SCS Swiss Chemical Society — Division of Analytical Sciences

Eurachem

Scientific Workshop in connection with Eurachem General Assembly 2023

Ensuring reliable and accurate results of analytical processes

22.–23. May 2023, METAS, Bern-Wabern, Switzerland

Lifecycle approaches for establishing 'Fitness for Intended Use' of Analytical Instruments and Systems, USP <1058>, in order to support and maintain 'Fitness for Purpose' of Analytical Procedures USP <1220>

Dr Christopher Burgess

Burgess Analytical Consultancy Ltd

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eMail: chris@burgessconsultancy.com

Short Biography

- an analytical scientist and a Fellow of the Royal Society of Chemistry (RSC)
- a Qualified Person within the European Union since 1985
- a qualified ISO ISO/IEC 17025 assessor
- more than 45 years experience in management and consulting positions within the pharmaceutical, biopharmaceutical and medical device industries after 20 years with Glaxo (Now GSK) in Analytical R &D, Quality Control and Quality Assurance.
- MSc and PhD degrees from Loughborough University in Analytical Chemistry.
- been involved in more than 280 **ECA** (**E**uropean **C**ompliance **A**cademy) training courses since 2001 which have had over 10,000 attendees from 82 different countries
- serves on the Extended Board of the **ECA** Foundation
- Chairman of the **ECA** Analytical Quality Control Group Board and contributing author to Guidelines on OOS, OOE & OOT results and Data Integrity, Data Governance and Analytical Procedure Lifecycle Management Guidelines
- a visiting Professor at the University of Strathclyde in the Strathclyde Institute of Pharmaceutical and Biomedical Sciences (SIPBS)
- an elected member of the USP Council of Experts, Expert Committees, Joint Subcommittees and Expert Panels 2010 to 2020 and re-elected for 2020-2025 cycle.
- a member of the USP Expert Panel & JSC on Validation and Verification of analytical procedures 2011-2025 and chairman of the JSC for the revision of <1058>
- he writes the Statistical Solutions columns for Pharmaceutical Technology USA

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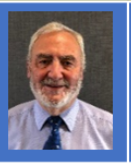
Board Members

Dr Christopher Burgess		Burgess Analytical Consultancy Limited, Qualified Person, USP Council of Experts 2010 to 2025 and Chairman of the AQCG Board
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Dr Joachim Ermer		Ermer Quality Consulting, Germany
Dr Gerd Jilge		Boehringer Ingelheim Pharma GmbH & Co. KG Retired Head of a Method Development Laboratory
Dr Bob McDowall		R D McDowall Limited Member of the ECA IT Compliance Interest Group
Ms Margarita Sabater		Genmab A/S, Denmark Senior CMC Specialist, Analytical

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Scope

- Short positional overview
- Traditional Pharmaceutical approached to analytical method (procedure) validation, verification and transfer
  - USP <1225> & <1226> & <1224>
  - ICH Q2(R1) [Revision & new Q14]
- USP initiatives: Applications to analytical processes
  - New General Chapter Analytical Procedure Lifecycle <1220>
  - *Analytical Instrument Qualification; General Chapter <1058>*

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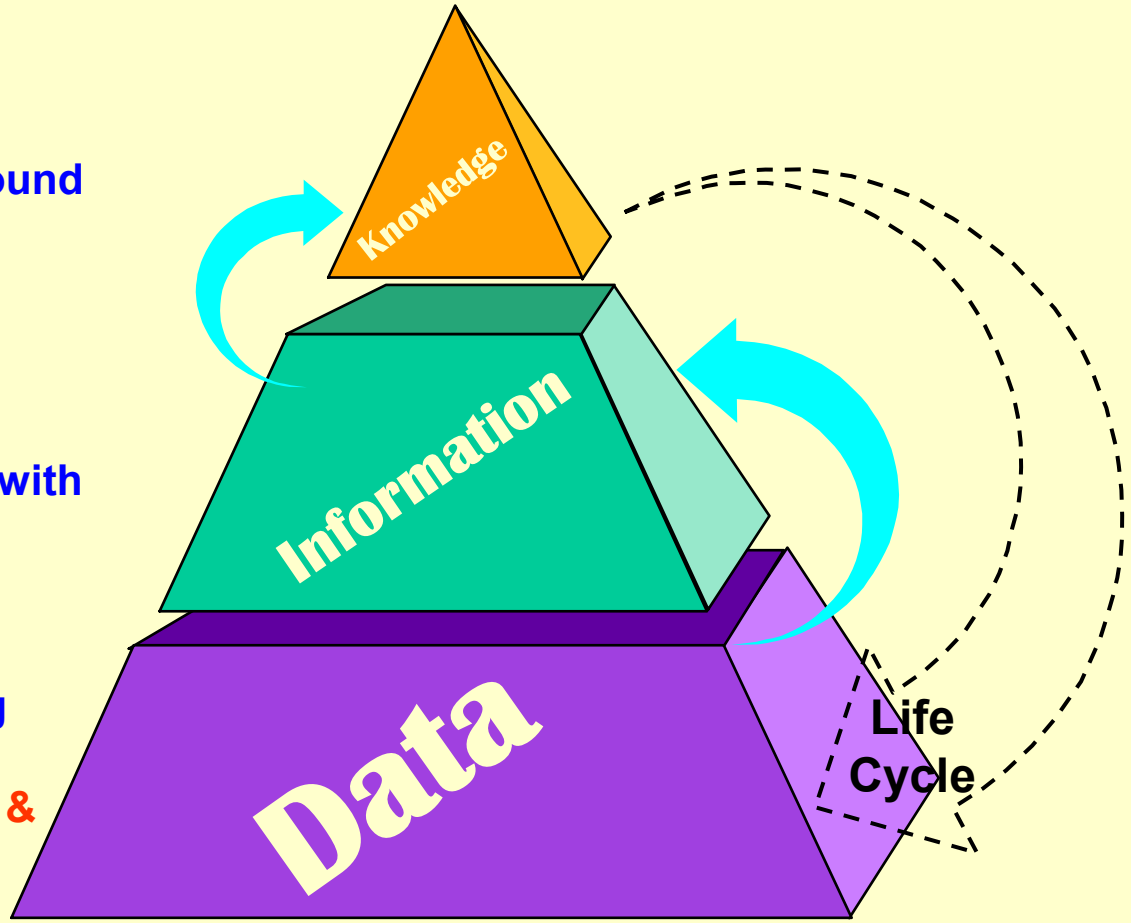
Data to Knowledge Hierarchy & Lifecycle

Product knowledge:
Based on scientifically sound analytical processes

Valid Sample Information:
Derived from good data using validated application software with verified algorithms.

Good Data:
Derived from relevant samples using validated methods developed on qualified and calibrated instruments & systems



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<1225> VALIDATION OF COMPENDIAL PROCEDURES

- Aligned with ICH Q2(R1) 1995
- Traditional analytical chemistry approach
- Validation requirements are limited by purpose
- Confusingly includes Robustness which is a development activity leading to SSTs

Table 1. Typical Analytical Characteristics Used in Method Validation

Accuracy
Precision
Specificity
Detection Limit
Quantitation Limit
Linearity
Range
Robustness

Category I—Analytical procedures for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.

Category II—Analytical procedures for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limit tests.

Category III—Analytical procedures for determination of performance characteristics (e.g., dissolution, drug release, etc.).

Category IV—Identification tests.

For each category, different analytical information is needed. Listed in *Table 2* are data elements that are normally required for each of these categories.

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<1225> VALIDATION OF COMPENDIAL PROCEDURES

Table 2. Data Elements Required for Validation

Analytical Performance Characteristics	Category I	Category II		Category III	Category IV
		Quantitative	Limit Tests		
Accuracy	Yes	Yes	*	*	No
Precision	Yes	Yes	No	Yes	No
Specificity	Yes	Yes	Yes	*	Yes
Detection Limit	No	No	Yes	*	No
Quantitation Limit	No	Yes	No	*	No
Linearity	Yes	Yes	No	*	No
Range	Yes	Yes	*	*	No

*May be required, depending on the nature of the specific test.

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<1226> VERIFICATION OF COMPENDIAL PROCEDURES

- Users of compendial analytical procedures are not required to validate these procedures when first used in their laboratories, but documented evidence of suitability should be established under actual conditions of use
- In the United States, this requirement is established in 21 CFR 211.194(a)(2) of the current Good Manufacturing Practice which states that the "suitability of all testing methods used shall be verified under actual conditions of use."

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<1224> TRANSFER OF ANALYTICAL PROCEDURES (TAP)

- The transfer of analytical procedures (TAP), also referred to as method transfer, is the documented process that qualifies a laboratory (the receiving unit) to use an analytical test procedure that originated in another laboratory (the transferring unit), thus ensuring that the receiving unit has the procedural knowledge and ability to perform the transferred analytical procedure as intended

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ICH Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical Validation; 14 November 2018

Q2(R1) Revision & Q14

- The current Q2(R1) "Guideline on Validation of Analytical Procedures: Text and Methodology" does not cover more recent application of analytical procedures, (e.g., Near Infrared (NIR) Spectroscopy or Raman Spectroscopy)
- The lack of guidance for these analytical data sets can lead to submissions with inadequate validation data for such analytical procedures, resulting in recursive information requests and responses, which can delay application approval
- This is particularly the case for procedures reliant on multivariate models, a category for which no ICH validation guideline exists
- Taking into consideration a difference between multivariate and traditional methods, the current approach of Q2 (R1) is not sufficient to establish the suitability of multivariate methods

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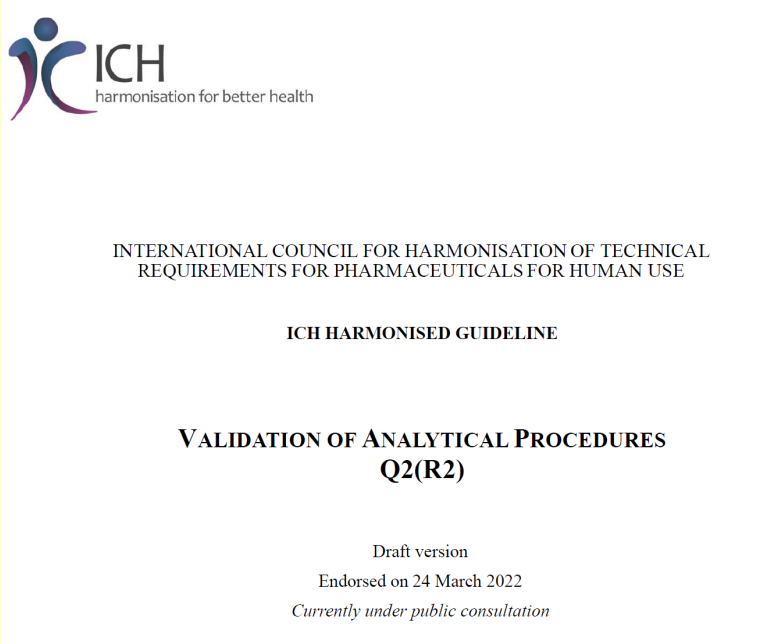
Arrived at Step 2; 2 years delay!



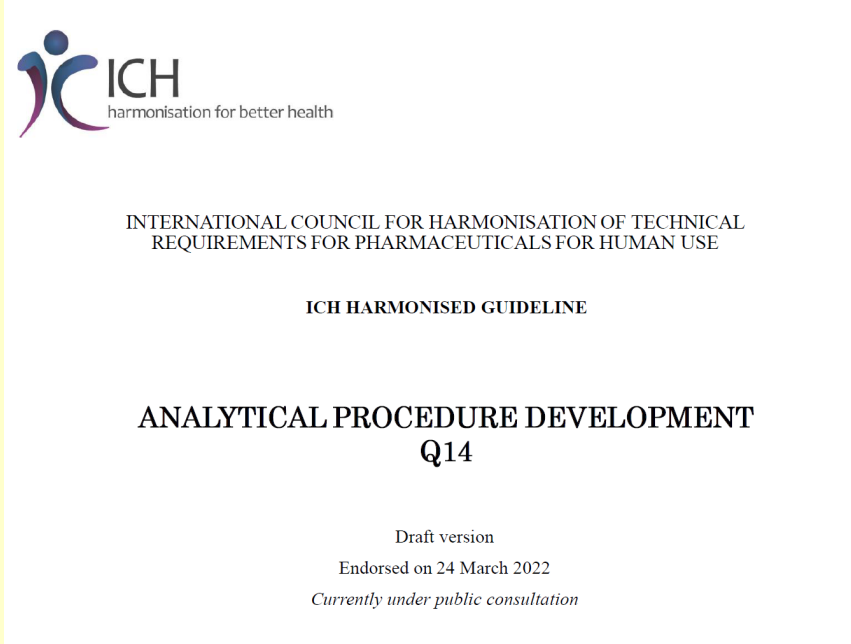
ICH
harmonisation for better health

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



ICH
harmonisation for better health

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

22 pages of text and two annexes
Annex 1; Selection of Validation Tests
Annex 2; Illustrative examples for analytical techniques
Total 34 pages

26 pages of text and three annexes
Annex A; Analytical Procedure Lifecycle
Annex B; Validation strategies for MODRs
Annex C; Example of Multivariate Model Life Cycle Components
Total 61 pages

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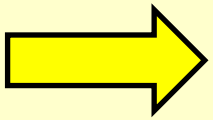
FDA Process Validation Paradigm shift

1987

"Process validation is **establishing documented evidence** which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics"



2011

"Process validation is the **collection and evaluation of data**, from the **process design** stage throughout production, which establishes scientific evidence that a process is capable of **consistently delivering** quality products."

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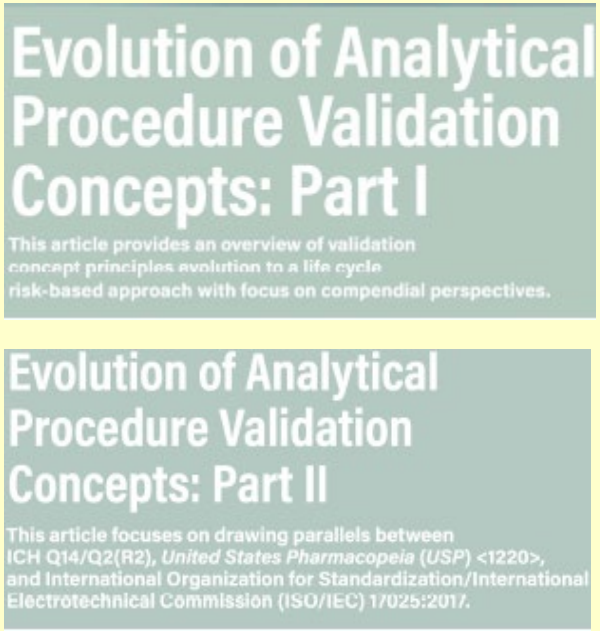

Amanda Guiraldelli is scientific affairs manager USP
&
Jane Weitzel is an independent consultant and chair of the USP Expert Committee on Measurement and Data Quality.

www.biopharminternational.com Quality and Regulatory Sourcebook March eBook 2023

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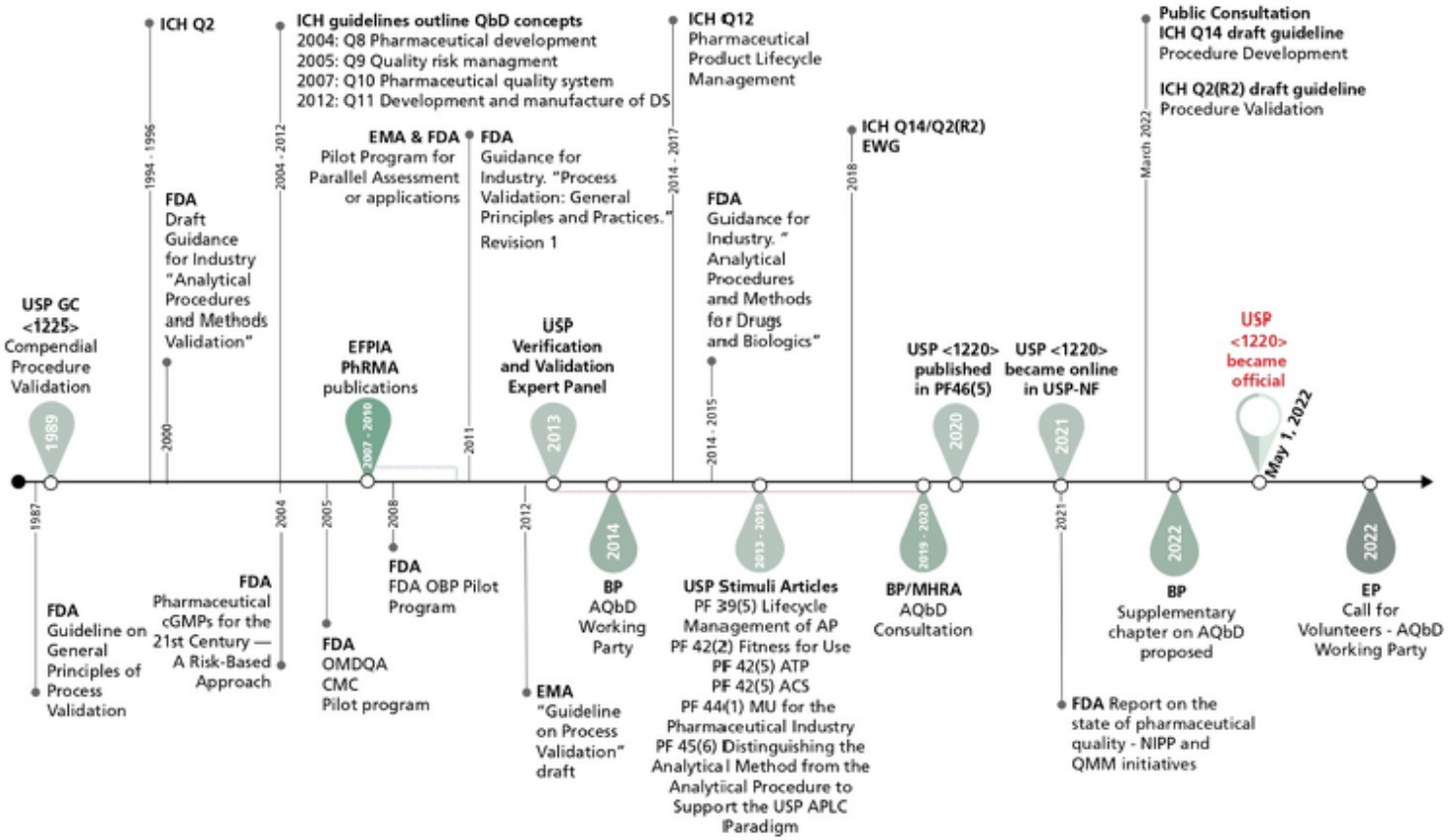
FIGURE 3. Timeline with publication of International Council for Harmonisation (ICH) guidelines outlining quality by design (QbD), *United States Pharmacopeia* (*USP*)/*British Pharmacopoeia* (*BP*) chapters, and FDA/EMA guidelines related to process and analytical procedures validation and/or life cycle.



https://www.e-digitaleditions.com/i/1495138-biopharm-international-march-2023/17?

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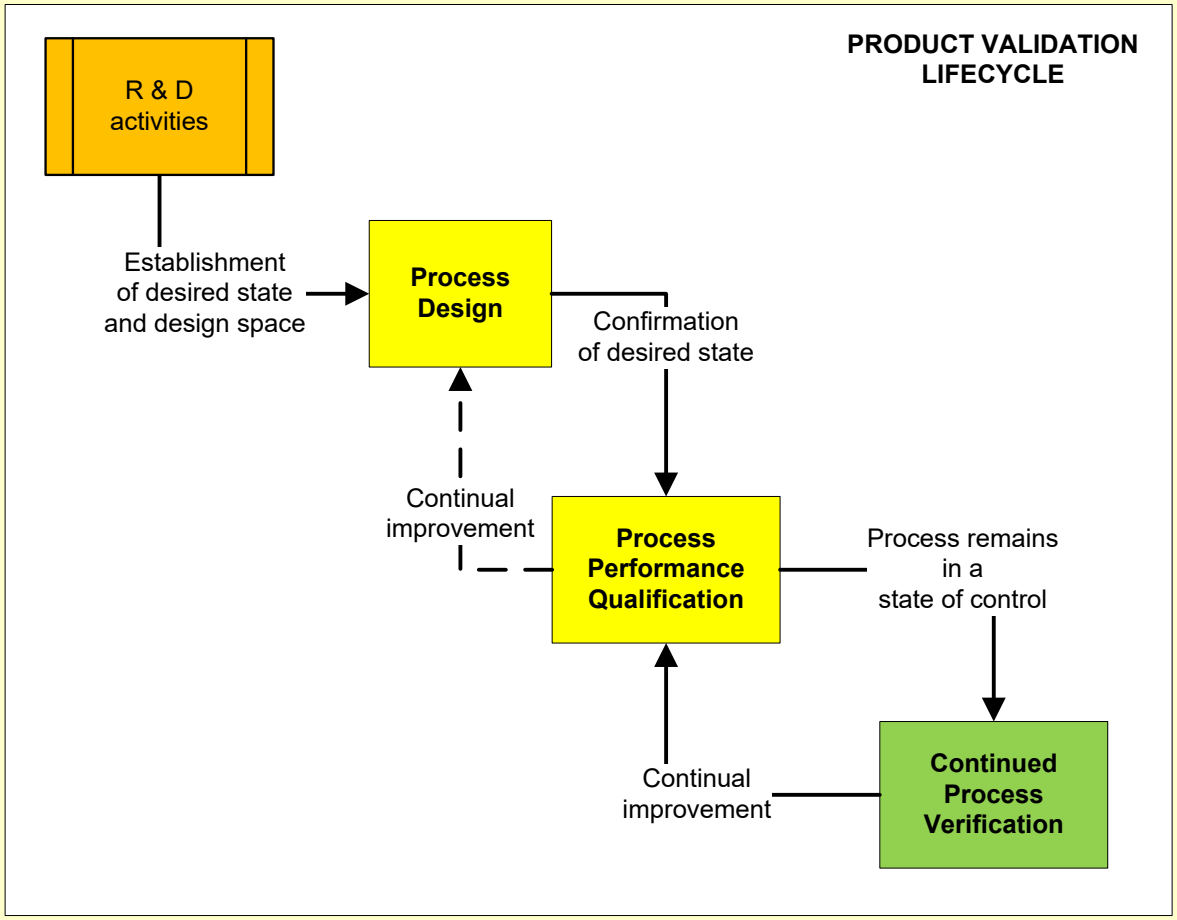
FDA Process Validation Guidelines January 2011



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ICH Q12 (Final Nov 2019)

Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

3.2.3.2 Identification of ECs for Analytical Procedures

- Similar to the principles described for a manufacturing process, ECs [Established Conditions] related to analytical procedures should include elements which assure performance of the procedure.
- The extent of ECs and their reporting categories could vary based on
  - the degree of the understanding of the relationship between method parameters and method performance
  - the method complexity

  and
  - control strategy.

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USP Lifecycle Management of Analytical Procedures

General Chapter <1220>

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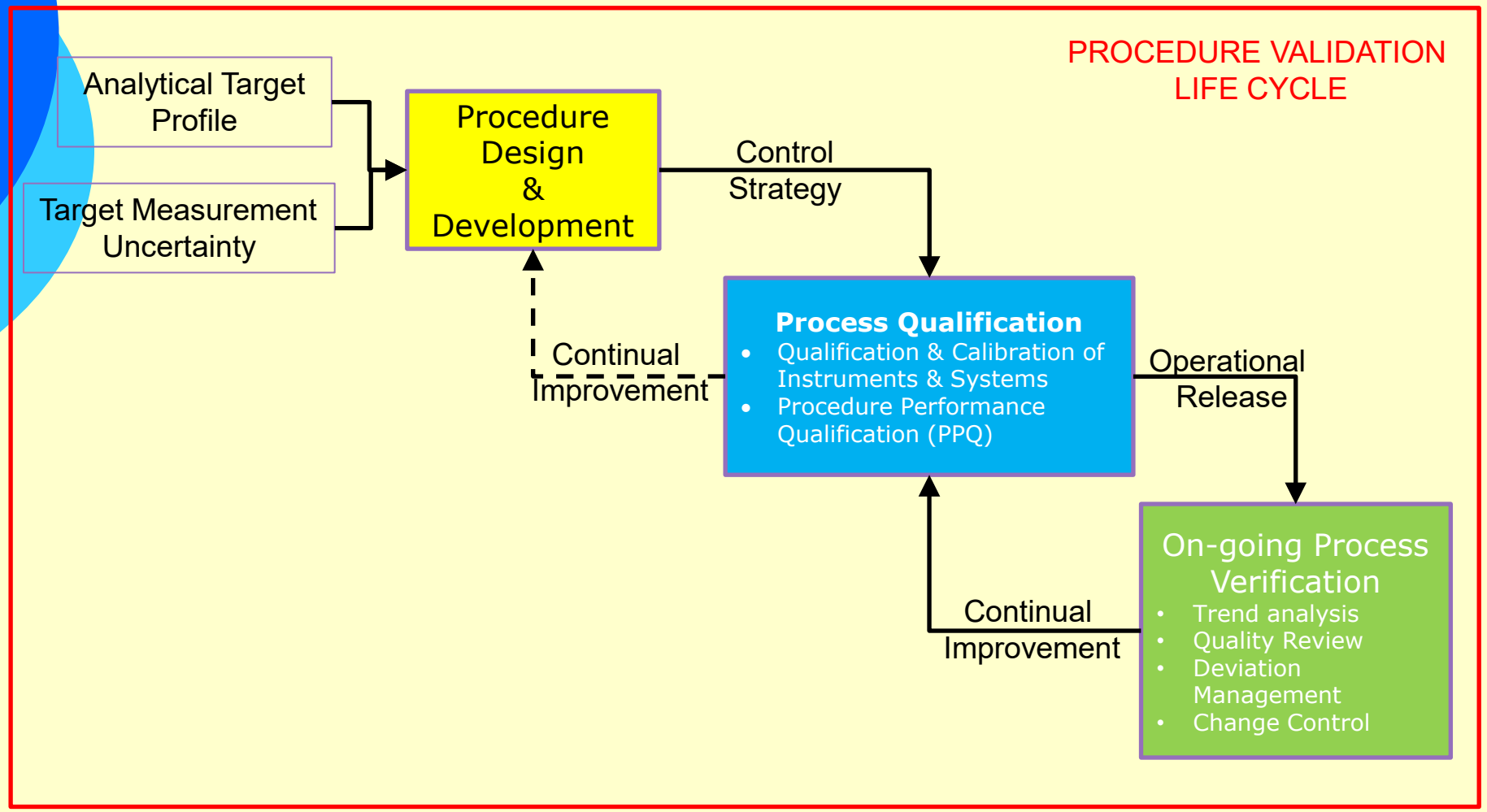
USP Initial Approach to Analytical Procedure Lifecycle



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Journey towards <1220>

Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification[a]

USP Validation and Verification Expert Panel: Gregory P Martin, MS (Chair); Kimber L Barnett, PhD; Christopher Burgess, PhD; Paul D Curry, PhD; Joachim Ermer, PhD; Gyongyi S Gratzl, PhD; John P Hammond; Joerg Herrmann, PhD; Elisabeth Kovacs; David J LeBlond, PhD; Rosario LoBrutto, PhD; Anne K McCasland-Keller, PhD; Pauline L McGregor, PhD; Phil Nethercote, PhD; Allen C Templeton, PhD; David P Thomas, PhD; ML Jane Weitzel

2013

Fitness for Use: Decision Rules and Target Measurement Uncertainty

Christopher Burgess,[a] Paul Curry,[a] Dave J LeBlond,[a] Gyongyi S Gratzl,[a] Elisabeth Kovacs,[a] Gregory P Martin,[a] Pauline L McGregor,[a] Phil Netthercote,[a] Horacio Pappa,[a,b] Jane Weitzel[a]

Analytical Target Profile: Structure and Application Throughout the Analytical Lifecycle

Kimber L. Barnett,[a] Pauline L. McGregor,[a] Gregory P. Martin,[a] David J. LeBlond,[a] M. L. Jane Weitzel,[a] Joachim Ermer,[a] Steven Walfish,[a] Phil Nethercote,[a] Gyongyi S. Gratzl,[a] Elisabeth Kovacs[a,b]

2016 & 2017

Analytical Control Strategy

Elisabeth Kovacs,[a] Joachim Ermer, PhD,[a] Pauline L McGregor, PhD,[a] Phil Nethercote, PhD[a] Rosario LoBrutto, PhD,[a] Gregory P Martin, MS,[a] Horacio Pappa, PhD[a,b]

Proposed New USP General Chapter: The Analytical Procedure Lifecycle <1220>

USP Validation and Verification Expert Panel: Gregory P Martin, MS (Chair); Kimber L Barnett, PhD; Christopher Burgess, PhD; Paul D Curry, PhD; Joachim Ermer, PhD; Gyongyi S Gratzl, PhD; John P Hammond; Joerg Herrmann, PhD; Elisabeth Kovacs; David J LeBlond, PhD; Rosario LoBrutto, PhD; Anne K McCasland-Keller, PhD; Pauline L McGregor, PhD; Phil Nethercote, PhD; Allen C Templeton, PhD; David P Thomas, PhD; ML Jane Weitzel, Horacio Pappa, PhD[a]

2017

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⟨1220⟩ ANALYTICAL PROCEDURE LIFE CYCLE

USP–NF 2022, Issue 1 on Nov. 1, 2021
and will become official on May 1, 2022

Philosophy & Scope I

- This general chapter holistically considers the validation activities that take place across the entire life cycle of an analytical procedure and provides a framework for the implementation of the life cycle approach.
- The analytical procedure life cycle approach described here is consistent with the quality by design concepts described in International Council for Harmonisation (ICH) guidelines.
- The procedure life cycle approach emphasizes the importance of sound scientific approaches and quality risk management for the development, control, establishment, and use of analytical procedures.

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⟨1220⟩ ANALYTICAL PROCEDURE LIFE CYCLE

USP–NF 2022, Issue 1 on Nov. 1, 2021
and will become official on May 1, 2022

Philosophy & Scope II

- Validation of an analytical procedure is the process by which it is established, through laboratory studies, that the performance of the procedure meets the requirements for the intended analytical applications.
- Validation, or demonstration that a procedure is suitable for the intended purpose, takes place during the entire procedure life cycle, beginning during the initial procedure design activities and extending through routine use. *These activities include the formal procedure validation, verification and transfer of procedures, as well as establishing and assuring adherence to an appropriate set of procedure controls and system suitability requirements*.
- The procedure life cycle is comprised of the analytical target profile (ATP) and three stages.

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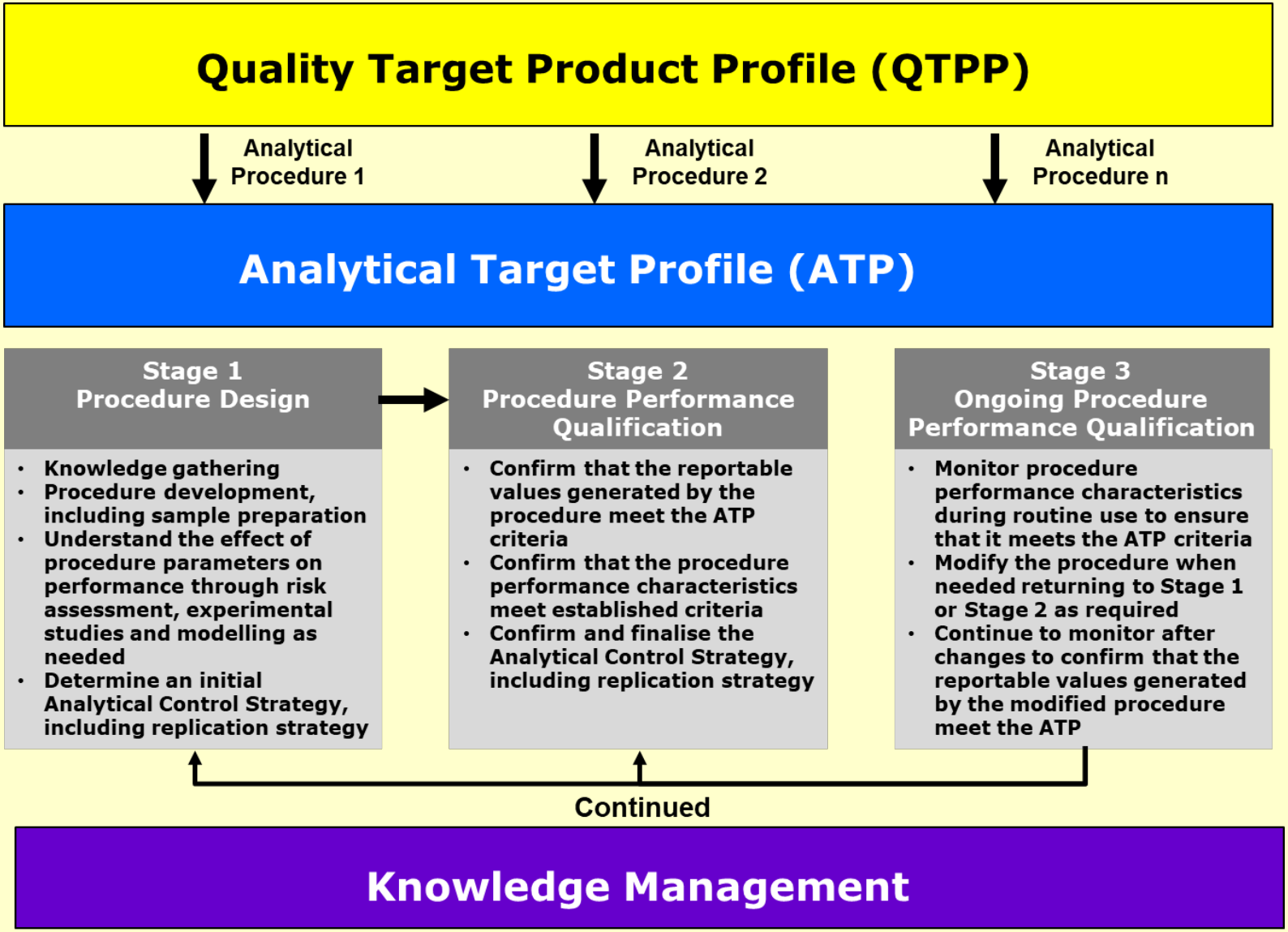

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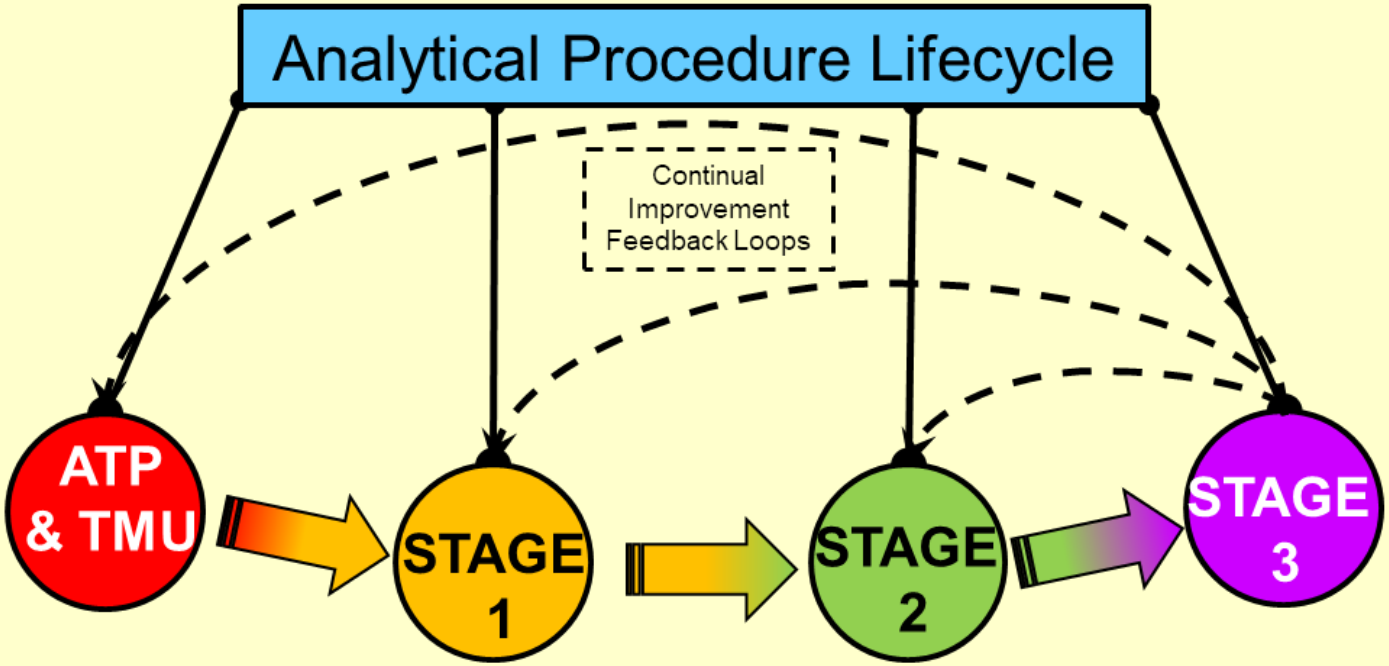
APLM is Dynamic!



Analytical Target Profile & Target Measurement Uncertainty
- Specifications
- Decision rules

Procedure Design and Development
- Knowledge gathering
- Risk Assessment
- DoE & modelling (Design Space)
- Analytical Procedure Control Strategy
- Replication Strategy
- Knowledge Management

Procedure Performance Qualification
- Protocol & Qualification Study
- Confirmation of the MODR & Analytical Procedure Control Strategy
- Release for operational use

Continued Procedure Performance Verification
- Trend analysis
- Deviation Management
- Change control

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Analytical Target Profile (ATP) & Target Measurement Uncertainty (TMU)

- A fundamental component of the life cycle approach is the definition of the analytical target profile (ATP) for the analytical measurement
- The ATP is a prospective description of the desired performance of an analytical procedure that is used to measure a quality attribute, and it defines the required quality of the reportable value produced by the procedure, aligned with the quality target product profile (QTPP)
- The ATP is based on the intended use for the procedure and, for quantitative or semi-quantitative procedures, should include upper limits on the precision and accuracy (bias) of the reportable value. [Total Error or Target Measurement Uncertainty]

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Stage 1: Procedure Design

Stage 1: Procedure Design
encompasses procedure development, which consists of the analytical technology and sample preparation. It includes understanding gained through knowledge gathering, systematic procedure development experiments, and risk assessments and associated lab experiments.

The output of Stage 1 includes:

- A set of procedure conditions that minimizes procedure bias, can provide suitable precision, and can meet the ATP criteria
- An understanding of the effect of procedure parameters on procedure performance
- Optimization of performance characteristics of the analytical procedure such as accuracy, precision, the appropriateness of the calibration model, selectivity, and sensitivity. This includes a preliminary replication strategy for samples and standards.
- An Analytical Control Strategy (ACS) which is a set of controls (system suitability tests (SST) and other procedure specific controls) needed to ensure proper performance

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Stage 2:
Procedure Performance Qualification

Stage 2: Procedure Performance Qualification
consists of studies designed to demonstrate that the procedure is suitable for its intended purpose in the laboratory.

This involves confirmation that the *reportable values* generated by application the analytical procedure meet the ATP criteria as well as confirmation of procedure performance attributes through the traditional validation, verification or transfer studies.

Data generated during Stage 1 can be used if available and suitable.

At the end of Stage 2, the replication strategy and the performance of the procedure is confirmed to meet the ATP and other criteria.

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Stage 3: Ongoing Procedure Performance Verification

Stage 3: Ongoing Procedure Performance Verification involves monitoring the analytical procedure during routine use and confirming that the performance continues to meet ATP criteria.

Monitoring ensures that the performance of the procedure is maintained at an acceptable level over the procedure lifetime.

It can also provide an early indication of potential performance issues or adverse trends and aid in identifying required changes for the analytical procedure.

Confirming procedure performance after changes (lifecycle change management) ensures that the modified procedure will produce results that meet the criteria defined in the ATP.

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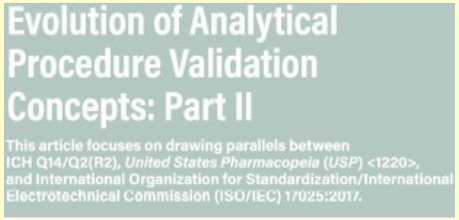

Comparison of concepts ISO/IEC 17025 & USP <1220>

TABLE IV. Comparison of terminology and elements between International Council for Harmonisation (ICH) Q14, Q2(R2), *United States Pharmacopeia* (*USP*) <1220>, and *International Organization for Standardization/International Electrotechnical Commission (ISO/IEC)* 17025–Part I. GUM is *Guide to the Expression of Uncertainty in Measurement*.

Concept	ISO	ISO/IEC 17025	ICH Q14&Q2(R2)	*USP* <1220>
Fit for purpose	ISO focuses on the needs of the customer. For analytical chemistry, this includes the client's use of the reportable value. The GUM in its definition of true value states that it must have an uncertainty appropriate for a given purpose. ISO 9001 is based on seven quality management principles (QMP), of which the first is Customer Focus.	"7.2.2.3 The performance characteristics of validated methods, as assessed for the intended use, shall be relevant to the customers' needs and consistent with specified requirements."	"fit for its intended purpose: to measure an attribute or attributes of the analyzed material with the needed specificity/ selectivity, accuracy and/ or precision over the reportable range."(Q14)	Demonstration of meeting the intended use as specified in the analytical target profile (ATP) through the analytical procedure life cycle (APLC).
Risk	ISO has many standards dealing with risk, including the ISO 31000 family of standards relating to risk management.	The risk-based thinking has enabled some reduction in prescriptive requirements and their replacement by performance-based requirements.	Q9/Q14 addresses risk extensively.	Addresses risk extensively.
Accuracy and Precision	Included in many ISO standards (e.g., ISO 14253-1:2017).	Decision rules are included, and their use is required by ISO/IEC 17025:2017 7.8.6.	Decision rules are not mentioned explicitly in Q2 or Q14 but can be used to achieve requirements.	Decision rules are included.
Probability	For example, ISO 3534-1:2006	Probability is part of decision rules.	Probability is mentioned under risk.	*USP* <1210> addresses probability.
ATP	Not included. ISO does require clear, concise, specific understanding of the customer's needs. The ATP is one mechanism to achieve this.	Although the components of an ATP are included (e.g., target MU, probability) the concept of ATP is not included.	Included in Q14, but not in Q2(R2).	Included. Focus on the fit for purpose of the reportable value.

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New Paper; Pharmaceutical Technology & BioPharm International in March 2023

Phil Borman, Amanda Guiraldelli Mahr, Jane Weitzel, Sarah Thompson, Joachim Ermer, Stephanie Sproule, Jean-Marc Roussel, Jaime Marach, and Horacio Pappa

Ongoing Analytical Procedure Performance Verification—Stage 3 of USP<1220>

Pharmaceutical Technology 47(3) 40-44 2023

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USP Lifecycle Management of Analytical Instruments & Systems

Enhancement of General Chapter <1058>

The heart of the uncertainty budget

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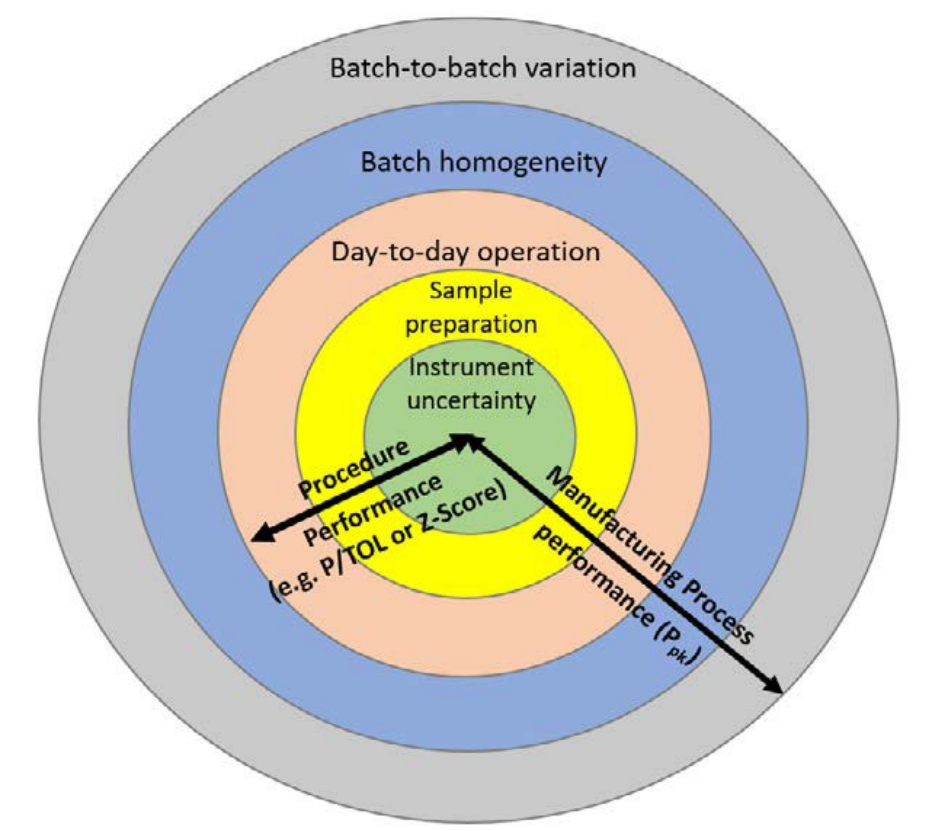
Product and analytical procedure sources of variability. P/TOL is precision to tolerance ratio

Figure 1.from
Pharmaceutical Technology
47(3) 40-44 2023



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Recent development at USP
Joint Sub Committee of the GC-CA EC and GC-MDQ EC to enhance <1058> compatibility with <1220> in 2020

1. *Nicole Addy – USP staff, ECM GC-CA*
2. *Edmund Biba – USP staff, GC-CA*
3. Bruno Boulanger – EC Member, **GC-MDQ**
4. *Lucy Botros – USP staff, GC-CA*
5. Chris Burgess – EC Member, **JSC Chair**, **GC-CA**
6. Joachim Ermer – EC Member, **GC-MDQ**
7. Greg Martin – EC Member, **GC-MDQ**
8. *Horacio Pappa – USP staff, GC-CA*
9. Oscar Quattrocchi – EC Member, **GC-CA**
10. Jean-Marc Roussel – EC Member, **GC-MDQ**
11. Rosty Slabicky – EC Member, **GC-CA**
12. Dwight Stoll – EC Member, **GC-CA**
13. Gabriel Vivó-Truyouls – EC Member, **GC-MDQ**
14. Jane Weitzel EC Member, EC Chair, **GC-MDQ**
15. *Kahkashan Zaidi – USP staff, GC-CA*

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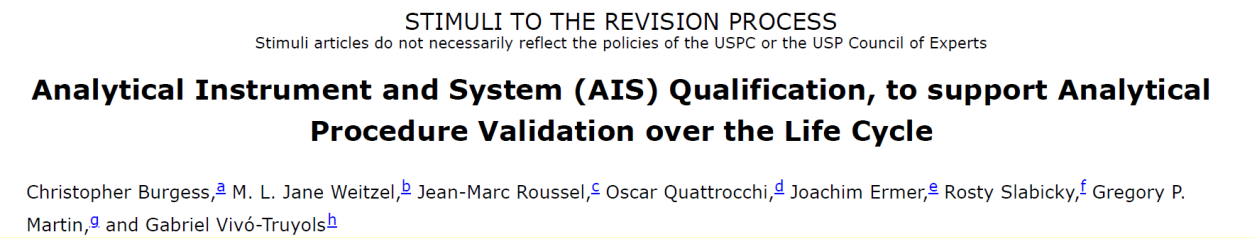
SRP papers in Pharmacopeial Forum

- SRP1; PF 48(1) Jan-Feb 2022



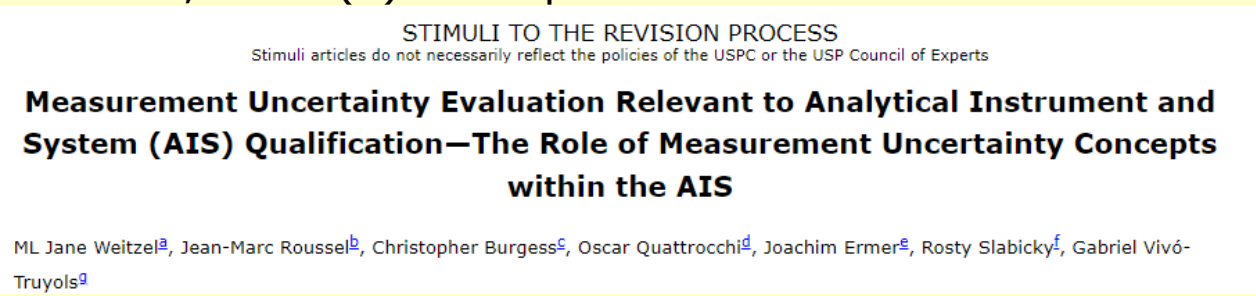
STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

Analytical Instrument and System (AIS) Qualification, to support Analytical Procedure Validation over the Life Cycle

Christopher Burgess,[a] M. L. Jane Weitzel,[b] Jean-Marc Roussel,[c] Oscar Quattrocchi,[d] Joachim Ermer,[e] Rosty Slabicky,[f] Gregory P. Martin,[g] and Gabriel Vivó-Truyols[h]

- SRP2; PF 48(2) Mar-April 2022



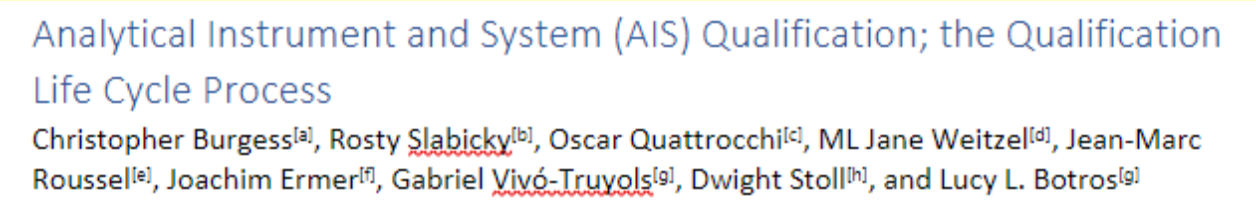
STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

Measurement Uncertainty Evaluation Relevant to Analytical Instrument and System (AIS) Qualification—The Role of Measurement Uncertainty Concepts within the AIS

ML Jane Weitzel[a], Jean-Marc Roussel[b], Christopher Burgess[c], Oscar Quattrocchi[d], Joachim Ermer[e], Rosty Slabicky[f], Gabriel Vivó-Truyols[g]

- SRP3; PF 48(4) Jul-Aug 2022



Analytical Instrument and System (AIS) Qualification; the Qualification Life Cycle Process

Christopher Burgess[a], Rosty Slabicky[b], Oscar Quattrocchi[c], ML Jane Weitzel[d], Jean-Marc Roussel[e], Joachim Ermer[f], Gabriel Vivó-Truyols[g], Dwight Stoll[h], and Lucy L. Botros[g]

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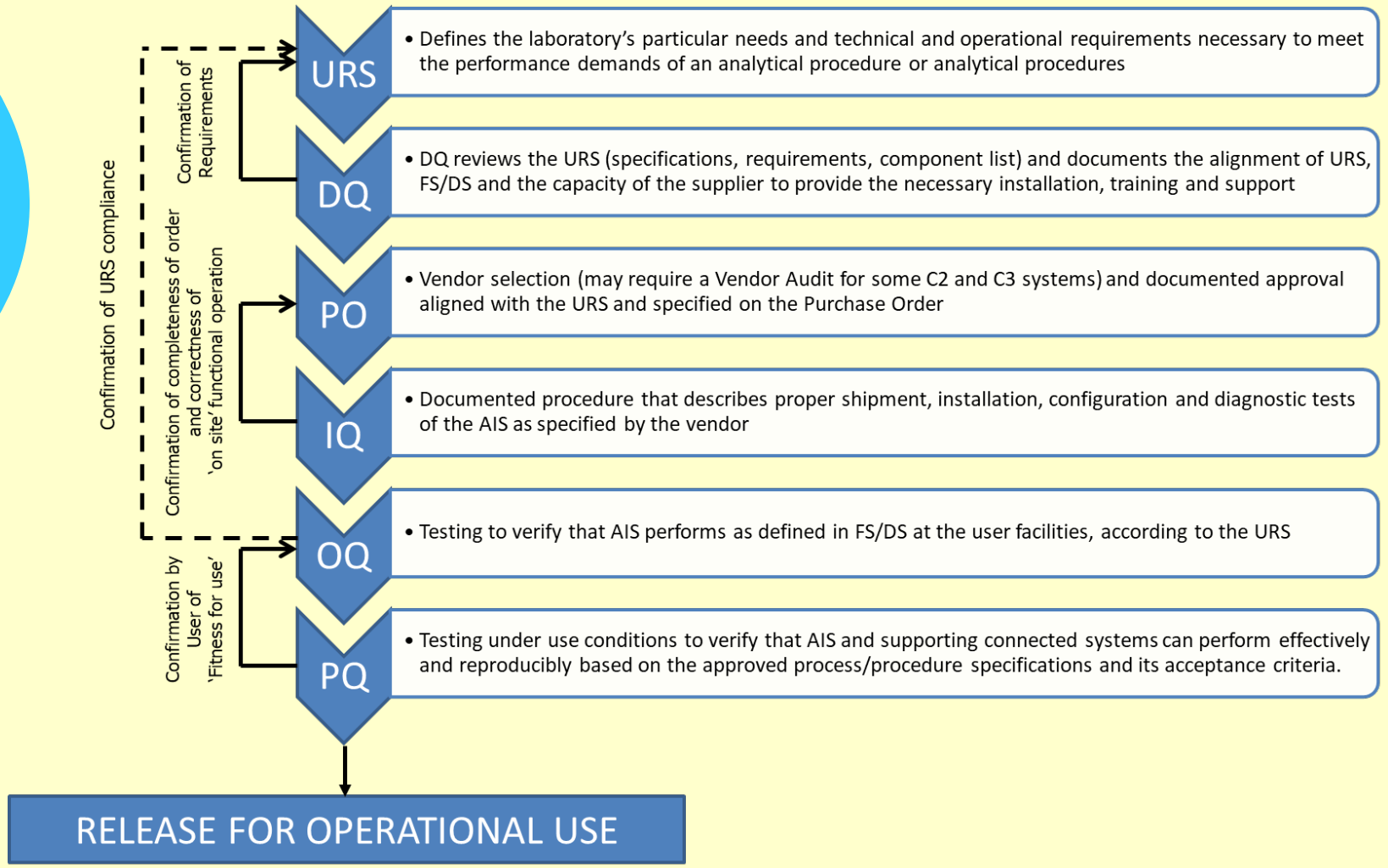
Life Cycle Activities;SRP3



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Life Cycle Activities and Proposed Instrument and System Categories;SRP3

LIFE CYCLE ACTIVITY	A_I	A_{II}	B1	B2	B3	C1	C2	C3
	Apparatus Class I	Apparatus Class II	Instrument Firmware control	Instrument In-built calculations	Instrument User defined routines	System Non configurable software	System Configurable software	System Configurable & customizable software
Risk Assessment	YES	YES	YES	YES	YES	YES	YES	YES
URS	CONSIDER	NO	YES	YES	YES	YES	YES	YES
Vendor FS/DS	CONSIDER	NO	NO	NO	NO	NO	CONSIDER	YES
DQ	NO	NO	YES	YES	YES	YES	YES	YES
Vendor audit	NO	NO	NO	NO	NO	NO	CONSIDER	YES
Purchasing SPEC & PO	YES	YES	YES	YES	YES	YES	YES	YES
Site Preparation	NO	NO	YES	YES	YES	YES	YES	YES
IQ/SAT	NO	NO	YES	YES	YES	YES	YES	YES
OQ/SAT	NO	NO	YES	YES	YES	YES	YES	YES
PQ/UAT	NO	NO	CONSIDER	CONSIDER	CONSIDER	CONSIDER	YES	YES
Authorization for use	YES	NO	YES	YES	YES	YES	YES	YES
Monitoring	CONSIDER	NO	YES	YES	YES	YES	YES	YES
Maintenance	CONSIDER	NO	YES	YES	YES	YES	YES	YES
Periodic review	YES	NO	YES	YES	YES	YES	YES	YES

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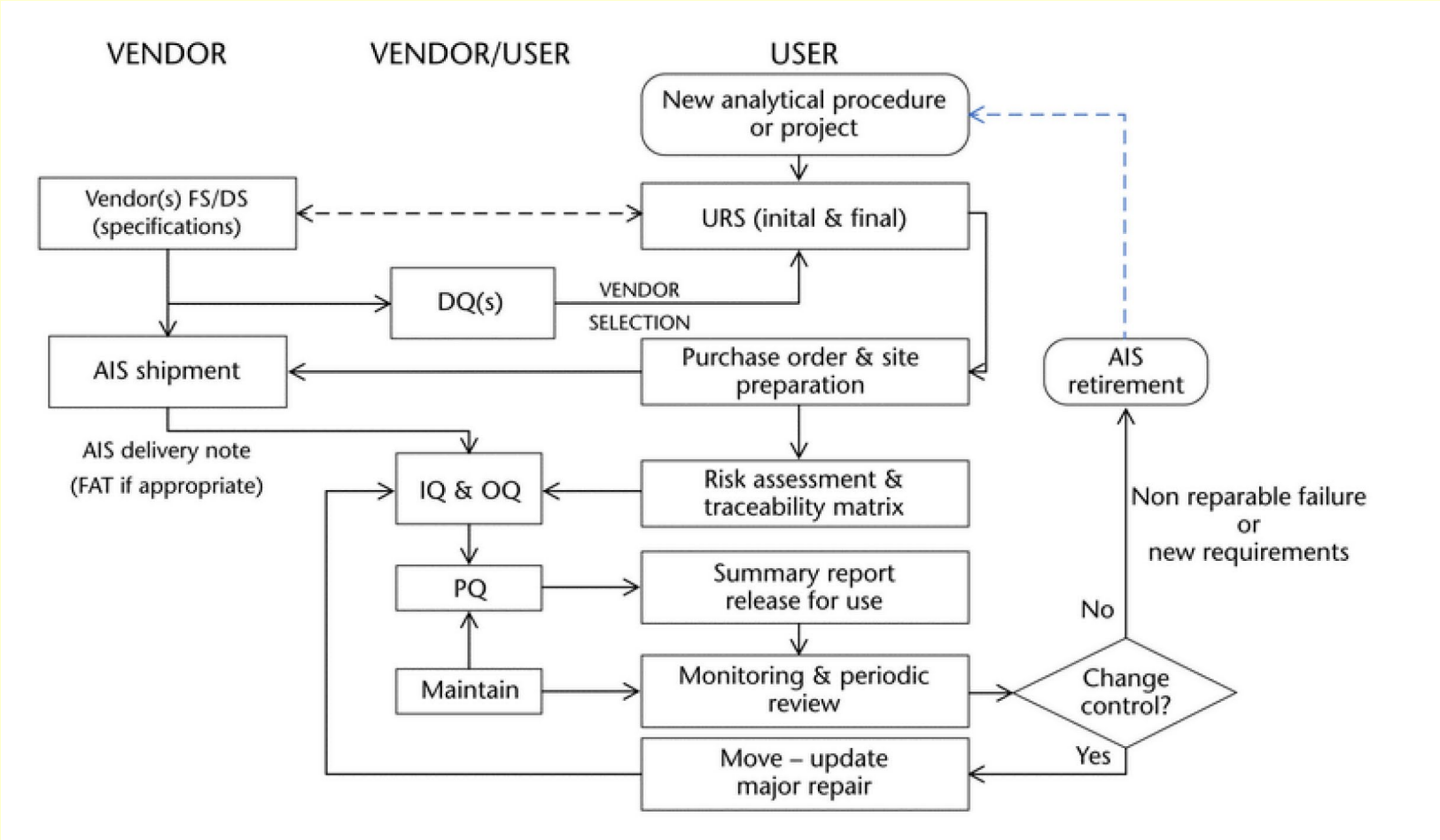
Qualification Process; Who can do what!;SRP3



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Measurement uncertainty

- All measurements are subject to error
- Measurement uncertainty is the measure of the reliability of an analytical result or measurement at a predetermined statistical probability as a result of experimental errors
- Experimental Errors
  - Random
  - Systematic
  - Independent (not correlated) or not
- All stages within an analytical procedure contribute to measurement uncertainty including calibration (Error propagation)

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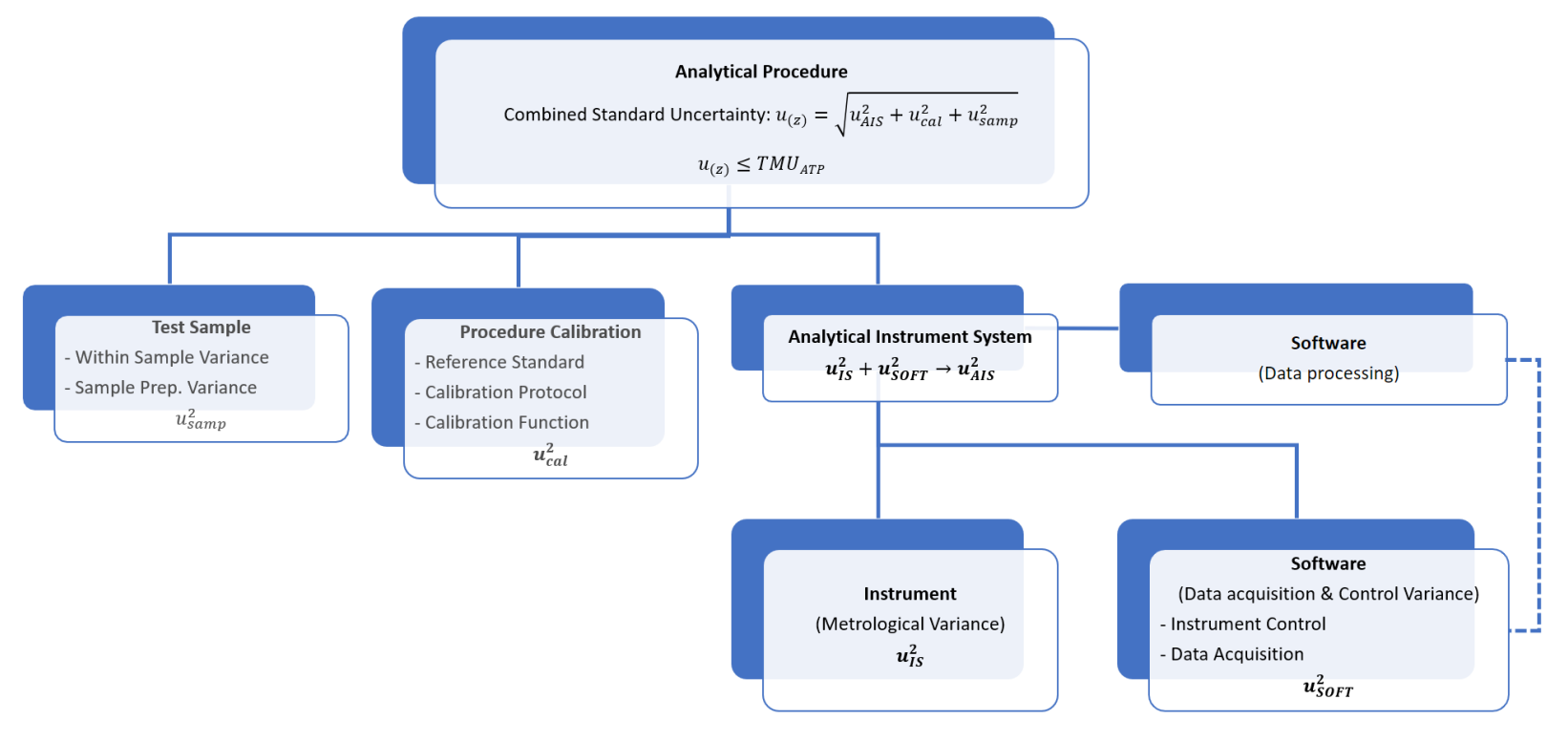
Error contributions; SRP 2



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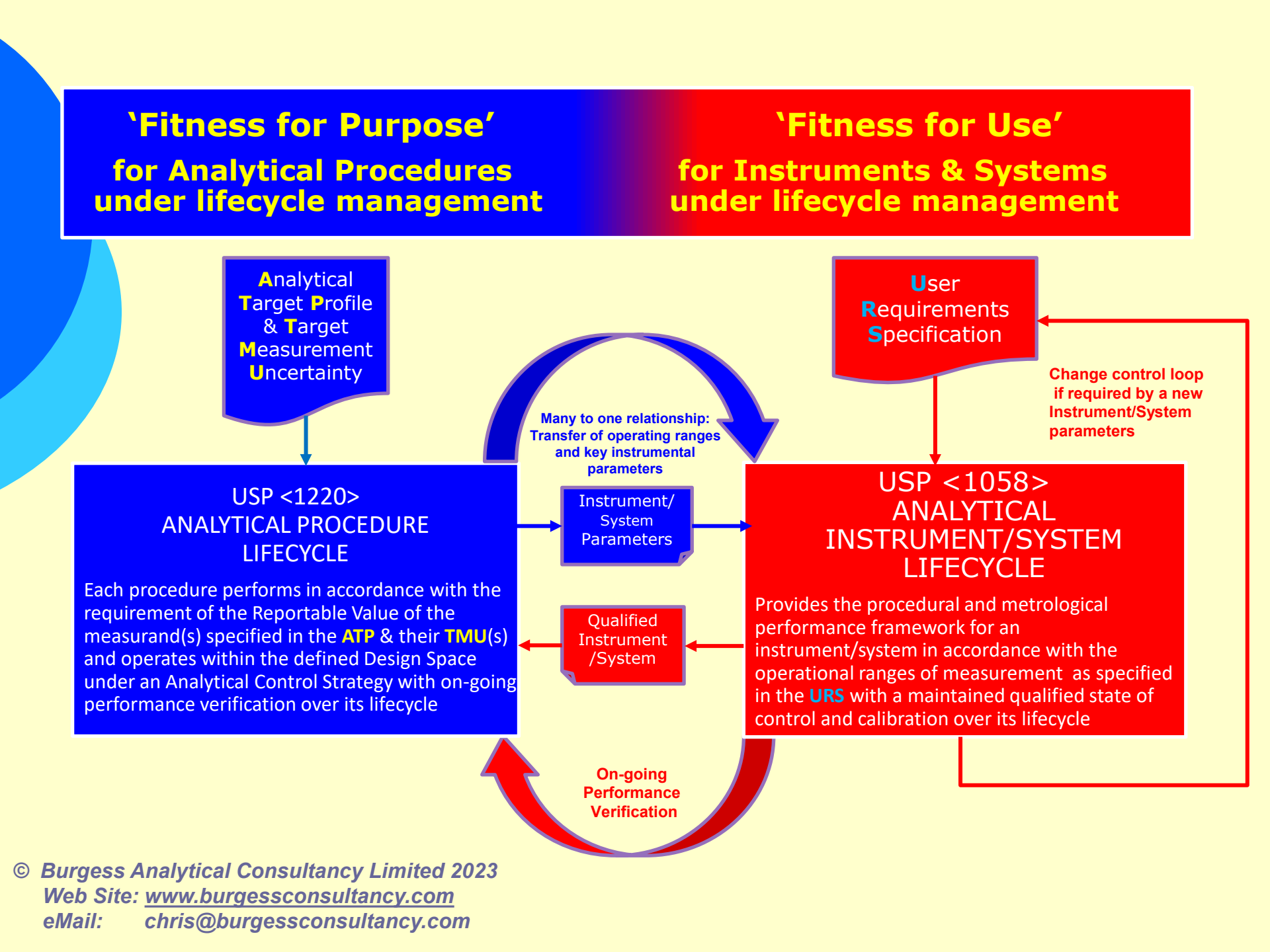

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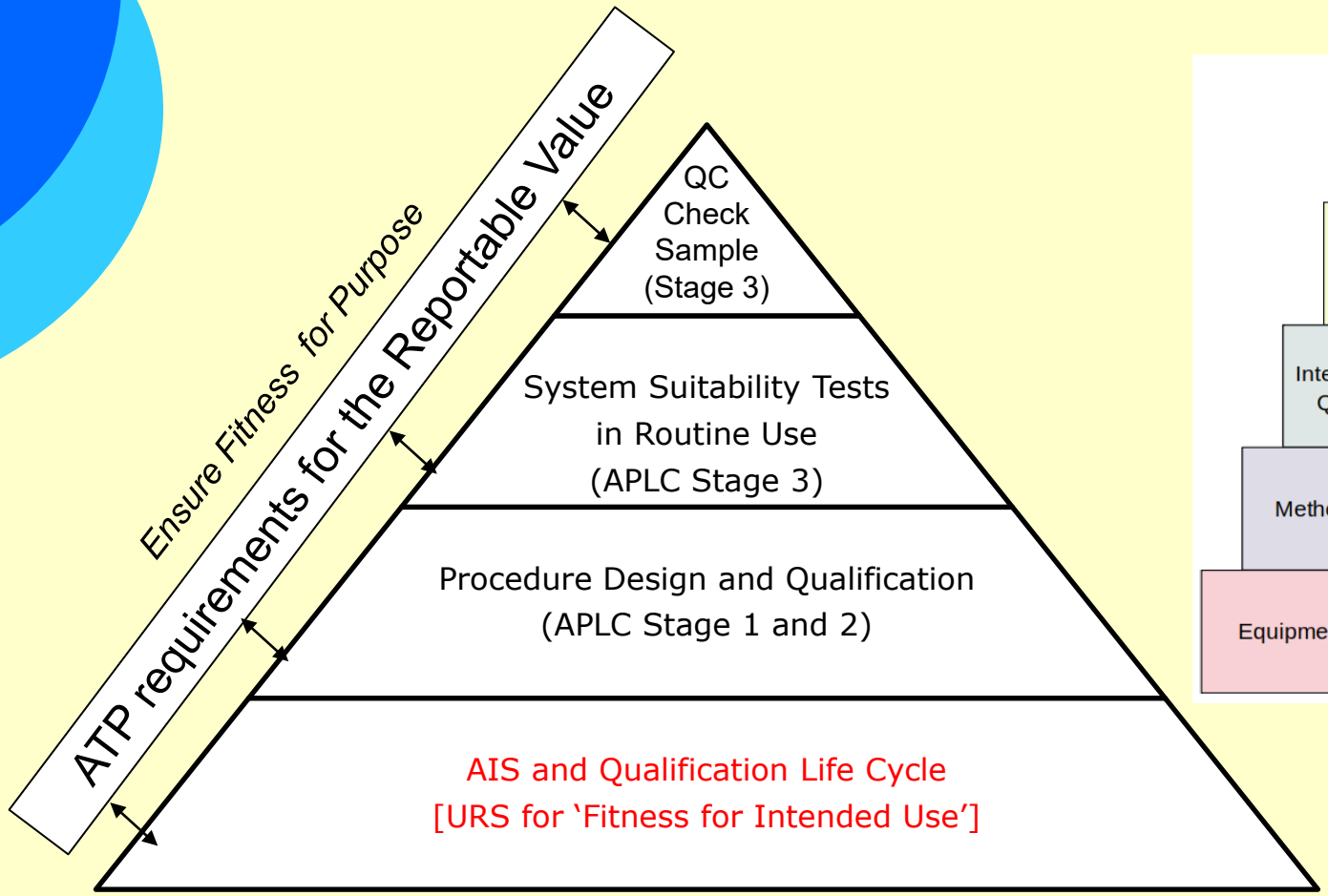
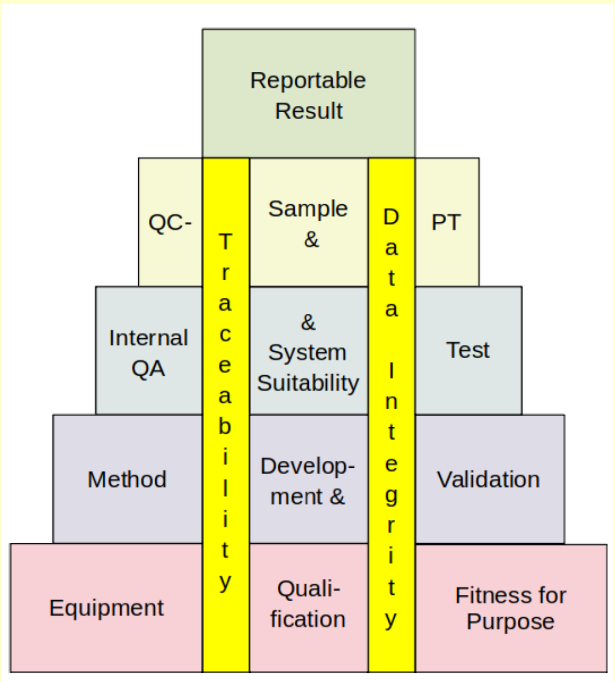
SUMMARY

USP & Eurachem approaches to Analytical Method (Procedure) Validation

Ensuring reliable and accurate results of analytical processes





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