# Mapping Key Elements in the ICH Q14 and USP <1220> Guidances to an Enhanced Workflow for Analytical Procedure Development

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# Referenced Guidance Documents

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

**ICH HARMONISED GUIDELINE**

## ANALYTICAL PROCEDURE DEVELOPMENT Q14

Final Version

Adopted on 1 November 2023

*This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.*

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

**ICH HARMONISED GUIDELINE**

## VALIDATION OF ANALYTICAL PROCEDURES Q2(R2)

Final Version

Adopted on 1 November 2023

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***Add the following:***

## ▲⟨1220⟩ ANALYTICAL PROCEDURE LIFE CYCLE

**INTRODUCTION**

This general chapter holistically considers the validation activities that take place across the entire life cycle of an analytical procedure and provides a framework for the implementation of the life cycle approach.

The analytical procedure life cycle approach described here is consistent with the quality by design concepts described in International Council for Harmonisation (ICH) guidelines. The procedure life cycle approach emphasizes the importance of sound scientific approaches and quality risk management for the development, control, establishment, and use of analytical procedures. Total error is used in this chapter; however, measurement uncertainty can also be used.

The procedure life cycle approach is applicable to all types of analytical procedures, and the extent of effort should be consistent with the complexity of the procedure and the criticality of the quality attribute to be measured. The life cycle approach can be considered optional, and any of the elements can be applied on the basis of how the procedure is used. Elements of the life cycle approach can also be applied retrospectively if deemed useful or in early stages of development with the appropriate modifications.

Elements of life cycle management of analytical procedures are also discussed in *Analytical Procedures and Methods Validation for Drugs and Biologics* (Guidance for Industry, FDA 2015).

Validation of an analytical procedure is the process by which it is established, through laboratory studies, that the performance of the procedure meets the requirements for the intended analytical applications. Validation, or demonstration that a procedure is suitable for the intended purpose, takes place during the entire procedure life cycle, beginning during the initial procedure design activities and extending through routine use. These activities include the formal procedure validation, verification, and transfer of procedures, as well as establishing and assuring adherence to an appropriate set of procedure controls and system suitability requirements.

The procedure life cycle is comprised of the analytical target profile (ATP) and three stages, which are introduced below and shown in *Figure 1*.

The ATP defines the criteria for the procedure performance characteristics that are linked to the intended analytical application and the quality attribute to be measured. It applies to all stages of the procedure life cycle. For quantitative procedures, the ATP describes the required quality of the reportable value since the reportable value generated using a qualified analytical procedure provides the basis for key decisions regarding compliance of a test article with regulatory, compendial, and manufacturing limits. The acceptable level of risk of making an incorrect decision can also be considered when establishing ATP criteria.

**Stage 1**: Procedure design encompasses procedure development, which consists of the analytical technology and sample preparation. It includes understanding gained through knowledge gathering, systematic procedure development experiments, and risk assessments and associated lab experiments. The output of *Stage 1* includes:

1. A set of procedure conditions that minimizes procedure bias to a suitable level, can provide acceptable precision, and can meet the ATP criteria
2. An understanding of the effect of procedure parameters (e.g., temperature, wavelength, flow rate, etc.) on procedure performance
3. Optimization of performance characteristics of the analytical procedure such as accuracy, precision, the appropriateness of any calibration model, specificity and limit of quantitation (as far as applicable); this includes a preliminary replication strategy for samples and standards
4. An initial analytical control strategy (ACS), which is a set of controls (system suitability tests [SSTs] and other procedure-specific controls) needed to ensure proper performance

**Stage 2**: Procedure performance qualification consists of studies designed to demonstrate that the procedure is suitable for its intended purpose. This involves confirmation that the reportable values generated by application of the analytical procedure meet the ATP criteria as well as confirmation of procedure performance characteristics through the traditional validation, verification, or transfer studies. Data generated during *Stage 1* can be used if available and suitable. At the end of *Stage 2*, the replication strategy and the performance of the procedure is confirmed to meet the ATP and other criteria.

**Stage 3**: Ongoing procedure performance verification involves monitoring the analytical procedure during routine use and confirming that the performance continues to meet ATP criteria. Monitoring ensures that the performance of the procedure is maintained at an acceptable level over the procedure lifetime. It can also provide an early indication of potential performance issues or adverse trends and aid in identifying required changes for the analytical procedure. Confirming procedure performance after changes ensures that the modified procedure will produce reportable values that meet the criteria defined in the ATP.

More details about the procedure life cycle are described in the subsequent sections.

# Abstract

This presentation will discuss the following key elements within the USP <1210>, USP <1220>, and ICH Q14 guidances which provide a new framework and workflow for analytical procedure development within the context of developing a robust LC method :

1. **Analytical Target Profile (ATP)**

   **A Negotiated Specification**

2. **Design of Experiments (DOE, DoE)**

   **Guided by Risk Assessment**

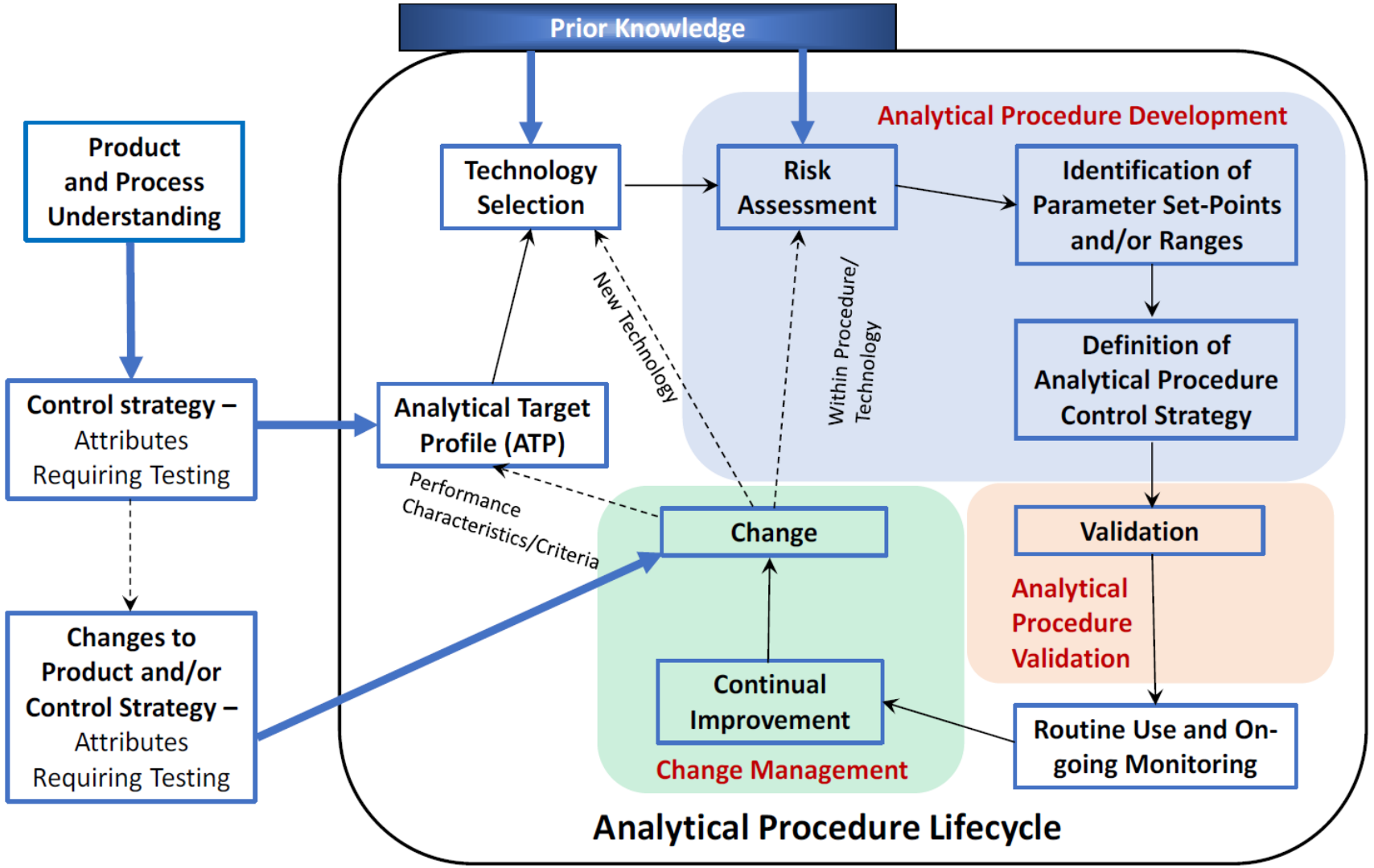
3. **Method Operable Design Region (MODR)**

   **Quantitative Robustness Integration**

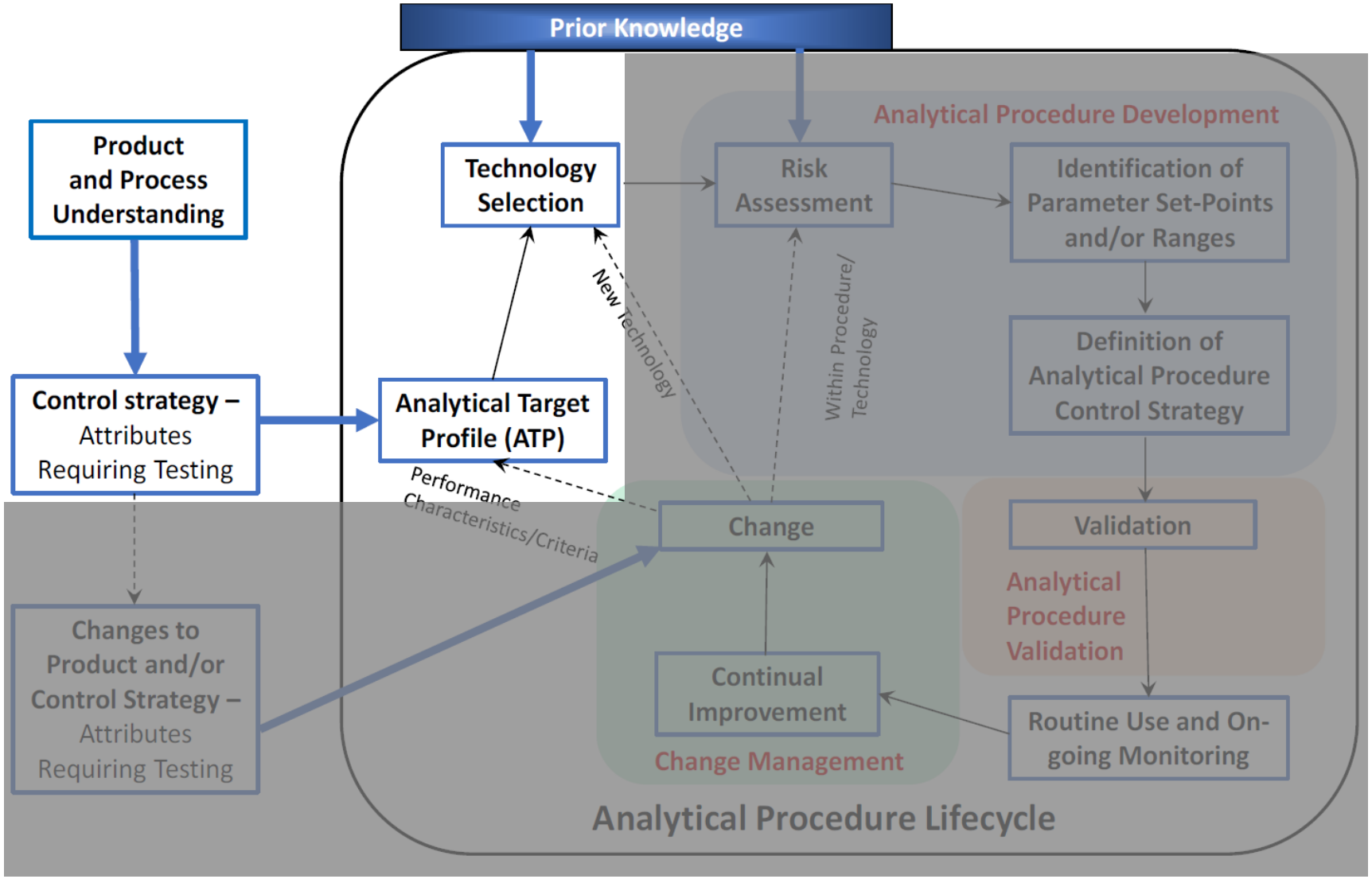
4. **Replication Strategy Optimization**

   **Meeting the ATP Performance Requirements**

# ICH Q14 – Analytical Procedure Lifecycle



# ICH Q14 – Analytical Procedure Lifecycle



# Analytical Target Profile

## Analytical Target Profile (USP <1220>

The ATP is based on the intended use for the procedure and, for quantitative or semi-quantitative procedures, should include upper limits on the precision and accuracy (bias) of the reportable value.

**Example 2**: 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%].

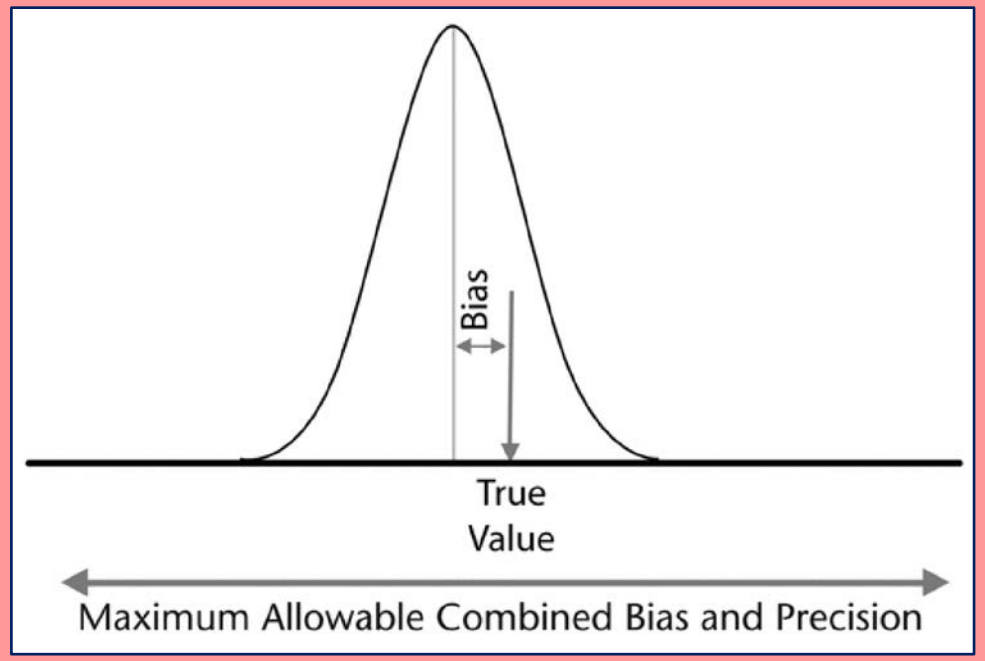
Negotiation

Replication Strategy

# Total Analytical Error (TAE)

**USP <1220>**

Total analytical error (TAE) represents the overall error in a test result that is attributed to imprecision and inaccuracy; TAE is the combination of both systematic error of the procedure and random measurement error.




## Two Critical Considerations:

1. The Negotiated Total Analytical Error (TAE) **Allowance** for the Analytical Method.
2. The Integration of Precision and Bias into a single **Interval Metric** – **USP <1210>.**

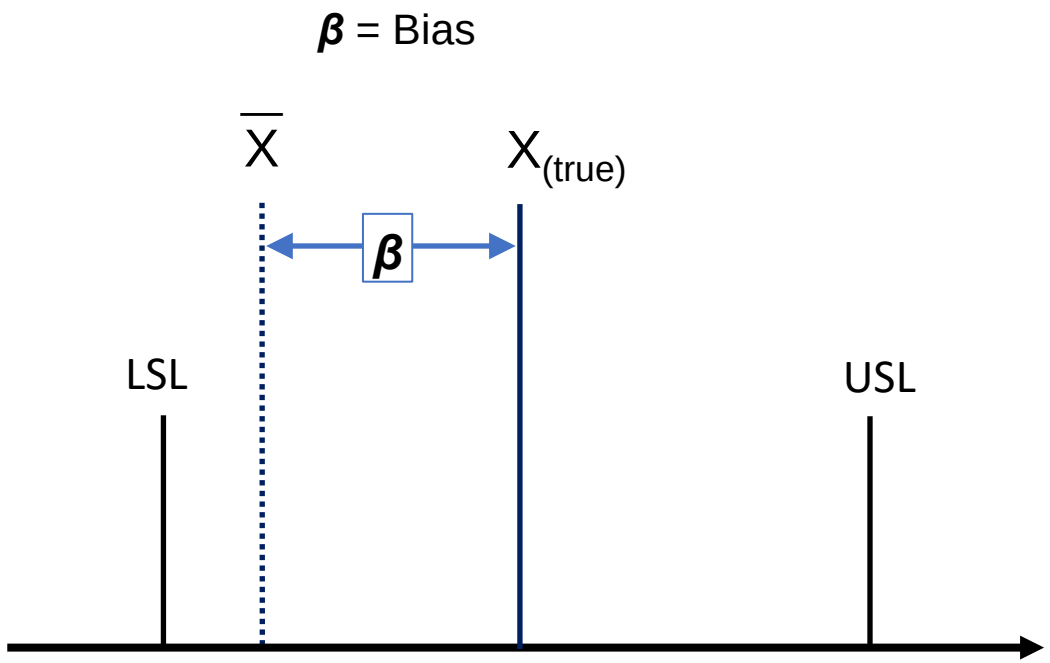
# <1210> Addresses a Critical Issue

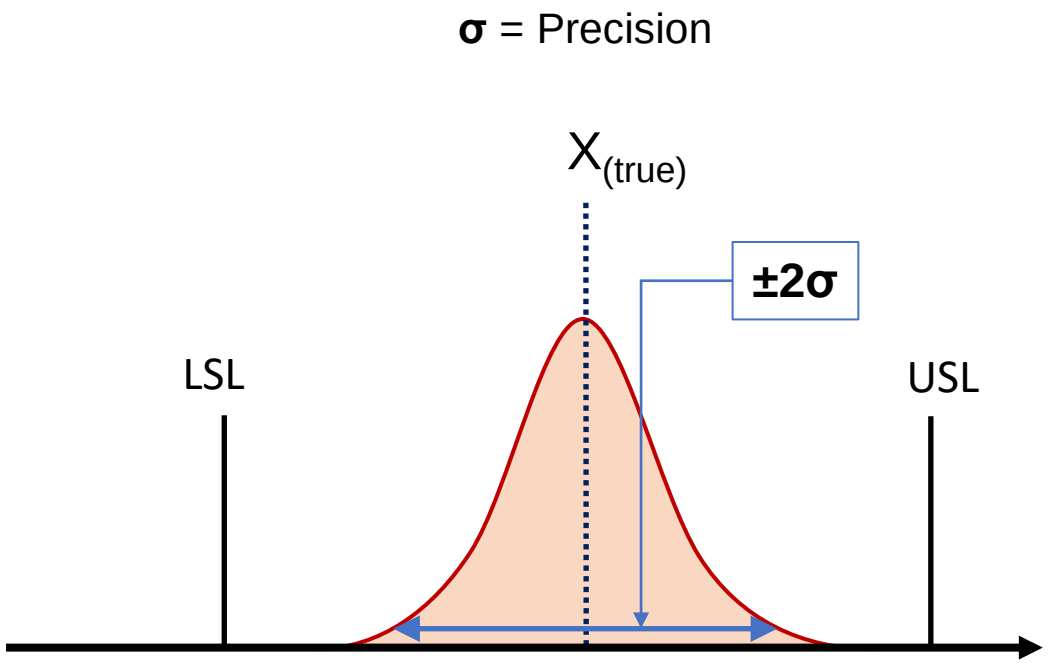


## 3. ACCURACY AND PRECISION

### 3.2 Combined Validation of Accuracy and Precision

An underperforming method can pass System Suitability for the Critical Method Attribute being evaluated when Accuracy ($\beta$ – bias) and Precision (σ – precision) are assessed separately = High Risk Approach.



# <1210> Interval Metric Solution



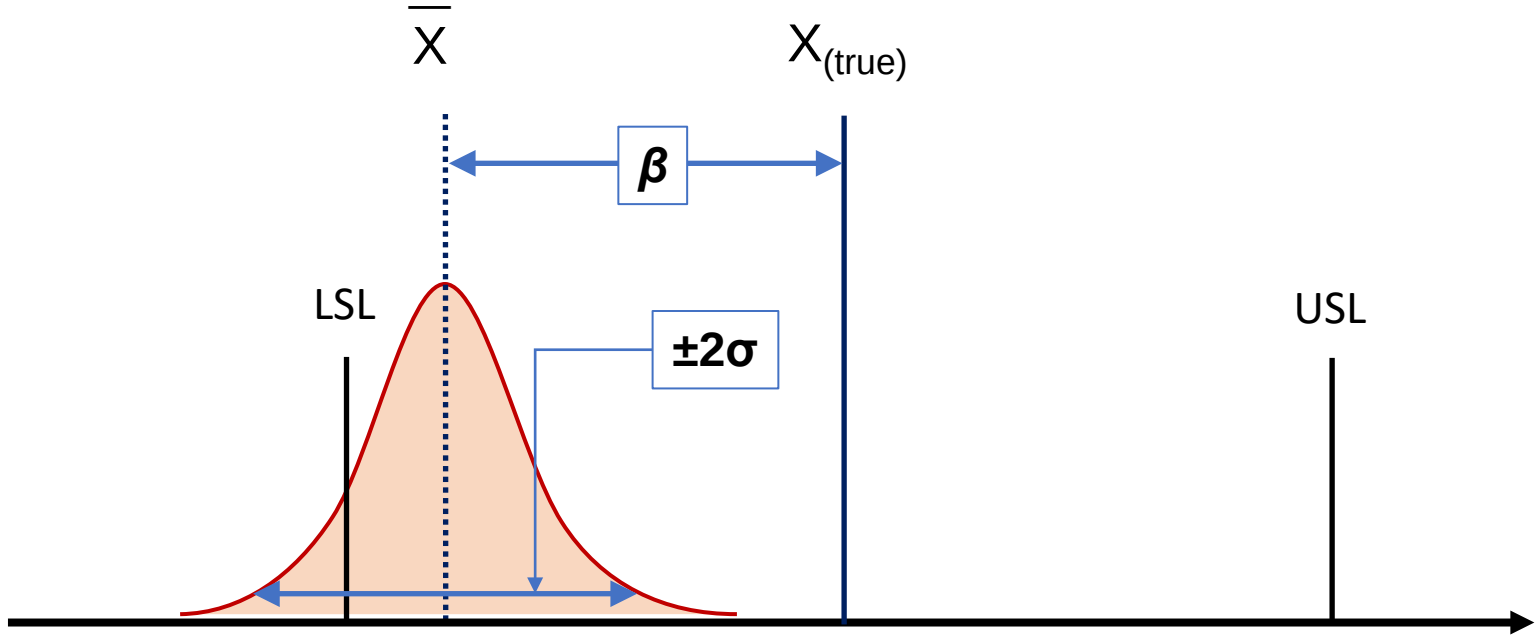
## 3. ACCURACY AND PRECISION

### 3.2 Combined Validation of Accuracy and Precision

As the illustration below shows – the method does not have acceptable System Suitability performance for the Critical Quality Attribute (CQA) being tested when both Accuracy (*β* – bias estimation) and Precision (σ – variation estimation) are assessed together = Low Risk Approach.

***β*** = Bias

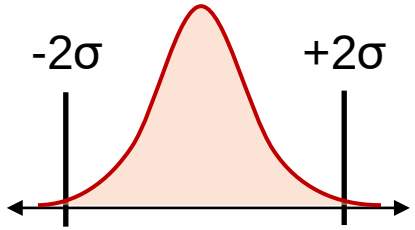
**σ** = Precision

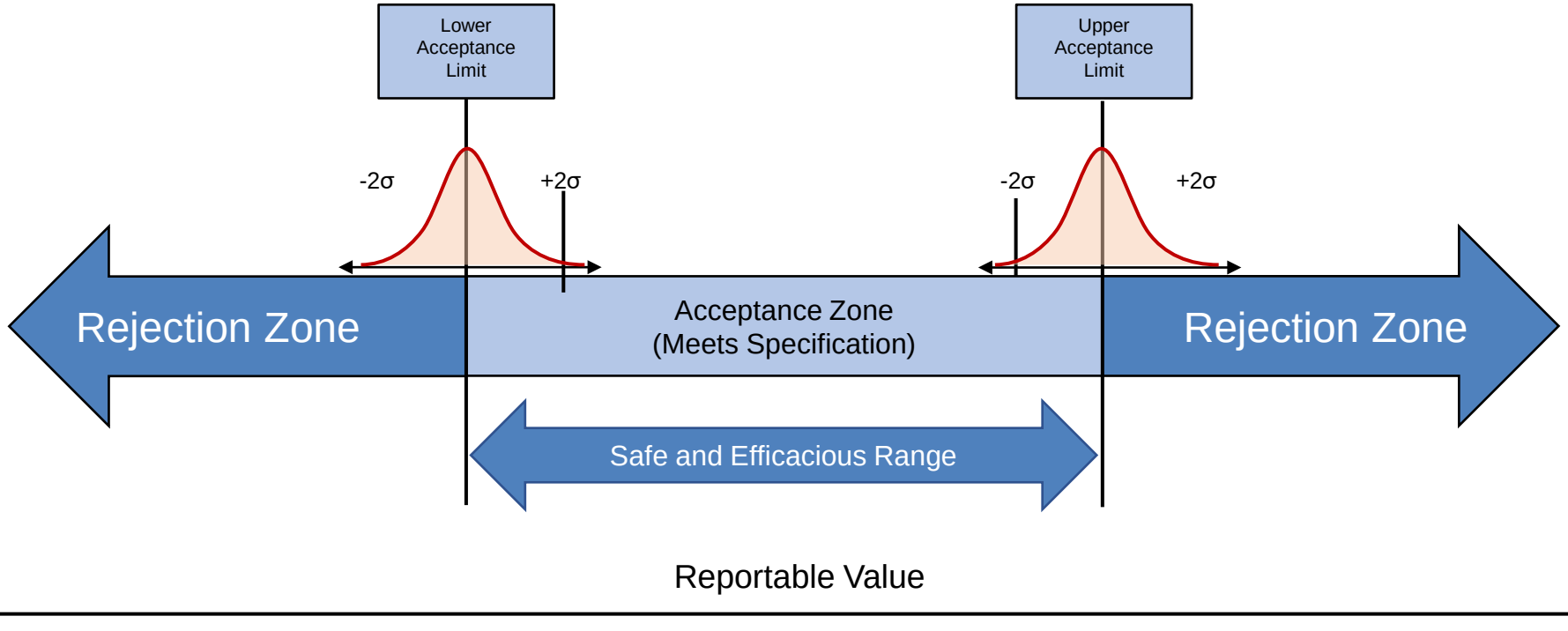


# TAE and Guard Bands

**Guard Bands** acknowledge the presence of Bias and Precision Limits and the need to incorporate a characterized TAE into the “Acceptance Zone”.

Total Analytical Error Distribution

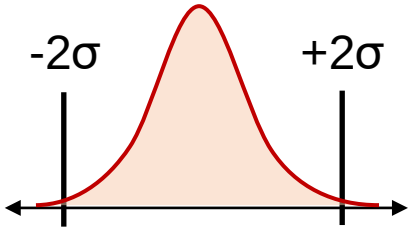


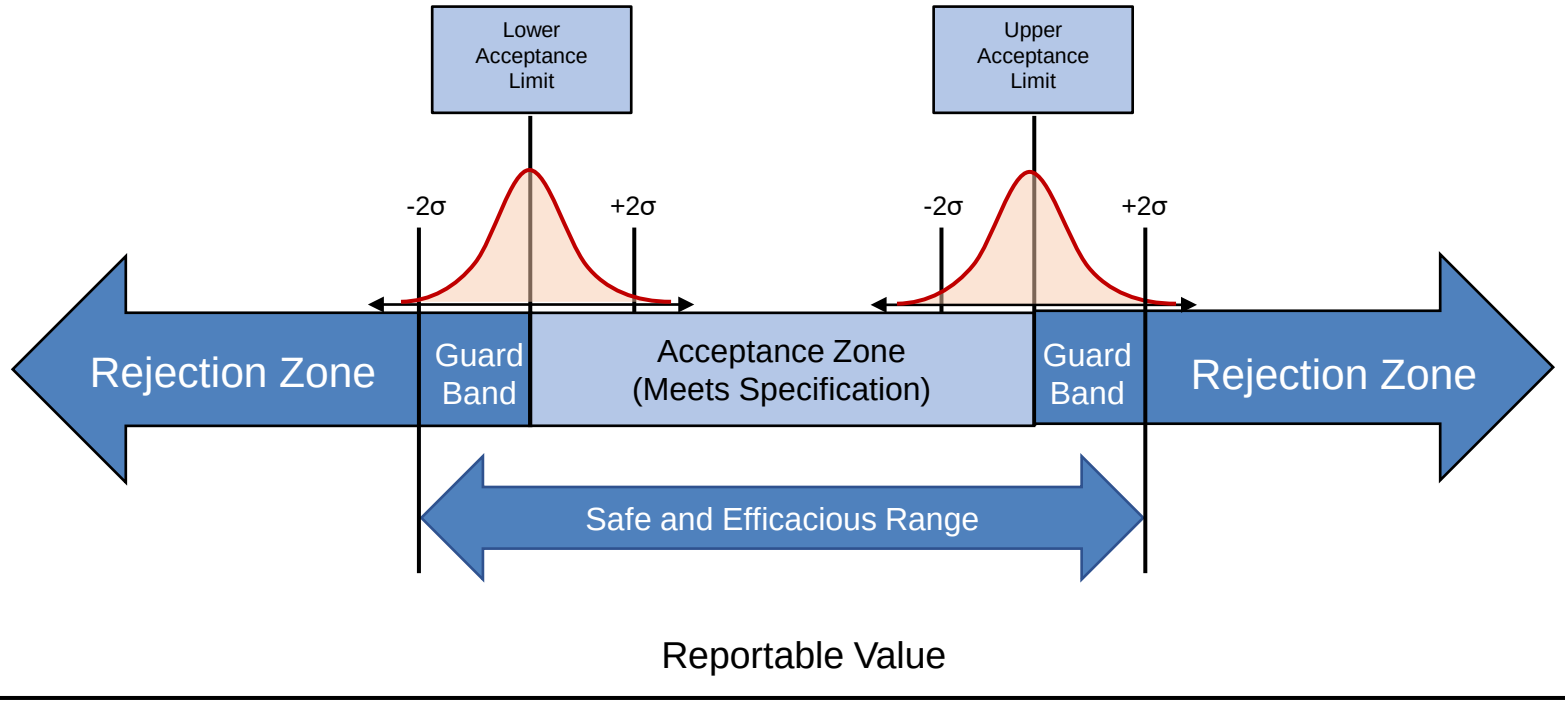



# TAE and Guard Bands

**Acceptance Zone is narrower** to incorporate the characterized TAE.

Total Analytical Error Distribution



# TAE and Guard Bands

## Production: Amount of Precision-to-Tolerance (P/T) Ratio Available for the Analytical Method

- API method has a tolerance range of 4.0% (i.e., 98.0% to 102.0%)
- Analytical method allowance = 30% of the P/T ratio using a 95% confidence interval.

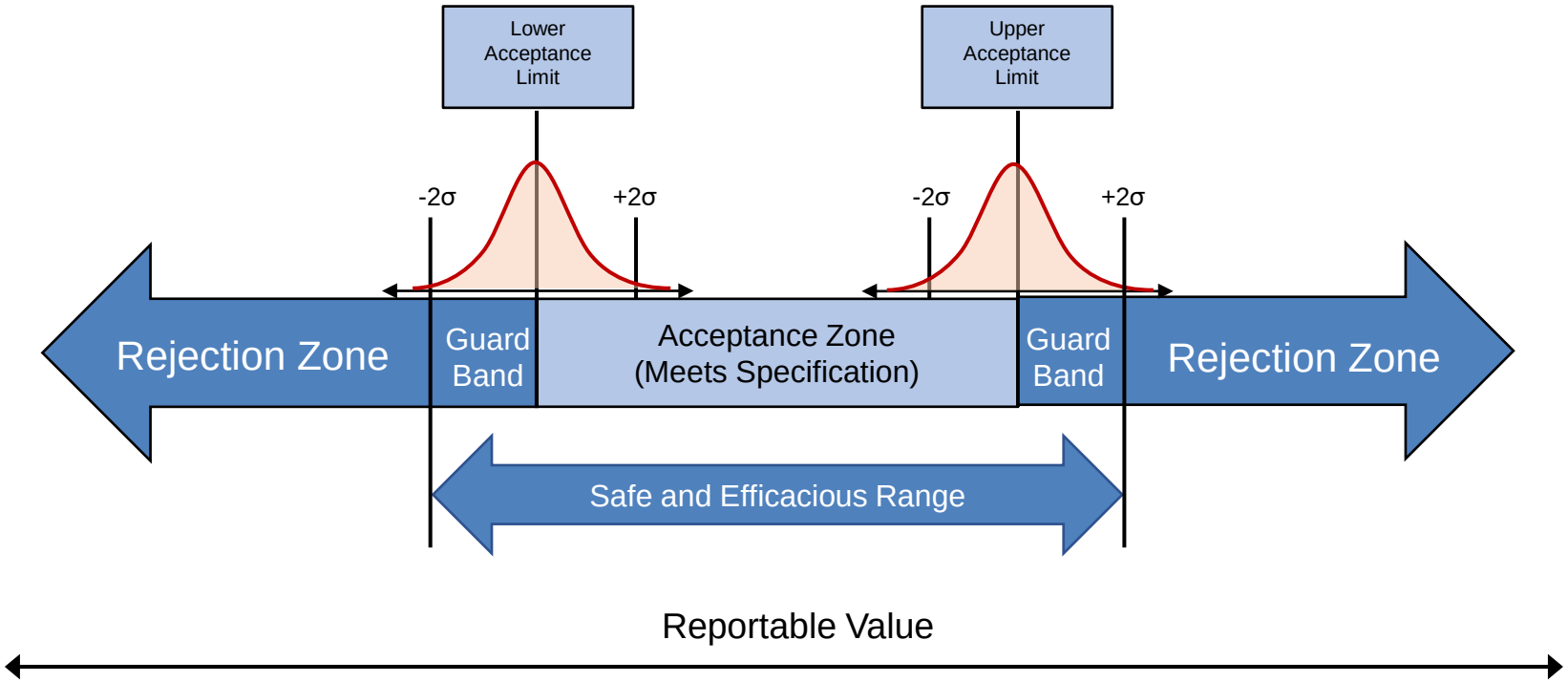
### Determining Required Precision ($\sigma_{max}$)

Tolerance Width = 4.00 (98.0 – 102.0)

Precision Width = 0.30 x 4.00 = 1.20

Split between LAL and UAL = ±0.60

**± 0.60 = ±2σ width for 95% C.I.**



# Analytical Target Profile



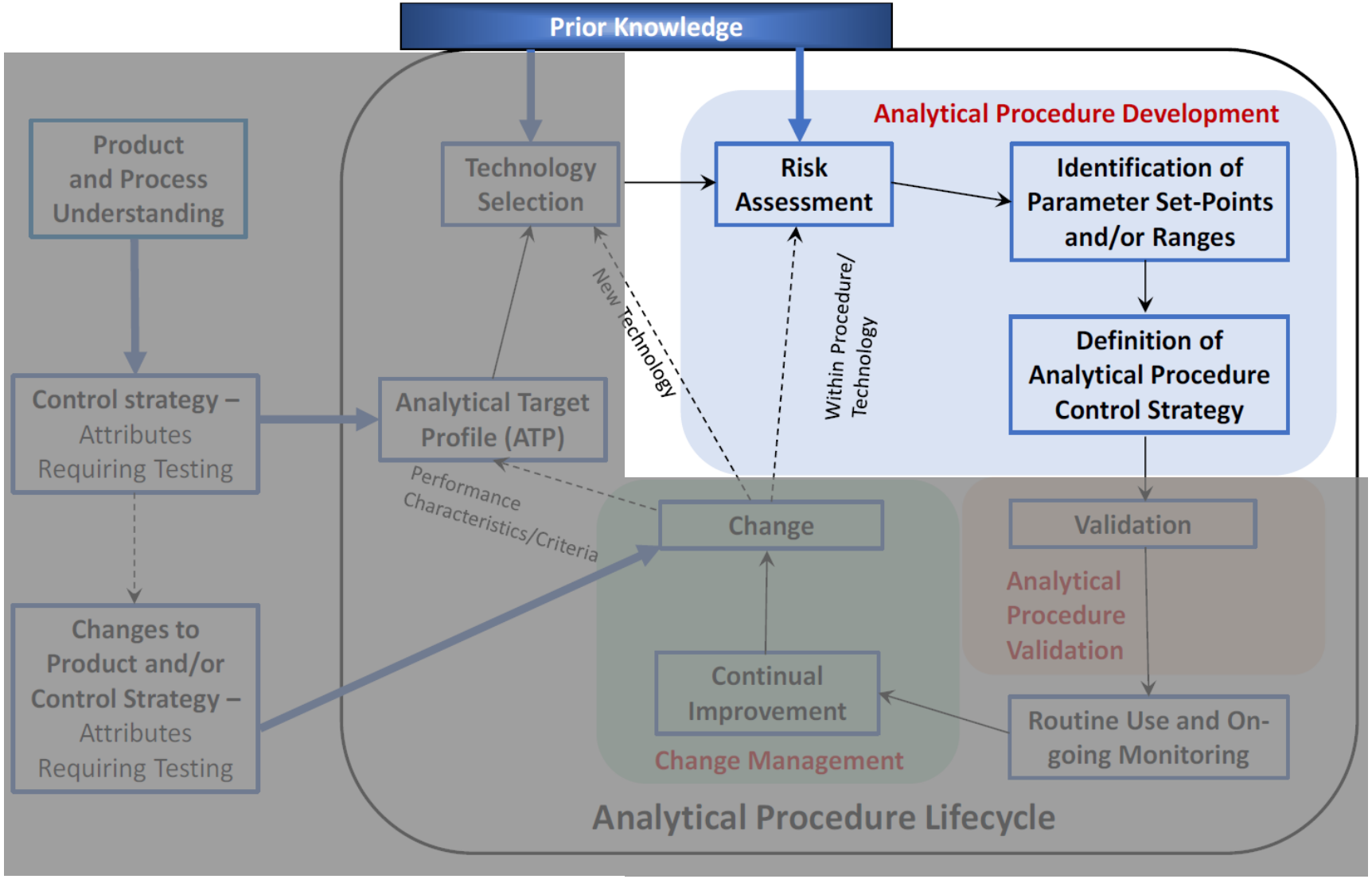
$$2\sigma_{max} = 0.60$$

## Selected Analytical Procedure = LC:

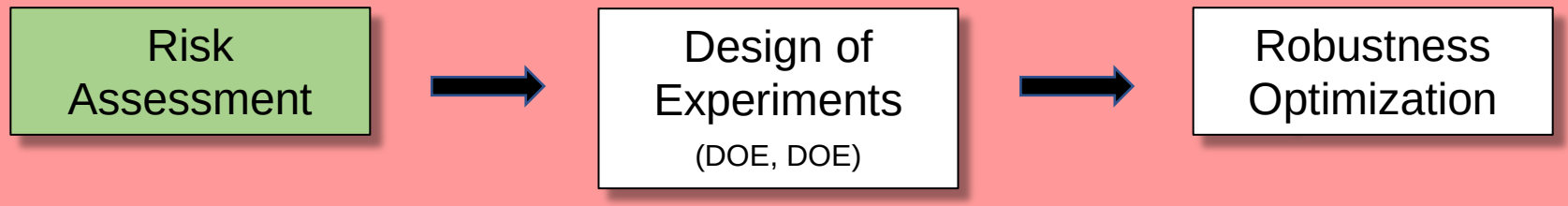
Combined Bias and Precision Allowance Becomes the ATP Quantitation Performance Metric:

- Robust Method Optimization
- Replication Strategy Optimization

# ICH Q14 – Analytical Procedure Lifecycle



# Risk Assessment




**ICH Q14**

Risk assessment and prior knowledge should be used to identify analytical procedure parameters, attributes and associated ranges to be investigated experimentally. Categorical variables (e.g., different instruments) can also be considered as part of the experimental design.

**USP <1220>**

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 modeling and/or experimentation.

# Risk Assessment – Parameter Selection

## Sources of Risk for Bias and Variation

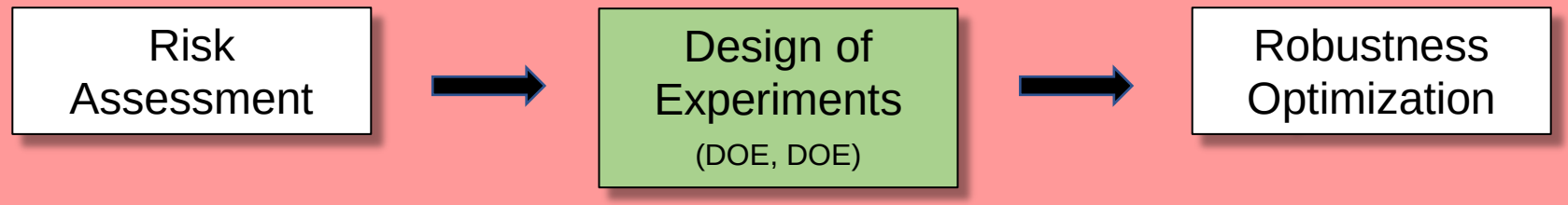
| Element | Presumed CMPs | CMAs | | | | | | Category (C, N, X) |
|---|---|---|---|---|---|---|---|---|
| | | Resolution USP | S/N | Tailing USP | Area % RSD - API | K-Prime - 1st Peak | K-Prime - Last Peak | |
| Chemistry | Column Type | 5 | 1 | 1 | 3 | 5 | 5 | X-S |
| | Strong Solvent | 5 | 1 | 1 | 3 | 5 | 5 | X-S |
| | Aqueous solvent | 5 | 5 | 5 | 1 | 5 | 5 | X-S |
| | pH | 5 | 5 | 5 | 3 | 5 | 5 | X-S-O |
| Process | Pump Flow Rate | 3 | 1 | 5 | 3 | 5 | 5 | X-O |
| | Injection Volume | 3 | 5 | 3 | 5 | 1 | 1 | C |
| | Oven Temperature | 5 | 1 | 3 | 3 | 5 | 5 | X-O |
| Gradient Program | Initial Hold Time | 1 | 1 | 1 | 1 | 5 | 1 | C-O |
| | Gradient Slope | 5 | 1 | 5 | 3 | 5 | 5 | X-S-O |
| Detection | Wavelength | 5 | 5 | 1 | 5 | 1 | 1 | C |
| | Sampling Rate | 3 | 5 | 1 | 5 | 1 | 1 | C |
| | Precision | 1 | 3 | 1 | 3 | 1 | 1 | C |

**C** = **C**ontrolled Factor, **N** = **N**oise Factor, **X** = e**X**perimental Factor (S = Screening, O = Optimization)

Impact Severity

| |
|---|
| Low = 1 |
| Medium = 3 |
| High = 5 |

# Design of Experiments (DOE, DoE)




**ICH Q14**

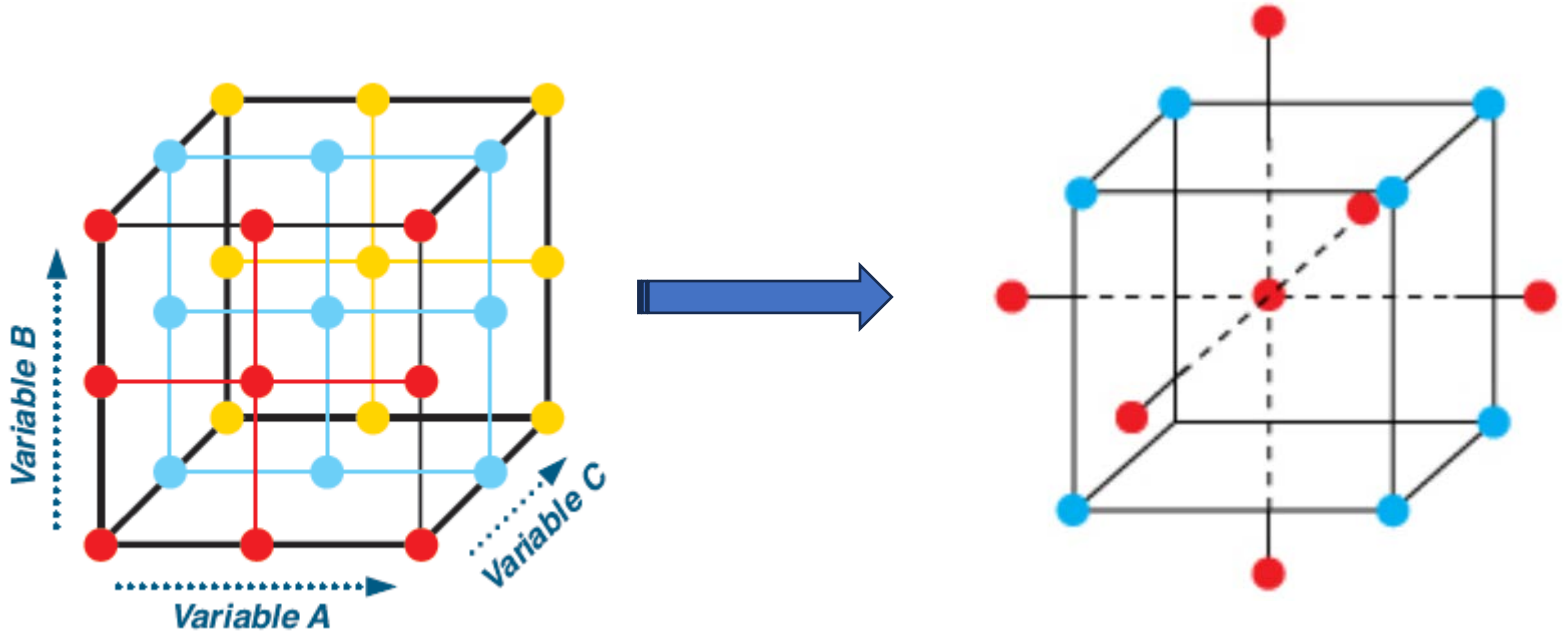
In an enhanced approach, the ranges for the relevant parameters and their interactions can be investigated in multivariate experiments (DoE).

**USP <1220>**

Experimentation is a direct way of generating data that can be used to assess the impact of procedure parameters on performance, and the use of statistical design of experiments (DOE) is an effective way to do this.

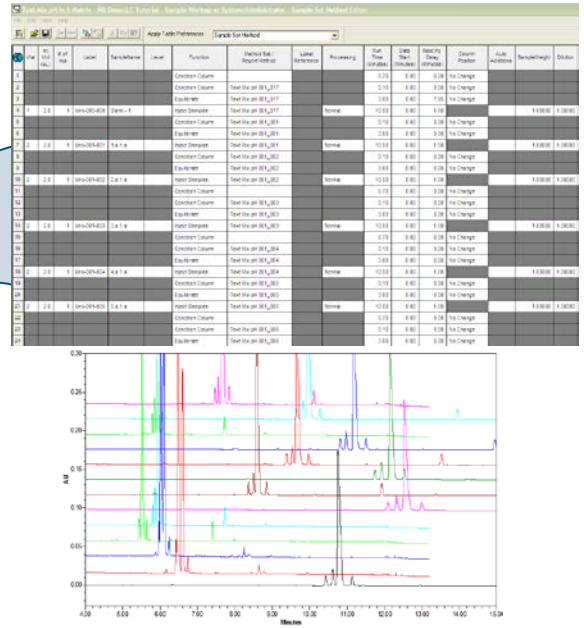
# DoE (DOE) – A Model Building Methodology

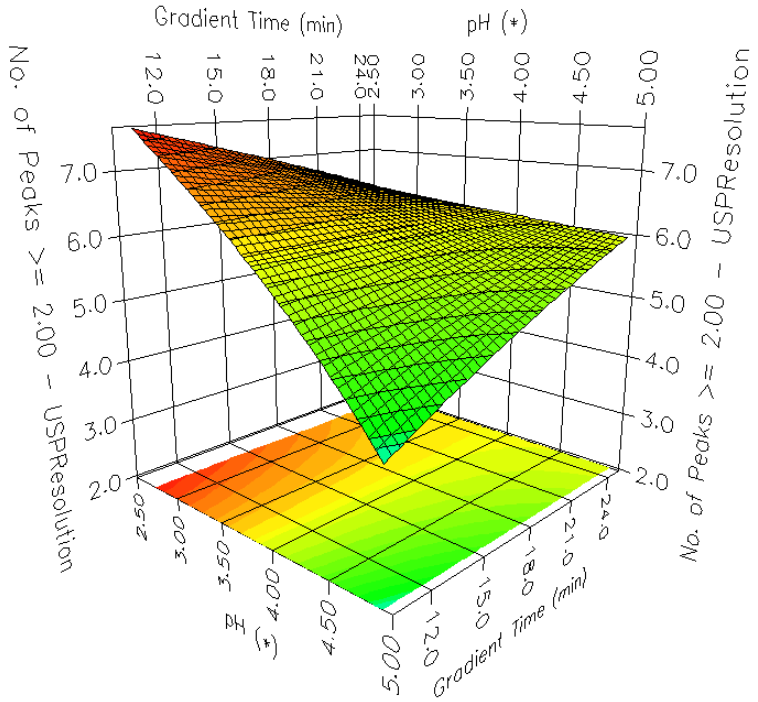
**DoE uses Statistical Sampling of All Possible Combinations to Support Accurate Estimation of Study Factor Effects**




$$R_S = b_0 + b_1(x1) + b_2(x2) + b_{11}(x1)^2 + b_{22}(x2)^2 + + b_{12}(x1 * x2)$$

# DoE (DOE) – A Model Building Methodology






$$\# - R_s \geq 2.00 = 9.3 + 4.2(PFR) - 5.4(\Delta t_G)^2 + 12.7(\Delta t_G * pH) + 1.3(pH * \Delta T) + 1.6[(\Delta T)^{2} * \Delta t_G] + \ldots$$

Linear Effect | Curvature Effect | Interaction Effects | Complex Effect

# Parameter Selection – Screening Study

| Method Parameter | Study Range |
|---|---|
| pH | 2.70 – 4.90 |
| Gradient Time (min) | 10.0 – 25.0 |
| Column Type | BEH C18<br>BEH Shield RP18<br>HSS T3<br>CSH Phenyl-Hexyl |

Prior knowledge (from original monograph) incorporated into Selected Column and Chemistry Study Factors and Range.

# Fusion QbD Experiment Automation – Export to Empower


Generates QbD-aligned DOE Experiment

Automatically Builds Sequence and All Instrument Methods

## Empower CDS

RD2 Optimization in S-Matrix\Internal Development\FMD\RD2 - Optimization - 9_9_0 as System/Administrator - Sample Set Method Editor

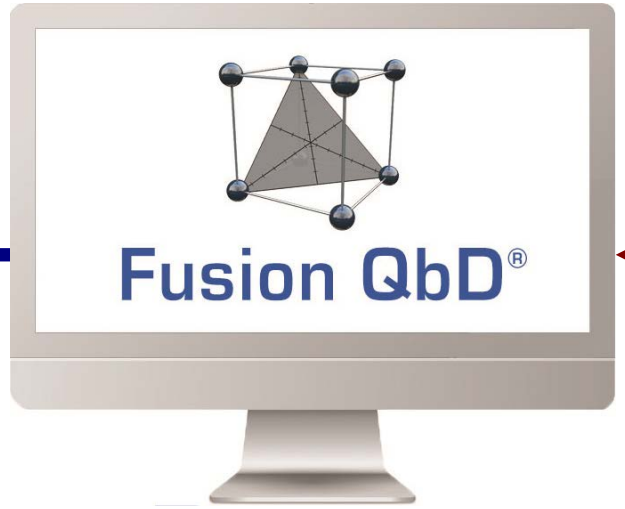
File Edit View Help

Apply Table Preferences: Sample Set Method

| | Plate/Well | Inj Vol (uL) | # of Injs | Label | SampleName | Level | Function | Method Set / Report or Export Method | Label Reference | Processing | Run Time (Minutes) | Data Start (Minutes) | Next Inj. Delay (Minutes) | MS Tune Method | MS Calibration Method | Column Position | Auto Additions | SampleWeight | Dilution |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | Condition Column | RD2 Optimization 001_031 | | | 6.60 | | | | | Position 5 | | | |
| 2 | | | | | | | Equilibrate | RD2 Optimization 001_001 | | | 4.00 | | | | | No Change | | | |
| 3 | 1:A,1 | 2.0 | 1 | Unk-001-001 | 1 | | Inject Samples | RD2 Optimization 001_001 | | Normal | 17.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 4 | | | | | | | Equilibrate | RD2 Optimization 001_002 | | | 4.00 | | | | | No Change | | | |
| 5 | 1:A,1 | 2.0 | 1 | Unk-001-002 | 2 | | Inject Samples | RD2 Optimization 001_002 | | Normal | 9.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 6 | | | | | | | Equilibrate | RD2 Optimization 001_003 | | | 4.00 | | | | | No Change | | | |
| 7 | 1:A,1 | 2.0 | 1 | Unk-001-003 | 3 | | Inject Samples | RD2 Optimization 001_003 | | Normal | 17.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 8 | | | | | | | Equilibrate | RD2 Optimization 001_004 | | | 4.00 | | | | | No Change | | | |
| 9 | 1:A,1 | 2.0 | 1 | Unk-001-004 | 4 | | Inject Samples | RD2 Optimization 001_004 | | Normal | 9.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 10 | | | | | | | Equilibrate | RD2 Optimization 001_005 | | | 4.00 | | | | | No Change | | | |
| 11 | 1:A,1 | 2.0 | 1 | Unk-001-005 | 5 | | Inject Samples | RD2 Optimization 001_005 | | Normal | 9.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 12 | | | | | | | Equilibrate | RD2 Optimization 001_006 | | | 4.00 | | | | | No Change | | | |
| 13 | 1:A,1 | 2.0 | 1 | Unk-001-006 | 6 | | Inject Samples | RD2 Optimization 001_006 | | Normal | 9.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 14 | | | | | | | Equilibrate | RD2 Optimization 001_007 | | | 4.00 | | | | | No Change | | | |
| 15 | 1:A,1 | 2.0 | 1 | Unk-001-007 | 7 | | Inject Samples | RD2 Optimization 001_007 | | Normal | 17.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 16 | | | | | | | Condition Column | RD2 Optimization 001_032 | | | 6.60 | | | | | Position 5 | | | |
| 17 | | | | | | | Equilibrate | RD2 Optimization 001_008 | | | 4.00 | | | | | No Change | | | |
| 18 | 1:A,1 | 2.0 | 1 | Unk-001-008 | 8 | | Inject Samples | RD2 Optimization 001_008 | | Normal | 13.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 19 | | | | | | | Condition Column | RD2 Optimization 001_033 | | | 6.60 | | | | | Position 5 | | | |
| 20 | | | | | | | Equilibrate | RD2 Optimization 001_009 | | | 4.00 | | | | | No Change | | | |
| 21 | 1:A,1 | 2.0 | 1 | Unk-001-009 | 9 | | Inject Samples | RD2 Optimization 001_009 | | Normal | 9.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 22 | | | | | | | Equilibrate | RD2 Optimization 001_010 | | | 4.00 | | | | | No Change | | | |
| 23 | 1:A,1 | 2.0 | 1 | Unk-001-010 | 10 | | Inject Samples | RD2 Optimization 001_010 | | Normal | 9.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 24 | | | | | | | Equilibrate | RD2 Optimization 001_011 | | | 4.00 | | | | | No Change | | | |
| 25 | 1:A,1 | 2.0 | 1 | Unk-001-011 | 11 | | Inject Samples | RD2 Optimization 001_011 | | Normal | 17.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 26 | | | | | | | Equilibrate | RD2 Optimization 001_012 | | | 4.00 | | | | | No Change | | | |
| 27 | 1:A,1 | 2.0 | 1 | Unk-001-012 | 12 | | Inject Samples | RD2 Optimization 001_012 | | Normal | 17.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 28 | | | | | | | Condition Column | RD2 Optimization 001_034 | | | 6.60 | | | | | Position 5 | | | |
| 29 | | | | | | | Equilibrate | RD2 Optimization 001_013 | | | 4.00 | | | | | No Change | | | |
| 30 | 1:A,1 | 2.0 | 1 | Unk-001-013 | 13 | | Inject Samples | RD2 Optimization 001_013 | | Normal | 13.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 31 | | | | | | | Condition Column | RD2 Optimization 001_035 | | | 6.60 | | | | | Position 5 | | | |
| 32 | | | | | | | Equilibrate | RD2 Optimization 001_014 | | | 4.00 | | | | | No Change | | | |
| 33 | 1:A,1 | 2.0 | 1 | Unk-001-014 | 14 | | Inject Samples | RD2 Optimization 001_014 | | Normal | 13.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 34 | | | | | | | Equilibrate | RD2 Optimization 001_015 | | | 4.00 | | | | | No Change | | | |
| 35 | 1:A,1 | 2.0 | 1 | Unk-001-015 | 15 | | Inject Samples | RD2 Optimization 001_015 | | Normal | 13.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 36 | | | | | | | Equilibrate | RD2 Optimization 001_016 | | | 4.00 | | | | | No Change | | | |
| 37 | 1:A,1 | 2.0 | 1 | Unk-001-016 | 16 | | Inject Samples | RD2 Optimization 001_016 | | Normal | 9.60 | 0.00 | 3.50 | | | | | 1.00000 | 1.00000 |
| 38 | | | | | | | Equilibrate | RD2 Optimization 001_017 | | | 4.00 | | | | | No Change | | | |

For Help, press F1

# Fusion QbD Experiment Automation – Import from Empower



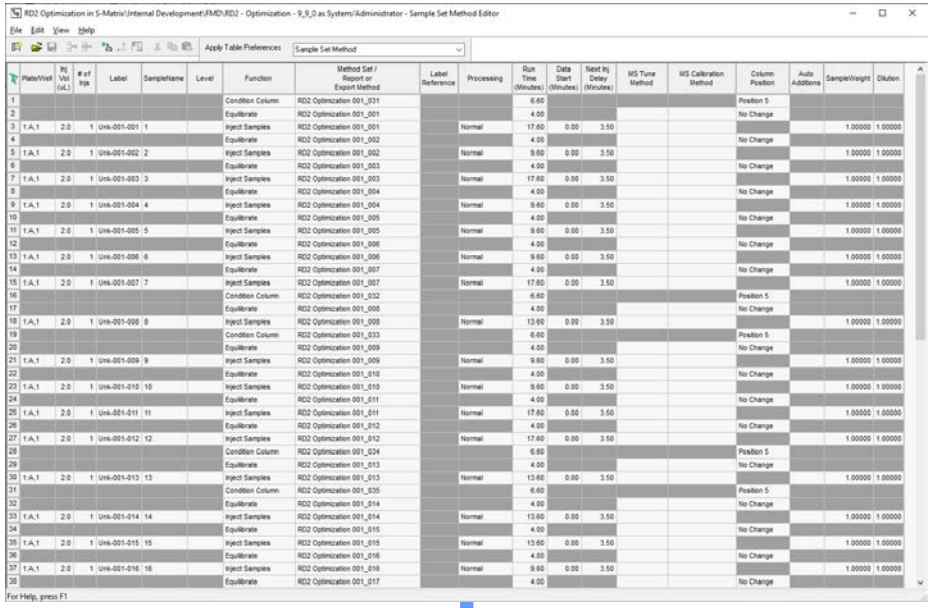

Automatically Retrieves All Chromatogram Results Data

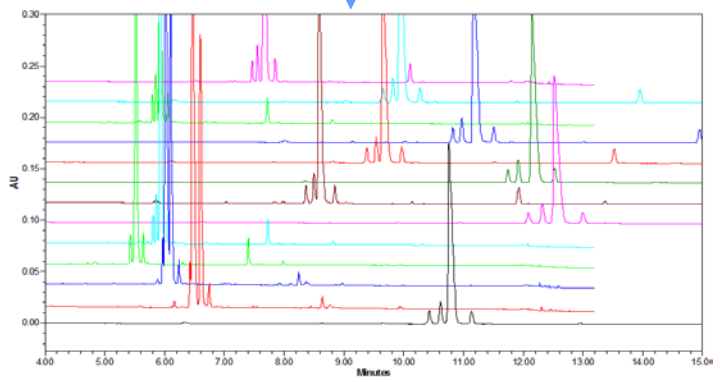
Automated analysis, graphing, and reporting.

Report formats:

RTF, DOC, HTML, PDF, XLSX, XML

## Empower CDS



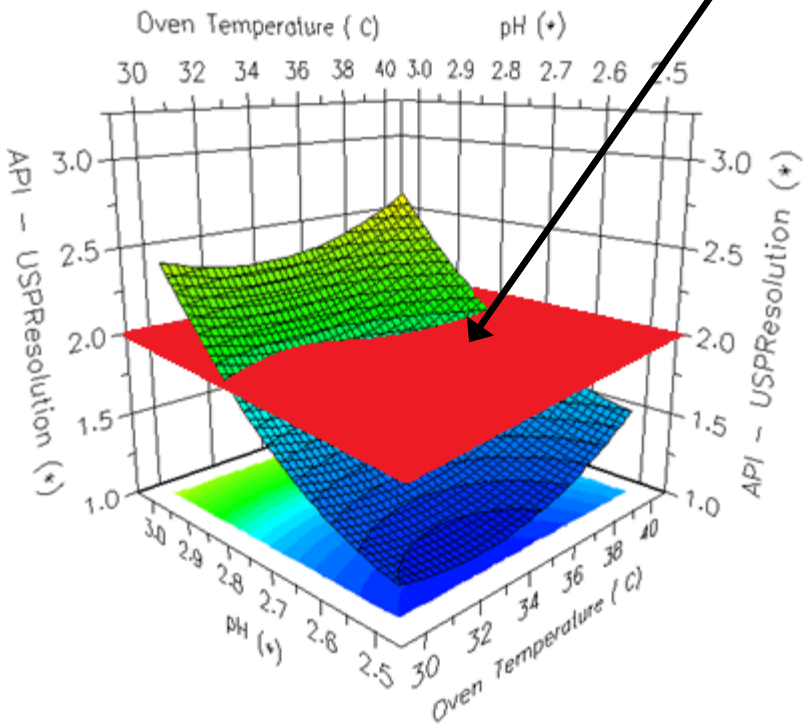


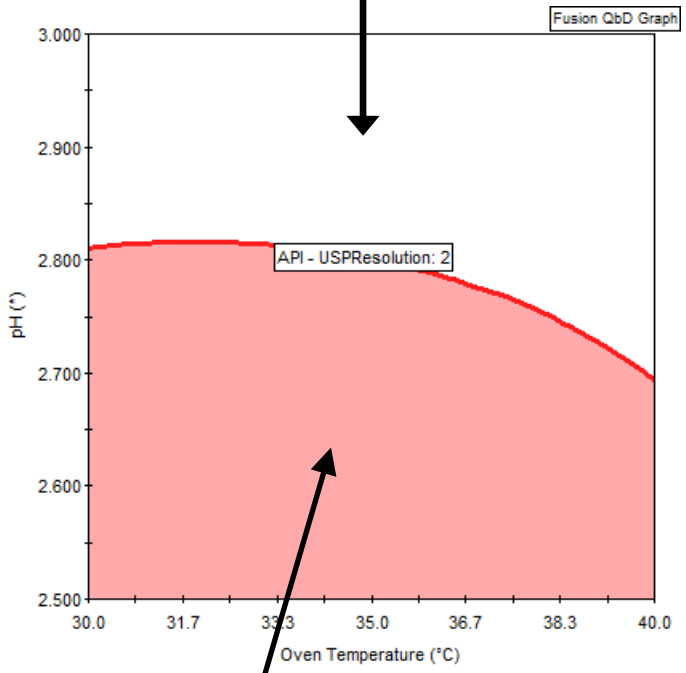
# Screening Study – Simple Analysis

Quantitative Knowledge

Required Performance Threshold

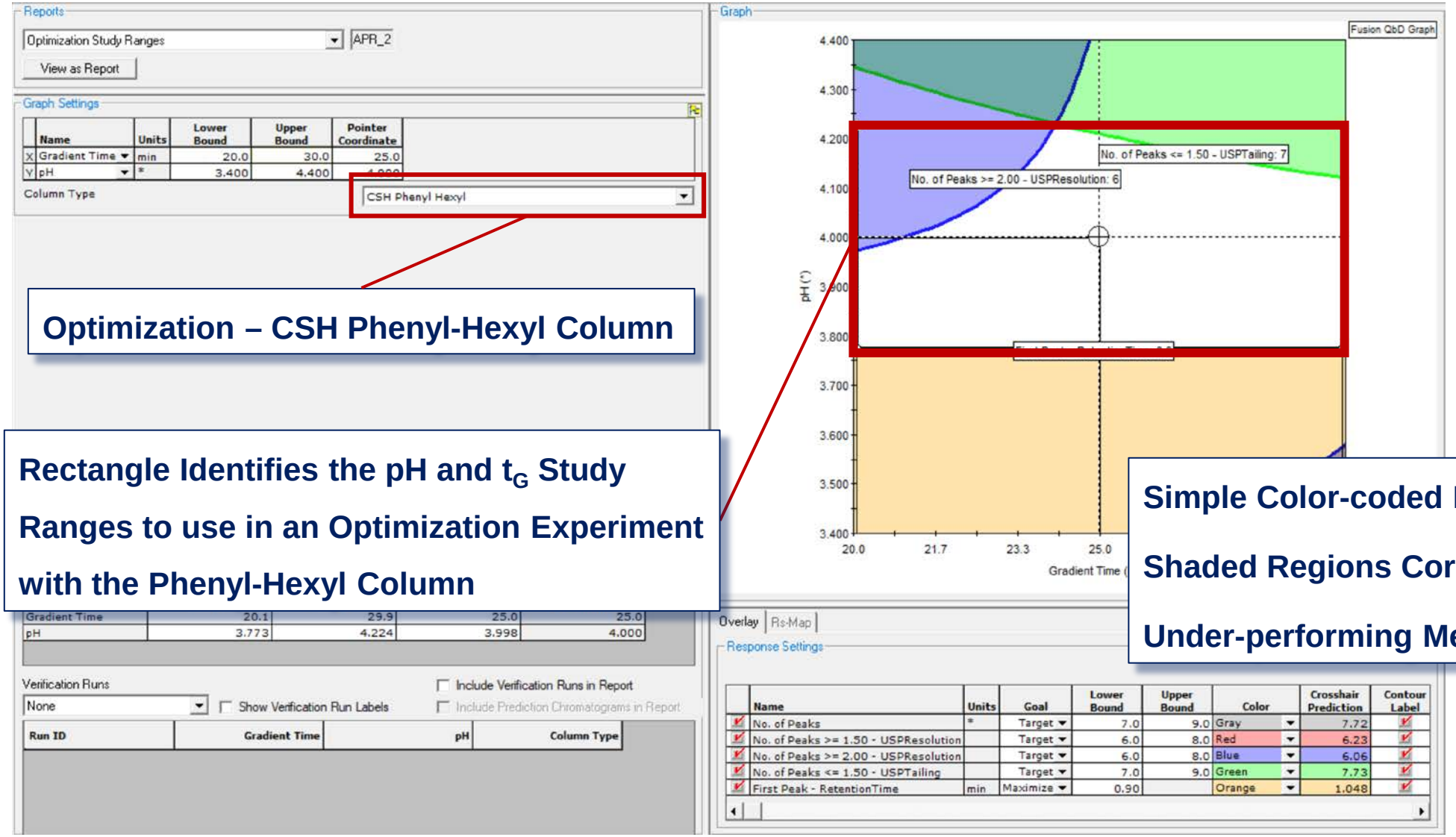
Region of Acceptable Performance **– One Response**




**Shaded region** = methods that **do NOT meet** performance requirements.

# Screening Study – Simple Analysis




**Optimization – CSH Phenyl-Hexyl Column**

**Rectangle Identifies the pH and $t_G$ Study Ranges to use in an Optimization Experiment with the Phenyl-Hexyl Column**

**Simple Color-coded Responses. Shaded Regions Correspond to Under-performing Methods**

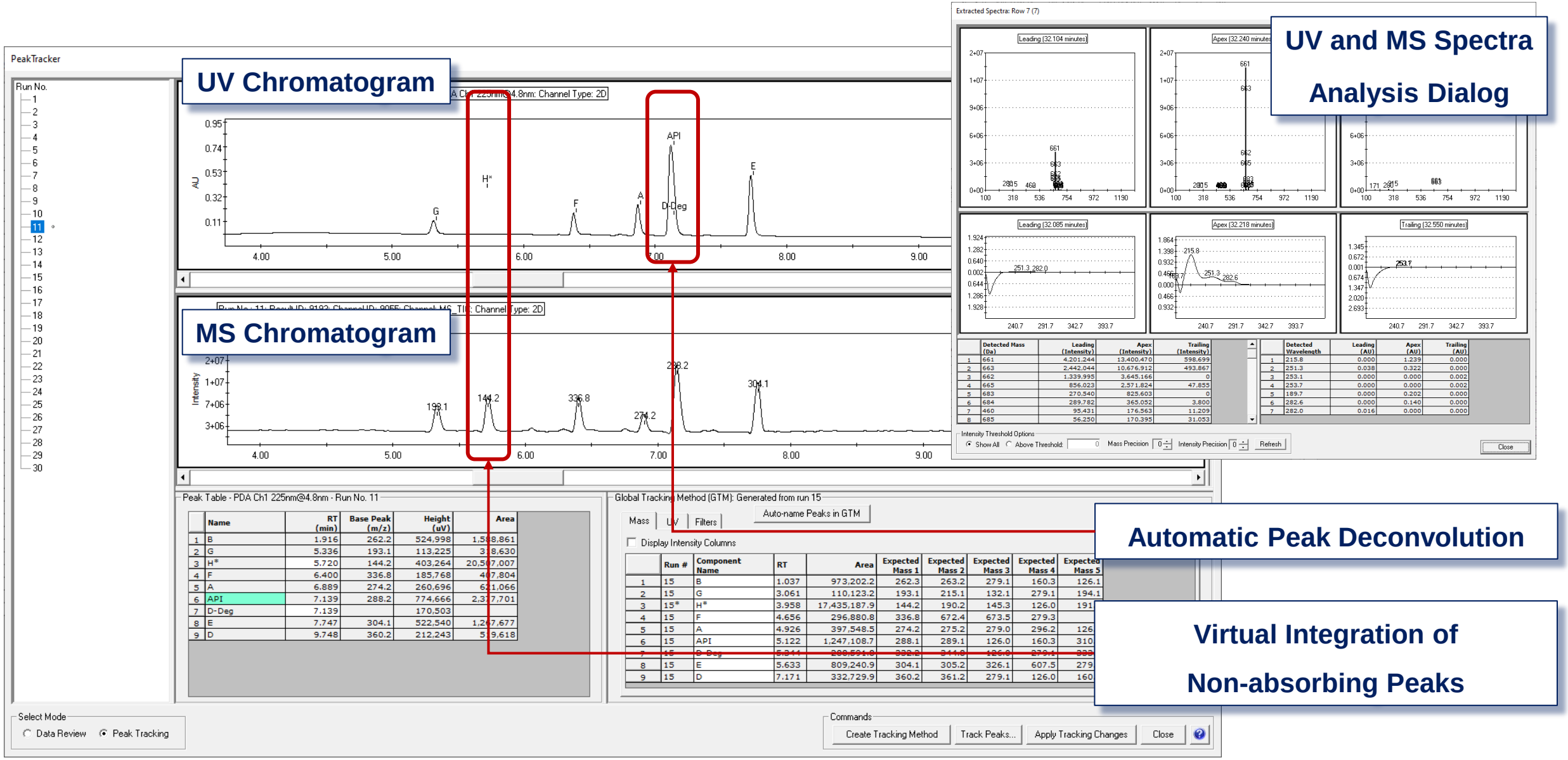
# Parameter Selection – Optimization Study

| Method Parameter | Study Range |
|---|---|
| Pump Flow Rate (mL/min) | 0.35 – 0.55 |
| Column Oven Temperature (°C) | 40.0 – 50.0 |
| Gradient Time (min)* | 8.0 – 16.0 |
| pH | 3.60 – 4.20 |
| Column Type | CSH Phenyl-Hexyl |

Light green background color indicates result obtained from screening study.

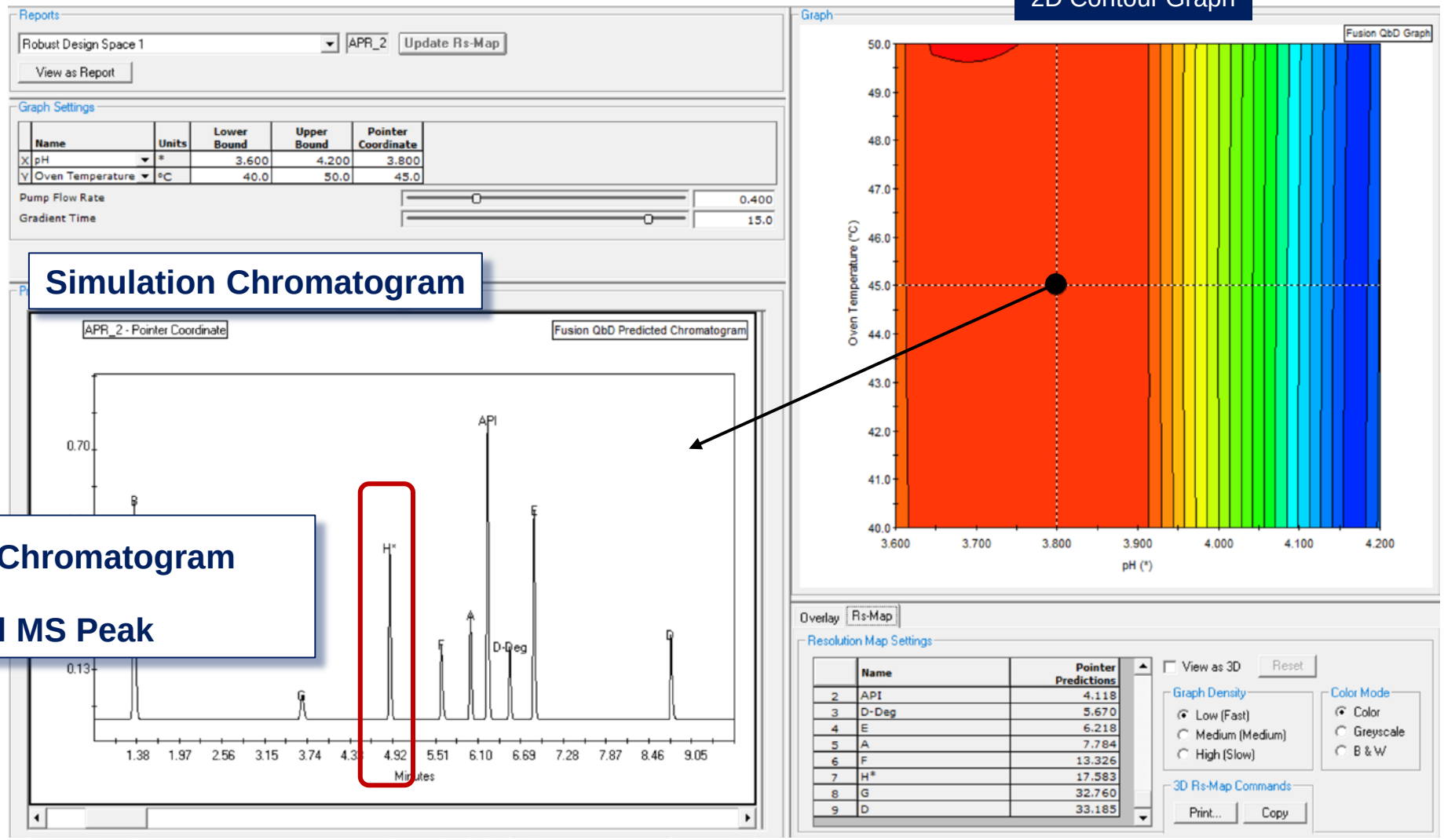
* – $t_G$ range adjusted to maintain slope range with new endpoint of 50% ACN.

# PeakTracker™ – UV & MS Data Based Tracking



# Traditional Resolution Map – 2D

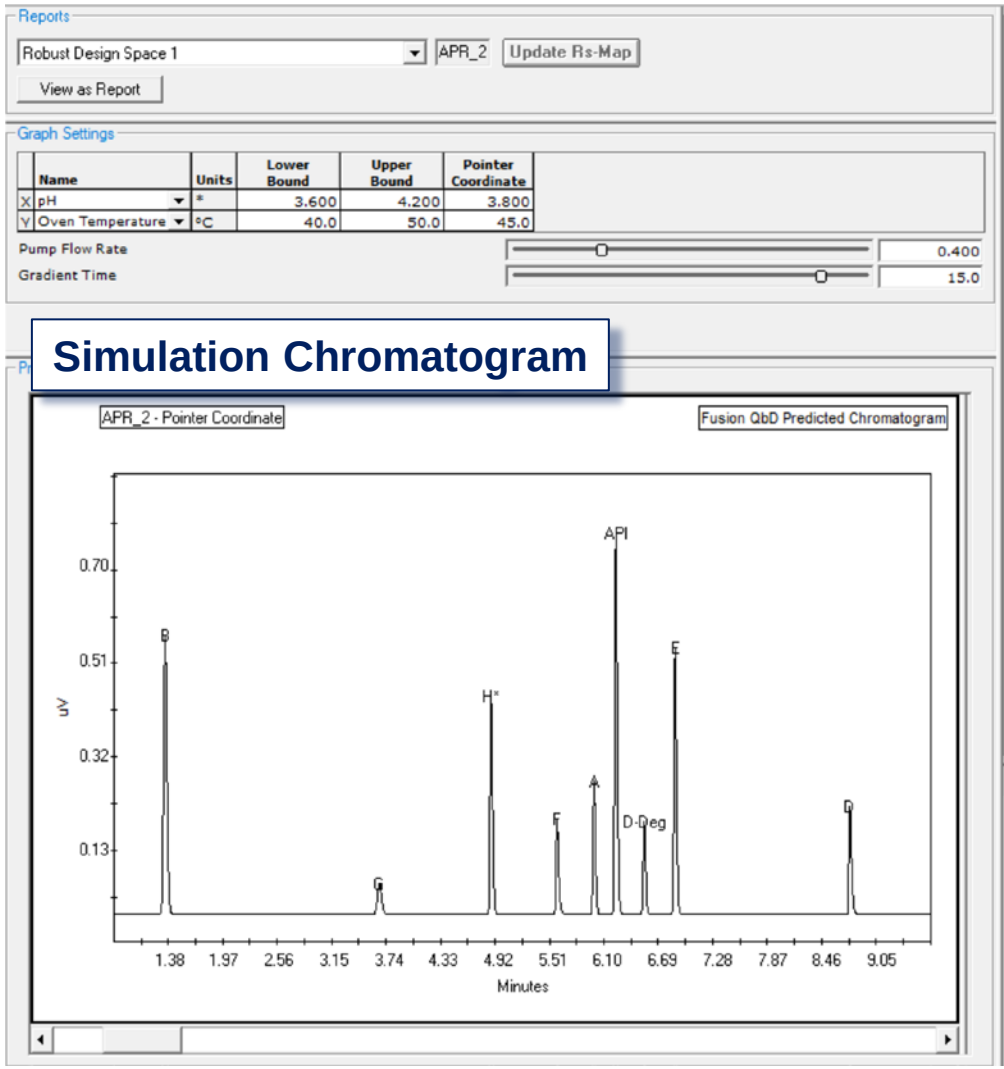
2D Contour Graph

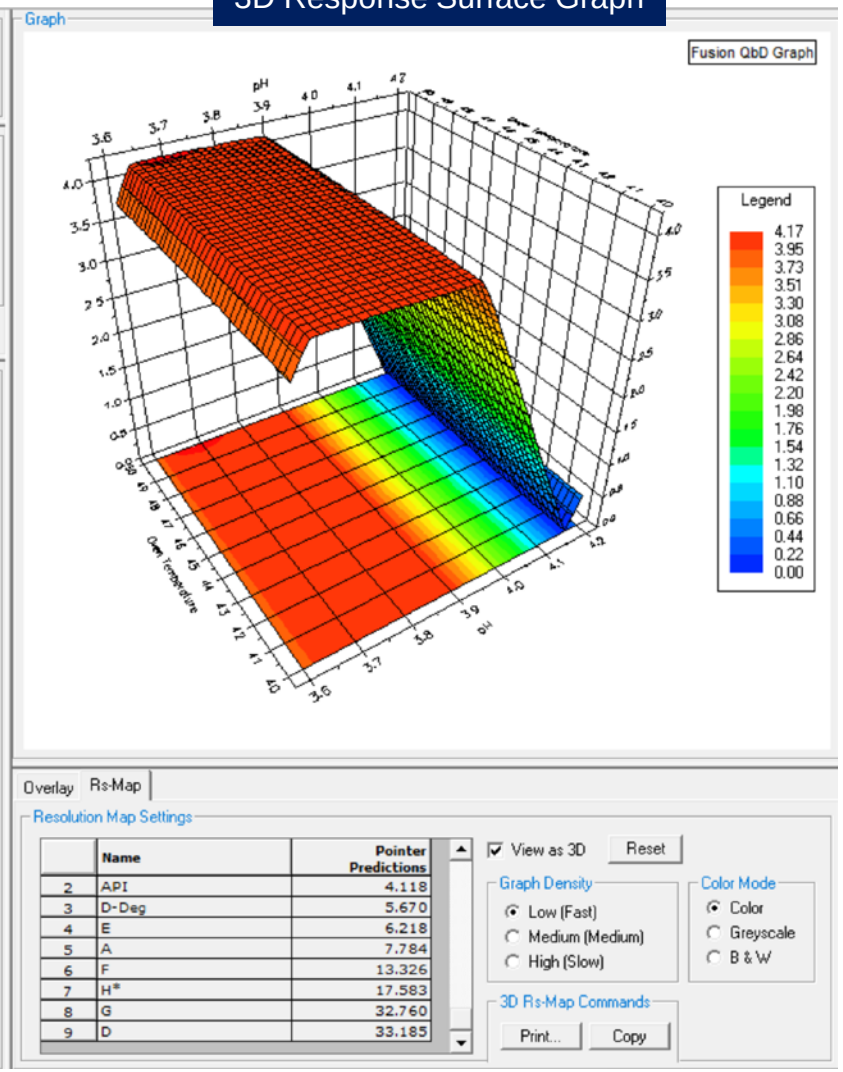



**Composite UV Chromatogram**

**Includes Virtual MS Peak**

# Resolution Map – Rotatable 3D

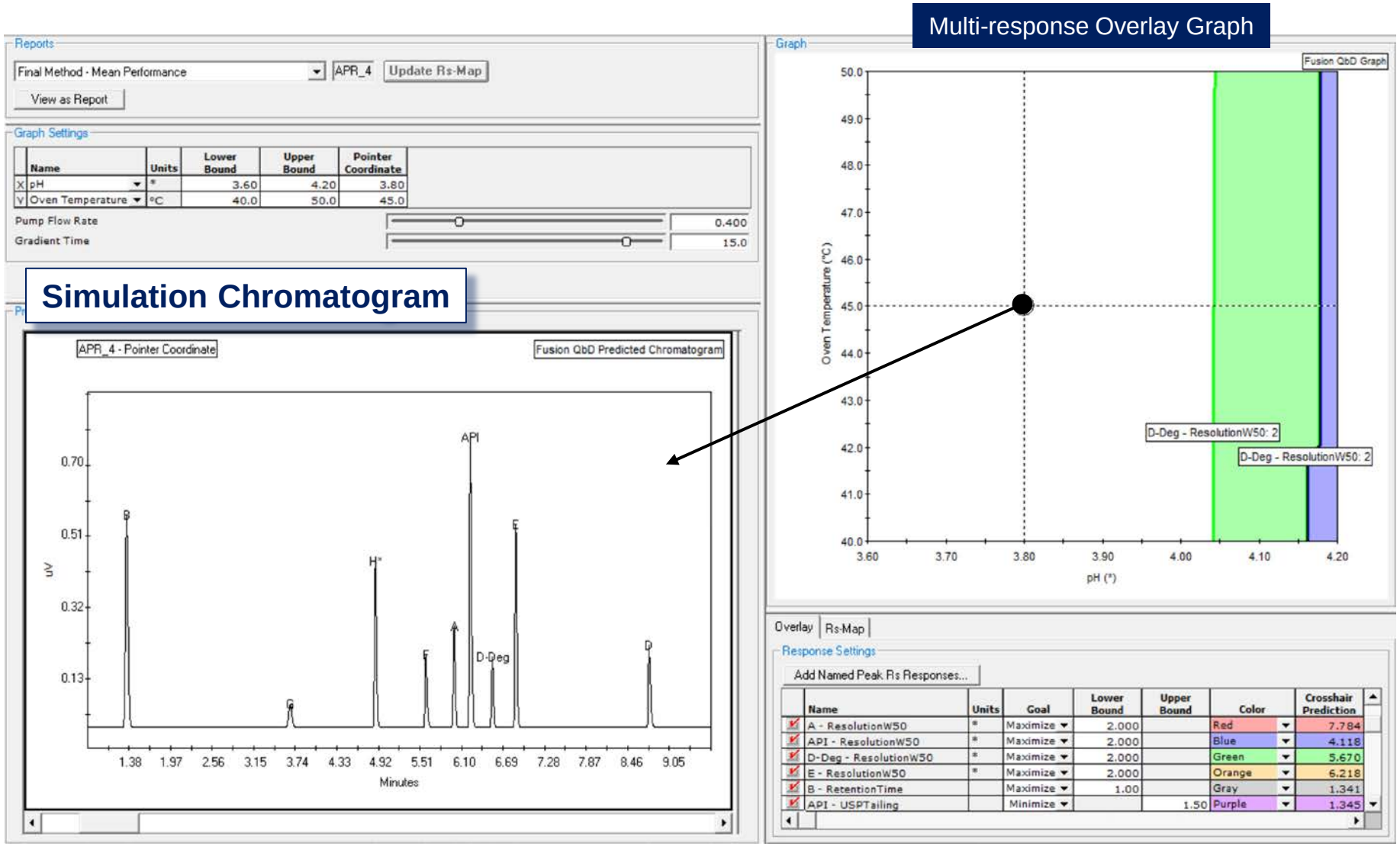


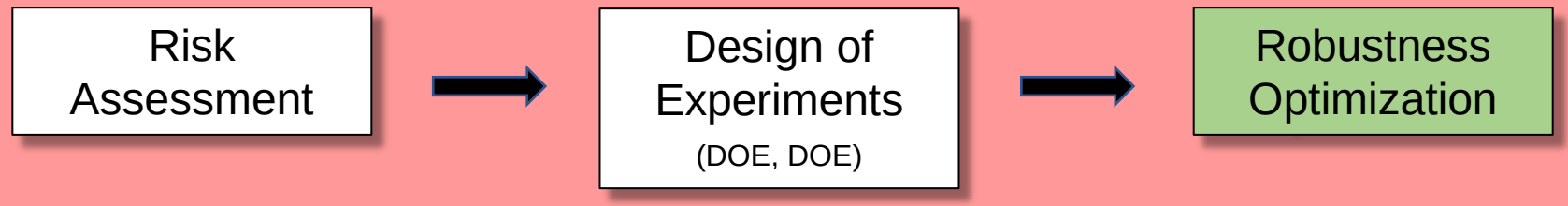
# Mean Performance Only MODR – Overlay

## Mean Performance:

- Resolution
- K-Prime
- Tailing
- Area %RSD
- Etc.



# Integrated Robustness Simulation




## ICH Q14

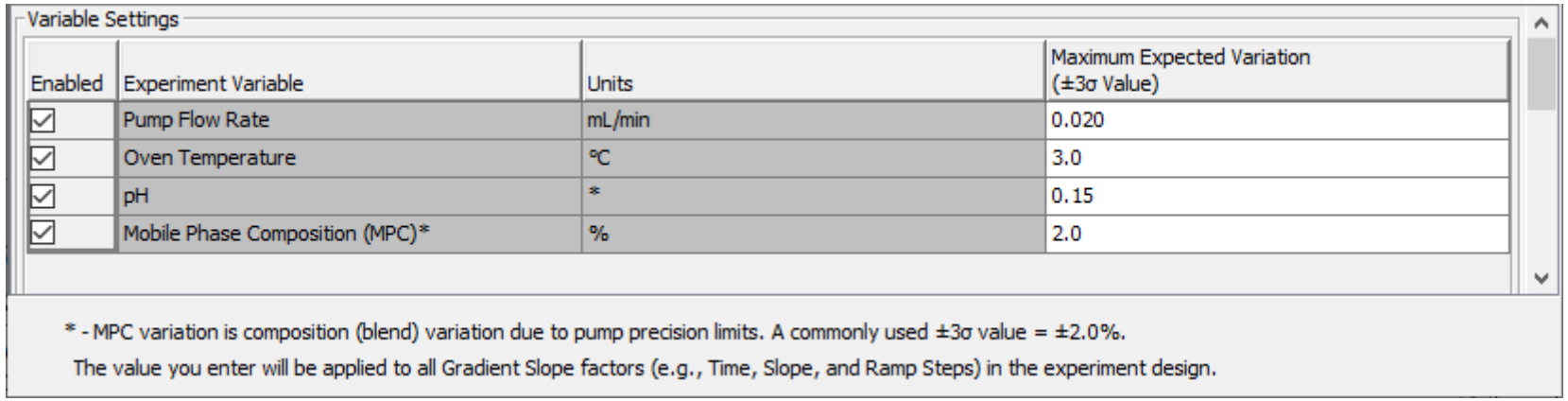
Data gained during the development studies (e.g., robustness data from a design of experiments (DoE) study) could be used as part of the validation data for the related analytical procedure performance characteristics and studies do not necessarily need to be repeated.

## USP <1220>

In some cases, it is helpful to demonstrate robustness of the procedure by developing models that describe the effect of parameters on the performance of the procedure, … This knowledge also enables the determination of robust operation regions for procedure parameters and, if desired, a method operable design region (MODR).

# Monte Carlo Robustness Simulation

## Wizard Page 1 – Define Maximum Expected Variation in Study Parameters



Variable Settings

| Enabled | Experiment Variable | Units | Maximum Expected Variation (±3σ Value) |
|---|---|---|---|
| ☑ | Pump Flow Rate | mL/min | 0.020 |
| ☑ | Oven Temperature | °C | 3.0 |
| ☑ | pH | * | 0.15 |
| ☑ | Mobile Phase Composition (MPC)* | % | 2.0 |

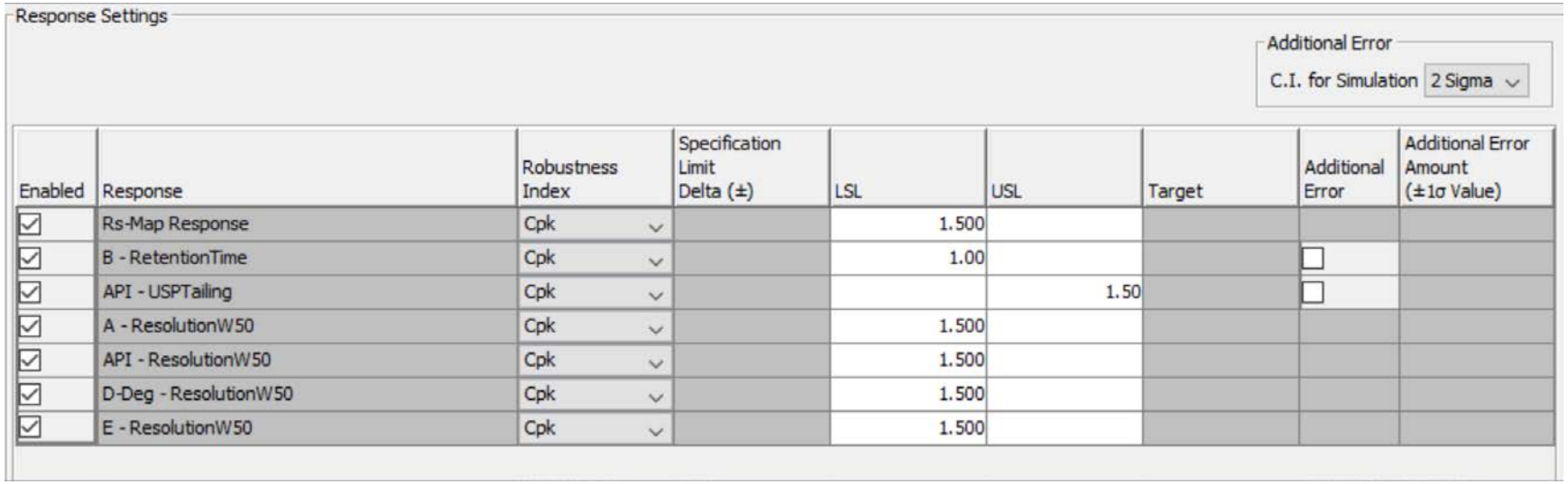
* - MPC variation is composition (blend) variation due to pump precision limits. A commonly used ±3σ value = ±2.0%.
The value you enter will be applied to all Gradient Slope factors (e.g., Time, Slope, and Ramp Steps) in the experiment design.

**Go beyond development LC system**

**expected variation in QC lab across LC systems during routine use.**

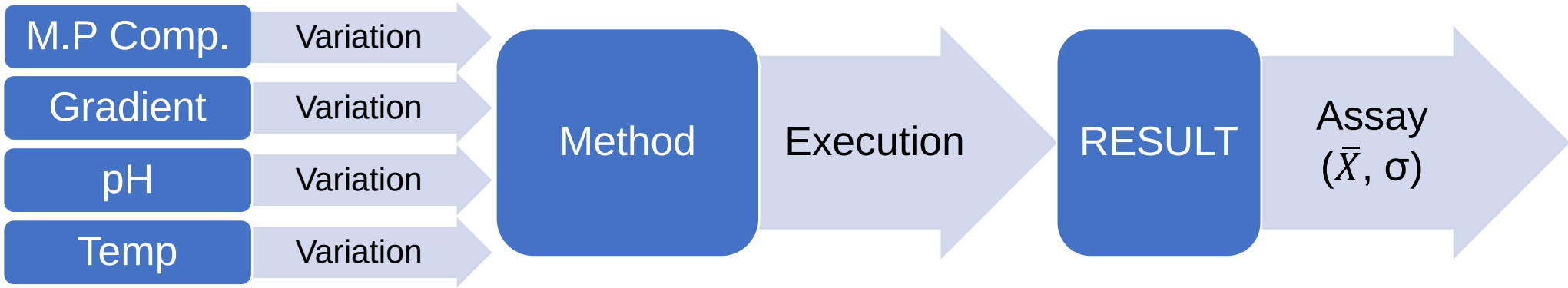
# Monte Carlo Robustness Simulation

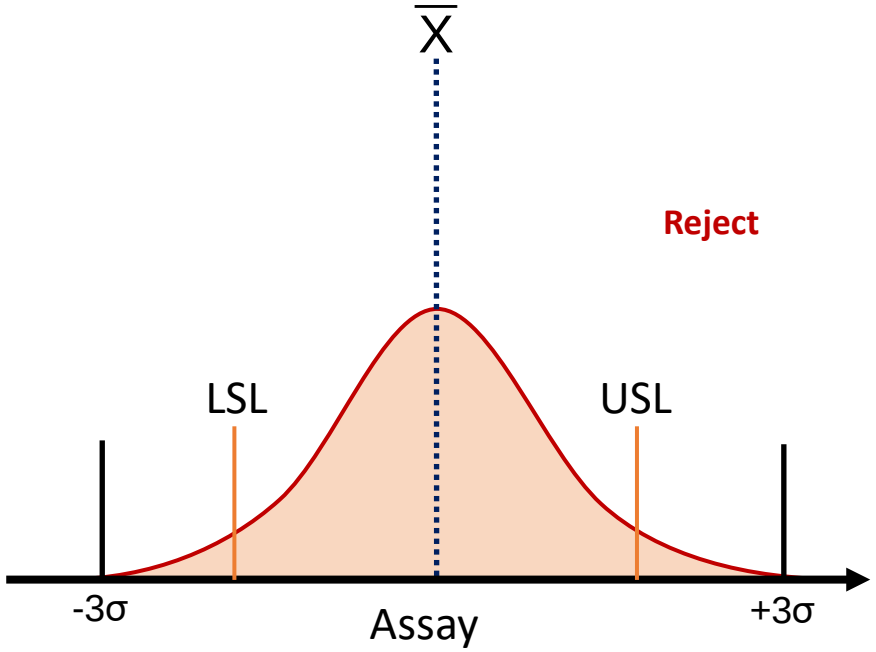
## Wizard Page 2 – Define Failure Mode and Spec Limits

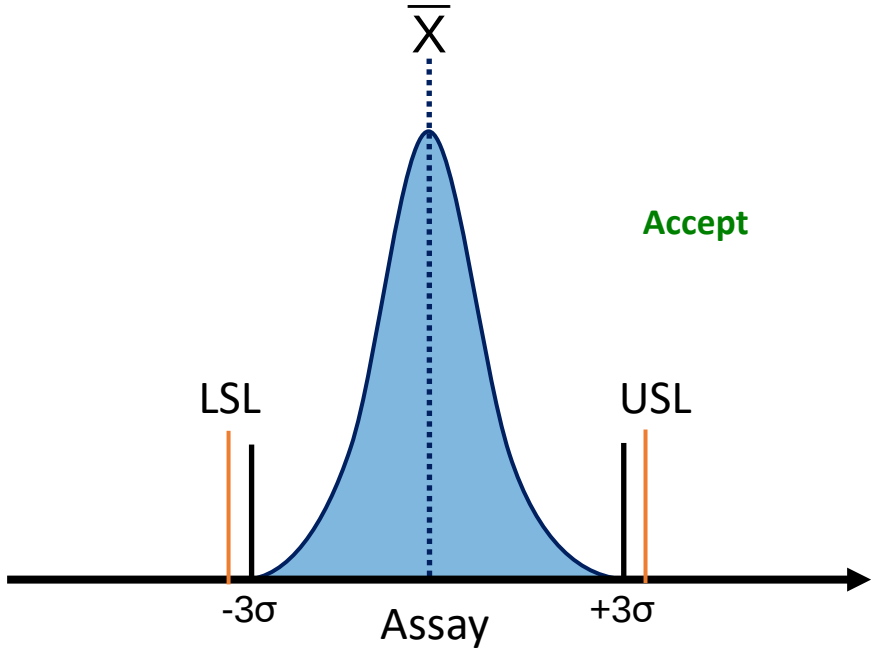



| Enabled | Response | Robustness Index | Specification Limit Delta (±) | LSL | USL | Target | Additional Error | Additional Error Amount (±1σ Value) |
|---|---|---|---|---|---|---|---|---|
| ☑ | Rs-Map Response | Cpk | | 1.500 | | | | |
| ☑ | B - RetentionTime | Cpk | | 1.00 | | | ☐ | |
| ☑ | API - USPTailing | Cpk | | | 1.50 | | ☐ | |
| ☑ | A - ResolutionW50 | Cpk | | 1.500 | | | | |
| ☑ | API - ResolutionW50 | Cpk | | 1.500 | | | | |
| ☑ | D-Deg - ResolutionW50 | Cpk | | 1.500 | | | | |
| ☑ | E - ResolutionW50 | Cpk | | 1.500 | | | | |

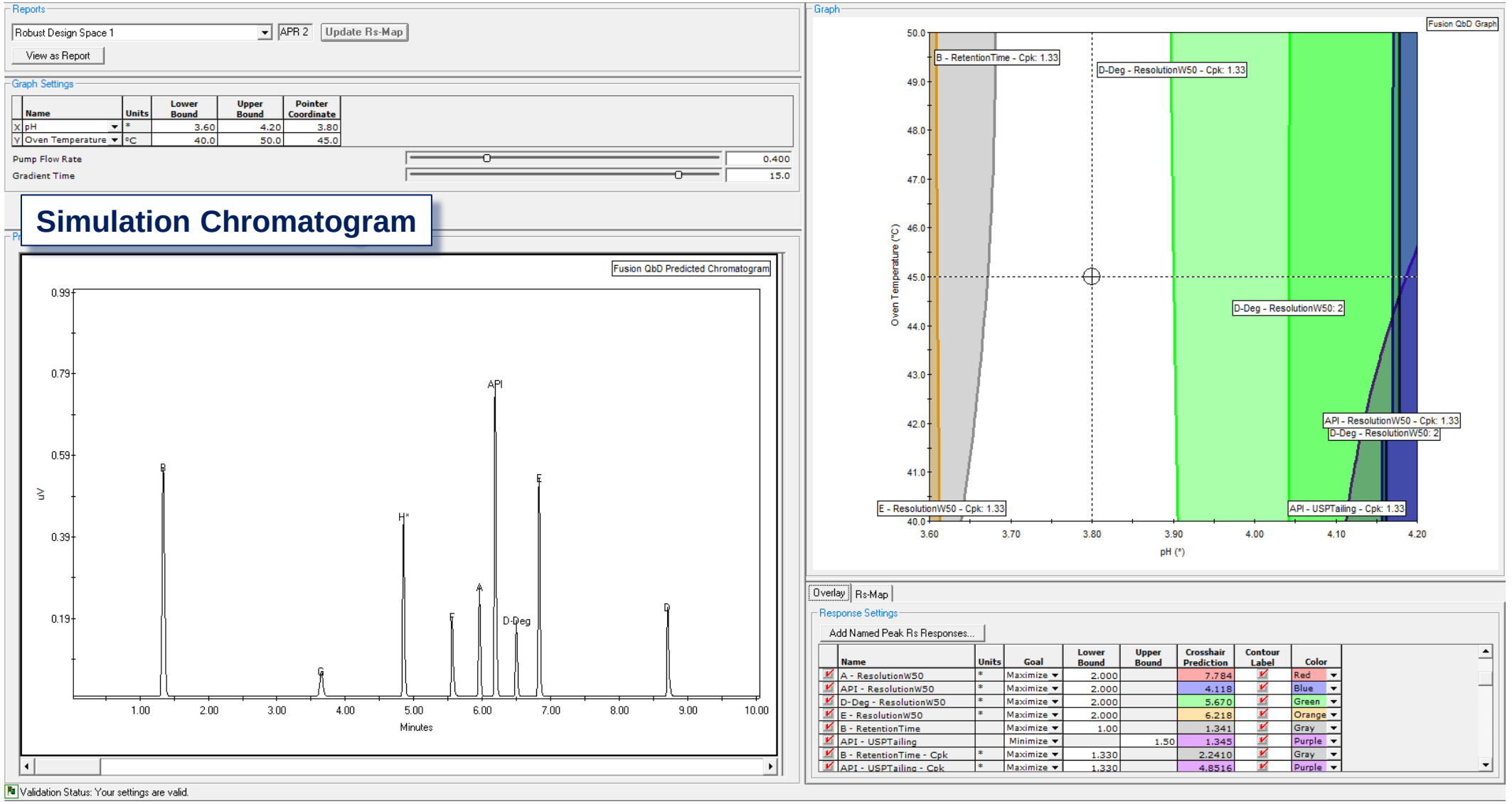
# Monte Carlo Robustness Simulation



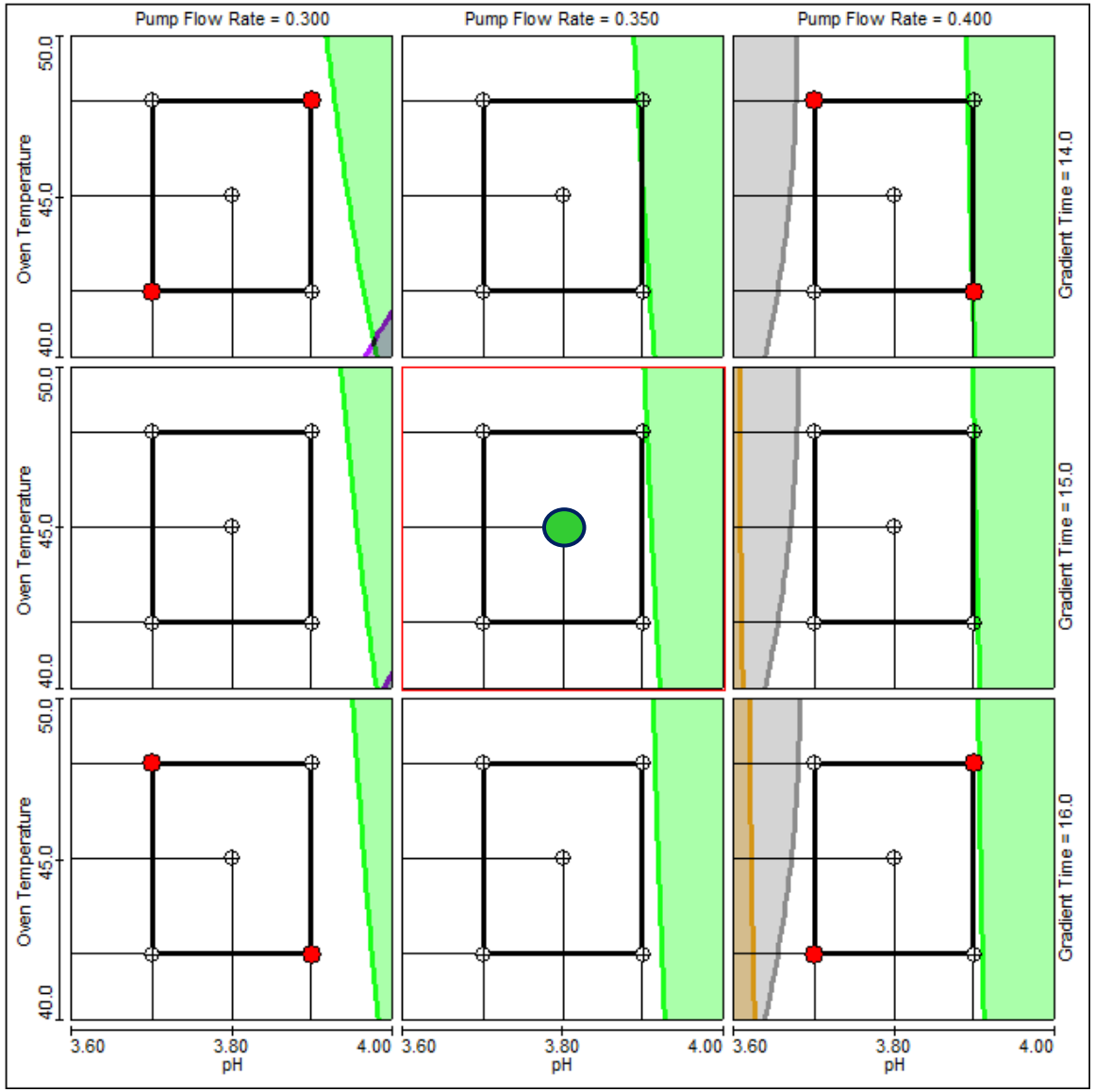
# Multi-Response Overlay View



# Robustness and MODR – 4-factor Trellis

## 4-Factor Method Operable Design Region (MODR).

- MODR (unshaded region) – methods are robust for all CQAs.
- Rectangle – independently adjustable ranges within which permanent post-approval changes can be made while maintaining robust performance for all CQAs.



# Replication Strategy Optimization

Robust Final LC Method → Replication Strategy Optimization → APLM Stage 2

**ICH Q14**

**Reportable Result**: the result as generated by the analytical procedure after calculation or processing and applying the described sample replication. *(ICH Q2)*

**ICH Q2(R2)**

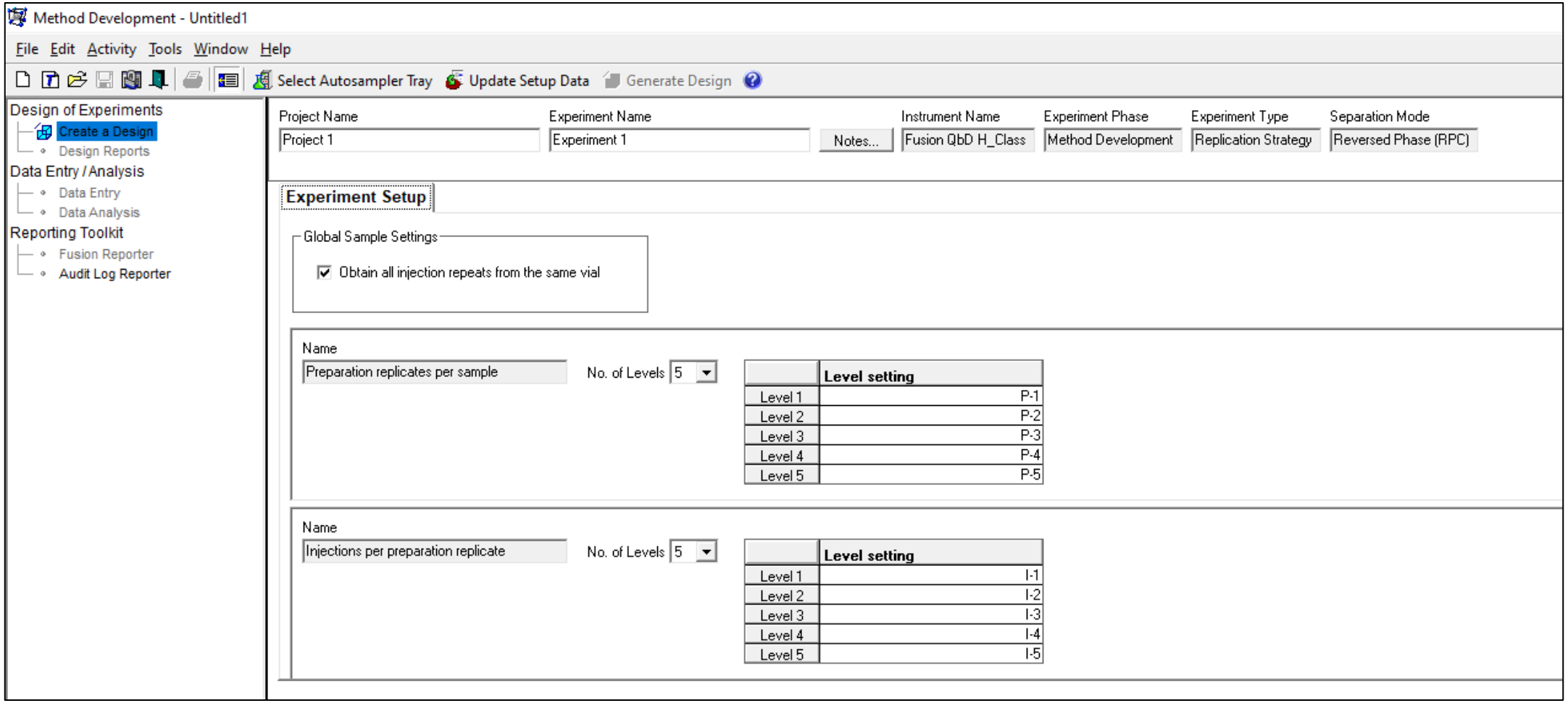
The experimental design of the validation study should reflect the number of replicates used in routine analysis to generate a reportable result.

**USP <1220>**

Stage 1:

Optimization of performance characteristics of the analytical procedure such as accuracy, precision, …; this includes a preliminary replication strategy for samples and standards.

# Replication Strategy for the Reportable Value



# TAE and Guard Bands

## Production: Amount of Precision-to-Tolerance (P/T) Ratio Available for the Analytical Method

- API method has a tolerance range of 4.0% (i.e., 98.0% to 102.0%)
- Analytical method allowance = 30% of the P/T ratio using a 95% confidence interval.

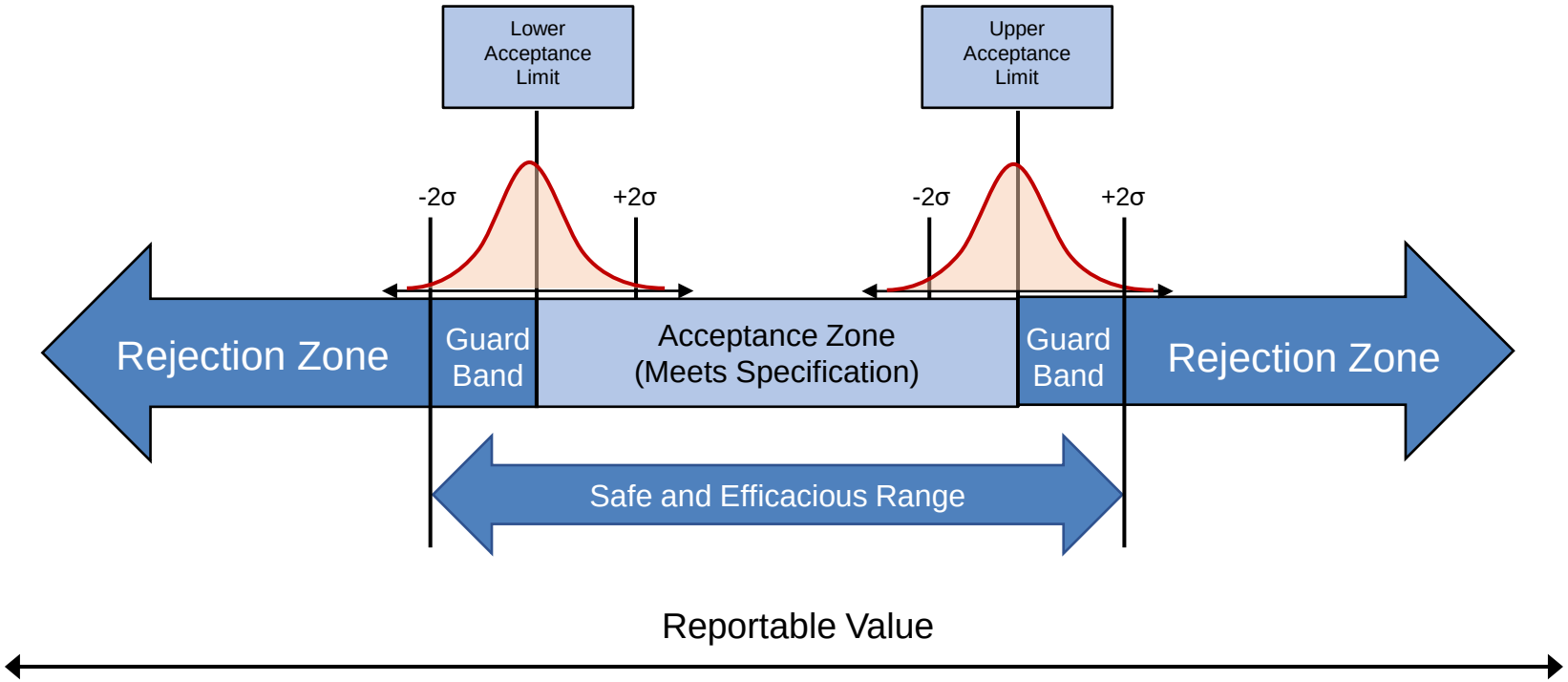
### Determining Required Precision ($\sigma_{max}$)

Tolerance Width = 4.00 (98.0 – 102.0)

Precision Width = 0.30 x 4.00 = 1.20

Split between LAL and UAL = ±0.60

**± 0.60 = ±2σ width for 95% C.I.**



# Replication Strategy for the Reportable Value

## Between Variables Components of Variation

| Variable Name | Variance | Standard Deviation | Degrees of Freedom | t-table Value | (+/-) 95% Confidence Limits | Error Contribution (%) |
|---|---|---|---|---|---|---|
| Sample Preparation | 0.065 | 0.256 | 4 | 2.7764 | 0.71 | 95.27 |
| Injection | 0.003 | 0.057 | 20 | 2.0860 | 0.11 | 4.73 |

## Overall Error in a Single Determination

| Statistic | Value |
|---|---|
| Mean | 100.142 |
| Variance | 0.069 |
| Standard Deviation | 0.262 |
| % RSD | 0.262 |

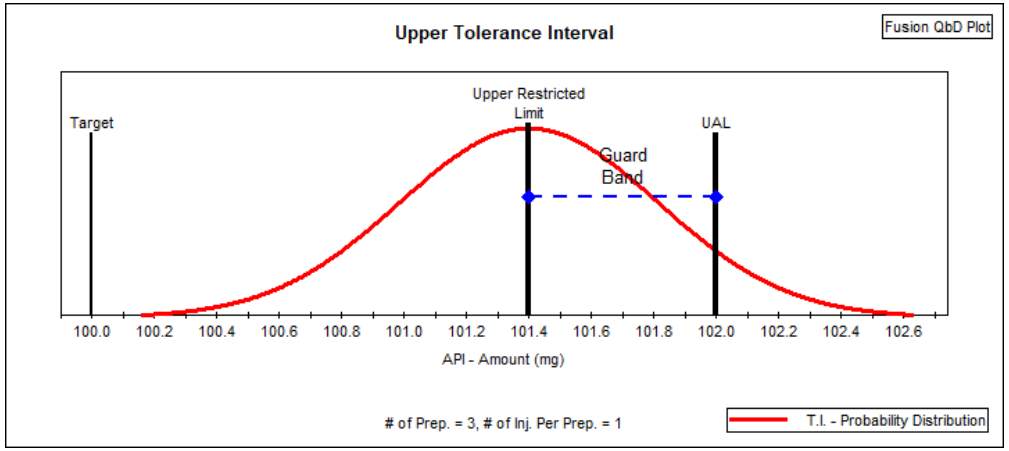
## TOST Analysis Results Summary

| Statistic | Value | Pass/Fail |
|---|---|---|
| TAE Width (2σ) - Target | ±0.600 | |
| Computed TAE Width (2σ) | ±0.434 | Pass |
| FPT | <0.0001 | |
| Cp | 4.4075 | |
| Variance | 0.023 | |
| Standard Deviation | 0.151 | |
| % RSD | 0.15 | |
| % CV | 0.15 | |

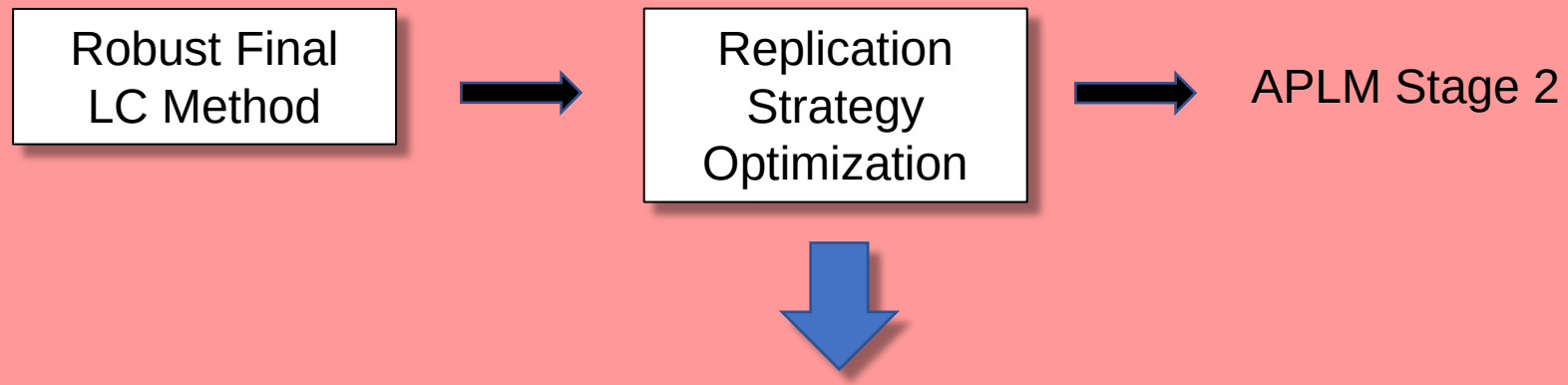
## Tolerance Interval Analysis Results

| Interval Setting | Value | Number of Preparations | Number of Injections per Preparation |
|---|---|---|---|
| Target | 100.000 | 3 | 1 |
| Acceptance Limits | ±2.000 | | |
| Desired Probability % | 95.00 | | |
| Tolerance Alpha % | 5.00 | | |
| | | | |
| Grand Mean | 100.142 | | |
| Computed Tolerance Interval | ±0.812 | Fail | |
| Required Guard Band Width | ±0.600 | | |

| No. of Injections | | No. of Preparations | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 1 | ±2σ | 0.7517 | 0.5313 | **0.4340** | 0.3759 | 0.3362 | 0.3069 | 0.2841 | 0.2658 | 0.2506 | 0.2377 |
| | T.I. | 1.7228 | 1.0550 | **0.8121** | 0.6810 | 0.5968 | 0.5372 | 0.4922 | 0.4568 | 0.4280 | 0.4040 |
| 2 | ±2σ | 0.7428 | 0.5252 | 0.4288 | 0.3714 | 0.3322 | 0.3032 | 0.2807 | 0.2626 | 0.2476 | 0.2349 |
| | T.I. | 1.4742 | 0.9516 | 0.7506 | 0.6383 | 0.5646 | 0.5115 | 0.4709 | 0.4387 | 0.4122 | 0.3900 |
| 3 | ±2σ | 0.7398 | 0.5231 | 0.4271 | 0.3699 | 0.3308 | 0.3020 | 0.2796 | 0.2615 | 0.2466 | 0.2339 |
| | T.I. | 1.3843 | 0.9156 | 0.7296 | 0.6239 | 0.5537 | 0.5028 | 0.4638 | 0.4326 | 0.4069 | 0.3854 |
| 4 | ±2σ | 0.7383 | 0.5220 | 0.4262 | 0.3691 | 0.3302 | 0.3014 | 0.2790 | 0.2610 | 0.2461 | 0.2335 |
| | T.I. | 1.3376 | 0.8973 | 0.7189 | 0.6166 | 0.5482 | 0.4985 | 0.4602 | 0.4295 | 0.4043 | 0.3830 |
| 5 | ±2σ | 0.7374 | 0.5214 | 0.4257 | 0.3687 | 0.3298 | 0.3010 | 0.2787 | 0.2607 | 0.2458 | 0.2332 |
| | T.I. | 1.3089 | 0.8862 | 0.7125 | 0.6122 | 0.5450 | 0.4959 | 0.4580 | 0.4277 | 0.4027 | 0.3816 |
| 6 | ±2σ | 0.7368 | 0.5210 | 0.4254 | 0.3684 | 0.3295 | 0.3008 | 0.2785 | 0.2605 | 0.2456 | 0.2330 |
| | T.I. | 1.2896 | 0.8787 | 0.7082 | 0.6093 | 0.5428 | 0.4941 | 0.4566 | 0.4265 | 0.4016 | 0.3807 |
| 7 | ±2σ | 0.7363 | 0.5207 | 0.4251 | 0.3682 | 0.3293 | 0.3006 | 0.2783 | 0.2603 | 0.2454 | 0.2328 |
| | T.I. | 1.2756 | 0.8733 | 0.7051 | 0.6072 | 0.5412 | 0.4929 | 0.4556 | 0.4256 | 0.4009 | 0.3800 |
| 8 | ±2σ | 0.7360 | 0.5204 | 0.4249 | 0.3680 | 0.3291 | 0.3005 | 0.2782 | 0.2602 | 0.2453 | 0.2327 |
| | T.I. | 1.2650 | 0.8693 | 0.7028 | 0.6056 | 0.5400 | 0.4920 | 0.4548 | 0.4250 | 0.4003 | 0.3795 |
| 9 | ±2σ | 0.7357 | 0.5202 | 0.4248 | 0.3679 | 0.3290 | 0.3004 | 0.2781 | 0.2601 | 0.2452 | 0.2327 |
| | T.I. | 1.2568 | 0.8662 | 0.7010 | 0.6044 | 0.5391 | 0.4912 | 0.4542 | 0.4244 | 0.3999 | 0.3791 |
| 10 | ±2σ | 0.7355 | 0.5201 | 0.4247 | 0.3678 | 0.3289 | 0.3003 | 0.2780 | 0.2601 | 0.2452 | 0.2326 |
| | T.I. | 1.2501 | 0.8636 | 0.6995 | 0.6034 | 0.5384 | 0.4906 | 0.4537 | 0.4240 | 0.3995 | 0.3788 |



# Sample Prep Method Optimization




**ICH Q14**

A sample and/or sample preparation is considered suitable if the measurement response of the sample satisfies pre-defined acceptance criteria for the analytical procedure attributes that have been developed for the validated analytical procedure.

**USP <1220>**

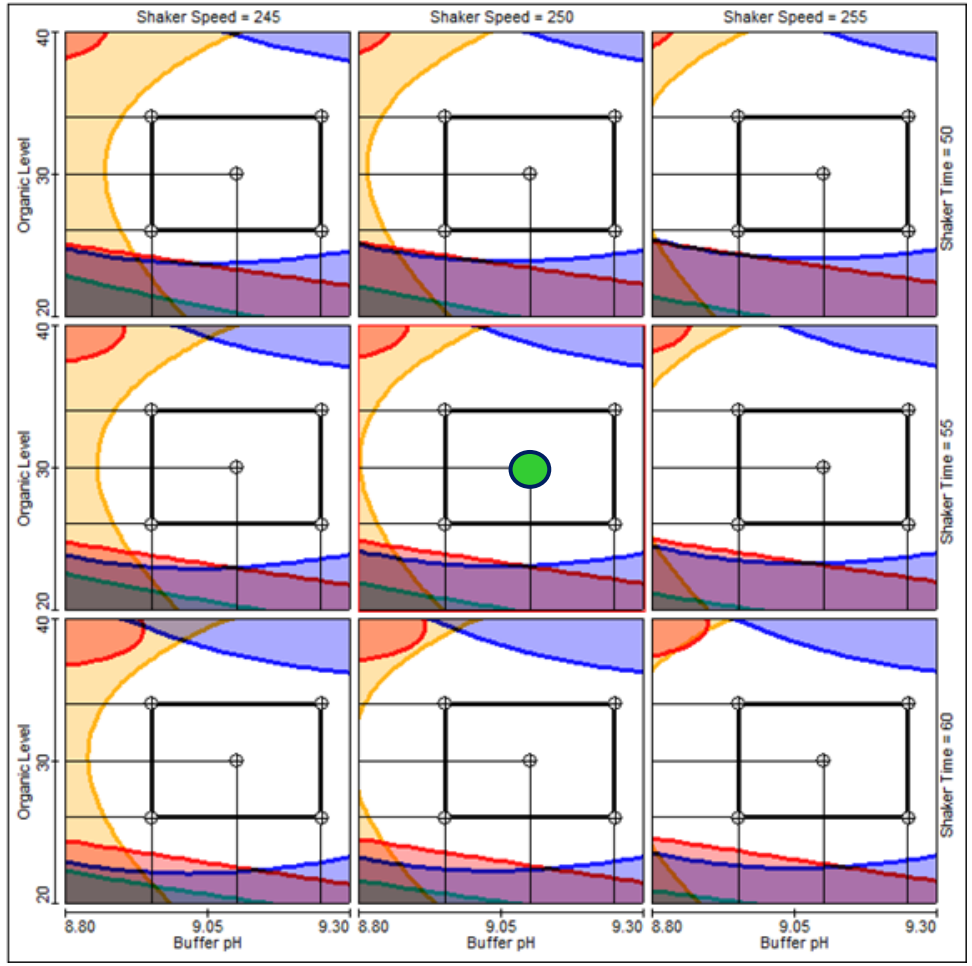
**Stage 1**: Procedure design encompasses procedure development, which consists of the analytical technology and sample preparation.

# APLM Stage 1 → Sample Prep Method Optimization

**Sample Preparation Method Optimization**

| Name | Units | Type | Level Settings |
|---|---|---|---|
| Buffer pH | | Discrete Numeric | Level 1: 8.00; Level 2: 8.50; Level 3: 9.00; No. of Levels: 3 |
| State: Variable | | | |

| Name | Units | Type | Lower Bound | Upper Bound |
|---|---|---|---|---|
| Organic Level | % | Continuous | 20 | 50 |
| State: Variable | | | | |
| Sonication Time | min | Continuous | 0 | 30 |
| State: Variable | | | | |
| Shaker Speed | rpm | Continuous | 50 | 250 |
| State: Variable | | | | |
| Shaker Time | min | Continuous | 20 | 120 |
| State: Variable | | | | |




Optimization reduces the amount of the TAE contributed by Sample Preparation.

# Replication Strategy for the Reportable Value

## Between Variables Components of Variation

| Variable Name | Variance | Standard Deviation | Degrees of Freedom | t-table Value | (+/-) 95% Confidence Limits | Error Contribution (%) |
|---|---|---|---|---|---|---|
| Sample Preparation | 0.029 | 0.170 | 4 | 2.7764 | 0.471 | 96.09 |
| Injection | 0.001 | 0.034 | 20 | 2.0860 | 0.071 | 3.91 |

## Overall Error in a Single Determination

| Statistic | Value |
|---|---|
| Mean | 100.091 |
| Variance | 0.030 |
| Standard Deviation | 0.173 |
| % RSD | 0.173 |

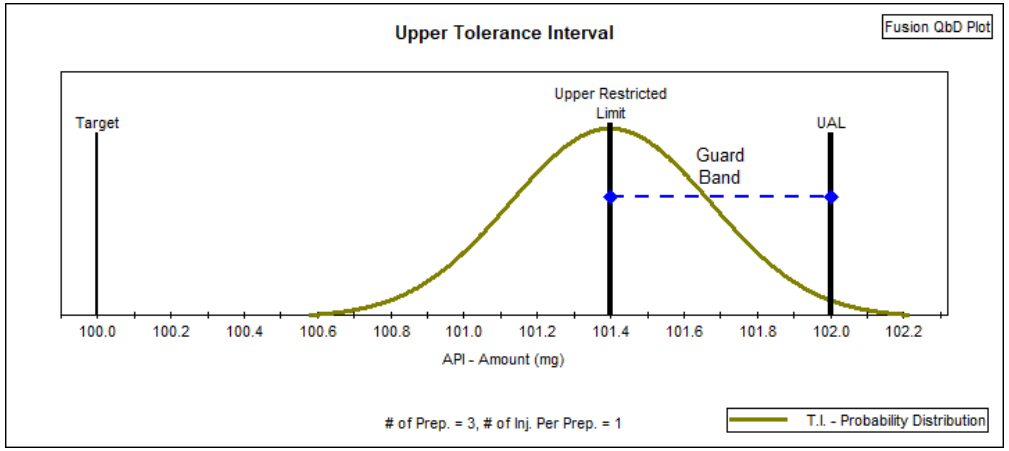
## TOST Analysis Results Summary

| Statistic | Value | Pass/Fail |
|---|---|---|
| TAE Width (2σ) - Target | ±0.600 | |
| Computed TAE Width (2σ) | ±0.287 | Pass |
| FPT | <0.0001 | |
| Cp | 6.6753 | |
| Variance | 0.010 | |
| Standard Deviation | 0.100 | |
| % RSD | 0.10 | |
| % CV | 0.10 | |

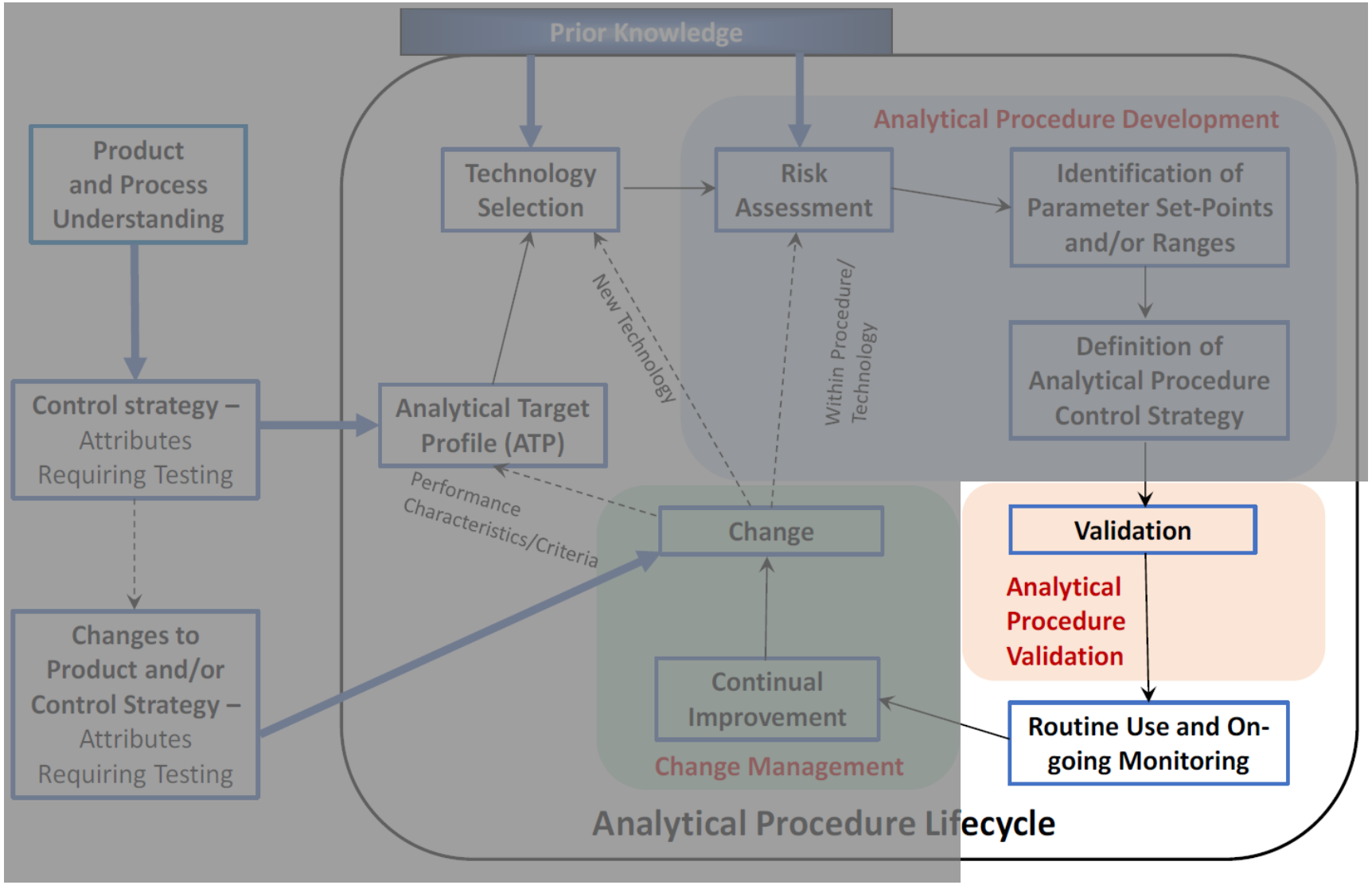
## Tolerance Interval Analysis Results

| Interval Setting | Value | Number of Preparations | Number of Injections per Preparation |
|---|---|---|---|
| Target | 100.000 | 3 | 1 |
| Acceptance Limits | ±2.000 | | |
| Desired Probability % | 95.00 | | |
| Tolerance Alpha % | 5.00 | | |
| | | | |
| Grand Mean | 100.091 | | |
| Computed Tolerance Interval | ±0.536 | Pass | |
| Required Guard Band Width | ±0.600 | | |

| No. of Injections | | No. of Preparations | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 1 | ±2σ | 0.4963 | 0.3511 | **0.2866** | 0.2482 | 0.2220 | 0.2026 | 0.1876 | 0.1755 | 0.1654 | 0.1570 |
| | T.I. | 1.1375 | 0.6961 | **0.5362** | 0.4496 | 0.3940 | 0.3547 | 0.3250 | 0.3016 | 0.2826 | 0.2668 |
| 2 | ±2σ | 0.4915 | 0.3475 | 0.2837 | 0.2457 | 0.2198 | 0.2006 | 0.1858 | 0.1738 | 0.1638 | 0.1554 |
| | T.I. | 0.9754 | 0.6296 | 0.4967 | 0.4224 | 0.3736 | 0.3384 | 0.3116 | 0.2902 | 0.2727 | 0.2581 |
| 3 | ±2σ | 0.4898 | 0.3464 | 0.2828 | 0.2449 | 0.2191 | 0.2000 | 0.1851 | 0.1732 | 0.1633 | 0.1549 |
| | T.I. | 0.9166 | 0.6063 | 0.4831 | 0.4131 | 0.3666 | 0.3329 | 0.3071 | 0.2864 | 0.2694 | 0.2552 |
| 4 | ±2σ | 0.4890 | 0.3458 | 0.2823 | 0.2445 | 0.2187 | 0.1996 | 0.1848 | 0.1729 | 0.1630 | 0.1546 |
| | T.I. | 0.8860 | 0.5943 | 0.4762 | 0.4084 | 0.3631 | 0.3302 | 0.3048 | 0.2845 | 0.2678 | 0.2537 |
| 5 | ±2σ | 0.4885 | 0.3454 | 0.2820 | 0.2443 | 0.2185 | 0.1994 | 0.1846 | 0.1727 | 0.1628 | 0.1545 |
| | T.I. | 0.8672 | 0.5871 | 0.4720 | 0.4056 | 0.3610 | 0.3285 | 0.3035 | 0.2834 | 0.2668 | 0.2528 |
| 6 | ±2σ | 0.4882 | 0.3452 | 0.2819 | 0.2441 | 0.2183 | 0.1993 | 0.1845 | 0.1726 | 0.1627 | 0.1544 |
| | T.I. | 0.8545 | 0.5822 | 0.4693 | 0.4037 | 0.3596 | 0.3274 | 0.3026 | 0.2826 | 0.2661 | 0.2522 |
| 7 | ±2σ | 0.4880 | 0.3450 | 0.2817 | 0.2440 | 0.2182 | 0.1992 | 0.1844 | 0.1725 | 0.1627 | 0.1543 |
| | T.I. | 0.8453 | 0.5788 | 0.4673 | 0.4024 | 0.3586 | 0.3266 | 0.3019 | 0.2821 | 0.2657 | 0.2518 |
| 8 | ±2σ | 0.4878 | 0.3449 | 0.2816 | 0.2439 | 0.2181 | 0.1991 | 0.1844 | 0.1725 | 0.1626 | 0.1542 |
| | T.I. | 0.8384 | 0.5761 | 0.4658 | 0.4014 | 0.3579 | 0.3260 | 0.3014 | 0.2816 | 0.2653 | 0.2515 |
| 9 | ±2σ | 0.4876 | 0.3448 | 0.2815 | 0.2438 | 0.2181 | 0.1991 | 0.1843 | 0.1724 | 0.1625 | 0.1542 |
| | T.I. | 0.8330 | 0.5741 | 0.4646 | 0.4006 | 0.3573 | 0.3256 | 0.3010 | 0.2813 | 0.2650 | 0.2513 |
| 10 | ±2σ | 0.4875 | 0.3447 | 0.2815 | 0.2438 | 0.2180 | 0.1990 | 0.1843 | 0.1724 | 0.1625 | 0.1542 |
| | T.I. | 0.8286 | 0.5724 | 0.4637 | 0.3999 | 0.3568 | 0.3252 | 0.3007 | 0.2811 | 0.2648 | 0.2511 |



# ICH Q14 – Analytical Procedure Lifecycle



# Complete Method Validation Experiment Suite

- Analytical Capability*
- Specificity
- Filter Validation
- Sample Solution Stability
- Accuracy*
- Linearity & Range
- Repeatability*
- Accuracy / Linearity / Repeatability*

  [Combined as per ICH Q2(R1)]
- LOQ*, LOD*
- Intermediate Precision and Reproducibility
- Validation Robustness – LC
- Validation Robustness – Non-LC

  [e.g. Sample Preparation, Dissolution]
- Method Transfer Study Support*

* – integration of USP <1210> Tolerance & Prediction Intervals]

# Analytical Method Transfer Example

Transferring Lab

Fusion QbD Sequence Execution

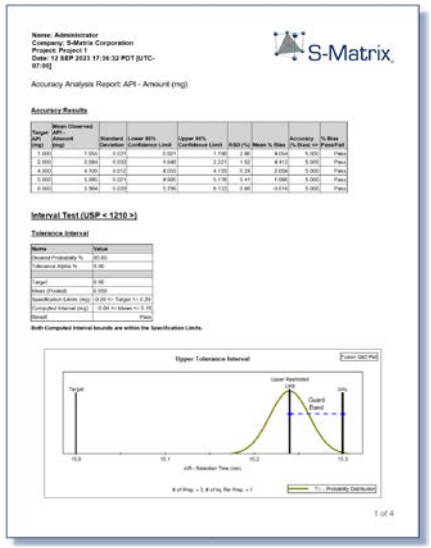
Fusion QbD Sequence Execution

Receiving Lab

Chromatography Data Software

ALR Design

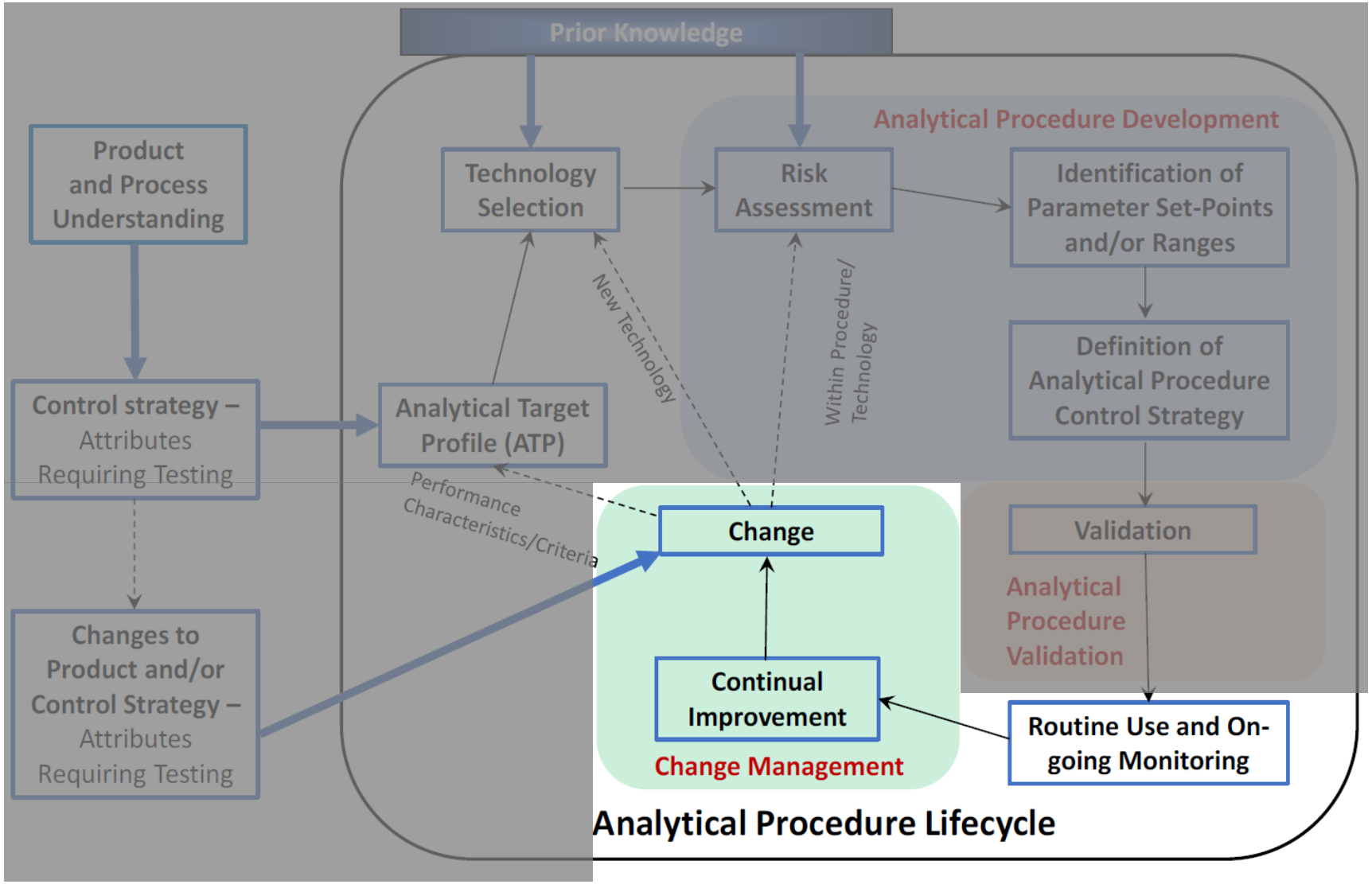
Chromatogram Results Data


1. Fusion QbD – Exports experiment to the CDS as Ready-to-Run sequence, methods, standards
2. Sequence is run at both labs.
3. Fusion QbD – Imports results for instant and complete analysis and reporting.

Accuracy
Linearity
Repeatability
Tolerance Interval
Pass/Fail Results

# ICH Q14 – Analytical Procedure Lifecycle



# Analytical Control Strategy

Robust Final LC Method → Analytical Control Strategy → APLM Stage 3

**ICH Q14**

Knowledge gained from application of an enhanced approach to analytical procedure development can provide better assurance of the performance of the procedure, can serve as a basis for the analytical procedure control strategy and can provide an opportunity for more efficient regulatory approaches to related post approval changes.

**USP <1220>**

The [Analytical Control Strategy] is a set of controls needed to ensure the procedure performs as expected and plays a key role in ensuring that the ATP is realized throughout the life cycle. The preliminary ACS is identified during the procedure development

process in Stage 1, …

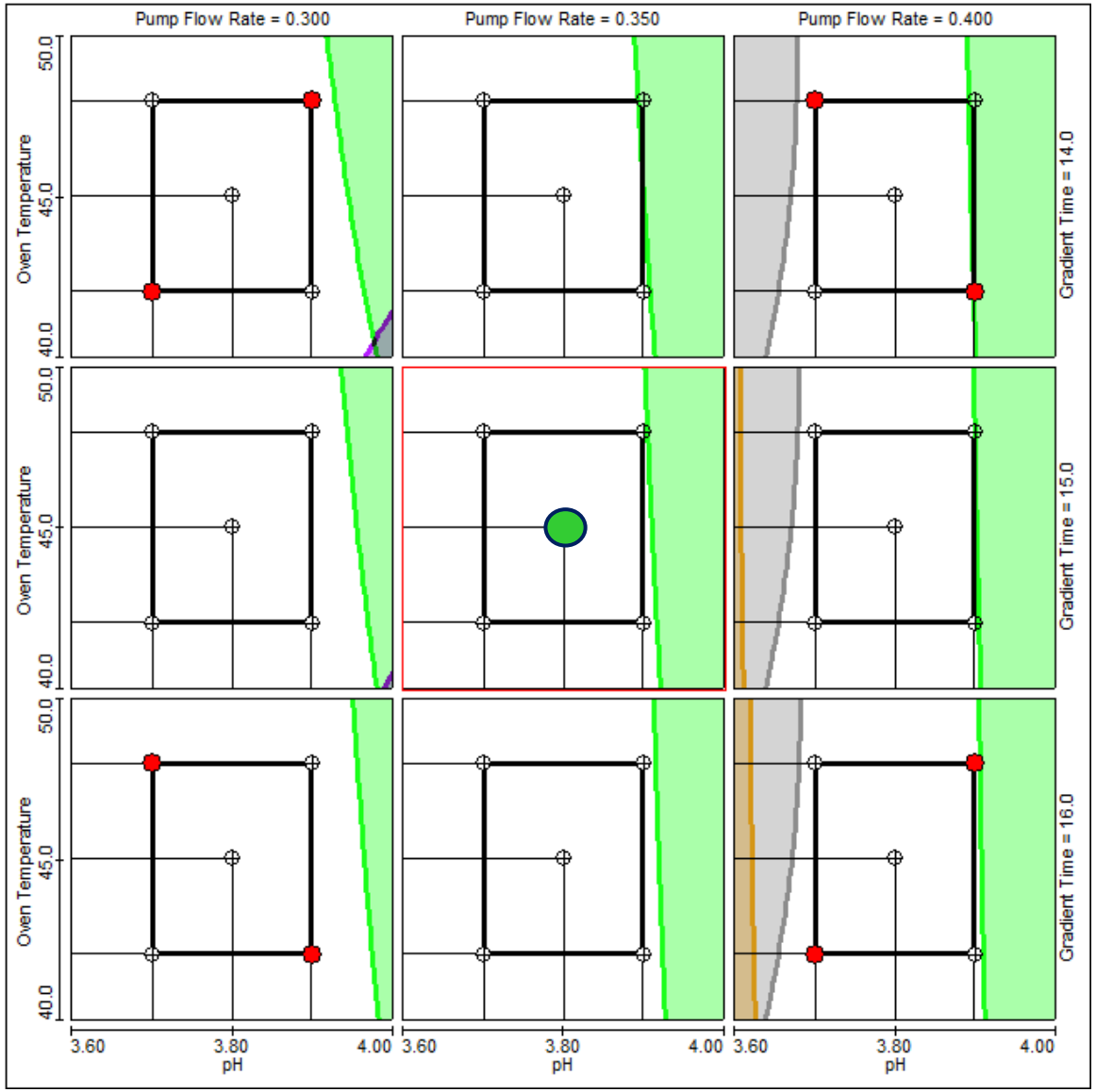
# Analytical Control Strategy (ACS)

Variable Settings

| Enabled | Experiment Variable | Units | Maximum Expected Variation (±3σ Value) |
|---|---|---|---|
| ☑ | Pump Flow Rate | mL/min | 0.020 |
| ☑ | Oven Temperature | °C | 3.0 |
| ☑ | pH | * | 0.15 |
| ☑ | Mobile Phase Composition (MPC)* | % | 2.0 |

* - MPC variation is composition (blend) variation due to pump precision limits. A commonly used ±3σ value = ±2.0%.
The value you enter will be applied to all Gradient Slope factors (e.g., Time, Slope, and Ramp Steps) in the experiment design.

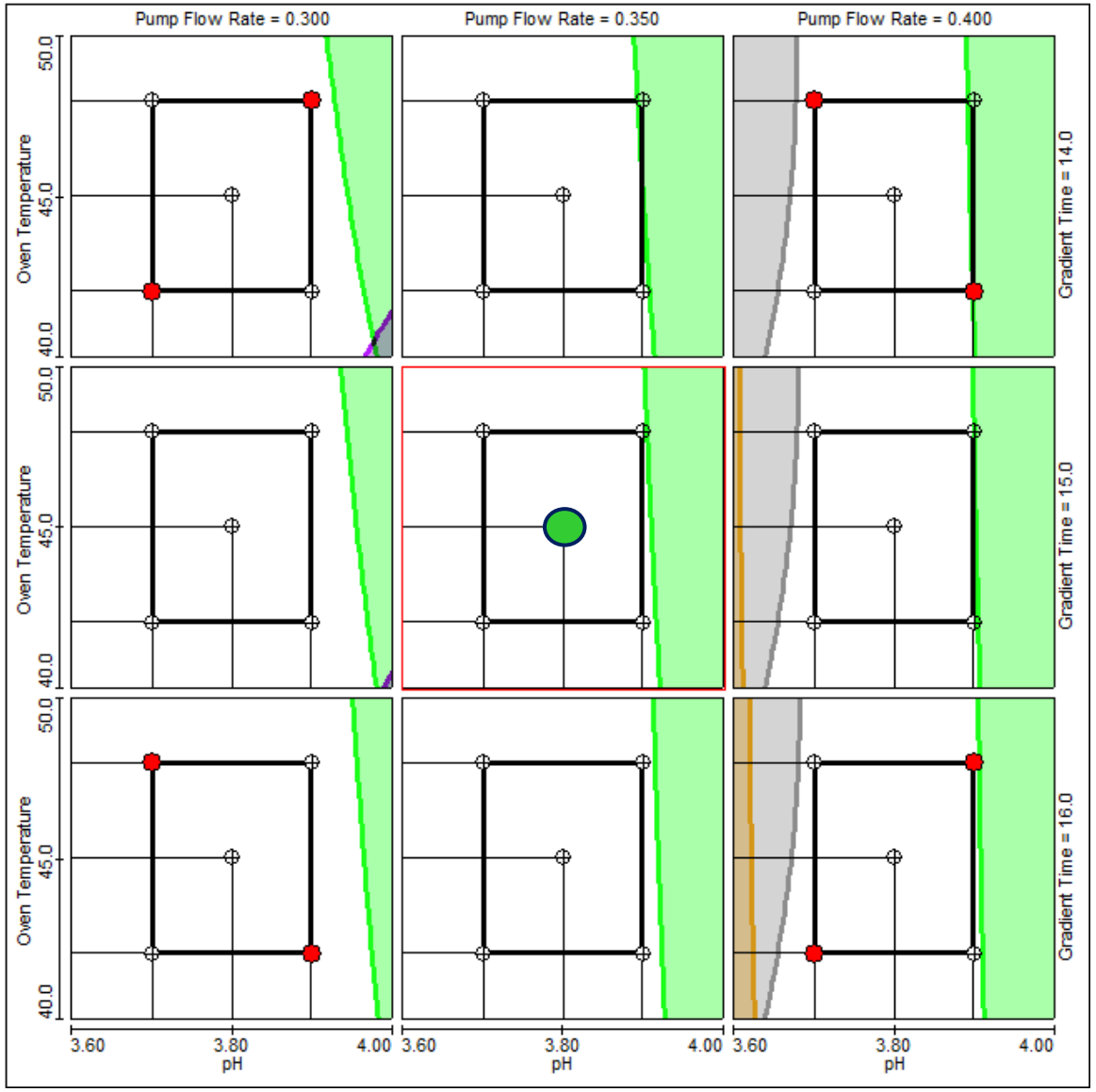
**LC System Control Specifications**



# Analytical Control Strategy (ACS)

| | Name | Units | Goal | Lower Bound | Upper Bound | Color |
|---|---|---|---|---|---|---|
| ☑ | A - ResolutionW50 | * | Maximize | 2.000 | | Red |
| ☑ | API - ResolutionW50 | * | Maximize | 2.000 | | Blue |
| ☑ | D-Deg - ResolutionW50 | * | Maximize | 2.000 | | Green |
| ☑ | E - ResolutionW50 | * | Maximize | 2.000 | | Orange |
| ☑ | B - RetentionTime | | Maximize | 1.00 | | Gray |
| ☑ | API - USPTailing | | Minimize | | 1.50 | Purple |
| ☑ | B - RetentionTime - Cpk | * | Maximize | 1.330 | | Gray |
| ☑ | API - USPTailing - Cpk | * | Maximize | 1.330 | | Purple |
| ☑ | A - ResolutionW50 - Cpk | * | Maximize | 1.330 | | Red |
| ☑ | API - ResolutionW50 - Cpk | * | Maximize | 1.330 | | Blue |
| ☑ | D-Deg - ResolutionW50 - Cpk | * | Maximize | 1.330 | | Green |
| ☑ | E - ResolutionW50 - Cpk | * | Maximize | 1.330 | | Orange |

**Routine Monitoring – Control Charts**



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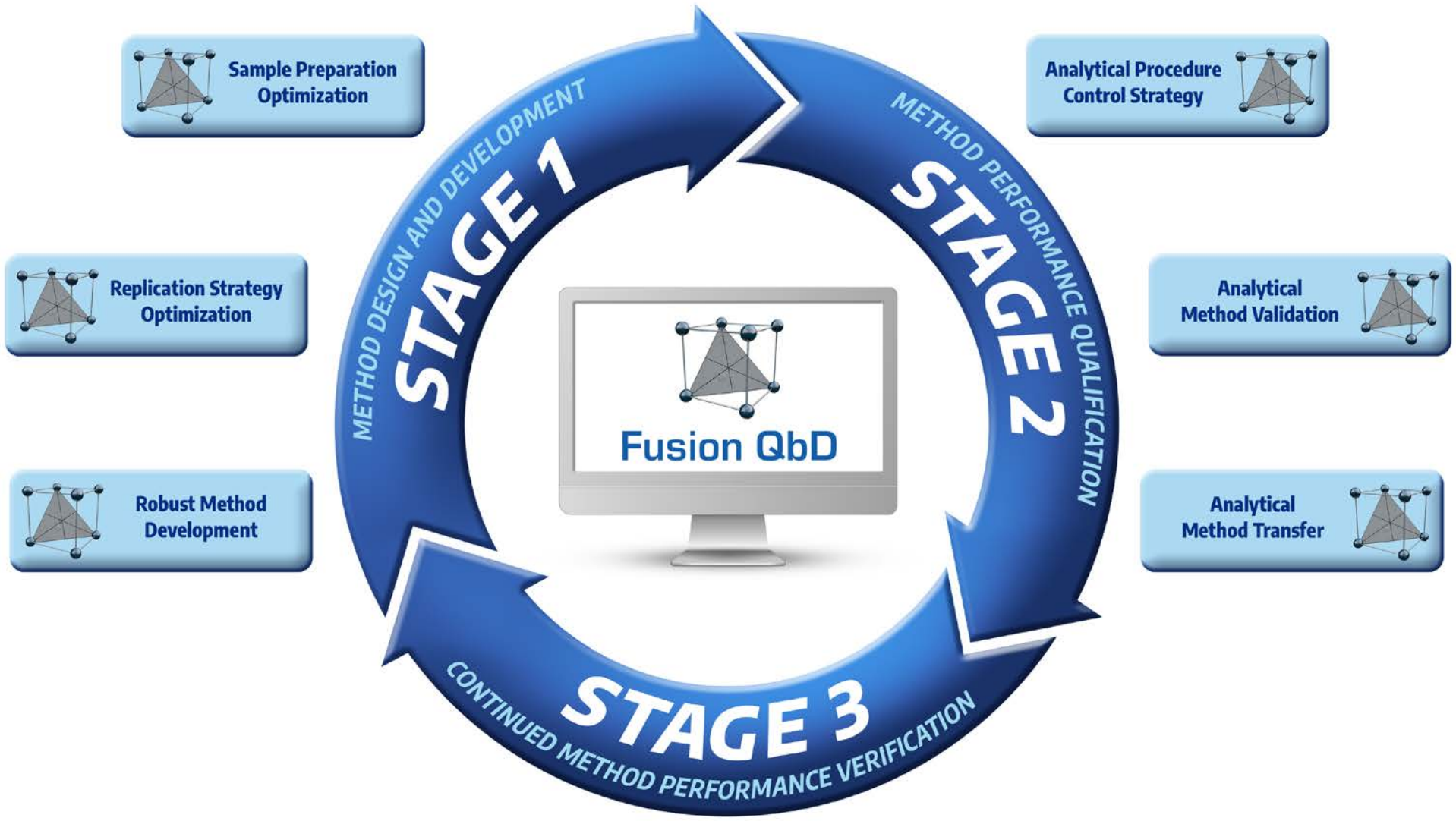
# THANK YOU!



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