

# Welcome



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# Lifecycle Management Concepts to analytical Procedures: A compendial perspective

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# USP Definitions



- <1225> Validation of Compendial Procedures  
Validation will be required when
  - an analytical procedure is used to test a non-official article.
  - an official article is tested using an alternative procedure (see *USP General Notices 6.30*).
- <1226> Verification of Compendial Procedures  
Verification will be required the first time an official article is tested using a USP procedure.
- <1224> Transfer of Analytical Procedures  
Transfer will apply when a non-compendial procedure is moved from one lab to another.

# <1225> Validation of Pharmacopeial Procedures



| Performance Characteristics | Category I | Category II |            | Category III | Category IV |
|-----------------------------|------------|-------------|------------|--------------|-------------|
|                             |            | Qty         | Limit      |              |             |
| Accuracy                    | <b>Yes</b> | <b>Yes</b>  | *          | *            | <b>No</b>   |
| Precision                   | <b>Yes</b> | <b>Yes</b>  | <b>No</b>  | <b>Yes</b>   | <b>No</b>   |
| Specificity                 | <b>Yes</b> | <b>Yes</b>  | <b>Yes</b> | *            | <b>Yes</b>  |
| LOD                         | <b>No</b>  | <b>No</b>   | <b>Yes</b> | *            | <b>No</b>   |
| LOQ                         | <b>No</b>  | <b>Yes</b>  | <b>No</b>  | *            | <b>No</b>   |
| Linearity                   | <b>Yes</b> | <b>Yes</b>  | <b>No</b>  | *            | <b>No</b>   |
| Range                       | <b>Yes</b> | <b>Yes</b>  | *          | *            | <b>No</b>   |

\* May be required depending on the type of test.

# Validation – USP Definition



“Validation of an analytical procedure is the process by which it is established, by laboratory studies, that the performance characteristics of the procedure meet the requirements for the intended analytical applications.”

# USP Validation & Verification Expert Panel



Gregory Martin (Chair)

Christopher Burgess, Ph.D.

Joachim Ermer, Ph.D.

Gyongyi S. Gratzl, Ph.D.

John P. Hammond, FRSC

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Pauline L. McGregor, Ph.D.

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Allen C. Templeton, Ph.D.

David P. Thomas, Ph.D.

Jane Weitzel, Ph. D.

Lucinda Buhse, Ph.D. (FDA liaison)

# Validation & Verification Expert Panel



- ▶ Adaptation of the lifecycle concept [ICH Q8] and of modern concepts for process validation to analytical procedures
  - ▶ to holistically align analytical procedure variability with the requirements of the product to be tested
  - ▶ to demonstrate that the analytical procedure meets the predefined criteria over the whole lifecycle
  - ▶ to facilitate continual improvement
  
- ▶ Stimuli article is published in PF 39(5), Sep - Oct 2013



## **Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification [PF 39(5)]**

ABSTRACT In this Stimuli article, the USP Validation and Verification Expert Panel discusses how the modern concept of a lifecycle model, which is based on process validation and described in ICH guidelines Q8, Q9, and Q10, can be applied to analytical procedures. The Expert Panel proposes that the traditional approaches to validation, transfer, and verification should be integrated into the analytical procedure lifecycle process rather than being viewed as separate entities. As a starting point or “predefined objective” according to ICH Q8, the requirements for a measurement of a critical quality attribute are established in the Analytical Target Profile. ....



# QbD in analytical design



“Systematic approach that begins with predefined objectives and emphasizes analytical procedure understanding and analytical control, based on sound science and quality risk management”

## **PROCESS**

### **Quality Target Product Profile:**

Prospective summary of the quality characteristics of a drug product to ensure quality, safety, efficacy

## **ANALYTICAL PROCEDURE**

### **Analytical Target Profile**

Defines the objective of the test and quality requirements for the reportable result

# Validation & Verification Expert Panel activities in 2016-2017

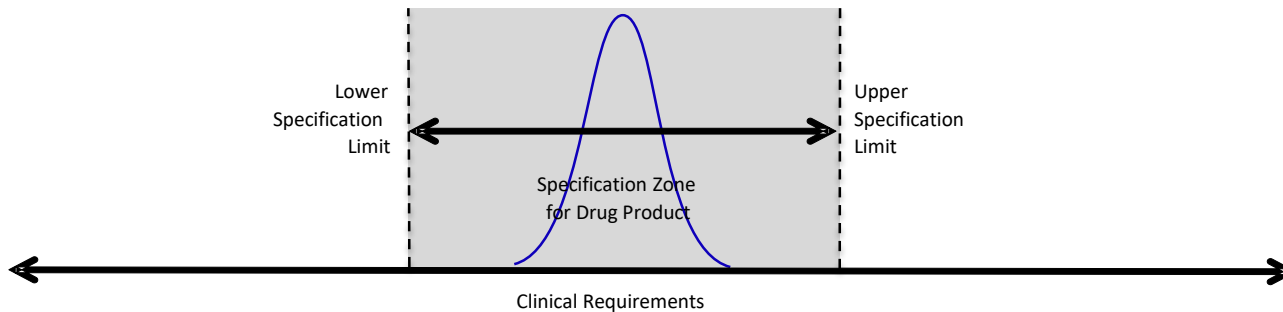


- PF 42(2) Fitness for Use: Decision Rules and Target Measurement Uncertainty
- PF 42(5) Analytical target profile (ATP): Structure and application throughout the analytical lifecycle
- PF 42(5) Analytical control strategy
- Second workshop was held in Europe in November, 2016
- PF 43(1): Stim article: The Analytical Procedure Lifecycle <1220>
- Third workshop in 2018?

# Fitness for Use: Decision Rules and Target Measurement Uncertainty PF42(2)



- ▶ What are decision rules, how are they developed, and how is the target measurement uncertainty determined.
- ▶ The link of decision rules with specifications
- ▶ Types of decision rules



# What is Target Measurement Uncertainty (TMU)



- ▶ Stated simply, the Target Measurement Uncertainty (TMU) is the acceptable error in the measurement associated with the reportable value.
- ▶ How much of your acceptance criteria should your measurement variability consume?

How much overlap is acceptable?  
That is the acceptable probability  
of making the wrong decision

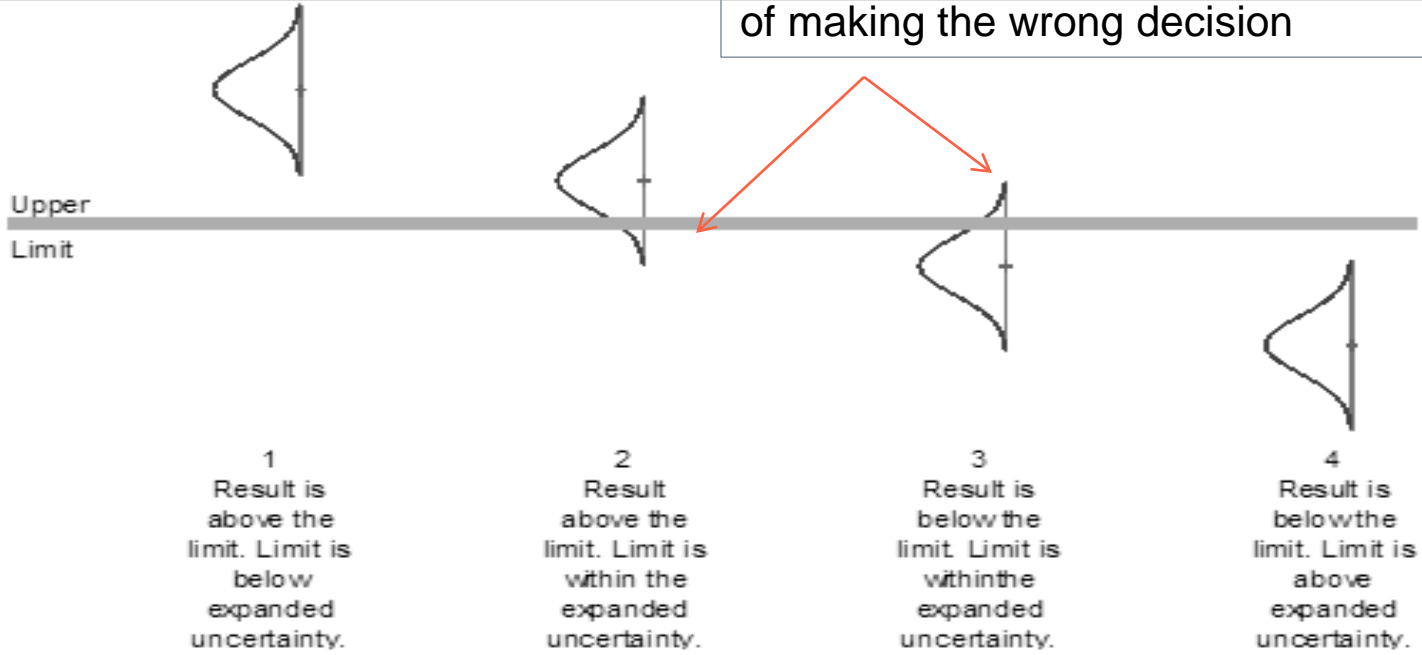


Figure shows the reportable value as the cross and the associated normal distribution with the width of the expanded uncertainty. The four possible outcomes when comparing the reportable value to the limit are illustrated. For scenarios 2 and 3, the overlap of the normal curve with the limit is determined by the acceptable probability of making a wrong decision.

# Analytical Target Profile: Structure and Application Throughout the Analytical Lifecycle PF 42(5)



The ATP is discussed further in this article, including its development, the linkage between the ATP and analytical control strategy, and application to each of the three analytical procedure lifecycle stages: design, qualification, and performance verification.

- The procedure must be able to accurately quantify [drug] in the [description of test article] in the presence of [x, y, z] with the following requirements for the reportable values: Accuracy =  $100\% \pm D\%$  and Precision  $\leq E\%$ .
- The procedure must be able to quantify [analyte] in the [description of test article] in the presence of [x, y, z] so that the reportable values fall within a TMU of  $\pm C\%$  with at least a  $X\%$  probability determined with  $Y\%$  confidence.

# Analytical Control Strategy PF42(5)



- ▶ What is the Analytical Control Strategy ?
  - A planned set of controls, derived from the requirements for fitness for purpose, an understanding of the analytical procedure, and the management of risk, all of which ensure the performance of the procedure and the quality of the reportable value, are in alignment with the ATP, on ongoing basis.
  
- ▶ What is the relationship between the ACS and the ATP?
  - The TMU is the maximum acceptable uncertainty for the reportable value in order to meet the ATP. The TMU (if stated in the ATP) can be used as a target for development criteria for the analytical procedure qualification and standard for monitoring the performance of the analytical procedure during routine use. The role of the ACS is to ensure that the TMU is met on a consistent basis over the entire lifecycle of the analytical procedure.

# How does the ACS apply to the product lifecycle?



## Stage 1: Risk analysis, identification and reduction

| Variable   | Potential Hazard  | Accuracy | Precision |
|--|---|----------|-----------|
| % Acetonitrile in the sample dissolution solvent     | Completeness of the Dissolution of the sample   | Red      | Yellow    |
| Sonication time                                      | Completeness of the Dissolution of the sample   | Red      | Yellow    |
| Analyst skill  | Incorrect sample preparation<br>Weighing, dilutions, use of volumetric flask  | Green    | Green     |
| Humidity of the laboratory                           | Moisture absorption can lead to inaccurate weighing or degradation  | Green    | Green     |
| Grade of acetonitrile used in the dissolving solvent | Potentially can impact if contaminants interfere with the analyte   | Green    | Green     |
| Column temperature                                   | Column performance, resolution, peak shape  | Yellow   | Red       |
| % Acetonitrile in the mobile phase                   | Column performance, resolution, peak shape  | Red      | Yellow    |
| Batch of packing material used in the HPLC Column    | Column performance, resolution, peak shape  | Red      | Yellow    |
| Quality of acetonitrile                              | Potential impact can affect the baseline, and/or provide high background noise depending on the analytical wavelength | Green    | Green     |



# How does the ACS apply to the product lifecycle?



## Stage 2: Qualification

The second stage in the lifecycle approach to validation of analytical procedures involves confirming (or qualifying) that the procedure meets the requirements of the ATP (typically, the accuracy and precision of the reportable value).

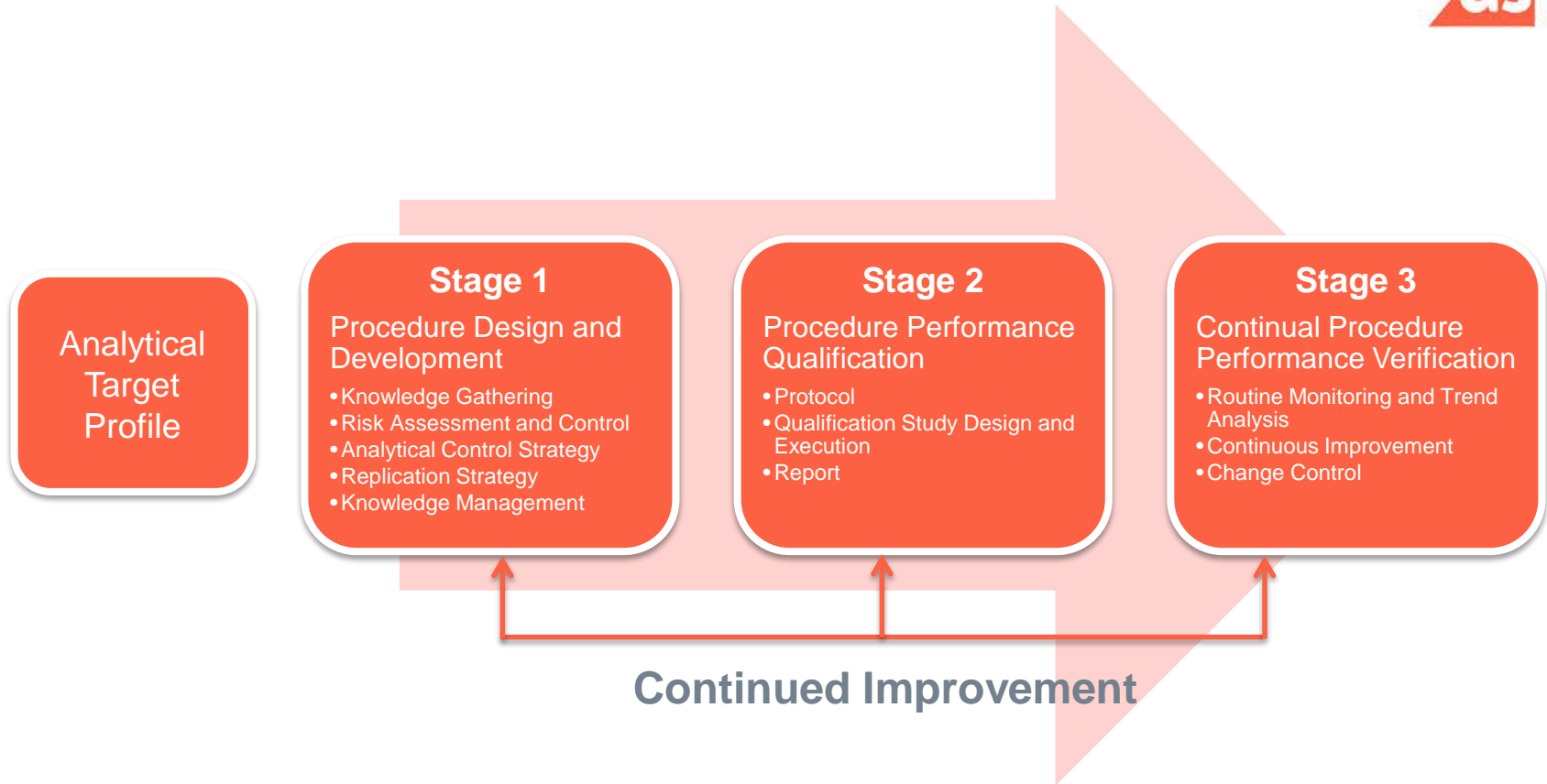
## Stage 3: Continual verification

Continually ensure that the reportable results produced by the procedure are fit for purpose

Provide an early indication of potential procedure performance issues or adverse trends

Trend plots of critical procedure performance indicators—such as resolution values, RSDs from system precision checks, results from routine testing, control or stability samples, or OOS or out-of-trend (OOT) investigations—can be established.

# Proposed New USP General Chapter: The Analytical Procedure Lifecycle (1220)



# Proposed New USP General Chapter: The Analytical Procedure Lifecycle (1220)



- ▶ This is an evolving concept
- ▶ No changes in <1224>, <1225>, and <1226>.
- ▶ Chemical Analysis Expert Committee is seeking input regarding the following questions:
  - Would a general chapter on the lifecycle approach be valuable?
  - Is the information presented herein sufficient for implementation of aQbD approach?
  - Would incorporation of references to statistical tools be valuable?
  - Can you provide input or approaches that would improve this proposed general chapter?

# Stimuli Article Comments



- Guidance is not needed vs. more guidance is needed
- Applicability, early vs. late stages
- Compendial vs. non-compendial procedures
- More detailed examples would be helpful, especially with statistics
- Terminology
- Optional vs. required concerns
- Replicates and OOS results
- Alignment with <1210>
- The approach will require more effort



- ▶ In general, an Analytical Target Profile (ATP) can be acceptable as a qualifier of the expected method performance by analogy to the QTPP as defined in ICH Q8 (R2)
- ▶ However, the Agencies would not consider analytical methods that have different principles (e.g., HPLC to NIR) equivalent solely on the basis of conformance with the ATP
- ▶ An applicant should not switch between these two types of methods without appropriate regulatory submission and approval.

# <1210> Statistical Tools for Analytical Procedure Validation



- **Companion of chapter <1225>**
- **Published in *Pharmacopeial Forum* 40(5) and 42(5)**
- **Outline:**
  - 1. 1. INTRODUCTION
  - 2. PRE-VALIDATION PROCEDURE DEVELOPMENT
  - 3. ACCURACY AND PRECISION
    - 3.1 Methods for Estimating Accuracy and Precision
    - 3.2 Combined Validation of Accuracy and Precision
  - 4. LIMITS OF DETECTION AND QUANTITATION
    - 4.1 Estimation of LOD
    - 4.2 Estimation of LOQ
  - 5. CONCLUDING REMARKS
  - REFERENCES

# <1210> Statistical Tools for Analytical Procedure Validation



- Describes utilization of statistical approaches in procedure validation as delineated in USP General Chapter <1225>
- Explains that capabilities of an analytic procedure must be validated based on the intended use of the analytical procedure
- Describes common types of uses and suggests procedure categories (I, II, III, or IV) based on the collection of performance parameters appropriate for these uses

# <1210> Statistical Tools for Analytical Procedure Validation



- Focuses on how to establish analytical performance characteristics of accuracy, precision, and detection limit
- Other analytical performance characteristics noted in *USP* General Chapter <1225> are out of scope for this chapter
- Also discusses equivalency testing



# Combined Accuracy and Precision



## ▶ Total Error Approach

- More rigorous statistical approach
- “Trade-off” between precision and bias possible

## ▶ Prerequisite

- Sample preparation is representative for routine application

A useful model for representing a reportable value is:

$$Y = \tau + \beta + \varepsilon$$

$Y$  = a reportable value

$\tau$  = true or accepted reference value

$\beta$  = systematic bias of the procedure

$\varepsilon$  = random measurement error

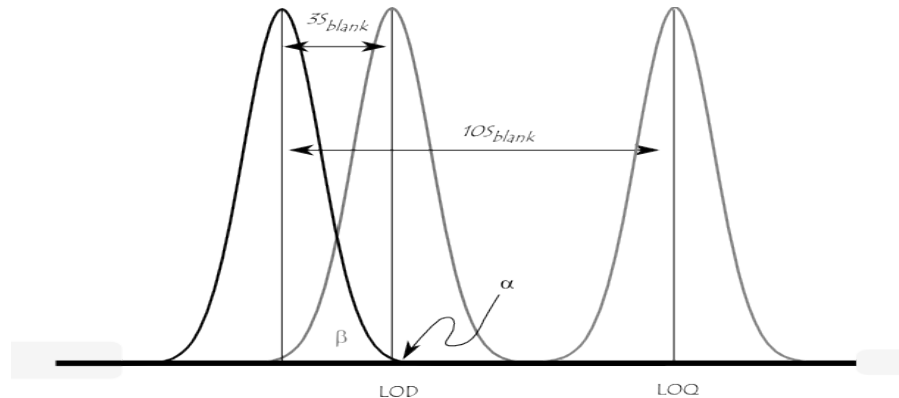
# Estimation of LOQ



LOQ “acceptable precision and accuracy” considerations:

The laboratory knows the required LOQ based on the intended application

The validation [method/procedure] is designed to prove accuracy and precision in the *neighborhood* of the required LOQ



# Statistical Equivalence



When using standard statistical tests for difference when seeking to show equivalence/similarity:

Good precision can lead to conclusion of non-equivalence for trivial differences

Poor precision can lead to conclusion of equivalence for large differences

## Guidelines

- Predetermine interval of “sufficiently similar”
- Calculate a 90% confidence interval for the measure of dissimilarity
- If the **entire** confidence interval falls in the similarity interval, then conclude equivalent; conclude unable to conclude equivalent
- The 90% confidence interval corresponds to a 5% false positive rate for the equivalence hypothesis

# Questions



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# Thank You



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