Proposed General Chapter <1220>
Analytical Procedure Lifecycle
- A holistic view of analytical methods performance

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The Analytical Target Profile (ATP)

Stage 1  
Procedure Design  
• Knowledge Gathering  
• Procedure development, including sample preparation  
• Understand the effect of procedure parameters on performance through risk assessments, experimental studies and modeling as needed  
• Determine an initial Analytical Control Strategy, including the replication strategy

Stage 2  
Procedure Performance Qualification  
• Confirm that the reportable values generated by the procedure meet the ATP criteria  
• Confirm that the procedure performance characteristics meet established criteria  
• Confirm and finalize the Analytical Control Strategy, including the replication strategy

Stage 3  
Continued Procedure Performance Verification  
• Monitor procedure performance during routine use to ensure it continues to meet ATP criteria  
• Modify the procedure when needed, returning to Stage 1 or Stage 2 as required  
• Continue to monitor after changes to confirm that the reportable values generated by the modified procedure meet the ATP

Knowledge Management

GC<1220> presents an alternate framework for analytical procedures that holistically incorporates all of the events that take place over the procedure Lifecycle...

...includes consideration of the target measurement uncertainty (TMU) and the bias simultaneously.
Current Practice for Validation

ICH and USP guidances
- Commonly treated as check-box exercise

Guidance recommends:
- setting criteria
- separately assessing performance characteristics
  - accuracy,
  - precision,
  - linearity,
  - specificity,
  - Sensitivity
  - robustness

Common Practice
- Establish default criteria
- Lack of transparency and rationale

- Don’t provide direct measure of:
  - the quality
  - the error associated with the measurement/results

- Less consideration may be given to understanding total measurement error and how it will influence the decisions to be made

- Variability and/or uncertainty in a measurement system can pose significant challenges when OOS results are observed.
Validation of Analytical Procedures

**USP <1225> Validation of Compendial Procedures**

“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.”

**ICH Q2 (R1): Validation of Analytical Procedures: Test and Methodology**

“The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose.”

**FDA: Guidance for Industry: Analytical Procedures and Methods Validation Chemistry, Manufacturing and Controls Documentation**

“Method validation is the process of demonstrating that analytical procedures are suitable for their intended use”
Validation of Analytical Procedures

Types of procedures that require validation:

- New procedure (i.e., GMP lot release)
- Existing procedure undergoes modification/improvement:
  - Critical parameters are changed
- Validated procedure is used outside its original scope
- Procedure specifically designed for a lab since standard method does not cover a requirement (change in instrument parameters, time, temperature, change in instrumentation, technology, etc.)
Validation of Analytical Procedures

Validation Parameters

<table>
<thead>
<tr>
<th>Performance Characteristics</th>
<th>Category I Qty</th>
<th>Limit</th>
<th>Category II Qty</th>
<th>Limit</th>
<th>Category III Qty</th>
<th>Limit</th>
<th>Category IV Qty</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Precision</td>
<td>Yes</td>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>LOD</td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>LOQ</td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Linearity</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
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</tr>
</tbody>
</table>

* May be required depending on the type of test.

Note: Robustness is often not part of the formal validation process but some elements are usually repeated.
Pharmacopeial Standards - Validation

Helpful USP Chapters for validation:

- <1225> Validation of Compendial Procedures
- <1210> Statistical Tools for Procedure Validation
- <1226> Verification of Compendial Procedures
- <1224> Transfer of Analytical Procedures
- <1220> Analytical Procedure Life Cycle*
- <1010> Analytical Data-Interpretation and Treatment
- <1210> Statistical Tools for Procedure Validation
- <1092> The Dissolution Procedure: Development and Validation
- <1223> Validation of Alternative Microbiological Methods
- <1033> Biological Assay Validation
- <1467> Residual Solvents—Verification of Compendial Procedures and Validation of Alternative Procedures
- <1117> Microbiological Best Laboratory Practices

*New proposed chapter – still not official
Existing USP chapters and published Stimuli Articles

USP Chapters

<1225> Validation of Compendial Procedures
- Focus in chromatographic procedures

<1226> Verification of Compendial Procedures
- To demonstrate suitability at the time of implementation

<1224> Transfer of Analytical Procedures
- Transfer between laboratories

<1210> Statistical tools for procedure validation

USP Stimuli articles

PF 39(5) Lifecycle Management of Analytical Procedures
- Method Development, Procedure Performance Qualification, and Procedure Performance Verification

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
- Quality risk management in the lifecycle of the analytical procedure
GC<1220> Analytical Procedure Lifecycle

CONTENT AND RATIONALE

1. INTRODUCTION

2. ANALYTICAL TARGET PROFILE (ATP)

3. STAGE 1: PROCEDURE DESIGN
   - Preparation for Analytical Procedure Development
   - Procedure Development
   - Quality Risk Management (QRM) and the analytical procedure
   - Robustness and Method Operable Design Region (MODR)
   - Replication Strategy
   - Procedure Control Strategy

4. STAGE 2: PROCEDURE PERFORMANCE QUALIFICATION (PPQ)
   - Protocol and Study Design
   - Qualification Results and Documentation

5. STAGE 3: CONTINUED PROCEDURE PERFORMANCE VERIFICATION (CPPV)
   - Routine Monitoring
   - Analytical Control Attributes
   - Control Charts
   - Changes to an Analytical Procedure
Analytical Target Profile (ATP)

- ATP is a prospective description of the desired performance for an analytical procedure that is used to measure a quality attribute.

- It is independent of measurement technology

- It should include:
  - Definition of the analyte
  - Description of the analytical matrix
  - The precision and accuracy (bias) acceptable for the reportable value.
  - Concentration range of the analyte
The procedure must be able to accurately quantify [drug] in a range from [A units] to [B units] in the [description of test article] in the presence of [x, y, z] with an accuracy = 100% ± [D%] and a precision ≤ [E%] for the reportable value.

The procedure must be able to quantify [analyte] in a range from [A units] to [B units] in the [description of test article] in the presence of [x, y, z] so that the distribution of the total analytical error of the reportable value falls within the total allowable analytical error range of ± [C%].
Lifecyle Approach

Precision and Bias

- Critical performance characteristics:
  - Bias: how close the measurement is, on average, to the actual value being measured
  - Precision: how much the measurement will randomly vary under routine use

- If there is bias in the procedure, the impact on analytical error should not be ignored.

- Appropriate limits for bias and precision in ATP can be determined based on several factors, including:
  - The criticality of the quality attribute being measured
  - The risk of an unacceptable error
  - The width of the specification acceptance range for the quality attribute measured by the procedure
  - The potential clinical safety or efficacy impact (if known) that analytical error may have

True Value is not known!

Maximum Allowable Combined Bias and Precision

-\[ \hat{x} \]

Precision: Width of the distribution of the reportable value
Measurement Uncertainty

- **Random errors** in experimental measurements are caused by unknown and unpredictable changes in the experiment.
- **Systematic errors** in experimental observations usually come from the measuring instruments.
- **Measurement uncertainty**: estimate of total error

**Fig. 1** Relationships between type of error, qualitative performance characteristics and their quantitative expression

Target Measurement Uncertainty (TMU)

Figure 1. Consolidation of attributes contributing to TMU through bias and precision.

- **TMU**
  - the maximum acceptable uncertainty for the reportable value in order to meet performance criteria and accomplish the fitness-for-purpose requisite

- The TMU 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.

- **42(2) Stimuli Article: Fitness for Use: Approaches for TMU calculation (misclassification rates and use of the coverage factor).**
Expanded Uncertainty

1. How much confidence do you want?
2. What is your calculated combined uncertainty?

\[ U = MU \times k_p \]

- \(MU\) = Measurement uncertainty (u)
- \(U\) = expanded uncertainty
- \(k\) = coverage factor
- \(p\) = acceptable probability of making a wrong decision

\(U\): provides an interval within which the true value is believed to lie with a higher level of confidence.

Expand \(u\) to meet a 68.26% confidence: \(k=1\)
Expand \(u\) to meet a 95.44% confidence: \(k=2\)
Expand \(u\) to meet a 99.73% confidence: \(k=3\)

Figure 3. A normal distribution curve centered on the reportable result shown by the x.
When the reportable result and its uncertainty are compared to the specification limit or limits, there are four possible outcomes:

1. Result is above the limit. Limit is below expanded uncertainty.
2. Result is above the limit. Limit is within expanded uncertainty.
3. Result is below the limit. Limit is within expanded uncertainty.
4. Result is below the limit. Limit is above expanded uncertainty.
Specifications and decision rules

- The closer the acceptance range is to the safe and efficacious range, the distribution of the total analytical error can have a larger impact on decision rule risks.

- In the situation where the safe and efficacious range is accurately known, guard bands can be applied to that range, based on the distribution of the total analytical error, to determine the acceptance range.

Figure 5: Decision Rule Determined using Guard band based on total analytical error.

Figure 6: Decision Rule with Indecision Zones based on total analytical error.
Decision Rules

Risk of using simple DR

Figure 8. A USP specification of 98.0%–102.0%. If a reportable result is at or close to 98.0%, there is a 50:50 probability that the true value is below the lower limit.
Decision Rules

Using Guard Bands

Tailing Factor

Can guide the selection of analytical factors which provide Good performance and robustness!

Resolution between critical pair

Ensure the Reportable Values are FIT FOR USE!
Stage 1: Procedure Design

- Understanding gained through knowledge gathering, experiments, and risk assessment.

Stage 1:
1. Preparation for Analytical Procedure Development
2. Procedure Development
3. Quality Risk Management (QRM) and the analytical procedure
4. Robustness and Method Operable Design Region (MODR)
5. Replication Strategy
6. Procedure Control Strategy
Quality Risk Management (QRM)

- systematic process for the assessment, control, communication, and review of risk to the quality of the reportable value across the lifecycle of the analytical procedure

Aim
- assess the proposed procedure conditions
- identify appropriate controls on the analytical procedure parameters and material attributes that will ensure the procedure meets the ATP.

Risk Management Methodologies
- flowchart, process mapping, cause and effect diagrams, failure mode effects analysis (FMEA), failure mode effects and criticality analysis (FMECA) etc.

Figure 4. Overview of a typical QRM process (ICH Q9).
Quality Risk Management (QRM)

- QRM process
  - Risk assessment (risk identification)
  - Identify potential variables
  - Estimate the risk associated with each variable
  - Plan for how to manage those risks
    - Control variables: risk are well understood and may be mitigated by controlling them within a certain range
    - Noise variables: difficult or impractical to control and the risks associated with them will need to be accepted
    - For variables where there may be higher risk, one way to reduce risk is to gain additional knowledge about the influence of those parameters using modelling and/or experimentation.

- This assessment is driven by prior knowledge and scientific expertise, but some factors with unknown influence may need to be considered higher risk until further knowledge available.

Figure 4. Overview of a typical QRM process (ICH Q9).
Case: Quality Risk Management

Risk assessment: Risk Analysis

- Estimate the risk associated with each of the variables.
- Variables that may affect resolution and peak shape, potentially affecting resolution (accuracy)
- Effects on peak shape can potentially lead to inconsistent integration (precision).
- separate the variables into those that can be controlled, those that cannot be controlled, and those that will be subject to further experimentation.

<table>
<thead>
<tr>
<th>Analytical Unit of Operation</th>
<th>Variable</th>
<th>Potential Hazard</th>
<th>Accuracy</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample preparation</td>
<td>% Acetonitrile in the sample dissolution solvent</td>
<td>Completeness of the Dissolution of the sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample preparation</td>
<td>Sonication time</td>
<td>Compleness of the Dissolution of the sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample preparation</td>
<td>Analyst skill</td>
<td>Incorrect sample preparation Weighing, dilutions, use of volumetric flask</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample preparation</td>
<td>Humidity of the laboratory</td>
<td>Moisture absoprtion can lead to inaccurate weighting or degradation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement (HPLC SetUp)</td>
<td>Grade of acetonitrile used in the dissolving solvent</td>
<td>Potentially can impact if contaminants interfere with the analyty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement (HPLC SetUp)</td>
<td>Column temperature</td>
<td>Columns performance, resolution, peak shape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement (HPLC SetUp)</td>
<td>% Acetonitrile in the mobile phase</td>
<td>Columns performance, resolution, peak shape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement (HPLC SetUp)</td>
<td>Batch of packing material used in the HPLC Column</td>
<td>Columns performance, resolution, peak shape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement (HPLC SetUp)</td>
<td>Quality of acetonitrile</td>
<td>Potential impact can affect the baseline, and/or provide high background noise depending on the analytical wavelength</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk Evaluation compares the risk versus the given risk criteria. The risk acceptance criteria (or the risk protection threshold) for this step is the TMU.

Table 2. Conditions for the DoE Experiment

<table>
<thead>
<tr>
<th>Variable</th>
<th>High Level</th>
<th>Mid Level</th>
<th>Low Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Acetonitrile in sample solvent</td>
<td>80</td>
<td>65</td>
<td>50</td>
</tr>
<tr>
<td>Sonication time (min)</td>
<td>20</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Column temperature (°)</td>
<td>45</td>
<td>35</td>
<td>(ambient; 25)</td>
</tr>
<tr>
<td>% Acetonitrile in mobile phase</td>
<td>80</td>
<td>70</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 3. Example of Risk Evaluation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severity (from DoE) (1 low, 5 high)</th>
<th>Probability of variation (1 low, 5 high)</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Acetonitrile in sample solvent</td>
<td>4</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Sonication time (min)</td>
<td>4</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>% Acetonitrile in mobile phase</td>
<td>5</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Column temperature (°)</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 4. Conditions for the DoE Experiment

<table>
<thead>
<tr>
<th>Variable</th>
<th>High Level</th>
<th>Mid Level</th>
<th>Low Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Acetonitrile in sample solvent</td>
<td>70</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Sonication time (min)</td>
<td>15</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Column temperature (°)</td>
<td>40</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>% Acetonitrile in mobile phase</td>
<td>75</td>
<td>70</td>
<td>85</td>
</tr>
</tbody>
</table>

Table 5. Example of Risk Evaluation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severity (from DoE) (1 low, 5 high)</th>
<th>Probability of variation (1 low, 5 high)</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Acetonitrile in sample solvent</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Sonication time (min)</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>% Acetonitrile in mobile phase</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Column temperature (°)</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

24(5) Stimuli Article: Analytical Control Strategy
Case: Quality Risk Management

Risk Control: Risk Reduction

Adding a system suitability requirement to detect the hazard to reduced the risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severity (from DoE) (1 low, 5 high)</th>
<th>Probability of variation (1 low, 5 high)</th>
<th>Detection</th>
<th>Risk Score (SxP)/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Acetonitrile in mobile phase</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*S: Severity; P: Probability; D: Detectability

42(5) Stimuli Article: Analytical Control Strategy
Robustness is a measure of the ability of a procedure not to be affected by small but deliberate variations.

MODR is a multidimensional combination and interaction of procedure parameters where all study factors combinations have been demonstrated to provide:

- Acceptable Mean Performance
- Acceptable Robustness
Method Operable Design Region (MODR)

Robustness and MODR

- Challenges for implementing the MODR:
  - Lack of guidelines with framework for
    - operating range creation
    - MODR proper validation
  - Knowledge gaps: demonstration that MODR works across important ‘ruggedness factors’ (such as the use of different systems, columns, environment, analysts etc)

- Key Aspects for MODR generation:
  - Use of suitable types of DOE or other modeling predictive methods which can precisely estimate effect of
    - 2-factors interactions or
    - higher-order interactions (if necessary depending on the complexity to model the analytical response).
  - robustness evaluation
ACS is a planned set of controls, derived from
- an understanding of the requirements for fitness for purpose of the reportable value,
- an understanding of the analytical procedure as a process,
- and the management of risk

The ACS is the totality of steps taken to eliminate the risk or control it at an acceptable level.

Figure 1. Linkages between the ACS, QRM, and KM.
Stage 2: Procedure Performance Qualification

- It consists of studies designed to demonstrate that the procedure is suitable for its intended use in the laboratory.

- Confirmation of procedure performance characteristics.

- At the end of stage 2 the replication strategy is confirmed, and it is confirmed that the performance of the procedure meets the ATP and other criteria.

- Encompasses all the analytical procedure activities commonly referred to as qualification, verification, validation and transfer described in other literature and guidances.
  - Protocol and Study Design
  - Qualification Results and Documentation
Stage 3: Continued Performance Verification

- **Routine Monitoring** Effective monitoring of an analytical procedure provides ongoing confidence that the reportable values generated are fit for purpose.

- **Analytical Control Attributes** example SST attributes such as system precision, signal-to-noise ratio, or peak symmetry

- **Control Charts** recommended practice for monitoring of method performance attributes and control sample results

- **Changes to an Analytical Procedure** changes should be risk assessed for their impact to determine the appropriate activities required. In addition, appropriate change management approaches and documentation should be used when make changes to a procedure.

Figure 8. Example of a control chart for an API titration content range from two replicate determinations. The control limit corresponds to the maximum expected difference between duplicates at the 99% confidence level, obtained from the average repeatability of 0.16% by multiplication with a factor of 3.64.
ICH Guideline Q14 - Concept Paper

New ICH guideline Q14 Analytical Procedure Development

Since there is no ICH guideline on Analytical Procedure Development, applicants often report analytical validation results alone and rarely present performance evaluation with analytical development outcomes.

Additionally, the lack of guidelines precludes the applicant from an opportunity to present scientific basis for flexible regulatory approaches to post-approval Analytical Procedure changes.
The new guideline will provide an opportunity to
- present the outcome of Analytical Procedure Development in **traditional approaches** and in **enhanced approaches**

**ICH Q11: Development and Manufacture of Drug Substance**

“**Traditional approach**”
- set points and operating ranges are defined and control strategy is typically based on demonstration of method reproducibility and testing to meet established acceptance criteria.

“**Enhanced approach**”
- risk management and scientific knowledge are used more extensively to identify and understand process parameters.

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**ICH Guideline Q14 - Concept Paper**

New ICH guideline
**Q14 Analytical Procedure Development**

Final Concept Paper - Endorsed in November 2018
Some of main technical and scientific elements, which require harmonization, include:

- The concept and strategy of enhanced approaches for Analytical Procedures
- Performance criteria of Analytical Procedures.
- In line with Q8 and Q11, greater understanding of Analytical Procedure can create the basis for more efficient, sound science and risk-based change management (e.g., using Quality by Design principles).
- Key elements and terminology
The new standard aims to harmonize the scientific approach to the development of analytical procedures. Analytical validation results are often reported without performance evaluation. The new standard will provide the opportunity to present the result of the development of analytical procedures in the traditional approach or in an improved approach.
The scope of the review will include validation principles covering the use of spectroscopic or spectrometry methods, some of which often require multivariate regression analysis. The current approach to Q2 (R1) is not sufficient to establish the suitability of multivariate methods. Methods based on multivariate models often do not use reference standards during analysis. This makes the robust development, validation and proper maintenance of such methods of utmost importance for reliable prediction throughout the entire method life cycle.

- Selection of analytical procedure validation experiments and criteria
- Considerations for multivariate procedures
- Specificity/selectivity
- Validation of the reportable range
  - Linear calibration method
  - Non-linear concentration-response curves
  - Multivariate calibration method
- Validation of lower range limits
- Accuracy and precision
QUESTIONS?

USP Workshop
Desenvolvimento de Métodos Indicativos de Estabilidade

Amanda Guiraldeilli, Ph.D.
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USP Workshop
Desenvolvimento de Métodos Indicativos de Estabilidade

PAUSA de 10 minutos