Recent Regulatory Updates and Trends in Analytical Method Validation

The Agilent Compliance Seminar 2016

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Overview

- Limitations of the current regulations and guidelines
- General trends in method validation, method transfer and verification
- Going through the new guidelines
  - EU GMP Chapter 6, Quality Control: Analytical method transfer
  - FDA guidance: Bioanalytical method validation
  - USP Chapter <1200>: Requirements for compendial validation
  - USP Chapter <1210>: Statistical tools for procedure validation
  - USP PF Stimuli paper: Lifecycle management of analytical procedures
  - USP Chapter <1225>: Validation of compendial methods, new Rev
  - PDA Technical Report 57 and 57-2: Analytical method development and qualification for biotechnology products
  - **FDA Guidance: Analytical procedures and methods from 2015**
- **Six step QbD process**

FDA CGMP Regulation for Analytical Methods

21 CFR Part 211.165 (e)

- The **accuracy, sensitivity, specificity, and reproducibility** of test methods employed by the firm shall be established and documented.
- Such validation and documentation may be accomplished in accordance with 211.194(a)(2).

21 CFR Part 211.194 (a) (2)

- The suitability of all testing methods used shall be **verified under actual condition of use**

Current FDA Guidelines For Method Validation

- **Analytical Procedures and Methods Validation for Drugs and Biologics (**Draft 2000**, Final 2015)**
- Bioanalytical Method Validation (2001), new draft 2013
- Methods Validation for Abbreviated New Drug Applications (1998, update 2006)
- Guideline for Submitting Samples and Analytical Data for Methods Validation (1987)
- Validation of Chromatographic Methods (1994)

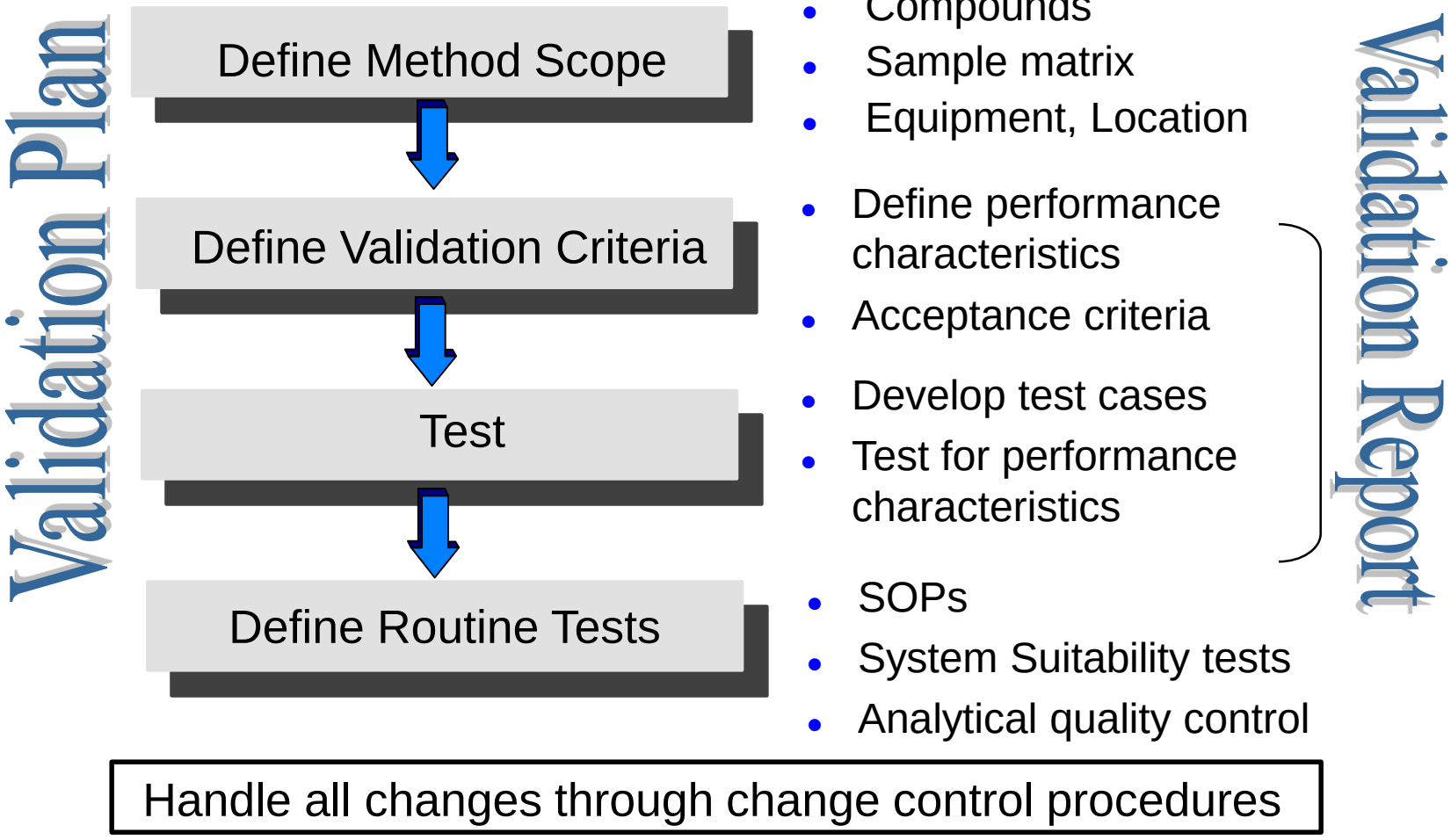
Other Guidelines For Method Validation

- ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology (2005)
  Must be followed in US and Europe
- USP <1225> : Validation of Compendial Methods,
- USP <1226> : Verification of Compendial Methods
- USP <1224> : Transfer of Analytical Procedures

Method Validation Parameters for different Method Tasks (ICH Q2)

Analytical Task	Identifi-cation	Impurity Quantitative	Impurity Qualitative	Assay
Accuracy	No	yes	No	Yes
Precision				
Repeatability	No	Yes	No	Yes
Intermediate	No	Yes	No	Yes
Reproducibility	No	Yes	No	Yes
Specificity	Yes	Yes	Yes	Yes
Limit of detection	No	No	Yes	No
Limit of quantitation	No	Yes	No	No
Linearity	No	Yes	No	Yes
Range	No	Yes	No	Yes
Robustness	**Expected to be done during Method Development**			

Validation of Analytical Methods



Handle all changes through change control procedures

Parameters and Tests (ICH Q2)

Parameter	Tests (examples)
Accuracy	Minimum at 3 concentrations, 3 replicates
Precision	
Repeatability	Minimum of 9 determinations over the specified range
Intermediate	Over 3 days, 2 operators, 2 instruments,
Reproducibility	Only required if testing is done in different laboratories
Specificity	Prove with specific methods: HPLC, DAD, MS, dif. columns
Limit of detection	Visual approach, S/N >= 3
Limit of Quantitation	S/N >= 10, Standard deviation of response
Linearity	Min 5 concentrations: visual, correlation coefficient (r)
Range	80 to 120% of test concentration, from linearity tests

General Trends in Method Validation and Transfer

- Use of integrated lifecycle
  Design – development – validation – routine use – updates – transfer
- Quality by Design
- Understand critical parameters
- Apply structured risk assessment for selection of DoE tests
- Use multivariate DoE studies to define method operational limits
- On-going control of critical parameters during routine operation and continuous improvement

New (proposed) Guidelines

- EU GMP Chapter 6, Quality Control: Analytical method transfer
- FDA guidance: Bioanalytical method validation (draft, 2013)
- USP Chapter <1200>: Requirements for compendial validation
- USP Chapter <1210>: Statistical tools for procedure validation
- USP PF Stimuli paper: Lifecycle management of analytical procedures, one proposal for <1220> (2013)
- USP Chapter <1225>: Validation of Analytical Methods - Proposal for new revision
- PDA Technical Reports 57: and 57-2 Analytical Method Validation and Transfer for Biotechnology Products (2012, 2015)
- FDA Guidance: Analytical Procedures and Methods Validation for Drugs and Biologics (Final 2015)

Red=QbD/Lifecycle

EU GMP Requirements for Method Transfer

Updates of EU Volume 4 GMPs Chapter 6: Quality Control

- **EU equivalent to USP chapter <1224>. However: formal regulation**
- **Effective since October 1, 2014**
- Review the original validation with compliance of ICH Q2
- **Perform gap analysis and perform missing validation steps prior to the transfer process**
- **Base acceptance criteria on current validation studies**
- Describe the transfer process in a transfer protocol
  - Identify methods to be transferred and testing
  - Identify training requirements
  - Identify samples and standards to be tested
  - Identify special transport and storage conditions
- **Investigate deviations** from protocol
- Document comparative outcome in the transfer report

FDA Guide for Validation of Bioanalytical Methods

- Used by sponsors of
  - Investigational new drug applicationns (INDs)
  - New drug applications (NDAs)
  - Abbreviated new drug applications (ANDAs)
  - Biologic liscence applications (BLAs)
- Applies to
  - Bioequivalency studies (BE) CFR 320.29
  - Bioavailability studies (BA) CFR 320.29
  - Non-clinical pharmacology / toxicology studies (CFR 58)
- Studies related to
  - Human drug approval process
  - Veternary drug approval process

Difference to Guidance from 2001

- Similar to the the EMA guidance (no real conflict)
- Includes requirements for System Suitability Testing (SST)
- **Inclusion of Incurred Sample Re-analysis**
- Specification of a minimum number of runs for Validation (Chromatography and Ligand Binding assays,)
- Recommend Calibration Standards and QCs should be prepared from Different Stock solutions
- Concentrations below the LLOQ should be reported as zeros
- Sample Analysis Reporting should include: All accepted and rejected analytical runs
- Some minor details, e.g.,
  - 2001 '…calculations of accuracy and precision excluding values that are determined as outliers **can** also be reported'
  - 2013 '…calculations of accuracy and precision excluding values that are determined as outliers **should** also be reported'

Incurred Sample Reanalysis (ISR)

- Necessary component of bioanalytical method validation
- Intend: verify the reliability of the reported analyte concentration
- **Conducted by repeating and verifying the analysis of a subject sample from a given study on different days**
- Original and repeat analysis use the same procedures
- Expected for each human BE study
- Expected at least once for each non-clinical method and subject
- **Total number of ISR samples should be 7% of study sample size**
- 2/3rds of the repeated samples should be within 20% for small molecules and within 30% for large molecules (SOP!)

USP's 'Thoughts' about Method Validation, Verification and Transfer

- Obsolescence of chapters <1225>, <1226>, <1224>
- Replace by new chapters
  - <1220> Lifecycle Management of Analytical Procedures with many details, not mandatory
  - <220> basic requirements, mandatory
  - Fits USP's approach for two chapters on the same topic
  - Below 1000: short, mandatory,
  - Above 1000: detailed, voluntary
- Include acceptance criteria in general chapters where approppriate (e.g., USP 233, Elemental Impurities)

USP Chapter <1200>: Requirements for Compendial Validation

- Establishes the types of data that the USP is expecting to see in order to determine the acceptability of a procedure prior to its inclusion in the the Pharmacopeia.
- Includes measurable parameters and clear criteria
- Acceptability of a procedure is evaluated by means of six standardized studies: **Precision, Accuracy, Specificity, Range, Accuracy, and Detectability.**
- **Eliminates LOQ and Linearity**

Not in line with ICH Q2 ?

USP Chapter <1210>: Statistical Tools for Procedure Validation

- Intended to be a companion to <1225>: Validation of Compendial Procedures,
- Provides sophisticated statistical methods and examples to aid method validation.
- Analytical performance characteristics that are discussed from a statistical perspective in the sections that follow are: Accuracy, Precision, Detection Limit. Quantitation Limit, Linearity, Range (Different from Chapter <1225>)

USP PF Stimuli Paper:
Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance, Qualification, and Procedure Performance Verification

- Authored by the USP Validation and Verification Expert Panel
- Discusses how the modern concept of a lifecycle model can be applied to analytical procedures
- Proposal to integrate validation, transfer and verification into the analytical procedure lifecycle process
- Includes three stages
  - design with development and understanding
  - Performance qualification
  - Continued performance verification

USP's PF Stimuli Paper - Elements

- Lifecycle approach
- Analytical target profile
- Risk management
- Analytical control strategy
  - Ensures that ATP is realized throughout the lifecycle
- Knowledge management through robustness studies
  - Acquiring, analyzing, and disseminating information
  - Ensures ongoing effectiveness of control strategy

ATP Analytical Target Profile

PF Stimuli Paper – 3 Stage Concept

- Procedure design
  - Development and understanding
  - Robustness studiés
  - Knowledge gathering
- Procedure performance qualification
  - Demonstrate that the procedure is fit for purpose
  - Methods meets criteria as defined in the ATP
- Continued procedure performance verification
  - Routine monitoring: system suitability test, QC samples, trend charts
  - Continuous improvement

ATP Analytical Target Profile

USP <1225> - In Process Revision

- Includes elements of the integrated lifecycle
  - As described in the 2012 stimuli paper
  - Text exactly as in the 2015 FDA method validation guide

LIFE CYCLE MANAGEMENT OF ANALYTICAL PROCEDURES

- Once a compendial procedure is successfully validated (or verified) and implemented, the procedure should be **monitored during the routine use to continually assure that the procedure remains fit for its intended purpose.**
- **Trend analysis on performance** should be carried out in order to provide documented evidence that the procedure performs to the required standard and to evaluate the need to optimize and revalidate all or a part of the analytical procedure.

USP <1225> - In Process Revision

LIFE CYCLE MANAGEMENT OF ANALYTICAL PROCEDURES

- If an analytical procedure can only meet the established system suitability requirements with repeated adjustments to the operating conditions stated in the analytical procedure, the analytical procedure should be reevaluated, amended, and revalidated, as appropriate.
- Over the commercial life of a product, new information and risk assessments (e.g., awareness of a new impurity) may necessitate the development and validation of a new or an alternative analytical procedure.
- New technologies used for testing may allow for greater understanding and/or confidence when testing (or assessing) product quality.
- Therefore, the appropriateness of analytical procedures should also be periodically evaluated, and new or alternative validated procedures may be considered.

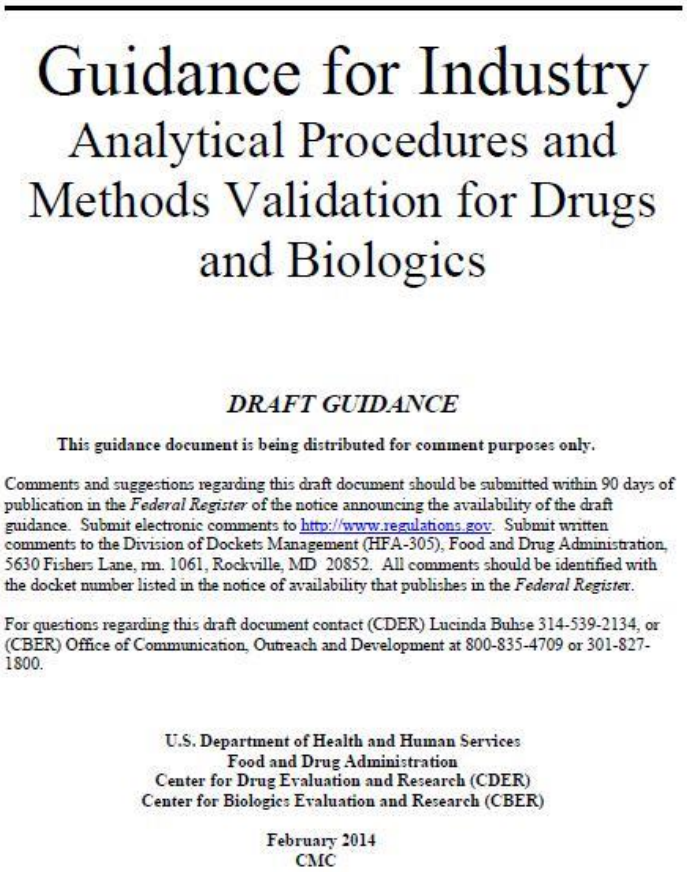
PDA Technical Report 57: Analytical Method Validation and Transfer for Biotechnology Products

- Describes method lifecycle steps from design and development to qualification and transfer
- Has sections on
  - Assessment of method validation readiness
  - Risk assessment process
  - Setting method validation acceptance criteria
  - Analytical method validation according to ICH Q2
  - Good practical examples, e.g., intermediate precision and an execution matrix
  - Analytical method transfer

FDA Guide – Analytical Method Validation

What's New?

- Promotes lifecycle management
- Has chapter on method development with focus on robustness testing
- Requires submission of method development data when supporting validation
- Refers to ICH Q2 for validation parameters and tests
- I**ncludes components of Quality by Design** (QbD)
- **Frequent mentioning of risk assessment**
- Includes chapters on verification of compendial methods and method transfer
- Includes chapter on alternative methods



Guidance for Industry

Analytical Procedures and Methods Validation for Drugs and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Lucinda Buhse 314-539-2134, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2014
CMC

Scope of the Guidance

- Replaces the draft guidance from 2000
- Replaces the FDA guidance „Submitting Samples and Analytical Data for Methods Validation” from 1987
- Drug substances, drug products, in abbreviated new drug applications (ANDA) and new drug applications NDA), and for biologic license applications (BLA)
- Recommended to look at for INDAs
- Complements ICH Q2 (R1)
- Method development and validation of non-compendial methods
- Verification of compendial methods
- Method transfer

Analytical Methods Development

- **Robustness** of a method should be evaluated during early stages of development, because results will influence the ideal technique and parameters
- A systematic approach should be adopted for robustness studies, e.g., **design of experiments** with method parameters
- Start with an initial **risk assessment** followed with **multivariate** experiments
- **Development data should be submitted** within the method validation section if they support the validation of the method.

Noncompendial Analytical Procedures

- Validation data and protocols must be generated following current good manufacturing practices
- Instruments must be qualified and operated under GMP
- ICH Q2(R1) considered primary reference for recommendations and definitions on validation characteristics for analytical procedures
- **Submitted data must include results from robustness testing (typically conducted during method development)**
- **Method conditions** and **post-approval changes** must be **submitted to FDA**

Revalidation

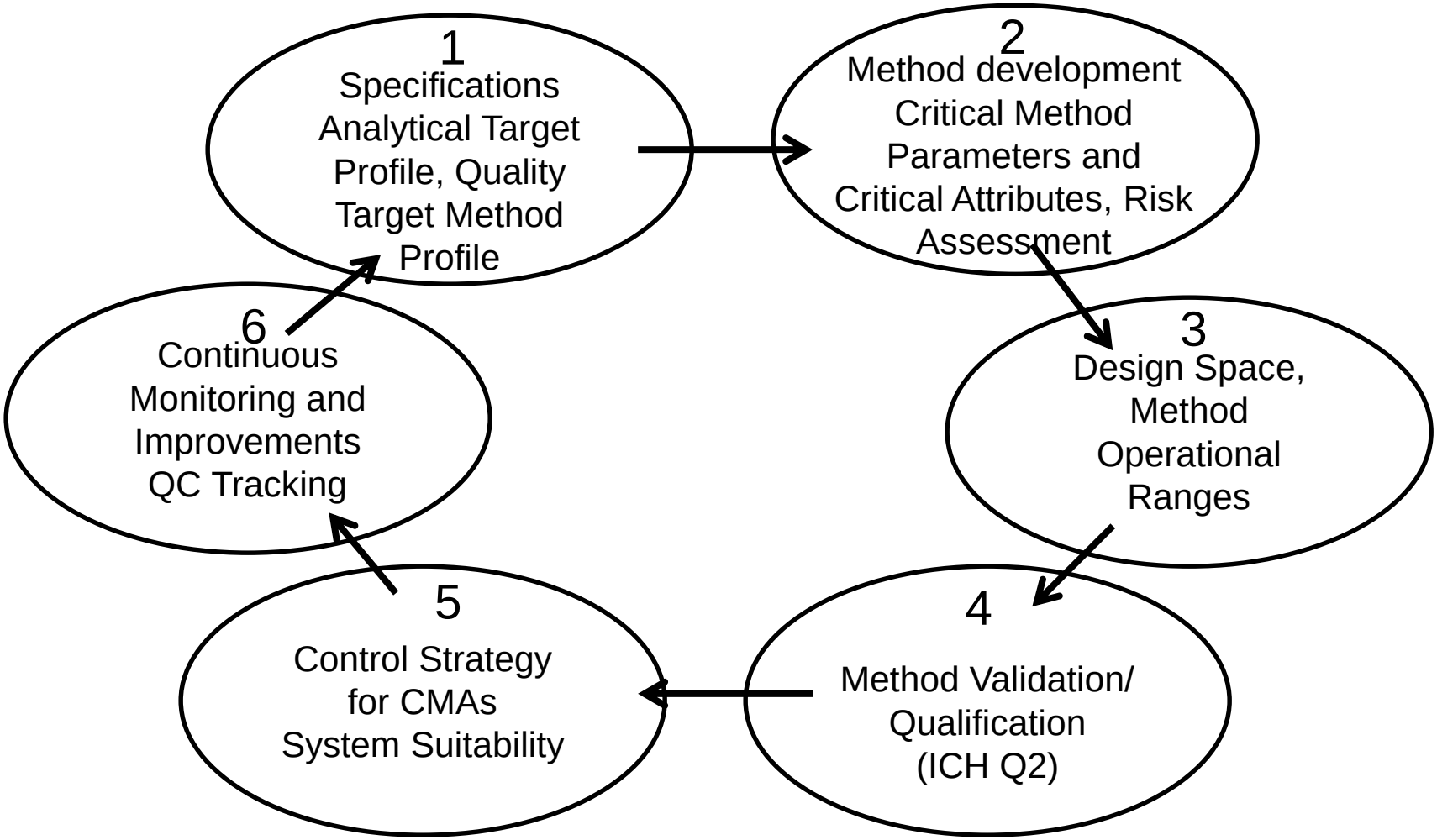
- When a change is made to an analytical procedure (e.g., a change in a piece of equipment or reagent or because of a change in manufacturing process or formulation), revalidation of all or part of the analytical procedure should be considered
- You should revalidate to ensure that the analytical procedure maintains its critical performance characteristics (e.g., specificity, precision, accuracy, etc).
- The degree of revalidation depends on the nature of the change.

No mention of time-based periodic revalidation

Life Cycle Management of Analytical Procedures

- During routine use of the method trend analysis on method performance should be performed at regular intervals to evaluate the need to optimize the analytical procedure or to revalidate all or a part of the analytical procedure.
- Over the life cycle of a product, new information (e.g., a better understanding of product CQAs or awareness of a new impurity) may warrant the development and validation of a new or alternative analytical method.
- Applicants should **periodically evaluate** the appropriateness of an analytical methods and consider new or alternative methods
- If an analytical procedure can only meet the established **system suitability requirements** with repeated adjustments to the operating conditions stated in the analytical procedure, the analytical procedure should be **reevaluated, revalidated, or amended,** as appropriate

Quality by Design for Analytical Methods

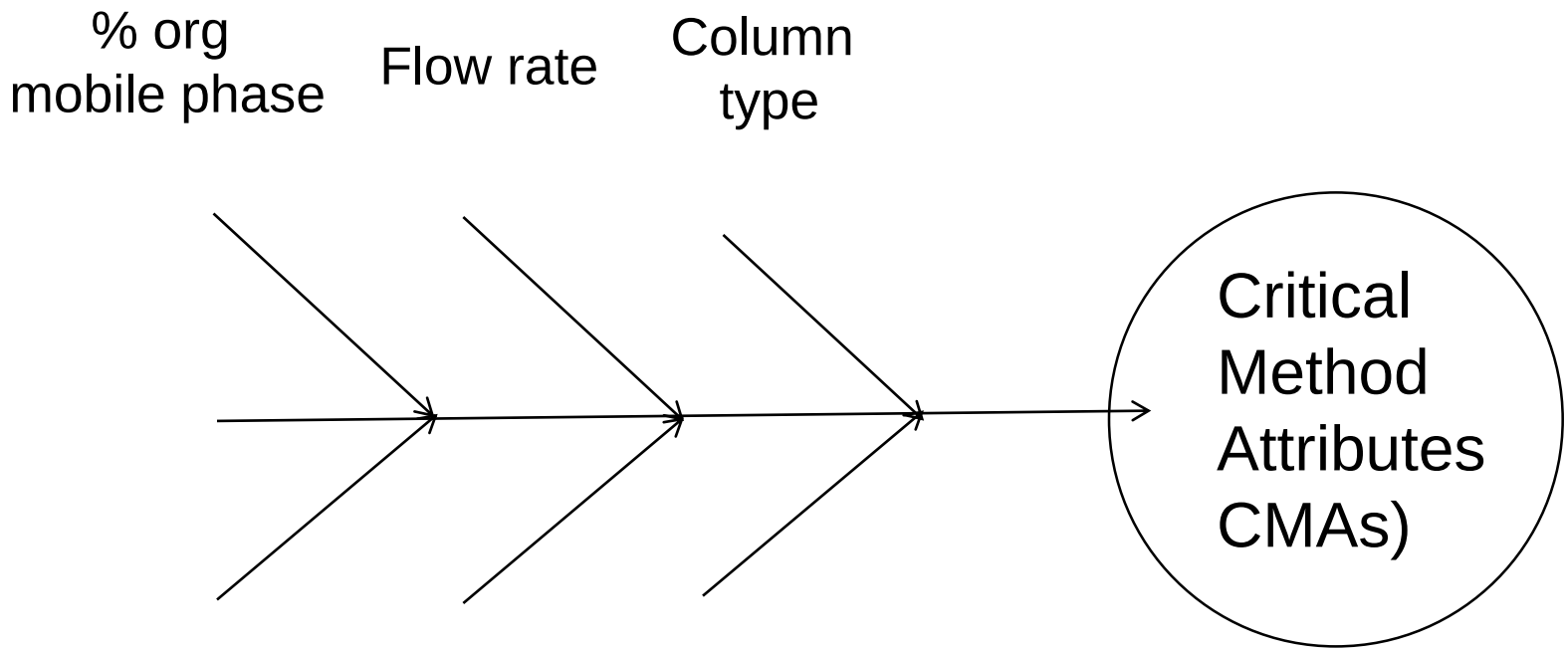


Define the Analytical Target Profile (ATP) and the Quality Target Method Profile (QTMP)

- Method operational intent (what the method has to measure) Inputs from end-user department
  - Ease of use, analysis cycle time, acceptable solvents, analysis cycle time
- Method performance characteristics, e.g., precision, accuracy, specificity, LOD/LOQ, linearity
- Acceptance criteria
- Which instruments will be used, where will the method be used (specific lab, specific site, global)

Example (incomplete): Quantitative impurity analysis compound at ≥0.05% with an accuracy and precision of 15% RSD at the limit of quantitation and 5% at 20x LOQ.

Method Parameters with impact on critical Method Attributes – Example HPLC



Apply Risk Assessment to Support Defined Criticality of Method Attributes

- Identify parameters with impact on the method's performance (Risk Identification)
  - Rely on subject matter experts, Brainstorming meeting
  - May also go back to development experiments
- Develop a prioritization matrix (Risk Evaluation)
  - Look at factors with highest impact on method performance
  - Link at specified instrument functionality, performance and qualification
  - Rank, e.g., in three categories: high (3), medium (2), low (1)
- Determine risk priority numbers for individual parameters

Example Prioritization Matrix

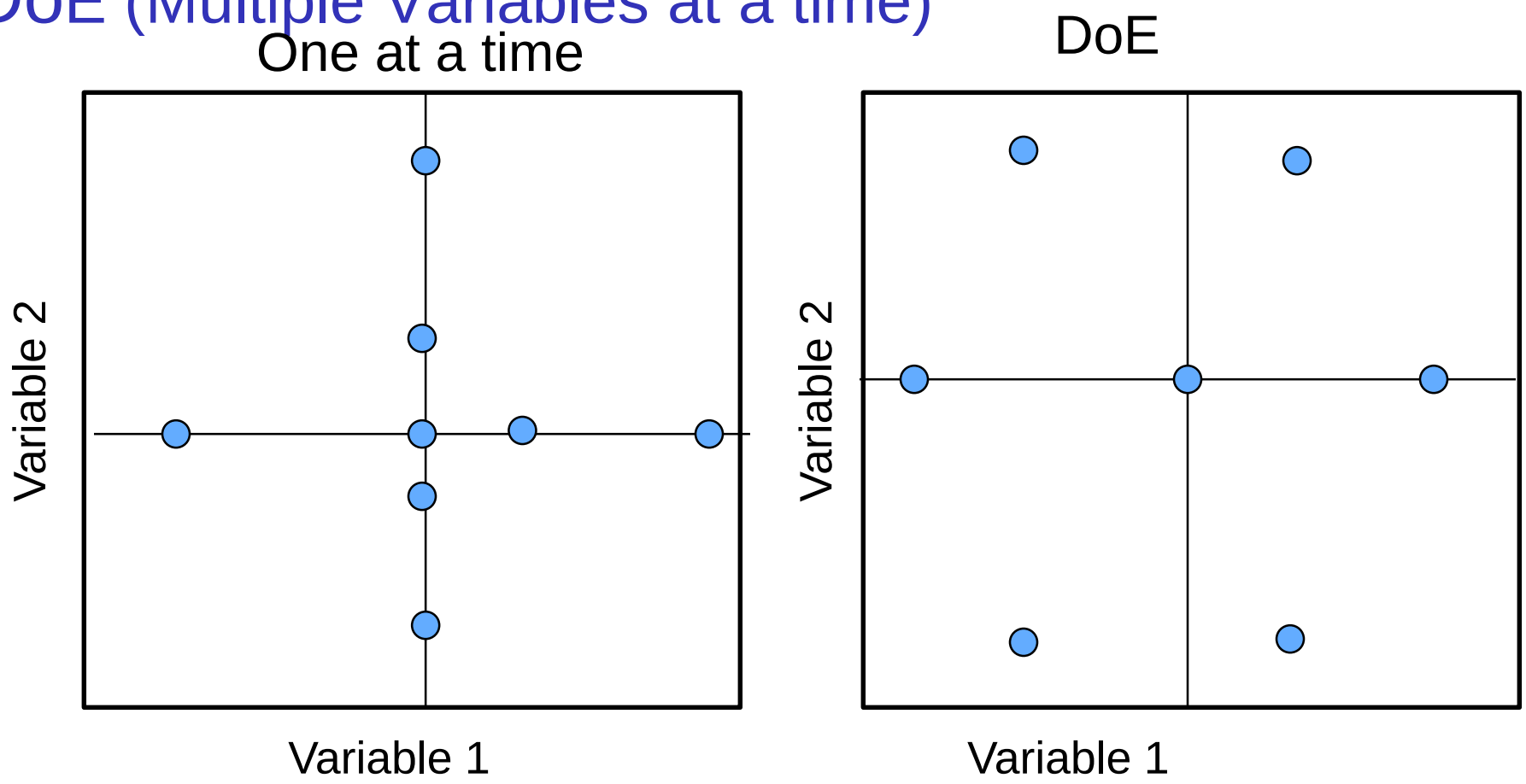
Impact of method variables on method attributes

Method variables / Method attributes	col. temp.	flow rate	pH	%organic phase	UV Wave-length
LOQ	1	2	3	3	2
Linearity	2	1	2	3	2
Repeatability	2	1	2	2	1
Accuracy	2	3	1	3	1
Specificity	3	1	2	3	1
Risk Priority Number (RPN)	**10**	**8**	**10**	**14**	**8**

1 = low, 2= medium 3 = high impact

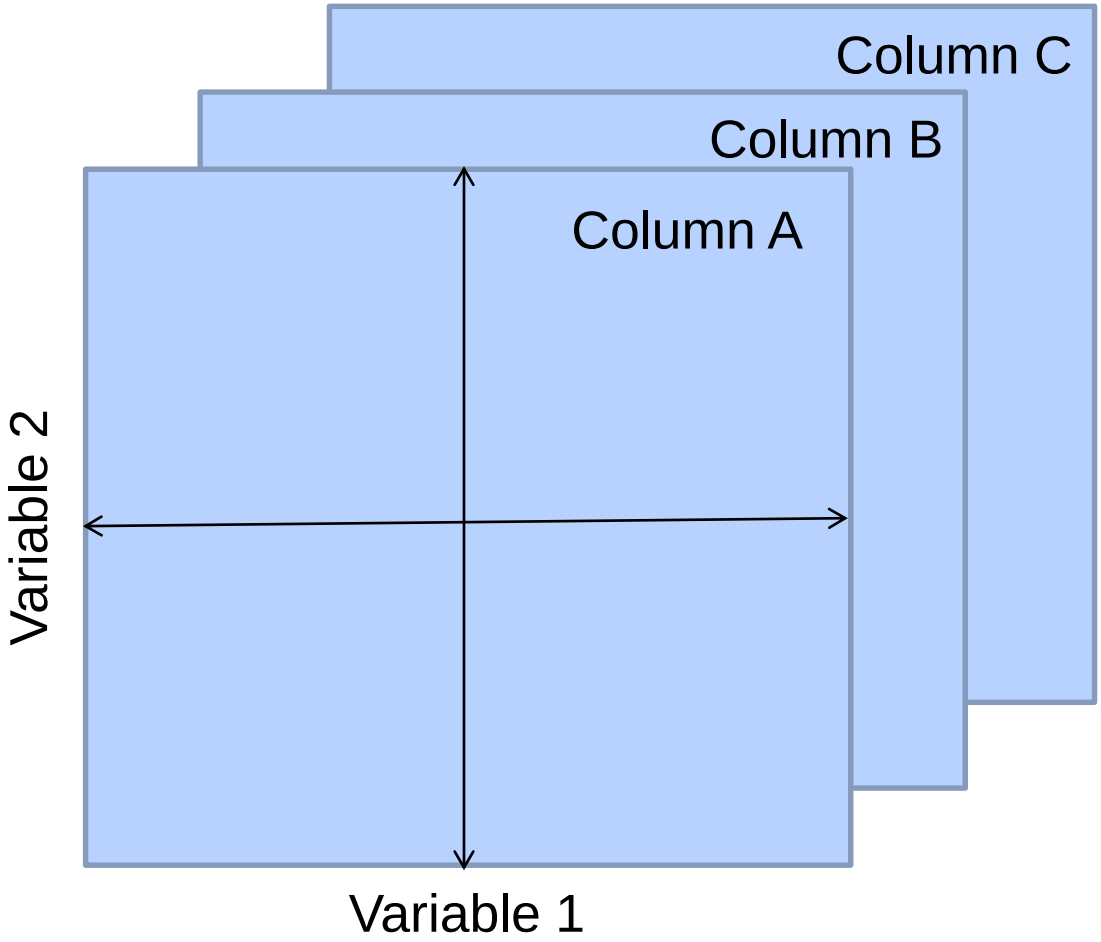
RPN ≥ 9 included in DOE study

Optimizing through one Variable at a Time vs. DoE (Multiple Variables at a time)



Impact of variables 1 and 2 (e.g., %org phase, col temp) on critical method attributes e.g. peak resolution or %recovery

Include different columns in Experiments



Repeat experiments on column 2 and 3.

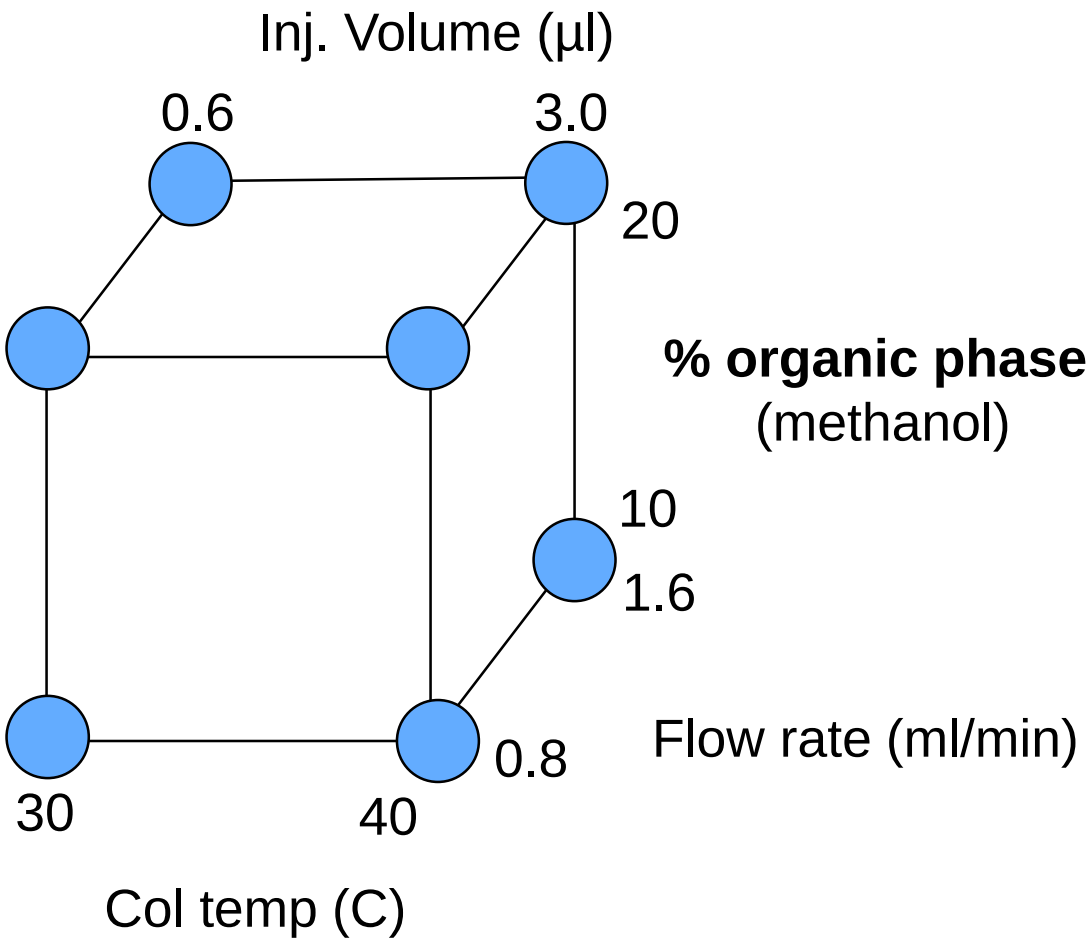
Simple DoE Example for HPLC Method

- Impact on Selectivity five variables two levels

Run #	% Org.Phase	pH	Col. Temp
1	-1	-1	+1
2	-1	+1	+1
3	-1	+1	-1
4	+1	-1	+1
5	+1	-1	-1
6	+1	+1	-1
Level -1 =	40 % ACN	4.0	25 ºC
Level +1 =	60% ACN 40% Water	6.0	40 ºC

FDA: Need sufficient statistical power to support analytical “Design Space”

Example with 4 Variables



Critical method attributes

Selectivity
LOQ
Accuracy
Precision

Qualify/Validate the Method for Intended Use

- Formally validate/qualify the method following **ICH Q2**
- Develop a method validation/qualification plan
- **Assure that equipment is qualified**
  (specifically spelled out in the new FDA guide)
- Assure that personnel is trained
- Perform qualification experiments, including robustness testing
- Evaluate data and document results
- Write a validation report

FDA MV guide 2015

ICH Q2(R1) is considered the primary reference for recommendations and definitions on validation characteristics for analytical procedures

Assure that the Method remains in a State of Control

- Run system suitability tests
  - Select critical test parameters based on risk assessment and design space experiments
- Run quality control samples
- Participate in proficiency testing programs
- Thoroughly look at OOS results, and if method specific, implement a corrective action plan
- Apply rigorous change control procedures
- Periodically review the method for suitability of the intended use.

Continually monitor and improve the Method

- Actively collect inputs from operators on reliability and performance
- Evaluate and follow-up to customer complaints and other feedback
- Look and follow-up at internal and external audit results
- Conduct regular method review, e.g., yearly
- Track and trend system suitability test results
- Track and trend quality control samples
- Respond to adverse trends before they become problems
- Continually improvement through
  - Problem solving and corrective action
  - Preventative action
  - Verification of corrective and preventive actions
- Implement a pharmaceutical quality system according to ICH Q10
  www.labcompliance.com/seminars/audio/309

Benefits - Summary

- Understanding, reducing and controlling sources of variability.
- Reducing analytical method-related out-of-specification and failure investigations.
- Lowering failure rates during method transfer.
- Facilitating continual method improvement.
- Eliminating regulatory re-approvals after changing method parameters within the predefined ATP.

Resources

- 2-day seminars in Boston (MA) and Vienna (Austria) Validation, Verification and Transfer or Analytical Methods.
- 70 page primer:
  Validation of Analytical Methods
  On-line Tutorial
  Validation of Analytical Methods