A Lifecycle Approach for Analytical Methods Validation – Implementing Best Practices

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Overview

- Method Validation
  - Requirements and Expectations
  - Good Scientific Practices
  - Team Agreement

- Method Validation Process
  - Validation - Product Lifecycle
  - Quality Plan
  - Design, Develop, Control
  - Definition of Intended Use
  - Specifications

- Method Validation Implementation
  - Protocol Development – Critical Components
  - Protocol Execution – Where? Who?
  - Selection of Characteristics, Acceptance Criteria

- Validation Exercise
Requirements and Expectations

• Guidance Documents
  – Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics (Feb 2014)
    • Guidance for Industry: Submitting Samples and Analytical Data for Methods Validation (Feb 1997)
  – Q2A: Text on Validation of Analytical Procedures (Mar 1995)
  – Q2B: Validation of Analytical Procedures: Methodology (Nov 1996)
  – Q6A, Q6B: Specifications (Dec 2000, Aug 1999)
  – Q8 (R2): Pharmaceutical Development (Nov 2009)
  – Q9: Quality Risk Management (Jun 2006)
  – Q10: Pharmaceutical Quality System (Apr 2009)
Expectation…

- It is the responsibility of the applicant to choose the validation procedure and protocol most suitable of their product.

- The main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose.

- Well characterized reference materials, with documented purity should be used throughout the validation study.
  - The degree of purity necessary depends on the intended use.

- All relevant data collected during validation and formulae used for calculating validation characteristics should be submitted and discussed as appropriate.
Participant Activity (10 mins)

What do you consider ‘Good Scientific Practice’?
Good Scientific Practices

Assay Development
• Scientifically sound and appropriate
• Repeatable
• Robust

Good Documentation Practice
• Real time documentation
• Clear to follow methods
• Training

Data
• Verified/Reviewed
• Calculations transparent
• Reproducible
Team Agreement

- Scientists – AD/QC/SME
- Statisticians
- Stakeholders
- Quality
- Scientists – AD/QC/SME/ Statisticians
- Stakeholders
- Quality
Team Agreement

• Why is this important?
Team Agreement Considerations...

• Groups
  – Analytical Development
  – Quality Laboratories
  – Technical Experts
  – Statisticians
  – Marketing?
  – Management

• Site to Site

• Clients/Sponsors
Method Validation Process

- Development
- Pre-validation/Qualification/Optimization
- Validation
- Revalidation

- Validation – Product Lifecycle
Method Validation Process: Quality Plan

• Do you have a Quality Plan?
Quality Plan

Analytical Method Validation

Instrument qualification, SOPs, training, critical assay materials

Master Validation Plan

ICH Q8, Q9, Q10
(Senior Management Commitment)
Method Validation Process (contd)

- Cross functional team
- Subject matter experts
- Project plan
- Monitor progress
- Organize documents
Design Experiments

Systematic approach

Method robustness

Initial risk assessment

Multivariate experiments

Design
Risk Management Process

Overview of a typical quality risk management process

(ICH Q9)
Method Development - highlights

- Description of method
- Step by step procedure (roadmap)
- Analytical Instruments and Equipment
- Reagents, Reference Material, Standard, Control
- Samples – in-process, bulk, finished product
- System
- Suitability, Automation
- Assay
- Acceptance criteria
- Data
- Analysis
Control & Finalize

- Instruments
- Equipment
- Chromatography
- Columns
- Sample handling
- Sample source (research, clinical, process validation...)
- Sample preparation – automated pipetting
- Laboratory
- Environment (temp, humidity)
- Stability studies - degradation studies
- Training

Determine sources of method variation

Understand changes in method parameters

Characterization & Analyses

Good documentation practices

- System suitability
- Assay acceptance
- Reference & reagent qualifications
- Assay critical parameters
- Automation

- Organization of raw data, notebooks, etc.
- Data verification
- Test method – Roadmap
- Procedure – visual guidance
- Data documentation sheets/forms/electronic
Define Intended Use

• Identify critical process steps and related assays
• Is this used for characterization only?
  – Or will this lead to a testing requirement and be held to a specification?
• How important is continued characterization testing?
  – Do they need to be ongoing as part of release or used for process check when necessary?
Specifications

“A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described.

It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.

‘Conformance to specifications’ means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval....”

(ICH Q6B)
Specification

Strategy designed to ensure product quality and consistency

thorough product characterization during development

adherence to good manufacturing practices (GMP's), e.g., suitable facilities, a validated manufacturing process, validated test procedures, raw materials testing, in-process testing, stability testing.

confirm quality of the drug substance/drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.
Prior to Method Validation Implementation...

- Pre-Validation Studies
  - Assay Qualification/Preliminary Validation
    - Clinical Phase I/II studies
  - Instrument Qualification
  - Lab Computer Systems and Software
  - Method parameters, assay acceptance criteria, specifications
  - Stability Indicating Methods
  - Robustness
# Method Validation Characteristics

<table>
<thead>
<tr>
<th>TYPE OF ANALYTICAL PROCEDURE; CHARACTERISTICS</th>
<th>IDENTIFICATION</th>
<th>TESTING FOR IMPURITIES</th>
<th>ASSAY; dissolution (measurement only); content/potency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Quantitation Limit</td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Precision Repeatability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Precision</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Specificity$^2$</td>
<td>-</td>
<td>+$^1$</td>
<td></td>
</tr>
<tr>
<td>Detection Limit</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitation Limit</td>
<td>-</td>
<td>-$^3$</td>
<td></td>
</tr>
<tr>
<td>Linearity</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

- Note: ‘-’ signifies that this characteristic is not normally evaluated; ‘+’ signifies that this characteristic is normally evaluated.
- 1 - In cases where reproducibility has been performed, intermediate precision is not needed.
- 2 - Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).
- 3 - May be needed in some cases.
Method Validation Implementation

- Protocol Development
  - Cover page - clear statement of scope
  - Test method summary - flow diagram, calculations
  - Summary (table) of assay characteristics to validate; number of determinations
  - Samples, Reagents, System Suitability Controls
  - Instruments, Laboratories involved, personnel to perform testing
  - Experimental details with acceptance criteria
  - Data analysis, recording test results and observations
  - Amendments or deviations to the protocol
Method Validation Implementation: Protocol Execution

• Where will the testing occur?
  – Identify sites/laboratories
  – Check for suitability/comparability

• Who will perform testing?
  – Analytical Development
  – Quality Control
  – Combination
Method Validation Implementation...

- How do you select for validation characteristics/parameters?
- What is the acceptance criteria?
- What are the appropriate system suitability controls?
Validation Exercise
Validation Exercise

• Enzymatic/HPLC Identity Assay
  – Peptide map of a protein molecule API
    • Need to determine the assay characteristics to be validated
    • Need to identify appropriate assay acceptance and system suitability criteria
Validation Exercise: Peptide Mapping

Chemical modification of protein

Enzymatic digestion of protein into peptides (e.g. trypsin)

RP HPLC separation of peptides

UV detection of peptides
Validation Exercise…

**Assay Purpose:** Identification Test

- **Assay Characteristics to Validate?**
  - Specificity
  - Accuracy
  - Precision
  - Linearity
  - Range
  - LOD/LOQ
  - Stability Indicating

- **Reduce**
  - 5.3 M Guanidine HCL, Tris pH 7.6, 16 mM DTT –
    - 1 hr, 37°

- **Alkylate**
  - 37 mM Iodoacetamide
    - 60 min, RT, dark

- **Desalt**
  - Dialysis
  - 6 M Urea,
    - 0.1 M Tris, pH 8.0, 2 hrs

- **Tryptic Digest**
  - 2 M urea,
    - 0.1 M Tris, pH 8.0,
      - 1:25 trypsin, 12 hrs

- **Stop reaction with TFA to 2%**

- **Analyze**
  - Compare UV traces at 220 nm of sample to reference std.

- **Detect**
  - UV at 220 nm

- **Separate**
  - Resolve peptides by C18 RP HPLC (0.02% TFA)

**Detailed Flow Diagram of Peptide Mapping**
Identification: Looking for fingerprint comparison
Validation Exercise . . .

For the peptide mapping test method:

• Which assay characteristic should be validated, and how would that be demonstrated?
• What system suitability controls would be appropriate?

Guidance Documents:
• USP <1055> Peptide mapping
• FDA Guidance Validation of Chromatographic Methods (1994)
Challenges?
Challenges…

• Analysts
  – turnover
  – knowledge not documented
  – training not consistent

• Test Method
  – critical parameters not locked down
  – insufficient information
  – not clear
  – lacking standardized work process
  – changes after validation
Challenges…

• Material
  – samples – clinical, process performance qualification, process changes…
  – reagents – vendor changes, one vendor source
  – chromatography columns

• Instruments, automation
  – method development on different model
  – technical support not consistent
  – aging models - vendor terminates model, support

• Data Analyses
• THANK YOU