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Automating statistical analysis and GxP reporting

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Science & Statistics – Elevating CMC through Partnership
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Disclaimer

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Agenda

1. Question addressed
   - Introduction: the business challenge
   - Analytical Procedure Validation & Regulatory guidance (ICH Q2R2)
   - Purpose of a measurement system and combined approach for accuracy and precision
   - The prediction interval (β-expectation tolerance interval)
   - A word on Design

2. Automated software
   - Why automating ?
   - Infrastructure
   - Quality Assurance
   - GxP regulation
   - End-to-end solution, from study design to a validated automated report

Introduction: the business challenge

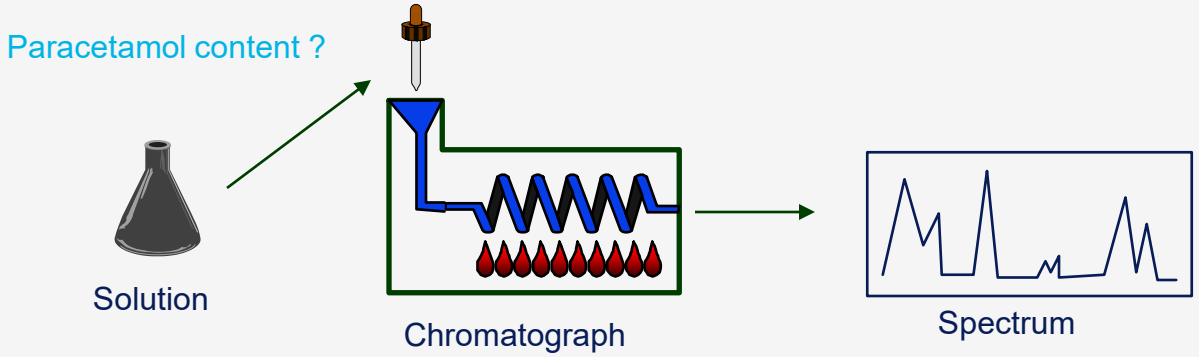
Suppose you are a company manufacturing Paracetamol tablets.

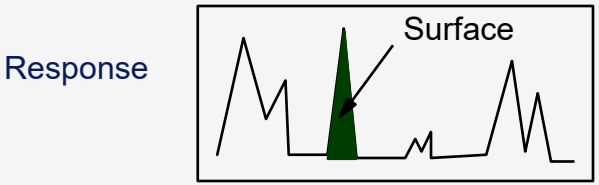
- You have manufactured a batch/lot of 1000 mg tables and want to sell them.
- Before you release the tablets to the market, you have to make sure that the tablets indeed contain 1000 mg of Paracetamol. (e.g. release testing)
  - Take a random sample of tablets, and test the amount of paracetamol inside.

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

What is an analytical procedure ? Test Method ? Bioassay ?

Analytical Procedures are used to quantify contents (API, excipients, potency, impurities,…)

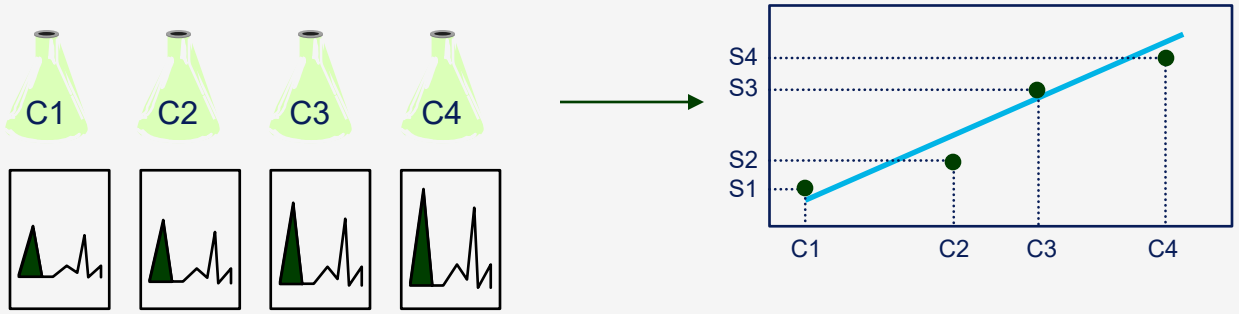




But which concentration corresponds to a measured surface ???

In the laboratory

1. Build a calibration line with samples that are known (e.g. by preparation, weighing)



2. Use the calibration line to back predict

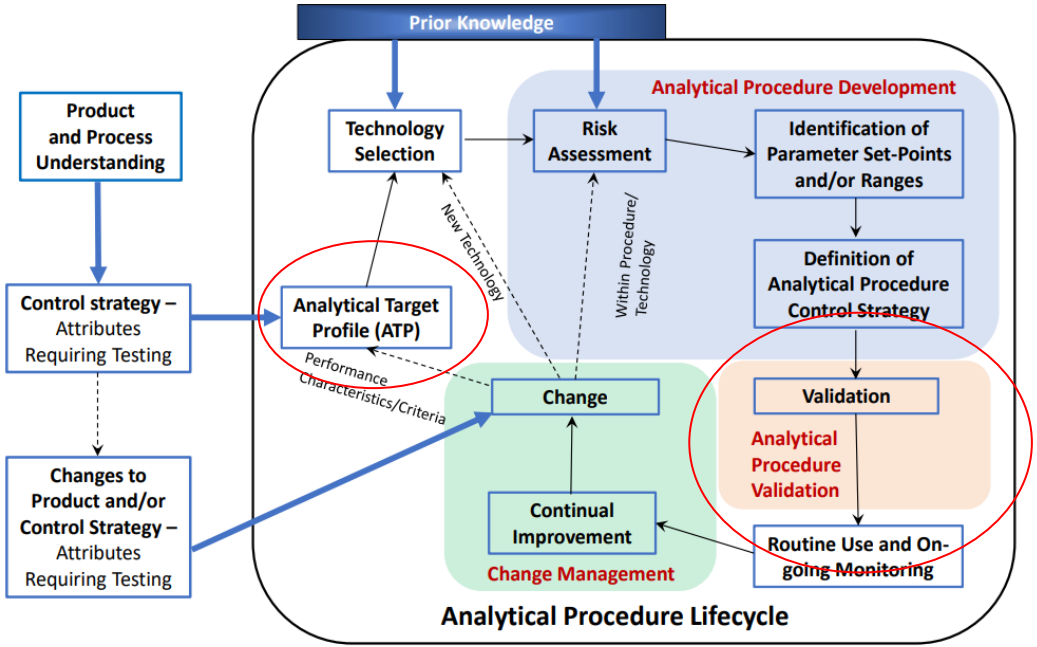
aQbD and lifecycle

Product & process understanding helps at defining the minimal performance characteristics needed for having a suitable-for-use analytical procedure : the ATP

Target of development is to meet the ATP so product and process can be controlled adequately

Independent of the technology

Three stages (as in FDA process validation and USP 1220)



How do we demonstrate the quantitation is working ? ICH-Q2 (R2) and ICH-Q14

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ANALYTICAL PROCEDURE DEVELOPMENT Q14

Draft version

Endorsed on 24 March 2022

Currently under public consultation

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ICH HARMONISED GUIDELINE

VALIDATION OF ANALYTICAL PROCEDURES Q2(R2)

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Assay validation

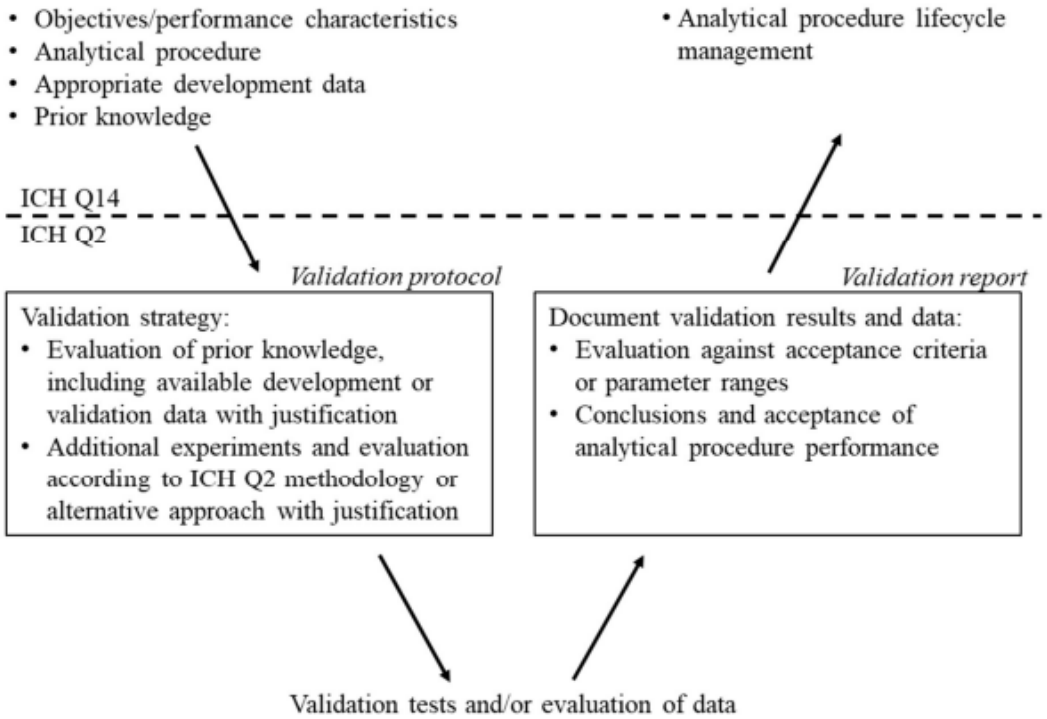
Aim → Show that the assay is fit for its purpose !

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

Validation Procedure in the ICH

Figure 1: Validation study design and evaluation

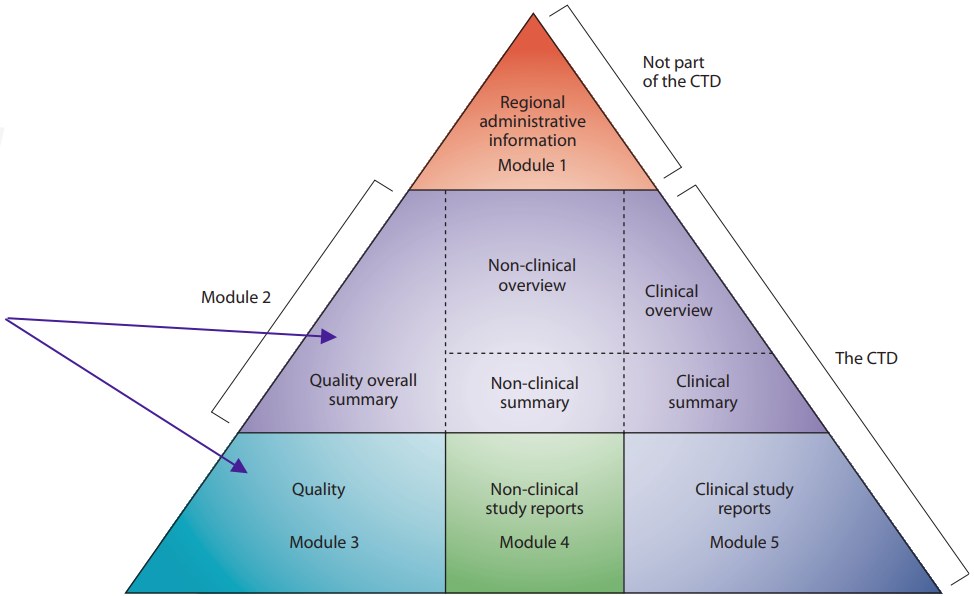


https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q2r2-guideline-validation-analytical-procedures-step-5-revision-1_en.pdf

Common Technical Document

Assay Validation Reports

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.

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

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

3.3.3 Combined approaches for accuracy and precision

An alternative to separate evaluation of accuracy and precision is to consider their total impact by assessing against a combined performance criterion.

Data generated during development may help determine the best approach and refine appropriate performance criteria to which combined accuracy and precision are compared.

Combined accuracy and precision can be evaluated by use of a prediction interval, a tolerance interval or a confidence interval. Other approaches may be acceptable if justified.

S.T.P. PHARMA PRATIQUES 8 (2) 81-107 1998

Méthodes chromatographiques de dosage dans les milieux biologiques
Exemple d'application de la stratégie de validation
Rapport d'une commission SFSTP

Présidents : E. Chapuzet et N. Mercier
S. Bervoas-Martin, B. Boulanger, P. Chevalier, P. Chiap, D. Grandjean, P. Hubert, P. Lagorce, M. Lallier, M.C. Laparra, M. Laurentie et J.C. Nivet

SFSTP, 5, rue Basse-des-Carmes, 75005 Paris, France

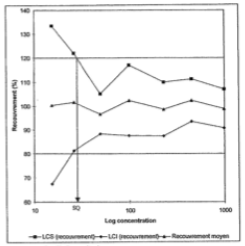


Figure 7 - Profil d'exactitude.

ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

VALIDATION OF ANALYTICAL PROCEDURES Q2(R2)

Draft version
Endorsed on 24 March 2022
Currently under public consultation

Combined approaches for Accuracy and Precision has been added in Q2(R2)

<u>The concept is not new !</u>

Presented in

- Chapuzet et al., in French in STP Pharma Pratiques, 8 (**1998**)
- Hubert et al., in FR/EN in STP Pharma Pratiques 13 (2003)
- Hubert et al., JPBA 36 (2004)
- Hubert et al., JPBA 45 (2007) x2
- Feinberg, J Chrom A 1158 (2007)
- Many, many more…

It started 20+ years ago at French SFSTP commission !

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1st: What is the question?

In AQbD mindset, let's define first the objective or target.

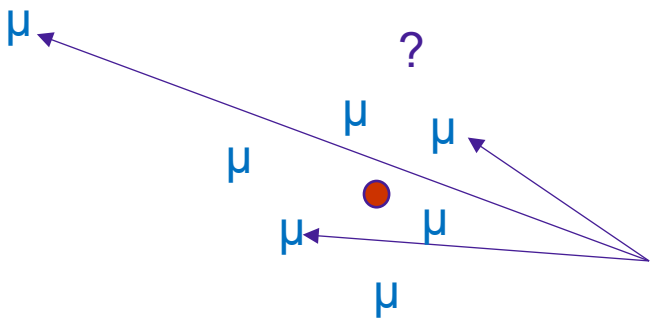
Let's start with the end in mind : *what is the purpose of a measurement system ?*

When having a measurement, we need to make a decision about the sample

This is one measurement (reportable value X) about a sample (unknown content μ), or measurand

Development → Validation → Routine Use

Given the measurement X,
what can be said about the unknown sample μ ?

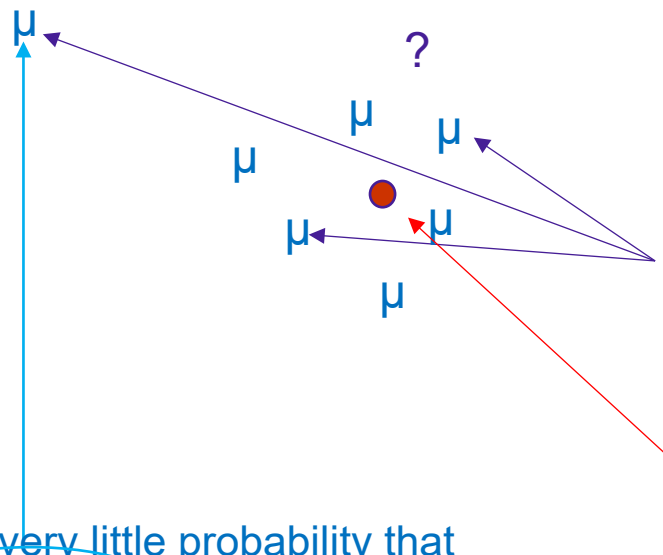


Where could be the true unknown value μ of that sample, given my measurement X ?

$$P(\mu|X)$$

Development → Validation → Routine Use

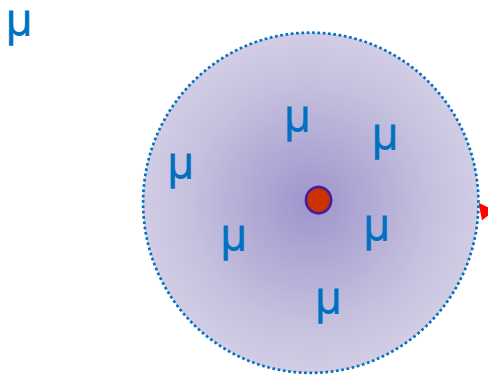
Given the measurement X,
what can be said about the unknown sample μ ?



There is very little probability that
the true unknown value μ is there, given my measurement is there.

Development → Validation → Routine Use

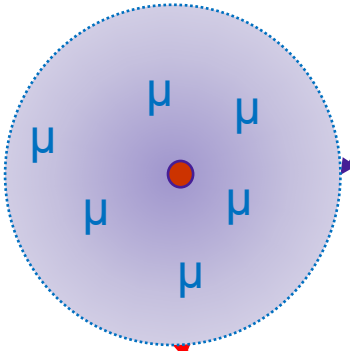
Of course we don’t know where μ is, but how about saying something like…



There is (say) 0.95 probability that the true unknown value μ is within this neighborhood.

$$P(\mu|X)$$

The Uncertainty



There is (say) 0.95 probability that the true unknown value μ is within this neighborhood.

$$P(\mu|X)$$

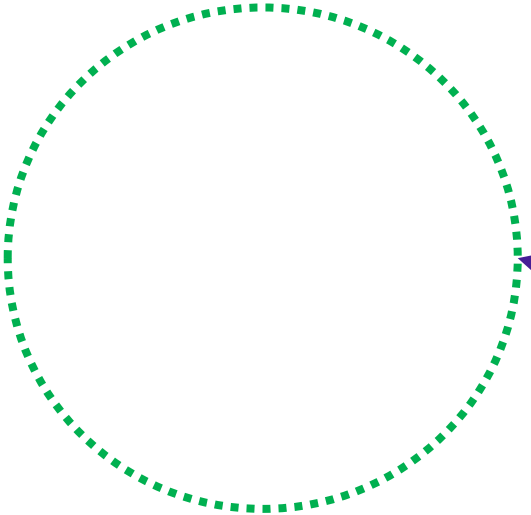
Nb: confidence as probability, not to be confounded with Confidence in frequentist statistics

This is the UNCERTAINTY of measurement

"The Uncertainty of a measurement is the range about the measured value within which the true value of the measured quantity is likely to lie at a stated level of confidence" (ISO)

Development → Validation → Routine Use

What is therefore the maximal Uncertainty (with assoc. Probability) ?



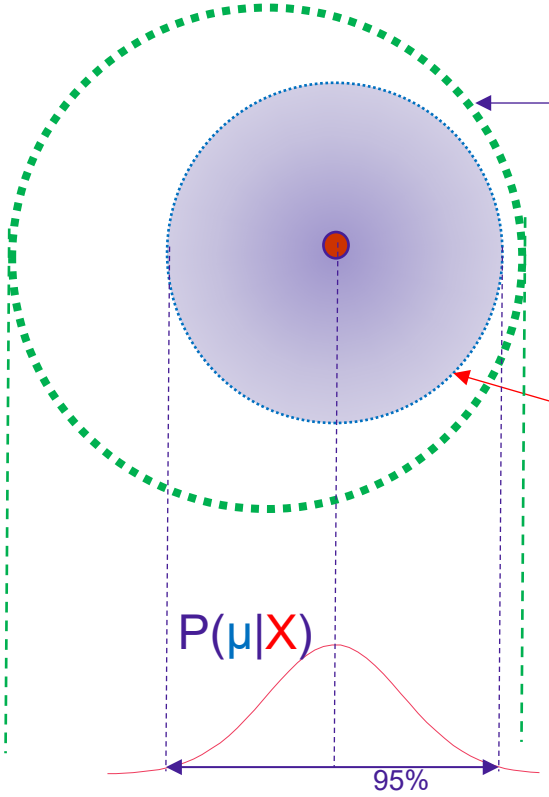
Let's define an ATP:

What is being analyzed ?

These are the specifications for my **product** (e.g. lot)

Development → Validation ← Routine Use

Uncertainty, product specifications and decision making (risk)



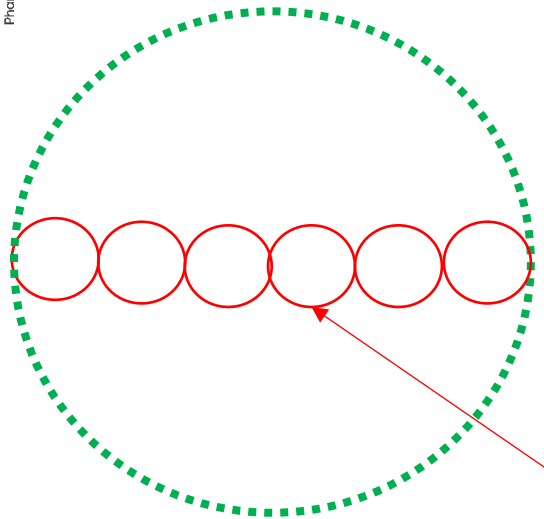
These are the specifications for my **product** (e.g. lot)

Given this measurement and the related Uncertainty, I can claim that there is more than 0.95 probability that my sample is within the specifications

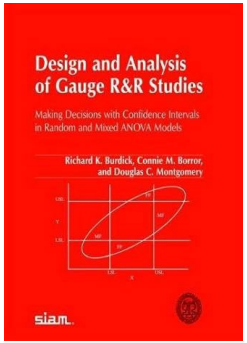
Decision ➔ I'm "confident" to claim the product is within specifications

Obviously, if uncertainty is too high, one cannot claim anything

Target Measurement Uncertainty and Specifications



How to define assay specs based on product specs ?
How to write a Total Analytical Error ATP ?



TMU= **Target** Measurement Uncertainty
It should be derived from Product Specifications (purpose) and should be a fraction of it.
Rule of thumb: say 1/6 of specifications for a “quality level” that is the probability (say at least 0.95 to contain the true value μ or measurand).
Often much larger for “difficult assays”

From Routine Use to Validation: defining objectives of validation

Do we agree about the use of measurement, its uncertainty and related risk in decision making ?

How to assess or quantify the Uncertainty of a measurement ?

- not the Uncertainty of an analytical procedure !

How to assess the confidence / probability / risk ?

This is the purpose of the Validation stage

Validation is the place where analysts

- use samples with ***known*** µ values (by sample preparation, dilution, orthogonal measure, etc.)
- use the words bias, precision, “total error”, ….because based on **known** samples !

Note of objective of validation of an analytical procedure

It is NOT to provide a small **Bias** and a good **Precision**.

We never release a Bias nor a Precision

These are not *the purpose of the measurement system !*

These are intermediate estimates *(Performance Characteristics)* required to quantify the Uncertainty and the probability

- *Sometimes* they are used as *surrogates* to report analytical performance… because of some official documents…

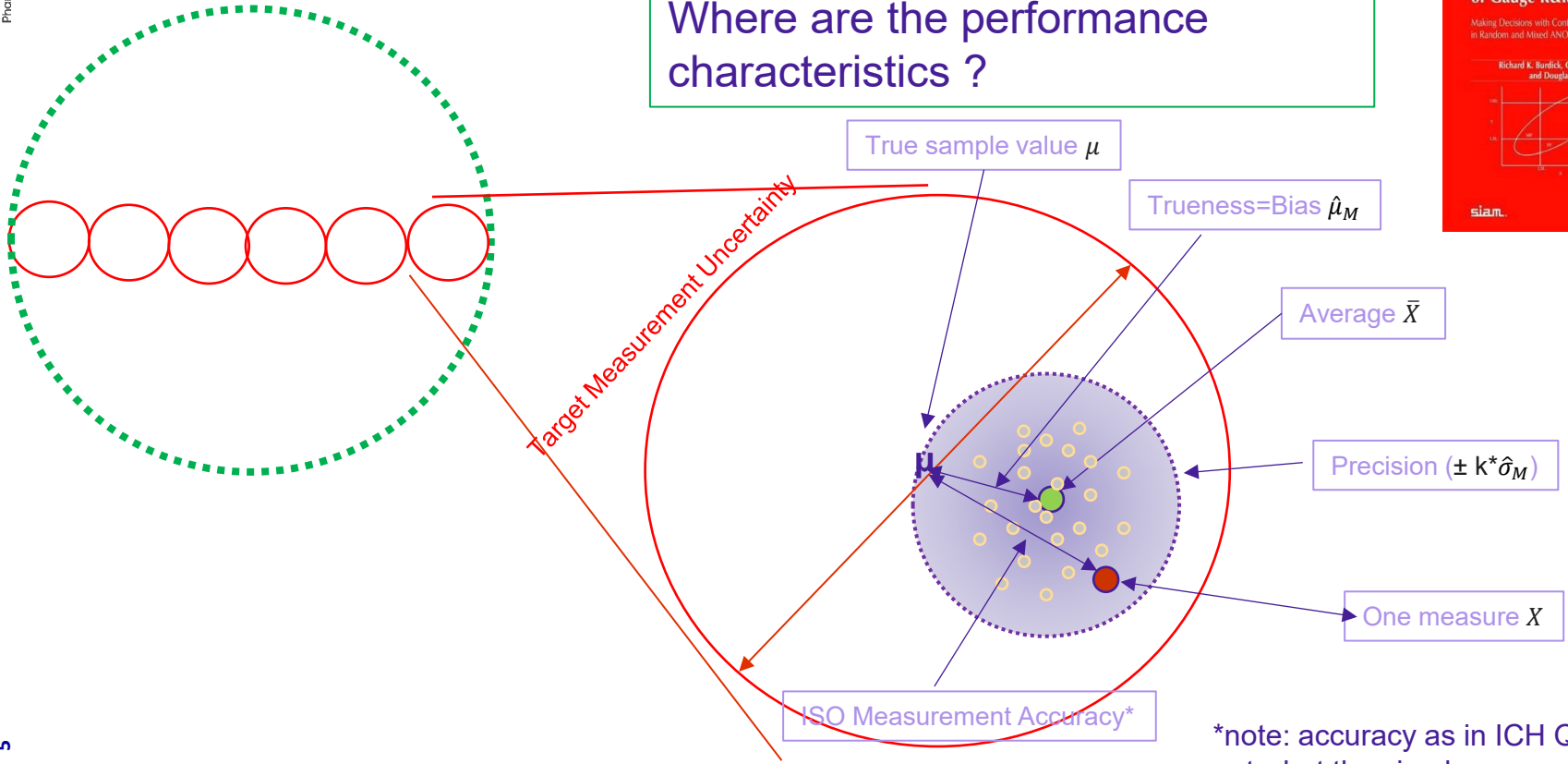
The route to estimate the Uncertainty of a future measurement

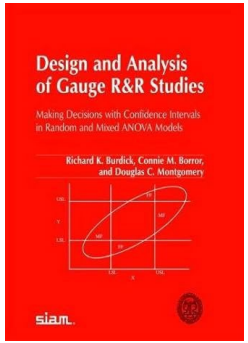
A “total analytical error“ ATP

“The procedure must be able to quantify Drug Substance impurities in a range from 0.1 µg/mL 25 µg/mL in all intermediates, in the presence of matrix and impurities x, y, z, so that the distribution of the total analytical error of the reportable value falls within the Target Measurement Uncertainty range of ± 30%”

Target Measurement Uncertainty and Specifications

Where are the performance characteristics ?





*note: accuracy as in ICH Q2, but not what they imply

Why the Combined approach for Accuracy and Precision is a valuable addition for Assay Validation ?

The objective of validation becomes…

Demonstrate that any **future** reportable value has a minimal **probability** π_{min}, say 0.95, to fall within the acceptance limits TMU, **given** the estimated performance of the **procedure** $\hat{\mu}_M, \hat{\sigma}_M$ (bias and precision)

$$E_{\hat{\mu},\hat{\sigma}}\{P[|X-\mu| < TMU] \mid \hat{\mu}_M, \hat{\sigma}_M\} \geq \pi_{\min}$$

The "missing link" between performance and results

Expected Analytical error of results in future

Estimated procedure performance characteristics (accuracy, precision)

Compute the predictive distribution and derive Prediction Interval

Compute the Prediction interval

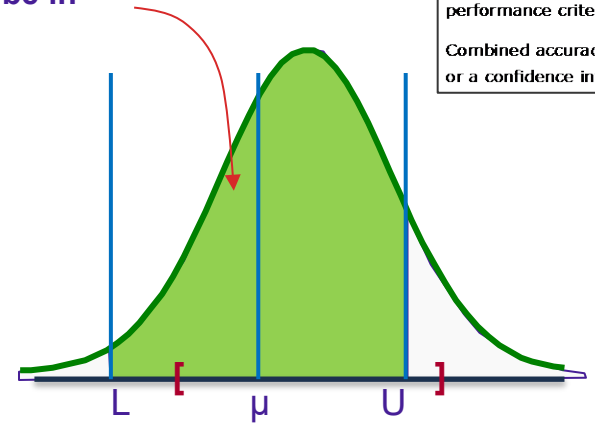
3.3.3 Combined approaches for accuracy and precision

An alternative to separate evaluation of accuracy and precision is to consider their total impact by assessing against a combined performance criterion.

Data generated during development may help determine the best approach and refine appropriate performance criteria to which combined accuracy and precision are compared.

Combined accuracy and precision can be evaluated by use of a prediction interval, a tolerance interval or a confidence interval. Other approaches may be acceptable if justified.

Predictive Probability to be in specifications



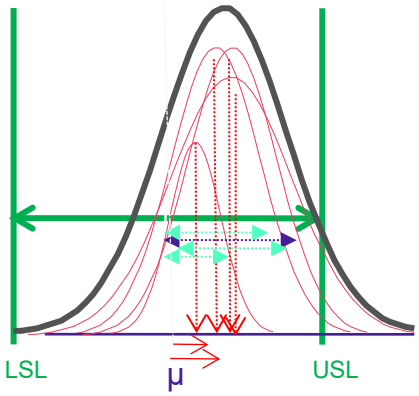
➔ The β-expectation tolerance interval
= Prediction interval
= (Credible) Interval of the Predictive distribution (of the future next result)
= Uncertainty of measurement, i.e. **total error**

Prediction Interval = Uncertainty of Measurement

- The width of Prediction distribution interval = Uncertainty of Measurement

- It integrates
  - The Precision
  - The Uncertainty of the **bias estimate**
  - The Uncertainty of the **precision estimate**

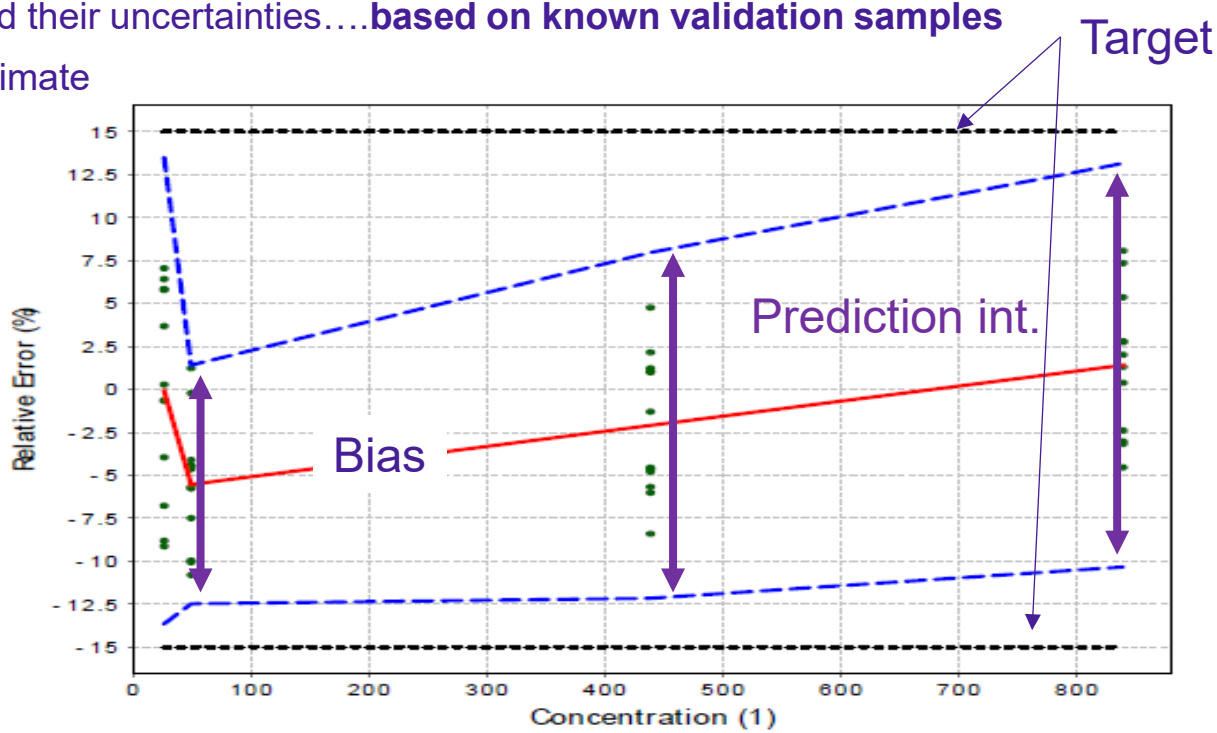
- The Uncertainty of measurement is NOT ONLY the Precision
  - Mathematically
  - From an interpretation perspective



Prediction Interval over the range (using enoval)

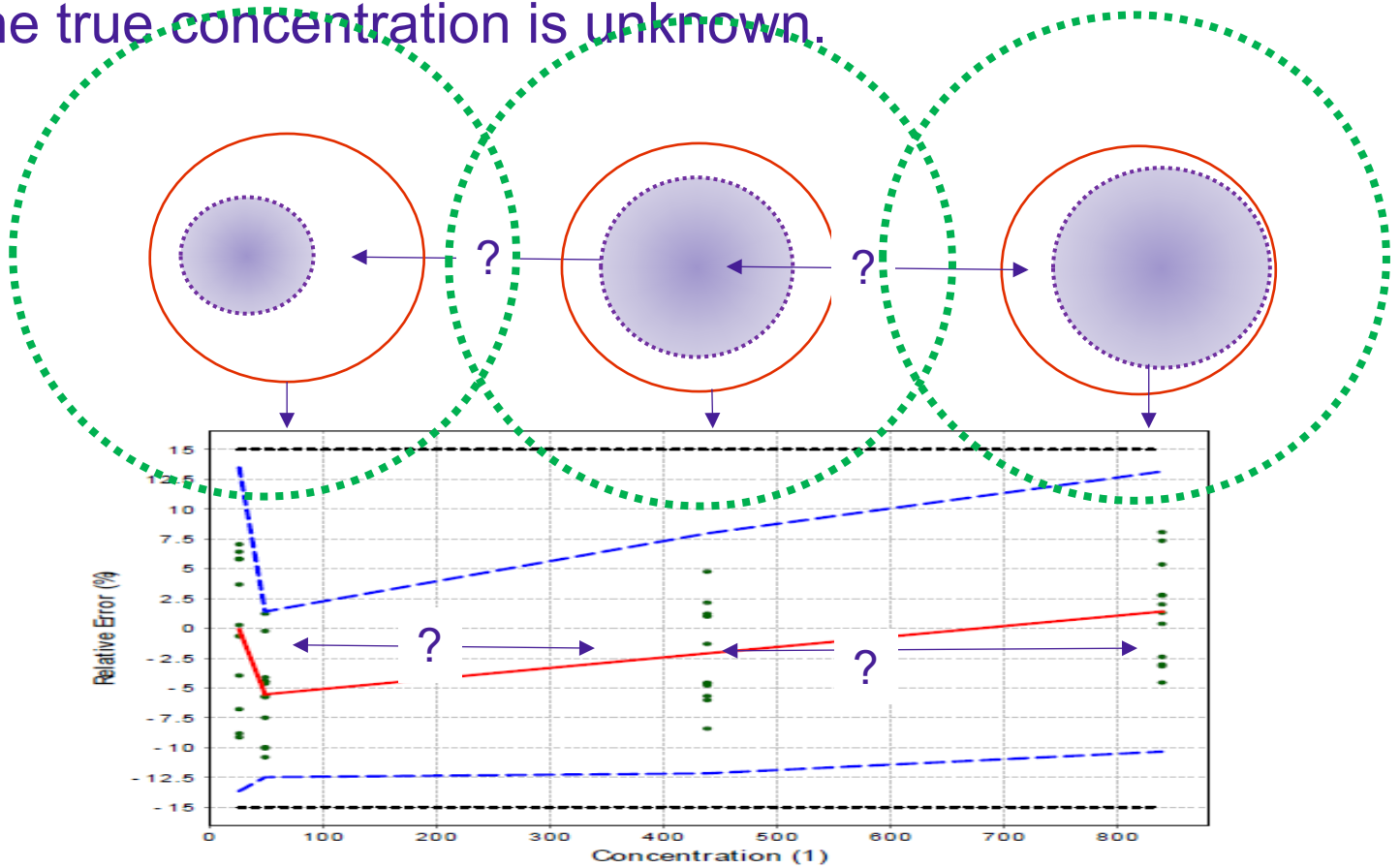
Compute over range

- The prediction Interval (i.e. Total analytical error), integrating bias, between- and within-series precision and their uncertainties….**based on known validation samples**
- The bias estimate



Ph. Hubert et al. / Journal of Pharmaceutical and Biomedical Analysis 45 (2007) 82–96
Burdick et al. / Statistical Methods for Validation of Procedure Accuracy and Precision, STIMULI TO THE REVISION PROCESS 39(3), 2013

Note the true concentration is unknown.



So given their true values are unknown, their intrinsic uncertainty is unknown
Only the guarantee to achieve the TMU is relevant.

Prediction interval - details

Several implementations exist

- Robert Mee (1984)
- Preferably use REML estimates (results would differ from least-square with unbalanced data)
- Correct degrees of freedom for unbalanced design (not the same number of replicates in each series/day)
- Ensure fixed closed-form solution whenever possible (GxP likes reproducibility)
- Verify coverage
- Document the solution so there is no ambiguity in the calculations

Prediction interval - details

In a Nutshell (R. Mee, 1984)

$$[\text{mean} - k * \text{sigma} ; \text{mean} + k * \text{sigma}]$$

$$\left[bias(\%)_j - Q_t\left(v, \frac{1+\beta}{2}\right)\sqrt{1+\frac{1}{pnB_j^2}}\,CV_{IP,j} \;\; ; \;\; bias(\%)_j + Q_t\left(v, \frac{1+\beta}{2}\right)\sqrt{1+\frac{1}{pnB_j^2}}\,CV_{IP,j} \right]$$

With…

$$bias(\%)_j = 100.\frac{\bar{x}_j - \hat{\mu}_j}{\hat{\mu}_j}$$

$$CV_{IP,j} = 100.\frac{\hat{\sigma}_{IP,j}}{\hat{\mu}_j}$$

And $\hat{\sigma}^2_{IP,j} = \hat{\sigma}^2_{W,j} + \hat{\sigma}^2_{B,j}$, obtained through REML

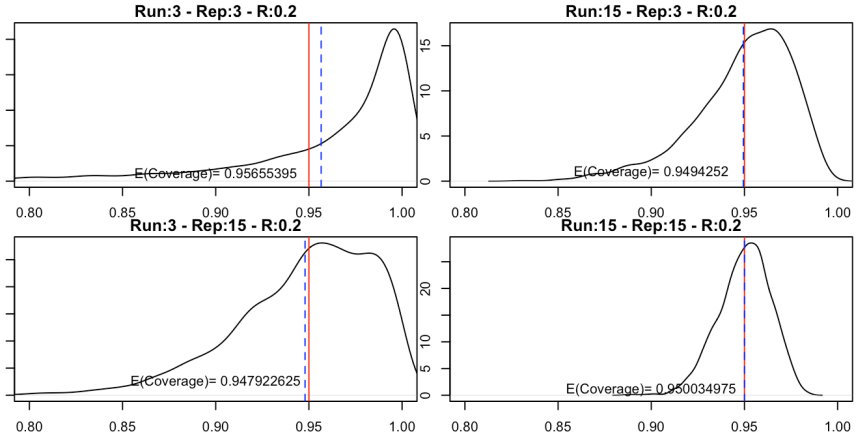
$$\hat{B}_j^2 = \frac{R_j + 1}{nR_j + 1}$$

$$v = \frac{\left(R_j+1\right)^2}{\frac{\left(R_j+\frac{1}{n}\right)^2}{p-1}+\frac{1-\frac{1}{n}}{pn}}$$

…and finally $R_j = \frac{\hat{\sigma}^2_{B,j}}{\hat{\sigma}^2_{W,j}}$

Sneak preview: Unit testing

- When developing advanced statistical approaches, it's important to verify the accuracy and correctness of the proposed solution
- Data simulation allows to generate random data sets, verify the exact coverage, and repeat thousands of times, obtaining a distribution of the coverage.



When number of runs (in the data) is low, accuracy is slightly off, but still very close to the nominal level (95%)

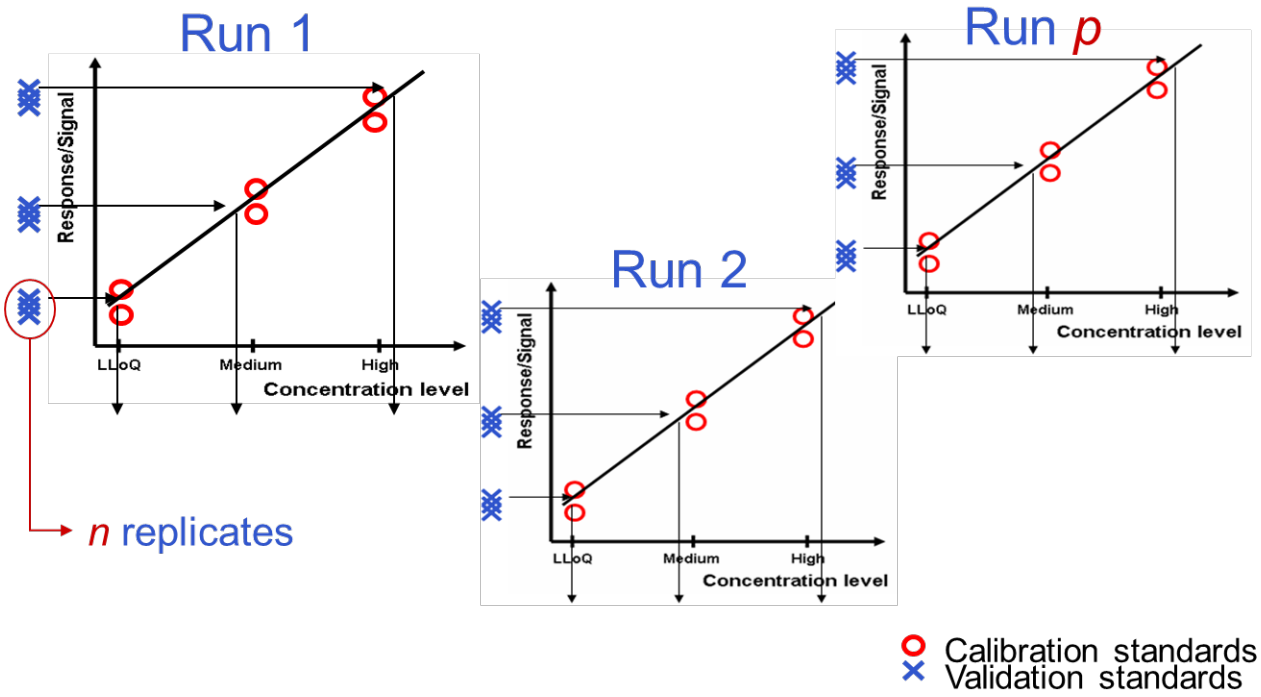
→ Very much in line with simulations made by Robert Mee (1984), but here obtained with unbalanced designs

Design

All-in-one design

Need to know how many

- levels
- runs
- replicates



Assay Validation – The Process

- Start with the objective – the Analytical Target Profile (ATP)

Ex: 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 an 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 interval that integrates:

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

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2nd: Automation

What does it take to have an expert system that is qualified

Why automating ?
Infrastructure
Quality Assurance
GxP regulation
End-to-end solution, from study design to a validated automated report

Why automating?

- Complex business question, not properly addressed by the industry, *in our opinion*
  - We thus believe there is a commercial opportunity
- Some parts of the tasks (here assay validation) are *repetitive* and could enter in a framework that would benefit the users
  - Cost reduction for end users: statistical computations + cost / time for reporting
  - Ensure alignment with regulatory bodies that are evolving
  - Business excellence for Cencora Pharmalex: we can also propose very competitive pricings to consulting customers by using our own software
- On other parts, small mistakes can easily be done
  - Formulas, reporting,…

A GxP expert system can answer all these points

Automation: a team challenge

Our holistic approach for building commercial statistical software

1. **Domain & regulatory expertise** (CMC / Clinical / Omics / ...)
2. **Statistical expertise** (Frequentist / Bayesian / ML / DS)
3. **Quality**: GxP-oriented covering consultancy, software development & infra
4. **Software dev. consultancy, environment & methodology** (GxP-ready)
5. **Infrastructure** for & maintenance of SaaS applications (GxP-ready)

Business question + repetitive task

... from **concept** to **production** (GxP-ready).

Consulting

- Freq/Bayesian/ML/DS/AI
- Clinical
- Biomarkers
- Omics
- CMC
- Trial Design
- PK/PD
- ...

R&D custom software

"ShinyApps"

- Fast delivery
- Flexible pricing (from PoC to tested, qualified)
- Modern dev process
- Qualified Infra

Commercial GxP software

"SmartSTATS"

- Modern dev process
- Efficient GxP process
- Automated Testing
- Automated QA docs
- Full SOP coverage
- Qualified Infra

Partnerships of experts in regulatory affairs, statisticians, IT architects and developers, Quality assurance, …

Quality Assurance

GxP : have a consistent product that allows to make reports that can be sent to authorities and ensure traceability of all activities (e.g. audit trails)

Guidance GAMP 5 for qualified infrastructure & product functionality in life-cycle of the system

Good automated manufacturing practice aims to deliver a cost-effective framework of good practice to ensure that computerized systems are effective and of high quality, fit for intended use, and compliant with applicable regulations.

Team: maintained competency matrix / demonstrated people proficiency and skills

Product: Qualified infrastructure, Validated results (URS, FRS, tests, docs, user guides), Change Control, Decommissioning

And Also: 21CFR-part11 (electronic data storage – confidentiality, signature, integrity), Privacy (e.g. GDPR in EU)

Quality assurance : SOP

SOPs

SOP-BEL-RDI-1005 Software **validation** in development environment

SOP-BEL-RDI-1000 Software **life cycle** in development environment

SOP-BEL-RDI-1004 Software **development** in development environment

SOP-BEL-RDI-1003 Software **Change Requests**

SOP-BEL-DCS-1015 **Incident** Management for DSQS

SOP-BEL-DCS-1006 **Version control** system for PLx Belgium (git)

SOP-BEL-DCS-1008 Software **versioning**

WI

Roles and responsibilities (inc. Competency Matrix)

Definitions and abbreviations

Risk assessment

DevOps conventions

Package conventions

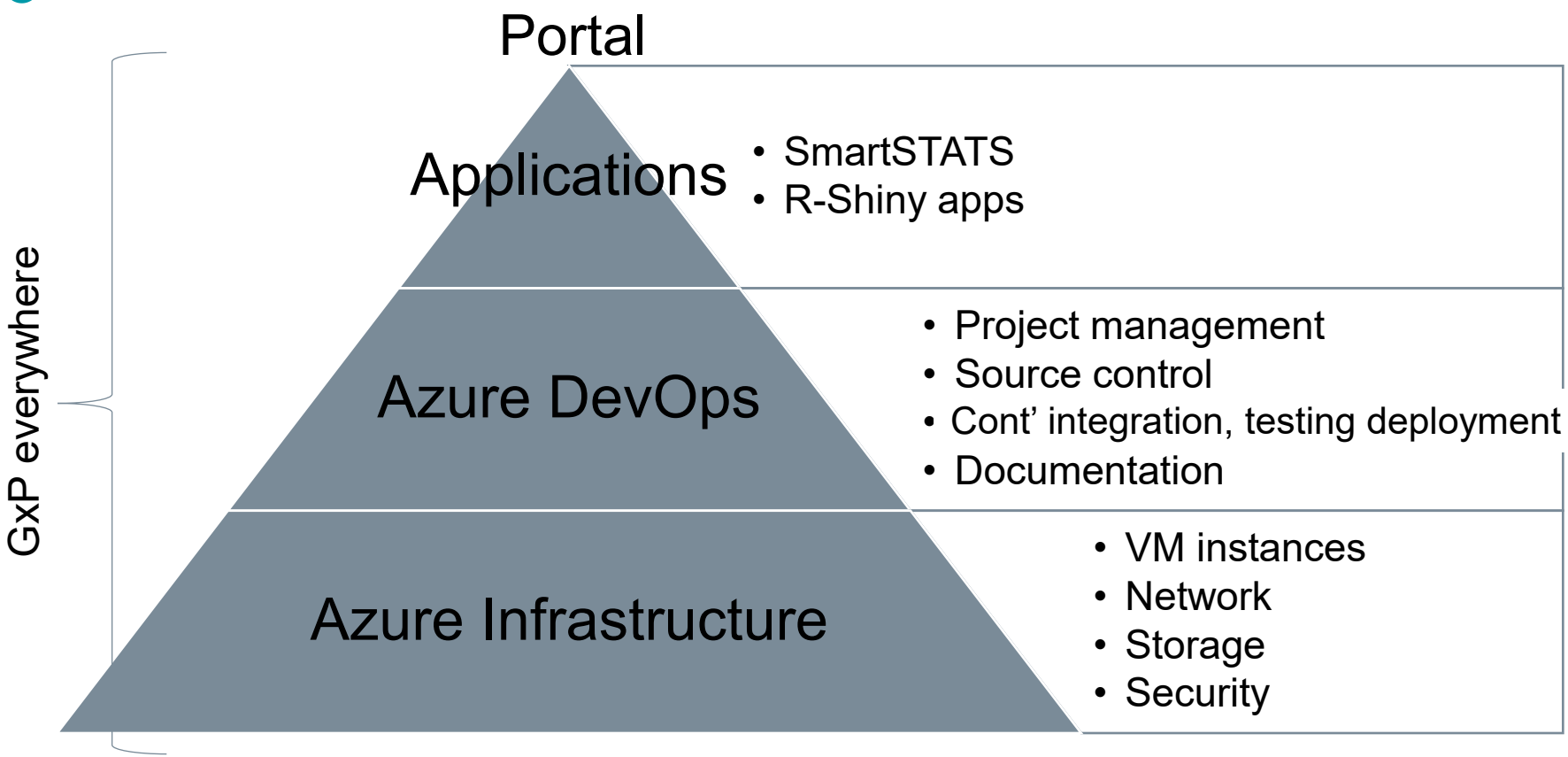
Coding conventions

REST API conventions

LSAF conventions

General guidance

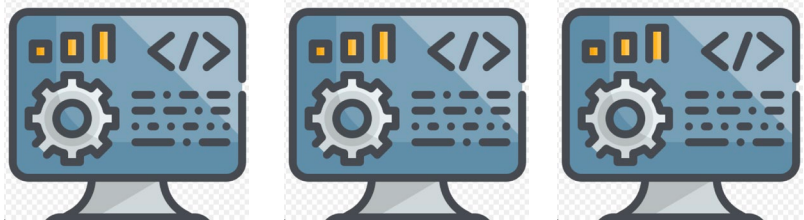
Detailed work instructions


Portal
Applications
• SmartSTATS
• R-Shiny apps
Azure DevOps
• Project management
• Source control
• Cont' integration, testing deployment
• Documentation
Azure Infrastructure
• VM instances
• Network
• Storage
• Security
GxP everywhere

Software development, environment & methodology (GxP-ready)

- Previous software versions used GAMP5 validation guidelines, stricto senso
  - V-model, not very flexible, testing & validation costs

- Implementation of an agile system that allows to ensure each module has a similar level of qualification
  - Using Epic / Features / User stories, in place of Project / URS / FRS
  - Fully electronic system (no paper) for the requirements, risks assessments, test, wiki
  - Minimize number of different systems (e.g. JIRA + Devops + linux SVN + Paper based doc + specific QMS + …)
- Development in term of sprint with releases that show full completion of (automated) unit testing and writing of the validation report.
  - Each release: new code review + full testing and automatic documentation + some high-level manual test (e.g. SSO)



Software development, environment & methodology (GxP-ready)

- Code review : all programmers reviews all relevant codes (see Competency matrix). All code is reviewed, often by multiple programmers.

- Build in risk assessment (SOP-G-GLO-SBS-1001 and related WI): each functionality is analyzed
  - E.g. very specific risks: ensure code routines never crash, error is managed and reported (e.g. stats routine)
  - E.g. very specific risks: ensure a software module is assigned to customer only if they get the license in order (authorization after authentication)
  - E.g. large scope: ensure the environment is 99% available

- Use code versioning for full traceability of the development (GIT)

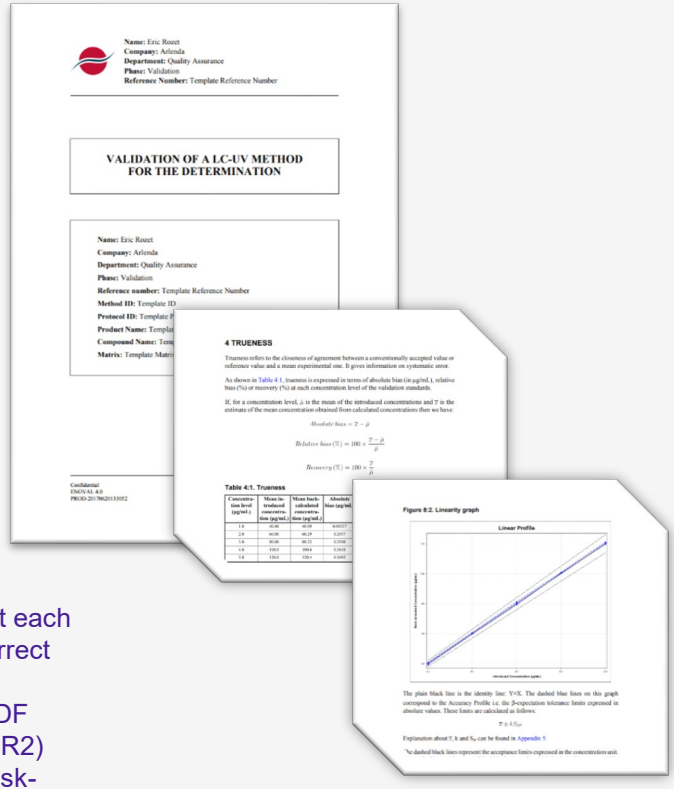
Testing strategy

Self-descriptive

```
JSON:validation
|--experimental_design
|   |--calibration
|   |   |--table
|   |   °--nr_observations
|   °--validation
|       |--table
|       °--nr_observations
|--calibration
|   |--summary
|   |--plots
|   |   °--...
|   °--diagnosis
|       |--levene
|       |--lack_of_fit
|       °--residuals
|           °--standardized
|               |--data
|               °--plot
|--validation
|   |--trueness
|   |   °--summary
|   |--precision
|   |   |--summary_relative
|   |   |--summary_absolute
|   |   |--upper_cl
|   |   °--by_series_recovery
|   |--uncertainty
|   |   °--summary
|   |--accuracy
|   |   |--summary
|   |   °--plots
|   |       |--profile
|   |       °--risk
|   |--linearity_of_results
|   |   |--summary
|   |   |--residuals
|   |   °--plots
|   |       |--linear_relationship
|   |       |--linear_profile
|   |       °--residuals
|   |--limits
|   |   |--quantitation
|   |   °--detection
|   |--indices
|   |--backcalculations
|   °--individual_recovery
|--user
|   |--parameters
|   |--calibration_data
|   °--validation_data
|--alignment
|   °--validation_data
°--info
    °--r-version
```

==> ROBUSTNESS TESTING

Mapping + Transform



- **Mapping**: tested **1x** to make sure that each part of the JSON is mapped to the correct place in the PDF
- **Transform**: tested **1x** from XML to PDF
- **Content**: ensure alignement with Q2(R2)
- **Automated** tests, expected results, risk-based approach (priority on high and medium risks)

Infrastructure for & maintenance of SaaS applications (GxP-ready)

- Definition of roles (e.g. Admin, users, etc.) and access rights (e.g. SSO authentication, authorisation)

- Choice of on-premises vs. cloud
  - On premise: full control, difficult maintenance, infrastructure obsolescence
  - Cloud: No physical maintenance, up to date security and performances, virtualization, but GDPR, access, file location, etc.

- Security
  - Guided by SOP and technical cybersecurity tools (encryptions, certificate (https), vulnerability scan, VM back up, DRP, Antivirus, anti-ransomware, safe and injection protected code, VPN, …)
  - Minimized exposed services (only Portal), Firewall, VPN for non-PROD environments
  - All these measures can be heavy on the infrastructure and may be conflictual !
  - Penetration tests from professional hackers

Infrastructure for & maintenance of SaaS applications (GxP-ready)

- Docker, Kubernetes (micro-services)
  - Modularization, simplicity, reproducibility, extensibility
  - Modules : only the portal can be attacked. Not possible to attack the modules themselves as only the portal can launch them. Each module runs in their own docker, which separates the environment and thus reduces all risks (attack, crashes, etc.).

- Automated Pipelines : builds & releases are automatically deployed within the VM in a docker

- Environments: Dev / Test / Prod
  - Never put in prod something not thoroughly tested

SaaS Model

No database !

We crunch the data, we generate the report, and at logout (or timeout) everything is securely deleted

Some anonymous data collected (e.g. number of reports generated for each module) for internal analytics, business development, etc.

Features & Key advantages

- V Fully validated according to GAMP 5 guidelines
- V Data security, 21 CFR part 11 compliant
- V Guidelines compliance (ICH, USP)
- V User-friendly
- V No installation required
- V No need to validate the system on site
- V No maintenance costs for customers
- V Accessible from any location (with Internet access
- V Always the latest version available (free of charge)

GxP SaaS

Software ready for use

- **ENOVAL** validates your physicochemical methods such as high - performance liquid chromatography and
  ultra - performance liquid chromatography
- **SEELVA** validates your ligand – binding - assay
  method such as enzyme - linked immunosorbent assay
  and radioimmunoassay
- **STABELITY** evaluates your product's shelf life
  and defines the release limits
- **TRANSVAL** focuses on the transfer of analytical methods from one lab to another.

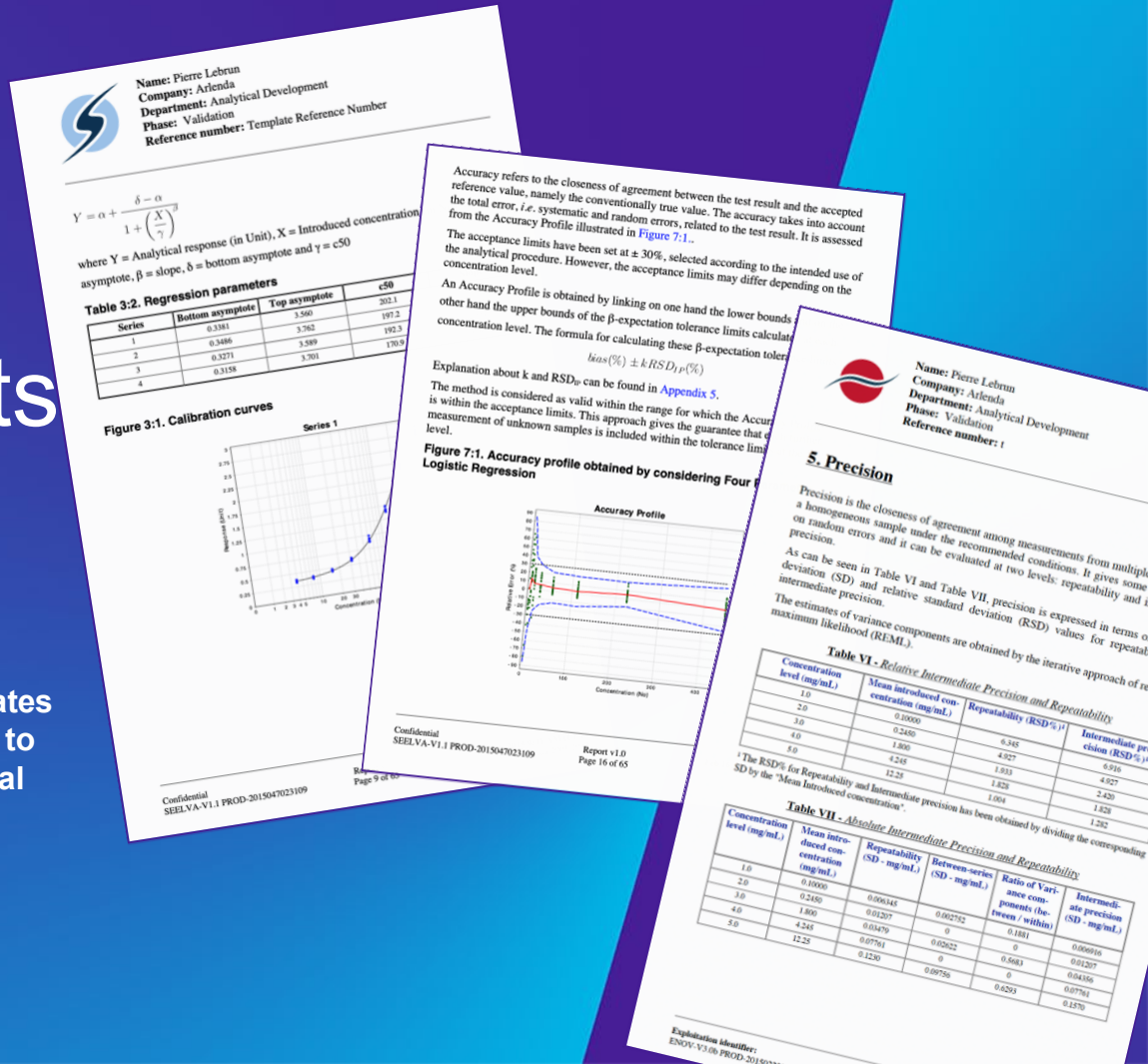
Software as a service — 21 CFR Part 11 / GAMP 5

SMARTENOVAL SMARTSEELVA SMARTSTABELITY SMARTTRANSVAL

cencora
PharmaLex

Example reports

SmartSTATS\Enoval & Seelva module generates a report in line with the EMA\FDA guidelines to prove or disprove the validity of our analytical procedure.



Conclusions

1. Statistical methodology is now ready, regulatory-wise to go to the next steps, thanks to ICH 2(R2)
2. We continue promoting the methodologies we developed 20 years ago, illustrating how Total Analytical Error is a beneficial framework for analytical procedure validation

3. Prediction interval (beta-expectation tolerance interval) is the simple way for decision making in this context

4. Developing expert systems in a GxP environment is challenging
5. Many different roles with specific expertise – a large team
   - A single talented statistician could develop a nice prototype using e.g. R/shiny
   - Now, the paths to validation are intricate
   - Modular systems + Agile development and qualification is key to ensure maintainable and extensible software

Thank you

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