World Health Organization
WHO Collaborating Centre for Regulatory Control of Pharmaceuticals

PIC/S
Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

QUALITY SYSTEM
SIRIM
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STANDARDS MALAYSIA
ACCREDITED LABORATORY
MS ISO/IEC 17025:2005
No: SAMM 450

Analytical Method Validation Common Problem 3

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OUTLINE

- LOD & LOQ parameter & related common problem(s)
- System suitability parameter & related common problem(s)
- Robustness
- Common problem(s) with attachment
- Other common problem(s)

Limit of Detection (LOD) & Limit of Quantification (LOQ)

Recap

Type of analytical procedure characteristics	Identification	Testing For Impurities Quantitation	Testing For Impurities Limit	Assay - dissolution (measurement only) - content/ potency
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm. Precision	-	+ (1)	-	+ (1)
Specificity (2)	+	+	+	+
Detection Limit	-	- (3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

- signifies that this characteristic is not normally evaluated

+ signifies that this characteristic is normally evaluated

(1) in cases where reproducibility has been performed, intermediate precision is not needed

(2) lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s)

(3) may be needed in some cases

DETECTION LIMIT VS QUANTITATION LIMIT

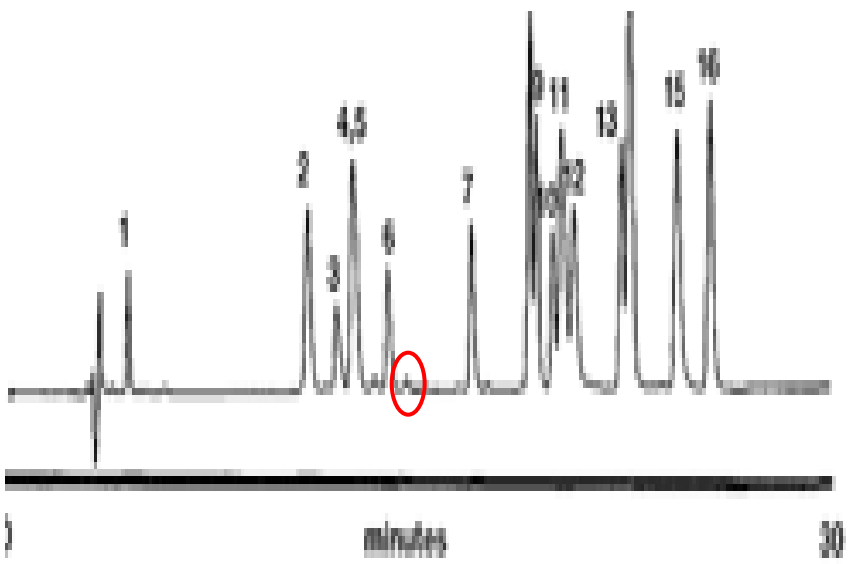
DL 'Know that it's there'

vs

QL 'Know how much is there'

DL vs QL

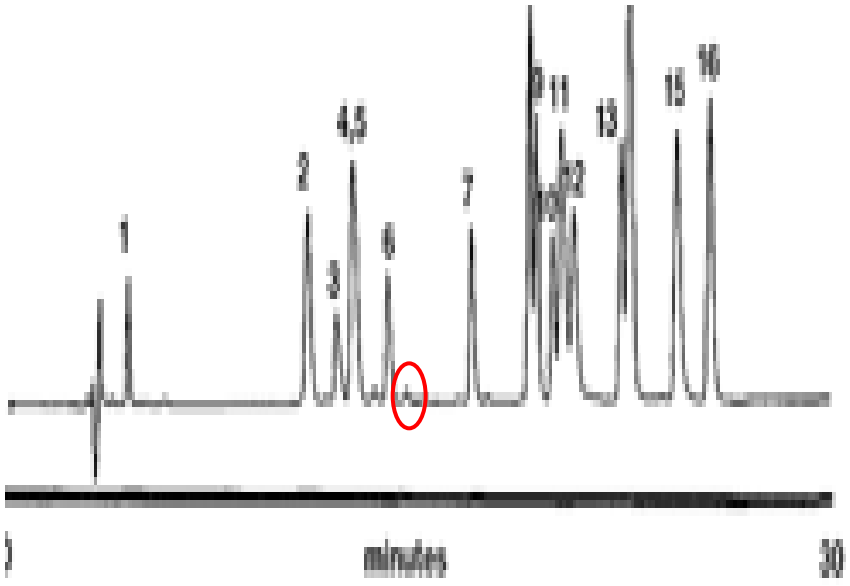
Is any of it present?



Is it there?

Detection Limit

How much of it present?



How much of it is there?

Quantification Limit

LOD : Definition

ICH 2005:

"…the lowest amount of analyte in a sample which can be detected but not necessarily quantitated…"

LOQ : Definition

ICH 2005

"…the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision & accuracy."

Is used particularly wrt assay of impurities &/or degradation products

LOD & LOQ: Approaches

Several approaches

1) Based on Visual Evaluation

2) Based on Signal-to-Noise (S/N)

3) Based on the Standard Deviation (SD) of the Response and the Slope

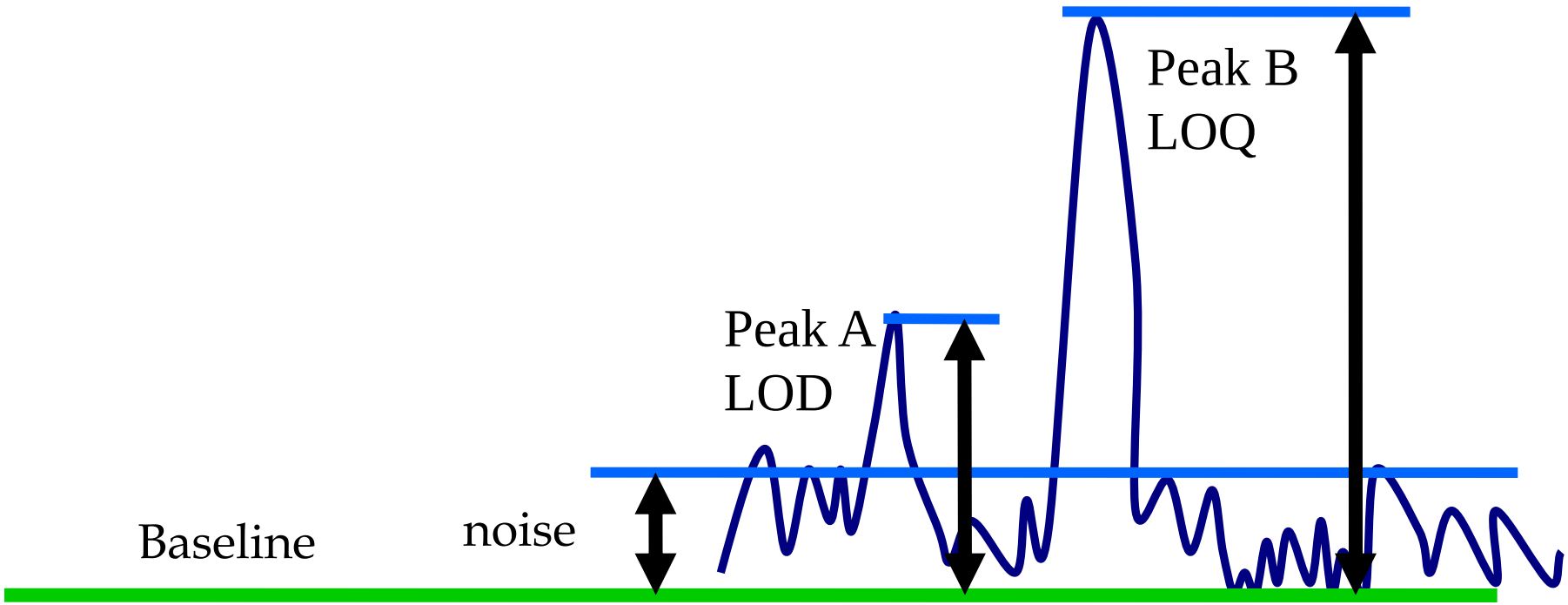
LOD & LOQ: Based on Visual Evaluation

- Visual evaluation may be used for non-instrumental methods but may also be used with instrumental methods.
- LOD
  ↳The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected .
- LOQ
  ↳The quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.
- Frequently this approach is used for TLC

LOD & LOQ: Based on Signal-to-Noise

- This approach can only be applied to analytical procedures which exhibit baseline noise.
- For example: GC, HPLC
- performed by comparing measured signals from spls with known low conc. of analyte with those of blank spls and establishing the min. conc. at which the analyte can be –
  (LOD) reliably detected; (LOQ) reliably quantified
- Typical S/N acceptance criteria:
  - LOD: 3 or 2:1
  - LOQ: 10:1

LOD & LOQ: Based on Signal-to-Noise



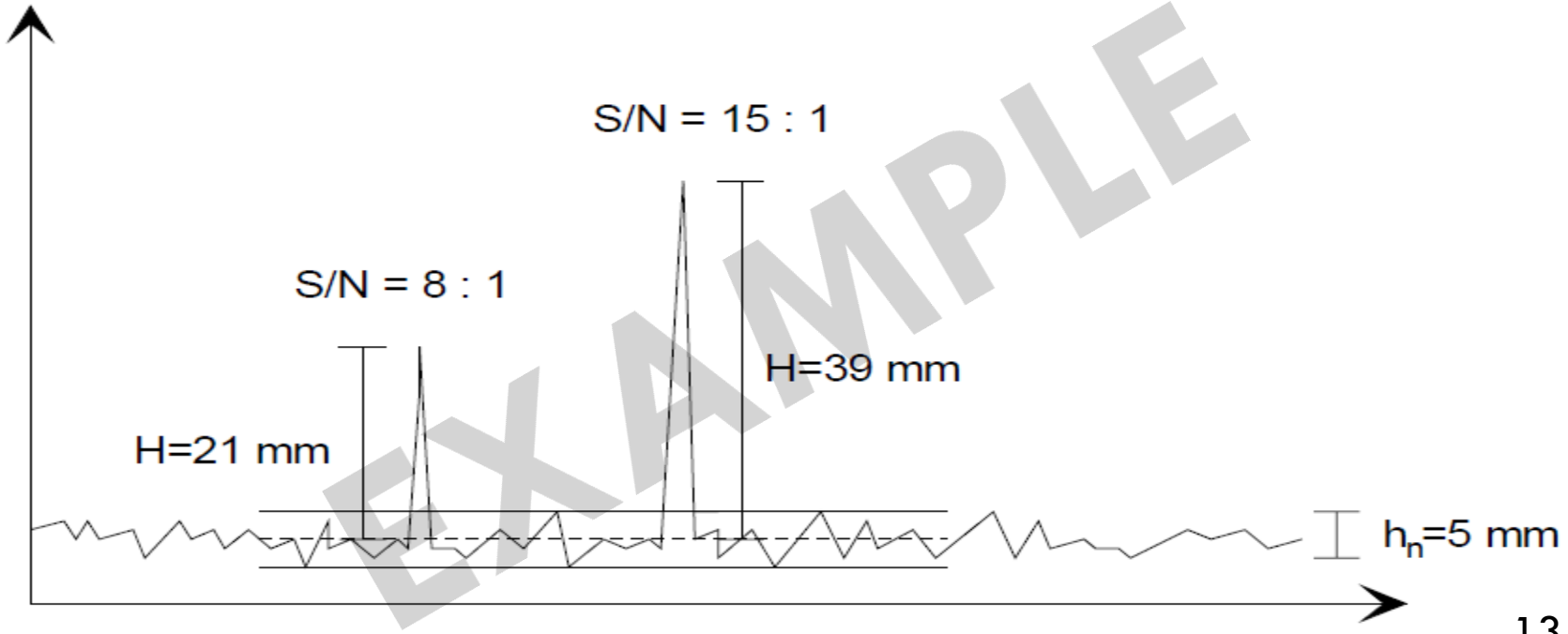
LOD & LOQ: Based on Signal-to-Noise

- The value for S/N can be calculated:

S/N = 2H/h

H: High of the peak from the mean baseline;

h: difference btw the largest and smallest noise values observed over a distance ≥ 5 times the width at the half-height of the peak and, if possible, situated equally around the peak of interest



LOD & LOQ: Based on SD of Response & Slope

- LOD calculation:

  $DL = 3.3 \times \sigma / S$

- LOQ calculation:

  $QL = 10 \times \sigma / S$

- Where σ = standard deviation of the response
  S = the slope of the calibration curve (of the analyte)

- Estimation of σ:
  - Based on the Standard Deviation of the Blank
    Analysing an appropriate no. of blank spls and cal. the SD
  - Based on the Calibration Curve
    Specific calibration curve can be studied using spls containing an analyte in the range of LOD/LOQ. The residual SD of a regression line or the SD of y-intercepts of regression lines may be used as the standard deviation σ.

LOQ: Recommended Data

- Summarized report with clear supportive data.
- Chromatogram with clear & symmetrical peak. Especially for visual evaluation method & Signal to noise method.
- Linear of regression. Standard Deviation (SD) of the Response and the Slope.
- Raw Data. E.g. chromatogram data: S/N, peak, conc., SD, recovery, calculation etc.

LOD & LOQ: Common Problem(s)

1) Method used is not clearly stated

2) Raw data was not provided eg. data to construct the curve, chromatogram with signal to noise ratio

3) Often leave out LOD

4) Do not provide confidence interval for LOQ determined based on calibration curve approach.

System Suitability Test (SST)

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ICH 2005:

◊ "…an integral part of many analytical procedures."

◊ "… The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such."

◊ "… System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated."

USP 2009:

◊ "… an integral part of chromatographic methods that should be run routinely to ensure the best performance of the chromatographic system"

◊ "Whenever there is a significant change in equipment or critical reagent, suitability testing should be performed before the injection of samples."

System Suitability Test (SST)

◊ Conclusion:

Sample analysis obtained while the system fails the requirements of system suitability are unacceptable

◊ Data required: at least 3 SS parameters

◊ Example of SS parameter & its AC:

1) RSD NMT 2.0%
2) tailing factor, t NMT 2.0
3) theorectical plate, N NLT 2000
4) resolution, R NLT 2
5) Capacity factor, k' NLT 1.5

SST: Common Problem(s)

1) Do not include system suitability criteria in analytical protocol and data is not provided in validation protocol.

2) No chromatogram provided.

ROBUSTNESS

ROBUSTNESS

- Show reliability of an analysis with respect to deliberate variations in method parameters.
- Should be considered during development phase and is depends on the type of procedure under study.
- Involved series of system suitability parameters being study to ensure validity of analytical procedure.
- Susceptible variation should suitably controlled or precautionary statement should stated in procedure (ICH 2005).

ROBUSTNESS: example

- Typical variation: stability of analytical solutions (sample, standard & etc).
  ◊ e.g.) Compare results after storage of test solution, e.g. for 24h at say 25°C:
  => AC: NMT +2% difference in assay

- others: pH of mp, mp composition, diff. columns, T, f/r & etc.
  ◊ e.g.) Compare results after making a small change to % of methanol (e.g. 40% vs 45% methanol) in mp
  => AC: NMT +2% difference in assay

Common Problems: Attachment

Common Problems: Attachment

1) Not able to locate attachment/reference stated by applicant.

2) Raw data, e.g. chromatograms, provided are not well labeled.

3) Resolution of attached chromatograms is low.

4) Pure chromatograms. No other related information to explain the chromatogram, e.g. retention time, peak area, system suitability.

Other Common Problems

Other Common Problems

1) Non compendial product declared analytical method complied to BP/USP method and thus do not perform analytical method verification.

2) Company claimed current pre-registered product is same as previously registered product and thus do not perform AMV.

3) Impurities limit too high

4) Some analytical procedure such as related substances, dissolution often being leave out.

Reference

Reference

- ICH Q2 (R1), 2006.
- Ludwig Huber, Validation and Quantification in Analytical Laboratories, 1998.
- Drug Registration Guidance Document (DRGD), First Edition, Revised July 2014.

Thank you!