

Supplementary Training Modules on Good Manufacturing Practice

Validation Part 4: QC-related validation



Validation

Introduction

- Why is analytical monitoring necessary?
- What is the purpose of analytical validation?



Validation

Objectives

To introduce the concepts of :

- Protocol development
- Instrument qualification
- Analytical procedure
- Extent of validation
- Method transfer
- Chemical and physical, biological, and microbiological test validation



Validation

Validation of analytical procedures requires:

- Qualified and calibrated instruments
- Documented methods
- Reliable reference standards
- Qualified analysts
- Sample integrity



Validation

Validation protocol for analytical method

- Statement of purpose and scope
- Responsibilities
- Documented test method
- List of materials and equipment
- Procedure for the experiments for each parameter
- Statistical analysis
- Acceptance criteria for each performance parameter



Validation

Qualification of the instrument

- ❑ Make, model and maker's manual
- ❑ Modifications
- ❑ Installation and operational qualification
- ❑ Calibration programs
- ❑ Maintenance schedules



Validation

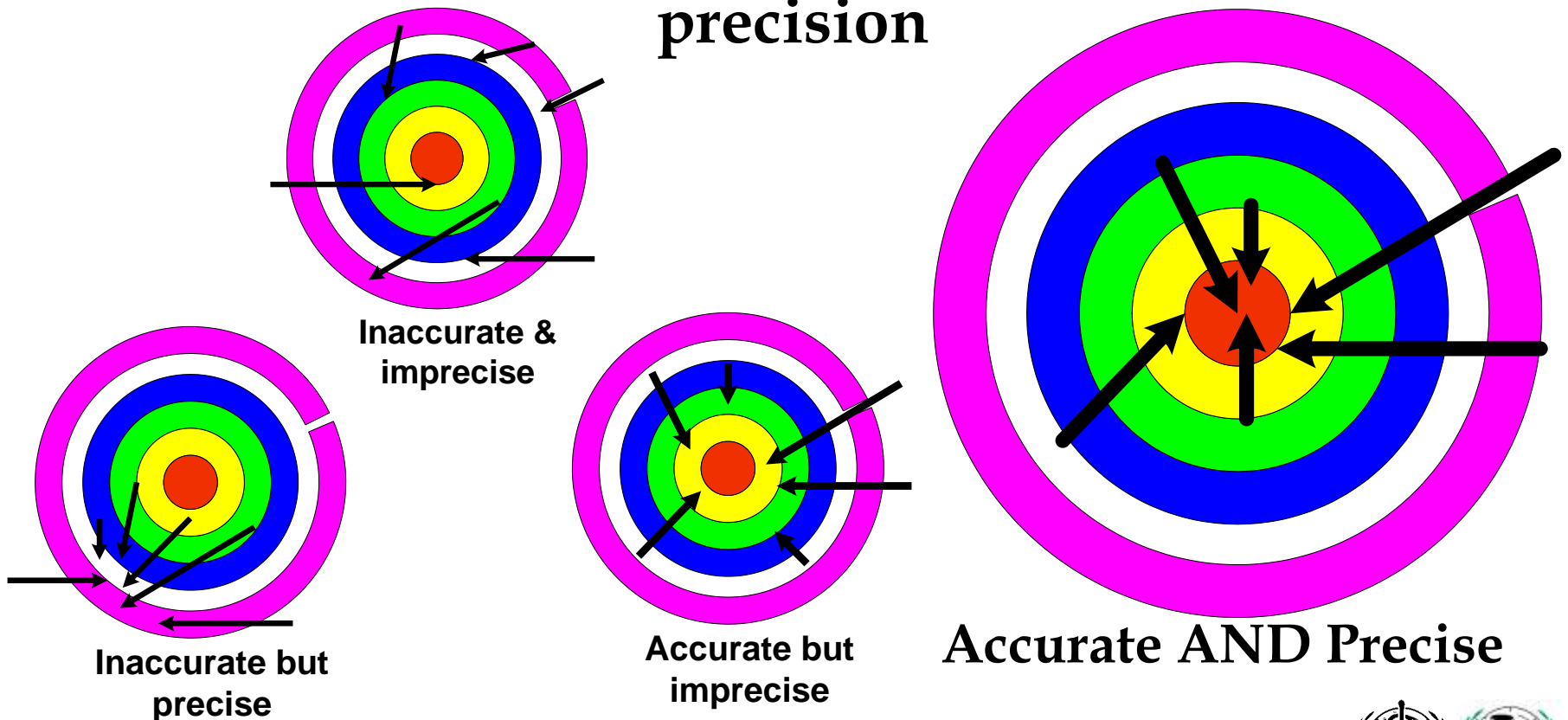
Characteristics of analytical procedures (1)

- Accuracy
- Precision
- Repeatability
- Reproducibility



Validation

Relationship between accuracy and precision



Validation

Characteristics of analytical procedures (2)

- Ruggedness
- Robustness
- Variability caused by:
 - *Day-to-day variations*
 - *Analyst-to-analyst*
 - *Laboratory-to-laboratory*
 - *Instrument-to-instrument*
 - *Chromatographic column-to-column*
 - *Reagent kit-to-kit*
 - *Instability of analytical reagents*



Validation

Characteristics of analytical procedures (3)

- Linearity and range
- Specificity
- Sensitivity
- Limit of detection
- Limit of quantitation



Validation

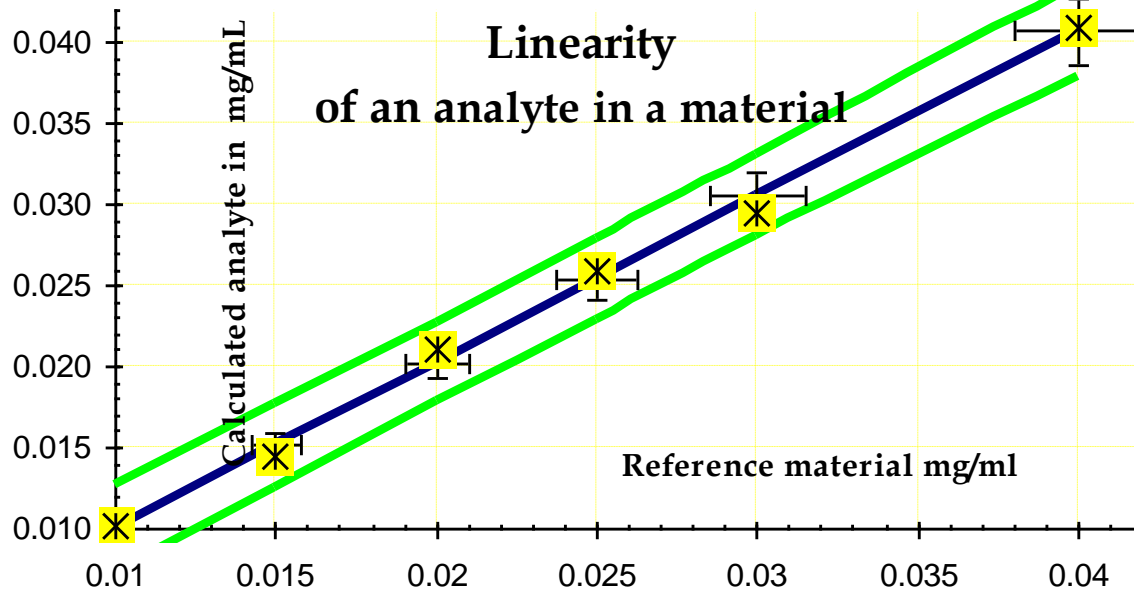


Table of values (x,y)

#	x Reference material mg/ml	y Calculated mg/ml
1	0.0100	0.0101
2	0.0150	0.0145
3	0.0200	0.0210
4	0.0250	0.0260
5	0.0300	0.0294
6	0.0400	0.0410



Validation

Linearity Statistics

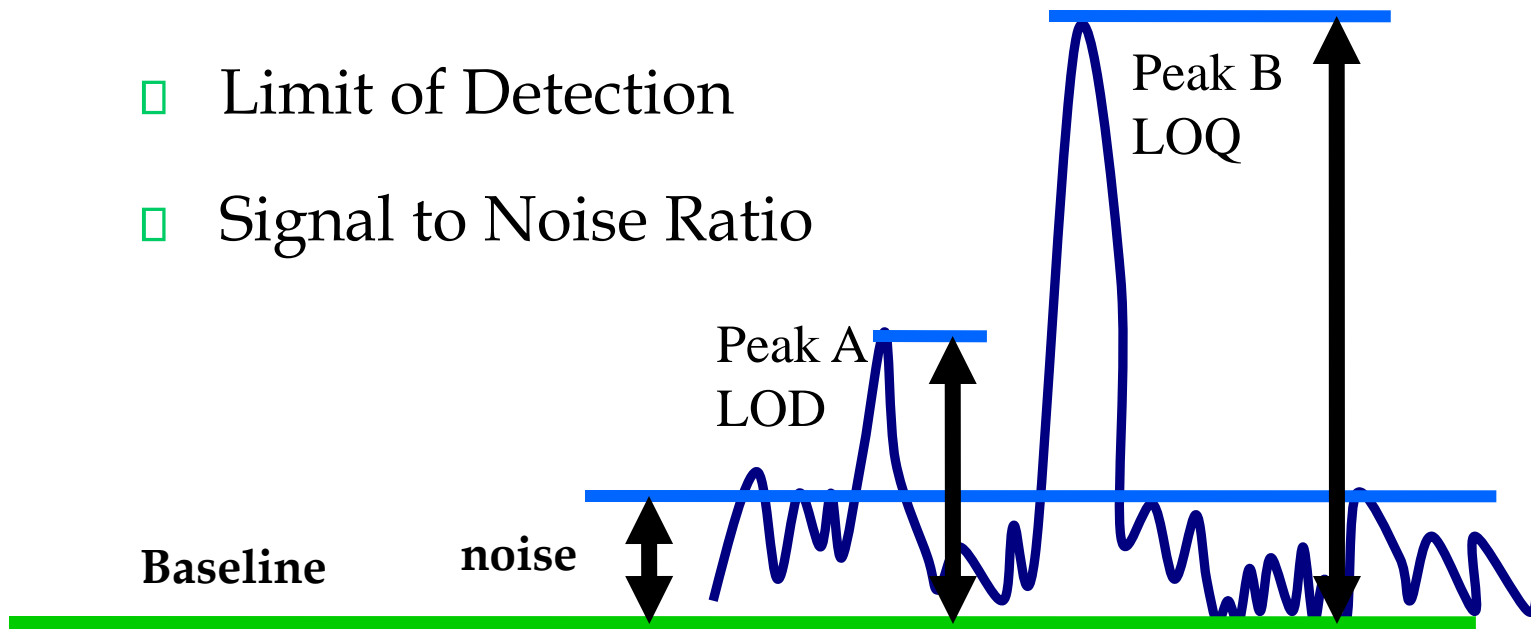
□ Intercept	-0.0002
□ Limit of Linearity and Range	0.005 – 0.040 mg/mL
□ Slope	1.0237
□ Correlation coefficient	
□ <i>Pearson</i>	0.9978
□ <i>Olkin and Pratt</i>	0.9985
□ Relative procedure standard deviation	3.4%



Validation

LOQ, LOD and SNR

- Limit of Quantitation
- Limit of Detection
- Signal to Noise Ratio



Validation

Different classes of analytical tests

- ❑ Class A: To establish identity
- ❑ Class B: To detect and quantitate impurities
- ❑ Class C: To determine quantitatively the concentration
- ❑ Class D: To assess the characteristics



Validation

Characteristic	A	B quant.	B Limit test	C	D
Accuracy		X		X	X*
Precision		X		X	X
Robustness	X	X	X	X	X
Linearity and range		X		X	X
Specificity	X	X	X	X	X
Limit of detection			X		
Limit of quantitation		X			



Validation

Extent of validation

- New methods require complete validation
- Pharmacopoeial methods require partial validation (or verification)
- Significant changes mean partial revalidation
 - *equipment changes*
 - *formula changed*
 - *changed suppliers of critical reagents*



Validation

Analytical method transfer

- Method transfer protocol and procedure
 - *precision*
 - *accuracy*
 - *ruggedness*
- Written and approved specific test method
- Proficiency check
- Formal acceptance by new laboratory



Validation

Chemical laboratory validation requirements (1)

- Balances
- Chromatography
 - *HPLC, HPTLC, GC, TLC*
- Dissolution or disintegration apparatus
- Karl Fischer moisture determination
- Melting, softening or freezing point apparatus
- Ovens, refrigerators, incubators



Validation

Chemical laboratory validation requirements (2)

- pH meter
- Polarimeter - optical rotation
- Refractometer
- Spectrophotometer UV/Vis, IR, FTIR, Raman, AA
- Timers
- Viscometer
- Volumetric equipment



Validation

Typical validation of HPCL assay (1)

- System suitability (performance check)
 - *system precision*
 - *column efficiency*
 - *symmetry factor*
 - *capacity factor*



Validation

Typical validation of HPLC assay (2)

- Method validation
 - *specificity*
 - *accuracy*
 - *precision*
 - *linearity*
 - *robustness*



Validation

Biological assays

- Can be difficult to "validate"
- "Validity" on a case by case basis
- Strictly adhere to the Biological Testing monographs in pharmacopoeias



Validation

Microbiological testing requiring validation

- ❑ Microbial limit testing
- ❑ Microbial count
- ❑ Sterility testing
- ❑ Preservative effectiveness testing
- ❑ Environmental monitoring program
- ❑ Biological testing



Validation

Validation of microbial test procedures (1)

- ❑ Virtually impossible to completely validate test procedures for every microorganism
- ❑ Neutralize /inactivate inhibitory substances, or dilute
- ❑ Periodic media challenge
- ❑ Media QC
- ❑ Reliable methods



Validation

Validation of microbial test procedures (2)

- Incubation temperature and time
- Media may not grow all microorganisms
- Variations in media may affect recovery
- Inhibitory disinfectants or preservatives
- Sample
 - *procedures*
 - *handling, storage, transport*



Validation

Microbiological viable count method validation (1)

- Methods
 - *pour plate / spread plate*
 - *membrane filtration*
 - *Most Probable Number*
- Sample size
- Test dilution
- Inoculation size



Validation

Microbiological viable count method validation (2)

- Membrane filtration conditions
- Incubation conditions
- Acceptance criteria



Validation

Sterility testing validation requirements

- ❑ Media growth promotion, sterility, pH
- ❑ Product validation
- ❑ Stasis testing
- ❑ Environmental monitoring
- ❑ Negative controls
- ❑ Challenge organisms

