Mapping Out the Validation Process

PDA 2011 Technical Report Overview

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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**

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2011 Draft Report Completion

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AMV/AMT TR Publication Update (Aug11)

- **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
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List of Specific Examples in the AMV TR

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

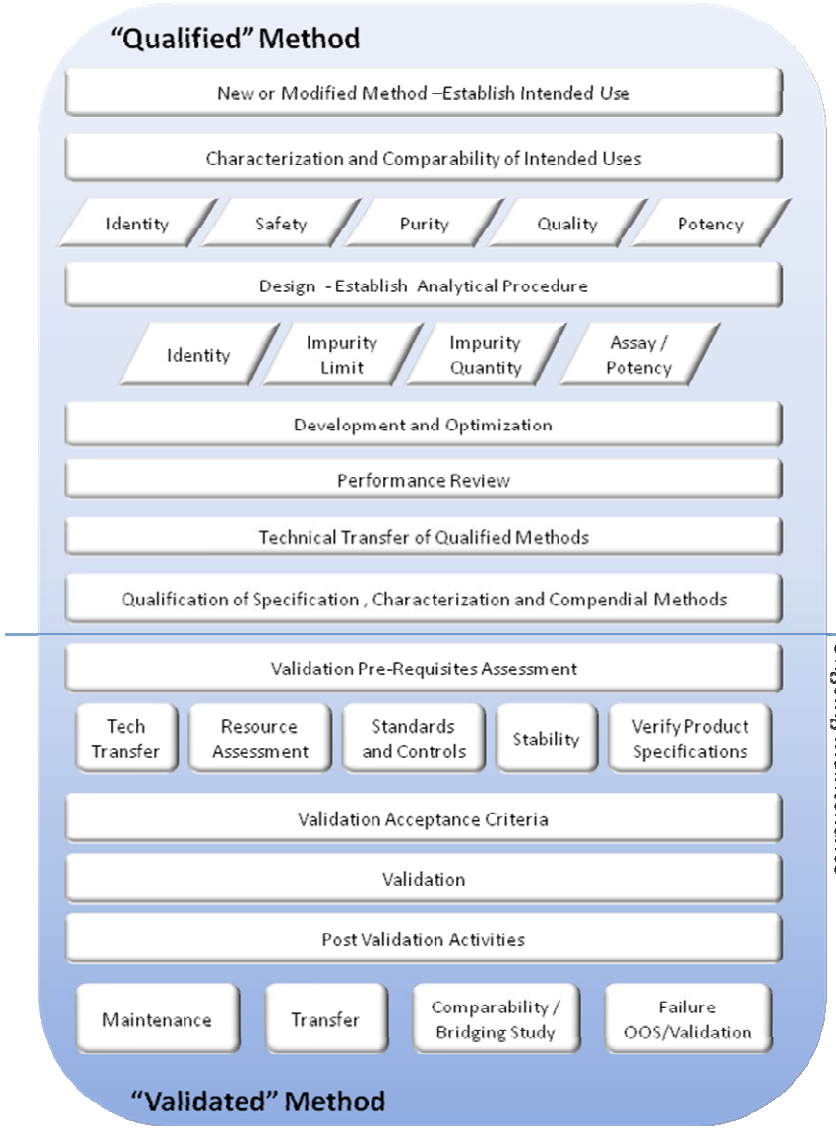
- Setting risk-based protocol acceptance criteria for a content assay
- **Using Intermediate Precision Results (using mixed linear model analysis)**
- (Prospective) critical reagent expiry study
- Significant digits in reported results (ASTM E 29-02 and E456)
- Analytical Method Transfer (AMT) of a validated 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



Not covered in AMV TR
(in AMD TR !)

Sections 1 and 3 in AMV TR

Section 4 in AMV TR

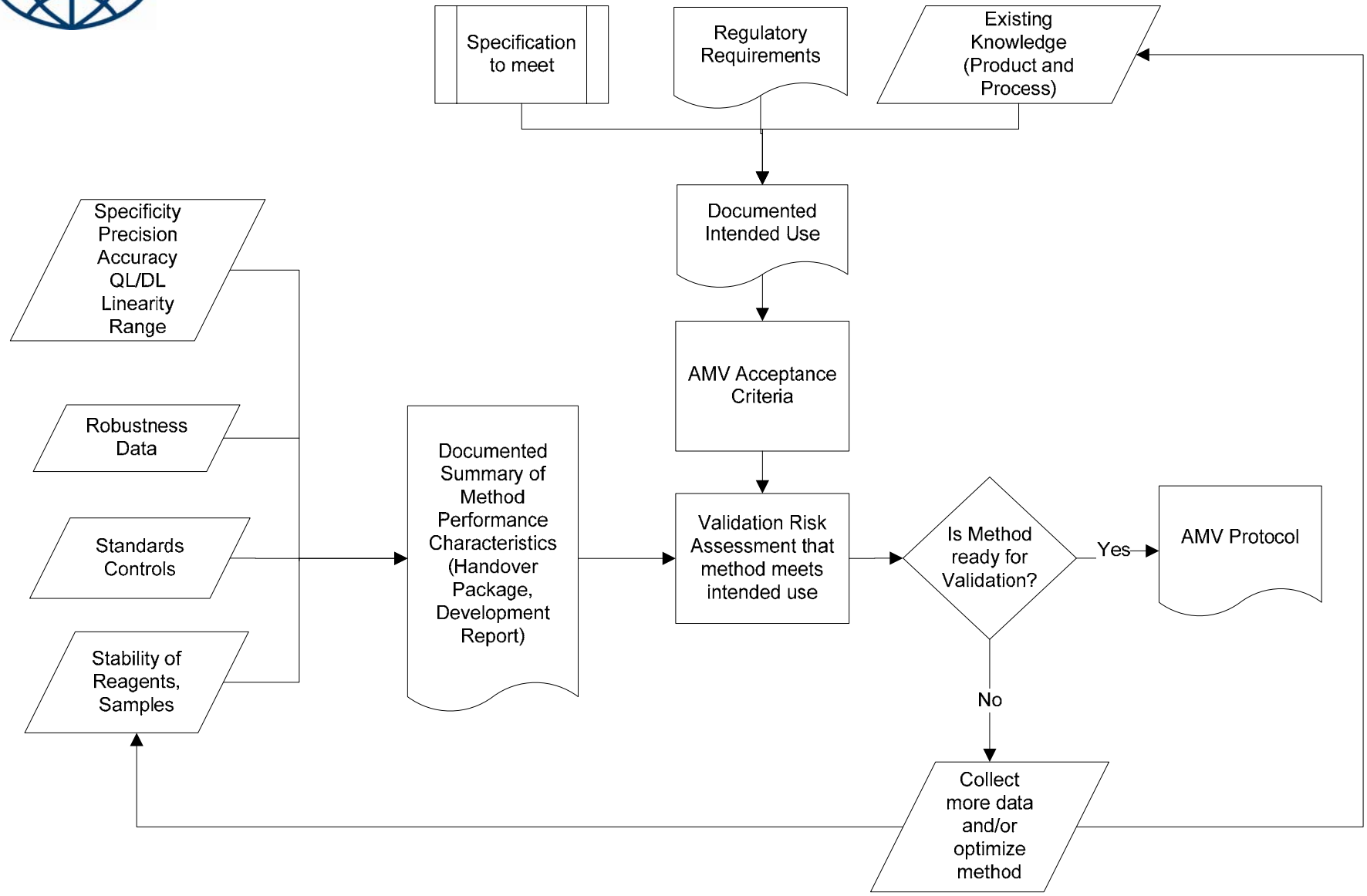
Sections 5-8 in AMV TR

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



General Risk Assessment Strategy Overview

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 <u>examples</u> while other acceptable alternatives also exist.

The Five General AMV Classes and Prospective AMV Studies

AMV Class Description			Typical Risk / Uncertainty Level (1=Low, 5=High)	Suggested Prospective AMV Studies
AMV Class No.	Analytical Method	Product / Process Sample		
A	New	New	4-5	Full Validation
B	New	Old (Validated)	3-4(1)	Full Validation Plus AMR(2) Studies
C	Analytical Platform Technology (not validated "as run")	New	2-3	Partial Validation
D	Old (Validated)	New	1-2	Partial Validation or Verification
E	Compendial	New	1-2	Verification per USP <1226>

(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.

Risk-Based AMV Studies
AMV Protocol Acceptance Criteria - Rationale

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:**

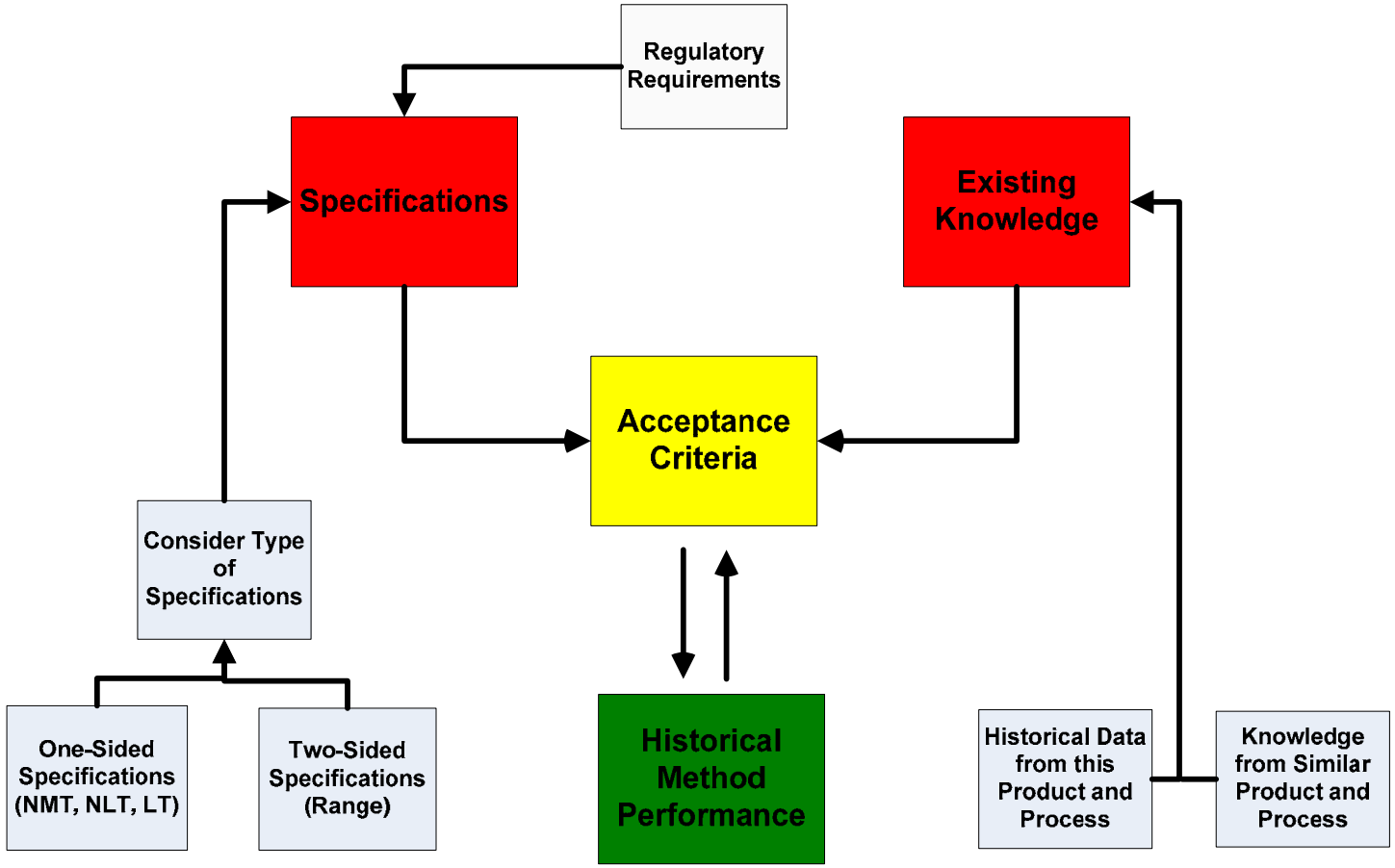
$$[\sigma \text{ mfg process observed}]^2 = [\sigma \text{ analytical method}]^2 + [\sigma \text{ mfg process actual}]^2$$

- **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.**

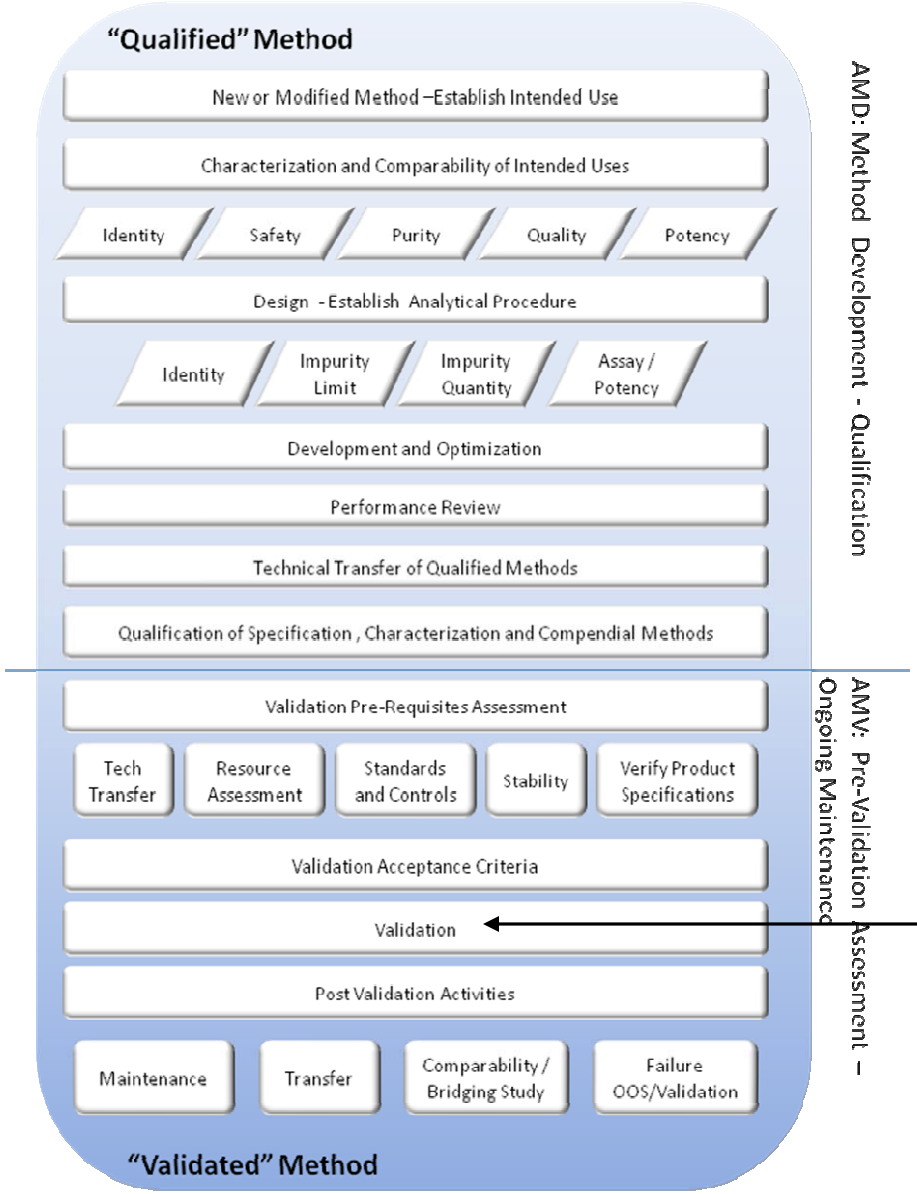
Consistent Risk Assessment to Set Acceptance Criteria

- **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



Analytical Method Life Cycle – AMV TR: Section No. 4



Formal AMV and Verification Studies (section no. 4)

ICH Q2(R1) Supporting Method Characteristics (ideally pre-AMV)

Analytical Method Performance Characteristic	Retrospective (AMD/AMQ, etc.) or Prospective Evaluation During AMV Studies
Robustness	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.
Signal Response Factors	Consider analyte response factors whenever multiple components may be reported or may impact the test results.
Statistical Data Reduction	Establish analyte response curve statistics for this method (ex., linear regression).
Degradation (For Stability – Indicating Methods)	Establish stability profile and degradation pathways of samples, impurities, and by-products as relevant for the intended use of the method.
Stability of All Material	Evaluate the short-term (during testing) and long-term (during storage) stability of standards, controls, reagents, and other critical material.
System Suitability	Establish that all test system suitability parameters are suitable for routine testing.
Sample Suitability	Establish that sample stability (during testing) and testing replicates are appropriate to routinely support accurate and reliable test results.
Significant Digits	Confirm during Repeatability Precision studies the significant digits in reported test results (and specifications) using ASTM E29-02 and ASTM E 456.
Analytical Method Replacement (pre- and/or post-validation	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.

Example for:
Intermediate Precision Mixed Linear Model Results

Effect	Variance	Std Dev.	CV
Overall	0.0249	0.158	14.6%
Instrument	0.0158	0.126	11.6%
Operator	0.0013	0.036	3.3%
Day	0.0004	0.020	1.9%
Residual	0.0157	0.125	11.6%

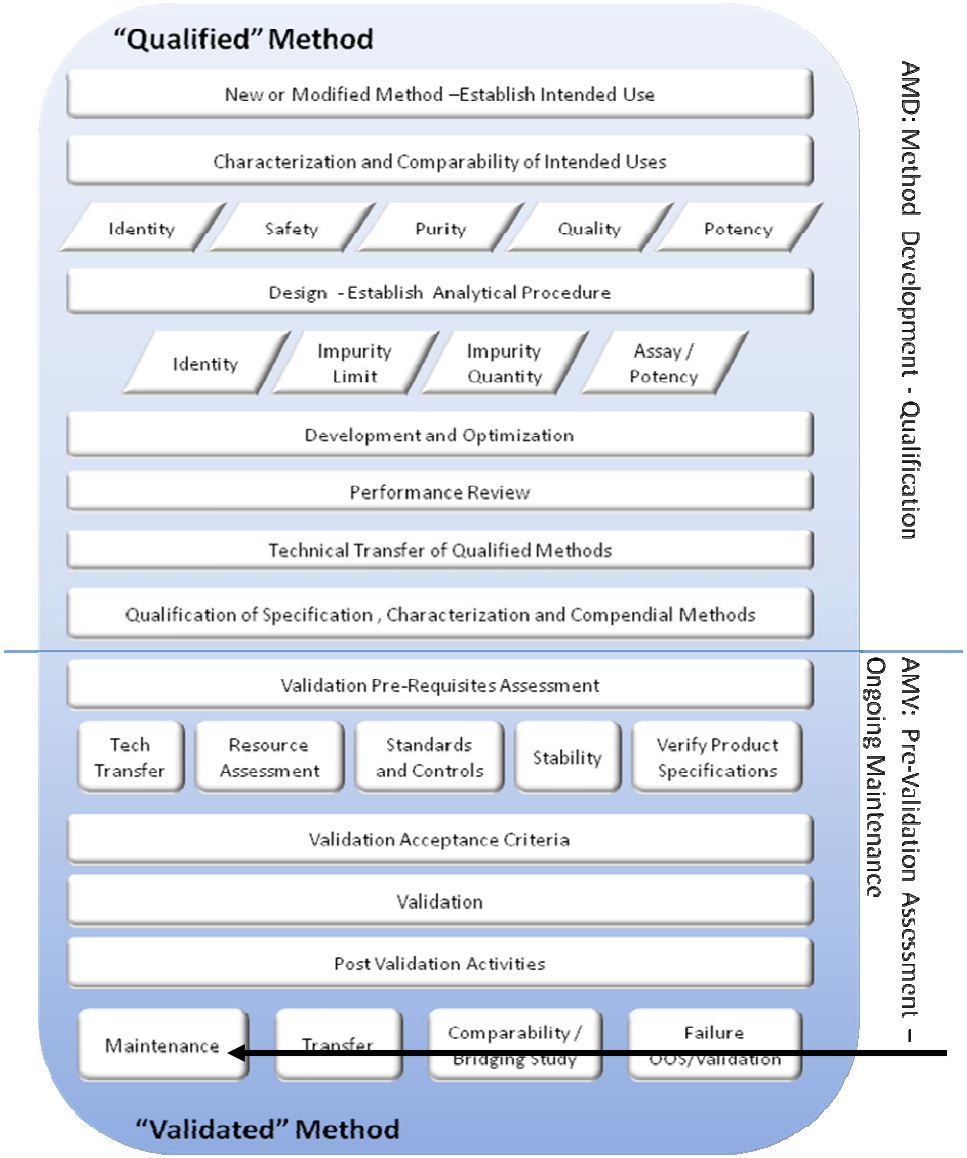
Interpretation of Intermediate Precision Results

- **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

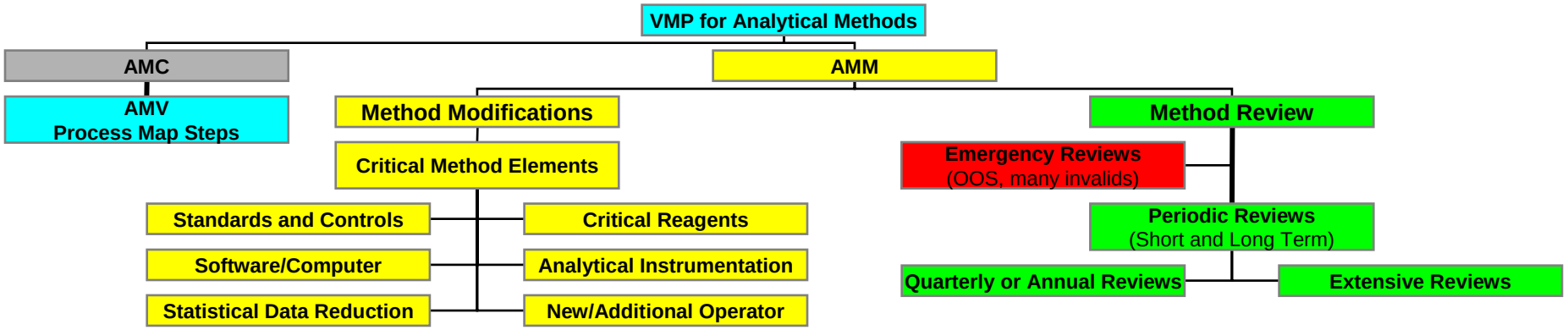
Method Types	Typical Specifications	Typical Minimum Verification Characteristics To be Evaluated
Identification	Yes/No Present/Absent Pass/Fail	A series of relevant (blind) samples should be correctly identified to demonstrate specificity. Reliable positive and, if applicable, negative identification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

Analytical Method Life Cycle – AMV TR: Section No. 7



AMM Program (section no. 7)

The AMM Program



Prospective

Retrospective

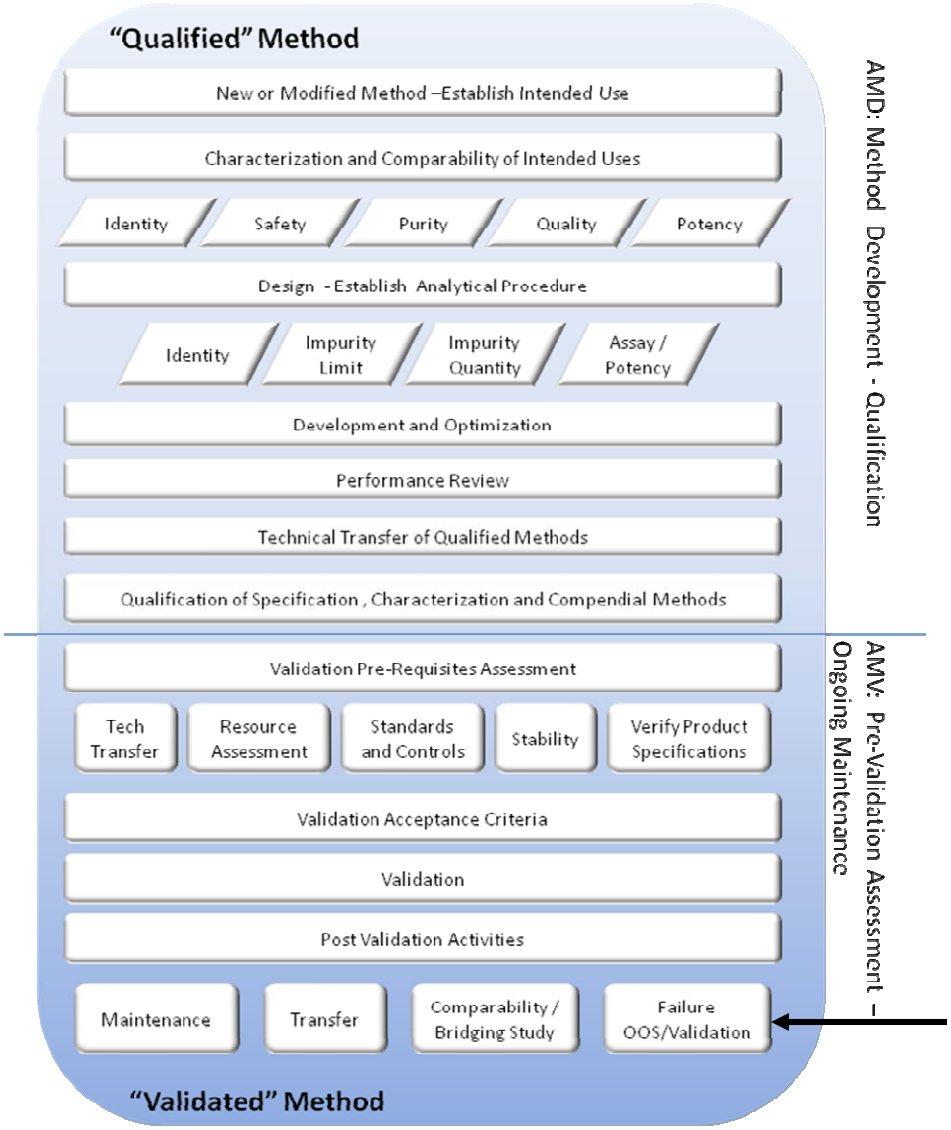
Retrospective Validation Status Review Checklist

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

Retrospective Validation Status Review Checklist (continued)

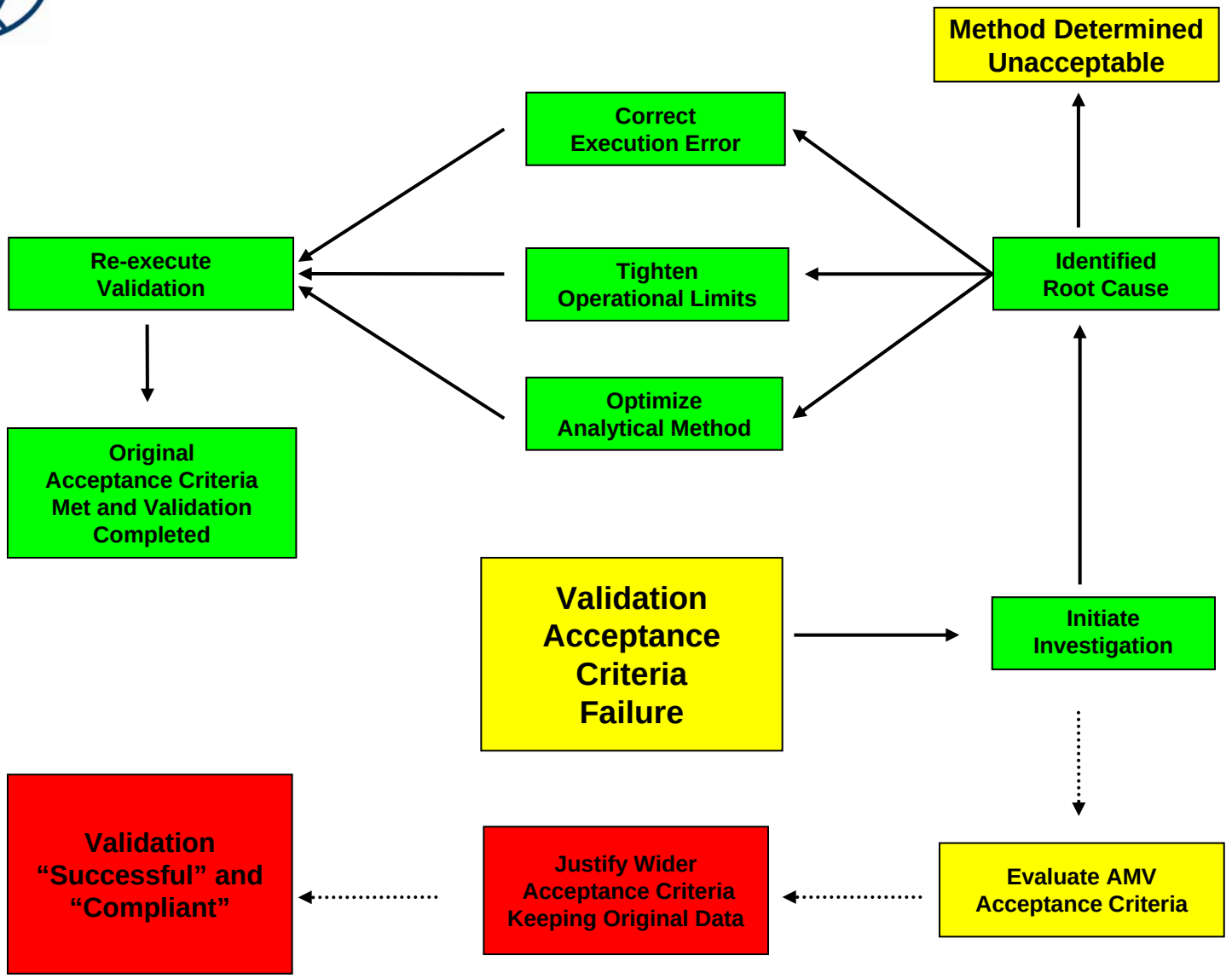
AMV and Method Performance Checklist Items (continued)	Results	Comments
Suitable System Suitability Demonstrated in AMV ?		
Number of Valid Test Runs Over Last 12 Months		
Number of Invalid Test Runs Over Last 12 Months		
Calculate Invalid Rate/Percentage:		
Statistical Assay Control Limits (ex., 3 Standard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

Dealing with AMV Failures



Dealing with AMV failures (AMV TR section 8)

Dealing with AMV Failures



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

Risks for failing to meet acceptance criteria:	**Risks for meeting "wide" acceptance criteria:**
Risk to firm: Potential inspection observations and overall compliance issues if failures are not completely resolved and justified before implementation.	*Risk to patient*: AMV results were near limits. This may lead potentially to unacceptable product because results may be inaccurate and/or unreliable.
Risk to firm: Project progression/completion not possible or continued "at risk". Project completion could be significantly delayed and additional resources and time may be needed.	*Risk to firm*: 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.
Risk to patient: Failed AMV studies may delay the supply of much-needed life-saving drugs.	*Risk to firm*: Any risk to patient is automatically also a risk to the firm.

Dealing with AMV Failures

Question 1-5 (Set A)

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

Dealing with AMV Failures

Questions 6-7 (set B)

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