Mapping Out the Validation Process

PDA 2011 Technical Report Overview

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MedImmune
(PDA’s AMV Task Force Chair)
AMV and AMT for Biotechnological Products
Overview of the Technical Report (2011)

Topics Covered:

- General Scope/Content of this Analytical Method Validation (AMV) Technical Report (TR)
- Analytical Method Validation (AMV) Process (from development/qualification to post-validation)
- AMV - Readiness Assessment Process
- Risk-Based AMV Study Designs
- Risk-Based Acceptance Criteria
- And, practical guidance for:
  - AMV Studies
  - Verification of Validated/Approved Methods
  - Analytical Method Transfer (AMT)
  - Analytical Method Replacement (AMR)
  - Analytical Method Maintenance (AMM)
  - Dealing with AMV Failures

Krause/PDA, 2011
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<tbody>
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2011 Draft Report Completion

Special Thanks To:

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</tbody>
</table>
PEI (European perspective), FDA (CDER and CBER), and PDA scientific and biotech advisory boards (voted 19 to 0 in favor of publishing) reviewed and positively commented on our TR document.

“Many thanks for giving me the opportunity to review your Draft Technical Report. I think you have developed a document which covers the topic of method validation and transfer in a very comprehensive way. The combination of a risk based guidance, taking into account the analytical method life cycle, and the basic ICH Q2(R1) guideline gives a good basis for an up to date approach to analytical method validation. From my point of view the advantage of this report is that it covers not only the classical validation process but also method transfer, comparability and maintenance. Another advantage is that the report gives a lot of guidance regarding the details of the different validation steps. I think you have developed a very helpful document not only for lab people but also for assessors. I hope that many companies will use this document in the future.”

(Dr. Siegfried Giess  
Head, Section of Immunochemistry  
Paul-Ehrlich-Institut)
List of Specific Examples in the AMV TR

**Examples listed in order of appearance in AMV TR (bold = covered in this presentation)**

- Setting risk-based protocol acceptance criteria for a content assay
- **Using Intermediate Precision Results** (using mixed linear model analysis)
- (Prospective) critical reagent expiry study
- Significant digits in reported results (ASTM E 29-02 and E456)
- Analytical Method Transfer (AMT) of a validated potency method.
- Analytical Method Replacement (AMR) for each of the three major cases:
  - Non-inferiority
  - Superiority
  - Equivalence
- Analytical Method Maintenance (AMM) – continuous monitoring for a content assay
Recent FDA Inspection Observations
(Analytical Methods – Laboratories)

Inspection observations for AMV studies and the affected laboratory processes can be found in the Top 5 of the most-frequently received FDA 483 observations and warning letters in recent years (2005-2011)!
AMV TR Introduction – The Analytical Method Life Cycle

- "Qualified" Method
  - New or Modified Method – Establish Intended Use
  - Characterization and Comparability of Intended Uses
  - Identity, Safety, Purity, Quality, Potency
  - Design – Establish Analytical Procedure
    - Identity, Impurity Limit, Impurity Quantity, Assay / Potency
    - Development and Optimization
    - Performance Review
    - Technical Transfer of Qualified Methods
    - Qualification of Specifications, Characterization and Compendial Methods

- Validation Pre-Requisites Assessment
  - Tech Transfer
  - Resource Assessment
  - Standards and Controls
  - Stability
  - Verify Product Specifications

- Validation Acceptance Criteria
- Validation
- Post Validation Activities
  - Maintenance
  - Transfer
  - Comparability / Bridging Study
  - Failure OOS/Validation

- "Validated" Method

- AMD: Method Development – Qualification
- AMV: Pre-Validation Assessment – Ongoing Maintenance

Not covered in AMV TR (in AMD TR !)
Sections 1 and 3 in AMV TR
Section 4 in AMV TR
Sections 5-8 in AMV TR

Krause/PDA, 2011
**AMV Overview**

*Analytical Method Validation* (AMV) is a required and continuous process for the manufacturer to provide documented evidence that an analytical method is suitable for its intended use with primary consideration to minimize risk to patients. (*Krause/PDA – 2007*)

*AMV* can be defined as the collection and evaluation of data, from the analytical method development stage throughout routine QC testing, which establishes scientific evidence that an analytical method is capable of consistently delivering accurate and reliable results. (*Krause/PDA TR – 2011, adapted from FDA’s Process Validation Guidance, 2011*)
Example of Assessment of AMV Readiness Flow Path

- Specificity
- Precision
- Accuracy
- QL/QL
- Linearity
- Range

- Robustness
- Data

- Standards
- Controls

- Stability of
- Reagents,
- Samples

- Specification
to meet

- Regulatory
Requirements

- Existing
Knowledge
(Product and
Process)

- Documented
Intended Use

- AMV Acceptance
Criteria

- Documented
Summary of
Method Performance
Characteristics
(Handover
Package,
Development
Report)

- Validation Risk
Assessment that
method meets
intended use

- Is Method
ready for
Validation?

- Collect
more data
and/or
optimize
method

- AMV Protocol

Krause/PDA, 2011
The purpose of risk assessment(s) is to provide measurable results for:

1) The desired amount of formal validation studies to be executed.
2) The level of method performance needed as manifested in the AMV protocol acceptance criteria.

The possible risk assessment matrices shown are examples while other acceptable alternatives also exist.
### The Five General AMV Classes and Prospective AMV Studies

<table>
<thead>
<tr>
<th>AMV Class No.</th>
<th>Analytical Method</th>
<th>Product / Process Sample</th>
<th>Typical Risk / Uncertainty Level (1=Low, 5=High)</th>
<th>Suggested Prospective AMV Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>New</td>
<td>New</td>
<td>4-5</td>
<td>Full Validation</td>
</tr>
<tr>
<td>B</td>
<td>New</td>
<td>Old (Validated)</td>
<td>3-4(^{(1)})</td>
<td>Full Validation Plus AMR(^{(2)}) Studies</td>
</tr>
<tr>
<td>C</td>
<td>Analytical Platform Technology (not validated “as run”)</td>
<td>New</td>
<td>2-3</td>
<td>Partial Validation</td>
</tr>
<tr>
<td>D</td>
<td>Old (Validated)</td>
<td>New</td>
<td>1-2</td>
<td>Partial Validation or Verification</td>
</tr>
<tr>
<td>E</td>
<td>Compendial</td>
<td>New</td>
<td>1-2</td>
<td>Verification per USP &lt;1226&gt;</td>
</tr>
</tbody>
</table>

(1) If a new analytical method (forced method replacement) is needed due to supply reasons, the risk level can be generally considered higher because no other option may exist. Unforced test method replacements can be considered to be a lower risk level as more time may be available to optimize the method performance.

(2) AMR = Analytical Method Replacement. A study to confirm that a new analytical method can perform equally or better than the existing one.

From Krause, PDA/DHI 2007.
Rationale for Acceptance Criteria:

- Acceptance criteria should “balance” the two opposing considerations below:

- **First consideration:** Demonstration of a desirable high level of overall process and method capability within a given set of specifications. This may lead to setting “narrow” acceptance criteria for the analytical method performance. If too narrow, meeting acceptance criteria may be difficult.

- **Second consideration:** Assurance of compliance and project completion by meeting protocol acceptance criteria. This may directly oppose the first consideration and lead to “wide” acceptance criteria. The method performance may therefore be considered validated, compliant, and acceptable although the actual method performance may not be suitable with respect to specifications and/or overall process capability expectations.
Risk-Based AMV Studies
More Points to Consider for Acceptance Criteria

- Variation and uncertainty in test results constitute risk to patient and firm.
- As specifications typically only exist for the observed manufacturing process variation, it is therefore critical to understand and control the underlying variation sources by using risk-based acceptance criteria for each of their maximum allowable variation.
- The historical data should be reviewed, understood, and used to set acceptance criteria to ultimately ensure the suitability for use of the analytical method.
- The relationship of typical variation sources are expressed below:

\[
[\sigma_{\text{mfg process observed}}]^2 = [\sigma_{\text{analytical method}}]^2 + [\sigma_{\text{mfg process actual}}]^2
\]

- For simplicity, the potential variation sources from the sampling process, transport, and storage, and/or the inconsistency in batch uniformity are considered to be part of the manufacturing process variation.
Consistent Risk Assessment to Set Acceptance Criteria

- Risk-based AMV protocol acceptance criteria should be predominately derived from the evaluation of two critical sources:
  - Specification(s)
  - Existing Knowledge (Product and/or Process)

- Existing knowledge may exist from historical data of this product and/or process or similar products and process(es).

- Other sources such as regulatory expectations may also impact acceptance criteria and should be considered when applicable.

- If the consistency of the sampling process and the batch uniformity is not an integral part of the manufacturing process variation or not known, these variation sources may also need to be considered.
Risk-Based AMV Protocol Acceptance Criteria

Specifications → Regulatory Requirements

Consider Type of Specifications

One-Sided Specifications (NMT, NLT, LT) → Two-Sided Specifications (Range)

Acceptance Criteria

Historical Method Performance

Existing Knowledge

Historical Data from this Product and Process

Knowledge from Similar Product and Process
# ICH Q2(R1) Supporting Method Characteristics (ideally pre-AMV)

<table>
<thead>
<tr>
<th>Analytical Method Performance Characteristic</th>
<th>Retrospective (AMD/AMQ, etc.) or Prospective Evaluation During AMV Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robustness</td>
<td>Deliberately perform minor changes to critical assay parameters such as incubation temperature or time. A DOE matrix can be used to test relevant operational conditions at their respective limits.</td>
</tr>
<tr>
<td>Signal Response Factors</td>
<td>Consider analyte response factors whenever multiple components may be reported or may impact the test results.</td>
</tr>
<tr>
<td>Statistical Data Reduction</td>
<td>Establish analyte response curve statistics for this method (ex., linear regression).</td>
</tr>
<tr>
<td>Degradation (For Stability – Indicating Methods)</td>
<td>Establish stability profile and degradation pathways of samples, impurities, and by-products as relevant for the intended use of the method.</td>
</tr>
<tr>
<td>Stability of All Material</td>
<td>Evaluate the short-term (during testing) and long-term (during storage) stability of standards, controls, reagents, and other critical material.</td>
</tr>
<tr>
<td>System Suitability</td>
<td>Establish that all test system suitability parameters are suitable for routine testing.</td>
</tr>
<tr>
<td>Sample Suitability</td>
<td>Establish that sample stability (during testing) and testing replicates are appropriate to routinely support accurate and reliable test results.</td>
</tr>
<tr>
<td>Significant Digits</td>
<td>Confirm during Repeatability Precision studies the significant digits in reported test results (and specifications) using ASTM E29-02 and ASTM E 456.</td>
</tr>
<tr>
<td>Analytical Method Replacement (pre- and/or post-validation)</td>
<td>Establish the mean difference/shift of reported results for new versus old method. Modify in-process and/or product specifications if necessary based on a statistical significant sample size.</td>
</tr>
</tbody>
</table>
Example for: Intermediate Precision **Mixed Linear Model** Results

<table>
<thead>
<tr>
<th>Effect</th>
<th>Variance</th>
<th>Std Dev.</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.0249</td>
<td>0.158</td>
<td>14.6%</td>
</tr>
<tr>
<td>Instrument</td>
<td>0.0158</td>
<td>0.126</td>
<td>11.6%</td>
</tr>
<tr>
<td>Operator</td>
<td>0.0013</td>
<td>0.036</td>
<td>3.3%</td>
</tr>
<tr>
<td>Day</td>
<td>0.0004</td>
<td>0.020</td>
<td>1.9%</td>
</tr>
<tr>
<td>Residual</td>
<td>0.0157</td>
<td>0.125</td>
<td>11.6%</td>
</tr>
</tbody>
</table>

Interpretation of Intermediate Precision Results

- **Operators** and **Days** are not critical method components. This is a good situation with regards to training requirements and lesser expectations for operator proficiency because there is a lower risk that test results are potentially affected when using new operators over time.

- There is a significant amount of variability observed among the three different **Instruments** used (CV = 11.6%). Although this is somewhat typical for a highly automated procedure with relatively minimum operator involvement, it is still something that will significantly contribute to overall assay variability. If needed, particular automation steps for this assay that contribute to this variability could be identified and improved/controlled.

- The unidentified **Residual Variation** (CV = 11.6%) could be evaluated by reviewing all supporting AMD data and/or the specific automated steps and operational conditions of this instrument method. It could also be compared to **Repeatability Precision** to support the identification of the variation source(s).

- If needed, further process step analysis could be done if the target is to improve the overall precision in routine operations.
### Verification Characteristics for Each General Compendial Method Type and Supported Specifications

<table>
<thead>
<tr>
<th>Method Types</th>
<th>Typical Specifications</th>
<th>Typical Minimum Verification Characteristics To be Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>Yes/No Present/Absent Pass/Fail</td>
<td>A series of relevant (blind) samples should be correctly identified to demonstrate specificity. Reliable positive and, if applicable, negative identification should be demonstrated.</td>
</tr>
<tr>
<td>Impurity (Quantitative)</td>
<td>No More Than Impurity (Quantitative)</td>
<td>Accuracy (against an acceptable reference standard) and repeatability and/or intermediate precision should be demonstrated using representative sample(s) below and above the QL.</td>
</tr>
<tr>
<td>Impurity (Limit)</td>
<td>Less Than</td>
<td>It should be demonstrated that impurity levels at the required DL are reliable and can be consistently detected.</td>
</tr>
<tr>
<td>Assay (Content, Potency, and/or Purity)</td>
<td>Range (for Content, Potency) No Less Than (for Purity)</td>
<td>Accuracy (against an acceptable reference standard) and repeatability and/or intermediate precision should be demonstrated using representative sample(s) below and above the (target) specifications.</td>
</tr>
</tbody>
</table>
Analytical Method Life Cycle – AMV TR: Section No. 7

“Qualified” Method
- New or Modified Method - Establish Intended Use
- Characterization and Comparability of Intended Uses
  - Identity
  - Safety
  - Purity
  - Quality
  - Potency
- Design - Establish Analytical Procedure
  - Identity
  - Impurity Limit
  - Impurity Quantity
  - Assay / Potency
- Development and Optimization
- Performance Review
- Technical Transfer of Qualified Methods
- Qualification of Specification, Characterization and CompendialMethods
- Validation Pre-Requisites Assessment
  - Tech Transfer
  - Resource Assessment
  - Standards and Controls
  - Stability
  - Verify Product Specifications
- Validation Acceptance Criteria
- Validation
- Post Validation Activities
  - Maintenance
  - Transfer
  - Comparability / Bringing Study
  - Failure / ODYS/Validation

AMM Program (section no. 7)

Krause/PDA, 2011
The AMM Program

Prospective

Retrospective

AMC

AMV

Process Map Steps

Method Modifications

Critical Method Elements

Standards and Controls

Critical Reagents

Software/Computer

Analytical Instrumentation

Statistical Data Reduction

New/Additional Operator

VMP for Analytical Methods

AMM

Method Review

Emergency Reviews

(Out of Spec, many invalids)

Periodic Reviews

(Short and Long Term)

Quarterly or Annual Reviews

Extensive Reviews

### Retrospective Validation Status Review Checklist

<table>
<thead>
<tr>
<th>AMV and Method Performance Checklist Items</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Method Number/Title/Revision:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process Step/Product Sampling Point(s):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Recent Validation/Verification Date:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specifications and/or Action Levels Supported:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH Q2(R1) Test Method Category:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suitable Accuracy Demonstrated in AMV?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suitable Repeatability Precision Demonstrated in AMV?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suitable Intermediate Precision Demonstrated in AMV?</td>
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<td></td>
</tr>
<tr>
<td>Suitable Specificity Demonstrated in AMV?</td>
<td></td>
<td></td>
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<tr>
<td>Suitable Linearity Demonstrated in AMV?</td>
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<tr>
<td>Suitable Assay Range Demonstrated in AMV?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suitable Detection Limit Demonstrated in AMV?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suitable Quantitation Limit Demonstrated in AMV?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suitable Robustness Demonstrated in AMD/AMV?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Retrospective Validation Status Review Checklist (continued)

<table>
<thead>
<tr>
<th>AMV and Method Performance Checklist Items (continued)</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suitable System Suitability Demonstrated in AMV ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Valid Test Runs Over Last 12 Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Invalid Test Runs Over Last 12 Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculate Invalid Rate/Percentage:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical Assay Control Limits (ex., 3 Standard Deviations):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test System in Control ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changes to Test System After AMV:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, provide more information:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current AMV Acceptable/Compliant ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, provide risk-based priority for revalidation for VMP:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method Performance Acceptable ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, provide risk-based priority for method improvement list:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QC Signature:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QA Signature:</td>
<td></td>
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Dealing with AMV Failures

"Qualified" Method
- New or Modified Method - Establish Intended Use
- Characterization and Comparability of Intended Uses
- Identity / Safety / Purity / Quality / Potency
- Design - Establish Analytical Procedure
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Validation Pre-Requisites Assessment
- Tech Transfer
- Resource Assessment
- Standards and Controls
- Stability
- Verify Product Specifications

Validation Acceptance Criteria
- Validation
- Post Validation Activities

"Validated" Method
- Maintenance
- Transfer
- Comparability / Bridging Study
- Failure OOS/Validation

AMV Method Development - Qualification
AMV Pre-Qualification Assessment
AMV Maintenance

Dealing with AMV failures (AMV TR section 8)

Krause/PDA, 2011
Dealing with AMV Failures

1. Validation Acceptance Criteria Failure
   - Method Determined Unacceptable

2. Identified Root Cause
   - Tighten Operational Limits
   - Optimize Analytical Method

3. Correct Execution Error
   - Re-execute Validation
   - Original Acceptance Criteria Met and Validation Completed

4. Validation “Successful” and “Compliant”
   - Justify Wider Acceptance Criteria Keeping Original Data
   - Evaluate AMV Acceptance Criteria

Initiate Investigation

Dealing with AMV Failures
Suggested Sets of Checklist Questions (total of n = 7 general questions)

**Set A (Questions 1-5):**
- Focused on impact assessment addressing safety, quality and efficacy identifying potential risk primarily to patients.
- The answers should support the direction and detail of workflow as summarized in the investigation process map.
- The answers may lead to a better understanding of the historical test method performance that may not have been sufficiently known or captured in the AMD or AMQ report.

**Set B (Questions 6-7):**
- Directed to assess the overall history and risk(s) to the firm’s compliance standing, the outcome of future regulatory inspections, and existing projects.
- The answers should suggest particular corrective and/or preventive actions (CAPA) that may fit best the overall need.
Back-up Slide(s)
Risk-Based AMV Protocol Acceptance Criteria

- The specifications are the most extreme limits in which the total of all variation contributors should fall.

- Acceptance criteria should be set to assure a minimum acceptable level of method performance given the specifications and performance expectations based on the existing knowledge and/or regulatory requirements.

- These method performance expectations are then compared to the existing historical data indicative of the method performance capability.

- Some “balancing” of the two opposing considerations may be necessary. However, if the historical method performance data sources do not provide sufficient evidence, or the method is simply not capable, then the method may not be ready to proceed to AMV studies.

- Some AMV protocol acceptance criteria (ex., linearity regression coefficient) cannot be directly connected to measurable method and/or process capability indicators. In those cases, acceptance criteria could be set from the historical system suitability data, or, when using Analytical Platform Technology (APT) methods, from comparable historical APT performance levels.
**General Risks to Patient and/or Firm**

<table>
<thead>
<tr>
<th>Risks for failing to meet acceptance criteria:</th>
<th>Risks for meeting “wide” acceptance criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk to firm:</strong> Potential inspection observations and overall compliance issues if failures are not completely resolved and justified before implementation.</td>
<td><strong>Risk to patient:</strong> AMV results were near limits. This may lead potentially to unacceptable product because results may be inaccurate and/or unreliable.</td>
</tr>
<tr>
<td><strong>Risk to firm:</strong> Project progression/completion not possible or continued “at risk”. Project completion could be significantly delayed and additional resources and time may be needed.</td>
<td><strong>Risk to firm:</strong> OOS test results from inaccurate and/or unreliable test method may actually be within specifications and acceptable. Firm cannot release product that is actually acceptable.</td>
</tr>
<tr>
<td><strong>Risk to patient:</strong> Failed AMV studies may delay the supply of much-needed life-saving drugs.</td>
<td><strong>Risk to firm:</strong> Any risk to patient is automatically also a risk to the firm.</td>
</tr>
</tbody>
</table>
# Dealing with AMV Failures

## Question 1-5 (Set A)

<table>
<thead>
<tr>
<th>Question</th>
<th>Examples of Questions</th>
<th>Possible Information Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Did we set balanced acceptance criteria?</td>
<td>Review protocol acceptance criteria justification(s), product specification(s), and historical data. Re-evaluate risks to patient and firm that were assessed to set acceptance criteria.</td>
</tr>
<tr>
<td>2</td>
<td>Did we fail to pass a critical protocol acceptance criterion (or several) such as intermediate precision when high variability could cause OOS results?</td>
<td>Check for criticality and corresponding likelihood for OOSs to occur.</td>
</tr>
<tr>
<td>3</td>
<td>Are results generated by this test method critical to assess product safety or product/process quality, or efficacy?</td>
<td>Consider production process stage, and impact to safety, quality or efficacy.</td>
</tr>
<tr>
<td>4</td>
<td>Did we have previous failures or unexpected results with this test method?</td>
<td>If this is not a new method, review previous AMV(s).</td>
</tr>
<tr>
<td>5</td>
<td>Were there any (failing) data sets generated during AMD/AMQ that were not discussed in the AMD/AMQ report?</td>
<td>Review laboratory notebooks from AMD/AMQ scientists and (if necessary) conduct interviews.</td>
</tr>
</tbody>
</table>
### Dealing with AMV Failures

**Questions 6-7 (set B)**

<table>
<thead>
<tr>
<th>Question</th>
<th>Examples of Questions</th>
<th>Possible Information Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><em>Has a similar failure occurred before and how did we handle this?</em></td>
<td>Review other/previous recovery processes.</td>
</tr>
<tr>
<td>7</td>
<td><em>Were there previous inspection observations for validation processes and/or failures not properly resolved?</em></td>
<td>Review previous regulatory and internal audit notes.</td>
</tr>
</tbody>
</table>