



Uncertainty in Process Control – The Limit of Setting Limits

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Pharma solutions for tomorrow, today.

Uncertainty in Process Control – The Limit of Setting Limits

Purpose

Setting reasonable specifications for pharmaceutical products – especially biological products – take into account

- the manufacturing process variability
- the analytical procedure's inherent variability
- the analytical procedure's robustness and ruggedness

Although test procedures used in pharmaceutical quality control have to be validated, these validation experiments are usually performed in early development stages in special laboratories using special equipment by specially skilled analysts. This may lead to an underestimation of the procedure's variability and the setting of inappropriate – in most cases too tight – specification limits.

Methods

- evaluate historical analytical performance data of Quality Control Labs
- perform robustness testing by design of experiments following the "Guidance for Robustness, Ruggedness Tests in Method Validation" (Vander Heyden et al. 2001)
- calculate uncertainty contributions according to "Quantifying Uncertainty in Analytical Measurement" (Eurachem 2001) to learn the procedure's long-term variability
- run statistical simulations for the proposed analytical process to determine whether the procedure is capable of controlling the expected specification limits

Results

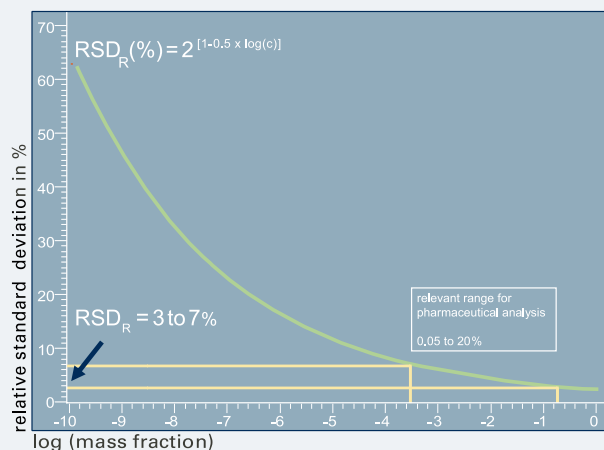
Precision data (intermediate precision)

Precision data (intermediate precision) to be expected based on performance data of routine quality laboratories:

Titration, potent.	~ 0.3%
Titration	~ 0.5%
Gravimetric assay	~ 0.5%
UV/ VIS	1.0% – 2.5%
HPLC (derivat.)	1.0% – 2.0%
GC (direct), CE	1.5% – 2.5%
HPTLC 2.0%	– 5.0%
GC (headspace)	> 3.0%
Fluorimetric assay	> 3.5%
Microbiological assay	> 5.0%
Biological assay	> 8.0%

Intermediate precision must be considered to be far higher than usually reported, non-specific techniques like titration show lower variability.

Development of more sophisticated equipment has not changed the relationship between concentration of an analyte in the matrix to be analyzed and the RSD to be expected, as expressed by the Horwitz function (Horwitz, 1997):



Perform robustness/ruggedness testing during validation to learn your procedure's weak points and to establish meaningful system suitability requirements.

Robustness: „internal factors“
Ruggedness: „external factors“

Guidance for Robustness/Ruggedness

Tests in Method Validation: Y. Vander Heyden et al., Pharm. Biom. Anal. 24, 723-753 (2001)
<http://minf.vub.ac.be/~fabi/validation/robust/>

Robustness

The robustness of an analytical method is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage (CPMP/ICH Q2A). Must be considered in procedure, e.g. system suitability parameters. Examples of parameters tested (CPMP/ICH Q2B) may be:

- stability of solutions
- influence of extraction/filtration/sample pretreatment
- mobile phase variations
- column variations
- influences of temperature, humidity, light

Ruggedness

The ruggedness of an analytical method is the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions, ...

Ruggedness is normally expressed as the lack of influence on test results by operational and environmental variables of the analytical method (USP <1225> Validation) and is usually tested by interlaboratory trials, may not be possible in early-stage development.

Testing robustness by experimental design may include continuous, discrete and mixed factors:

Robustness Testing by DOE

Possible factors

- **quantitative** (continuous)
pH, temperature of solution, concentration
- **qualitative** (discrete)
reagent batch, type of equipment, analyst
- **mixed**
fraction of modifier in mobile phase
- usually not more than 3 - 4 factors
- "pre-selected" during method development
- higher number > too complex

Knowing your procedure's intermediate precision and having tested its robustness, estimate its long-term variability by either using historical data or by following the Eurachem guide "Quantifying Uncertainty in Analytical Measurement" (Eurachem 2001) taking into consideration the following points:

Sources of uncertainty and variability

- sampling/sample preparation
- contaminations/carry-over effects
- long-term sample/matrix effects and interferences
- instrument/equipment/balance bias, drifts and ageing effects
- reagent/reference standard purity
- measurement/environmental conditions
- computational effects/smooth algorithm
- personal bias – random and systematic

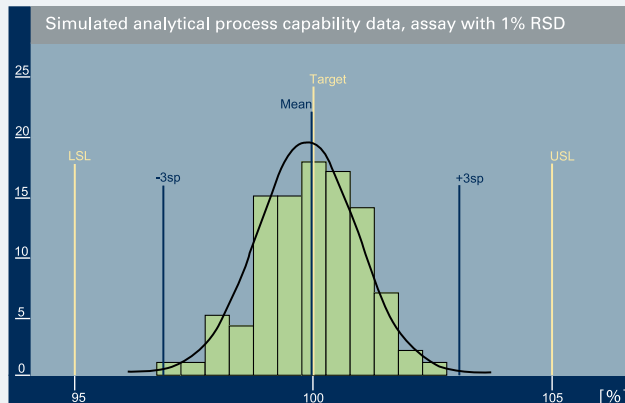
Simulation – Analytical Capability

An estimate of the procedure's true variability can be used for computation of simulated analytical results and their distribution.

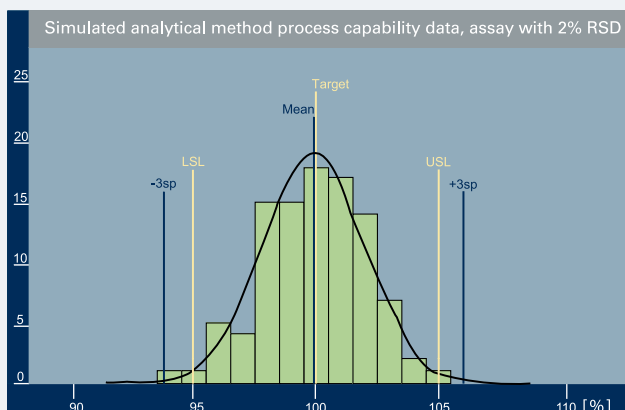
- take estimated long-term RSD of your procedure
- calculate Cp values and % of data lying outside the intended specification limits

Examples:

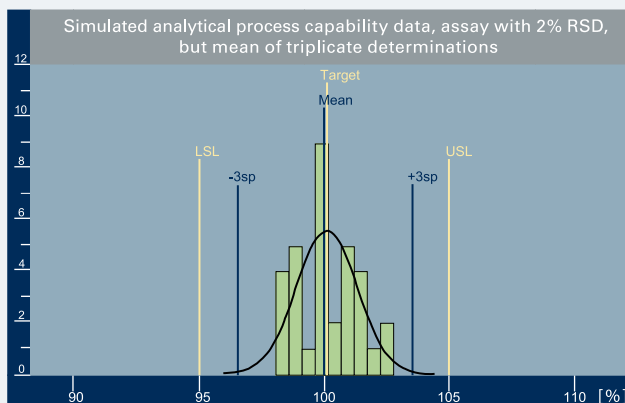
- synthetic random data for a process mean of 100% and a variability of 1 & 2%
- specification limits 95 to 105%
- the examples do not even consider a manufacturing variation or bias!



The procedure's expected variability is still within the proposed specification limit.



A significant number of OOS results arising from purely random effects has to be expected.



Using multiple determinations – in this case triplicate analysis to calculate one reportable result – clearly reduces the incidence of potential OOS results.

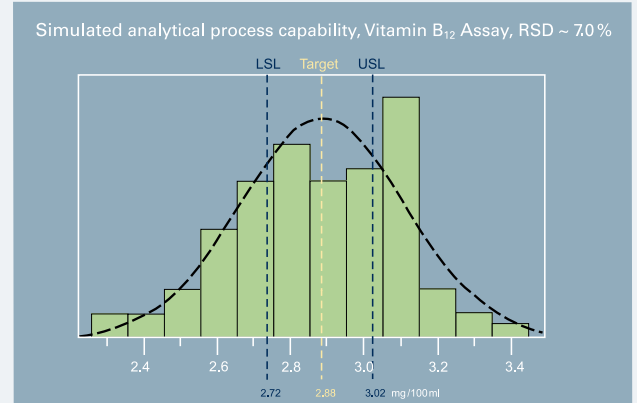
This approach allows for the visualisation of possible interaction between specification limits which are set too tightly variability, and may also be used to analyse given analytical procedures in case of multiple OOS results to assess the process capability:

Example:

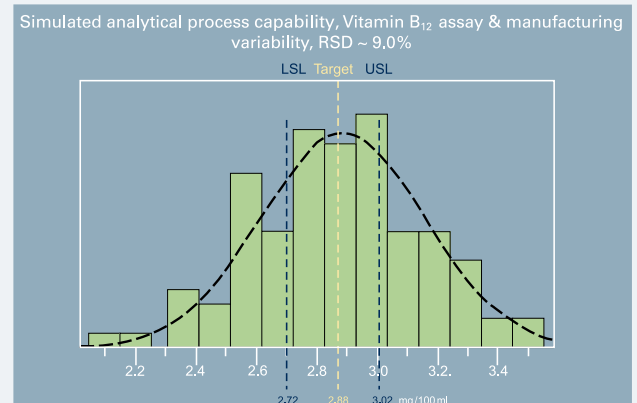
Syrup contains 2.88 mg Vitamin B12/100 ml.

- B12 assay by microbiological method, 6 replicates, RSD of the procedure: 6.9%
- specification limits 95 - 105%, corresponding to 2.72-3.02 mg/100 ml

Simulation by 100 randomly taken data sets:



The simulation clearly shows that a procedure with 6.9% RSD will generate $\geq 60\%$ OOS results – without considering any manufacturing variability. If manufacturing variability is added, the overall RSD is appr. 9.0%, resulting in the following simulation showing even higher degrees of OOS results:



Conclusion

The sequence

- determine "real life" intermediate precision
- perform robustness testing to generate the most stable analytical process
- estimate long-term variability
- perform simulating calculation to determine your procedure's process capability

Offers a helpful tool to determine whether

- your analytical procedure is capable of controlling the proposed specification
- specifications have been set properly



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