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Performance Standards for Established Clinical Laboratory Tests

by

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Simple Ideas, Better Solutions

Session Objectives

- **Define Performance Standards**
- **Explain how to find existing TEA for your Laboratory's established tests.**
- **Describe what to put in the parameters screen boxes for EE modules that use allowable error.**
- **Explain how to compute TEA when CLIA or CAP says to use $\pm 3SD$**

What Are Established Tests?

- Analytes cleared or approved by the FDA
- Included in peer group assessments from PT providers such as the CAP, AABB, NYS, or EQAS.
- Home-brew, LDTs, new, and novel tests are not included in this group.
- *MDx, semi-quant may use different “models” for determining performance standards.

Your Data has error

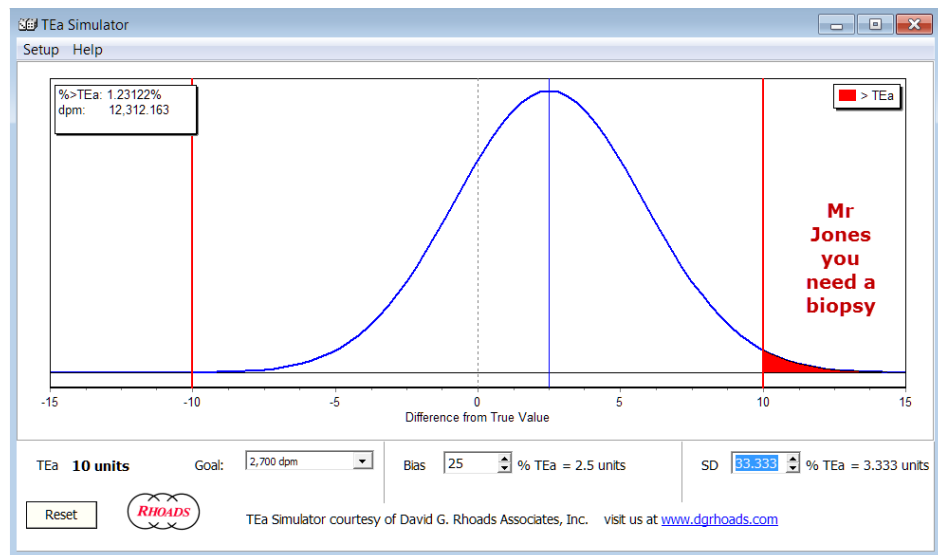
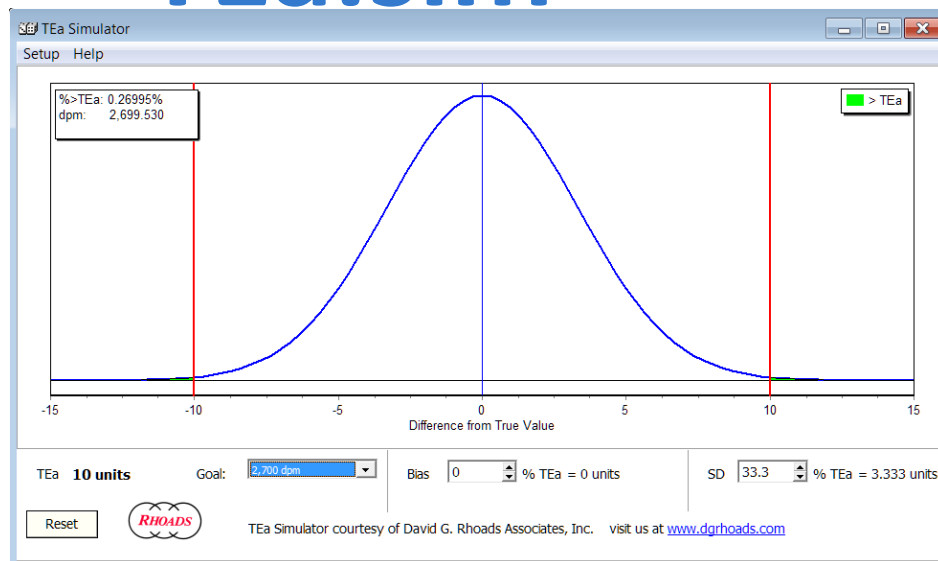
(you knew this!)

- If you report a single measured result, it includes the true result plus some error.
- The error around the result is its uncertainty
- Uncertainty is composed of random error, the bias to the true value, and factors that occur infrequently like carryover, and non-specificity
 - This session will only discuss bias and random error
- How much error can your lab accept for a method?
 - 5% ? A 2 sigma test 45,000 dpm
 - 0.3% ? A 3 sigma test 2,700 dpm
 - 0.0003% A 6 sigma test 3.4 dpm
- A specification for the amount of allowed error is called Total Allowable Error. Non technical terms might be “Performance standards, performance limits, or performance Goals.

Performance Standards

- **Allowable Error for Clinical Laboratory Tests**
- **Per CLIA, your laboratory is responsible for defining a policy or *specification* for the amount of *Total Allowable Error (TEa)* medically or administratively acceptable for your methods.**
- **The TEa established by the lab is used as the pass/ fail criteria for many modules in EP evaluator.**

TEa.sim



TEA formula and Sigma

$$\text{TEa} = \text{SEa} + f * \text{REa}$$

f = factor of 2 for +/- 2SD

f = factor of 3 for +/- 3 SD

- +/- 2SD corresponds to 95% of data (2 sigma)
- +/- 3SD corresponds to 99.7% of data (3 sigma)
- +/- 6SD corresponds to 99.9993% of data (6 sigma)

- Sigma = (TEa% – bias%)/lab CV

TEa includes both bias and imprecision

- **The EP Evaluator Calibration Verification experiment assesses bias to the true value.**
 - True value standards are required.
 - Value assigned
 - Mean results from a large peer group are often accepted
 - Best practices recommend measuring at least 3 replicates.
 - SEa is a fraction of the TEa.
- **Early definitions of TEa used a 2 SD model meaning that 95% of the measured results were expected to be within the TEa**
- **CLIA, CAP, New York State and others use a 3 SD model to predict that 99.7% of your data will be within TEa.**

How Are Performance Standards Used?

- Performance Standards include two concepts:
 1. **Allowable systematic error (SEa)**
 - Accuracy
 - Bias vs a “true” value:
 2. **Allowable random error (REa)**
 - Precision
 - Target SD values for routine QC
- These two components define the quality specifications of our primary product:

Patient Results

Trueness, Accuracy, and Bias

- People get these terms confused
- Over the years, accuracy and bias have taken on new connotations.
- Point estimate – your single measured result which includes bias and imprecision
- If you are regulated by CLIA and must perform calibration verification which includes the term accuracy, that is referring to the element of bias:
 - Bias implies that imprecision is zero.
 - True values reference materials must be used.

ISO Definitions for Trueness and Accuracy

Trueness

- The **bias** between a lab's **average value** from a **huge** series of test results and an accepted reference value which is also the mean of a huge set of data)
- Data Source: **EQC** – monthly summary compared to group mean. (peer or All method)
- Monthly summary can be expressed as a mean +/- SD
- if TEA is the basis for the analytical goal, then a defined % of TEA is used to assess Trueness.
- $SEA = (25 - 50)\% TEa$

Accuracy

- Bias between a lab's **single** measured value and the true value
- Data Source : **EQA** (PT surveys)
- Single lab value compared to group mean (peer or All method)
- Imprecision is embedded in the single lab result.
- Therefore if TEA is the basis for the analytical goal, then 100% of TEA is used to assess accuracy.
- $SEa = 100\% TEa$

Performance goals CLSI EP15

- Trueness (bias). Trueness goals for bias should be stated as the maximum allowable bias, at each analyte concentration to be tested, that is not exceeded with certain probability.
 - Maximum allowable bias may be expressed in either absolute or relative terms—that is, either as a deviation, in concentration units, or as a percent deviation, as either an absolute concentration or as a percentage of the concentration
- Accuracy - total error – the sum of any set of defined errors that can affect the accuracy of an analytical result;
 - CLSI EP15 defines total error as the combination of bias and imprecision

Overall Accuracy

- **Overall Accuracy = Bias – when your “standards” are peer group assessments**
- **Use SEA = 100% of TEA**
- **Why?**
 - Your peer group mean includes the element of imprecision. AND
 - You are only interested in determining if your results are within the total error and do not care to evaluate bias

Simple Accuracy Module

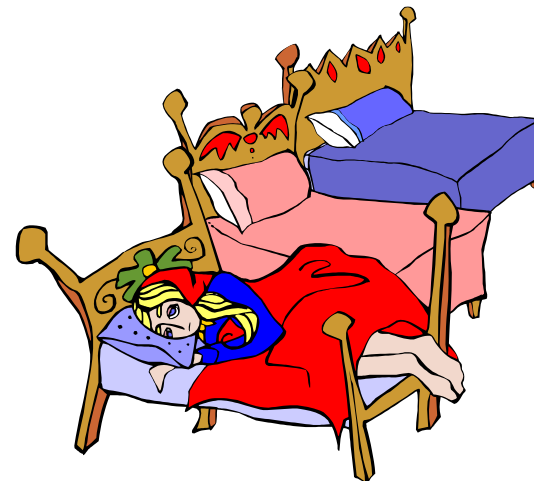
- Use for Overall Accuracy
- When your regulatory agency says you are accurate if your recovery is within the manufacturer's guidelines
- the “standards” you use are provided by the manufacturer and the target values are expressed as a low to a high range.
- At least 2 levels with 2 replicates each are required
- **Pass** means that both levels recover within the target range.

The Trueness Module in EE 11

- Satisfies the French COFRAC requirement, and the ISO 15819 recommendation to assess Trueness and Uncertainty
- Data from External Quality Control (EQC) or External Quality Assurance (EQA) programs
- Quantifies the lab's bias compared to their peer group.
- Evaluates uncertainty using available bias and precision components.
- Calculates sigma using EQC data

TEa Implications

- If too large, the ability to correctly interpret results is compromised
- If too small, the costs for keeping the process in control become excessive
- The “just right” TEa allows accurate interpretation of clinical issues, and reasonable process control costs.



Sodium Example – Case 1

- Sodium Ref interval = 136 – 144
- Case 1: TEa is too big. (TEA = +/- 9)
 - QC 140 ± 3 mmol/L (1 SD)
 - ± 3 sd becomes 131 to 149
 - Completely covers the ref interval so that any discrimination between health and disease is impossible
- TEA should never be wider than the reference interval
- Typical SD is 1 mmol/L @ 140 – mid normal range

Sodium Example Case 2

- Sodium Ref interval = 136 – 144
- Case 2: TEa is too small. (TEA = +/- 0.3)
 - QC: 140 ± 0.1 mmol/L (1 SD)
 - ± 3 SD becomes 139.7 to 140.3
 - Fails because cost to maintain process control is excessive.
- TEA should never be smaller than the last reportable digit.
- Typical sd is 1 mmol/L @ 140 – mid normal range
- CLIA TEa is +/- 4 mmol/L

Error Budget

- **Systematic error (SEa):**
 - Error in one direction (i.e., bias)
- **Random Error (REa):**
 - Unpredictable positive or negative error;
 - Close to the target SD for your routine QC specimens
- **TEa = SEa + (factor × REa):**
 - Our examples use a factor of 3, which equals a total random error of +/- 3SD (99.7% of the precision data)
- **Typical error budgets in EP Evaluator:**
 - 25% to 50% for SEa
 - The remainder for REa
- **Sigma = (TEa% – bias%)/lab CV**

Use of Performance Standards in EP Modules

- **TEa required:**
 - CLSI EP-10 for linearity and precision
 - Method Comparison: CLSI EP-9, 2IC and MIC
- **TEa optional:**
 - Alternate Method Comparison (AMC)
 - Trueness
- **SEa required:**
 - Linearity/Calibration Verification
- **REa optional:**
 - Simple Precision, Complex Precision
- **REa required:**
 - Precision in Linearity/Calibration Verification

Where Can You Find CLIA Limits?

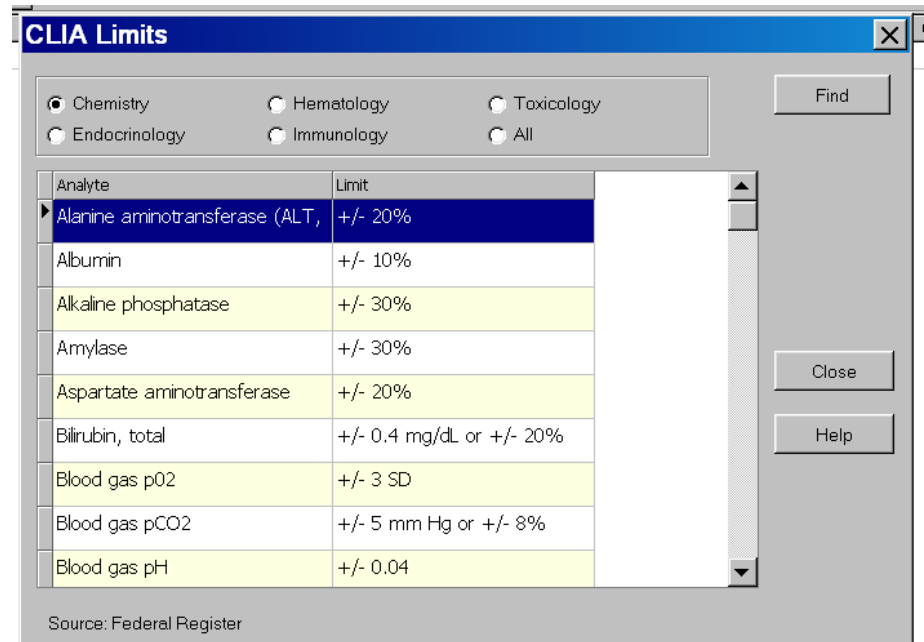
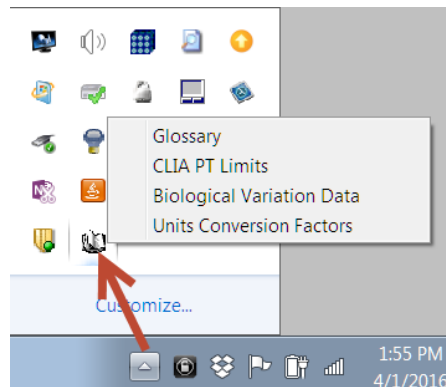
- www.cms.hhs.gov/clia

- **EP Evaluator**

 - Tools/CLIA PT Limits

 - windows toolbar 

 - EE reference tools book



A screenshot of a software application window titled "CLIA Limits". The window has a blue title bar and a grey background. It contains a table of analytes and their limits, along with several buttons and a source note.

Analyte	Limit
Alanine aminotransferase (ALT,	+/- 20%
Albumin	+/- 10%
Alkaline phosphatase	+/- 30%
Amylase	+/- 30%
Aspartate aminotransferase	+/- 20%
Bilirubin, total	+/- 0.4 mg/dL or +/- 20%
Blood gas pO2	+/- 3 SD
Blood gas pCO2	+/- 5 mm Hg or +/- 8%
Blood gas pH	+/- 0.04

Source: Federal Register

The application window also features a "Find" button, a "Close" button, and a "Help" button. At the top, there are radio buttons for "Chemistry", "Hematology", "Toxicology", "Endocrinology", "Immunology", and "All".

Other resources for Performance Standards

- In your EE software program folder on your computer or network drive : EE\Resources
 - “Rhoads Suggested Performance Standards.pdf”
- www.datainnovations.com/products/ep-evaluator/documentation
- Tables of Essential Clinical Laboratory Statistics
 - Allowable Total Error Table from eight sources
 - CLIA '88,
 - College of American Pathologists (CAP),
 - Wisconsin State Laboratory of Hygiene,
 - Wadsworth Center of the New York State Department of Health,
 - American Association of Bioanalysts (AAB),
 - the Royal College of Pathologists of Australasia and the Australasian Clinical Biochemist association Quality Assurance Program,
 - Canadian Fixed limits from the College of Physicians and Surgeons of Saskatchewan,
 - and the 2004 update of the Spanish Society of Clinical Chemistry and Molecular Pathology (SEQC) table of Desirable Quality Specifications based on Biological Variation.

Fill in the boxes

- In the parameters screen

Allowable Error Criteria		
	Conc	Pct
Allowable Total Error (TEa)	<input type="text" value="6.0"/>	<input type="text" value="10.0"/>
% for Systematic Error	<input type="text" value="25"/>	
% for Random Error	<input type="text" value="25"/>	

- In the policy definition\analyte settings screen

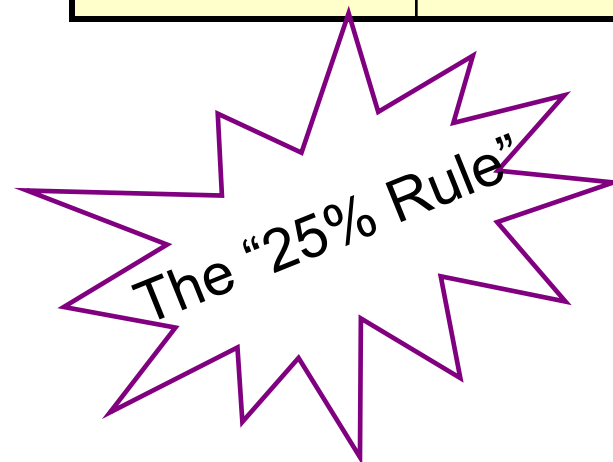
Analyte Parameters - Key											
Edit											
Analyte	Allowable Total Error		Err Bgt		Reportable Range		Low Proximity Limit		High Proximity Limit		L
	Conc	Pct	SE %	RE %	Low	High	Conc	Pct	Conc	Pct	
I GLUCOSE	6	10	50	25	0	600	6			50	

Establish your Error Budget

For your daily QC sd target and your maximum allowed bias
(How Is Your Daily QC SD Related to TEa?)

- First establish your TEa goal.
- Then, it is relatively simple to target your daily QC SD goal.
- IF
 - Systematic error is 25% of total error (i.e., systematic error budget is 25%)
 - $SEa/TEa = 25\%$
- THEN
 - 75% of TEa is left for total random error .
 - $1\text{ SD} = REa/3$ or
 - 25% of TEa

75% REa	1 SD = TEa/4
	1 SD = TEa/4
	1 SD = TEa/4
25% SEa	SEa



Ref: Ehrmeyer, S., Laesslg, RH., et.al.

"1990 Medicare/CLIA Final Rules for Proficiency Testing: Minimum Intralaboratory Performance Characteristics (CV and Bias) Needed to Pass"

CLIN. CHEM.36/10, 1736-1740 (1990)

SDs from TEa

- Example 1: 25% rule
- Typical +/- 3 SD model

- Example 2: 50% SEa example
- Some available standards have more expected bias

75% REa	1 SD = TEa/4
	1 SD = TEa/4
	1 SD = TEa/4
25% SEa	SEa

50% REa	1 SD = TEa/6
	1 SD = TEa/6
	1 SD = TEa/6
50% SEa	SEa

If you expect a large bias, then your sd goal will need to be smaller in order for for 99.7% of data to fall within your target TEA goal.

Create a target SD goal to define REa

For a +/- 3 SD model

- 99.7% of your data is targeted to be within TEA
- Define TEA
- Define SEA (bias)
- What percent of the total is left?
- Divide by 3 and enter into the REA box.

For a +/- 2 SD model

- 95% of your data is targeted to be within TEA
- Define TEA
- Define SEA (bias)
- What percent of the total is left?
- Divide by 2 and enter into the REA box.

Linearity and Calibration Verification Module

TEa and SEa entry

File Edit Module Experiment RRE ERI View Utilities Tools Help

Instrument: ASSAYER2 Analyte: GLUCOSE

GLUCOSE: Recovery Plot

Spec ID	Assigned	Mean	% Rec.	Resid
CalKit-1	25.0	25.0	100.0	4.5
CalKit-2	100.0	101.0	101.0	3.4
CalKit-3	250.0	247.7	99.1	-4.2
CalKit-4	400.0	406.3	101.6	0.3
CalKit-5	600	588.7	98.1	-23.0
CalKit-6	750	785.0	104.7	19.1

Accuracy and Linearity

Spec ID	Assgn'd	Mean	% Rec.	Resid
CalKit-1	25.0	25.0	100.0	4.5
CalKit-2	100.0	101.0	101.0	3.4
CalKit-3	250.0	247.7	99.1	-4.2
CalKit-4	400.0	406.3	101.6	0.3
CalKit-5	600	588.7	98.1	-23.0
CalKit-6	750	785.0	104.7	19.1

Linearity Parameters

General Parameters

Units: mg/dl Max decimal places: Auto Reagent Lot: []

Analyst: Kate Doe Date: 01 Jun 2000 Max # Replicates: 3

Instrument: ASSAYER2 Analyte: GLUCOSE

Specimens and Assigned Values

CalKit-1	25.0
CalKit-2	100.0
CalKit-3	250.0
CalKit-4	400.0
CalKit-5	600
CalKit-6	750

Report Options

Calibration Verification

Confirm Linearity Confirm Precision

Confirm Accuracy Calculate Probability Proficiency Test F

Confirm Reportable Range

Comment: []

Allowable Error Criteria

Allowable Total Error (TEa) Conc: 6 Pct: 9

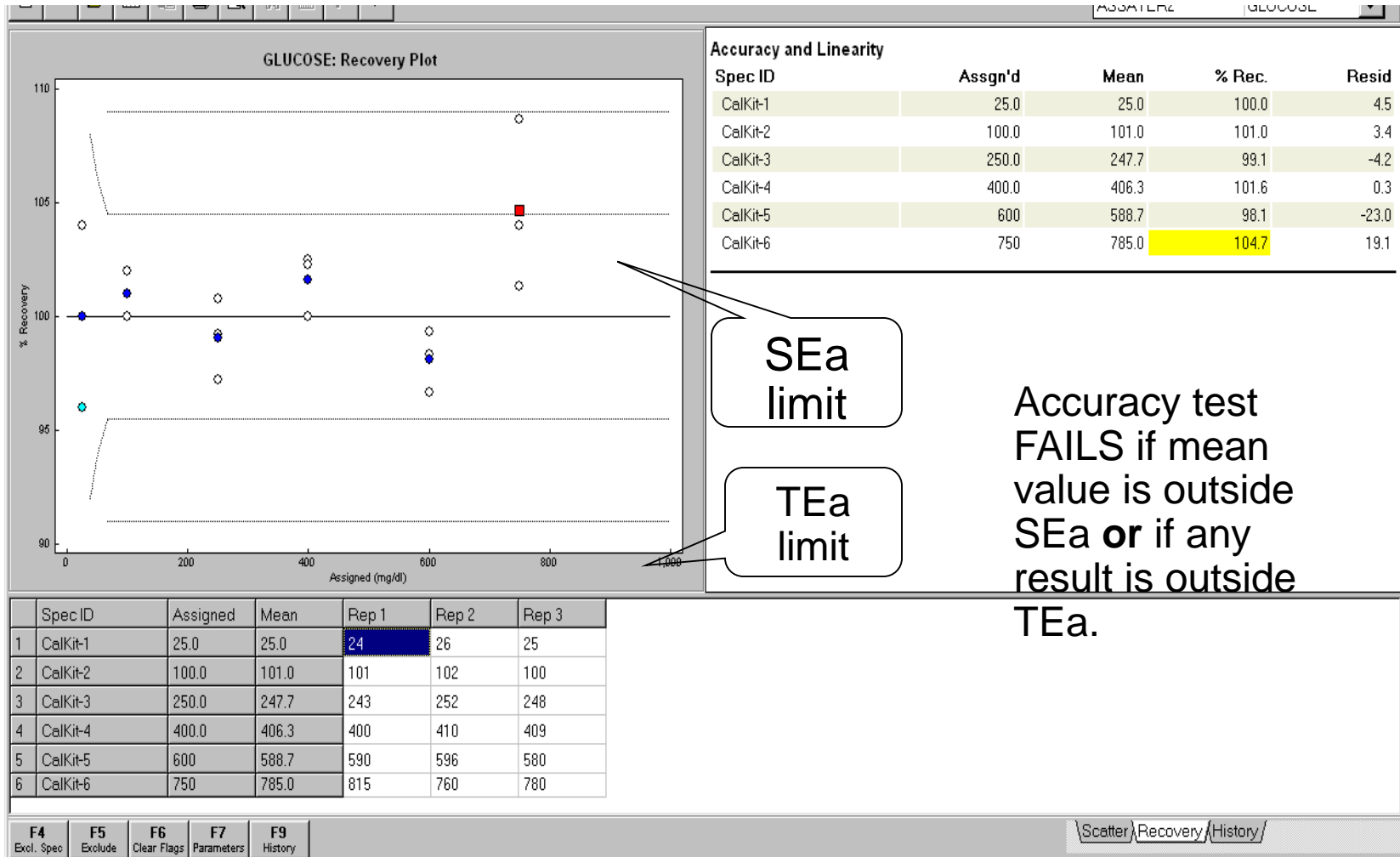
% for Systematic Error: 50

F4 Excl. Spec F5 Exclude F6 Clear Flags F7 Parameters F9 History

Enter TEa and Percentage for Systematic Error

Linearity and Calibration Verification Module

TEa and SEa - Pass Fail



SEa limit

TEa limit

Accuracy test FAILS if mean value is outside SEa or if any result is outside TEa.

Bias – Rules of Thumb (When your standards are True Values)

- **Unacceptable** – SEa goal greater than 50% of TEa
- **Acceptable** – SEa goal between 25 and 50% of TEa
- **Excellent** – SEa goal less than 25% of TEa
- **Why?**
 - Standards are weighed in or value assigned and do NOT include element of imprecision AND
 - You want to evaluate your observed bias vs the Sea goal



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Our Recommended Approach

This approach is relatively simple and easy to understand and implement. Furthermore, the data needed is accessible to most laboratories.

Approaches to Determining TEa

- **Historically, many approaches have been used to establish TEa:**
 - **Medical requirements**
 - **Biological variation**
 - **Reference interval**
 - **Regulatory requirements (i.e. CLIA '88)**
 - **Achievable error (State of the art)**
 - **Peer group survey (PGS) results from proficiency testing**
- **Approaches are listed in order based on the Hierarchy of Quality Models proposed in 1999 at the international Stockholm conference sponsored by the IUPAC, IFCC, and WHO.**

Overview of the Three-Step Process

- 1. If medical requirements exist, use them.**
- 2. Otherwise if regulatory limits (CLIA) exist, use them unless the peer group survey (PGS) values are significantly lower.**
- 3. Otherwise, calculate the median CV from an adequate number of **PGS results** and multiply by three. Round up or down gently.**

Step 1

Medical Requirement Approach

Nationally Established TEa for Six Important Analytes

Analyte	95% limit	99.7% limit
Cholesterol	8.9% (1)	13.4
HDL Cholesterol	13% (1)	19.5
LDL Cholesterol	12% (1)	18
Triglycerides	15% (1)	22.5
Creatinine	7.6% (2)	11.4
HbA1c	6% (3)	9

- National Cholesterol Education Program, Recommendations on Lipoprotein Measurement by the Working Group on Lipoprotein Measurement. (September, 1995) NIH pub: 95-3044. (TEA = bias + 2 (CV%))
- Myers et al (2006) Recommendations for Improving Serum Creatinine Measurement: A Report of the Laboratory Working Group of the National Kidney Disease Education Program. CCJ 52, 5.
- NGSP (2009) <http://www.ngsp.org/> Beginning January 2014, 37 of 40 results (38 of 40 i.e., (95%) for Level I laboratories) will need to be within +/-6% (relative) of the NGSP SRL in order to pass certification (current limits are +/-7%).

Step 2

Regulatory Requirement Approach

- **CLIA '88 PT Limits describe TEa Values for about 75 analytes:**
 - 50 analytes have limits specified as a percent, a concentration, or both.
 - For the rest, limits are specified as 3SD, which refers to the Peer Group Survey (PGS).
- Values were set administratively in early 1990's so they may not reflect improved technology.
- Most of these values seem acceptable; a few seem large.
- Whatever other problems exist, they are by definition administratively acceptable.
- The CLIA TEa values represent the largest limits you would want

*In EP Evaluator, a table of these limits can be found in
Tools/CLIA PT Limits.*

Selected PT Values from CLIA '88

Analyte	CLIA '88 Limits
Erythrocyte count (RBC)	$\pm 6\%$
Prothrombin time	$\pm 15\%$
Calcium	± 1.0 mg/dL
ALT (SGPT)	$\pm 20\%$
Blood gas pO ₂	± 3 SD
Glucose	± 6 mg/dL or 10% (greater)
HCG	± 3 SD
Digoxin	$\pm 20\%$ or 0.2 ng/mL (greater)

Step 3

Peer Group Survey Approach

- Based on the PT specification of target $\pm 3SD$, the issue is how to **generalize** this calculation.
- Sources are PT or EQAS results for your instrument family (i.e., CAP survey):
 - Use a total of 6 to 10 eligible specimens covering multiple cycles. The estimate is improved if more results are used.
 - Calculate the median CV from these PGS results and multiply by three. Round up or down gently.
- The fundamental advantage of this approach is its accessibility. It is available for almost every test performed in most clinical laboratories.

SURVEYS 2005

C-B

Chemistry

PARTICIPANT SUMMARY



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INSTRUMENT	NO. LABS	MEAN	S.D.	C.V.	MEDIAN	LOW VALUE	HIGH VALUE
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Luteinizing Hormone - mIU/mL

Y-01	Abbott Architect	32	19.33	1.18	6.1	19.5	16.1	21.5
	Abbott AxSYM	177	16.73	1.14	6.8	16.8	13.6	19.6
	Bayer ACS:180	36	18.21	1.37	7.5	18.3	14.8	21.6
	Bayer ADVIA Centaur	428	18.96	1.18	6.2	18.9	15.3	22.6
	Bayer Immuno-1	7	-	-	-	19.0	17.7	20.0
	Beckman Access/2	242	14.61	0.79	5.4	14.6	12.7	16.9
	Biomerieux VIDAS/mini VIDAS	9	-	-	-	15.6	15.2	16.7
	DPC Immulite 1000	80	18.94	1.09	5.7	19.0	15.9	21.6
	DPC Immulite 2000	150	19.32	1.44	7.4	19.1	15.4	23.5
	Roche Elecsys/E170	74	17.59	0.58	3.3	17.6	16.5	19.0
	Roche Elecsys 1010/2010	84	17.20	0.76	4.4	17.3	15.0	18.9
	Tosoh AIA-Pack	27	18.04	1.04	5.8	18.1	15.9	19.8
	Vitros Eci	110	18.25	0.83	4.5	18.2	16.2	20.3
	All Instruments	1507	17.68	2.04	11.6	17.9	10.4	28.8

Y-02	Abbott Architect	32	92.50	6.54	7.1	93.4	74.3	105.5
	Abbott AxSYM	177	81.35	6.78	8.3	81.8	62.2	98.9
	Bayer ACS:180	35	87.73	6.41	7.3	88.0	72.0	102.4
	Bayer ADVIA Centaur	427	93.93	6.40	6.8	94.0	74.7	111.7
	Bayer Immuno-1	7	-	-	-	91.2	85.8	96.3
	Beckman Access/2	245	70.83	4.07	5.7	70.6	60.9	82.9
	Biomerieux VIDAS/mini VIDAS	9	-	-	-	74.7	72.0	84.5
	DPC Immulite 1000	80	102.07	7.19	7.0	102.5	84.2	123.0
	DPC Immulite 2000	151	111.25	11.40	10.2	111.0	81.7	141.0
	Roche Elecsys/E170	74	77.73	2.68	3.4	78.0	72.0	84.5
	Roche Elecsys 1010/2010	86	76.03	3.68	4.8	76.6	66.7	85.6
	Tosoh AIA-Pack	26	85.78	4.51	5.3	87.5	76.5	91.8
	Vitros Eci	108	67.65	3.33	4.9	67.5	59.5	77.3
	All Instruments	1510	86.05	14.91	17.3	85.2	39.0	141.0

CAP Survey Data Example

HCG (VITROS Eci)			
	<i>n</i> = 63		
Spec ID	Mean	SD	CV
C-11	26.97	1.65	6.1
C-12	68.29	4.54	6.6
C-13	90.61	6.39	7.1
C-14	52.13	3.57	6.8
C-15	82.47	4.84	5.9

Total Achievable Error: PGS Approach Based on CAP Survey Results

- Calculate CVs for all points.
- Find the **median CV**, then multiply by 3.
- In this case, $3 \times 6.6 = 19.8$, which rounds to 20%.

HCG (VITROS Eci)			
	<i>n</i> = 63		
Spec ID	Mean	SD	CV
C-11	26.97	1.65	6.1
C-12	68.29	4.54	6.6
C-13	90.61	6.39	7.1
C-14	52.13	3.57	6.8
C-15	82.47	4.84	5.9

Median

Calculation of Low End TEa: Do You Need a Concentration Component?

- For many analytes, a TEa of x% will not work at all concentrations:
 - For example, in an experiment to verify reportable range accuracy.
 - For LDH, the TEa is 20%. Suppose the assigned value of a low standard is 5 units. Your mean measured value is 7 units (40% above the defined value). While the difference is clinically insignificant, it will fail the test for accuracy.
- Thus, a concentration component should be defined for TEa in addition to the percentage.
- The value that can be used is **3 times the observed SD** at a low concentration. Ideally that material will have a concentration relatively close to the lower end of the reportable range.
- If the lowest standard assigned value is “0” you **MUST** have a conc component. Otherwise the experiment will fail. (10% of 0 = 0)

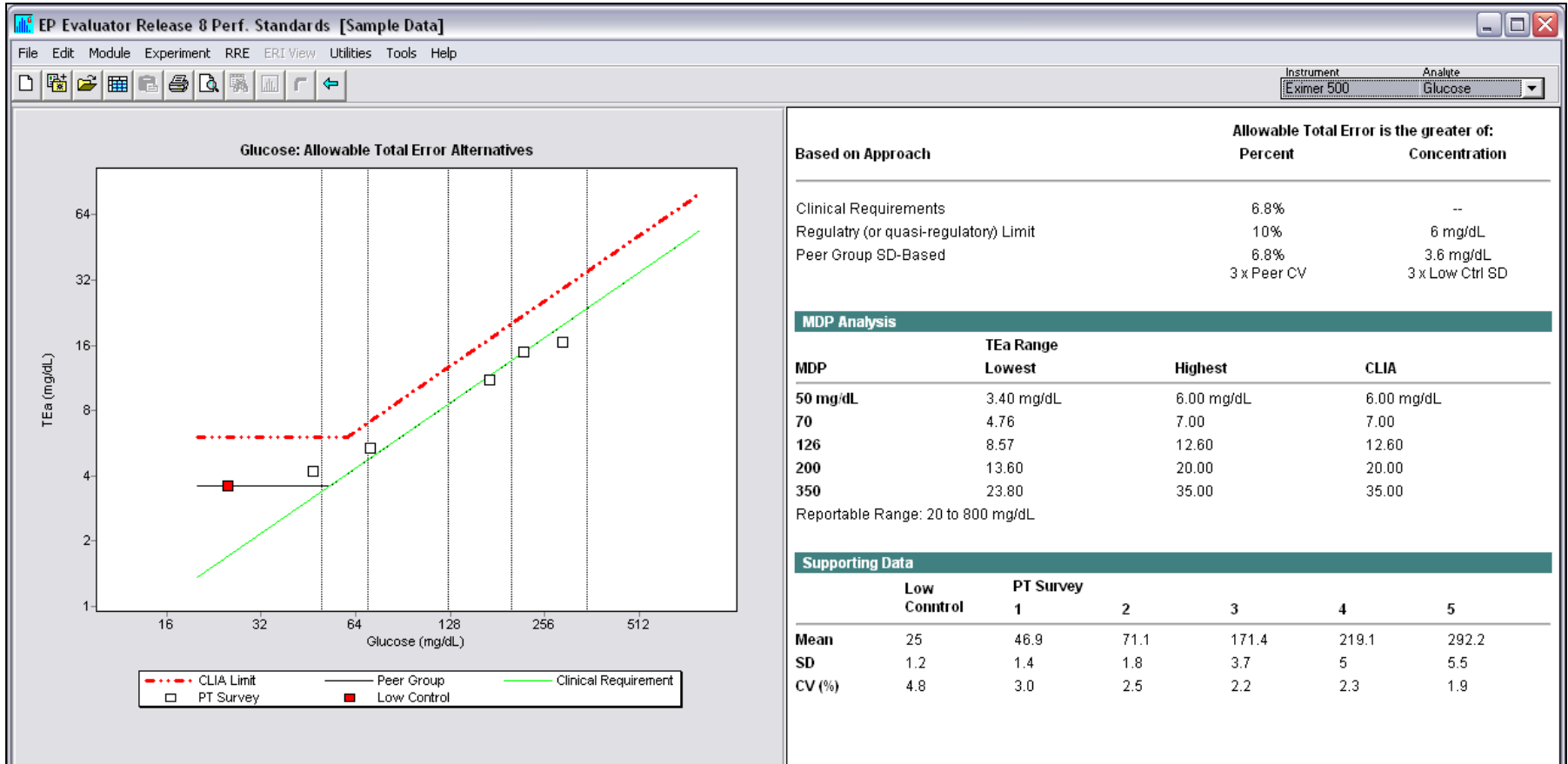
Low Value Assessment: Concentration vs. Percentage

- Ways to get a usable value for the TEa at the low end:
 - If the manufacturer offers a low end precision SD, use it ($\times 3$)
 - Otherwise, use $3 \times$ SD from a low concentration sample:
 - Peer group survey (either a PT survey or a monthly QC survey)
 - Low-end precision SD (total) from the complex precision experiment
- For most analytes, it is desirable to use:
 - Concentration at the low end
 - Percentage at the high end
- This prevents setting unrealistic expectations at the low end. Using a percentage target at these low levels often gives an unachievable value.

Calculating Total Allowable Error

- There is no single correct TEa for all analytes but usually a range of values.
- The object is to obtain a TEa that is **attainable** *and* **defensible**:
 - **Attainable** means that the performance goals are analytically achievable.
 - **Defensible** means that the performance goals are clinically responsible.
- There are software tools in EP Evaluator to calculate TEa.

Performance Standards Module



Calculating TEa for Established Tests: Summary

- 1. If an analyte has nationally specified medical requirements, use them!**
- 2. Otherwise, if available, use TEa based on CLIA PT limits.**
- 3. Otherwise, use TEa based on PGS.**
 - Median %CV \times 3 (or SD \times 3 for low end)
 - You may gently round up your TEa (i.e. 18% rounds up to 20%).

Benefits of Establishing TEa

- Defines the metrics for the two key values on which the quality of our primary product, patient results are based:
 - Allowable random error (i.e. target SD's for QC)
 - Allowable systematic error (i.e. bias)
- Allows one to make the very powerful statement similar to the following:

“This glucose test result is expected to be within 6 mg/dL or 10% of the true result 99.7% of the time.”

Calculating TEa: Let's Do It!

Our object is to define a TEa which is **Attainable** and **Defensible**.

Summary of steps for the Recommended Approach:

1. **Use Medical Requirements or Regulatory Limits If they exist.**
2. **Otherwise, calculate median CV from the summary of the PGS results for your instrument and test.**
 - **Use Results from a minimum of 6 specimens from two or more PT cycles**
3. **Multiply the median CV by 3 and round up or down gently.**

Case 1: Sodium (Olympus)

Reportable Range:	50 to 200 mmol/L
Medical Requirements:	None
Regulatory Reqs:	4 mmol/L (CLIA '88) = $4/140 = 2.85\%$

Peer Group Survey Results for Your Instrument					
Mean	121.9	136.7	114.5	133.0	148.1
SD	1.1	1.1	1.1	1.0	1.2
CV%	0.9	0.8	1.0	0.8	0.8
Mean	151.8	140.4	136.7	118.0	129.3
SD	1.5	1.2	1.2	1.2	1.2
CV%	1.0	0.9	0.9	1.0	0.9

Median 3 of 0.8, 4 of 0.9, 3 of 1.0 = 0.9

Case 1: Sodium (cont'd)

- **Medical Requirements: none**
- **Regulatory Requirements: 4 mmol/L/2.85%**
- **PGS median: $0.9 \% \times 3 = 2.7\%$**
- **What TEa value would you choose?**

4 mmol/L: the Regulatory Requirement
(2.85% and 2.7% are nearly the same)

Case 2: CO2

Reportable Range:	0 to 45 mmol/L
Medical Requirements:	None
Regulatory Reqs:	None by CLIA, 3SD by CAP

Peer Group Survey Results for Your Instrument					
Mean	14.9	20.3	27.1	22.1	18.3
SD	1.2	1.3	1.7	1.4	1.3
CV%	8.0	6.2	6.4	6.4	7.3
Mean	21.9				
SD	1.3				
CV%	6.0				

Median 6.0, 6.2, 6.4, 6.4, 7.3 8.0.

Case 2: CO2 (cont'd)

- **Medical Requirements: none**
- **Regulatory Requirements: CAP 3SD**
- **PGS median CV $\times 3$: $6.4 \times 3 = 19.2 \%$**
- **What TEa value would you choose?**

20%: the PGS gently rounded

(PGS method is the same as the 3SD Regulatory Requirement)

Case 3: HDL Cholesterol (Siemens Dimension)

Reportable Range:	Not available
Medical Requirements:	13%
Regulatory Reqs:	30%

Peer Group Survey Results for Your Instrument					
Mean	46.6	60.3	31.6	57.6	46.8
SD	1.7	2.0	1.3	1.9	1.6
CV%	3.7	3.4	4.0	3.2	3.3
Mean	50.8	32.4	33.4	43.7	54.8
SD	2.4	1.9	2.0	2.3	3.0
CV%	4.7	5.7	5.9	5.2	5.4

Median 3.2, 3.3, 3.4, 3.7, 4.0 | 4.7, 5.2, 5.4, 5.7, 5.9

Case 3: HDL Cholesterol (cont'd)

- **Medical Requirements: 13%**
- **Regulatory Requirements: 30%**
- **PGS median CV $\times 3$: $4.35 \times 3 = 13.05 \%$**
- **What TEa value would you choose?**

13%: the medical requirement

Guidelines for your TEa

With few exceptions

- Your QC Target SD (REa) should not exceed 25% of TEa
 - Since max TEa is 30%, the upper limit of the target SD is 7.5%
- Maximum allowable bias (SEa) should not exceed 50% of TEa
 - We recommend a SEa in the range of 25 to 50% of the TEa.
- TEA should not be wider (larger) than the analyte's central 95% reference interval
- TEA should not be smaller than the magnitude of the last significant digit (If last reportable digit is one unit. TEA should not be smaller than 1)
- In LIN CAL/Ver module, if lowest standard is zero or close to zero, you must have a conc component for TEA, - or the experiment will fail.

Proximity Limits for Reportable Range: A Special Consideration

- Proximity limits are not related to TEa.
- However, per CLIA the laboratory must verify the accuracy of the upper and lower limit of its reportable range.
- In EE, in order to pass accuracy, the recovered mean must be within \pm SEa of the assigned value.
- You must define “how close” your standards need to be to the lowest and highest reportable range limits. This gap is called the *proximity limit*. *It is expressed as the desired deviation from the target.*
- CAP suggests 50% for the low limit and 10% for the high limit.
 - A concentration component may be better at the low end. If the lowest standard is “0” you MUST have a conc component. Otherwise the experiment will fail. (10% of 0 = 0)
 - In general, choose one or the other, not both.

Choosing Proximity Limits

- EE Help offers some guidance on proximity limits. But the choice is an informed decision.
- Your choice should reflect:
 - How close should your reportable ranges be to the analytical range from the manufacturer?
 - At the high end you want to make the fewest dilutions.
 - At the low end, you want to take advantage of the sensitivity of the method, when low values are clinically important..
 - How close are the lowest and highest Medical Decision Points (MDP) relative to the reportable range limits?
- “If you want to verify a “5”, is it OK to have a standard that is a “10” ?? Depends on the analyte and the medical decision points. If the closest MDP is 25, that may be OK, but if the MDP is 5, then perhaps you want a standard that actually is closer to the MDP.

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Thank You!