

1.8

ICH Q2B Guideline
Validation of Analytical Procedures
Methodology

Comments for its application

Introduction

- ❑ All relevant data collected during validation and formulae used for calculating validation characteristics should be submitted and discussed as appropriate.
- ❑ It is the responsibility of the applicant to choose the validation procedure and protocol most suitable for their product.
- ❑ Well-characterised reference materials, with documented purity, should be used. The degree of purity necessary depends on the intended use.

The validation characteristics

1. Specificity
2. Linearity
3. Quantitation limit
4. Detection limit
5. Range
6. Accuracy
7. Precision
 - Repeatability
 - Intermediate Precision
 - Reproducibility
8. Robustness
9. System Suitability Testing

1. Specificity

1.1 Identification

Discrimination between compounds of closely related structures which are likely to be present.

1.2 Assay and Impurity test

For chromatographic procedures, representative chromatogram.
Resolution of the two compounds which elute closest together.
In case of non specific assay is used, a combination can be applied:
Titration for assay, suitable test for impurities.

1.2.1 Impurities are available

- Assay: Spiking pure substance (drug substance or drug product) with appropriate levels of impurities and/or excipients. Assay result unaffected.
- Impurity test: spiking drug substance or drug product with appropriate levels of impurities and demonstrating separation

1.2.2 Impurities not available

- Samples stored under relevant stress conditions
 - assay: the two results are compared
 - impurity test: impurity profiles are compared
- Peak purity test: diode array, mass spectrometry

2. Linearity

Linearity should be established across the range.

- **Minimum 5 concentrations:**
 - dilution standard stock solution
 - separate weighing of synthetic mixtures
- **Linear relationship, regression analysis**
 - correlation coefficient
 - y-intercept
 - slope of regression line
 - residual sum of squares.

3. Quantitation limit, 4. Detection limit

The ICH guideline on validation has been succeeded by the ICH guidelines on Impurities in New drug substances and Drug Products.

There have been threshold levels defined for

- **Reporting thresholds**
- **Identification thresholds**

They should be applied instead of quantitation and detection limits.

5. Range

Analytical procedure	Range
Assay of drug substance or finished product	80 - 120 % of test solution
Impurity (quantification)	Reporting threshold to 120% of acceptance criteria
Assay and impurity	One test with 100 % standard Linearity: Reporting threshold to 120 % assay acceptance criterion
Content uniformity	70 - 130 % of test concentration
Dissolution testing	± 20% over specified range
Drug release testing	20% after 1 hour up to 90% after 24 hours 0-110 % of label claim

6. Accuracy

Established across the specified range

Analytical procedure	Validation procedure
General	<ul style="list-style-type: none"> • 9 determinations over 3 concentrations covering specified range 3 concentrations, 3 replicates • reporting <ul style="list-style-type: none"> - % recovery or - difference between mean and accepted true value - confidence interval
Drug substance	Application of analytical procedure to analyte of known purity (reference material)
Drug product	<ul style="list-style-type: none"> • Placebo + drug substance • adding known quantities of drug substance to drug product
Impurities (quantification)	<ul style="list-style-type: none"> • Adding known quantities of impurities to drug product • Placebo + impurities <p>The individual or total impurities are determined e.g. weight/weight or area percent, in all cases with respect to the major analyte</p>

7. Precision

Analytical procedure	Validation characteristic	Validation procedure
Assay and impurity	Repeatability	<ul style="list-style-type: none"> • 9 determination from accuracy • 6 determinations at 100% of test concentration
	Intermediate precision	<ul style="list-style-type: none"> • Different days • Analysts • Equipment Not necessary to study these effects individually 2 x 6 determinations at 100 % of test concentration
	Recommended data	<ul style="list-style-type: none"> • standard deviation • relative standard deviation • confidence interval

8. Robustness

Should be considered during development phase

- Variations:**
 - Stability of analytical solutions
 - different equipment
 - different analysts
- HPLC:**
 - influence of pH in mobile phase
 - variations in mobile phase
 - different column
 - temperature
 - flow rate

9. System Suitability Testing

Integral part of analytical procedures