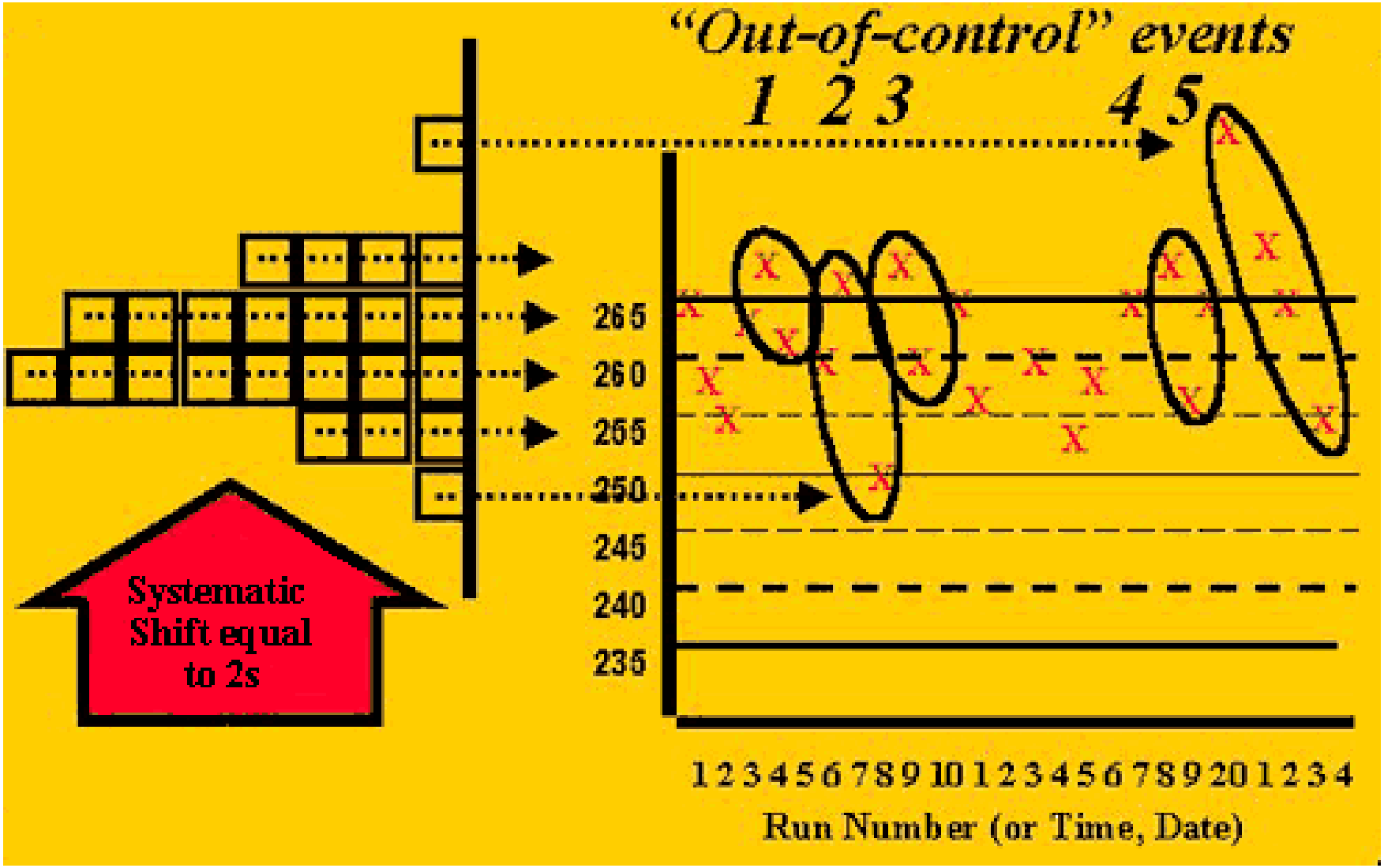
What Do You Do Now?

- Change Old Bad Habits - Recognize Problems:
  - Bad Habit #1: Repeat the control
  - Bad Habit #2: Try a new control
- Develop Good Habits - Solve Problems:
  - Good Habit #1: Inspect control charts or rules violated to determine type or error
  - Good Habit #2: Relate type of error to possible causes
  - Good Habit #3: Consider factors in common on multitest systems
  - Good Habit #4: Relate causes to recent changes
  - Good Habit #5: Verify the solution and document the remedy

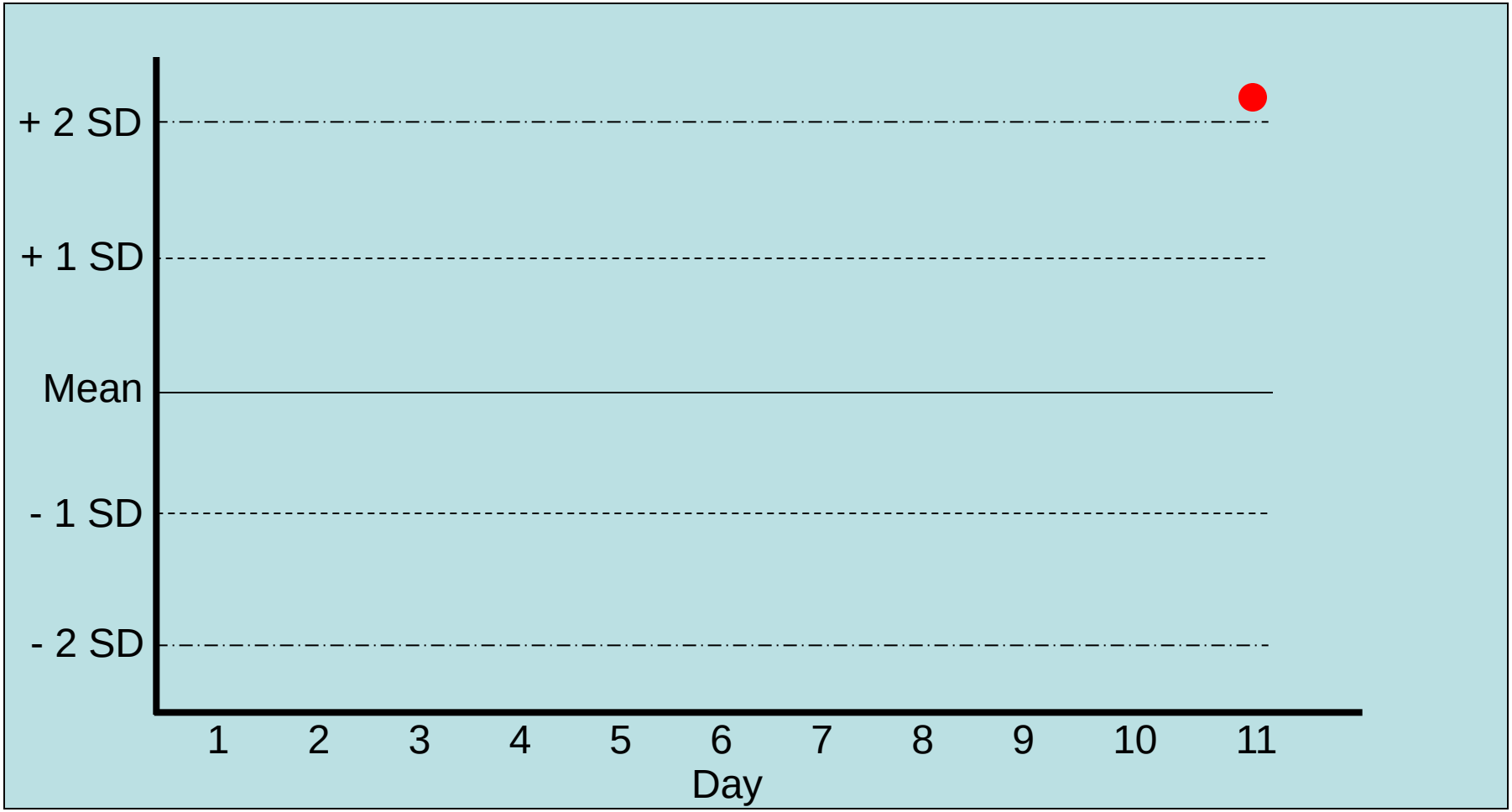
What are some causes?

Quality Control Issue	Possible Causes
Values shifting within range (Systematic)	•Inadequate mixing of controls •Controls left at suboptimal temperature for too long •Variation between controls (ranges) •Lot number change
Values shifting out of range (Systematic)	•Any of the reasons described above •Improper reconstitution of controls •Error in control concentration •Reagent contamination •Deterioration of controls •Instrument problem
Trend (Systematic)	•Instrument change: o Reaction temperature o Sampling problem o Reagent delivery problem o Detector Problem
Imprecision (Random)	•Improper mixing of reactions constituents •Contamination during testing •Pipetting variation •Electrical Supply

Analyze Your QC Data!!!!



HCV High Pos Control



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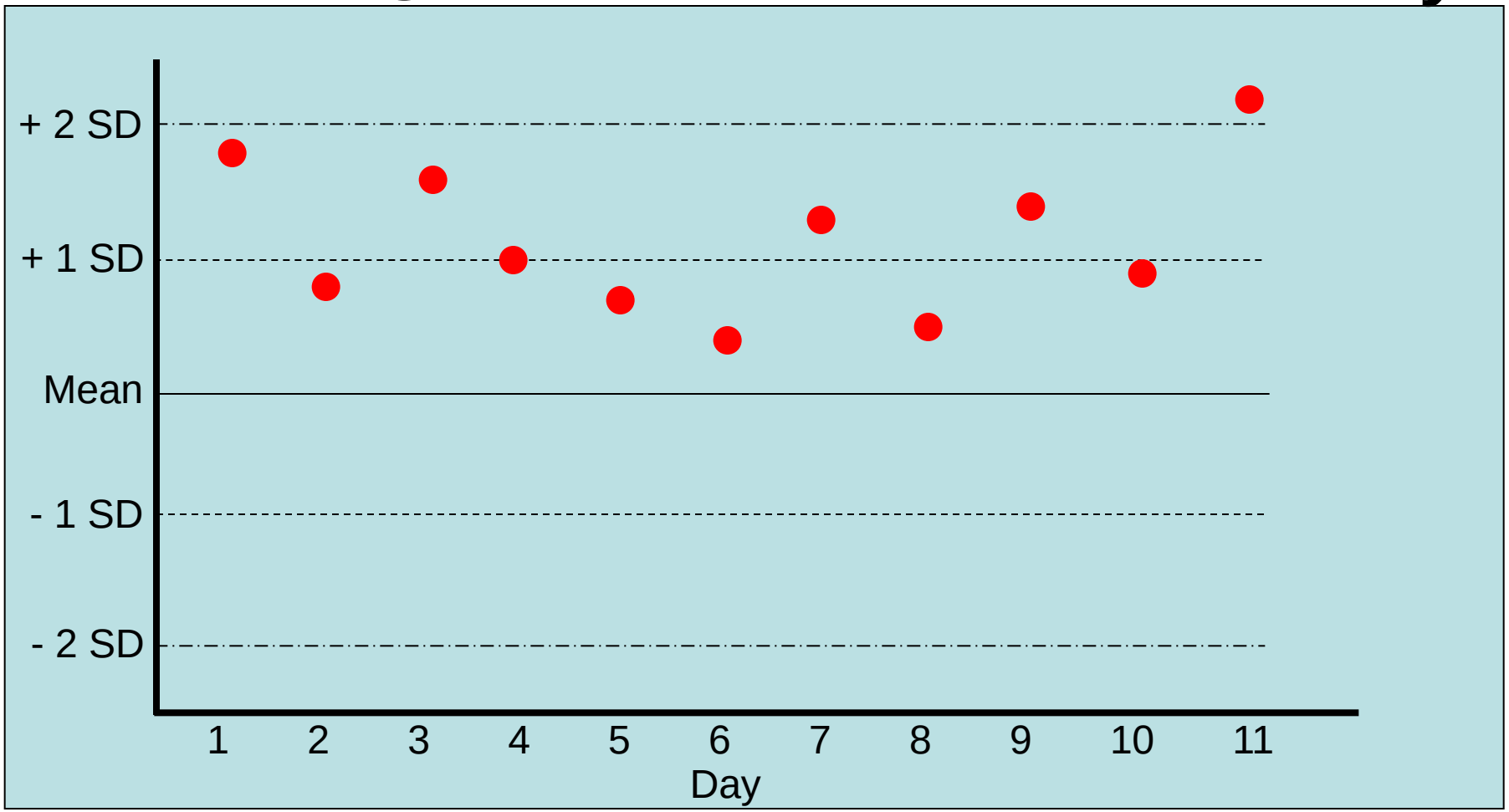
HCV 1_{2S} High Pos Control Run



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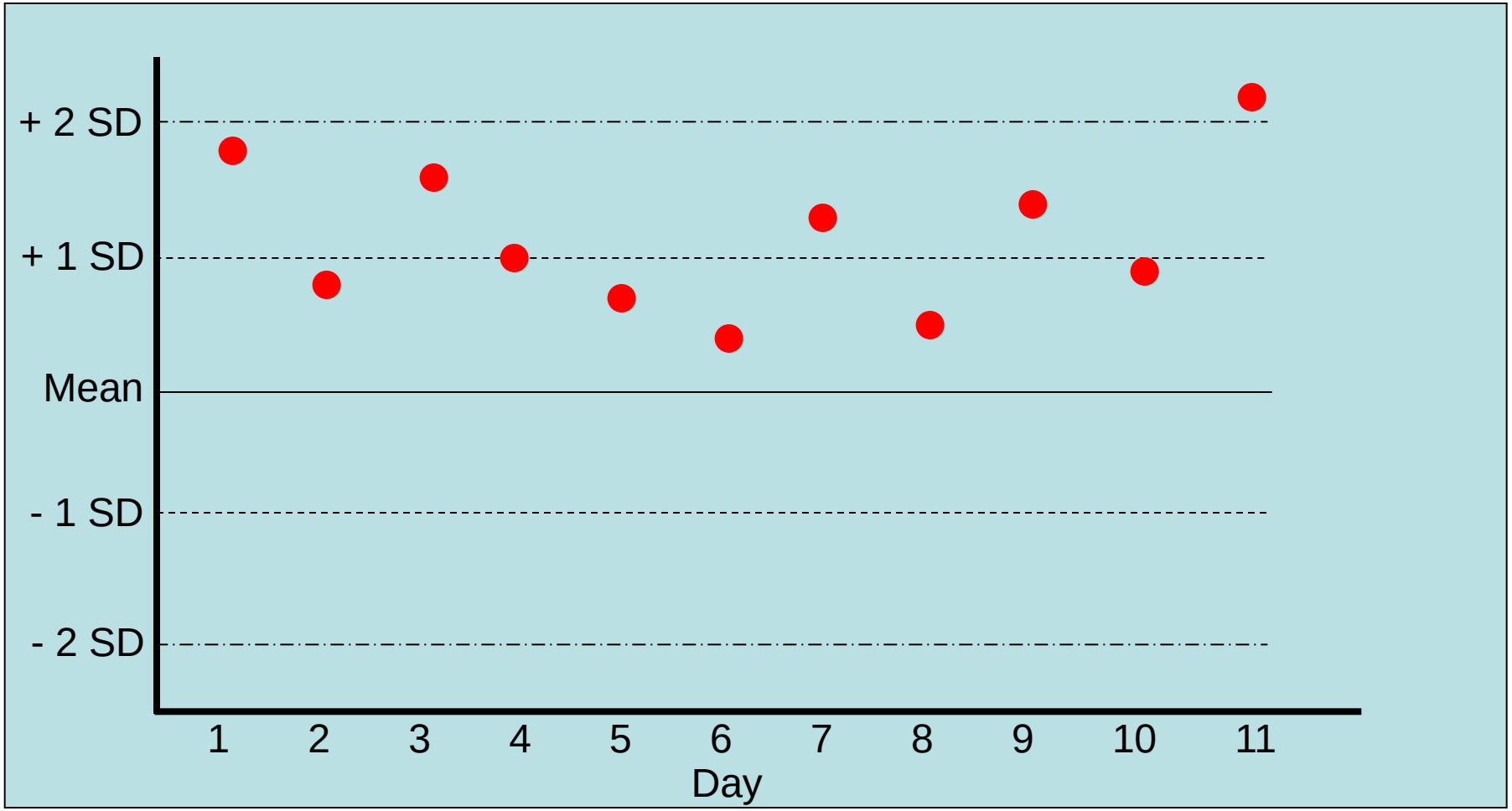
HCV 1_{2S} High Pos Control RemedyRL



New control values plotted using new control ranges

Are we controlling quality or just running controls?

- How do we know our control procedure is contributing to our quality?

control signal? analytical run	reject	accept
with error	true reject (TR)	false accept (FA)
without error	false reject (FR)	true accept (TA)

Probability for error detection = $P_{ed} = n_{tr}/(n_{tr} + n_{fa})$

Probability for false rejection = $P_{fr} = n_{fr}/(n_{fr} + n_{ta})$

- Ideally, P_{ed} will be 100% and P_{fr} will be 0%

On what does the performance of control procedures depend?

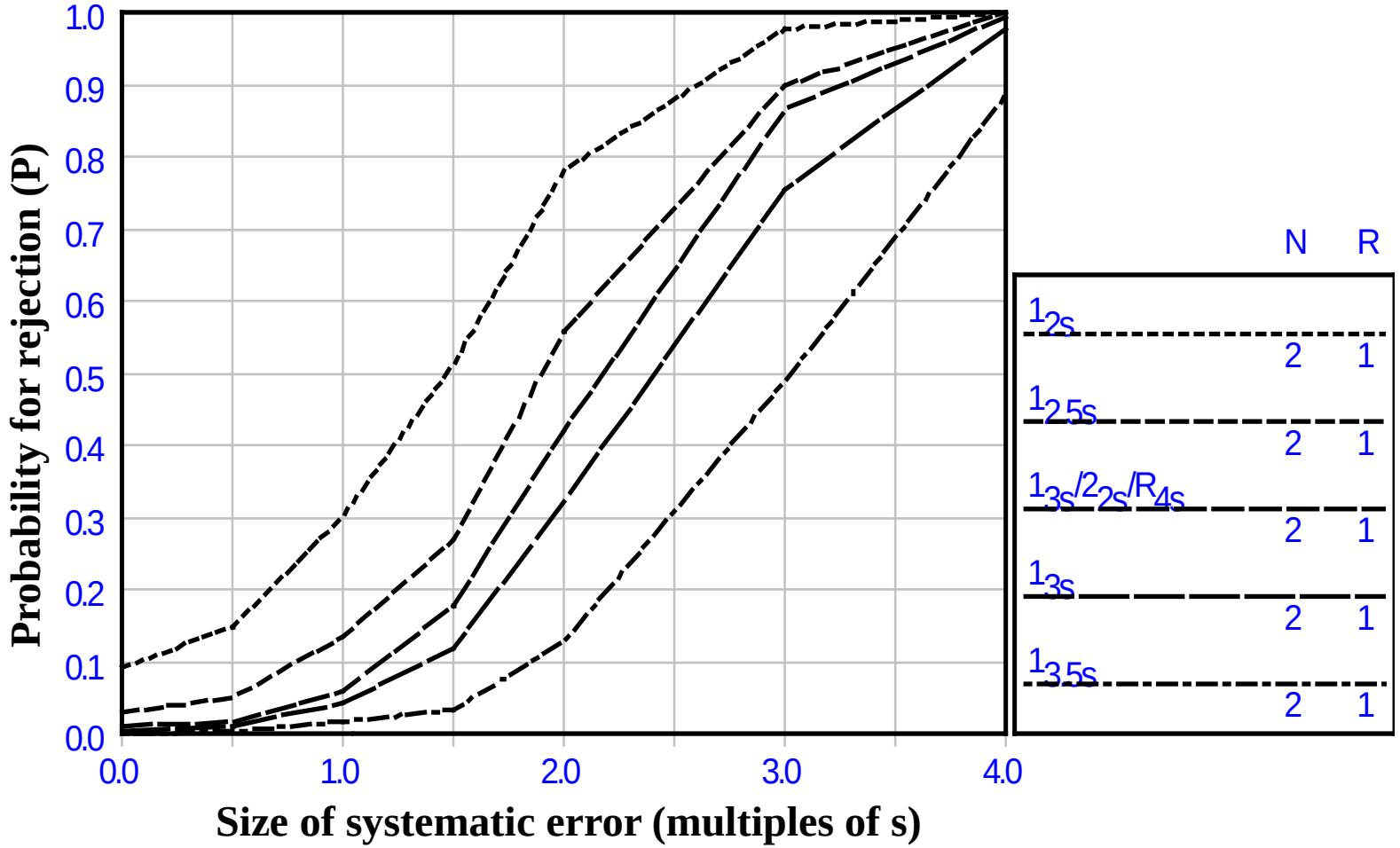
P_{ed} increases when:

- N increases
- Control limits are narrowed
- Fewer measurements in a row are required to exceed a limit

P_{fr} decreases when:

- N decreases
- Control limits are widened
- More measurements in a row are required to exceed a limit

“Power function graphs”
Response of N=2 QC Rules



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Important Definitions

- **Six Sigma:**
  - ➔Quantitative goal for process performance
    - Achieve “six sigma” performance
  - ➔Universal measure of process performance
    - Measure Defects Per Million (DPM) or Defects Per Million Opportunities (DPMO)
  - ➔A six sigma process is one that produces no more than 3.4 defects per million opportunities
  - ➔Goal of ≤ 3.4 DPMO is the current industry standard for many manufacturing processes
    - o Motorola: Six Sigma = 3.4 DPM
  - ➔Established by Motorola in 1985 to reduce number of manufacturing defects

What is a “defect”?

- A product that doesn’t meet specifications
  - Must define the specification or tolerance limits
  - Then compare product to specification
- A test result that is in error
  - Can use CLIA proficiency testing criteria as specifications or tolerance limits
  - Compare observed errors to allowable limits of error – if greater, it’s a defective result

Sigma Metric

Sigma = (TE_A - bias)/SD

- Sigma has no units
- All parameters in the equation should be of the same unit
- If units are in %, CV will replace SD at a specific medical decision concentration
- Bias will be expressed as % at the same medical decision concentration

Recommended Sigma values

- Higher sigma is better
- Sigma of **6.0** is the goal for world class quality
- Sigma of **3.0** is the minimum allowable sigma for routine production

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Sigma Metric and QC Design

- Sigma ≥ **6**, QC process is flexible. Keep false rejections low by using wide control limits - at least 3s.
- Sigma **~ 5,** N=2 or 3 with control limits of **2.5s** or **3.0s**.
- Sigma **~ 4,** N=4 to 6, use either the $1_{2.5s}$ single rule or a $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ multirule procedure.
- Sigma **< 4.0**, run all the control you can afford. In addition, increase the frequency of instrument function checks, performance validation checks, and preventive maintenance.
- Sigma **< 3.0**, look for a new and better method. You can't do enough QC to assure the quality of the test results

Sample Sigma performance levels

- Deaths per million airline passengers
  - >6 Sigma
- Lost baggage at airport
  - 4.2 Sigma (0.4% error)
- Firestone tire production (tire blow out that causes an accident)
  - 4.9 Sigma (0.04% error)

Healthcare processes

- 3.7 Sigma (1-2% error) is typical
- Emory University Hospital Na^+ Sigma = 2.4 = 184,060 DPM = 18.4% error rate
- Hmmm…worse than lost airport baggage???

The necessary Sigma performance level is not often known

- Manufacturing goal: 6 Sigma
- Airplane flights: >6 Sigma
- Your car stops when you press the brake pedal: >6 sigma

6 sigma experts

- **Green Belt**: a title for someone who is involved with a Six Sigma project "part-time.“
- **Black Belt**: someone who does Six Sigma "full time." Their entire work effort is focused on finding defects, wherever they might be, and eliminating them from the process.
- **Master Black Belt**: often designates an outside consultant who specializes in Six Sigma process improvements; these individuals provide training to others involved in process improvement.

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Who is this Man?

James O. Westgard, Ph.D.

Visit him at:
www.Westgard.com to learn more about more really cool QC stuff !!

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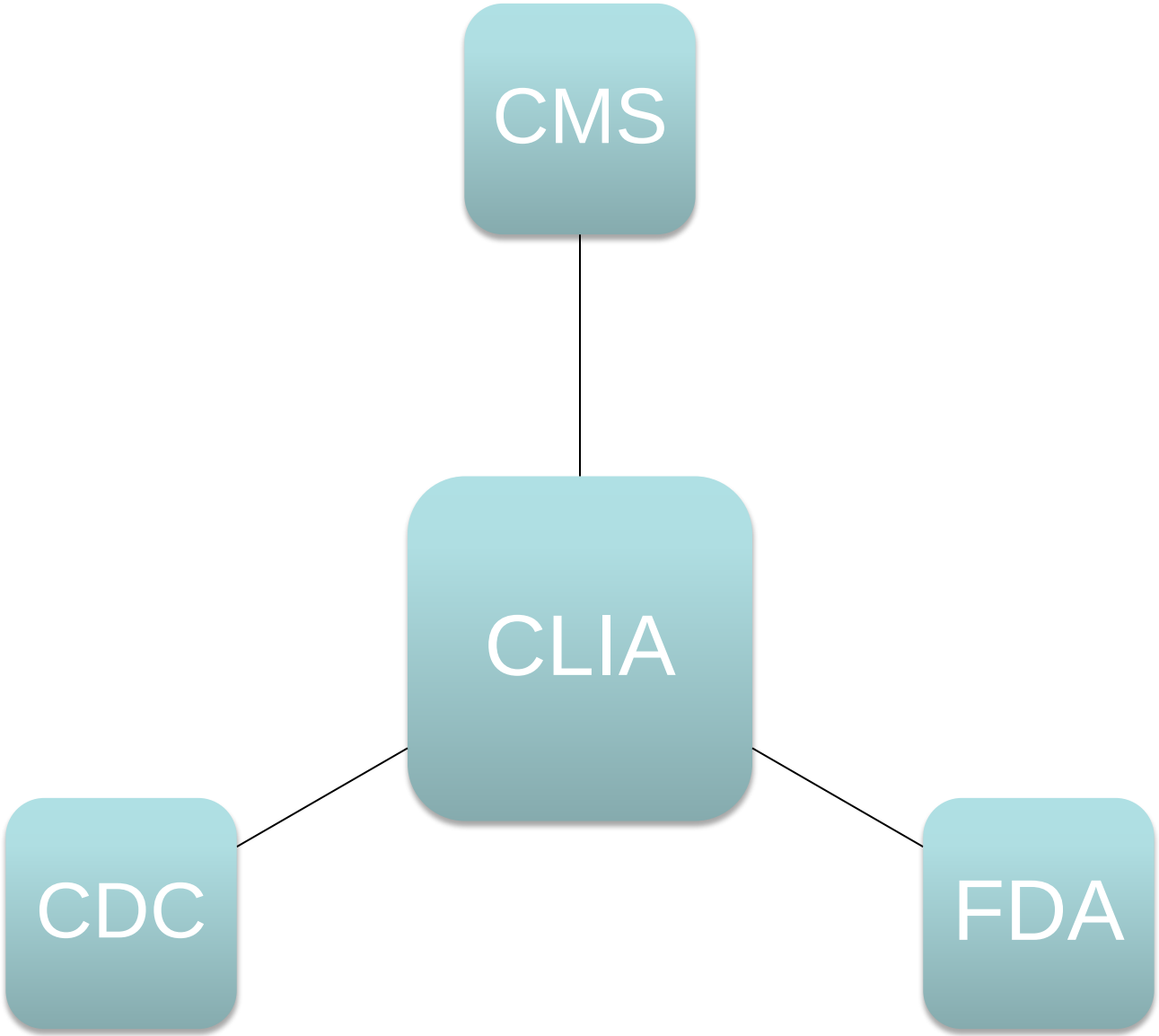
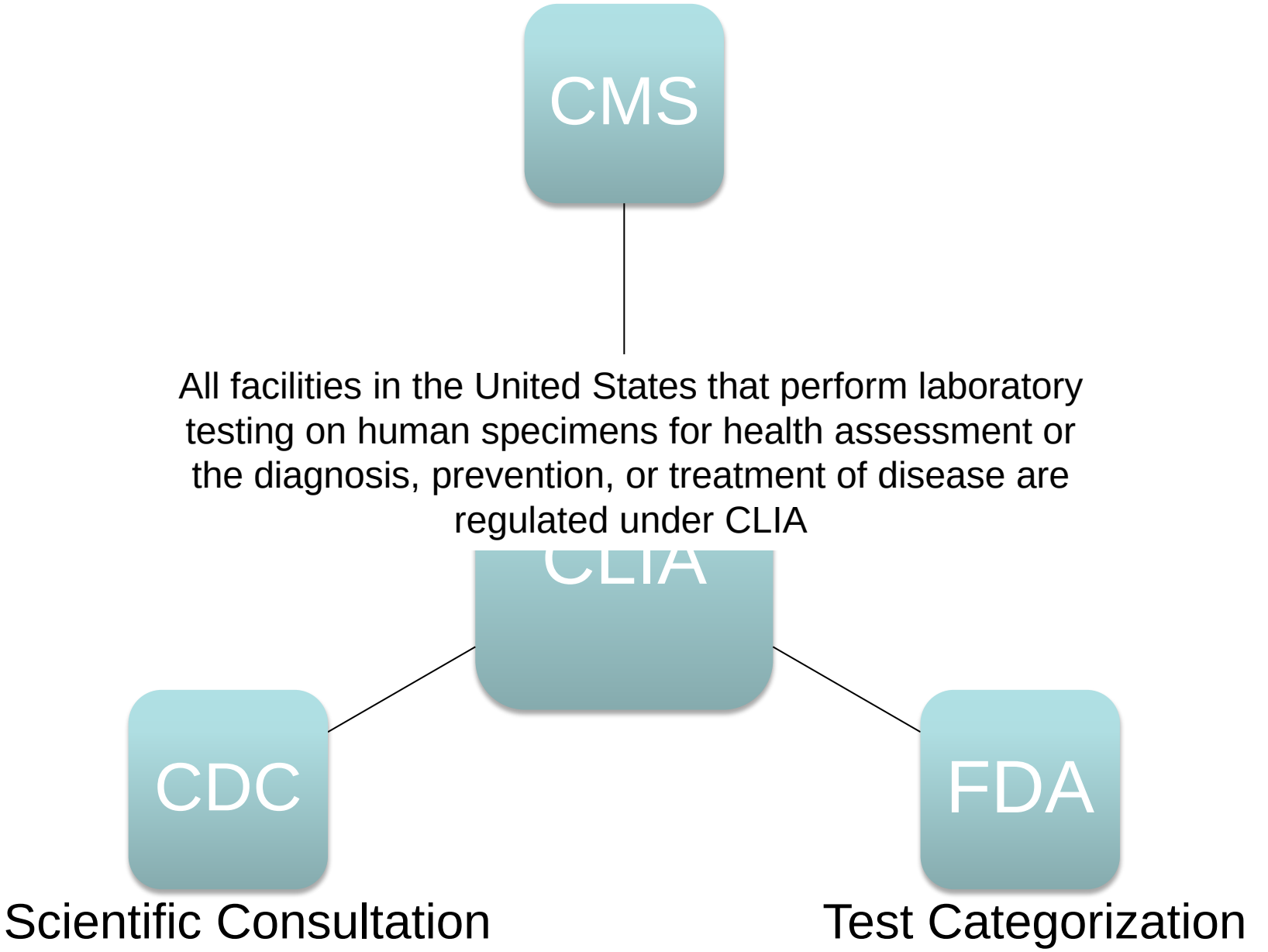
The light at the end of the tunnel!
Oswego, New York
Feb. 23, 2007

Regulatory



Clinical Laboratory Oversight



FDA test classification

Classification	Determining Factors	Oversight
Low Risk: the consequence of an incorrect result or incorrect interpretation is unlikely to lead to serious morbidity/mortality.	The test result is typically used in conjunction with other clinical findings to establish or confirm diagnosis. No claim that the test result alone determines prognosis or direction of therapy.	The laboratory internally performs analytical validation and determines adequacy of clinical validation prior to offering for clinical testing. The accreditor during the normally scheduled inspections will verify that the laboratory performed appropriate validation studies.
Moderate Risk: the consequence of an incorrect result or incorrect interpretation may lead to serious morbidity/mortality AND the test methodology is well understood and independently verifiable.	The test result is often used for predicting disease progression or identifying whether a patient is eligible for a specific therapy. The laboratory may make claims about clinical accuracy.	The laboratory must submit validation studies to the CMS-deemed accreditor for review and the accreditor must make a determination that there is adequate evidence of analytical and clinical validity before the laboratory may offer the test clinically.
High Risk: the consequence of an incorrect result or incorrect interpretation could lead to serious morbidity/mortality AND the test methodology is not well understood or is not independently verifiable.	The test is used to predict risk of, progression of, or patient eligibility for a specific therapy to treat a disease associated with significant morbidity or mortality, AND; The test methodology uses proprietary algorithms or computations such that the test result cannot be tied to the methods used or inter-laboratory comparisons cannot be performed.	The laboratory must submit test to FDA for review prior to offering the test clinically. CMS and accreditor determine compliance.

Clinical Lab Oversight

- CMS

- Accreditation Organizations (deemed organizations)

Accepted Accreditation Organizations

- College of American Pathologists (CAP)
- The Joint Commission (JC)
- Commission on Laboratory Accreditation (COLA)
- American Association of Blood Banks (AABB)
- American Osteopathic Association (AOA)
- American Society for Histocompatibility and Immunogenetics (ASHI)

Types of CLIA certificates

☐(1) Certificate of waiver (2) Certificate for PPM procedures (3) Certificate of registration or registration certificate (4) Certificate of compliance (5) Certificate of accreditation

☐**Certificate of Waiver** – This certificate is issued to a laboratory to perform only waived tests.
☐**Certificate for Provider-Performed Microscopy Procedures (PPMP)** – This certificate is issued to a laboratory in which a physician, midlevel practitioner or dentist performs no tests other than the microscopy procedures. This certificate permits the laboratory to also perform waived tests.
☐**Certificate of Registration** – This certificate is issued to a laboratory that enables the entity to conduct moderate or high complexity laboratory testing or both until the entity is determined by survey to be in compliance with the CLIA regulations.
☐**Certificate of Compliance** – This certificate is issued to a laboratory after an inspection that finds the laboratory to be in compliance with all applicable CLIA requirements.
☐**Certificate of Accreditation** – This is a certificate that is issued to a laboratory on the basis of the laboratory's accreditation by an accreditation organization approved by HCFA (now CMS).

2011 CLIA Stats

Total Labs	217,688
- Waived	141,585
- PPMP	39,630
- Compliance	20,302
- Accredited	16,171

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PT for CLIA Waived Tests?

- Surveys in testing sites with a Certificate of Waiver indicated:
  - high personnel turnover rates
  - lack of understanding about Good Laboratory Practices, and
  - inadequate training
- All can lead to errors in patient testing and poor patient outcomes

http://www.cdc.gov/mmwr/PDF/rr/rr5413.pdf

Question

- **If my lab only performs waived testing, am I required to perform PT?**

PT is not required for any test that is waived.

Growth of Waived Testing

TABLE 1. Increases in waived analytes and test systems, Certificate of Waiver laboratories, and Medicare Part B reimbursed waived testing, 1993–2004

Waived testing measurement parameter	1993	1998	2000	2003	2004
No. of analytes for which waived test systems are available	9	40	53	74	76
No. of waived test systems*	203	608	832	1,495	1,638
No. of laboratories with a Certificate of Waiver†	67,294	78,825	85,944	102,123	105,138
Percentage of laboratories with a Certificate of Waiver†	44%	50%	52%	57%	58%
No. of Medicare Part B reimbursed waived tests	NA§	NA	14,663,751	20,781,297	23,041,693
Percentage of Medicare Part B reimbursed laboratory testing that is waived	NA	NA	6.5%	7.8%	8.1%
Medicare Part B payment amount for waived tests	NA	NA	$69,765,453	$112,247,706	$128,169,398

*Numbers reflect multiple names under which individual tests are marketed and might include waived tests no longer sold.
†Does not include Clinical Laboratory Improvement Amendments (CLIA) exempt laboratories in New York and Washington.
§Not available.
Source: CDC and Food and Drug Administration CLIA Test categorization databases; Centers for Medicare & Medicaid Services (CMS) Medicare Part B Utilization for CLIA-covered Laboratory Services; and CMS On-line Survey, Certification, and Reporting database.

2013 No. of analytes for which waived test systems are available 111

http://www.cdc.gov/mmwr/PDF/rr/rr5413.pdf

Who is doing the training?

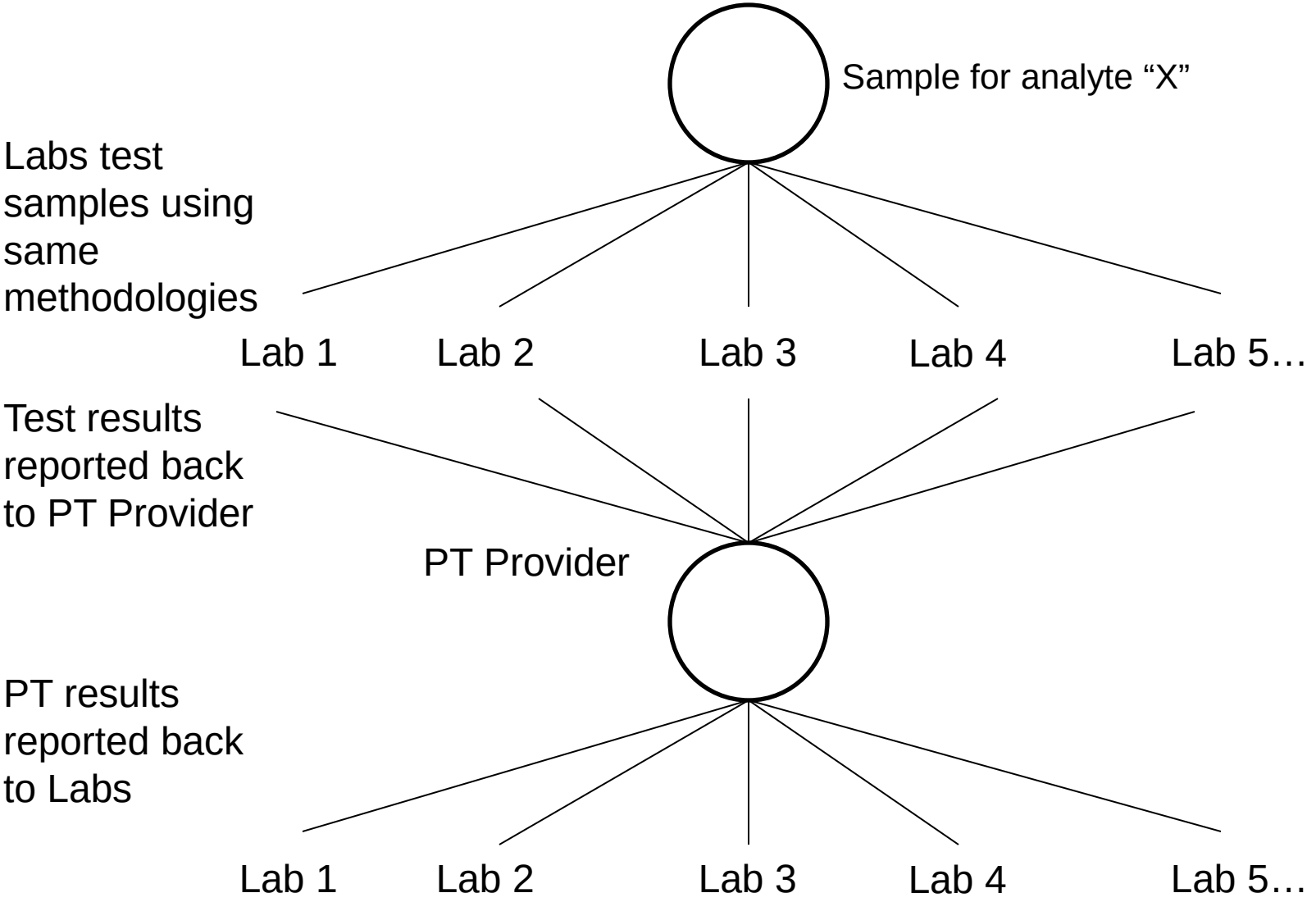
TABLE 4. Number and percentage of training providers for Certificate of Waiver testing personnel, by type of training provider, from the Centers for Medicare & Medicaid Services surveyed sites,* 2003–2004

Training provider	No.	(%)
Nurse	699	(33)
Manufacturer/Sales representative	329	(15)
Physician	220	(10)
In-service/Training coordinator	152	(7)
Other employees	144	(7)
Self-trained/Video	98	(5)
Director/Medical director	97	(5)
Medical assistant	92	(4)
Supervisor/Manager	42	(2)
Office manager	52	(2)
Laboratory director	49	(2)
Laboratory personnel	39	(2)
Hospital laboratory staff	37	(2)
Medical technologist/Medical laboratory technician	37	(2)
Laboratory consultant	19	(1)
Emergency medical technician/Paramedic	24	(1)
Pharmacist	23	(1)
Physician assistant	6	(<1)
Other	93	(4)
Physician testing only†	54	(2)
Training not documented	51	(2)

* N = 2,139 sites. A total of 3,317 sites were surveyed. However, all sites did not provide information on training sources, and some sites identified more than one training provider. All responses were included in the data.
† Sites did not specify who provided training to these physicians.

http://www.cdc.gov/mmwr/PDF/rr/rr5413.pdf

PT Programs –
Peer Group or Accuracy based



Proficiency Test Results – Peer Group

College of American Pathologists
325 Waukegan Road, Northfield, Illinois 60093-2750
800-323-4040 • http://www.cap.org
Advancing Excellence

CAP Number: 8661979-01 **Kit#** 1
Institution: Emory University
Attention: Ross Molinaro PhD
City / State: Atlanta GA 30322

Kit ID: 25348122
Kit Mailed: 9/17/2012
Original Evaluation: 10/24/2012

EVALUATION
ORIGINAL

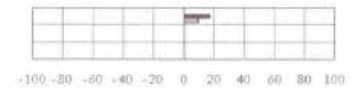
Y-B 2012 Ligand-Special

Test / Unit of Measure / Peer Group	Specimen	Your Result	Mean	S.D.	No. of Labs	Limits of Acceptability S.D.I	Lower	Upper	Your Grade
Testosterone	Y-04	412.0	412.74	25.25	27	0.0	336.9	488.6	Acceptable
ng/dL	Y-05	246.0	235.83	19.81	29	+0.5	176.4	295.3	Acceptable
MASS SPECTROMETRY	Y-06	68.4	66.46	6.31	28	+0.3	47.5	85.4	Acceptable

Evaluation and Comparative Method Statistics

Plot of the Relative Distance of Your Results from Target as Percentages of allowed Deviation

Survey -100----------Mean----------+100



Specimen	Calculated Quest Result (ng/dL)	Grade
Y-04	334.4	Not Acceptable
Y-05	207.7	Acceptable
Y-06	72.1	Acceptable

Specimen	Calculated UCSF Result (ng/dL)	Grade
Y-04	413.1	Acceptable
Y-05	248.4	Acceptable
Y-06	72.2	Acceptable

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Proficiency Test Results – Accuracy Based

2012 GH2-B (fresh pooled samples)

		GH2-04			GH2-05			GH2-06 (HbAS)		
NGSP Reference Value (%HbA1c)*		5.40			8.30			5.65		
	no. labs	Mean %HbA1c	Mean bias	% CV	Mean %HbA1c	Mean bias	% CV	Mean %HbA1c	Mean bias	% CV
* Abbott Architect c	83	5.40	0.00	4.4	8.28	-0.02	3.8	6.80	1.15	3.4
* Axis-Shield Afinion	23	5.54	0.14	4.1	8.10	-0.20	3.4	5.65	0.00	3.5
* Bayer (Merika) A1cNOW*	23	5.05	-0.35	4.0	7.49	-0.81	6.2	6.31	0.66	4.9
* Beckman AU system	37	5.34	-0.06	3.3	8.15	-0.15	3.9	6.66	1.01	3.6
* Beckman Synchron LX Systems	17	5.49	0.09	4.0	8.22	-0.08	3.2	5.62	-0.03	6.5
* Beckman UniCel DxC Synchron	268	5.39	-0.01	3.3	8.24	-0.06	3.3	5.48	-0.17	3.1
* Bio-Rad D-10	230	5.55	0.15	2.9	8.50	0.20	2.5	5.80	0.15	3.0
* Bio-Rad in2it	11	5.30	-0.10	5.2	8.13	-0.17	3.9	5.55	-0.10	7.1
* Bio-Rad Variant II	103	5.32	-0.08	2.7	8.36	0.06	2.3	5.68	0.03	3.7
* Bio-Rad Variant II Turbo	174	5.40	0.00	2.9	8.42	0.12	2.5	5.66	0.01	4.2
* Bio-Rad Variant II Turbo 2.0	48	5.50	0.10	2.1	8.52	0.22	1.9	5.96	0.31	3.8
* Roche Cobas c311	15	5.50	0.10	5.0	8.33	0.03	5.8	5.70	0.05	12.2
* Roche Cobas c500/700	262	5.50	0.10	2.5	8.12	-0.18	2.5	5.61	-0.04	2.6
* Roche Cobas Integra 400	51	5.47	0.07	3.2	8.40	0.10	3.8	5.65	0.00	3.3
* Roche Cobas Integra 800	145	5.51	0.11	2.5	8.26	-0.04	2.0	5.65	0.00	2.4
* Siemens Advia A1c_3 Reagent	59	5.56	0.16	5.7	8.54	0.24	5.6	5.90	0.25	6.9
* Siemens DCA 2000/2000+	58	5.46	0.06	2.8	8.28	-0.02	3.0	5.77	0.12	3.1
* Siemens DCA Vantage	261	5.44	0.04	2.6	8.17	-0.13	2.6	5.78	0.13	2.8
* Siemens Dimension ExL new reagent	113	5.67	0.27	3.3	8.08	-0.22	3.1	5.90	0.25	3.7
* Siemens Dimension RxL new reagent	131	5.70	0.30	3.4	8.18	-0.12	3.6	5.92	0.27	3.0
* Siemens Dimension RxL orig reagent	11	5.55	0.15	2.8	8.09	-0.21	2.6	5.82	0.17	2.5
* Siemens Dimension Vista new reagent	192	5.72	0.32	4.0	8.61	0.31	2.8	5.95	0.30	3.4
* Siemens Dimension Xpand new reagent	69	5.66	0.26	3.3	8.10	-0.20	2.8	5.90	0.25	3.5
* Siemens Dimension Xpand orig reagent	13	5.65	0.25	2.6	8.13	-0.17	2.1	5.76	0.11	2.6
* Tosoh G7 Auto HPLC	145	5.65	0.25	2.1	8.61	0.31	1.8	5.65	0.00	2.1
* Tosoh G8 Auto HPLC	284	5.62	0.22	1.5	8.58	0.28	1.3	5.64	-0.01	1.8
* Trinity Biotech HPLC (Affinity)	30	5.53	0.13	1.8	8.28	-0.02	2.3	5.69	0.04	1.8
* Vitros 5,1 FS Chem Syst	212	5.28	-0.12	2.0	8.10	-0.20	2.4	5.41	-0.24	2.6

* = NGSP certified at the time of the survey

http://www.ngsp.org/CAP/CAP12b.pdf

Question

- **If I have more than one testing site, do I need to enroll in PT for each site?**

PT enrollment and participation is required for **each CLIA certificate**

Professional Practice in Clinical Chemistry

Frequency

- PT must be performed for the required tests
- Typically three sets of five specimens are sent to labs for PT each year
- For the majority of lab disciplines, satisfactory grade is ≥80%
  - ABO group and D (Rho)t tying is 100%
  - Blood bank compatibility testing is 100%

Passing PT

- If a set of 5 specimens is received, at least 4 out of the 5 must pass
- If <4 pass, the lab must achieve ≥80% acceptability on the next 2 PT surveys
- If fail again within 2 surveys, the lab's PT is considered unsuccessful for that analyte
  - Increased scrutiny put on lab
  - Investigation

Professional Practice in Clinical Chemistry

CLIA Performance Measures Proficiency Testing (PT)

- Laboratories conducting moderate and/or high complexity testing are required to participate in PT for certain tests they perform

- PT is also educational and involves sending samples with results unknown to the laboratory, three times per year to evaluate whether the laboratory's results are accurate and compare to its peers. The CLIA regulation requires that the PT samples be tested in the same manner and by the same individuals as patient testing. PT samples are provided by private non-profit organizations, Federal, or State agencies. PT programs undergo an annual and ongoing regulatory review conducted by CMS.

Question

- **How do I verify the accuracy of the tests that do not have PT required?**

One way to check the accuracy of testing:

  - Split a patient's specimen (NEVER SPLIT A PT SAMPLE) with another laboratory that offers the same test(s). Review your results and the other laboratory's results for acceptability.

Self Assessment Questions

1. Reproducible inaccuracies that are consistently in the same direction define which of the following?
   a) **Systematic error**
   b) Imprecision
   c) Random error
   d) Dissociative statistics

2. Which of the following is true regarding Sigma metrics?

a) All parameters in the equation should be of different units

b) With a Sigma < 3.0, your method is considered performing at 3.4 defects per million opportunities

c) Sigma has no units

d) None of the above

3. All facilities in the United States that perform laboratory testing on human specimens for health assessment or the diagnosis, prevention, or treatment of disease are regulated under which of the following?

a) Food and Drug Administration
b) College of American Pathology
c) Clinical Laboratory Improvements Amendment
d) Centers for Disease Control and Prevention

4. The satisfactory grade for proficiency testing in the clinical laboratory is always at least:

   a) 100%
   b) 50%
   c) 25%
   d) None of the above