Quality Control

Future directions

Ensuring the relevancy of quality control in today’s clinical laboratory
Objectives:

Review the history of Quality control
   Appreciating the role of Laboratory QC in patient care

Current Practice
   • Integration of QC and QA
   • The QC squeeze

The Future - “Lean QC”
   • How good should we be?
   • Do we know how the information is used

A rational way to choose QC Rules— and avoid the QC squeeze
   • Based on the Total Allowable Error(TAE) or Allowable Imprecision(ASD)

Quality Assurance: heading errors off at the pass
   • QC rules for longer term Quality Assurance
   • Managing Lot Changes to improve QC and Quality
What is quality testing all about?

- Physicians making the best decisions
  - With the clinical information they have
  - With the diagnostic information they have
Clinicians making the best decision they can

• What factors influence the decisions they make?
  • The *accuracy* of the test
  • The *perception* of the accuracy of the test
If the result is not credible...

The doctor discounts the importance of the test in their decisions

- This perception reduces the value of the test, as much as the actual inaccuracy of the test
If the result is not credible...

It takes **one** incidence to lose credibility!

It takes **many** incidences to get it back!
What is it about QC that ensures accurate patient results are being generated?
Which statements are true?

• QC is ‘in’ so patient results are OK
  • MAYBE
• QC is ‘out’ so patient results are wrong
  • MAYBE
• QC is ‘out’ but patient results are OK
  • MAYBE
• QC is ‘in’ but patient results are wrong
  • MAYBE
History of Quality Control

The control chart was invented by Walter A. Shewhart while working for Bell Labs in the 1920s

Purpose:
- To determine whether a process should undergo a formal examination for quality-related problems
History of Quality Control

Concept applied by W. E. Deming in Japan 1950’s & 60’s
• Originally proposed 3 Sigma as the out of control limits.

Modified by S. Levey and E. R. Jennings in 1950 for application in the Clinical Laboratory
QC Today

as commonly practiced

A QC result is “out”
  • QC is rerun
  • If “in” then continue running the test

What is the problem?
  • To Statisticians
    • The Type II error
      • Failing to reject a false null hypothesis
  • To us
    • Actually out of control when we think we are in control
Is my method out of control?
Missing an Out-of-Control Method

50% chance that the repeat QC will be “within” the 2SD range.
84% chance that the repeat QC will be “within” the 3SD range.
What to do?

After troubleshooting and correcting any issues
- Eg. Fresh control material, new reagents or …
- LAST RESORT – recalibrate

Run controls in duplicate
- Both control results should be within 2 SD of mean
  - $2_{2S}$ to establish “in control” condition
Is my method out of control?
The best QC Strategy

Minimize False rejections
- “out of control” when the method is in control

Minimize False acceptances
- “in control” when the method is out of control
The 2SD Problem: Are we playing by the wrong Rules?

False rejections with +/- 2SD Limits

- 1 QC Sample
  - Reject 5% of runs
- 2 QC Samples
  - Reject 9% of runs
- 3 QC Samples
  - Reject 14% of runs
- 2 QC Samples X 25 tests
  - Reject 95% of runs
QC Current Practice

The QC squeeze

- Newer instruments have better precision
- We set our SD limits based on the ever reducing actual CV’s of these new instruments
- We will always have the same QC repeat rate no matter how precise the instruments become
How good does a test have to be?

We need to be able to relate our daily QC performance to some generally accepted criteria or **STANDARD** of performance.
The Future - “Lean QC”

- How good should we be?
- Do we know how the information is used?
  - Well established medical applications
    - Diagnosis vs monitoring
    - Today’s diagnostic test is tomorrow’s monitoring test
  - Clinical Cutoffs
  - Established accuracy and precision standards
    - Eg A1C
  - The future or unanticipated use
- Bottom line - NOT Always!
How good should we be?

Be as good as we can be

• Our Ultimate limitation is **biological variation**
  
  • To the physician: we can’t be better than the variability that exists within the patient
  
  • If biological variation for serum porcelain is
    • SD = 100 lbs/gallon (CV = 40-%)
  
  • It doesn’t matter much if our test precision is
    • 5 lb/gallon or 10 lbs/gallon (CV = 2% or 4%)

• Biological variation has become the determinant of how accurate and precise a test can be

• [http://www.westgard.com/biodatabase1.htm](http://www.westgard.com/biodatabase1.htm)
How good does a test have to be?

• **Total Allowable Error** (aka allowable medical error)
• Based on -
  • Clinical use of the test
  • Biological variability
    • Day-to-day variation
    • Diurnal variation
  • Pre-analytical effects
  • etc.

• Most common tests have published values for Total Allowable Error

  • [http://www.westgard.com/biodatabase1.htm](http://www.westgard.com/biodatabase1.htm)
Avoiding the QC Squeeze

A new way to choose QC Rules

- Based on the Total Allowable Error (TAE)
  - [http://www.westgard.com/biodatabase1.htm](http://www.westgard.com/biodatabase1.htm)
The Total Error Budget

• Total error is the sum of bias (systematic error) and imprecision

• Determine the bias and then the allowable imprecision follows

allowable imprecision = total allowable error - bias.
Relationship of: Total Allowable Error, Imprecision and Bias

MEDx Chart: The Total Allowable Error Budget

- 0.50 TEa - 2 Sigma
- 0.33 TEa - 3 Sigma
- 0.25 TEa - 4 Sigma
- 0.17 TEa - 6 Sigma

Allowable Inaccuracy (bias, %)
- Excellent
- Good
- Marginal
- Poor
- Unacceptable

Allowable Imprecision (%)
- 0
- 15

Instruments:
- Instrument -1
- Instrument -2
- Instrument -3
- Instrument -4
How do we know if our test is good enough?

Determine the Sigma statistic

\[ \text{Sigma} = \frac{\text{TAE} - \text{Bias}}{\text{CV}} \]

- CV = variation of your method
- Bias = difference from…
  - Reference method
  - All method mean

http://www.westgard.com/lesson74.htm
QC Rules for an “Outrageously Good” test

Evaluating single QC results

• If Sigma >= 8 then $1_{4S}$ rule may be used

• Eg For Serum CRP (at critical level = 2.0 mg/l)
  • TAE = 56%
  • Your actual CV = 6 %
  • Bias = 8%
  • Sigma = $(56 – 8)/6 = 8$
QC Rules for an “Excellent” test

Evaluating single QC results

• If Sigma >= 6 then $1_{3.5}$ rule may be used

• Eg For Serum Alkaline Phosphatase (at ULN = 150 U/l)
  • TAE = 12%
  • Your actual CV = 1.4 %
  • Bias = 3%
  • Sigma = (12 – 3)/1.4 = 6.4
QC Rules for a "Very Good" test

Evaluating single QC results

- If Sigma is between 5.5 - 6 then $1_{3.0s}$ rule may be used

- Eg For Serum Alkaline Phosphatase (at ULN = 150 U/l)
  - TAE = 12%
  - Your actual CV = 1.7%
  - Bias = 3%
  - Sigma = $(12 - 3)/1.5 = 5.3$
QC Rules for a “Good” test

Evaluating single QC results

- If Sigma is between 5.0 – 5.5 then $1_{2.5}s$ rule may be used

- Eg For Serum Alkaline Phosphatase (at ULN = 150 U/l)
  - $TAE = 12\%$
  - Your actual $CV = 1.9 \%$
  - $Bias = 3\%$
  - $Sigma = (12 - 3)/1.5 = 5.3$
QC Rules for an “OK” test

Evaluating single QC results

• If Sigma < 4 then multiple QC samples need to be evaluated
  • eg $1_{2.0s}$ rule and multirule QC should be used

• Eg For Serum Alkaline Phosphatase (at ULN = 150 U/l)
  • TAE = 12%
  • Your actual CV = 1.9 %
  • Bias = 5%
  • Sigma = $(12 - 5)/2 = 3.7$
The Total Error Budget: Reducing Bias to Reduce QC Failures

• Total error is the sum of bias (systematic error) and imprecision

• Determine the bias and then the allowable imprecision follows

allowable imprecision = total allowable error - bias.
Reducing Bias as a means to Reduce QC Failures

Determine the Sigma statistic

\[ \text{Sigma} = \frac{\text{TAE} - \text{Bias}}{\text{CV}} \]

- CV = variation of your method
- Bias = difference from…
  - Reference method
  - All method mean

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Reducing Bias to improve SIGMA

- Eg For Serum Alkaline Phosphatase (at ULN = 150 U/l)
  - TAE = 12%
  - Your actual CV = 1.9 %
  - Bias = 5%
    - Sigma = (12 – 5)/1.9 = 3.7 use $1_{2S}$ and Multirule QC
  - Bias = 2%
    - Sigma = (12 – 2)/1.9 = 5.3 use $1_{3S}$
Quality Control vs Quality Assurance

Thinking longer term

- Use Mulltrule QC to look for changes that should be investigated
  - $R_{4s}$ - variability
  - $4_{1s}$ – shift
  - $10_x$ – shift

- Apply the Sigma Statistic to manage reagent & calibrator lot changes

- Reduces the frequency of immediate QC problems
  - Solves the underlying problem
  - Rejected runs will be reduced
Impact of lot Changes on “Precision”
Quality Assurance: Anticipating problems

Lot to Lot Changes
  • Evaluating new Lots of reagents
    • When?
    • How?
    • What Criteria?
Lot to Lot Changes

When

- Ideally
  - Before the new lot is shipped
- Practically
  - When the new lot is received
- Suboptimally
  - When you are about to start the new lot
Lot to Lot Changes

How?
• Old Lot vs new Lot
  • QC
  • Small patient correlation
    • N = 20 or N= 10 in duplicate
    • Plot or use Linear regression
      • Determine Slope and intercept
How do we know if our test is good enough?

Determine the Sigma statistic

\[
\text{Sigma} = \frac{\text{TAE} - \text{Bias}}{\text{CV}}
\]

- CV = variation of your method
- Bias = difference from…
  - Reference method
  - All method mean

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Lot to Lot Changes

What Criteria?

Determine the Sigma statistic

\[ \text{Sigma} = \frac{\text{TAE} - \text{Bias}}{\text{CV}} \]

- \text{CV} = \text{variation of your QC @ Medical decision Limit}
- \text{Bias} = \text{difference between new lot and old lot}
Bias between Lots: eg Lipase

**Y** = Slope * **X** + Intercept

**Bias** = **Y** - **X**

= Slope * **X** + Intercept - **X**

**%Bias** = 100 * \( \frac{(Y - X)}{X} \)

= 100 * \( \frac{(Slope \times X + Intercept - X)}{X} \)
Lot to Lot Changes

Previous Example - Lipase

- Total Allowable Error at 65 U/l = 29%
- CV** = 3%
- Actual bias = \(100 \times \frac{(\text{Slope} \times X + \text{Intercept} - X)}{X}\)
- Actual bias = \(100 \times \frac{(1.109 \times 65 + 0.634 - 65)}{65}\)
  \[= 11.8\%\]
- Sigma = \(\frac{\text{TAE} - \text{Bias}}{\text{CV}^*} = \frac{29\% - 11.8\%}{3\%}\)
- Sigma = \(5.7\)

Sigma Statistic Interpretation

- Sigma > 6 Excellent
- Sigma 4 – 6 Good
- Sigma 3 – 4 Marginal
- Sigma 2 - 3 Poor
- Sigma < 2 Unacceptable

** use current CV of QC @ Medical decision limit (MDL)
Patient Correlation: An opportunity to reduce false rejections

Scenario:
- QC shifts with new Lot
- but Sigma is Acceptable  eg > 3

- Implies Shift is only significant for QC material
- Opportunity to re-establish QC means
- Reduces False Rejections
Impact of Reagent Instability on Lot Changes
In Summary

Intelligent QC

- Minimize false acceptance
  - Puts an extra burden on the lab
- Minimize false rejection
  - Reduces burden on the lab
  - Take advantage of the better performance of new instruments
- Avoid the QC squeeze
  - Chose the right QC Rules
    - Use the Sigma statistic to assess the Performance of your tests
    - Use QC Rules tailored to the Performance of the test
  - Less bias means more room for imprecision (ie larger Sigma)
  - Reduce Lot to Lot bias to reduce apparent imprecision
  - Reassess QC means if patient correlation is acceptable
    - Sigma .> 3
  - Reject poor lots