

TestAmerica

THE LEADER IN ENVIRONMENTAL TESTING

Determining Detection and Quantitation Limits

**Designing a Straightforward Procedure that
Actually Works**

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NEMC 2008

- Federal Advisory Committee for Detection and Quantitation
- Established May 2005
- Recommend Detection and Quantitation procedures for compliance monitoring under 40CFR Part 136
- Provide advice and recommendations on policy issues related to detection and quantitation

- Participants drawn from
 - ~ States
 - ~ Regulated industry
 - ~ Publicly owned treatment works
 - ~ Testing laboratories
 - ~ Environmental Community

What do we need a Procedure to do?

- MQOs
 - ~ Produce an estimate of bias
 - ~ Produce an estimate of precision
 - ~ False Positives
 - ~ False negatives

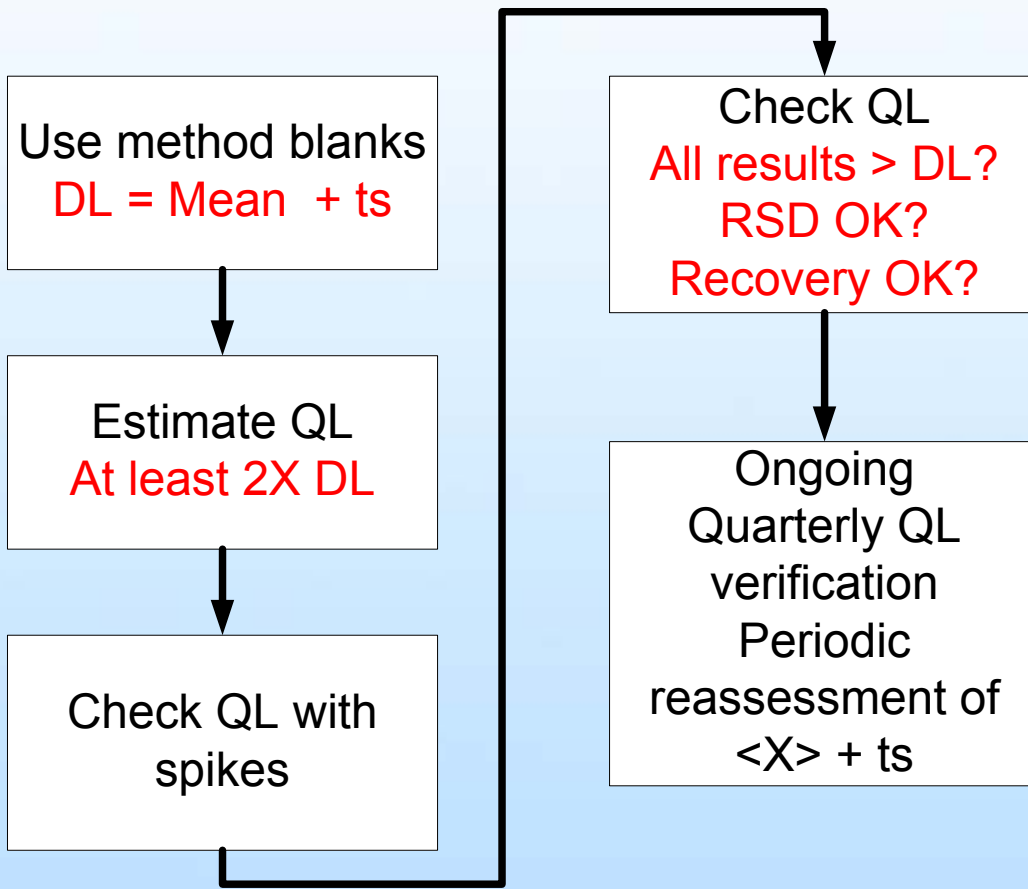
What do we need a procedure to do?

- Incorporate temporal variability
- Reflect routine performance
- Address matrices
- Evaluate the entire test method
- Address blank bias
- Address intermittent blank contamination

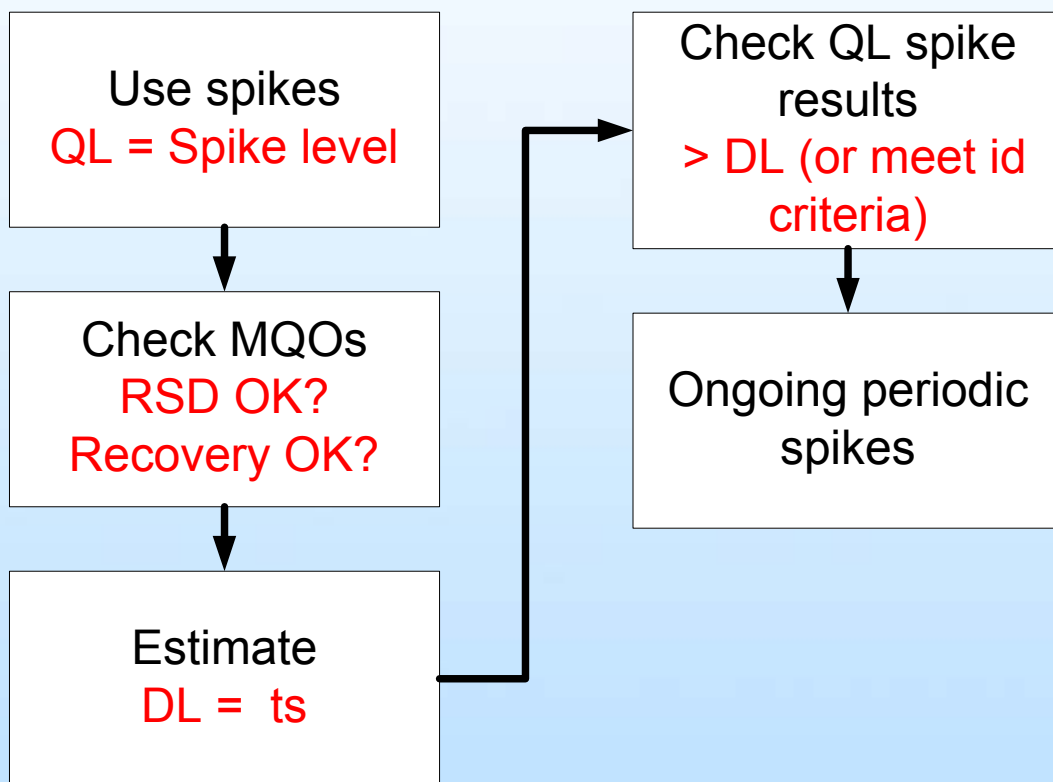
Other considerations for procedures

- How complex is the data to process?
- How complex is the procedure to implement in the laboratory?
- Is the procedure clearly written?
- Does the procedure communicate detection/quantitation concepts?

Methods with numerical blank results




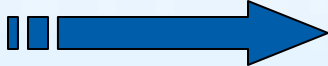


Methods with no or infrequent numerical blank results



Decision 1

- Modify the definitions for detection and quantitation from those used by ISO/IUPAC

Europe vs US

- Rugby  American Football
- Cricket  Baseball
- Metric  Imperial
- DL definition  ???

Definition of Detection Limit

- The detection decision point is defined as the Critical Value (Lc) alternatively referred to as the **Critical Level**. This is set at the standard deviation of the blank times a constant, which is directly related to sample size and the confidence level desired (normally 99%).
- **Detection Limit (DL)**: The minimum result which can be reliably discriminated from a blank (for example, with a 99% confidence level).

Detection Limit Definition

- **IUPAC definition fails if:**
 - ~ Blank results do not average zero
 - ~ Non-normal distribution
 - ~ Intermittent blank results
- **FAC definition accommodates all these issues**
 - ~ **Detection Limit (DL):** The minimum result which can be reliably discriminated from a blank (for example, with a 99% confidence level).

Definition of Quantitation Limit

- Quantification capability is defined as the Minimum Quantifiable (true) Value (L_q) or alternatively the Quantification Limit. This is set at a known level of RSD, normally 10%. Empirically others have simply set it at 10 times the standard deviation of the blank assuming constant variability in this region.
- **Quantitation Limit (QL):** The smallest detectable concentration of analyte greater than the Detection Limit (DL) where the accuracy (precision & bias) achieves the objectives of the intended purpose.
- **Lab Quantitation Limit (QL_{lab}):** The smallest detectable concentration of analyte greater than the Detection Limit (DL) where the accuracy (precision & bias) demonstrated by the laboratory achieves the objectives of the intended purpose.

Quantitation Limit Definition

- Limitations of IUPAC definition
 - ~ No consideration of bias
 - ~ Assumes constant standard deviation
 - ~ 10% RSD is not achieved even in the middle of the calibration curve for some analytes
 - ~ No relation to objectives
- **Quantitation Limit (QL):** The smallest detectable concentration of analyte greater than the Detection Limit (DL) where the accuracy (precision & bias) achieves the objectives of the intended purpose.

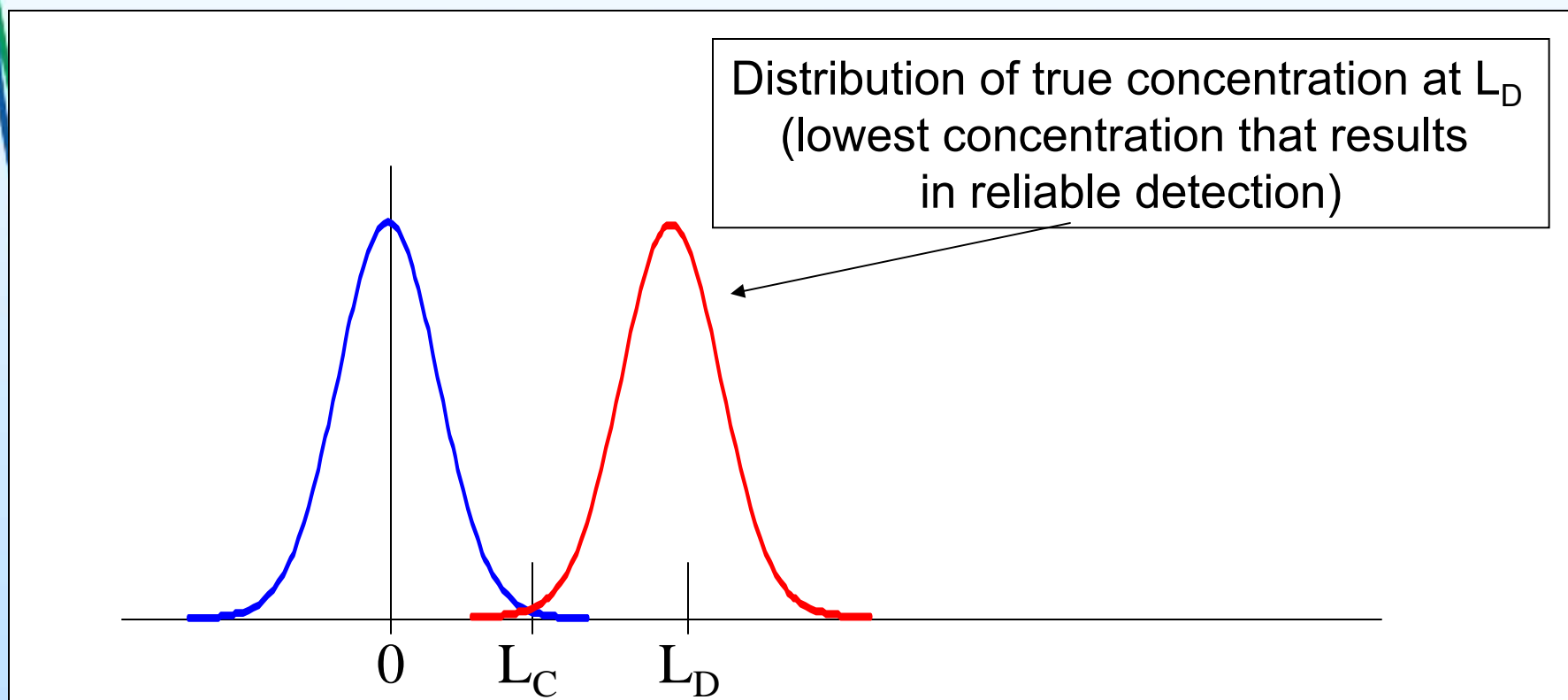
Decision 2

- Use a 2 level detection / quantitation scheme with a critical level and a quantitation limit
- Do not use a three level detection / quantitation scheme with a critical level, a limit of detection and a quantitation limit

Why use a 2 level DL/QL rather than a 3 level DL/QL?

- Currie defined three levels, L_C , L_D and L_Q
- L_C = Critical level
 - ~ Lowest result that can be reliably distinguished from a blank
- L_D = Limit of Detection
 - ~ Lowest true concentration that can be reliably detected (ie lowest true concentration that reliable returns a result greater than L_C)
- L_Q = Limit of Quantitation
 - ~ The lowest true concentration at which the precision of result is adequate for quantification (often considered to be 10%RSD)

Illustration of L_D



Problems with L_D

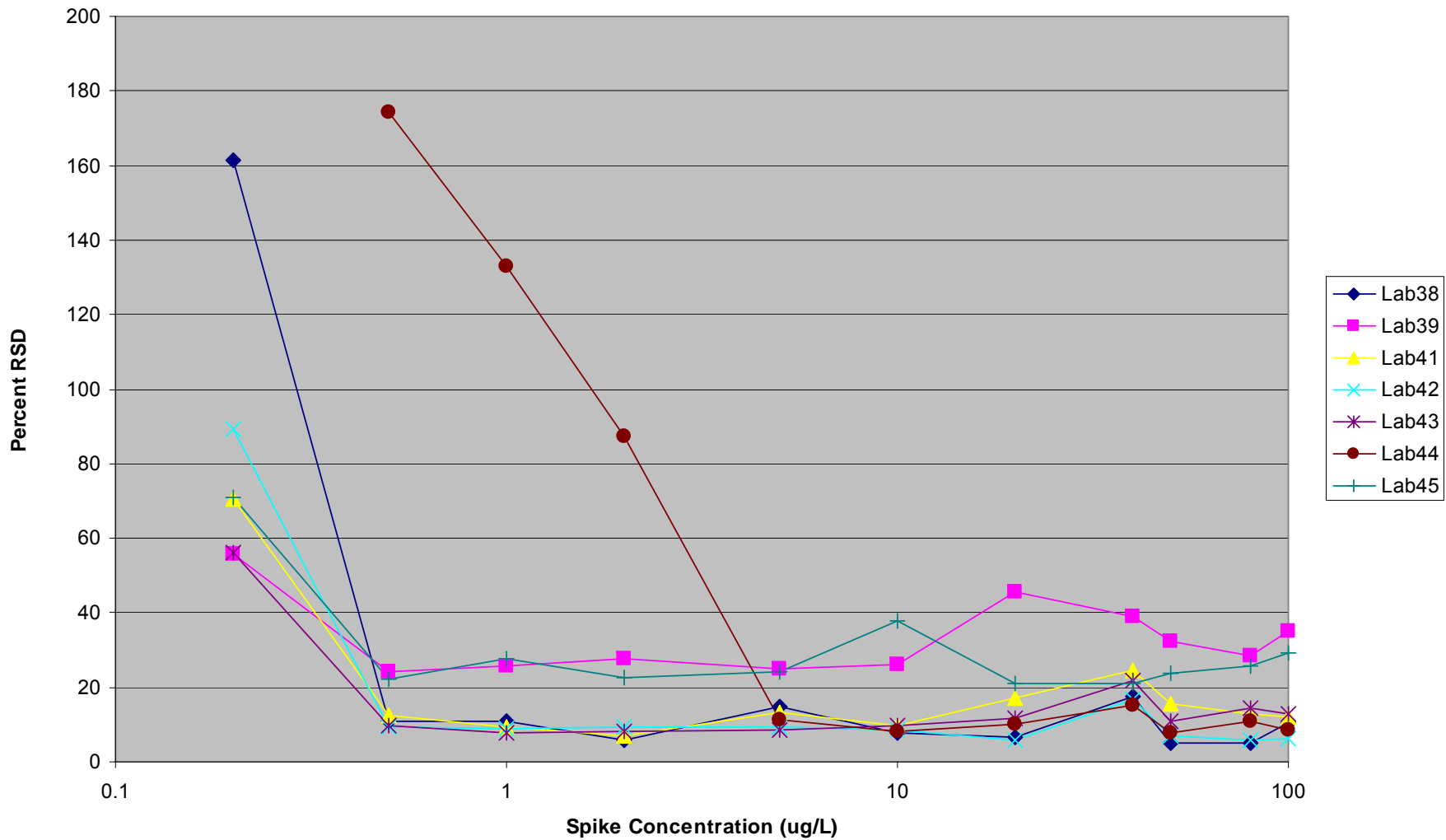
- L_D can be readily determined if we make the assumption that $L_D = 2 \times L_C$
- L_D assumptions
 - ~ No blank bias
 - ~ Constant variance
 - ~ No issues with qualitative identification

**If we cannot assume that $L_D = 2 \times L_C$
then L_D is almost impossible to
determine**

Reasons for the 2 level procedure

- L_D turns out to be close to L_Q in most cases
- The current MDL/ML process is a two level scheme
- Critical level (MDL)
- Quantitation limit (ML)
 - ~ Changing to a three level scheme would have severe implementation problems for laboratory reporting and regulatory use of data

Phenol RSDs by Spike Level



From Ken Miller, CSC

Decision 3

- Use method blanks to determine the detection limit wherever possible
 - ~ The level of contamination or instrument bias has a very significant impact on the detection limit, and the degree of impact can only be determined with blanks
 - ~ A large population of routine blanks is available, since they are analyzed along with every preparation batch
 - ~ No problems regarding selection of the correct spiking level
 - ~ Blanks work best!

Decision 4

- Include a process for verifying the determined detection and quantitation limits
 - ~ There is no requirement to verify MDL or ML in the current Part 136 Appendix B, but....
 - ~ The need for verification is widely recognized
 - Requirements for DL and QL verifications in NELAC
 - Requirements in recent methods

- Evaluate blanks
 - ~ If 5% or more have results above the DL, elevate the DL accordingly
 - Intermittent blank problem
 - Non-normal data
- Evaluate QL spikes
 - ~ If 5% or more give results that are below the DL or fail qualitative identification criteria raise the QL accordingly
 - ~ Check the precision and accuracy
 - ~ Check the LER

Decision 5

- How much data is required?
 - ~ Currently the Part 136 Appendix B procedure requires 7 replicates. These are generally analyzed all on one day, and the evaluation is generally repeated every year, although neither of these requirements is found in the procedure



Amount of Data

- Startup
 - ~ Minimum of 7 blanks (for the DL) and 7 spikes (for the QL).
 - ~ Required per instrument
- Ongoing
 - ~ Minimum of 4 spikes per year. One blank in each preparation batch
 - ~ If multiple instruments, minimum of two spikes per instrument

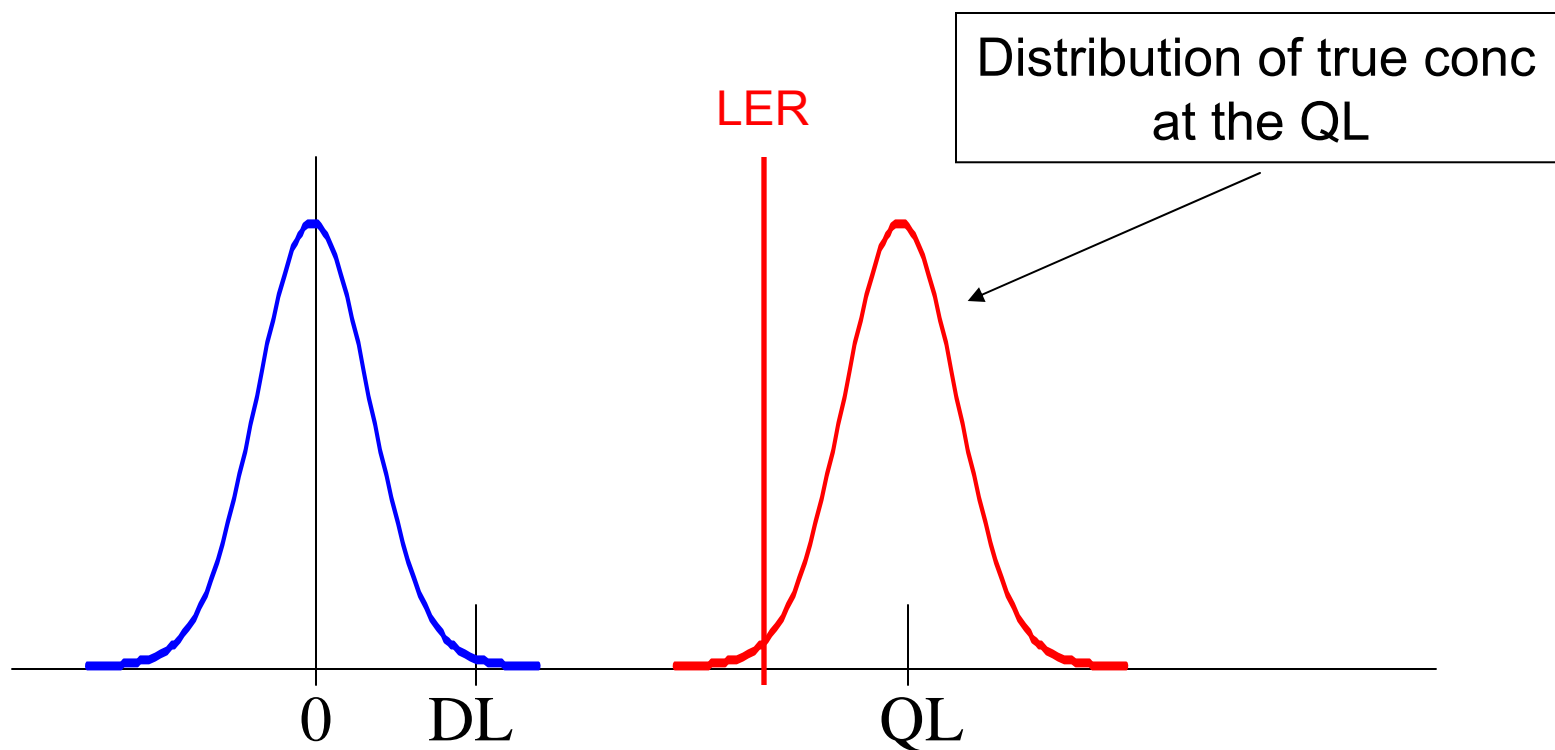
Balance between cost and rigor

Decision 6 Lowest Expected Result

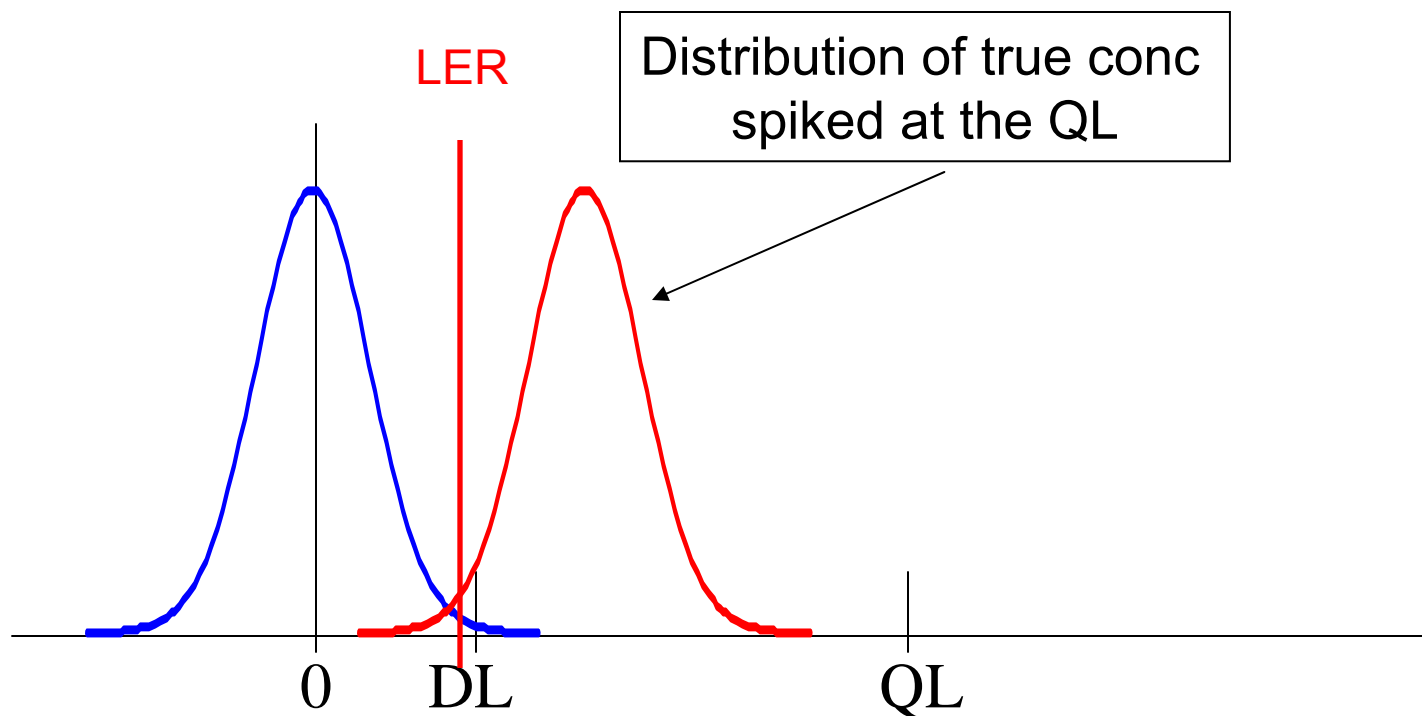
$$\text{LER} = \frac{\bar{X}_s * QL}{SL} - \left(s \times t_{(n-1, 1-\alpha=0.95)} \right)$$

- Where s is defined in std dev of spikes
- Where X is the mean concentration result from the QL spikes.
- t is the 95th percentile of a t distribution with $n-1$ degrees of freedom.
- SL is the spike level used for the QL spike sample.

- Lowest Expected Result (LER)
 - ~ Analyte with 100% recovery

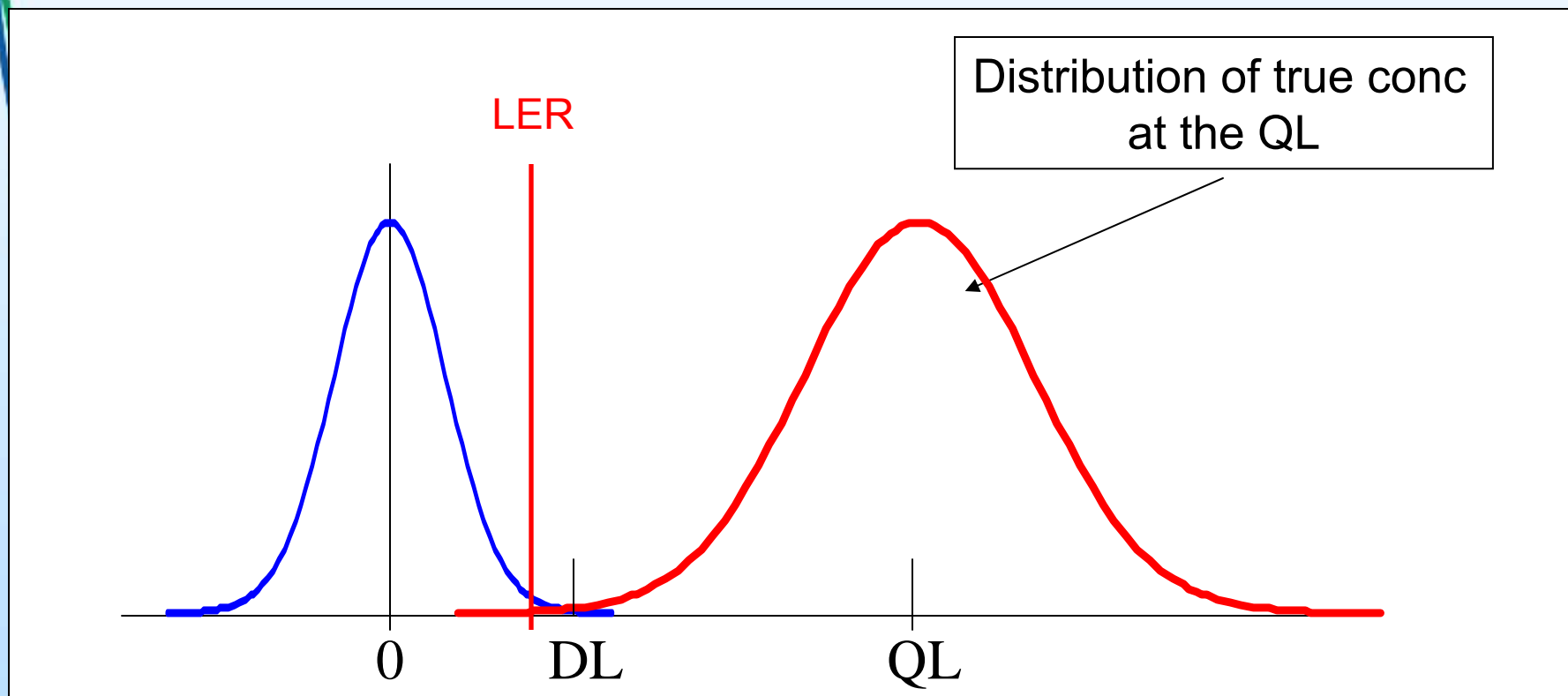


- Lowest Expected Result (LER)
 - ~ Analyte with 50% recovery



QL needs to be adjusted up

- Lowest Expected Result (LER)
 - ~ Analyte with poor precision



QL needs to be adjusted up

LER check, method 524.2

- 13 samples, spiked at QL
- No false negatives for any analyte that passes the LER test
- 10 analytes that failed the LER test had between 1 and 13 false negatives

Detection Limit

- Uses ongoing routine data
 - ~ MDL was a snapshot in time
- Blank bias explicitly included
 - ~ MDL calculation does not involve blank bias
- Verification a key part of the procedure
 - ~ MDL does not require verification

Quantitation Limit

- Considers variance and accuracy
 - ~ ML considers only variance
- Failure to consider qualitative identification
 - ~ Yes, Qualitative identification is verified
- Variance is based on assumption of constant variance and is not verified
 - ~ Yes, actual variance is measured

Next Steps

- Pilot test of the procedure
- Procedure modifications, if indicated by Pilot results
- Proposed rule
- Public Comment
- Final rule

- All opinions expressed are those of the author, not necessarily of the FAC

QUESTIONS?