

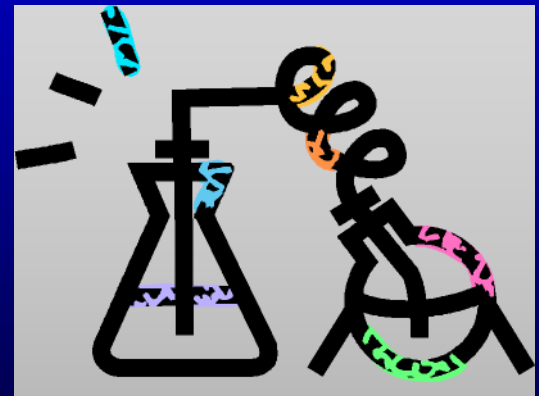
Quality Assurance in Drug Development

Criteria for Safety Assessments

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Content

- Definitions
- General principles
- Key elements
- Compliance issues
- Conclusion



Definition of Safety Pharmacology Studies

“Safety pharmacology studies are defined as those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above”

General Principles

- Rational approach when selecting and conducting safety pharmacology studies;
- Use of scientifically valid methods:
 - preferable internationally recognized/standardized methods
 - use of new technologies and methodologies in accordance with sound scientific principles is encouraged (if needed)
- Limit measurement uncertainty to a minimum.

The Famous Trio:

When expressing results of analytical measurements you will need to bear in mind the 3 inter-linking parameters

Has the method been validated and it is fit for purpose?

VALIDATION

Will the results be traceable to an accepted reference standard?

TRACEABILITY

MEASUREMENT
UNCERTAINTY

How sure will you be of the accuracy of the results obtained?

General Principles

2 basic elements to consider:

- Analytical **process** from receipt of the sample to provision of the result
- Analytical **procedure**: from method validation to regular performance of the analysis

Keywords:

- **QUALITY ASSURANCE**
- **VALIDATION**



Analytical process quality assurance

- Quality management system
- Accreditation (ISO 17025 or ISO 15189)
- Training and qualification of lab personnel
- Adequate infrastructure and service provision
- Adequate instrumentation (including computer systems)
- Review of the system & continual improvement

Accuracy and reliability of an analysis contributing elements

- Human factors
- Technical supplies and environmental conditions
- Analytical method(s) and its validation
- Use and maintenance of the instrumentation
- Measurement traceability (full audit trail)
- Sampling
- Handling of test and calibration items

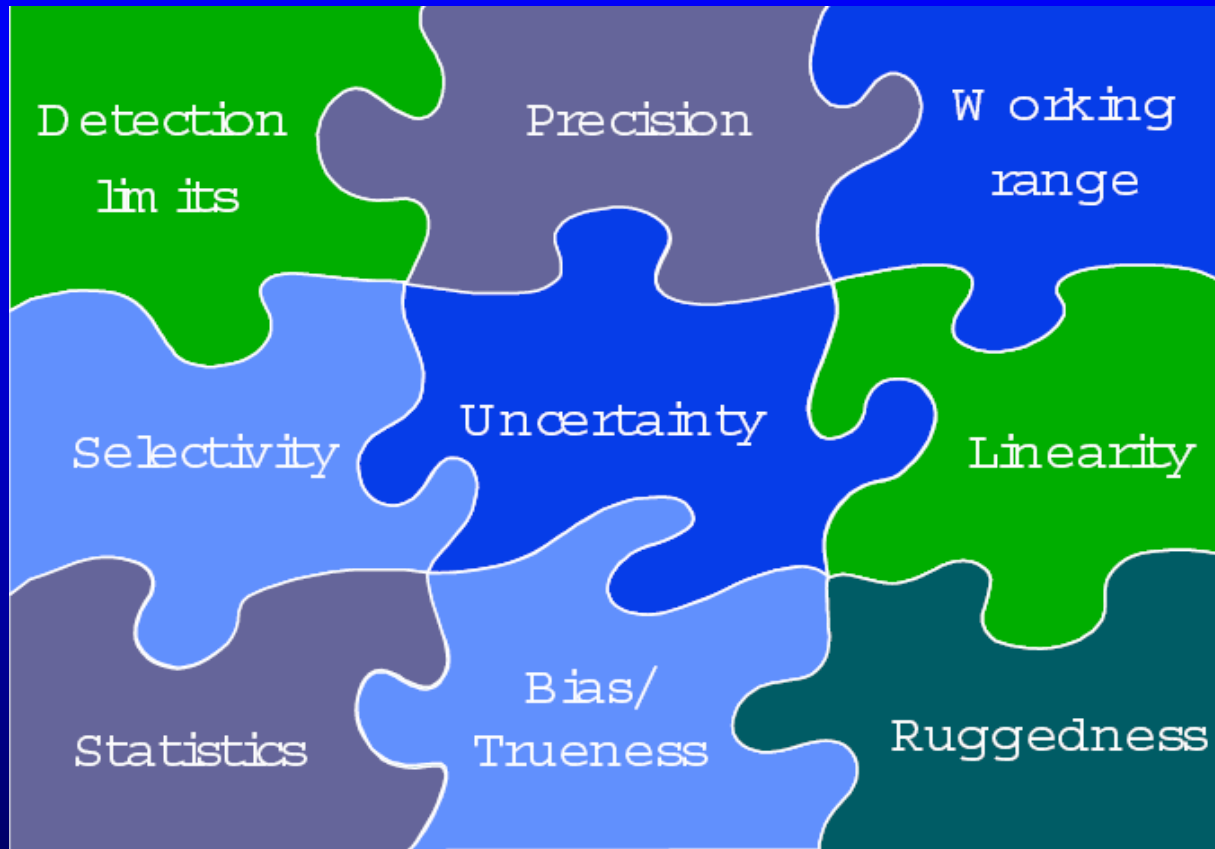
Validation: definition

“Establishing the documented evidence which provides a high degree of assurance that a specific process (analysis) will consistently produce a product (result) meeting its pre-determined specifications and quality attributes.”

Method Validation

Method validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled.

Validation: a puzzle?



Method Validation

Published Guidance documents:

- ICH-Q2(R1) “Validation of Analytical Procedures: Text and Methodology (2005)
- CDER Draft “Analytical Procedures and Method Validation” (2000)
- CDER “Bio-analytical Method Validation for Human Studies” (1999)
- OECD series on principles of Good Laboratory Practice (1997)
- CDER “Submitting Samples and Analytical Data for Method Validations” (1987)
- CLSI (former NCCLS) Guidance Documents

ICH Topic Q2(R1)

Validation of Analytical Procedures

- The main objective of validation of an analytical procedure is to demonstrate that the procedure is **suitable** for its intended purpose.
- In practice, it is usually possible to design the experimental work so that appropriate validation characteristics can be considered simultaneously to provide a sound, overall knowledge of the capabilities of the analytical procedure, for instance: **specificity, linearity, range, accuracy and precision.**
- Well-characterized **reference materials**, with documented purity, should be used throughout the validation study.

Method Characteristics to be considered for Validation

- Specificity (Selectivity)
- Linearity
- Range
- Accuracy
- Precision
 - Repeatability
 - Intermediate Precision
 - Reproducibility (Ruggedness)
- Detection Limit
- Quantitation Limit
- Robustness
- System Suitability



Specificity

- Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include matrix effects, other components, degradation products, etc....
- When it is not always possible to demonstrate that an analytical procedure is specific for a particular analyte (complete discrimination), a combination of two or more analytical procedures is recommended to achieve the necessary level of discrimination (comparison to matrix blank; use method generally accepted as specific)

Linearity

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

(standard curve, linear regression)

Analytical range

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

(standard curve, LOQ)

Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

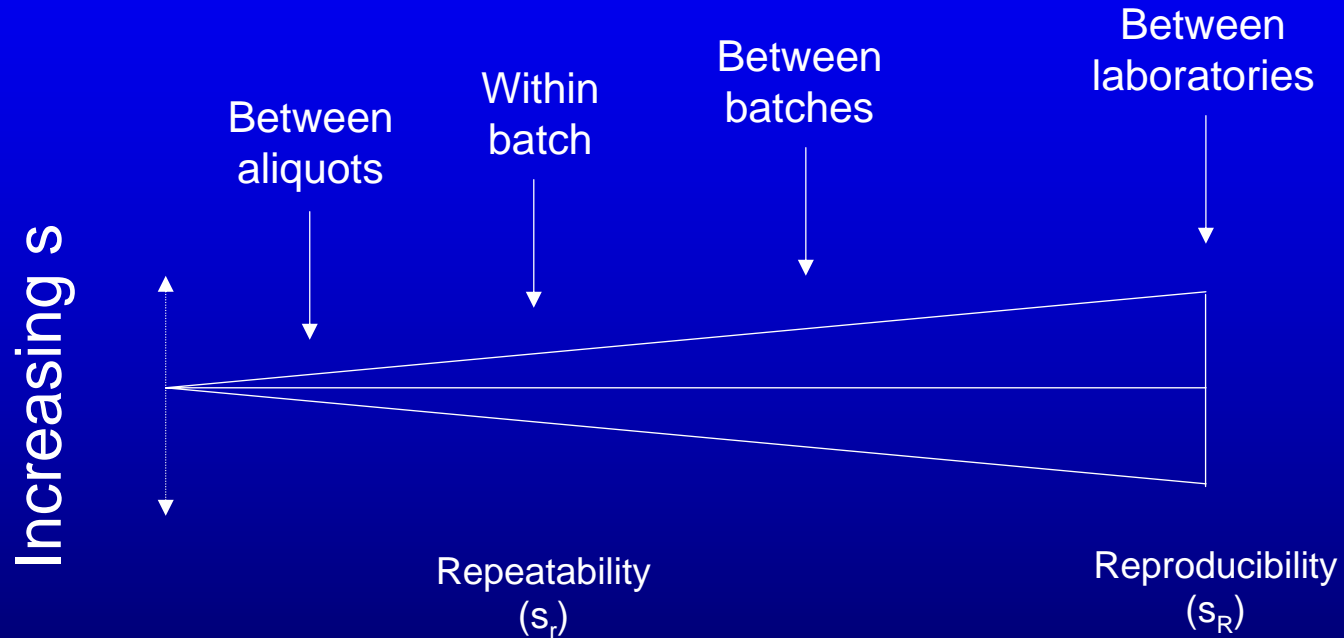
(Recovery, spike)

Precision

- **Repeatability** expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.
- **Intermediate Precision** expresses within-laboratories variations: different days, different analysts, different equipment, etc.
- **Reproducibility** expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

~~(Repeat analyses)~~

Different Precision measurements



Detection limit (LOD)

The Lowest level of an analyte that can be detected above the background on a particular test instrument

(signal/noise ratio)

Quantitation limit (LOQ)

The lowest level of an analyte that can be quantitatively determined with an acceptable level of accuracy and precision.

(signal/noise ratio)

Robustness

The robustness of an analytical procedure is a measure of its capability to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

(minor changes in instrumental parameters,
reagent composition, etc.)

Ruggedness

The ability of a method to produce the expected results in the hands of a competent analyst in a different laboratory, or with different instruments of the same type.

(inter-lab or intra-lab collaborative study)

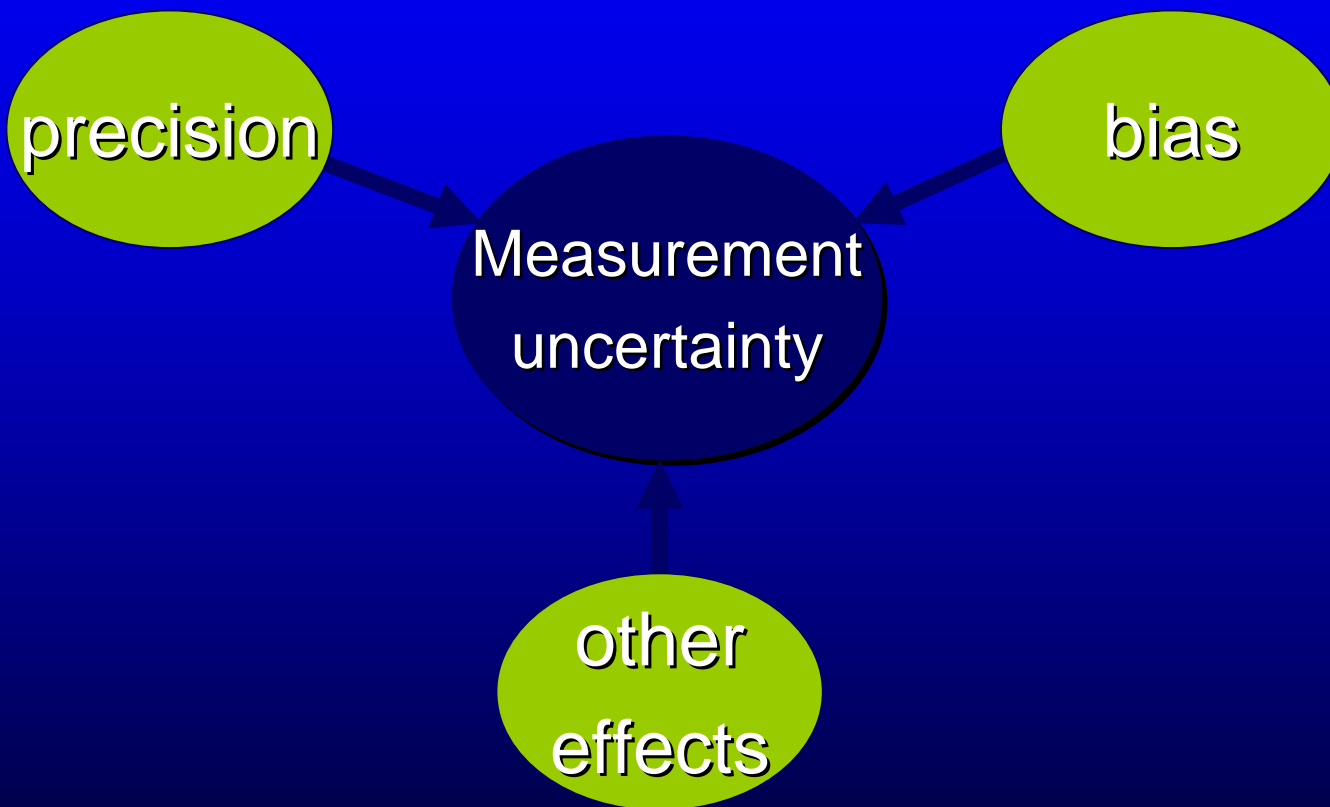
Method validation

Does one need to do each of these all the time?
??????

- Accuracy
- Precision
- Specificity
- Limit of Detection
- Limit of Quantitation
- Linearity
- Range
- Robustness
- Ruggedness



Relation between uncertainty and validation



Method validation

Answer: Do what makes sense scientifically!!

Remember the validation definitions:

...verified under the actual conditions of use

...for the intended analytical applications

...the particular requirements for a specific intended use

Method validation

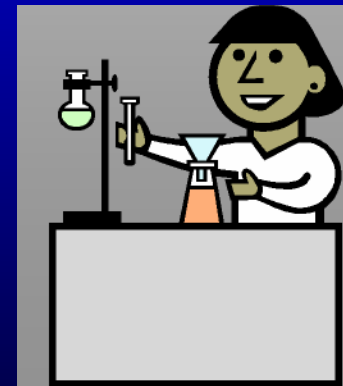
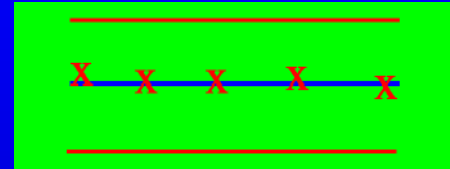
- Major element: **quantitative** determination:
➔ Accuracy and Precision are critical, LOD and LOQ not required
- Trace element: **qualitative** determination:
➔ LOD and Specificity are critical, Precision not required
- Trace element: **quantitative** determination:
➔ Accuracy, Precision, LOD and LOQ, probably all critical

System suitability

System suitability testing is 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

Routine analysis

- Internal quality control
- 2nd and/or 3th level quality control (proficiency testing)
- Technical and 2nd level validation of the result
- Reporting



Compliance issues in the general process

- Insufficient training/qualification of the technical staff
- Defective document management
- Defective quality control and corrective actions
- Insufficient review/audit of the processes

Compliance issues in the technical process

- Target and Control Limits
 - versus validated parameters
 - versus historical process performance
- Equipment Maintenance
- Calibration
- System for reporting and evaluating deviations
 - hardware
 - software
 - security
 - life cycle management

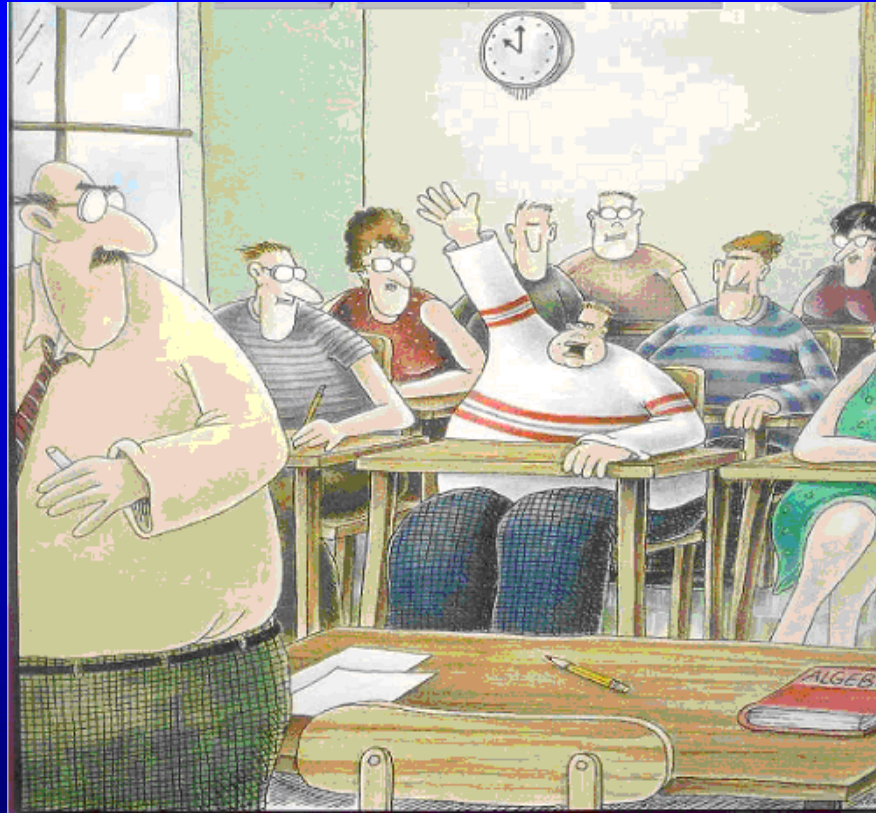
Conclusions

Quality assurance guaranteed by:

- Adequate management system
- A “controlled” test system with process control
- Method validation according to predefined criteria
- Training and education of lab personnel
- Documented procedures
- Proper instrument calibration and maintenance
- Assurance of the lab data integrity



Thanks for your attention!



“Mr. Osborne, May I be excused, my brain is full?”