Statistics and External Quality Assessment Programmes for Medical Laboratories

HKAS Training

6 November, 2012

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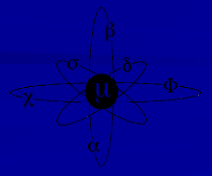

Statistical Methods and EQAP

- Method Validation/verification – general discussion
  - CLSI EP5, EP9, EP15, EP17
- Measurement Uncertainty for Medical Laboratories
  - CLSI C51, ISO 21748
- EQAP
  - General
  - CLSI GP27

ISO 15189:2011

- **5.5.1.1 General**
- The laboratory shall select examination procedures which have been validated for their intended use…The specified requirements (performance specifications) for each examination procedure shall relate to the intended use of that examination.

ISO 15189 - Verification

- **5.5.1.2 Verification of examination procedures**
- Validated examination procedures … shall be subject to independent verification by the laboratory before being introduced into routine use.

The laboratory shall obtain information from the manufacturer/method developer for confirming the performance characteristics of the procedure.

ISO 15189 - Verification

- **5.5.1.2 continued**
- The independent verification by the laboratory shall confirm, through obtaining objective evidence … that the performance claims for the examination procedure have been met. The performance claims for the examination procedure confirmed during the verification process shall be those relevant to the intended use of the examination results.

ISO 15189 - Validation

5.5.1.3 Validation of examination procedures

The laboratory shall validate examination procedures derived from the following sources:

a) non-standard methods;

b) laboratory designed or developed methods;

c) standard methods used outside their intended scope;

d) validated methods subsequently modified.

ISO 15189 - Validation

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ISO 15189 - Validation

- **5.5.1.3 continued**
- The validation shall be as extensive as is necessary and confirm, through the provision of objective evidence (in the form of performance characteristics), that the specific requirements for the intended use of the examination have been fulfilled.

ISO 15189 – Characteristics

- **5.5.1.3 continued**

NOTE Performance characteristics of an examination procedure should include consideration of: measurement trueness, measurement accuracy, measurement precision including measurement repeatability and measurement intermediate precision; measurement uncertainty, analytical specificity, including interfering substances, analytical sensitivity, detection limit and quantitation limit, measuring interval, diagnostic specificity and diagnostic sensitivity.

ISO 15189 - Uncertainty

- **5.5.1.4 Measurement uncertainty of measured quantity values**

The laboratory shall determine measurement uncertainty for each measurement procedure in the examination phase used to report measured quantity values on patients' samples. The laboratory shall define the performance requirements for the measurement uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty.

ISO 15189 - Uncertainty

- **5.5.1.4 continued**
- NOTE 1 The relevant uncertainty components are those associated with the actual measurement process, commencing with the presentation of the sample to the measurement procedure and ending with the output of the measured value..

ISO 15189 - Uncertainty

- **5.5.1.4 continued**
- NOTE 2 Measurement uncertainties may be calculated using quantity values obtained by the measurement of quality control materials under intermediate precision conditions that include as many routine changes as reasonably possible in the standard operation of a measurement procedure, e.g. changes of reagent and calibrator batches, different operators, scheduled instrument maintenance.

Trueness Study – Statistical Model

- Basic statistical model:

  m is replaced by $\mu+\delta$

  δ = bias of a measurement method

  μ = true value, or accepted reference value

  When δ is of interest:

  $y = \mu + \delta + B + e$

Medical Applications

- Precision for medical applications in the USA are produced by CLSI – Clinical and Laboratory Standards Institute.
- CLSI EP5 A2 (2004): *Evaluation of precision performance of quantitative measurement methods*
- CLSI EP9 A2 (2002): *Method comparison and bias estimation using patient samples*
  - *'Interim revision', 2010 – no protocol changes*

CLSI EP5-A2 - Scope

- "… for manufacturers of *in vitro* diagnostic (IVD) devices and developers of clinical laboratory measurement methods who wish to establish the precision capabilities of their methods. It is also for the users of those methods who wish to measure their own precision."
  - EP5-A2 also has procedures for verification of manufacturer claims

CLSI EP5-A2 - History

- EP5 (1999) – took 18 years to prepare (original work proposal, 1981).
- Revised in 2002-2004
- Currently under revision (since 2005)
  - First attempt at revision timed out in 2008
  - New revision convened by industry statistician
  - Likely to be completed 2013
- CLSI Standards are heavily influenced by IVDD Industry

CLSI EP5-A2 Revision

- Objective for current version is to update terminology from initial version and to prepare for harmonization with ISO 5725-2
  - More than one instrument
  - More than one laboratory
  - Precision across measuring interval
- Harmonization with ISO 5725-2 is proving to be controversial

CLSI EP5-A2 - Protocol

- EP5-A2 uses a simple protocol
  - At least 2 levels of material
  - At least 20 operating days
  - 2 runs per day
  - 2 samples per run
  - 2 replicates per sample

CLSI EP5-A2 Protocol

- No requirement for interlaboratory comparison study
- No requirement for description of precision across measuring interval

- Includes considerations for more than one device or more than one laboratory
- Includes recommendation for describing precision across measuring interval

CLSI EP5-A2 Components

- The main objective of the precision evaluation experiment is to estimate the precision of the device or measurement method as used on a single instrument in a single laboratory.
- Components estimated:
  - Repeatability
  - Between run; within day; between day
  - Within laboratory

CLSI EP5-A2 – Data analysis

- Remove outliers
  - Replicate outliers only

    diff between replicates > $5.5\sigma_r$ (not Cochran)

- Components estimated by conventional statistical procedures

CLSI EP5-A2 – Data analysis

- Compare repeatability and within-laboratory estimates with manufacturer's claims
  - Chi-Square statistic

CLSI EP9 - Scope

- Objective is an “independent evaluation of bias performance by individual laboratories”
- “The user is free to compare these performance estimates with either the manufacturer’s claims or the user’s own internal criteria.”
- No reference to trueness

CLSI EP9-A2 - History

- EP9 (1995) – started in 1986).
- Revised in 2002
- Currently under revision (since 2008)
  - ‘Interim revision’ in 2010 to provide new introduction
  - No substantive changes
- Comparison, not validation, but lacks requirement of common reference (not VIM concept of ‘comparison’)

CLSI EP9-A2 - Protocol

- Simple protocol
  - At least 5 operating days
  - At least 40 patient samples
  - Samples tested with reference and comparative methods
  - 2 replicates per analysis

CLSI EP9-A2 - Analysis

- Outlier check for replicates
- Visual comparison
- Linear regression
- Bias estimate is the difference between methods at medical decision points

CLSI EP17

- EP17 (2004): *Protocols for determination of limits of detection and limits of quantitation*

CLSI EP17 - Scope

- "… recommendations for determining the lower limit of detection of clinical laboratory methods, for verifying claimed limits, and for the proper use and interpretation of the limits. It also provides guidance for determining lower limits of quantitation based on a laboratory's goals for performance at low-levels."

CLSI EP17 - History

- EP17 (2004) – work started 1989).
  - Based on ISO 11843 series “Capability of detection” from ISO TC69/SC6
- Currently under revision (since 2008)

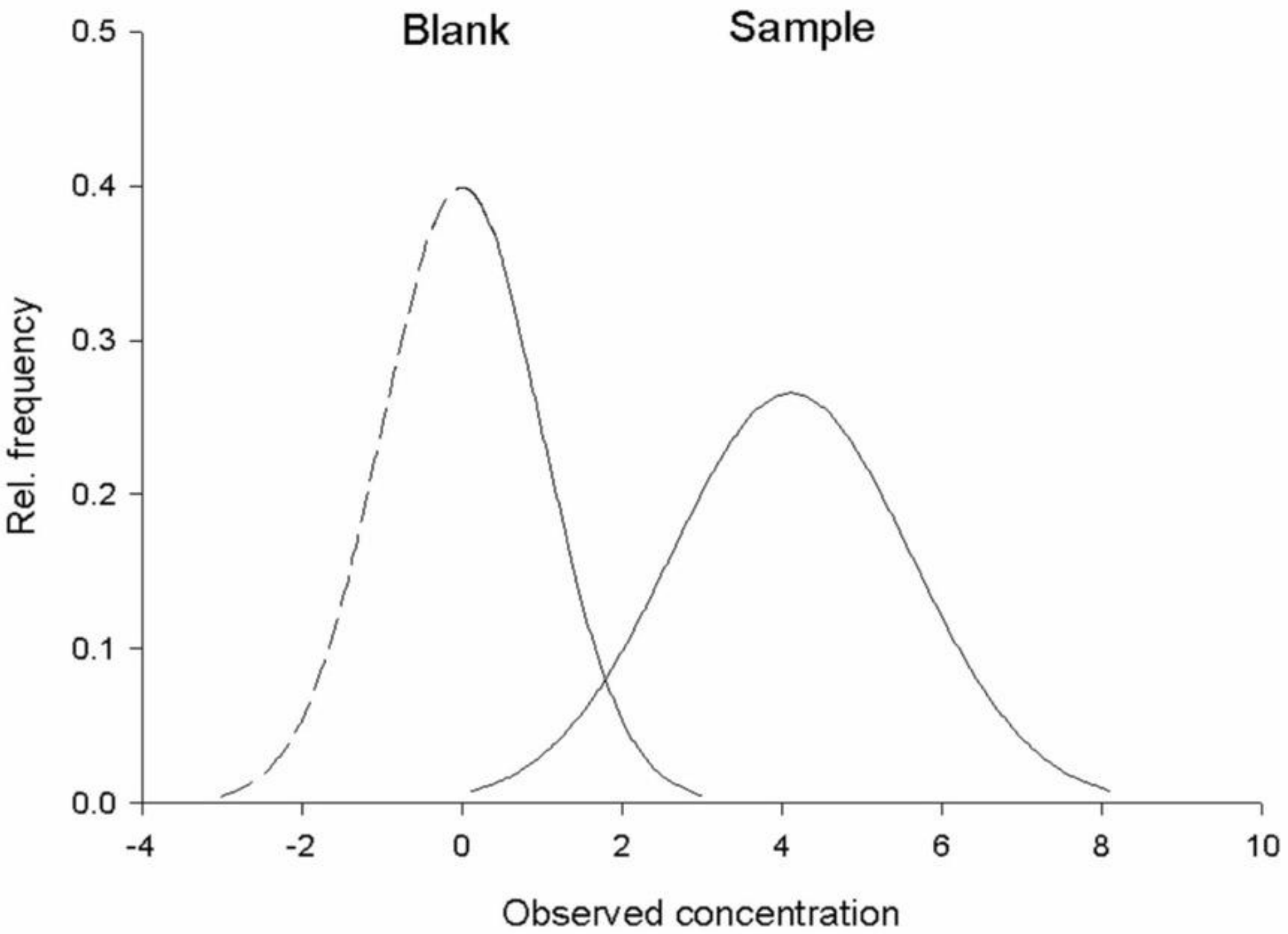
- Applied to all IVD methods with LOD claims, since 2004

Limit of Detection - Conventional

- Repeated measurements on a blank sample or very low level sample
- Calculate SD
  - LOD = 3SD; LOQ = 7 SD
  - LOD = 5 SD; LOQ = 10SD
  - Etcetera…no consensus
  - ‘Signal to Noise Ratio’ > 4 (or 3 or 7 or ??)
- No consideration for what happens for samples that have low level positive

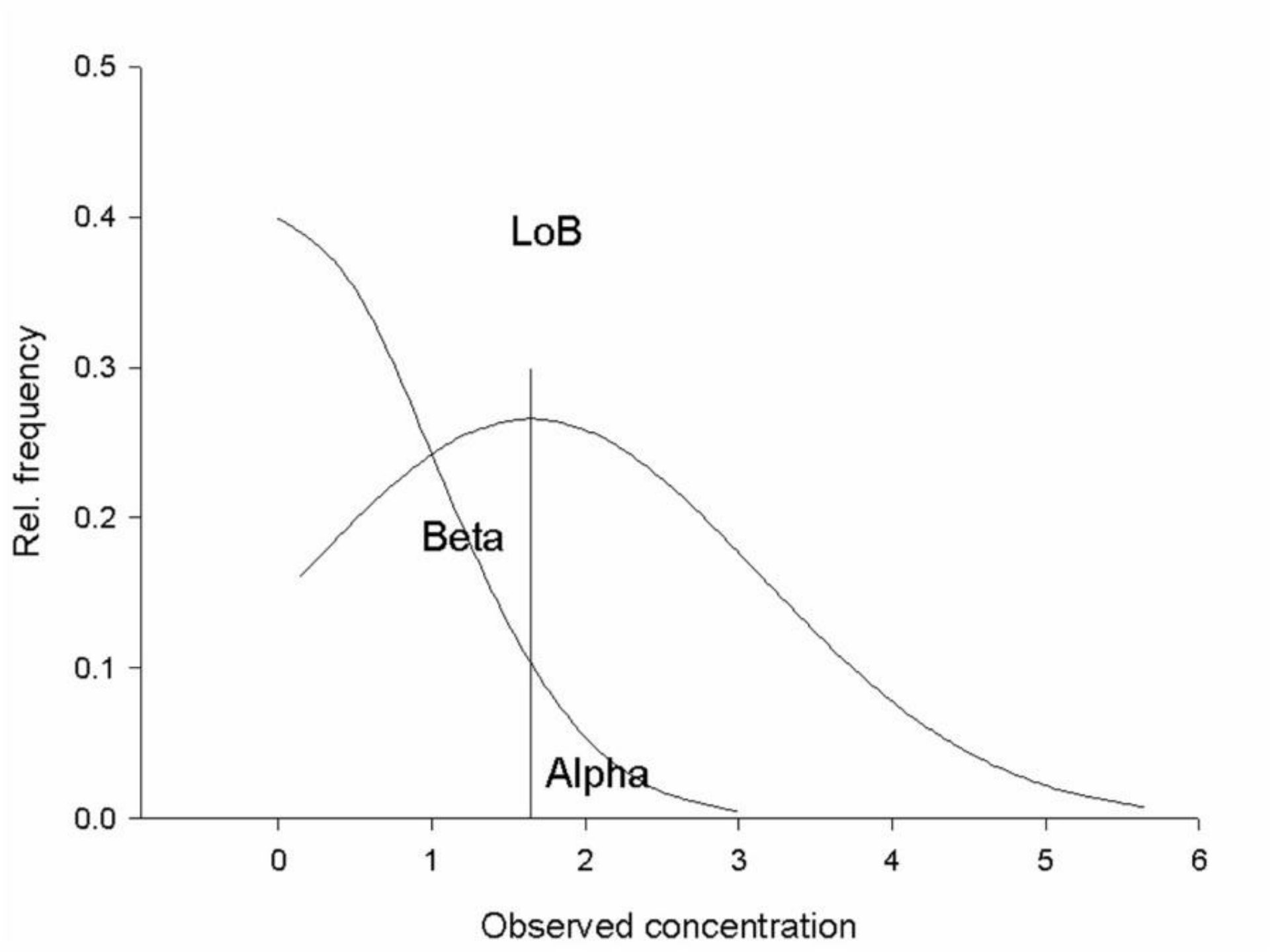
CLSI EP17 - Protocol

- EP17 uses a nonparametric procedure (based on ranks)
- Assumes that the distribution of results on blank samples is different than the distribution of samples with small amounts of the measurand


Blank
Sample
0.5
0.4
0.3
0.2
0.1
0.0
Rel. frequency
-4
-2
0
2
4
6
8
10
Observed concentration

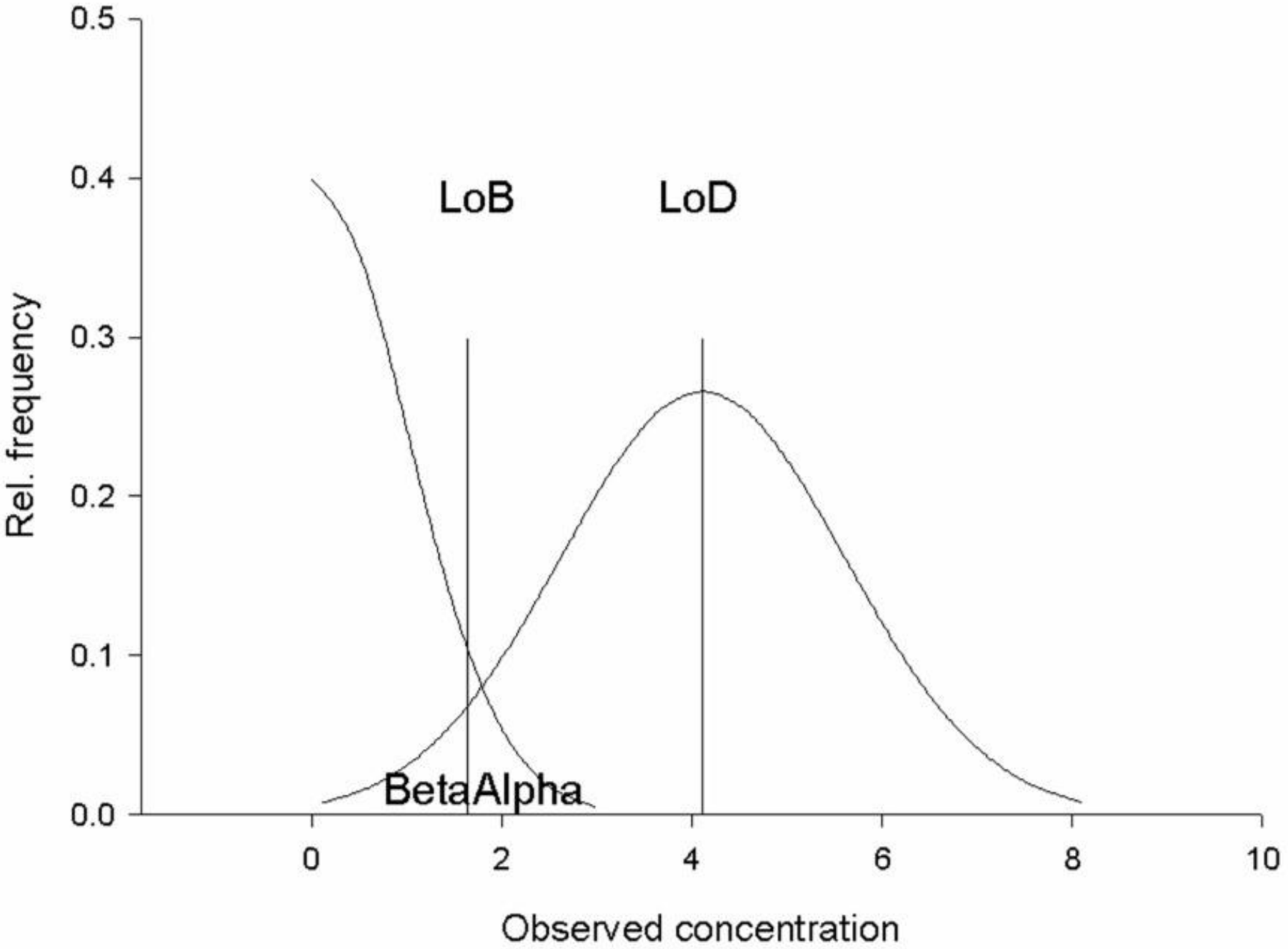
CLSI EP17 - Protocol

- EP17 uses a nonparametric procedure
  - Analysis of 60 “blank” samples
  - Determine “Limit of Blank” (LOB) (critical value, 95th percentile)


0.5
0.4
0.3
0.2
0.1
0.0
Rel. frequency
LoB
Beta
Alpha
0
1
2
3
4
5
6
Observed concentration

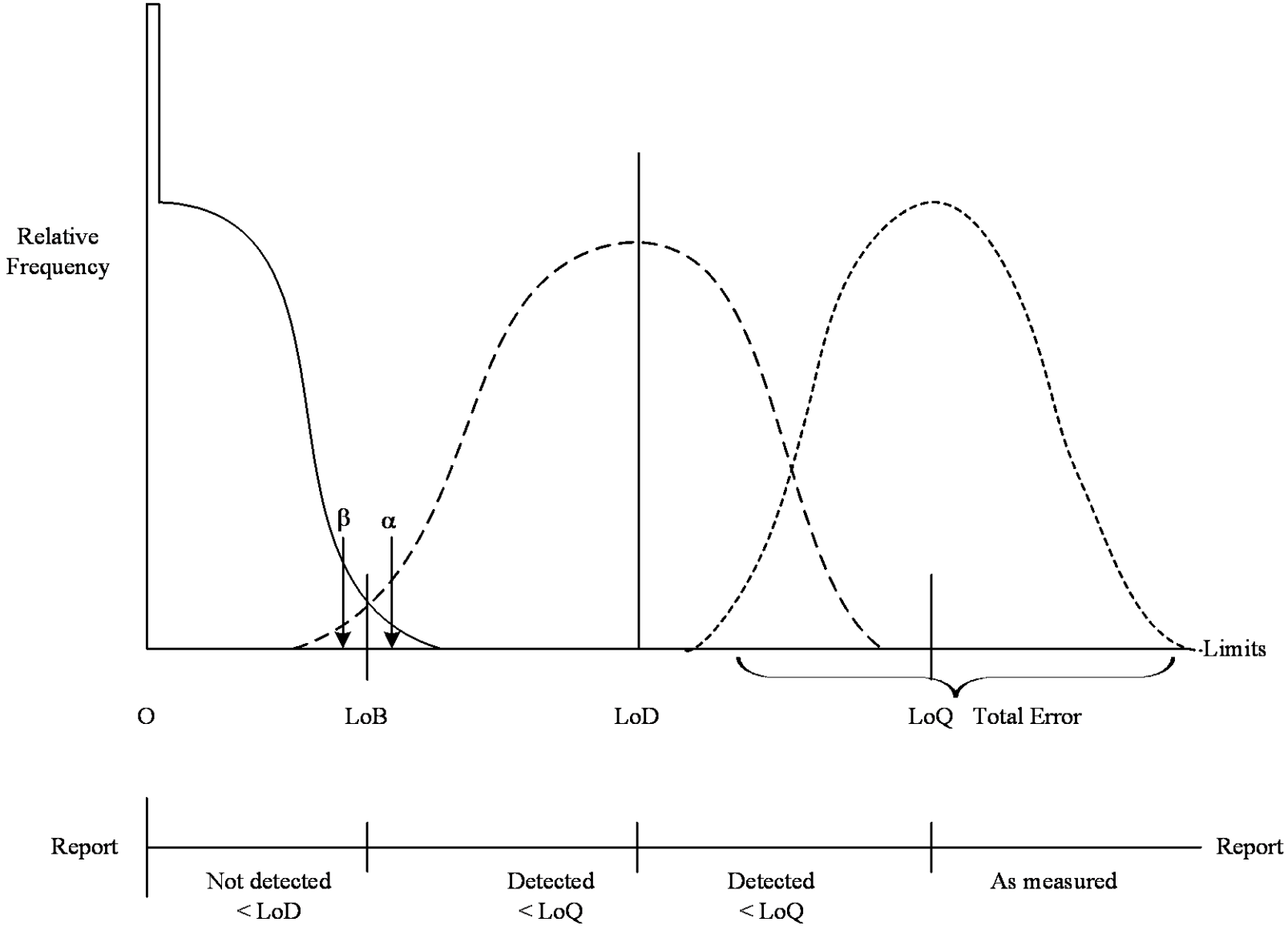
CLSI EP17 - Protocol

- EP17 uses a nonparametric procedure
- Analysis of > 60 samples with level > LOB
  - LOD = level where >95% of results > LOB


0.5
0.4
0.3
0.2
0.1
0.0
Rel. frequency
LoB
LoD
Beta
Alpha
0
2
4
6
8
10
Observed concentration

CLSI EP17 - Protocol

- EP17 uses a nonparametric procedure
- LOQ based on analytical goals for error (target uncertainty)


Relative Frequency
β
α
Limits
O
LoB
LoD
LoQ
Total Error
Report
Report
Not detected
< LoD
Detected
< LoQ
Detected
< LoQ
As measured
α = Prob (False Positive)
β = Prob (False Negative)
Total Error < Laboratory Goal
Distribution of Blank
Distribution of Sample at LoD
Distribution of Sample at LoQ

CLSI EP17 Protocol

- All in one laboratory - no requirement for interlaboratory comparison study
- Could be manufacturer or test laboratory

Medical Applications - Verification

- In US (CLIA'88) laboratories must 'verify' that a method works according to manufacturer specification, prior to using the method for patient examinations.

- CLSI EP15 (2005): *User verification of performance for precision and trueness*

EP15 A2 (2005)

- Experiment to verify precision claim
  - 5 days
  - 2 different levels
  - 1 run per day
  - 1 sample for each level
  - 3 replicates per sample
- Estimates obtained:
  - Repeatability
  - Within laboratory precision

EP15 A2 (2005)

- Compare repeatability and within-laboratory precision estimates with manufacturer claim
  - Chi-square tests

EP15 A2 (2005)

- Experiment to verify trueness claim
  - 20 patient samples (across range)
  - Each sample tested in duplicate
  - Need reference method
- Not really trueness, unless a CRM or definitive reference method is used
- Can compare with manufacturer claim only if the same reference method is used
  - Use t test on differences

C51A Expression of Measurement Uncertainty in Laboratory Medicine

"This document describes a practical approach to developing relevant and useful estimates of measurement uncertainty and for using the information to maintain and improve the quality and application of clinical laboratory measurements."

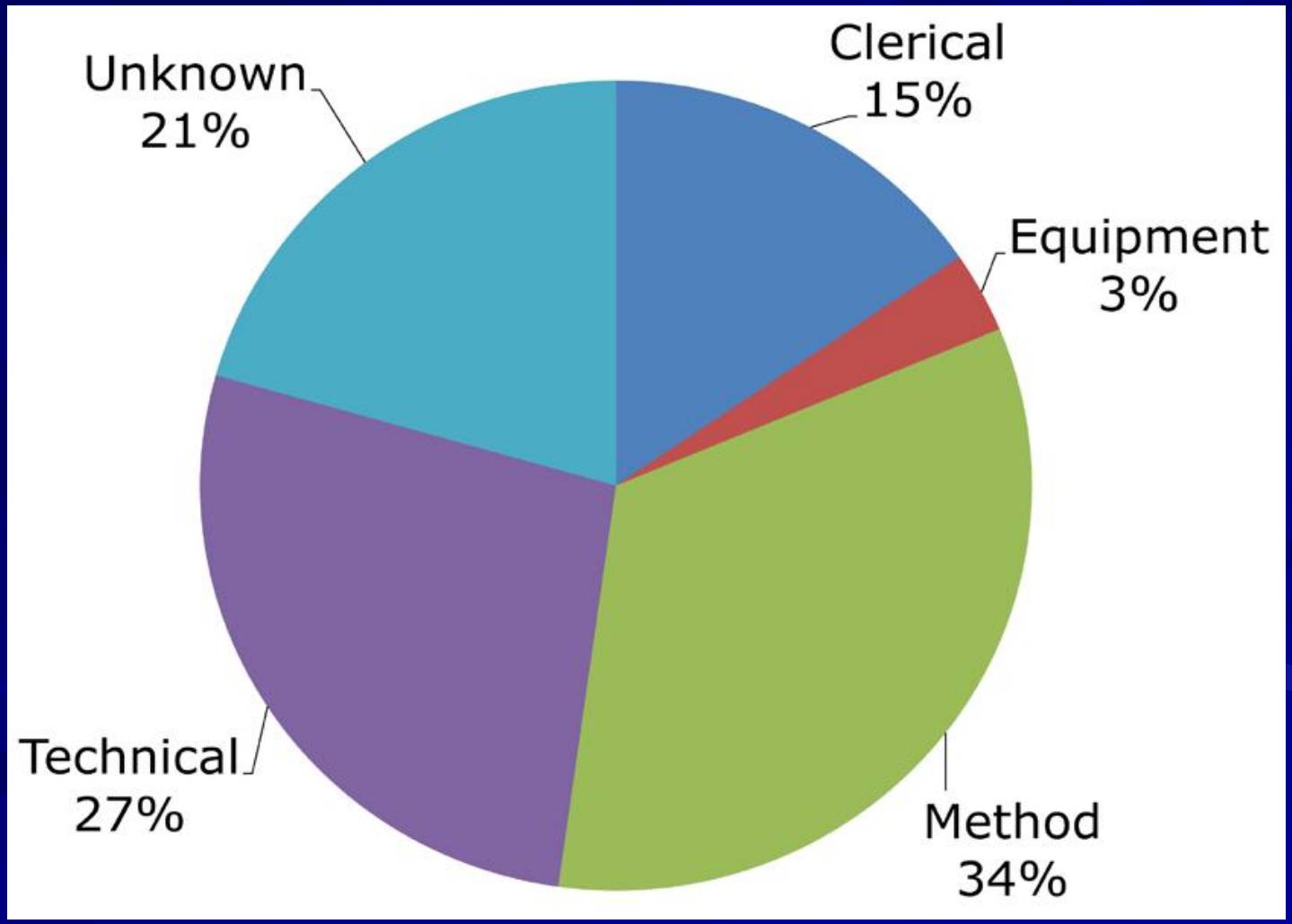
C51 Uncertainty (2011)

- Overview of MU
- Bottom-up evaluation (GUM)
- Top-down evaluation
  - QC data
  - Method validation (if by interlaboratory study)
  - Confirmation with EQA
- Bias assessment
- Reporting MU and other uses
- Example with QC data

Evaluating EQAP Results

- Many guides exist, specific for programme
  - CLSI GP27A2:2008 (under revision)
  - CAP PT
  - Bio-Rad EQAS
  - RCPA EQA
  - Others

QMP-LS EQA Root Causes - 2011



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