

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

Susanne Bauerschmidt

Pierre Lebrun

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Disclaimer

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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+

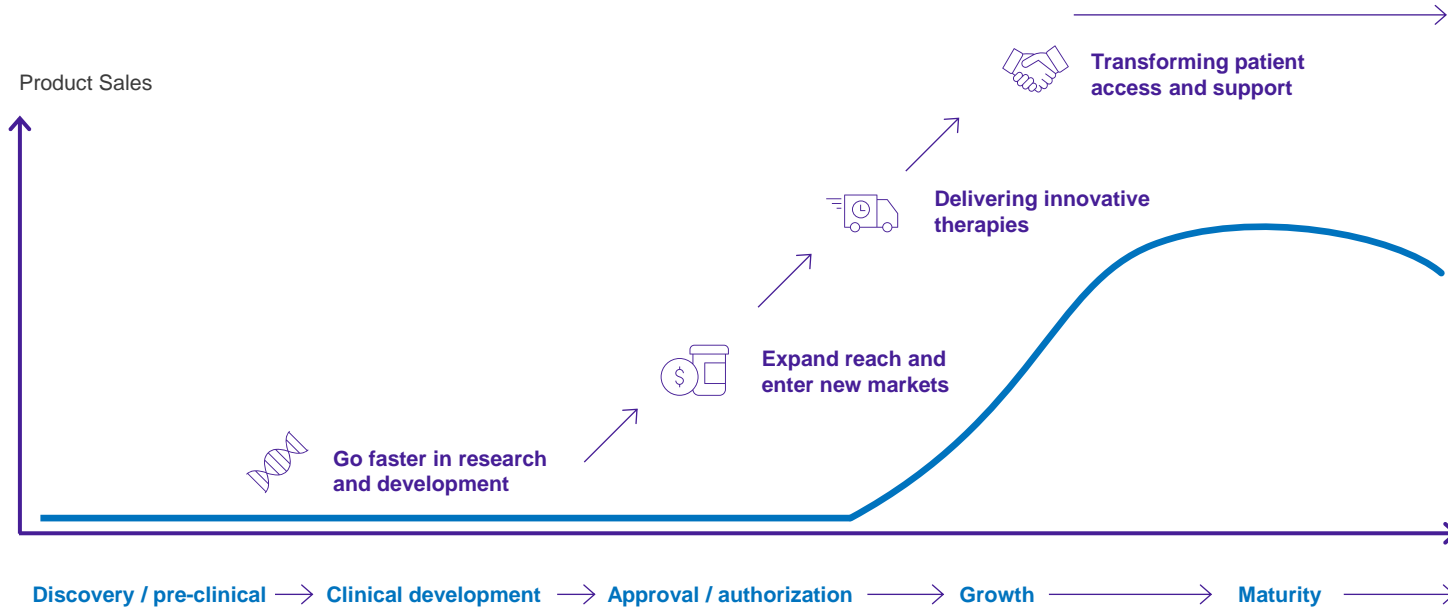
Experienced & certified **local representatives** support our global coverage



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:**

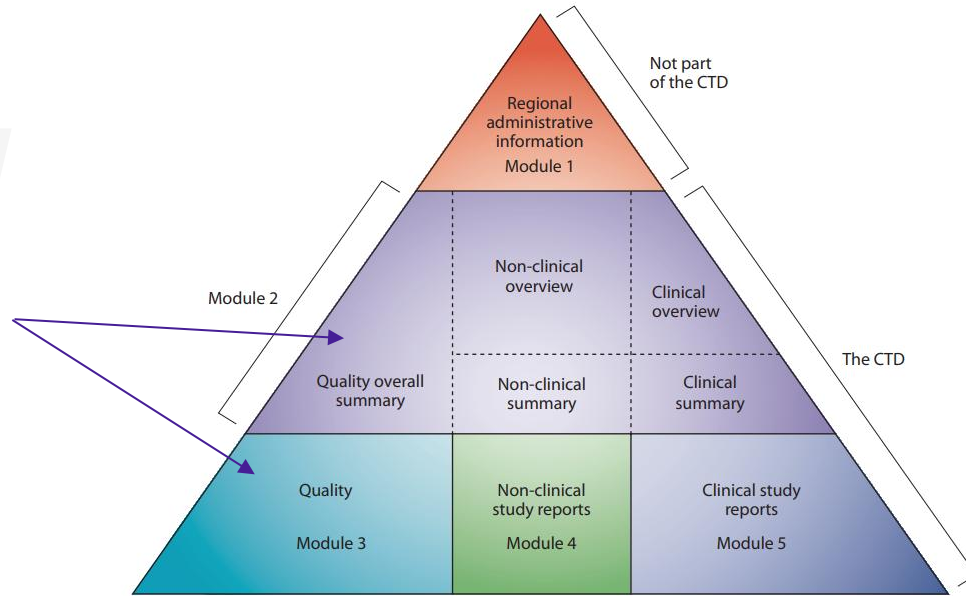
- Chapter <1225>: Validation of Compendial procedures

- Chapter <1210>: Statistical Tools for Procedure Validation

- Chapters <1032><1033><1034>: consideration for design, analysis, and validation of Biological assays

Common Technical Document

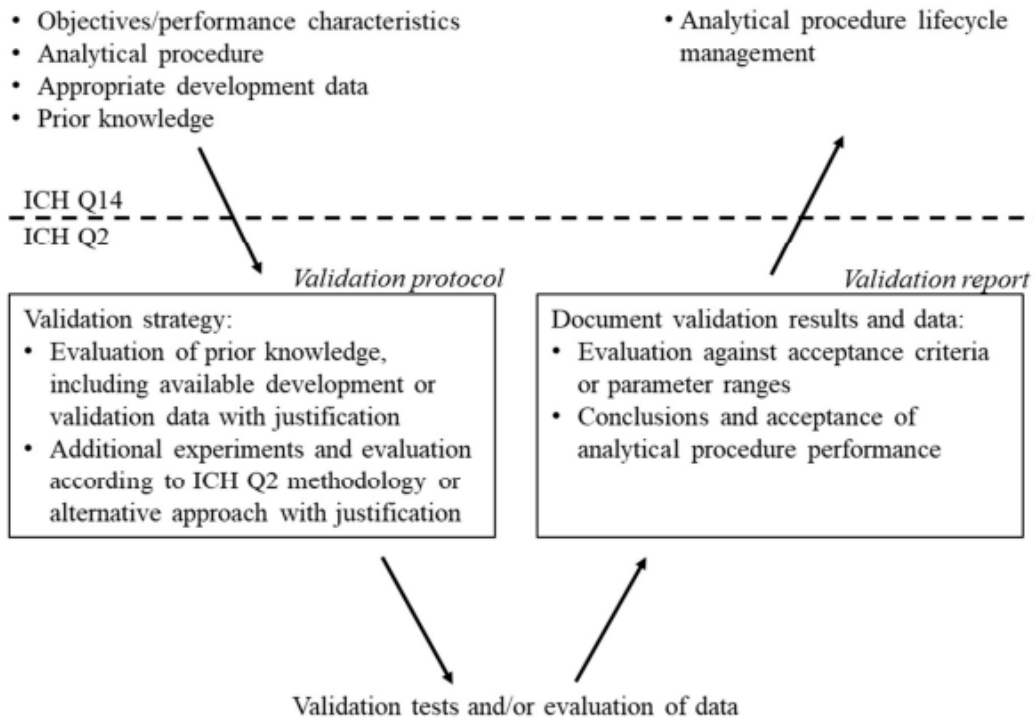
CTD Triangle



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.

Validation Procedure in the ICH

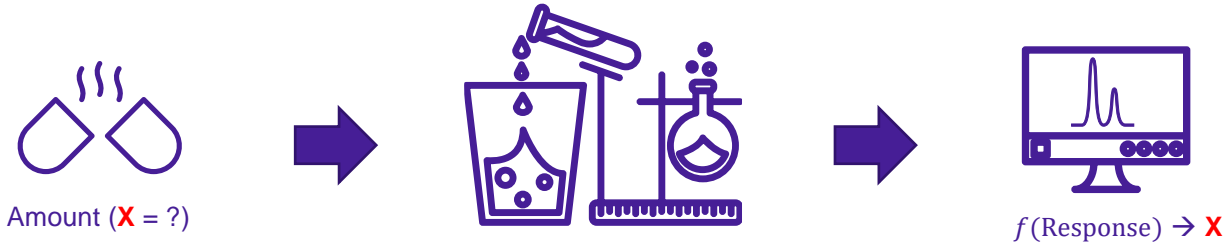
Figure 1: Validation study design and evaluation



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	IDENTITY	IMPURITY (PURITY)		ASSAY Content or potency
		Other quantitative measurements (1)	Limit Test	
Analytical Procedure Performance Characteristics to be Demonstrated (2)		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	-	+	-	+

- 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

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.

- Report ICH Q2(R2) criteria, with uncertainty margins (confidence intervals)

- Compute the Uncertainty of Measurement using Total Analytical Error

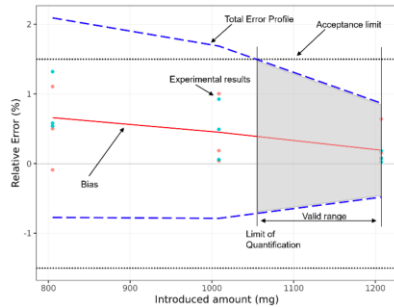
--> It is a prediction intervals that integrates:

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

σ_w	0.1			0.2		
σ_b	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

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



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Company: Arlanda
Department: Analytical Development
Phase: Validation
Reference number: Template Reference Number

$$Y = a + \frac{b - a}{1 + \left(\frac{X}{\gamma}\right)^c}$$

where Y = Analytical response (in Unit), X = Introduced concentration asymptote, β = slope, δ = bottom asymptote and $\gamma = c50$

Table 3-2: Regression parameters

Series	Bottom asymptote	Top asymptote	c50
1	0.3811	2.560	202.1
2	0.3486	3.762	197.2
3	0.3271	3.589	192.3
4	0.3158	3.701	170.9

Figure 3-1: Calibration curves

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Accuracy refers to the closeness of agreement between the test result and reference value, namely the conventionally true value. The accuracy is the total error, i.e. systematic and random errors, related to the test result from the Accuracy Profile illustrated in Figure 7-1.

The acceptance limits have been set at $\pm 30\%$, selected according to the analytical procedure. However, the acceptance limits may differ due to concentration level.

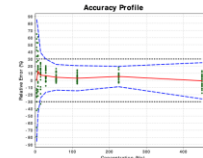
An Accuracy Profile is obtained by linking on one hand the lower bound and other hand the upper bounds of the β -expectation tolerance limits calculated at concentration level. The formula for calculating these β -expectation limits is:

$$\text{bias}(\%) \pm k \cdot \text{RSD} \cdot \rho(\%)$$

Explanation about k and RSD ρ can be found in Appendix 5.

The method is considered as valid within the range for which the Accuracy is within the acceptance limits. This approach gives the guarantee that measurement of unknown samples is included within the tolerance limit level.

Figure 7-1: Accuracy profile obtained by considering Four Point Logistic Regression



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Phase: Validation
Reference number: 1

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5. Precision

Precision is the closeness of agreement among measurements from multiple sampling of a homogeneous sample under the recommended conditions. It gives some information on random errors and it can be evaluated at two levels: repeatability and intermediate precision.

As can be seen in Table VI and Table VII, precision is expressed in terms of standard deviation (SD) and relative standard deviation (RSD) values for repeatability and intermediate precision.

The estimates of variance components are obtained by the iterative approach of restricted maximum likelihood (REML).

Table VI - Relative Intermediate Precision and Repeatability

Concentration level (mg/mL)	Mean introduced concentration (mg/mL)	Repeatability (RSD %) ¹	Intermediate precision (RSD %) ¹
1.0	0.1000	0.248	0.956
2.0	0.2480	0.427	0.627
3.0	1.800	1.103	2.420
4.0	4.245	1.628	1.628
5.0	12.25	1.004	1.282

¹The RSDs for Repeatability and Intermediate precision has been obtained by dividing the corresponding SD by the "Mean Introduced concentration".

Table VII - Absolute Intermediate Precision and Repeatability

Concentration level (mg/mL)	Mean introduced concentration (mg/mL)	Repeatability (SD - mg/mL)	Between-series (SD - mg/mL)	Ratio of Variance components (between / within)	Intermediate precision (SD - mg/mL)
1.0	0.1000	0.00445	0.002752	0.1881	0.006036
2.0	0.2480	0.01207	0	0	0.01207
3.0	1.800	0.03479	0.02622	0.5583	0.04436
4.0	4.245	0.07761	0	0	0.07761
5.0	12.25	0.1230	0.09796	0.6203	0.1570

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e-nova V3.08-PROD
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Assay validation – Summary of our Solution

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

Measured Quality Attribute	IDENTITY	IMPURITY (PURITY)		ASSAY
		Other quantitative measurements (1)	Limit Test	Content or potency
Analytical Procedure Performance Characteristics to be Demonstrated (2)		Quantitative 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	-	+	-	+

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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

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 CFR Part 11 compliant)

Saves costs in report writing

Significantly reduces human errors

Can be used within analytical QbD framework

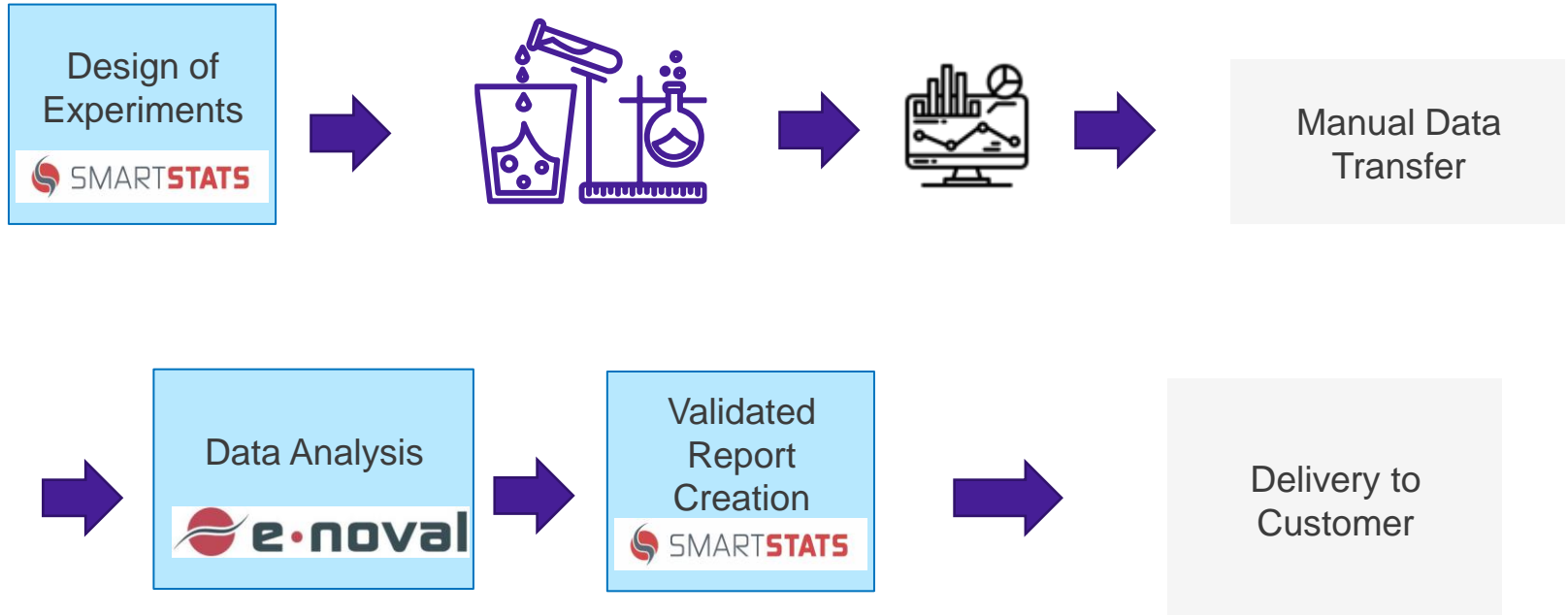
Go further than Excel (e.g. REML, quantile computation, etc.) to always give correct results.

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

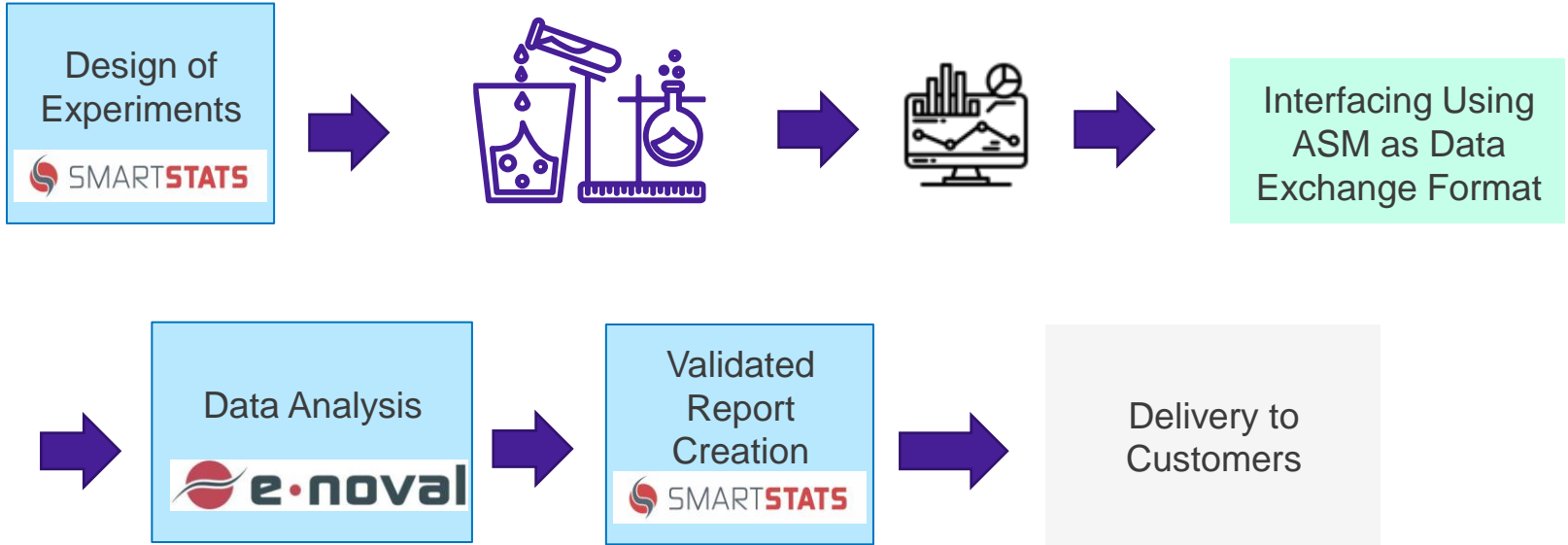
Best-in-class decision making

Statistics hot-line

Current Process with Smartstats/Enoval



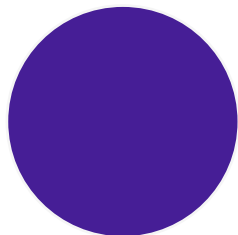
Future Process Using Allotrope Simple Model



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