FUSION QBD®

REPLICATION STRATEGY OPTIMIZATION

How to Define Suitable Number of Sample Preps & Injections.
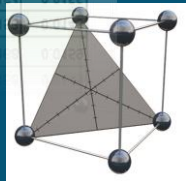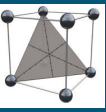
Regulatory Perspective

Robust Final LC Method	→	Replication Strategy Optimization	→	APLM Stage 2

ICH Q14

Reportable Result: the result as generated by the analytical procedure after calculation or processing and applying the **described sample replication**. *(ICH Q2)*

ICH Q2(R2)

The experimental design of the validation study should reflect the **number of replicates** used in routine analysis to generate a reportable result.

USP <1220>

Stage 1:

Optimization of performance characteristics of the analytical procedure such as accuracy, precision, …; this includes **a preliminary replication strategy** for samples and standards.
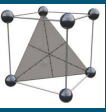
USP <1220>

Total analytical error (TAE) represents the overall error in a test result that is attributed to **imprecision** and **inaccuracy**; TAE is the combination of both **systematic error** of the procedure and **random measurement** error.

β = Bias
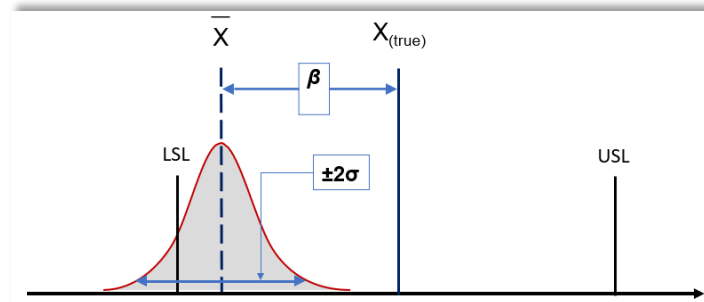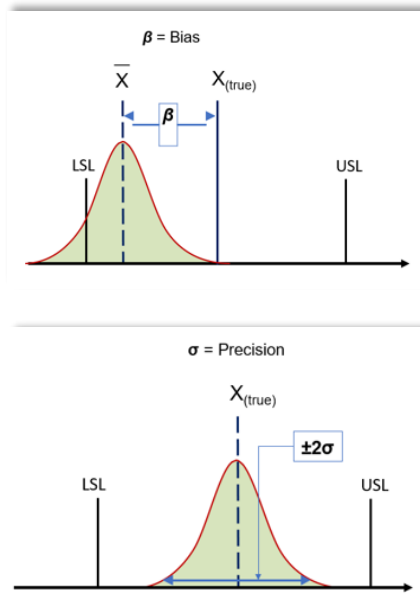
σ = Precision

Two Critical Considerations:

1. The Negotiated Total Analytical Error (TAE) **Allowance** for the Analytical Method.
2. The Integration of Precision and Bias into a single **Interval Metric** – **USP <1210>.**

Replication Strategy Optimization
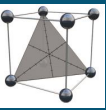
Total Analytical Error Distribution

-2σ   +2σ
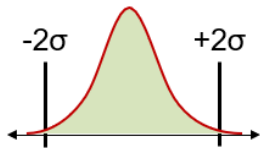
TAE reflects combination of β and σ. It represents the range, where the true value can be expected with the defined degree of probability and uncertainty.

Guard Bands acknowledge the presence of Bias and Precision Limits and the need to incorporate a characterized TAE into the "Acceptance Zone".

Acceptance Zone is narrower to incorporate the characterized TAE.
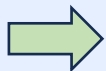
The Accpetance Limits for the Analytical Method need to be set smaller than the actual product specification limits

TOST: With a chance of 50% the true value is outside the Acceptance Zone

LAL   UAL

-2σ   +2σ   -2σ   +2σ

Rejection Zone | Acceptance Zone (Meets Specification) | Rejection Zone

Safe and Efficacious Range
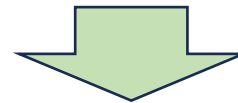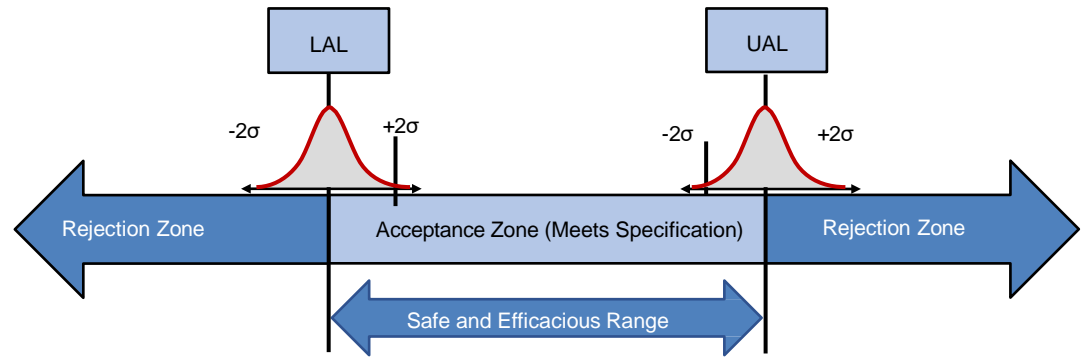
Interval Tests: Tolerance Interval (T.I.) or Prediction Interval (P.I.)

LAL   UAL

-2σ   +2σ   -2σ   +2σ

Rejection Zone | Guard Band | Acceptance Zone (Meets Specification) | Guard Band | Rejection Zone

Safe and Efficacious Range

Reportable Value

Replication Strategy Optimization
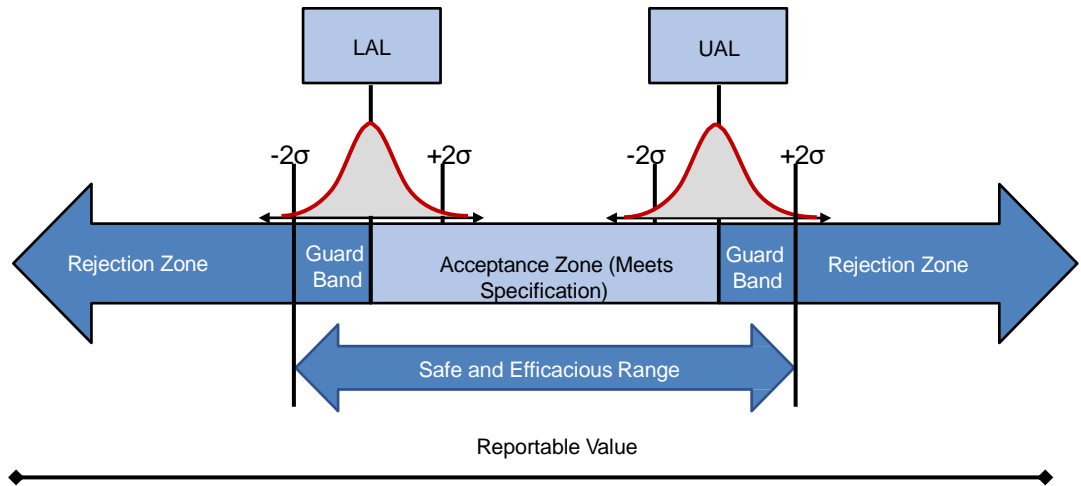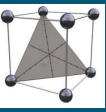
Fusion QbD has adopted the approaches described in USP <1210> and USP <1220> regarding TAE, Guard Bands and Interval Tests.

To be defined:

➢ Target Value

➢ Acceptance Limit

➢ TAE Limits

➢ Interval Type

➢ Desired Probability [%]

➢ Tolerance Alpha [%]
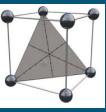
Definitons

➢ **Target Value:** Expected/Desired Outcome

➢ **Acceptance Limit:** +/- Range in Target Value Units defining the Acceptance Zone

➢ **TAE Limits**: Combined error from sample preparation and injection (in target level units)

  • For example, given a target of 100%, ± Acceptance Limits of ±2.00 (98.0 – 102.0), and an allowance of 40% for error (60% for production), you would enter ±0.80 (40%*2.00 = 0.80).

➢ **Interval Types, selection according to risk profile**

  ▪ Tolerance Interval: Wider range than T.I.

  ▪ Prediction Interval: More rigorous than P.I.

➢ **Desired Probability [%]:** Proportion of the overall data distribution required to fall within the interval

➢ **Tolerance Alpha [%]:** Desired level of confidence in the result. The reverse one-sided expression for the confidence interval.
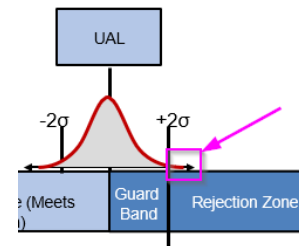
TOST – Two One-Sided Test

The TOST analysis is a variance-only analysis which <u>does not incorporate the estimated bias</u> from the target (true or expected value), and therefore treats the grand average of the data as the assumed Target (<u>zero bias assumption</u>).

The TOST analysis determines the magnitude of the error* in a Reportable Result, given the magnitude of the TAE in an individual measurement, as estimated from the data, and the selected replication strategy.

The analysis compares the Reportable Result error to the defined ± TAE Limits.

Pass: the computed error is ≤ the defined ± TAE Limit value.

Fail: the computed error is > the defined ± TAE Limit value.

* Error = Range where the True Value can be expected with the defined degree of confidence.
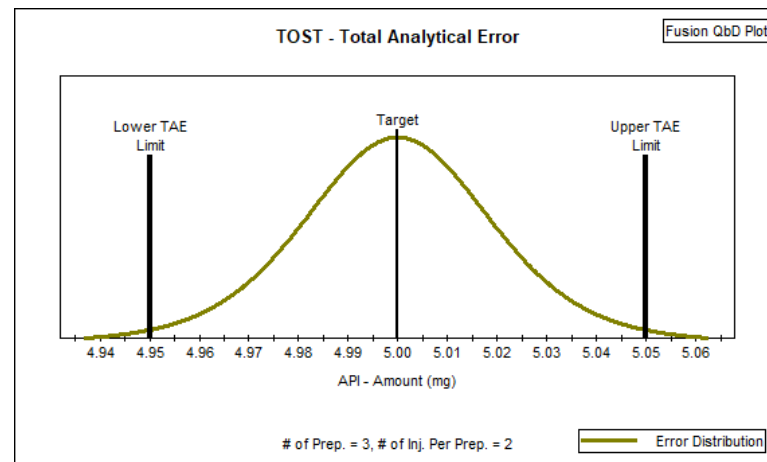
TOST Analysis Results Summary

No. of preparation replicates per sample	3
No. of injections per preparation replicate	2

Statistic	Value	Pass/Fail
TAE Width (2σ) - Target	±0.050	
Computed TAE Width (2σ)	±0.039	Pass
FPT	<0.0001	
Cp	1.8365	
Variance	< 0.001	
Standard Deviation	0.018	
RSD	0.36	
CV	0.36	
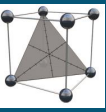
Interval Tests

The Interval Test analysis incorporates the estimated Accuracy (bias from the target value) and the TAE estimated from the data. The analysis compares the computed Tolerance (or Prediction) Interval, based on the user's specified Desired Probability and Tolerance Alpha, relative to the users defined ± Acceptance Limits.

Computed Interval – displays the interval generated by subtracting the defined ± TAE Limit values from the user specified Acceptance Limit values for the response. **This defines the required guard band width.**

Pass: the computed Interval is ≤ the Required Guard Band Width value.

Fail: the computed error is > the Required Guard Band Width value.

Guard Band Width – the distance the Acceptance Limits must be moved inside the original limits (moved closer to target) given the Computed Tolerance Interval.

Note – the Tolerance Interval is computed from
1) the magnitude of the overall error in a single measurement, defined by the error analysis,
2) a given replication strategy, and
3) the user's specified the Desired Probability and Confidence Alpha goals defined in the Analysis Wizard for a Reportable Result.

Tolerance Interval Analysis Results

Interval Setting	Value	Number of Preparations	Number of Injections per Preparation
Target	5.000	3	2
Acceptance Limits	±0.100		
Desired Probability %	90.00		
Tolerance Alpha %	5.00		
Grand Mean	5.005		
Computed Tolerance Interval	±0.045 Pass		
Required Guard Band Width	±0.050		

The computed Tolerance Interval falls within the defined Total Analytical Error Limits.

Upper Tolerance Interval — Fusion QbD Plot. # of Prep. = 3, # of Inj. Per Prep. = 2. T.I. – Probability Distribution
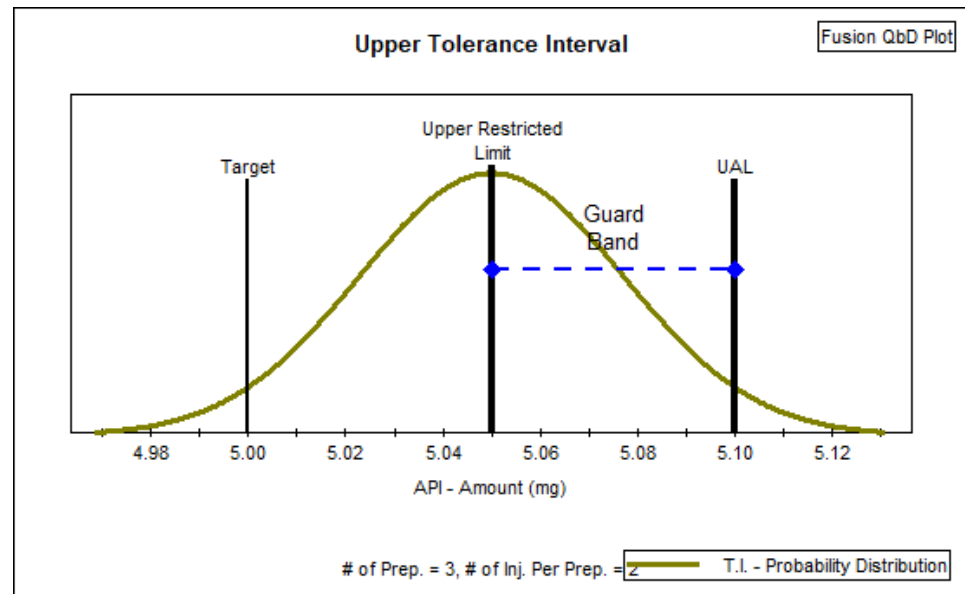
Replication Strategy Predicted TOST and Interval Results

No. of Injections		No. of Preparations									
		1	2	3	4	5	6	7	8	9	10
1	±2σ	0.0885	0.0626	0.0511	0.0442	0.0396	0.0361	0.0334	0.0313	0.0295	0.0280
	T.I.	0.1326	0.0812	0.0625	0.0524	0.0459	0.0413	0.0379	0.0352	0.0329	0.0311
2	±2σ	0.0676	0.0478	0.0390	0.0338	0.0302	0.0276	0.0255	0.0239	0.0225	0.0214
	T.I.	0.0877	0.0566	0.0446	0.0380	0.0336	0.0304	0.0280	0.0261	0.0245	0.0232
3	±2σ	0.0590	0.0417	0.0340	0.0295	0.0264	0.0241	0.0223	0.0208	0.0197	0.0186
	T.I.	0.0721	0.0477	0.0380	0.0325	0.0289	0.0262	0.0242	0.0225	0.0212	0.0201
4	±2σ	0.0541	0.0383	0.0313	0.0271	0.0242	0.0221	0.0205	0.0191	0.0180	0.0171
	T.I.	0.0642	0.0430	0.0345	0.0296	0.0263	0.0239	0.0221	0.0206	0.0194	0.0184
5	±2σ	0.0510	0.0361	0.0295	0.0255	0.0228	0.0208	0.0193	0.0180	0.0170	0.0161
	T.I.	0.0593	0.0401	0.0323	0.0277	0.0247	0.0225	0.0207	0.0194	0.0182	0.0173
6	±2σ	0.0489	0.0346	0.0282	0.0244	0.0219	0.0200	0.0185	0.0173	0.0163	0.0155
	T.I.	0.0559	0.0381	0.0307	0.0264	0.0235	0.0214	0.0198	0.0185	0.0174	0.0165
7	±2σ	0.0473	0.0334	0.0273	0.0236	0.0211	0.0193	0.0179	0.0167	0.0158	0.0149
	T.I.	0.0535	0.0367	0.0296	0.0255	0.0227	0.0207	0.0191	0.0179	0.0168	0.0159
8	±2σ	0.0460	0.0325	0.0266	0.0230	0.0206	0.0188	0.0174	0.0163	0.0153	0.0145
	T.I.	0.0517	0.0355	0.0287	0.0248	0.0221	0.0201	0.0186	0.0174	0.0164	0.0155
9	±2σ	0.0450	0.0318	0.0260	0.0225	0.0201	0.0184	0.0170	0.0159	0.0150	0.0142
	T.I.	0.0503	0.0347	0.0280	0.0242	0.0216	0.0197	0.0182	0.0170	0.0160	0.0152
10	±2σ	0.0442	0.0313	0.0255	0.0221	0.0198	0.0180	0.0167	0.0156	0.0147	0.0140
	T.I.	0.0491	0.0339	0.0275	0.0237	0.0212	0.0193	0.0178	0.0167	0.0157	0.0149

Contact us for more Information

Fusion QbD® is a mature LC method development software especially designed for AQbD approaches in the pharmaceutical industry.

If you want to get the full understanding of how the design region is modelled in Fusion QbD, please contact us for our **training or consultancy services**.

Cromingo e.K. – All Fusion QbD products and services from a single source in close collaboration with S-Matrix Corporation.

Reach out to us directly for further information **info@cromingo.com**

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