ANALYTICAL PROCEDURES AND VALIDATION

HOW TO GUARANTEE THE ROBUSTNESS OF DATA AND COMPLIANCE WITH REGULATIONS

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SETTING BEFORE ANALYTICAL VALIDATIONS

- Assay specification of a tablet is 95.0 – 105.0 % label claim
- Assay result on batch L4/18 is 105.3 %

Possible reactions of the Head of production:

A. Something went wrong in production.

B. Was the analytical procedure correctly performed?

C. Are we sure of the analytical procedure?

***The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose*. (ICH Q2_R1)**

Suitability means that no "bad" batches will be released and no "good" batches will be rejected (a problem of OOS).

What are the questions we ask about the "suitability" of the procedure?

- **SPECIFICITY**: can we apply the procedure to the matrix (the medicinal product)? The problem is the potential interference of matrix components to the analyte signal.
- **UNCERTAINTY OF THE RESULT** (quantitative procedures). Includes linearity, precision and accuracy
- **LIMIT OF DETECTION / QUANTITATION**: the lowest analyte concentration the procedure can quantify / quantitatively assess.

… not only today, but in all future applications of the procedure

Regulatory framework
official documents

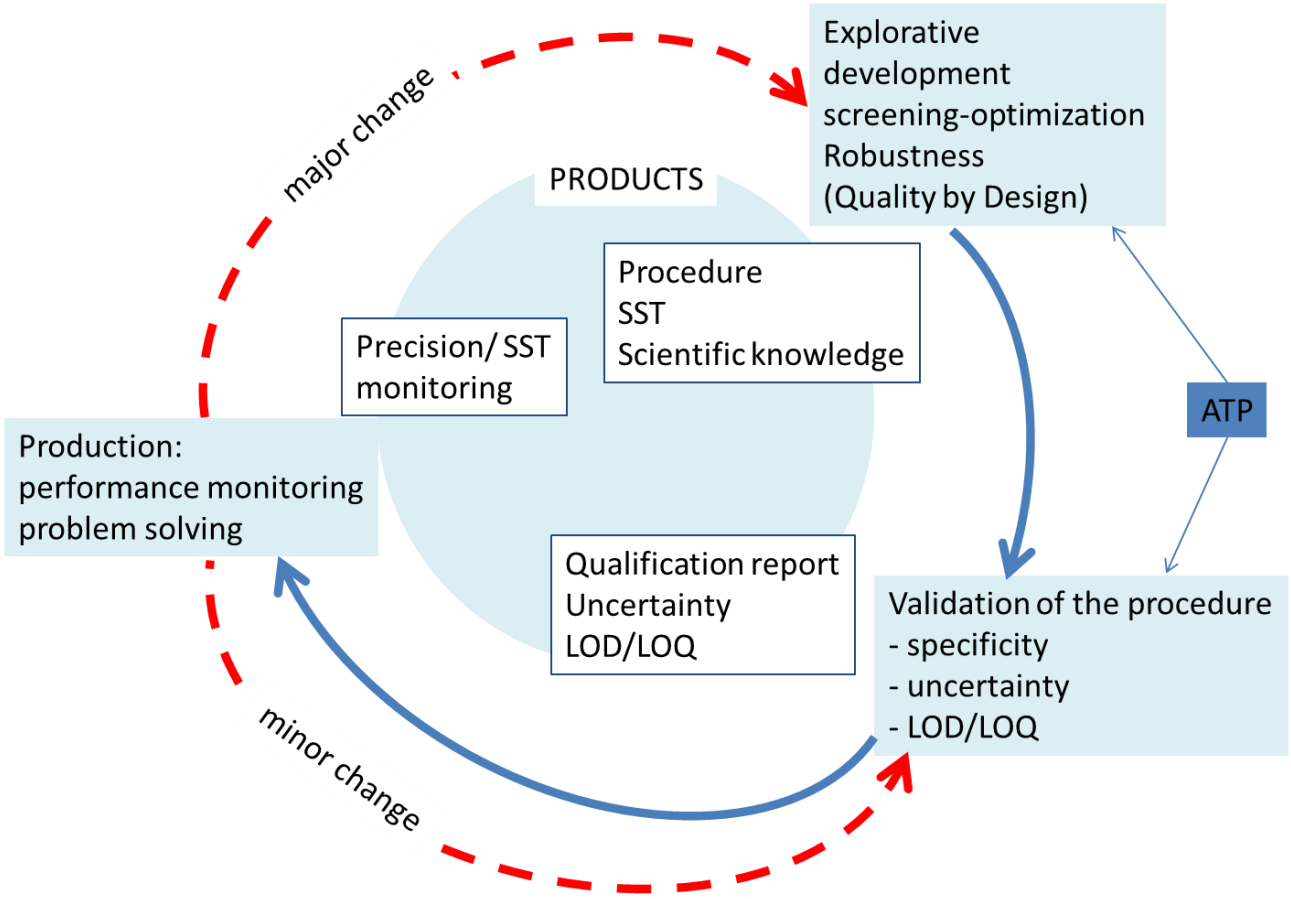
- Guideline ICH Q2_R1 *
- FDA, Analytical Procedures and Methods Validation for Drugs and Biologics – Guidance for industry, July 2015
- ANVISA RDC Nº 166, 24/07/2017

- USP <1010> Analytical data — Interpretation and treatment**
- USP <1210> Statistical tools for analytical validation

**CH Press Release - Kobe, Japan, June 2018*
The Assembly agreed to begin work on three new topics for ICH harmonisation…
- Analytical Procedure Development and Revision of Q2(R1) Analytical Validation (Q2(R2)/Q14

*** Under revision: Pharmacopeial Forum 44(5) 2018*

The analytical procedure lifecycle



The analytical development is part of the validation exercise
Validation is confirmed in the production phase

Correct language matters

Table 1. Analytical Procedure Validation Terminology

Terminology	Description
Laboratory sample	The material received by the laboratory
Analytical sample	Material created by any physical manipulation of the laboratory sample, such as crushing or grinding
Test portion	The quantity (aliquot) of material taken from the analytical sample for testing
Test solution	The solution resulting from chemical manipulation of the test portion such as chemical derivatization of the analyte in the test portion or dissolution of the test portion
Reading (individual determination)	The measured numerical value from a single unit of test solution
Reportable value	Average value of readings from one or more units of a test solution

USP <1210> Statistical tools for procedure validation.

The parameters of the analytical validation

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 impurities, degradants, matrix, etc. (ICH Q2_R1).

- Includes degradation (stress testing).
- Robustness/quality by design of the chromatographic part of the method ensures that specificity can be reasonably maintained in all future applications of the analytical methods.
- The specificity exercise, including robustness/QbD, should afford a significant system suitability test to check specificity in a single analysis.

The design of the quantitative power of the procedure

- **ROBUSTNESS OF THE PREPARATION OF THE TEST SOLUTION**
  Can the procedure be easily repeated? (E.g. extraction)
- **LINEARITY OF THE CALIBRATION** (more in general: the mathematical relationship between the analyte concentration and the instrumental response).
- **LINEARITY OF THE RESPONSE IN THE MATRIX**
  calibration: external or standard additions?
  …essentially is relative accuracy… the primary focus in <1225> and ICH Q2 is the first type of linearity, which can be called calibration linearity [Pharmacopeial Forum 39(3)]
  But: requested by ANVISA in case of complex matrixes (proof of paralellism).
- **STABILITY OF THE ANALYTICAL SOLUTIONS**

PROCEDURE DESCRIPTION

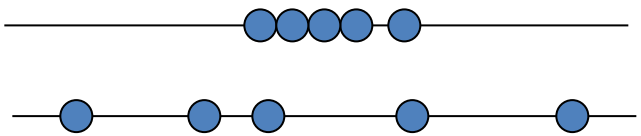
You should describe analytical procedures in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results within the proposed acceptance criteria. You should also describe aspects of the analytical procedures that require special attention. (FDA 2015)

"Add 10 mL solvent and mix"

- does mixing time matter? No time should mean instantaneous dissolution.
- mix with what system? Vortex? Manual? Magnetic?

This should have been investigated during robustness studies.

UNCERTAINTY COMPONENTS: PRECISION



precise

not precise

- Not to forget: *Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. (ICH Q2_R1)*

Interesting example:
a spiked sample is not always a representative sample.

FOOD CHEMICAL CONTAMINANTS

Immunoaffinity Column Cleanup with Liquid Chromatography for Determination of Aflatoxin M_1 in Liquid Milk: Collaborative Study

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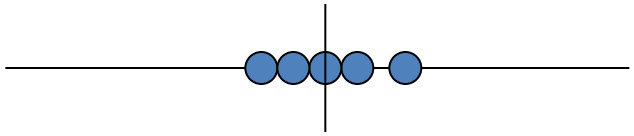
PRECISION

- **REPEATABILITY**: same laboratory, same operator, same equipment, short interval of time
- **INTERMEDIATE PRECISION**: within-laboratories variations: different days, different analysts, different equipment, etc.

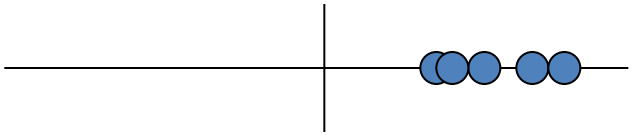
Estimated parameters:

- repeatability standard deviation and coefficient of variation,
- intermediate precision standard deviation and coefficient of variation

UNCERTAINTY COMPONENTS: ACCURACY



precise and accurate



precise but not accurate

- Result expression: recovery
- 3 levels: for the assay 80 % - 100 % -120 % of the nominal.
- True value:
  - accurately prepared artificial samples

  or

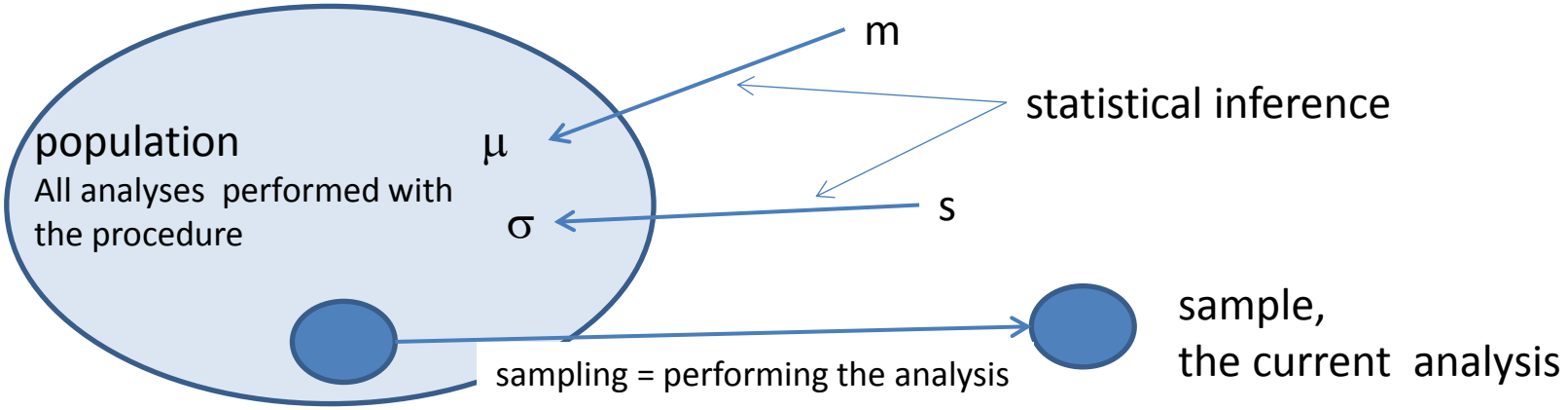
  - comparison with results of an official method (less common)

LIMIT OF DETECTION (LOD) AND LIMIT OF QUANTITATON (LOQ)

- (For impurities and contaminants),
- the lowest concentration that can be detected or quantified with suitable precision, respectively**, in all future analyses** with reasonable confidence.

- ICH methods:
  - based on the signal to noise in analytical procedures which exhibit baseline noise,
  - based on the calibration line (the ICH procedure is not aligned with IUPAC and with best practice),
  - in any LOQ should be confirmed with precision experiments.

STATISTICS IN ANALYTICAL VALIDATION



Usual parametric statistics requires a known distribution of the popolution (usually normal).

Statistics allow us:

- to estimate the parameters of the population (estimation theory) → diagnosis
- to decide with reasonable confidence if our sample can belong to an hypothesized population (hypothesis testing) →decision

ACCEPTANCE CRITERIA
(not defined by ICH Q2_R1)

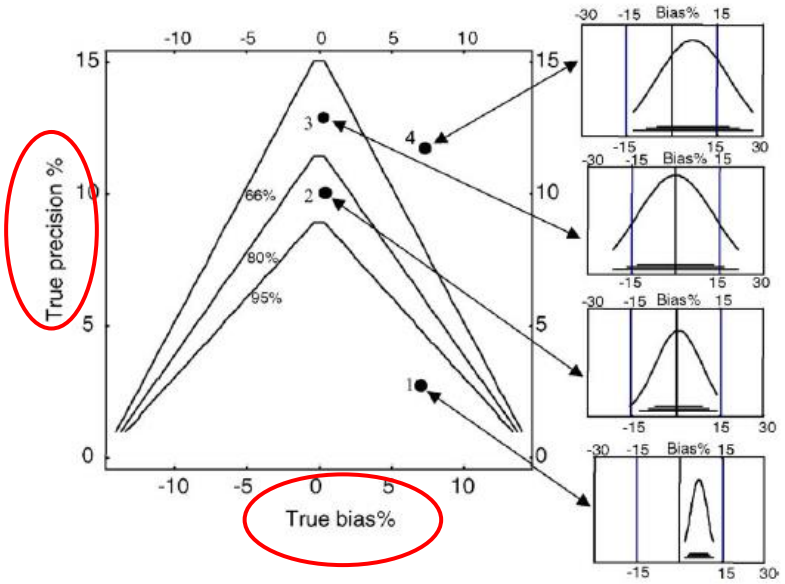
- Usual acceptance criteria:
- precision: standard deviation ≤ 2.0 %
- accuracy: mean recovery ≤ 2.0 %
- (specification: 95.0 % 105.0 %)

- Let suppose s = 1.9 %, m=1.9 %:
  - we can expect a high number of out of specification results even for a perfect batch (100 %)
  - … **the head of Production is right to doubt of our result!**

… **new criteria are necessary.**

An interesting proposal
(but discussion is ongoing)

- Total measurement uncertitude is the combination of precision and accuracy:
- $TMU = \sqrt{{s_{precision}}^2 + {s_{bias}}^2}$
- the acceptance criterion is based on the joint interval of precision and bias.



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Harmonization of strategies for the validation of quantitative analytical procedures
A SFSTP proposal—part I

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Lifecycle of the analytical procedure: analytical transfer and verification of compendial methods

- Background: we are convinced to have exhaustively identified variability sources (laboratory, instruments, reagents, procedure description, operators skill,…), **but is it true**?
  - Analytical transfer: the method has been validated in the sending unit, but is it still suitable in the receiver unit?
  - First application of a method described in a pharmacopoeia: the method has been validated, but does it work in our laboratory?
- Common statistical background: validation proofed that parameters of the population are "suitable", but does our laboratory belong to this population?

- In both cases we perform a risk analysis, i.e. a written and documented assessment of critical factors which could result in a (more frequent) failure of the method.
- Verification: factors identified as non negligible sources of additional uncertainty will be experimentally checked, i.e.
  - specificity is probably always critical,
  - linearity can be non-critical for LC-UV and critical for LC-MS, etc.
- Operator training should always be at the top of attention.
- In analytical transfer an acceptable difference between sending and receiving units should be set in advance and tests should show that the measured difference with its uncertainty are within the acceptable range (equivalence test or TOST).

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