cencora
PharmaLex

Streamlining Analytical Method Validation for ICH Compliance with ASM, eCTD Submissions, GAMP5 Qualification, and Standardized Data Integration

Susanne Bauerschmidt

Pierre Lebrun

2024 Fall Allotrope Connect, 20-Nov 2024

Disclaimer

The information provided in this presentation does not constitute legal advice. PharmaLex GmbH, and its parent Cencora, Inc., strongly encourage the audience to review available information related to the topics discussed during the presentation and to rely on their own experience and expertise in making decisions related thereto.

About us

40+

Nationalities
Are on staff, including former us food and drug administration (FDA) and European medicines agency (EMA) **experts**

43,000

Projects have been completed successfully

Lead 40+

Health agency meetings annually, including with EMA / FDA / PMDA / NMPA

9/10

of the top pharmaceutical companies are our clients

60%

of our client base are small and midsize enterprises

50+%

of our projects are global

25+

Years of industry experience

3,000+

Employees worldwide work with

1,600+ clients

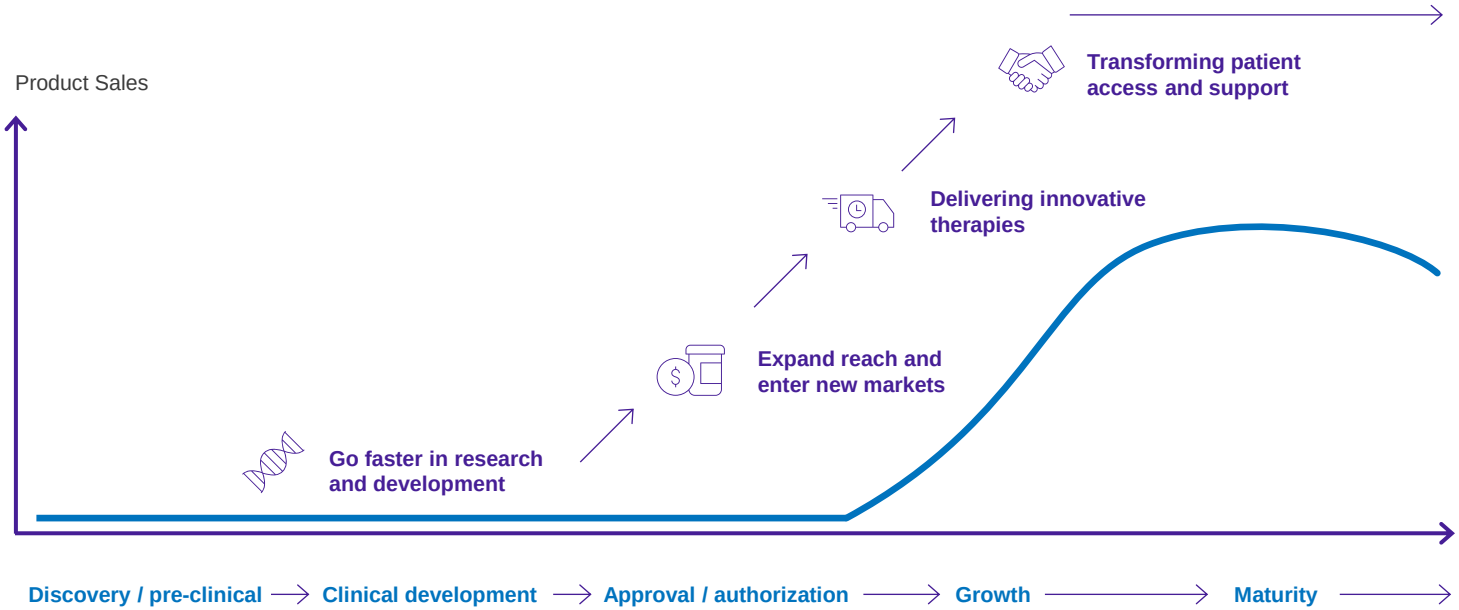
200+

Experienced & certified **local representatives** support our global coverage

90+%

of our principal consultants hold PHDS

Our goal is to help you speed time to market and maximize your product's success



Assay Validation

Assay Validation

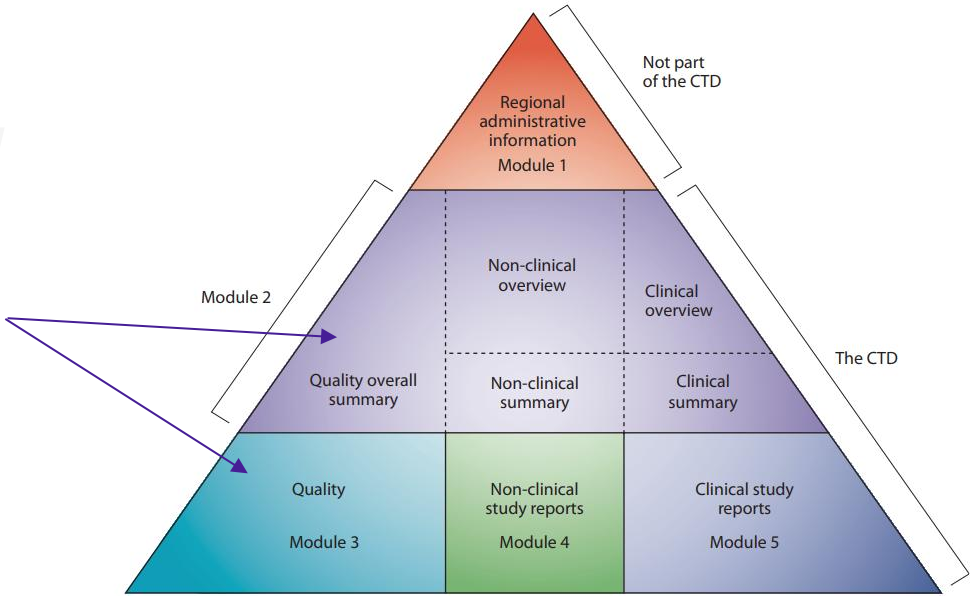
Aim → Show that the assay is fit for its purpose !

Main (Bio)Pharma regulatory guidelines (non-exhaustive):

- **ICH**
  - **ICH Q2(R2): Validation of Analytical Procedures**
  - ICH M10: Bioanalytical method validation
- FDA
  - Analytical Procedures and Methods Validation for Drugs and Biologics - Guidance for Industry (2015)
  - Guidance for Industry: Bioanalytical Method Validation (2018)
- USP:
  - Chapter <1225>: Validation of Compendial procedures
  - Chapter <1210>: Statistical Tools for Procedure Validation
  - Chapters <1032><1033><1034>: consideration for design, analysis, and validation of Biological assays

Common Technical Document

Assay Validation Report

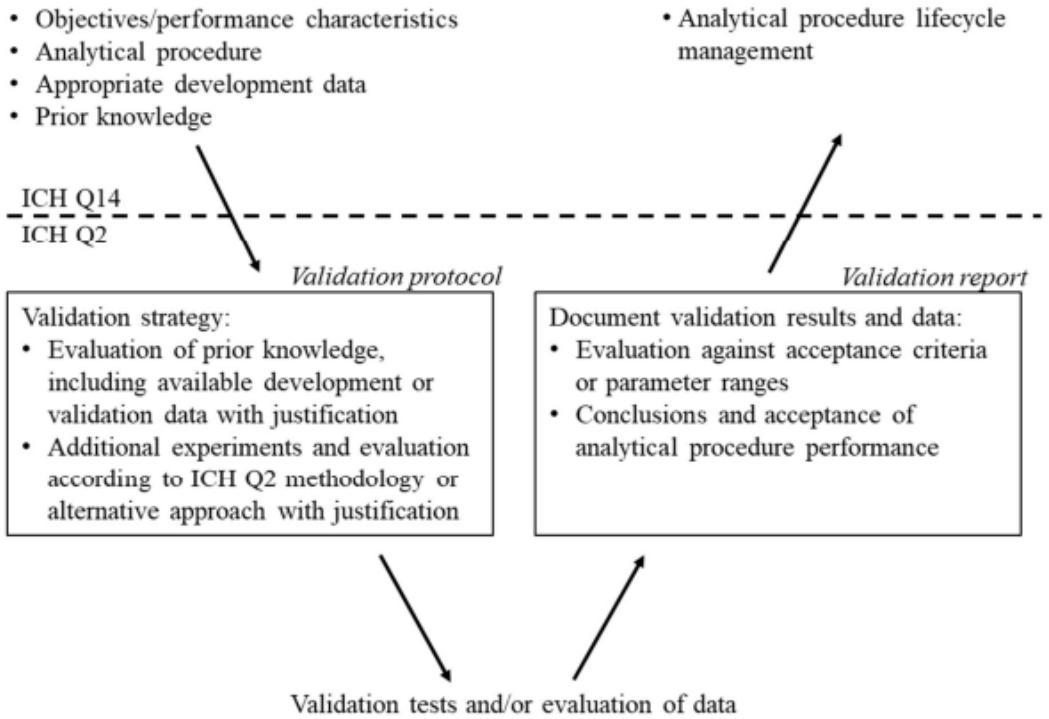


The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

https://admin.ich.org/sites/default/files/2021-02/CTD_triangle_color_Proofread.pdf

Validation Procedure in the ICH

Figure 1: Validation study design and evaluation

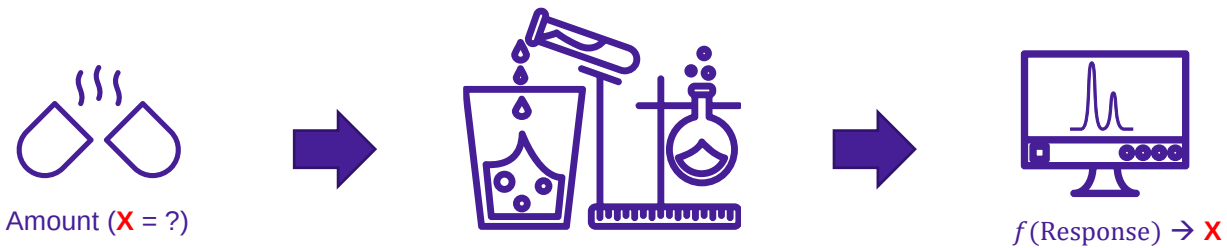


https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q2r2-guideline-validation-analytical-procedures-step-5-revision-1_en.pdf

Business Challenge

Suppose you are a company manufacturing Paracetamol tablets.

- You have manufactured a batch/lot of 1000 mg tables and want to sell them.
- Before you release the tablets to the market, you have to make sure that the tablets indeed contain 1000 mg of Paracetamol. (e.g. release testing)
  - Take a random sample of tablets, and test the amount of paracetamol inside.



- So before you can use this procedure, you need to prove that it can indeed detect and quantify paracetamol with sufficient accuracy and precision. (i.e. that the procedure “is fit for its purpose”.)

Assay Validation – Criteria

Table 1: Typical performance characteristics and related validation tests for measured quality attributes

Measured Quality Attribute / Analytical Procedure Performance Characteristics to be Demonstrated (2)	Identity	Impurity (Purity)		Assay
		Other quantitative measurements (1)		Content or potency
		Quantitative Test	Limit Test	Other quantitative measurements (1)
Specificity (3)				
Specificity Test	+	+	+	+
Range				
Response (*Calibration Model*)	-	+	-	+
Lower Range Limit	-	QL†	DL	-
Accuracy (4)				
Accuracy Test	-	+	-	+
Precision (4)				
Repeatability Test	-	+	-	+
Intermediate Precision Test	-	+ (5)	-	+ (5)

- signifies that this test is not normally conducted

+ signifies that this test is normally conducted

† in some complex cases DL may also be evaluated

QL, DL: quantitation limit, detection limit

(1) other quantitative measurements can follow the scheme for impurity, if the range limit is close to the DL/QL; other quantitative measurements can follow the scheme for assay (content or potency), if the range limit is not close to the DL/QL

Specificity/Selectivity,

Results Linearity, Calibration model,

Range,

Quantification Limit

Detection Limit

Accuracy,

Precision (Repeatability and Intermediate Precision),

Combined Accuracy and Precision (Total Analytical Error),

Stability,

Robustness

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q2r2-guideline-validation-analytical-procedures-step-5-revision-1_en.pdf

Assay Validation – The Process

- Objective – the Analytical Target Profile (ATP)

The procedure must be able to quantify paracetamol in a range from 300 µg/mL to 1200 µg/mL in our pharmaceutical product

*so that the distribution of the **total analytical error** of the reportable value falls within the **total maximum uncertainty** range of ±2% with 95% coverage.*

- Data Collection – Design of Experiment
  - Define number of days and replicates assessed, based on prior information on the performance
  - Replicating this design at each concentration levels (e.g. 300, 500, 800, 1000 and 1200 mg) allows creating a all-in-one design where all collected data will be used to compute accuracy, precision, total analytical error, linearity, range, etc.

σ_w / σ_b	0.1			0.2		
	n	p	P(success)	n	p	P(success)
0.1	3	2	0.9980	3	2	0.9715
0.2	4	2	0.9863	4	2	0.9617
	4	3	0.9886	4	3	0.9793
				4	4	0.9850
				4	5	0.9882
				4	6	0.9897

- Report ICH Q2(R2) criteria, with uncertainty margins (confidence intervals)
- Compute the Uncertainty of Measurement using Total Analytical Error

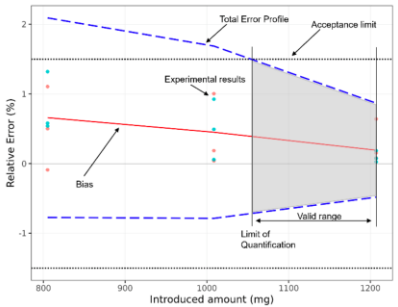
--> It is a prediction intervals that integrates:

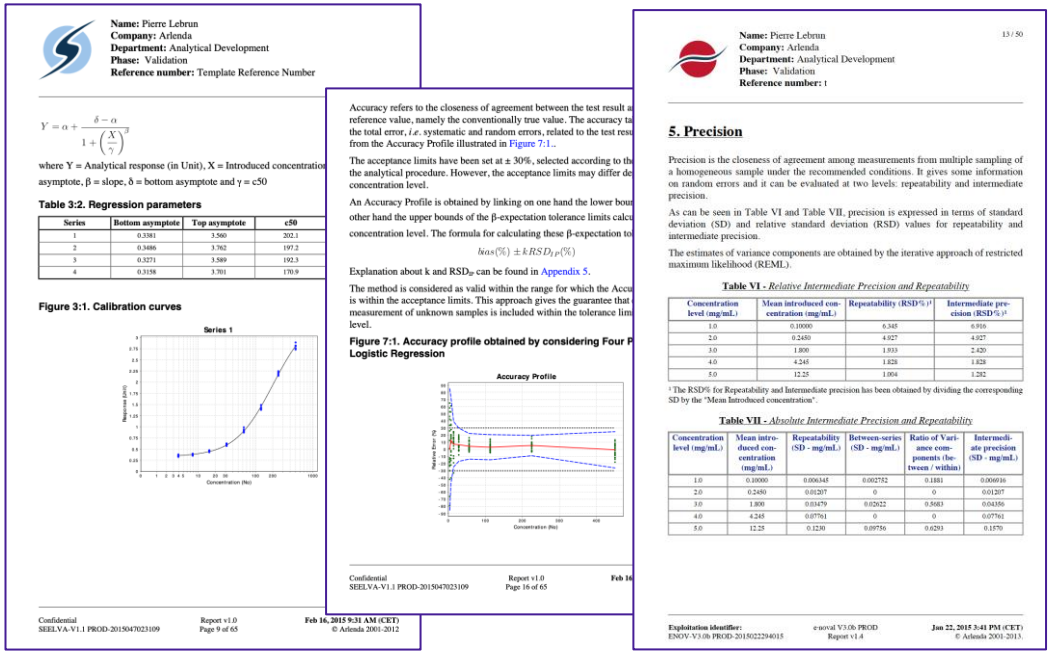
  - The precision (repeatability and intermediate precision)
  - The bias and its uncertainty of estimate (accuracy)
  - The uncertainty of the precision estimates

Assay Validation - Results

- The software will then issue a full report that can be filled into the Module 3 section of the eCTD

- The Total Analytical Error is used as the main decision tool
  - It is the uncertainty of measurement
  - It defines the assay range optimally
  - Ease the go/no go decision as it is a single performance criteria combining both accuracy, precision & linearity





Assay validation – Summary of our Solution

Table 1: Typical performance characteristics and related validation tests for measured quality attributes

Measured Quality Attribute / Analytical Procedure Performance Characteristics to be Demonstrated (2)	Identity	Impurity (Purity)		Assay
		Other quantitative measurements (1)		Content or potency
		Quantitative Test	Limit Test	Other quantitative measurements (1)
Specificity (3)				
Specificity Test	+	+	+	+
Range				
Response (*Calibration Model*)	-	+	-	+
Lower Range Limit	-	QL†	DL	-
Accuracy (4)				
Accuracy Test	-	+	-	+
Precision (4)				
Repeatability Test	-	+	-	+
Intermediate Precision Test	-	+ (5)	-	+ (5)

- signifies that this test is not normally conducted

+ signifies that this test is normally conducted

† in some complex cases DL may also be evaluated

QL, DL: quantitation limit, detection limit

(1) other quantitative measurements can follow the scheme for impurity, if the range limit is close to the DL/QL; other quantitative measurements can follow the scheme for assay (content or potency), if the range limit is not close to the DL/QL

Specificity/Selectivity,

Results Linearity, Calibration model

Range,

Quantification Limit

Detection Limit

Accuracy,

Precision,

Total Analytical Error,

Stability,

Robustness

Smartstats/Enoval

A validated solution that supports:

- Experimental Design
- Joint Statistical analysis
- Report Generation

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q2r2-guideline-validation-analytical-procedures-step-5-revision-1_en.pdf

Value for the customer

Standardize analytical reporting across the organization

Up-to-date with latest authority requirements (EMA, FDA, …) e.g. ICH Q2(**R2**), Q1E, …

SaaS: no maintenance costs

Suitable for GxP use (GAMP5 validated, 21 CRF Part 11 compliant)

Saves costs in report writing

Significantly reduces human errors

Can be used within analytical QbD framework

Go further than Excel (e.g. REML, quantile computation, etc.) to always give correct results.

Easy to use: made by statisticians for non-statisticians (lab scientists)

Best-in-class decision making

Statistics hot-line

Current Process with Smartstats/Enoval

Design of Experiments

SMARTSTATS

Manual Data Transfer

Data Analysis

e·noval

Validated Report Creation

SMARTSTATS

Delivery to Customer

Future Process Using Allotrope Simple Model

Design of Experiments

SMARTSTATS

Interfacing Using ASM as Data Exchange Format

Data Analysis

e·noval

Validated Report Creation

SMARTSTATS

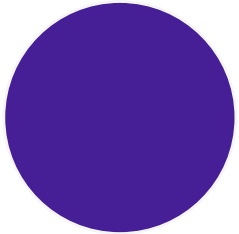
Delivery to Customers

Potential Additional Value for Allotrope Users

- No manual data extraction as the Allotrope data format can be integrated as software input
  - Data remains FAIR
  - No *break* in Quality Assurance

- State of the art from data quality & standardization to statistical methods & automated reporting
  - Inscribed in most advanced regulatory strategy

Contact Us!



Martina Fortin
Director, Business Development
Martina.Fortin@pharmalex.com