AUTOMATING ICH-Q2(R2) VALIDATION OF ANALYTICAL PROCEDURES

SmartSTATS\Enoval integration into procedure development and validation workflows allows to improve the efficiency and quality of the validation processes across the organization.

Alfredo Montero, Davor Josipovic, Cédric Dubourg, Inês Fortes

cencora PharmaLex

1. Define the Analytical Target Profile (ATP)

Starting point of validation is a clear ATP definition in function of the Total Analytical Error (TAE) as advised by USP 1220 and ICH Q14. For example:

The procedure must be able to quantify potassium bicarbonate in a range from 800 mg to 1200 mg in our pharmaceutical product so that we can expect at least 95 % of all our future measured values to fall within ±1.5 % relative error range.

2. Determine the optimal validation design

Every validation attempt, due to inherent measurement error, has a probability to fail, even if the analytical procedure is truly fit for purpose. One can use a-priori knowledge about the analytical procedure's performance to estimate the probability of validation success for various designs as shown in the following table.

σ_w	0.1			0.2			0.3			0.4			0.5		
σ_b	n	p	P(success)	n	p	P(success)	n	p	P(success)	n	p	P(success)	n	p	P(success)
0.1	3	2	0.9980	3	2	0.9715	3	3	0.9606	3	5	0.9592	5	5	0.9612
							3	4	0.9847	3	6	0.9778	5	6	0.9808
							4	2	0.9759	4	4	0.9848	6	4	0.9605
										5	3	0.9869	6	5	0.9845
										6	2	0.9734			
0.2	4	2	0.9863	4	2	0.9617	4	4	0.9669	5	4	0.9583			
	4	3	0.9886	4	3	0.9793	4	5	0.9767	5	5	0.9748			
				4	4	0.9850	4	6	0.9820	5	6	0.9819			
				4	5	0.9882	5	2	0.9607	6	3	0.9621			
				4	6	0.9897	5	3	0.9874	6	4	0.9830			
							6	2	0.9873						
0.3	6	2	0.9761	6	2	0.9521	6	5	0.9528						
	6	3	0.9787	6	3	0.9655	6	6	0.9598						
	6	4	0.9802	6	4	0.9695									
	6	5	0.9813	6	5	0.9736									
	6	6	0.9815	6	6	0.9765									

Table 1: Recommended number of series (n), replicates by series (p) and the probability of a successful validation attempt, P(success), as a function of the expected values for the between-series (σ_b) and the within-series (σ_w) standard deviations (in %) when acceptance limits are set to 1.5 % and bias is set 0 %.

3. Compute calibration curves

Simple procedures do not require calibration. But more complex procedures such as ELISA need to be calibrated. Enoval offers 16 different calibration models to choose from.

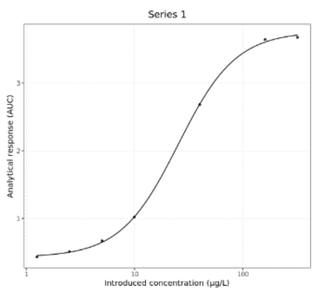

Figure 1: Four parameter logistic calibration curve on a logarithmic scale.

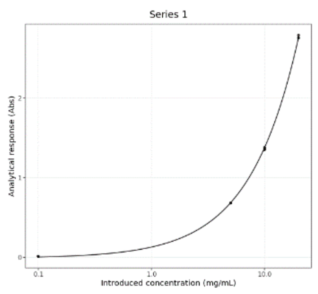

Figure 2: Power calibration curve on a logarithmic scale.

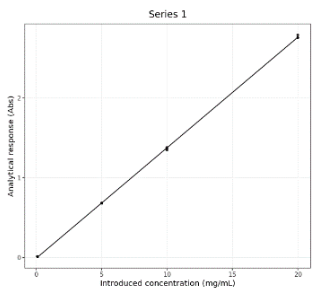

Figure 3: Simple linear calibration curve.

Enoval allows you to select the best calibration curve based on your validation objectives.

4. Compute accuracy and precision

Balanced design or not: no need to bother with formulas. Enoval will always use the correct statistical theory to provide you with the correct statistical results.

Amount level (%)	Mean introduced amount (mg)	Mean result (mg)	Absolute bias (mg)	Relative bias (%)	Recovery (%)	95% Confidence Interval of Recovery (%)
80	805.2	810.5	5.312	0.6598	100.7	[100.1 , 101.2]
100	1009	1013	4.548	0.4510	100.5	[100.0 , 100.9]
120	1207	1209	2.334	0.1934	100.2	[99.96 , 100.4]

Table 2: Accuracy summary table from an Enoval report.

Amount level (%)	Mean introduced amount (mg)	Repeatability (RSD%)	Between-series (RSD%)	Intermediate precision (RSD%)
80	805.2	0.4988	0	0.4988
100	1009	0.4306	0	0.4306
120	1207	0.2234	0.05055	0.2291

Table 3: Relative precision summary table from an Enoval report.

5. Uncertainty

For accredited and medical laboratories operating under ISO 17025 and ISO 15189, reporting uncertainty is required. Enoval has a dedicated chapter on Uncertainty, reporting the required statistics.

Amount level (mg)	Mean introduced amount (mg)	Standard uncertainty of the bias (mg)	Standard uncertainty (mg)	Expanded uncertainty (mg)	Relative expanded uncertainty (%)
80	805.2	1.640	4.338	8.675	1.077
100	1009	1.773	4.691	9.382	0.9302
120	1207	1.183	3.008	6.015	0.4983

Table 4: Uncertainty summary table from an Enoval report.

6. Total Error Profile

Decide whether the procedure complies to the ATP: See in an eyewink which level you need to optimize, long before you enter the QC stage.

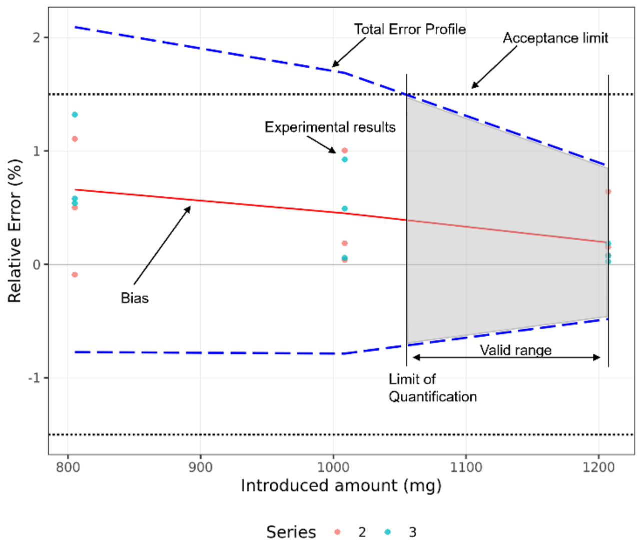

Figure 4: Total Error Profile summarizes the analytical procedure performance. The dotted black lines are the acceptance limits of ±1.5 % as defined in the ATP. The red line is the interpolated expected bias. The blue dashed lines are the interpolated β-expectation tolerance interval, i.e., the interval where we expect 95 % of all our future measurements to fall. We see that when measuring at 800 mg and 1000 mg, more than the allowed 100 % - 95 % = 5 % of measurements are expected to fall outside the acceptance limits. This suggests the procedure is not fit for purpose in that range.

7. Risk of falling outside of specification

Understanding the risk associated with procedure performance deviations enables a proactive approach to quality management by identifying potential vulnerabilities or areas of improvement in the procedure.

Amount level (%)	Mean introduced amount (mg)	Absolute β-expectation tolerance limits (mg)	Relative β-expectation tolerance limits (%)	Risk (%)
80	805.2	[799.0 , 822.0]	[-0.7726, 2.092]	13.80
100	1009	[1001 , 1026]	[-0.7857, 1.688]	9.113
120	1207	[1201 , 1218]	[-0.4817, 0.8684]	2.754

Table 5: Summary of Total Analytical Error. β-expectation tolerance interval – i.e., the expected interval for the 95 % of our future measurements – is given in both absolute and relative terms. The Risk (%) is the expected probability (%) of a future measurement to fall outside the acceptance limit of ±1.5 % (as stated in the ATP). As one can see the risk of falling outside of specification is higher than 100 % - 95 % = 5 %, i.e., the maximal risk required by the ATP, when measuring at 800 and 1000 mg.

8. Linearity analysis

Verify whether the results (possibly back-calculated from the calibration curve) are in line with the true quantities.

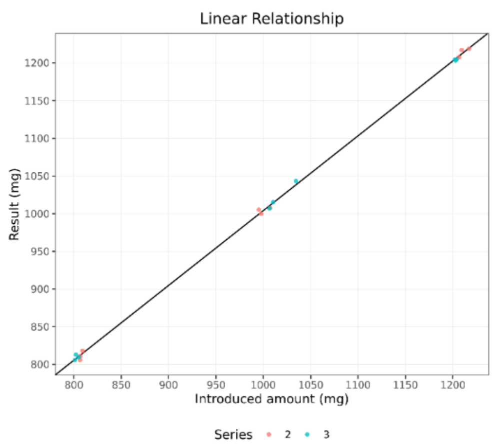

Figure 5: Linearity analysis graph: measured results versus the true quantity. Best linear fit using intercept (11.02) and slope (0.9940) with 95 % confidence intervals of these coefficients being [4.804, 17.23] for the intercept and [0.9880, 1.000] for the slope implying there is little reason to not think that was is measured, is the true quantity.

9. Writing an ICH-Q2(R2) compliant report in minutes

Enoval summarizes all these results, and more, into a comprehensive report in line with the ICH Q2(R2) guidance, ready for submission to the authorities, so that scientists do not have to spend days writing reports but can focus on developing procedures.

10. Value for you

- **Easy to use**: made by statisticians for non-statisticians.
- **Standardize procedure validation reporting across the organization.**
- Up to date with latest authority requirements (**ICH-Q2(R2)**, EMA, FDA, …).
- Suitable for GxP use (GAMP5 validated, 21 CRF Part 11 compliant).
- SaaS: no maintenance for you (i.e., we maintain it for you).
- **Reduces report writing to a couple of minutes instead of days.**
- Goes further than possible with Excel (e.g., REML, unbalanced designs, etc.)
- Can be integrated into existing LIMS or data platforms.

SCAN ME

software-plxstat@pharmalex.com | pharmalex.com | pharmalexglobal