Designing QC Activities to More Precisely Manage Analytical Accuracy and Patient Risk

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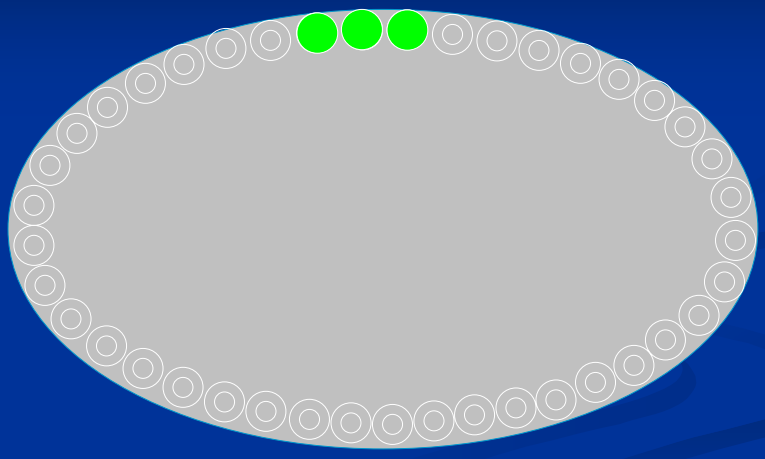
Quality Control in the Modern Laboratory

- Patients, providers, and regulators are increasingly focused on the importance of managing patient risk
- For the clinical laboratory patient risk is related to the accuracy of the patient results produced and reported by the lab
- Laboratory quality control (QC) should be designed to assure that patient results meet the quality (accuracy) required for their intended use (ISO 15189 Clause 5.6.1)
- The era of laboratory automation provides an opportunity for laboratories to reassess whether current QC practices are effectively managing patient risk

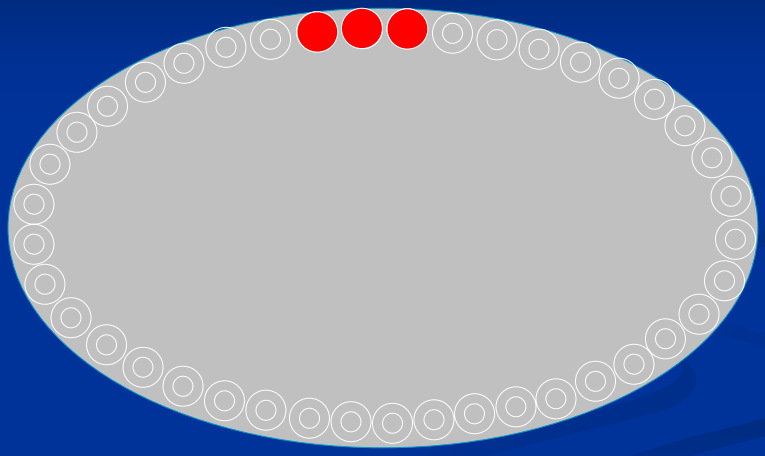
Traditional Laboratory QC

- Traditional QC strategies were designed decades ago in an era when most laboratory testing was performed in batches
- Both patient samples and QC samples were included in each batch
- The QC sample results were used to decide whether the patient sample results in the batch were acceptable

QC procedures designed to validate a batch process…



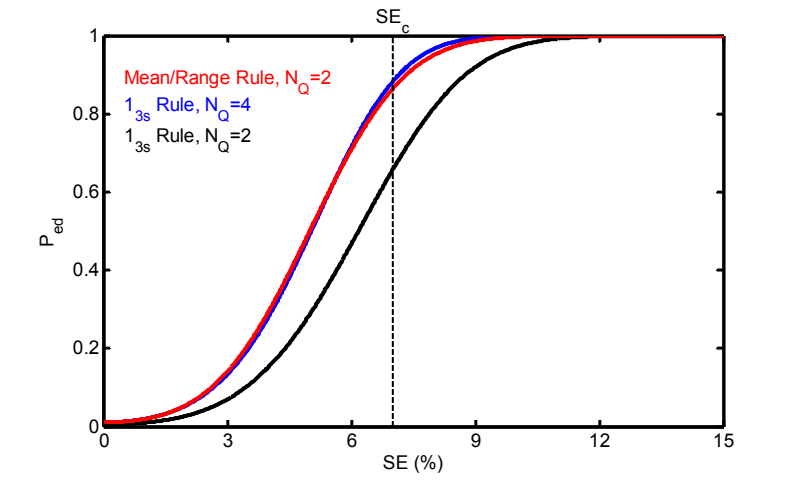
…or invalidate a batch process



Traditional QC Design

- The questions that must be answered in order to set up a QC procedure for batch testing are
  - How many QC samples should be tested in the batch?
  - What QC rules should be applied to the QC sample results in order to decide if the patient results in the batch are acceptable?
- Traditional QC design focuses on finding answers to these two questions that will provide the statistical power needed to detect a "critical" out-of-control error condition in a batch
  - Westgard proposes power function graphs and Op-Spec charts to find an appropriate QC strategy

QC Power Functions

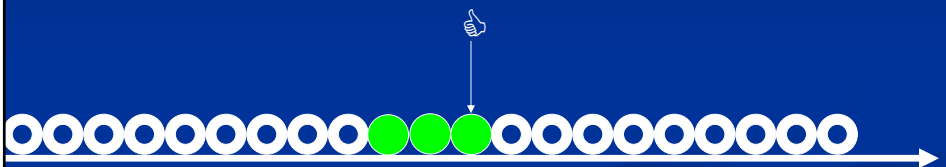


The Era of Laboratory Automation

- The majority of new laboratory instruments perform discrete testing
- With automated discrete analyzers there no longer is an association between QC results and a batch of patient samples
- QC results reflect the status of the test system at a point in time

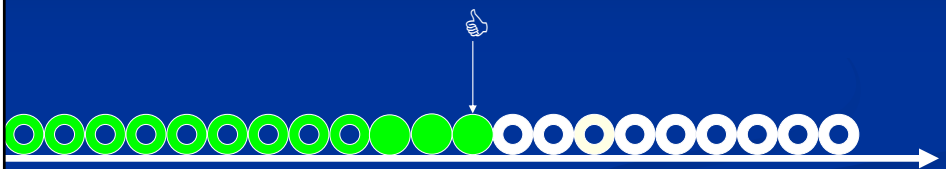
Discrete Instrumentation

Controls can validate that no error condition exists at the time of evaluation…



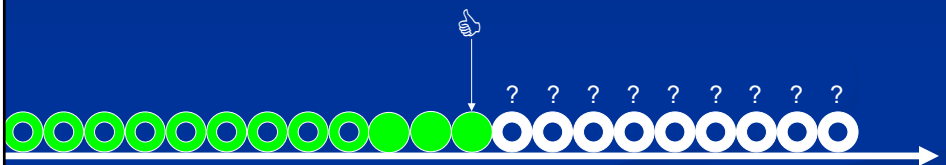
Discrete Instrumentation

…which implies that the preceding specimens are OK,



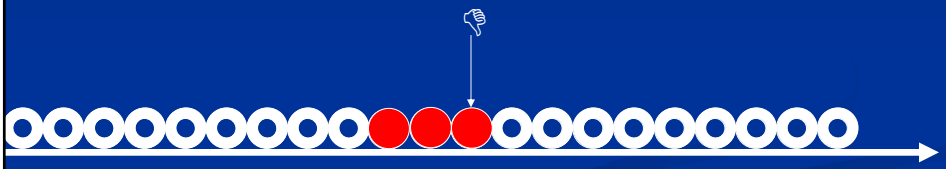
Discrete Instrumentation

but cannot validate the specimens immediately following.



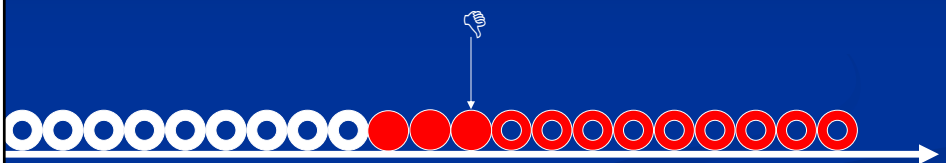
Discrete Instrumentation

Likewise, controls can validate that an error condition exists at the time of evaluation…



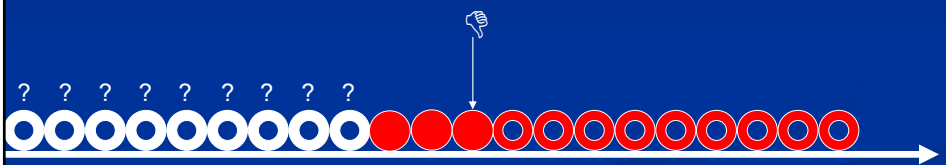
Discrete Instrumentation

…which invalidates the immediately following specimens



Discrete Instrumentation

…but cannot tell us which preceding specimens are OK.



QC Strategies for Today's Laboratory

- The questions that must be answered in order to set up a QC procedure in the modern laboratory are
  - How many QC samples should be tested, what QC rules should be applied, and **WHEN SHOULD QC TESTING OCCUR**?
- Traditional QC design gives no guidance on when to test QCs
- CLIA §493.1256(d)(3)(i) requires "at least once each day patient specimens are assayed … for each quantitative procedure include two control materials of different concentrations"
- To illustrate the shortcomings of traditional QC design practices and guidance consider the following situation

Example Scenario

- Two laboratories: laboratory A and laboratory B
  - Both labs test 2 QC's every morning.
  - Both labs use the same QC rules.
  - Lab A tests 50 patient specimens per day.
  - Lab B tests 350 patient specimens per day.
- The same instrument malfunction occurs midday in both labs affecting all subsequent patient results
- The QC rules used by the two laboratories have identical statistical power
- Both labs meet CLIA requirements
- Do the patient populations in the two laboratories have the same risk?

An Approach to Designing QC Strategies to Manage Patient Risk

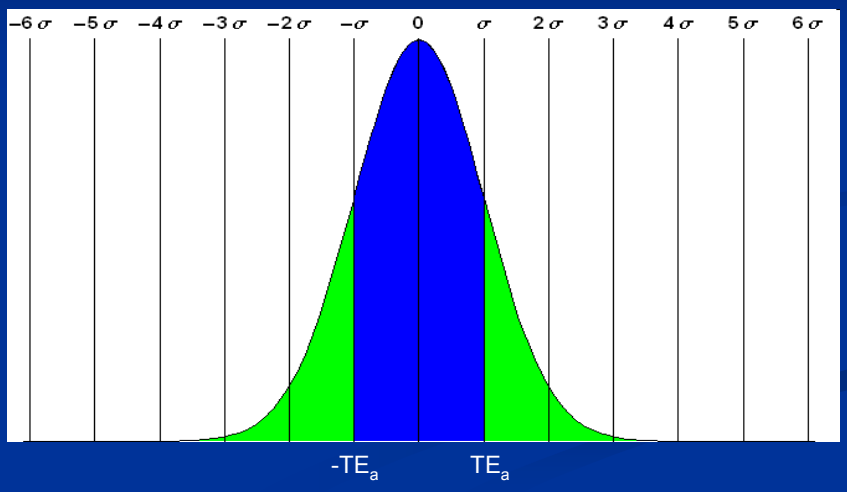
- QC design should focus on assuring the quality of reported patient results
  - Design QC strategies to control the expected number of incorrect patient results reported when a malfunction occurs in the lab
- QC design should reflect modern laboratory operations
  - Don't assume "batches"
  - Objectively assess the impact of QC testing frequency

The "Quality" of a Patient Result

- The quality of a patient result depends on the difference between the true concentration and the value reported by the laboratory
- One way to quantify quality is the probability that a result's error exceeds a specified total allowable error, TE_a
  - If the error in a patient's result exceeds TE_a it places the patient at risk
  - TE_a is directly related to the concept of sigma metrics

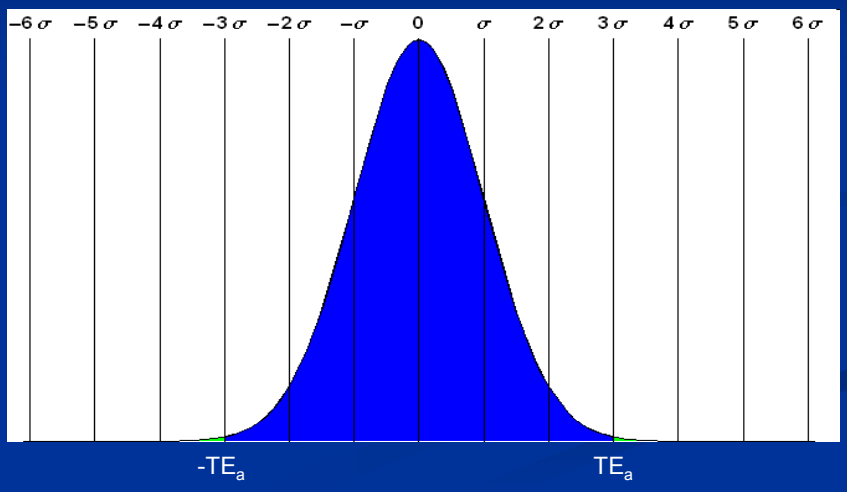
One Sigma Range

68.27%



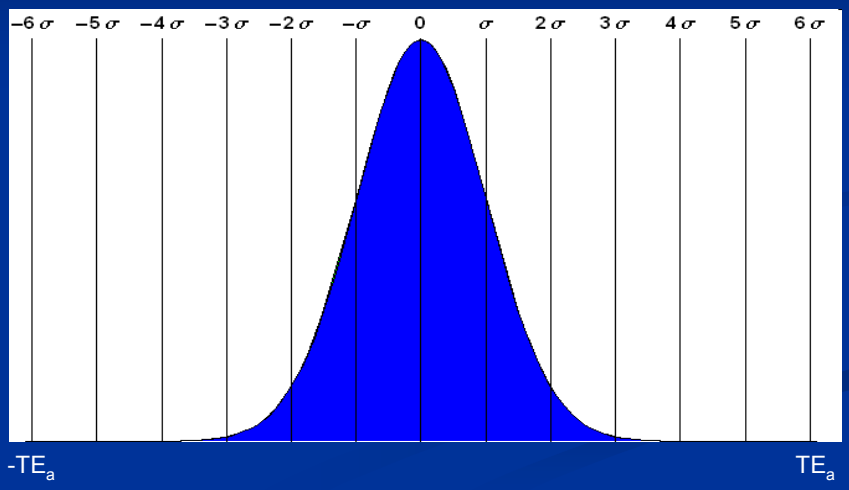
Three Sigma Range

99.73%

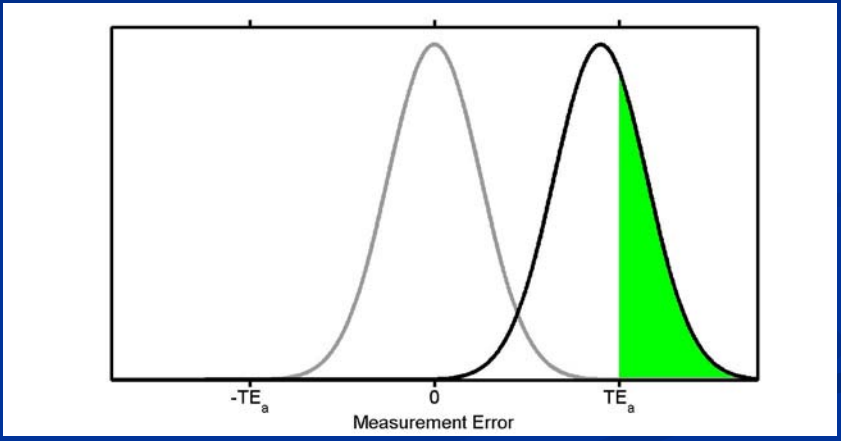


Six Sigma Range

99.9999998%



Probability of an Unacceptable Result due to a Systematic Error Condition (SE)



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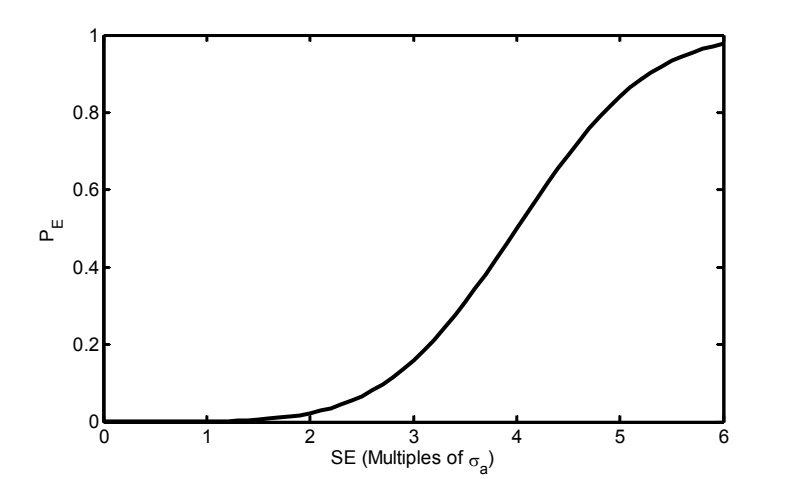
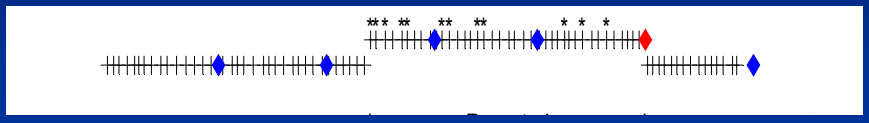


The Expected Number of Unacceptable Patient Results Reported: $E(N_U)$

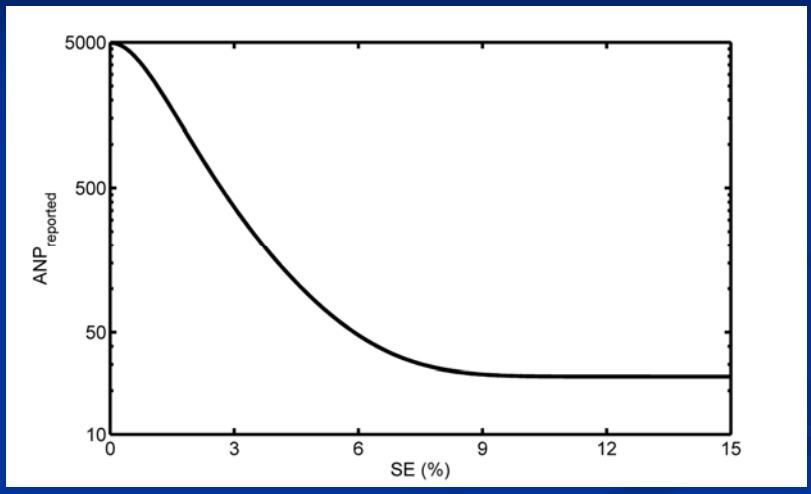


- * denotes an unacceptable patient result
- The expected number of unacceptable patient results reported depends on
  - The probability of producing an unacceptable result during the error condition, P_E
  - The average number of patient results reported during the error condition, $ANP_{reported}$

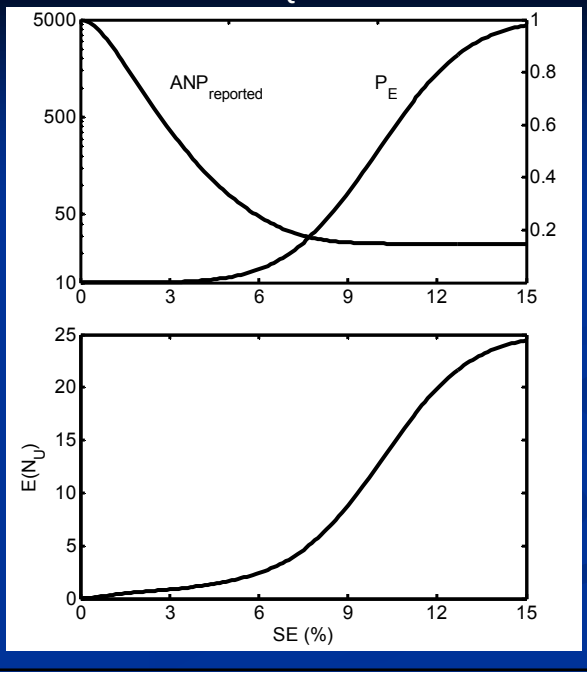
Average Number of Patient Results Reported ($ANP_{reported}$)

- The average number of patient results reported during an error condition depends on
  - the power of the QC rule
  - the frequency of QC events
- We want the average number of patient results between false rejections to be large
- Small error conditions may persist a long time before detection
- Large error conditions are likely detected at the first QC event

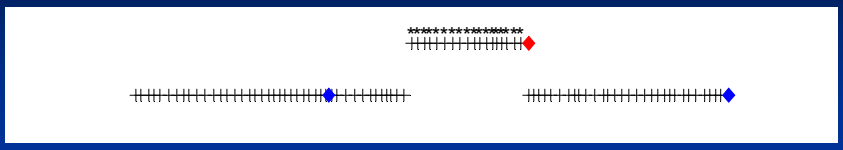
Average Number of Patient Results Reported ($ANP_{reported}$)



Mean/Range Rule, N_Q=2, N_B=50, TE_a=±10%



Immediate Reporting of Results



- For large out-of-control error conditions
  - The probability of detecting the error at the first QC event approaches 1.0
  - But all patient results from the occurrence of the error until the next QC event are unacceptable
  - The expected number of unacceptable patient results depends on the length of the interval between QC events

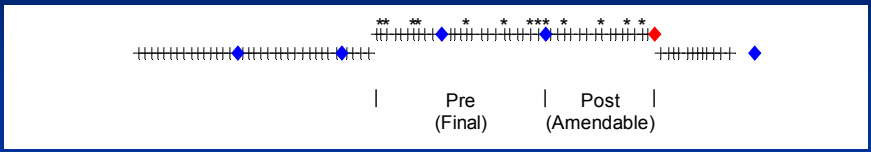
Immediate Reporting of Results

- QC strategies based on the periodic testing of control samples have an inherent vulnerability when results are reported immediately
- The vulnerability exists in the interval between the occurrence of an out-of-control error condition and the next scheduled QC event
- What to do?
  - Shorten the interval between QC events
  - Supplement the QC events
  - Damage control

Damage Control

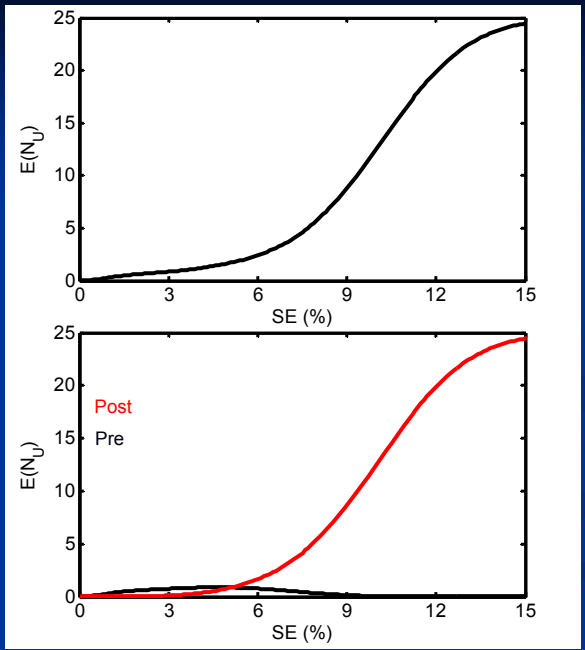
- CLIA says;
  - §493.1256(c)(1) – "The control procedure must detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance."
  - §493.1282(b)(2) - "All patient test results obtained in the unacceptable test run and since the last acceptable test run must be evaluated to determine if patient test results have been adversely affected. The laboratory must take the corrective action necessary to ensure the reporting of accurate and reliable patient test results."

Damage Control



- The total number of results produced during an error condition can be divided into two groups
  - Pre: Results prior to the last accepted QC event
  - Post: Results since the last accepted QC event
    - If the lab is doing bracketed QC, these patient results aren't reported
    - If the lab is immediately reporting, these patient results should be repeated and updated

Pre and Post, N_B = 50, TE_a = ±10%



Example Scenario Revisited

- Two laboratories: laboratory A and laboratory B
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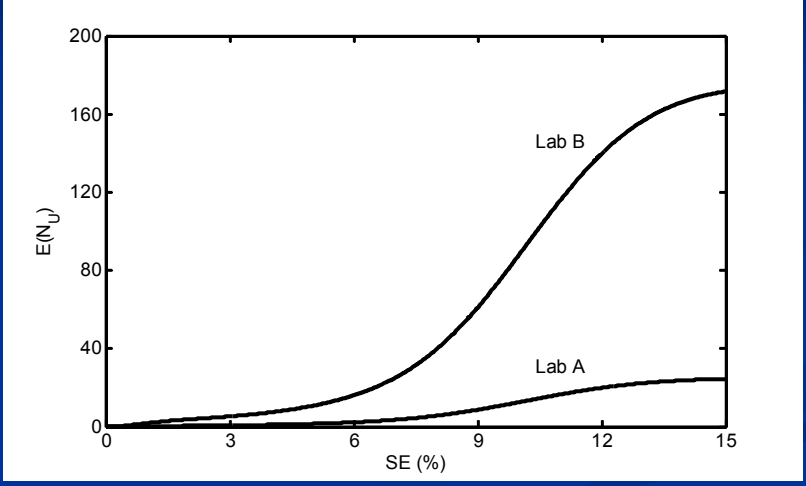
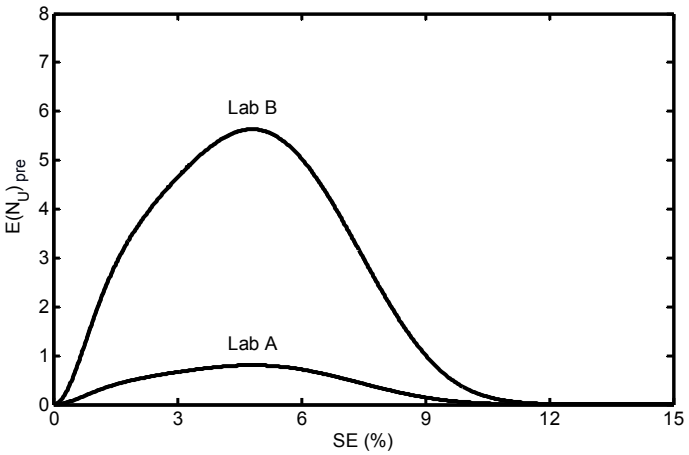
Total Expected Unacceptable



Expected Unacceptable Prior to Last Good QC Event



Using $E(N_u)$ to Design QC Strategies that Manage Patient Risk

- We can design QC strategies to limit $E(N_u)$
- For example
  - A laboratory designs a QC strategy so that $E(N_u)_{pre} \leq 1$ for all possible error conditions
  - then the quality claim the laboratory can make to its customers is

    the expected number of unacceptable "final" patient results reported by the lab because of an error condition should never exceed 1
- How to select among alternative designs that achieve the same $E(N_u)$ goal?
  - Choose the strategy with the lowest QC utilization rate
  - Choose the strategy with the lowest false rejection rate

Which QC Strategy to Choose?

(CV_1, CV_2)	QC rule	P_{fr}	N_Q	N_B	N_Q/N_B
(3.0,2.25)	Mean/Range	0.01	2	57	.035
(3.0,2.25)	$1_{2.81s}$	0.01	2	34	.059
(3.0,2.25)	Mean/Range	0.01	4	70	.057
(2.6,1.9)	Mean/Range	0.01	2	394	.005
(2.6,1.9)	Mean/Range	0.001	2	109	.018

Which QC Strategy to Choose?

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(2.6,1.9)	Mean/Range	0.01	2	394	.005
(2.6,1.9)	Mean/Range	0.001	2	109	.018

Summary

- The risk of reporting an incorrect patient result depends on
  - The accuracy requirements for the result (TE_a)
  - The laboratory's analytical capability (imprecision, bias)
  - The power of the laboratory's QC rules
  - The frequency of QC testing in the laboratory
- Analytical capability and the frequency of QC testing have a big impact on the risk of reporting incorrect patient results
- The number of QCs tested and the QC rules used in the laboratory have less impact on patient risk
- It's possible to design QC strategies that effectively manage patient risk by limiting the expected number of incorrect patient results produced and reported by the laboratory when an out-of-control error condition occurs

References

- Yundt-Pacheco J, Parvin CA. The impact of QC frequency on patient results. *MLO Med Lab Obs* 2008; 40(9):24-7.
- Parvin CA. Assessing the impact of the frequency of quality control (QC) testing on the quality of reported patient results. *Clin Chem* 2008; 54(12):2049-54.