S-Matrix

Pittcon Conference and Exposition

Session #: O24-00
Track: Pharmaceutical

Impacts of USP Modernization Initiatives on Analytical Development for Drug Products

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Abstract

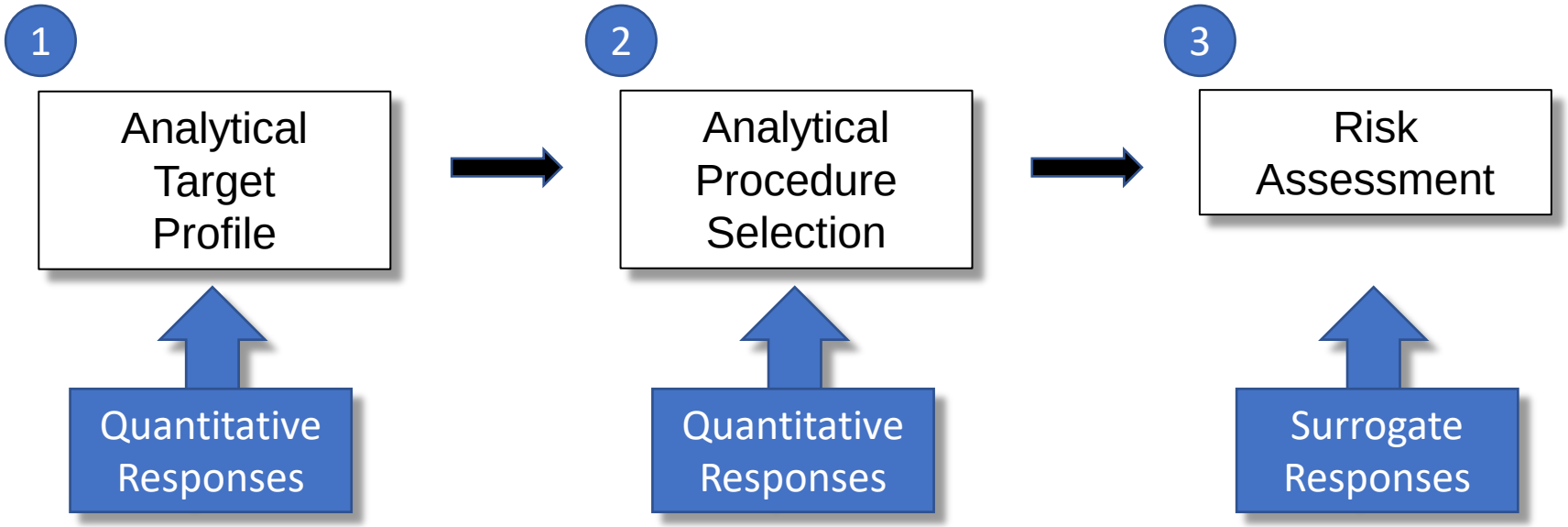
This presentation will describe the following key elements within the USP <1210> and USP <1220> guidances which provide a new framework and workflow for analytical procedure development:

1. **Analytical Target Profile (ATP)**
   a. A specification negotiated with Production.
   b. A bridge linking qualitative and quantitative method development data.
2. **Method Operable Design Region (MODR)**
   a. Establishing a true, multi-dimensional, robust MODR.
   b. Capturing the Analytical Control Strategy knowledge required for APLM Stage 3.
3. **Replication Strategy Optimization**

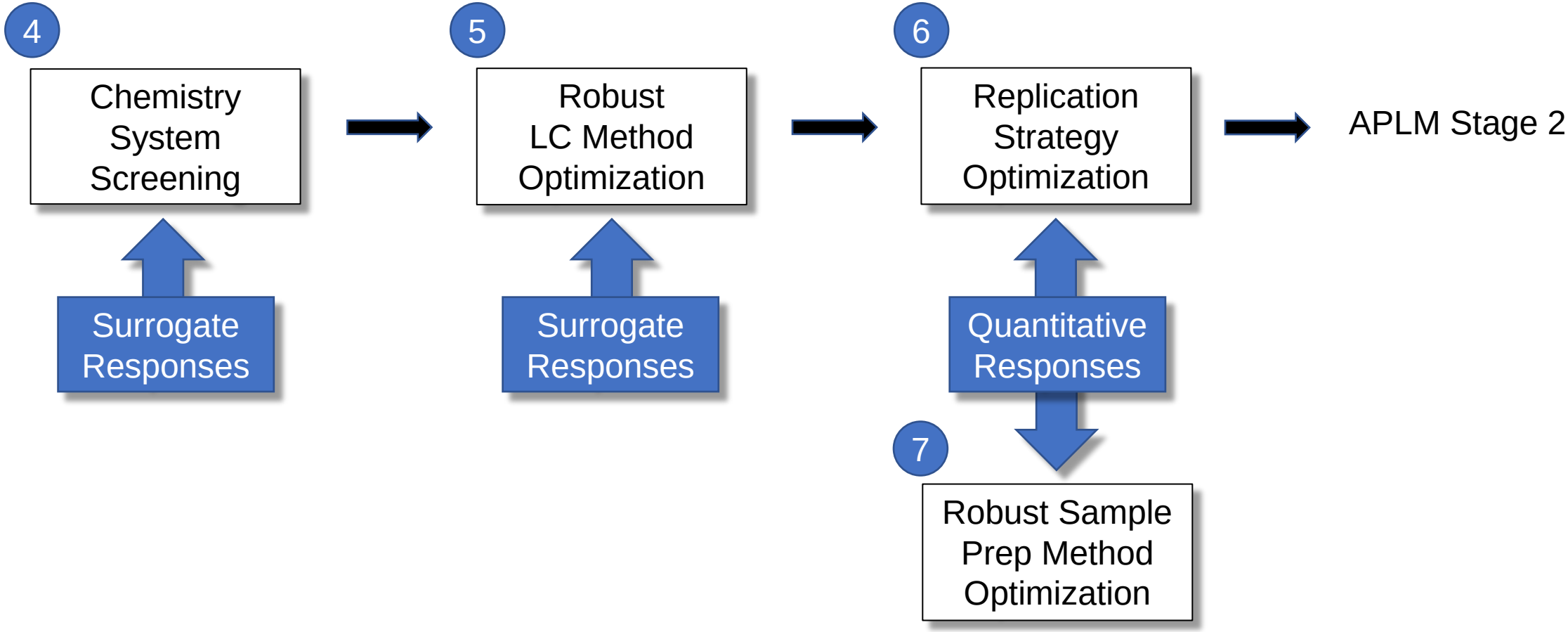
   Identifying the most efficient strategy for generating Reportable Values (a.k.a. Reportable Results) which meet ATP Performance Requirements.

These key elements will be described within the context of developing a robust UHPLC method.

APLM Stage 1 Workflow



APLM Stage 1 Workflow - Continued



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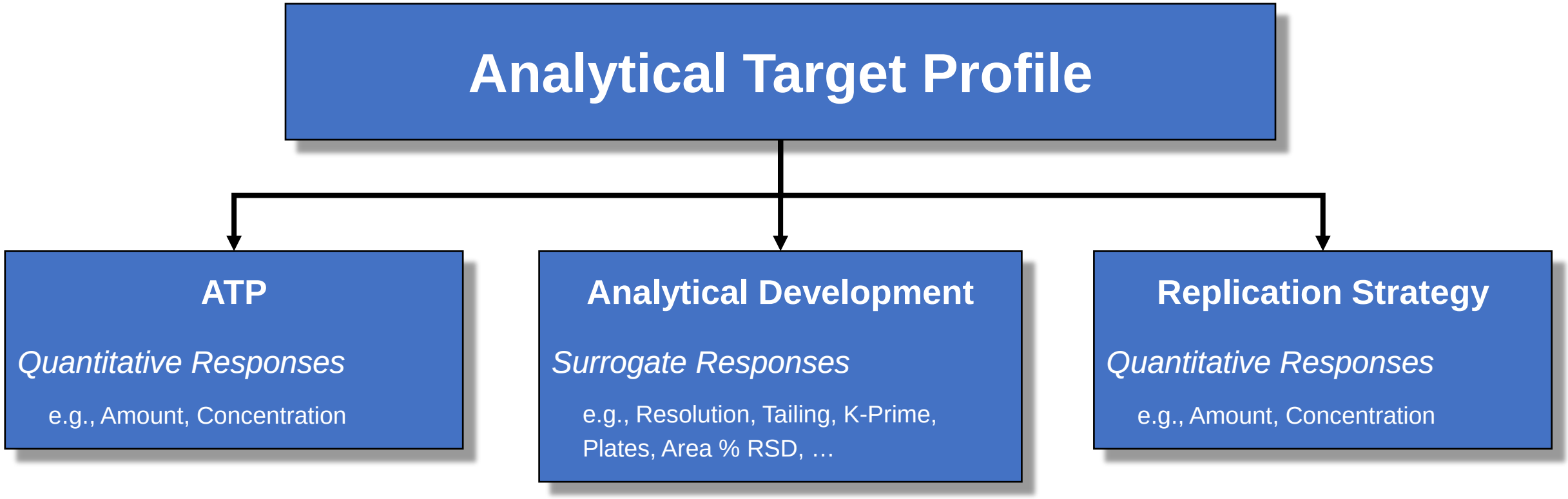
Run a Sample Preparation Optimization study when the minimum Replication Strategy required to meet the method precision requirements in the ATP is not feasible, and Sample Prep is the major source of error.

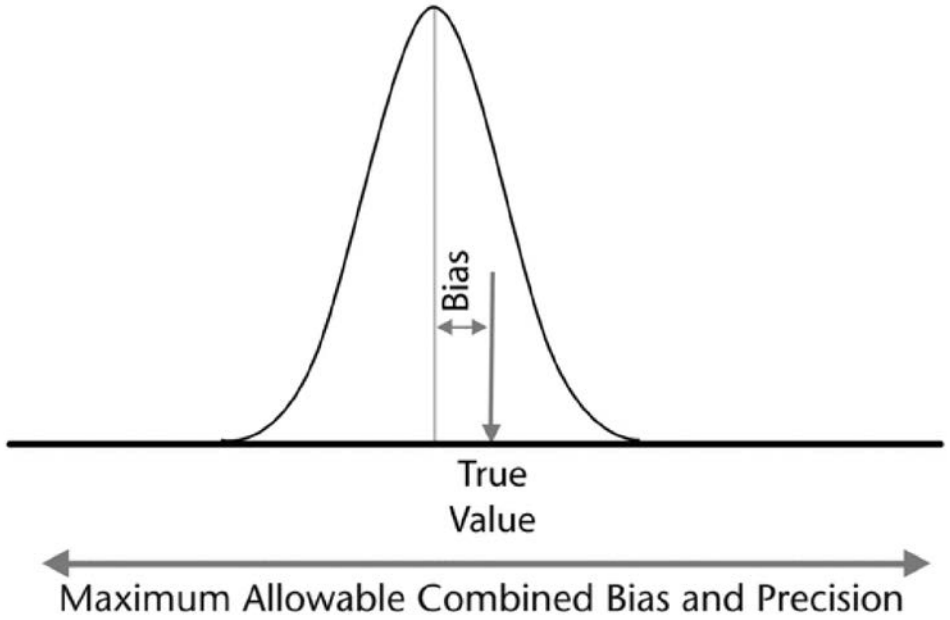
ATP as a Bridge



ATP for Analytical Procedure

Analytical Target Profile (USP <1220>

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%].

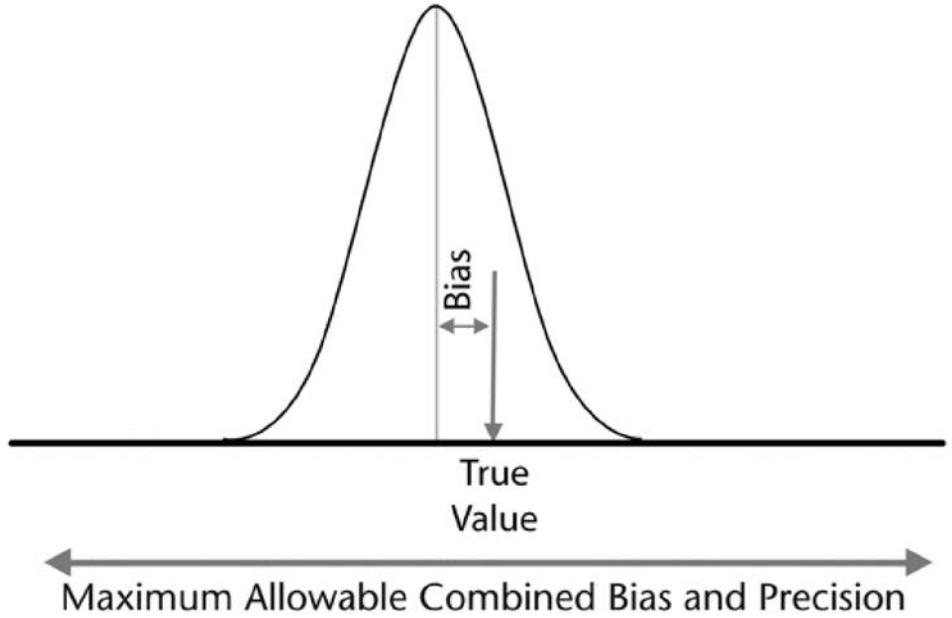


Total Analytical Error (TAE)

USP ⟨1220⟩ Analytical Procedure Life Cycle

Total Analytical Error (TAE):

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:

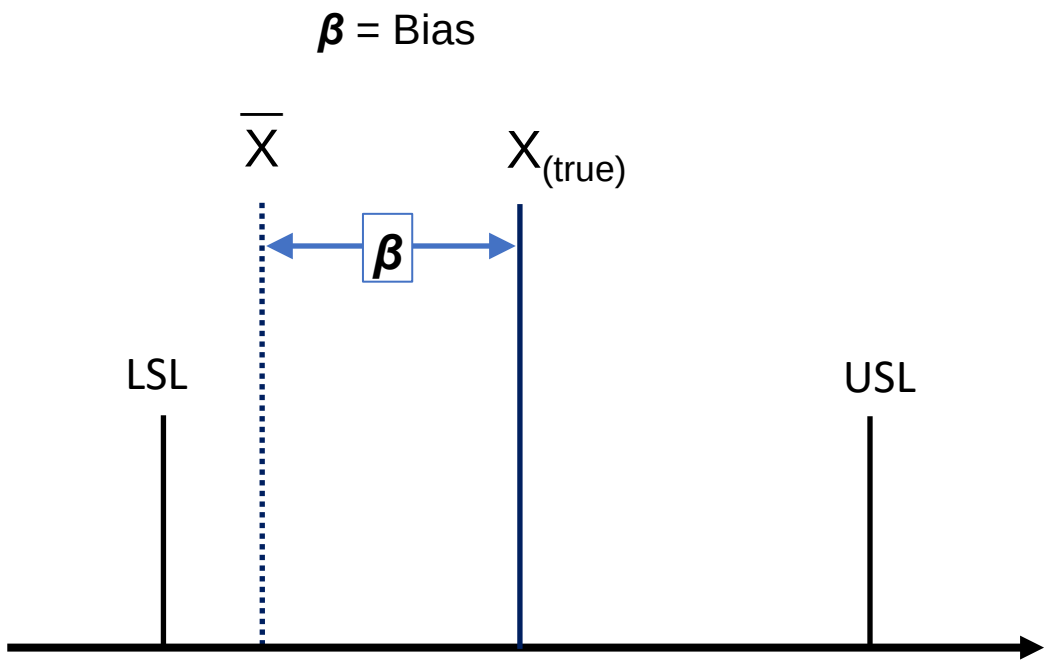
1. The Integration of Precision and Bias into a single **Interval Metric** – USP <1210>.
2. The Negotiated Total Analytical Error (TAE) **Allowance** for the Analytical Method.

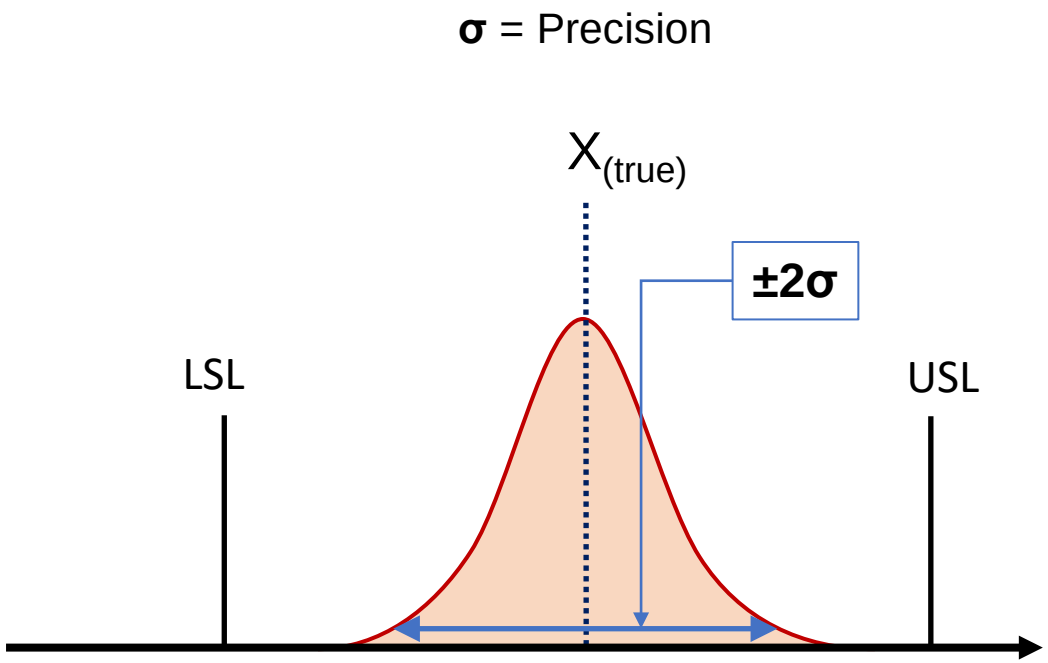
<1210> Addresses a Critical Issue

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 (β – bias) and Precision (σ – precision) are assessed separately = High Risk Approach.





<1210> Interval Metric Solution

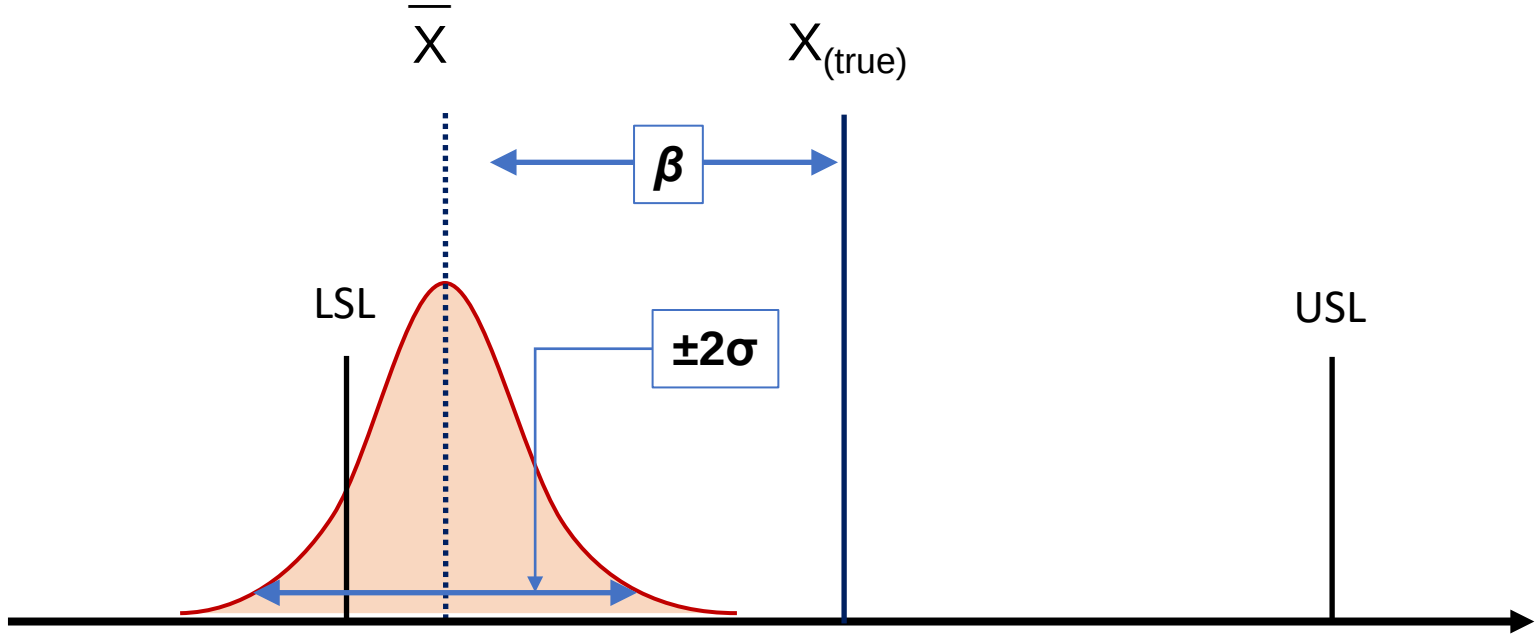
3. ACCURACY AND PRECISION

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

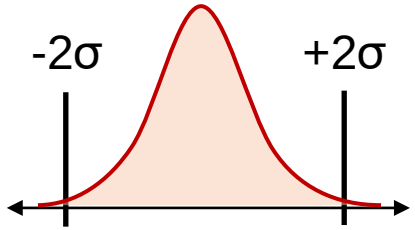
σ = Precision

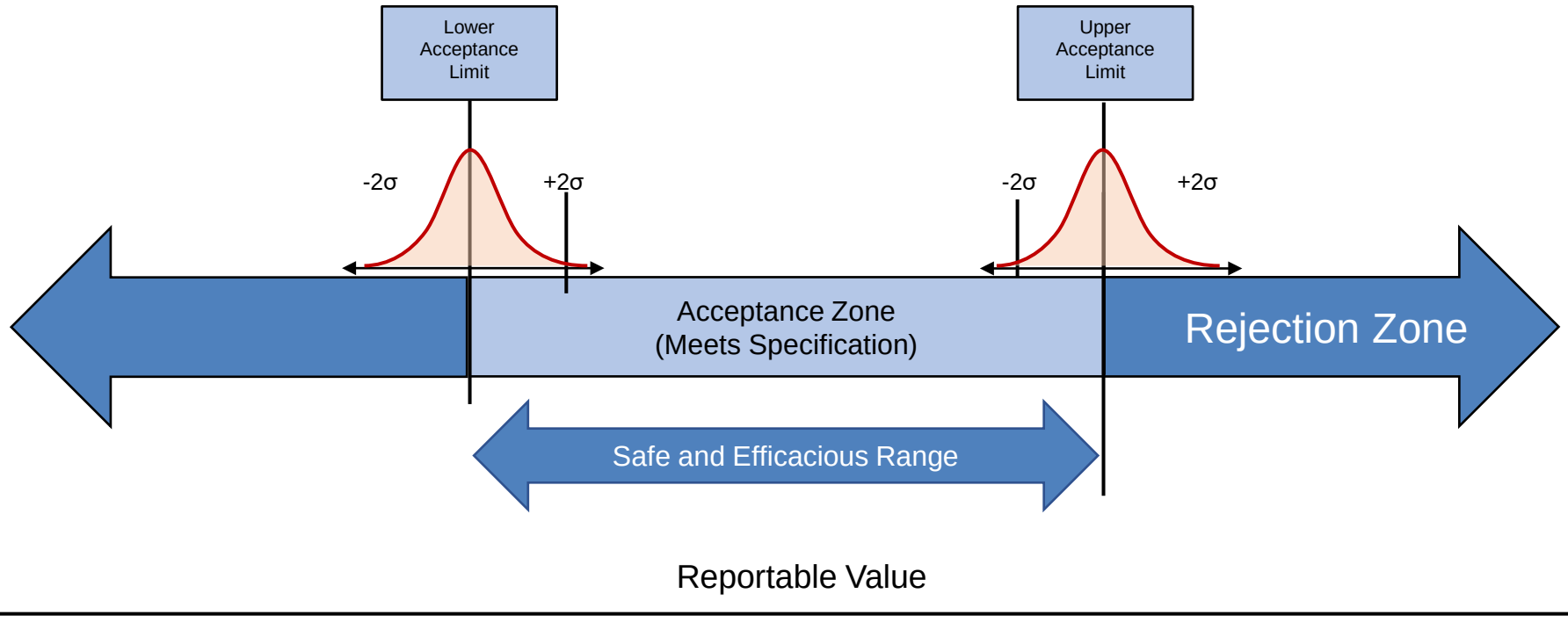


TAE and Guard Bands

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

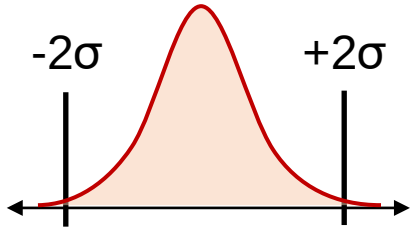


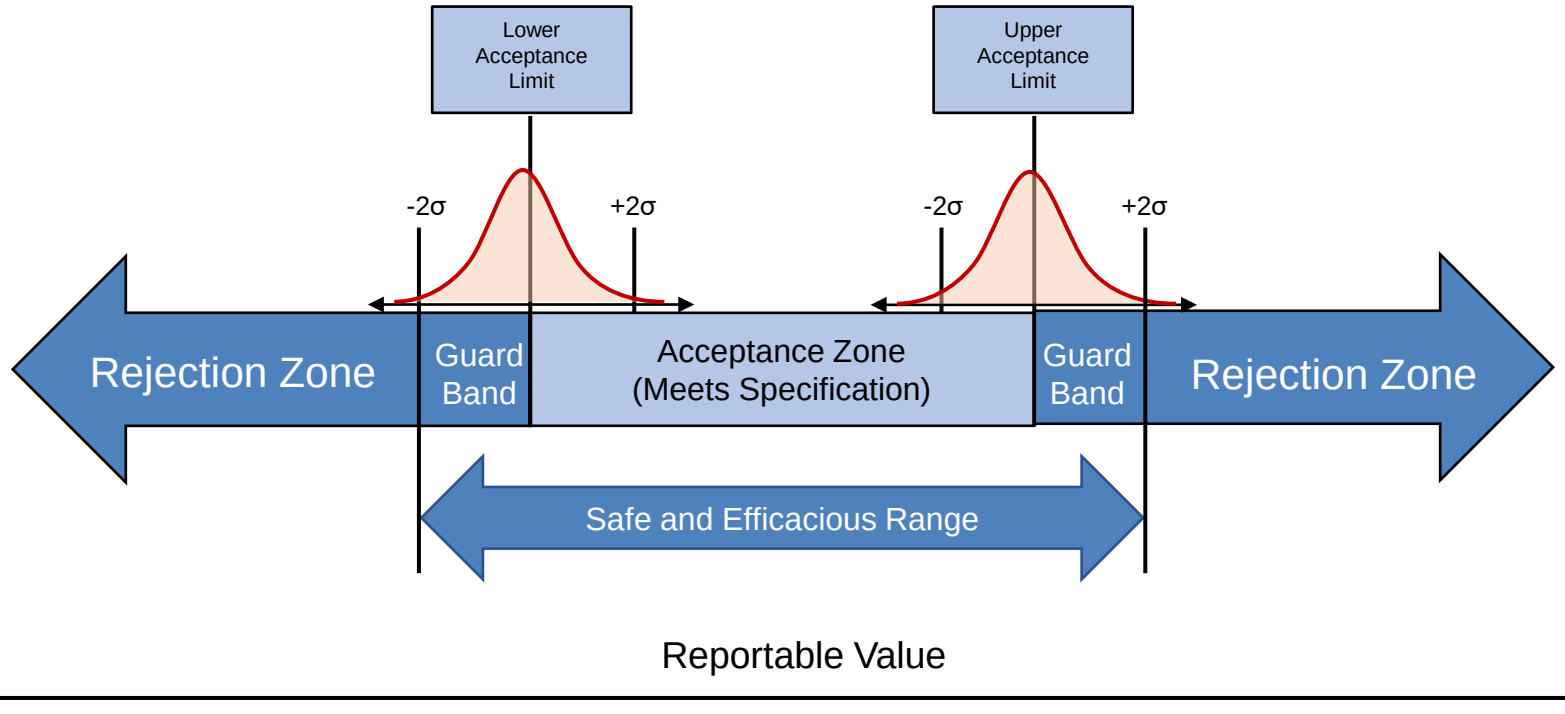


TAE and Guard Bands

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.

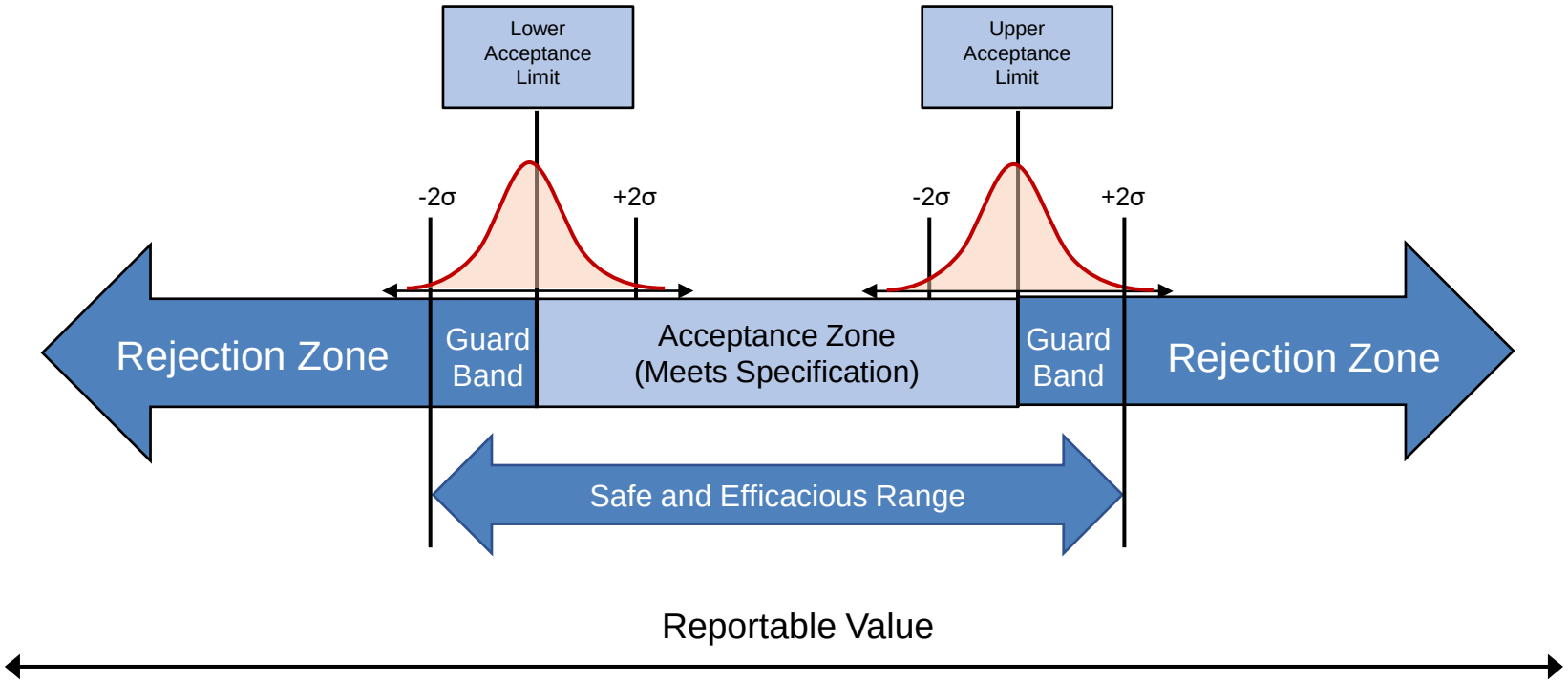
Determining Required Precision (σ_{max})

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.



ATP for Analytical Procedure

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

Selected Analytical Procedure = UHPLC:

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

- Robust Method Optimization
- Replication Strategy Optimization

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
	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

General Method Development Workflow

USP ⟨1220⟩ Analytical Procedure Life Cycle

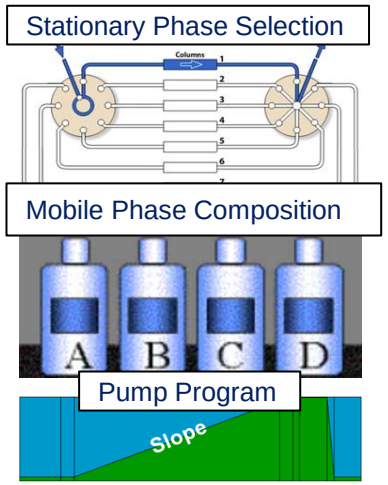
Fusion QbD® Software Platform

Full Experiment Automation with the CDS.

Full 21 CFR 11 Compliance with Bi-directional Audit Trail

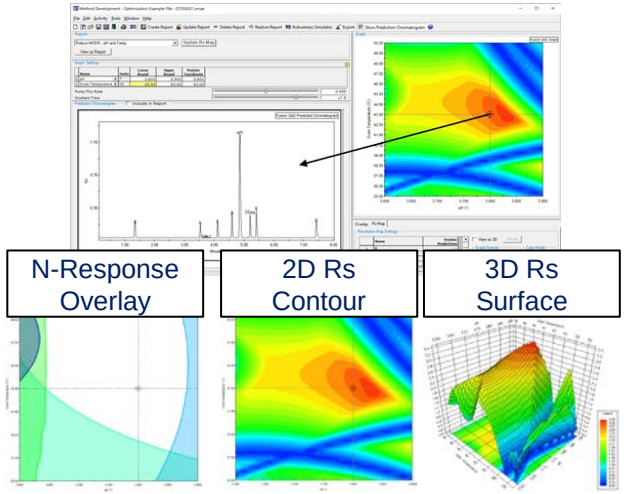
Chemistry System Screening

Quickly identify critical method parameters and select study ranges for optimization.



Robust LC Method Optimization

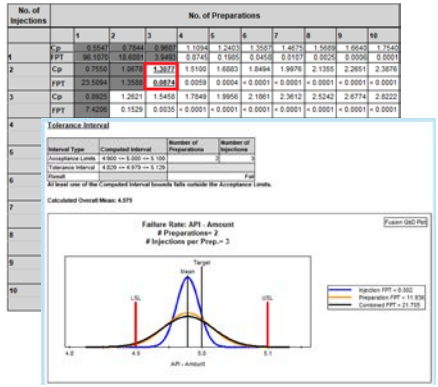
Establish Robust Method Operable Design Region (MODR) for all Critical Analytical Method Attributes.



Replication Strategy Optimization

Define % contributions of Preparation Error and Injection Error to Overall Method Precision (Total Analytical Error).

Select optimal Replication Strategy.

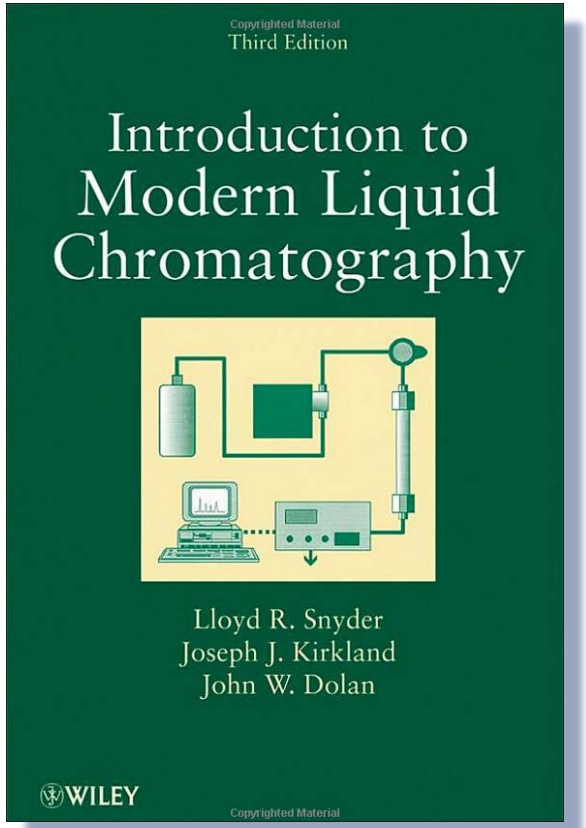


Current Thinking by Recognized Experts

Chemistry System Screening

"For methods involving a large number of samples, and where adequate resolution must be combined With run times that are as short as possible, **it can be profitable to spend more time initially on "scouting" experiments**.

- Different **columns**
- Different **B-solvents**
- Variations in **pH** and **temperature**
- Use of **Gradient elution** during the experiments can help avoid the need to separately optimize values of %B for each variable studied."



Snyder, Kirkland, and Dolan. (2010). *Introduction to Modern Liquid Chromatography*, 3rd Edition; John Wiley & Sons, Inc., Hoboken, New Jersey (p. 67)

Screening Study – Parameter Flexibility

Full utilization of Quaternary Pumps, Solvent Selection Valves, and Column Switching Valves.

Study **any combination** of LC parameters which can **interactively effect** method performance!

- Isocratic and Gradient Methods
- Strong Solvent Type
- Any pump program steps – e.g.
  - Equilibration Time & %
  - Isocratic Hold Time & %
  - Gradient Time / Slope
  - Initial / Final Hold Time & %
  - Re-equilibration Time & %
- Column Temperature
- Column Type
- Flow Rate
- Injection Volume
- pH
- Mobile Phase Blends
- Salt, Buffer, Additive – Type & ΔC
- Wavelength

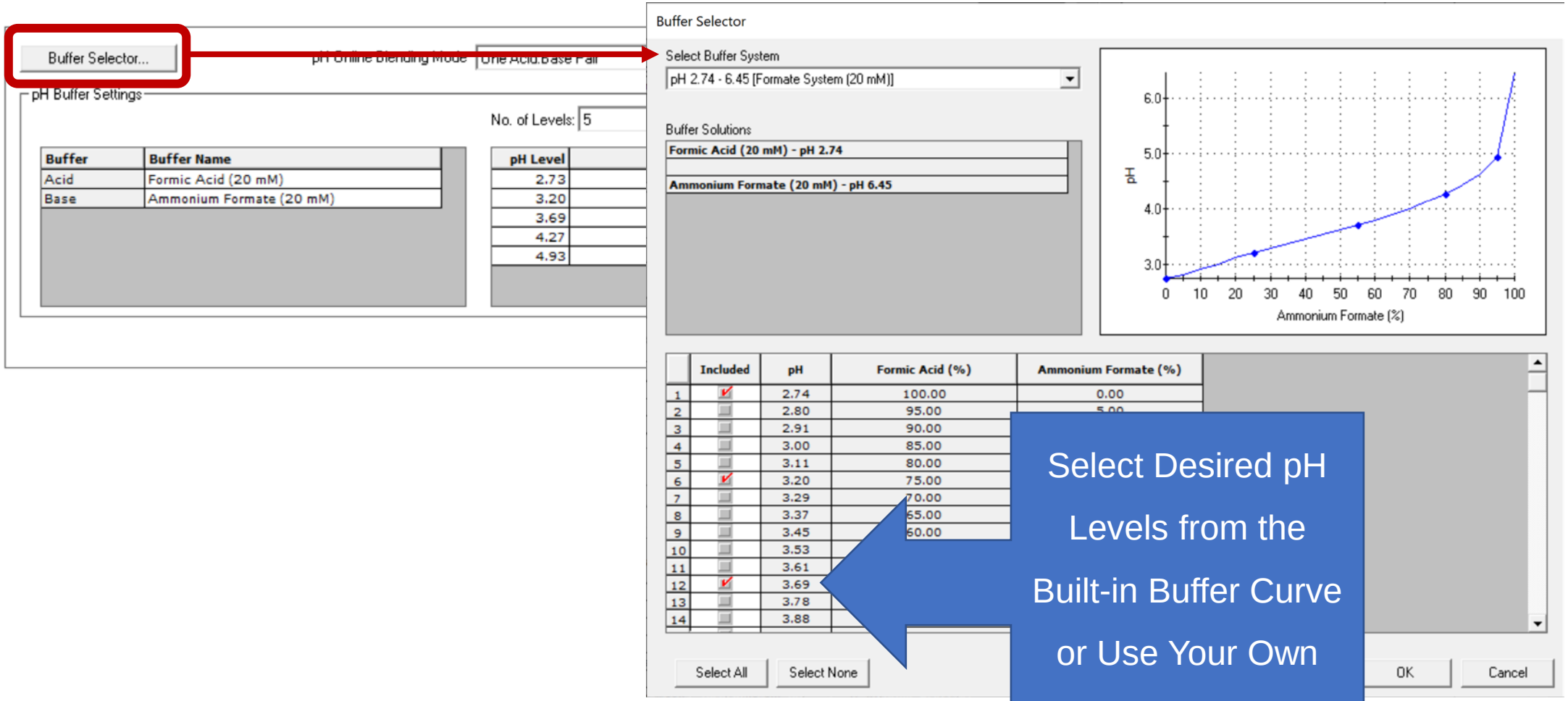
Parameter Selection – Screening Study

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

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

Experiment Setup – pH

Select One of the Built-in Buffer Systems or Enter Your Own



Select Desired pH Levels from the Built-in Buffer Curve or Use Your Own Curve

Experiment Setup – Gradient Time

Pump Program

No. of Gradient Steps: 1

Time Precision

	No.	Step Name	Time State	Time - Lower Bound	Time - Upper Bound	% Strong Solvent
☑	1	Equilibration	Constant	5.00	---	5.0
	2	Initial Hold	Constant	2.00	---	5.0
	3	Gradient	Variable	10.00	25.00	---
	4	Final Hold	Constant	1.00	---	95.0
	5	Ramp Up to Wash	Constant	0.50	---	---
☑	6	Column Wash	Constant	4.00	---	99.0
	7	Ramp Down from Wash	Constant	0.50	---	---
☑	8	Re-equilibration	Constant	3.00	---	5.0

Program duration: Min = 26.00 minutes, Max = 41.00 minutes

Gradient Study Factor: Gradient Time

Setting Mode: (•) Time ( ) Slope

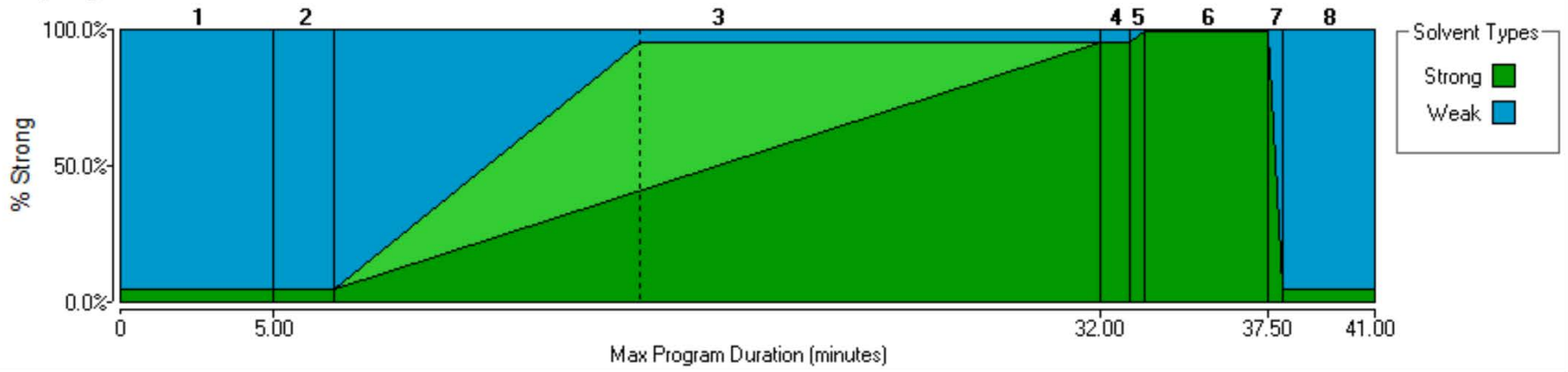
Update

Gradient

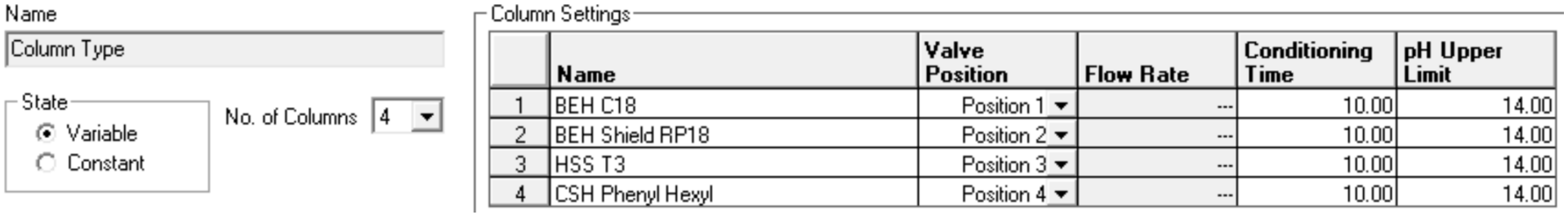
No. of Levels 5

Time(min)	Slope(%/min)
10.00	9.00
13.75	6.55
17.50	5.14
21.25	4.24
25.00	3.60

Pump Program Chart



Experiment Setup – Column Type



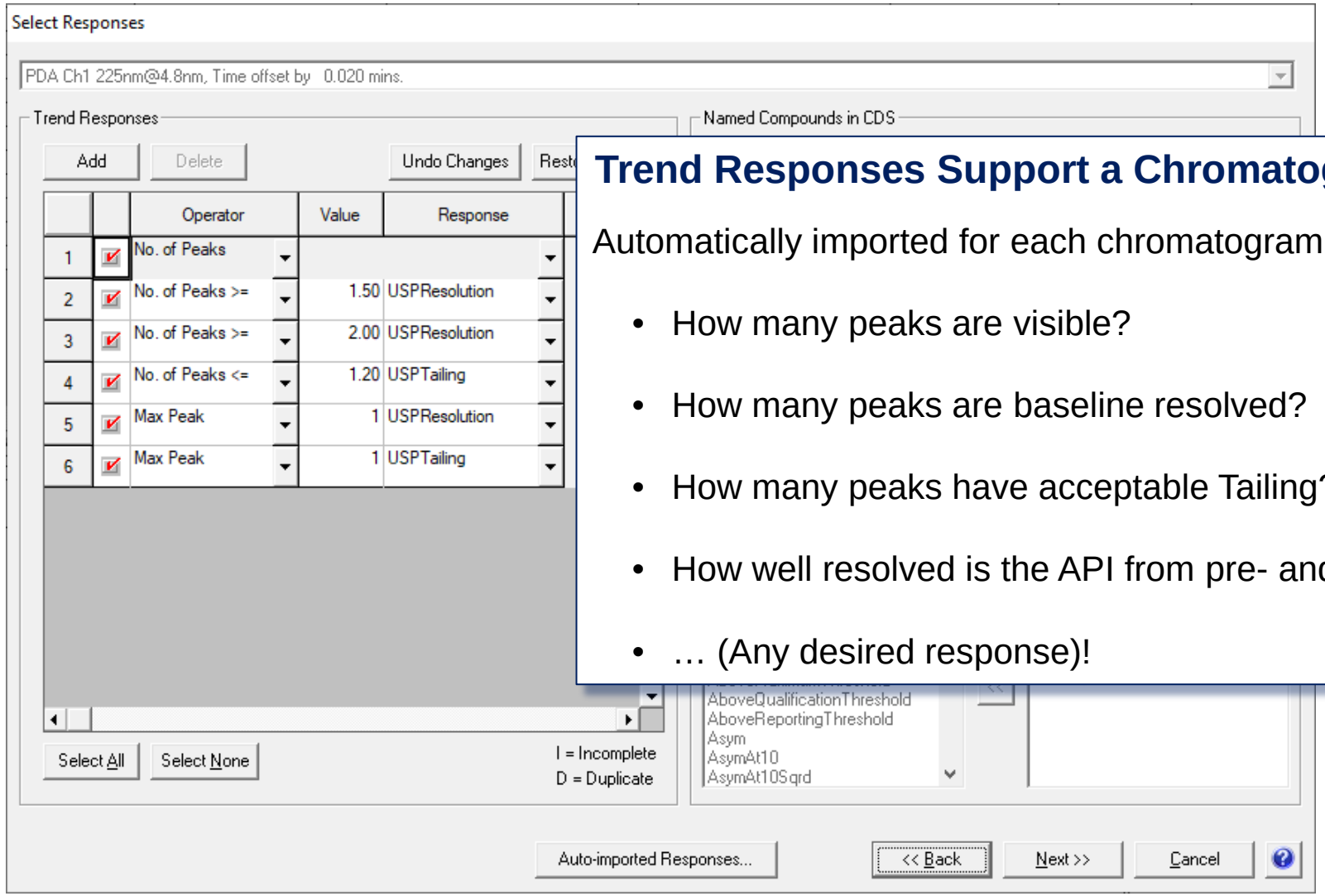
	Name	Valve Position	Flow Rate	Conditioning Time	pH Upper Limit
1	BEH C18	Position 1	---	10.00	14.00
2	BEH Shield RP18	Position 2	---	10.00	14.00
3	HSS T3	Position 3	---	10.00	14.00
4	CSH Phenyl Hexyl	Position 4	---	10.00	14.00

Chemistry Intelligence –

- Blocks design on Column Temp when it is a study factor
- Groups runs by MP Chemistry (e.g., pH, Strong Solvent)
- Incorporates column conditioning between MP Chemistry changes

Valve Intelligence – Automatically generates multiple sequences as needed when # of columns in exceeds # of available valve positions.

Screening Study – Trend Responses



Trend Responses Support a Chromatographer's Screening Goals

Automatically imported for each chromatogram:

- How many peaks are visible?
- How many peaks are baseline resolved?
- How many peaks have acceptable Tailing?
- How well resolved is the API from pre- and/or post-eluting peaks?
- … (Any desired response)!

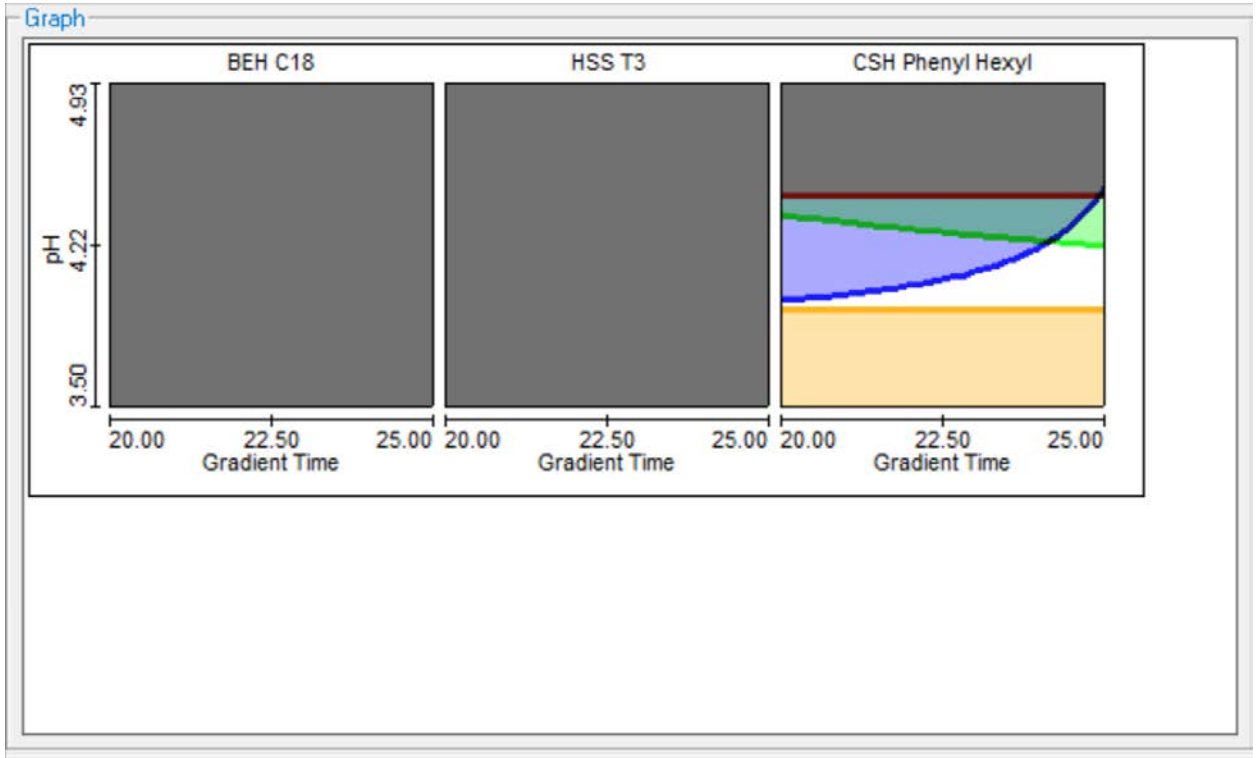
Screening Study – Simple Analysis

Modeling Trend Responses:

1. Enables graphical visualization of factor effects and workable regions.

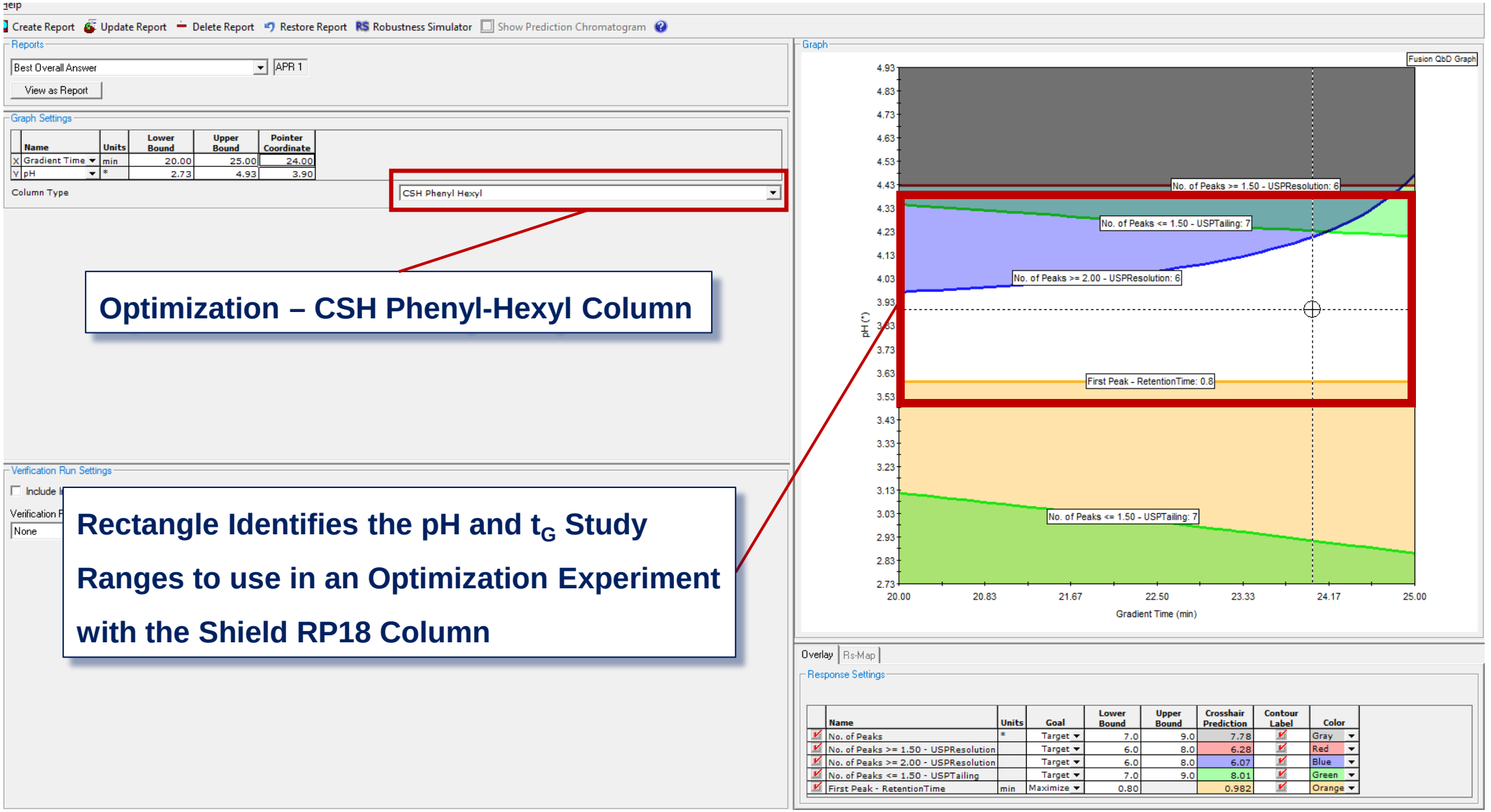
2. Extends DoE Sampling to all possible combinations (APC) – e.g., DoE = 40 runs, APC = 200 runs.

3. Avoids a risky “pick the winner strategy” based on a small sample size.



	Name	Units	Goal	Lower Bound	Upper Bound	Color
☑	No. of Peaks	*	Target	7.0	9.0	Gray
☑	No. of Peaks >= 1.50 - USPResolution		Target	6.0	8.0	Red
☑	No. of Peaks >= 2.00 - USPResolution		Target	6.0	8.0	Blue
☑	No. of Peaks <= 1.50 - USPTailing		Target	7.0	9.0	Green
☑	First Peak - RetentionTime	min	Maximize	1.00		Orange

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 Shield RP18 Column

Screening → Optimization

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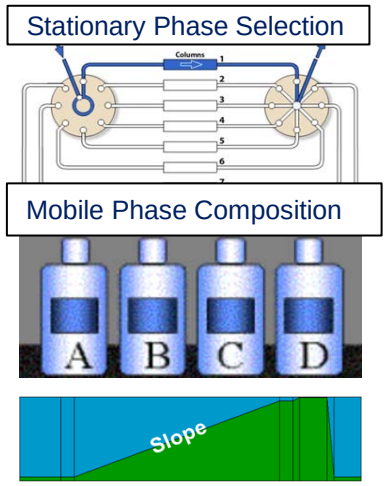
Full 21 CFR 11 Compliance with Bi-directional Audit Trail

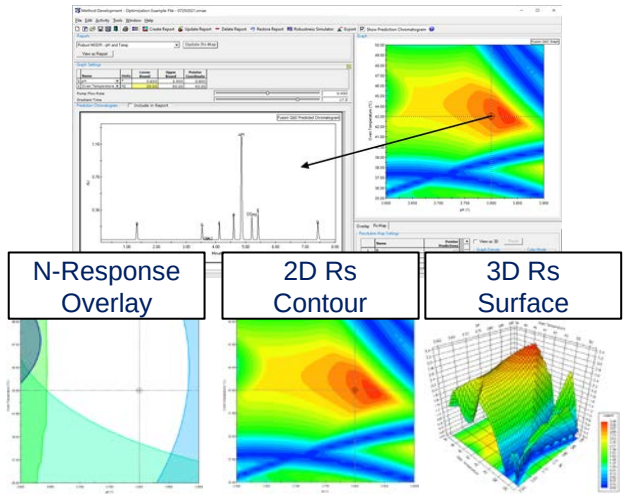
Chemistry System Screening

Quickly identify critical method parameters and select study ranges for optimization.



Robust LC Method Optimization

Establish Robust Method Operable Design Region (MODR) for all Critical Analytical Method Attributes.



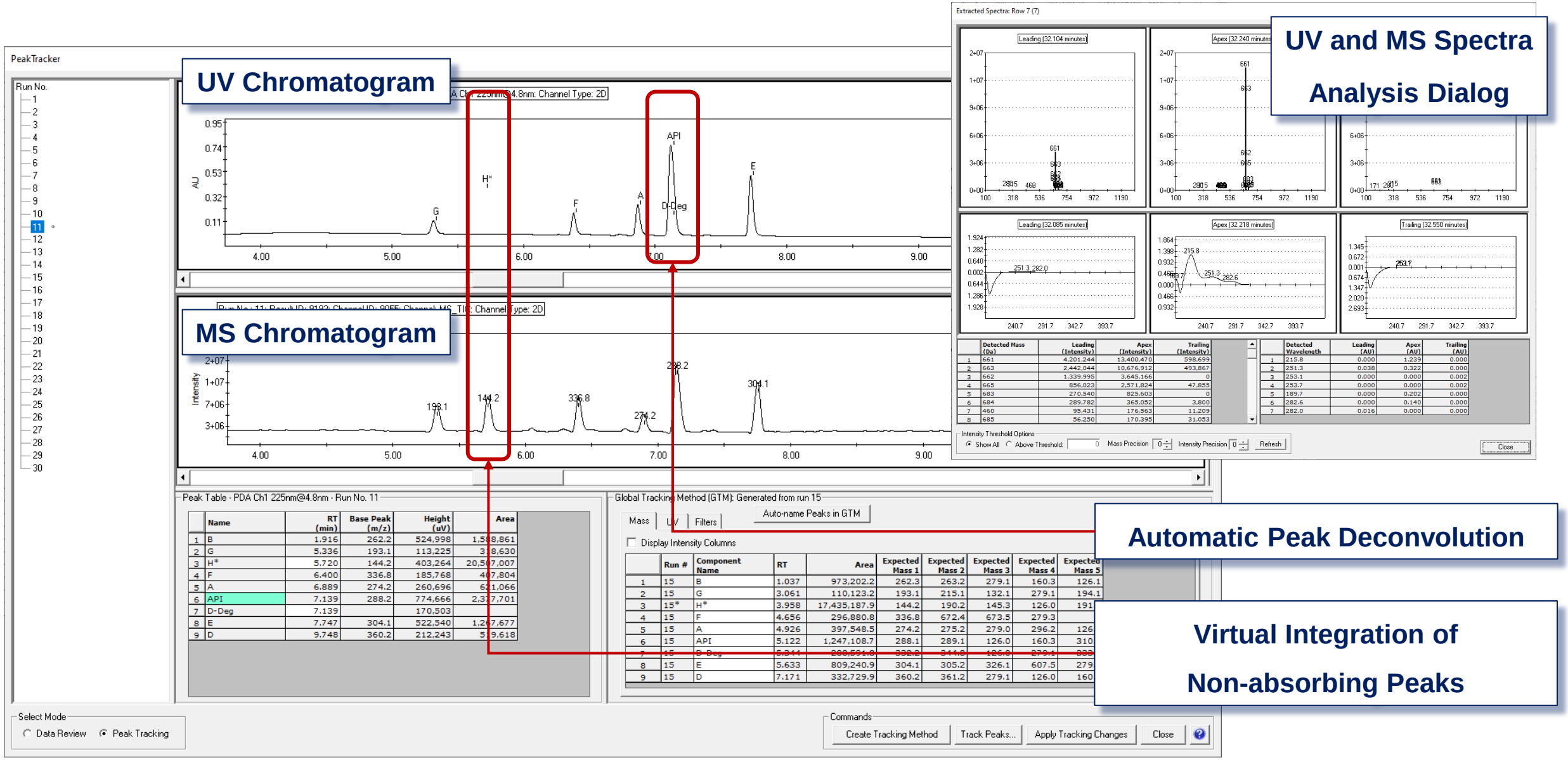
Parameter Selection – Optimization Study

Robust LC Method Optimization

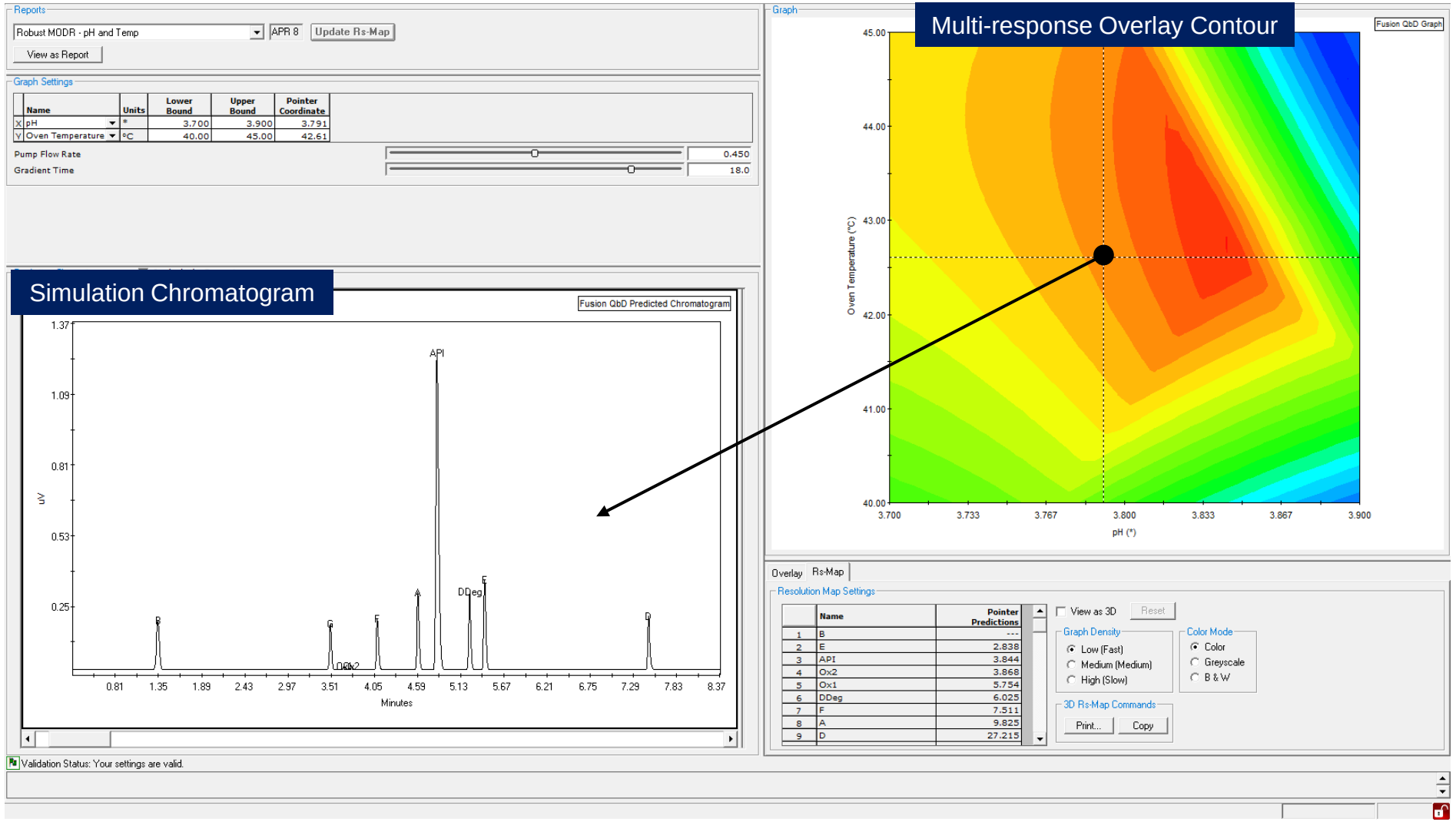
Method Parameter	Study Range
Pump Flow Rate (mL/min)	0.30 – 0.50
Column Oven Temperature (°C)	25.0 – 45.0
Gradient Time (min)*	20.0 – 25.0
pH	3.50 – 4.30
Column Type	CSH Phenyl-Hexyl

Light green background color indicates result obtained from screening study.

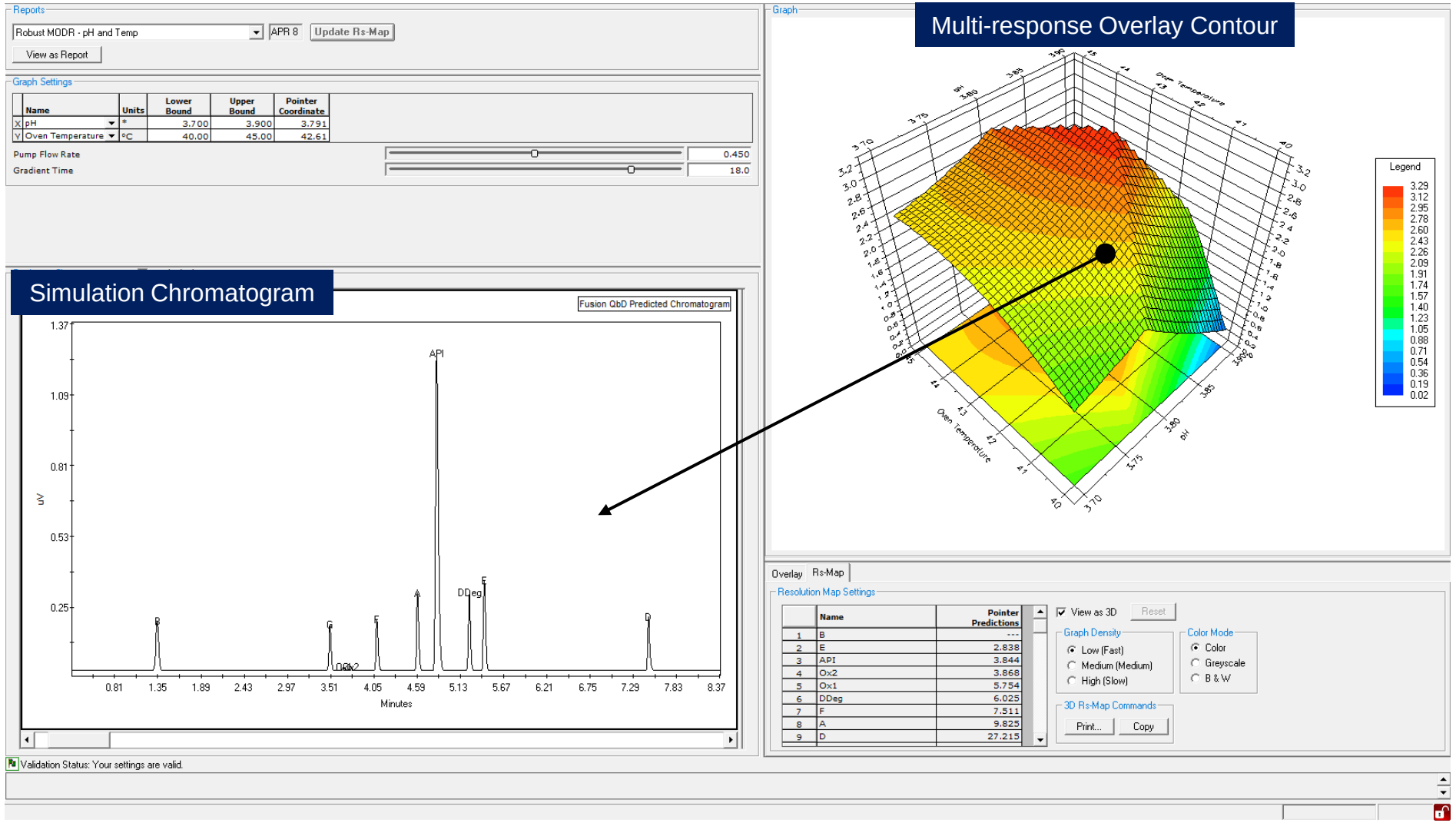
PeakTracker™ – UV & MS Data Based Tracking



Traditional Resolution Map – 2D

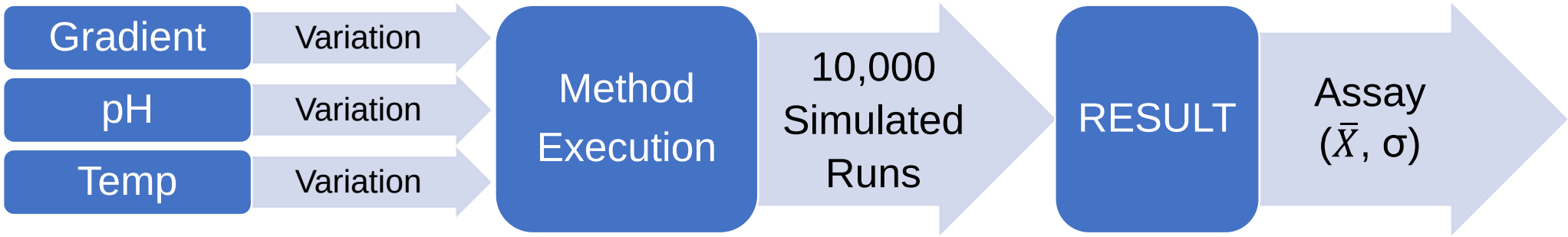


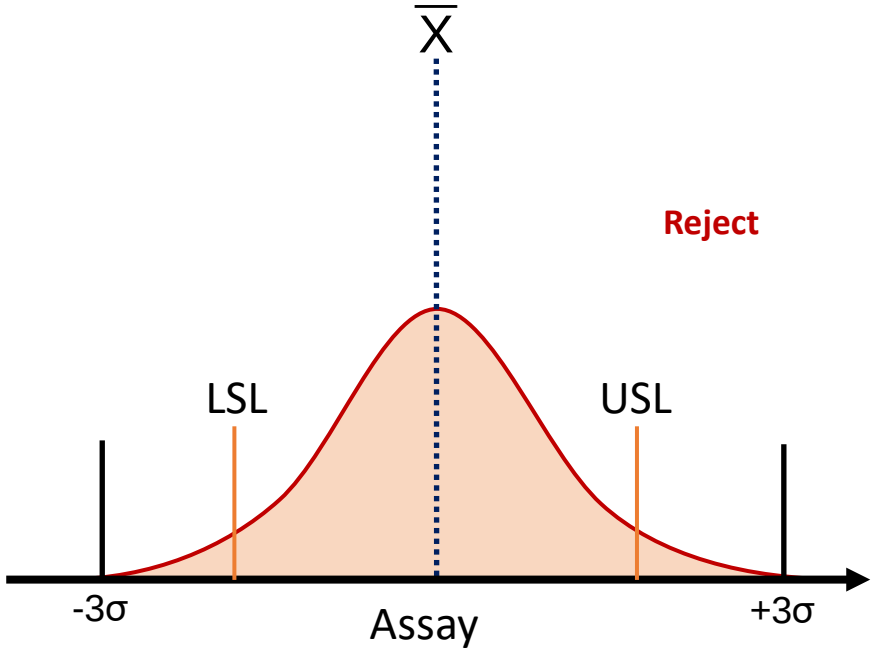
Resolution Map – 3D

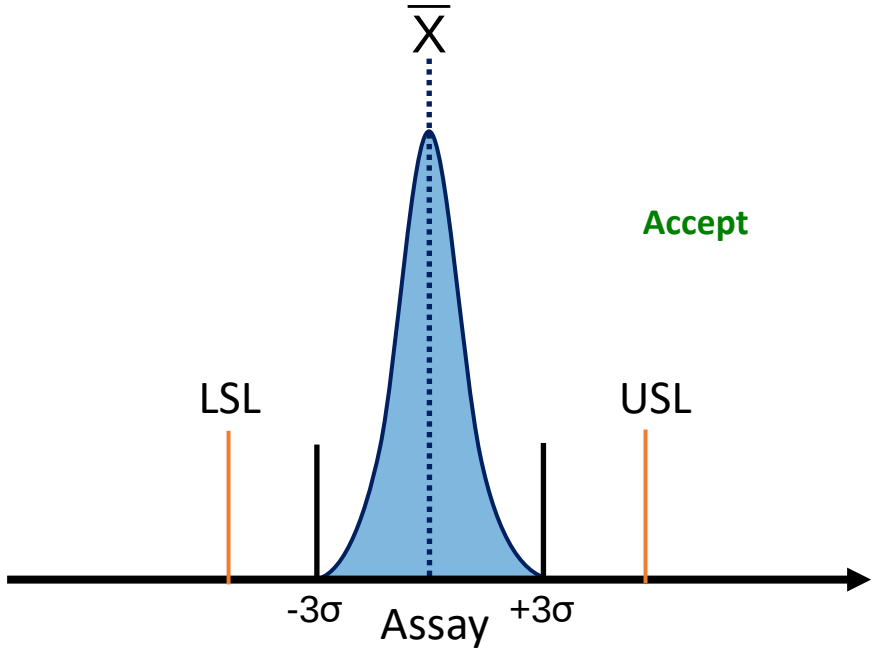


Monte Carlo Robustness Simulation

Example Study Parameters –
Expected Variation on Transfer



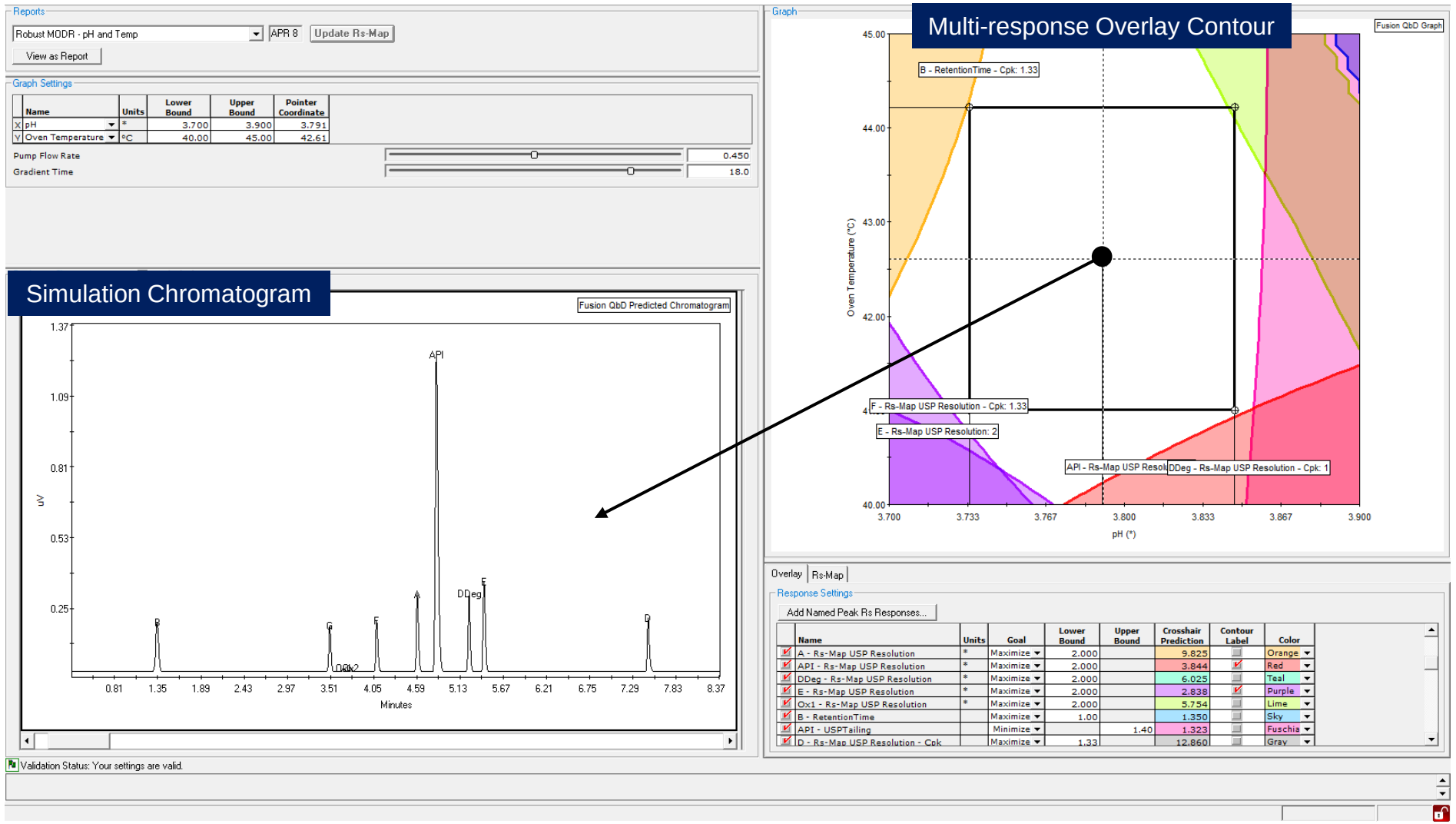




Robustness and MODR – Overlay

Mean Performance and Robustness:

- Resolution
- K-Prime
- Tailing
- Area %RSD
- Plates
- Run Time
- Etc.



Robustness and MODR – 4-factor Trellis

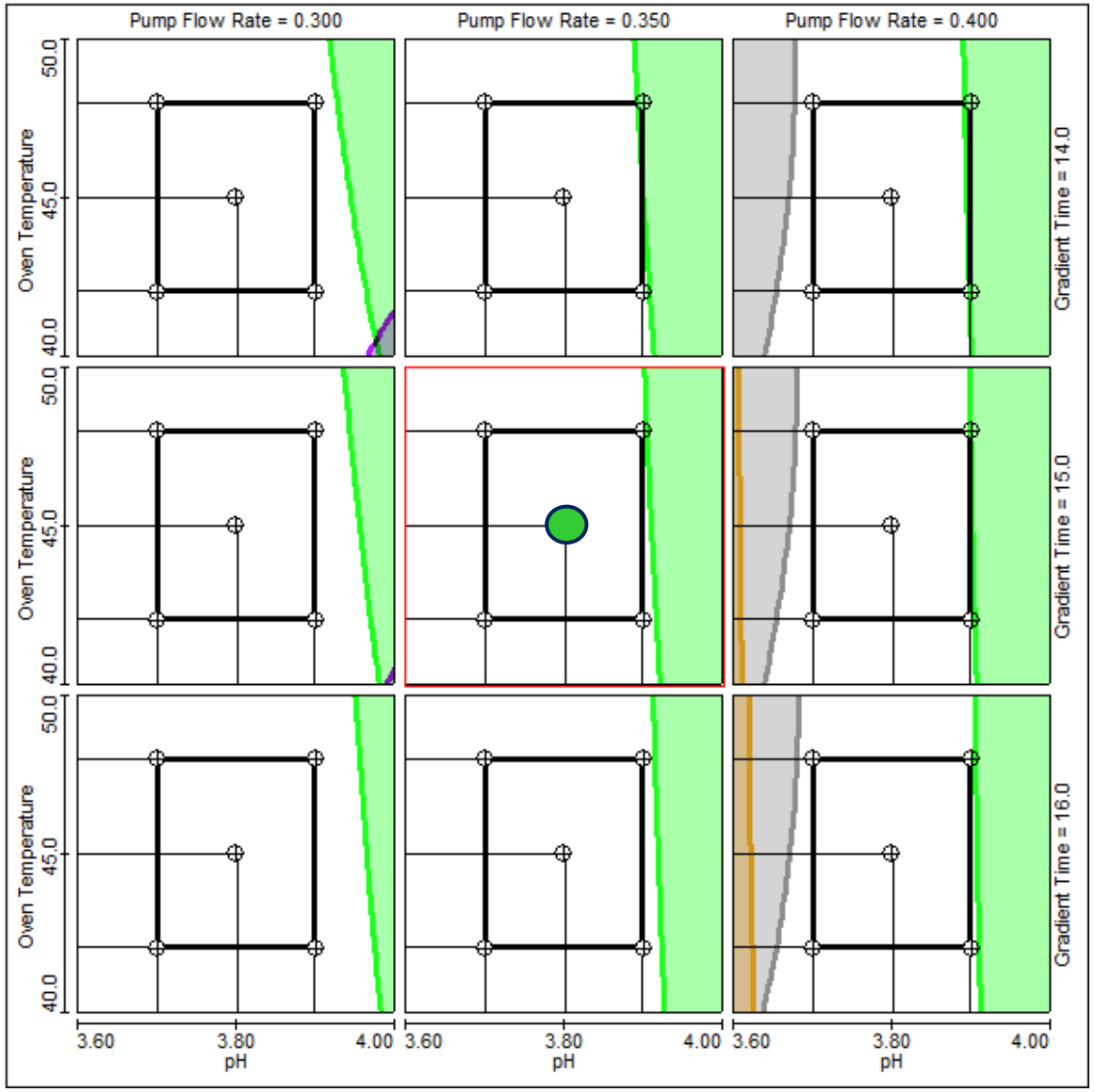
User Settable Expected Variation Ranges

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.

- Robustness Wizard – goes beyond development LC system – to expected variation in QC lab during ongoing use.
- MODR and Independently Adjustable Ranges rectangle
  - MODR (unshaded region) – methods are robust for all CQAs.
  - Rectangle & Trellis – independently adjustable ranges within which permanent post-approval changes can be made while maintaining robust performance for all CQAs.



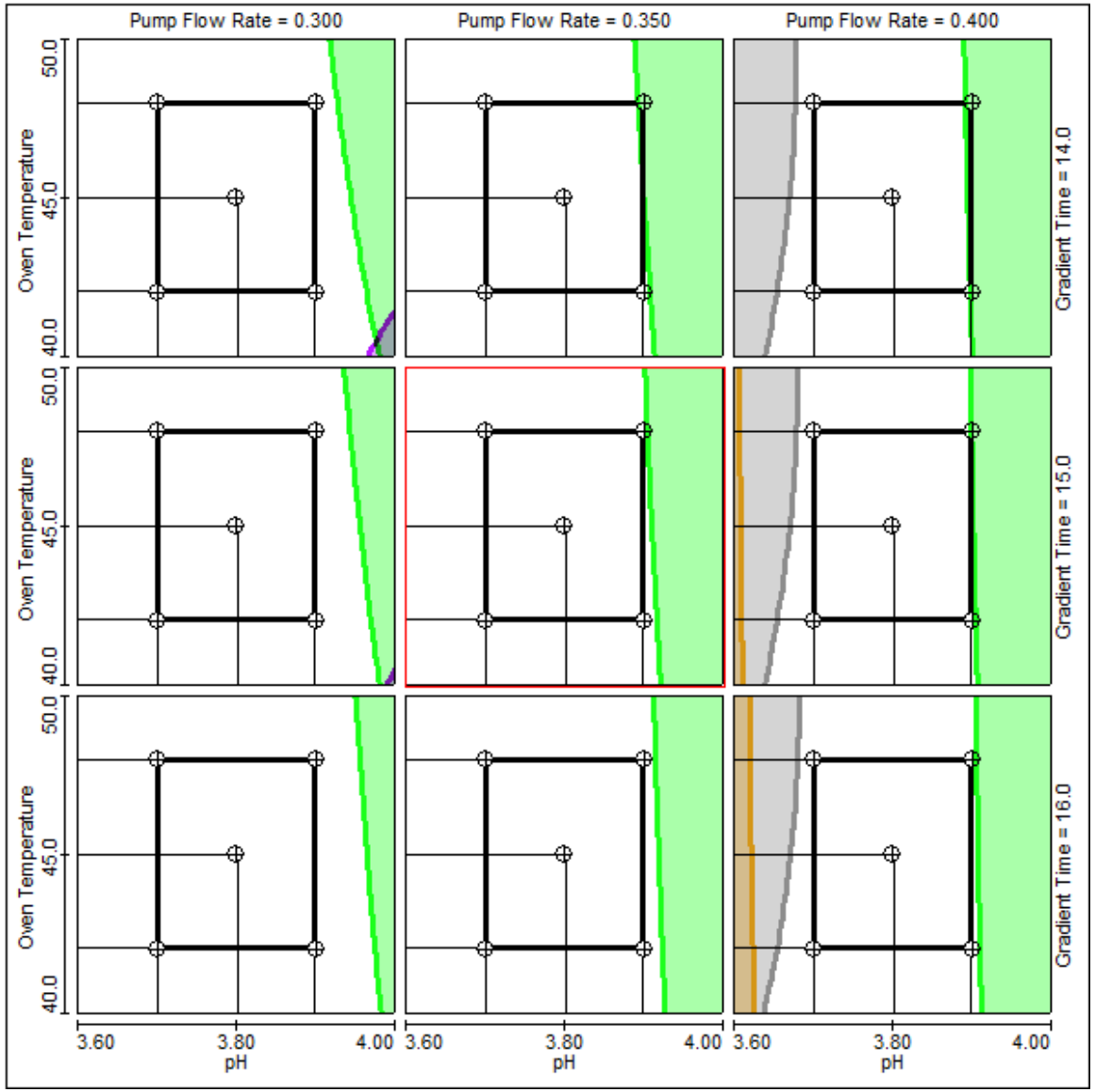
Analytical Control Strategy (ACS)

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.

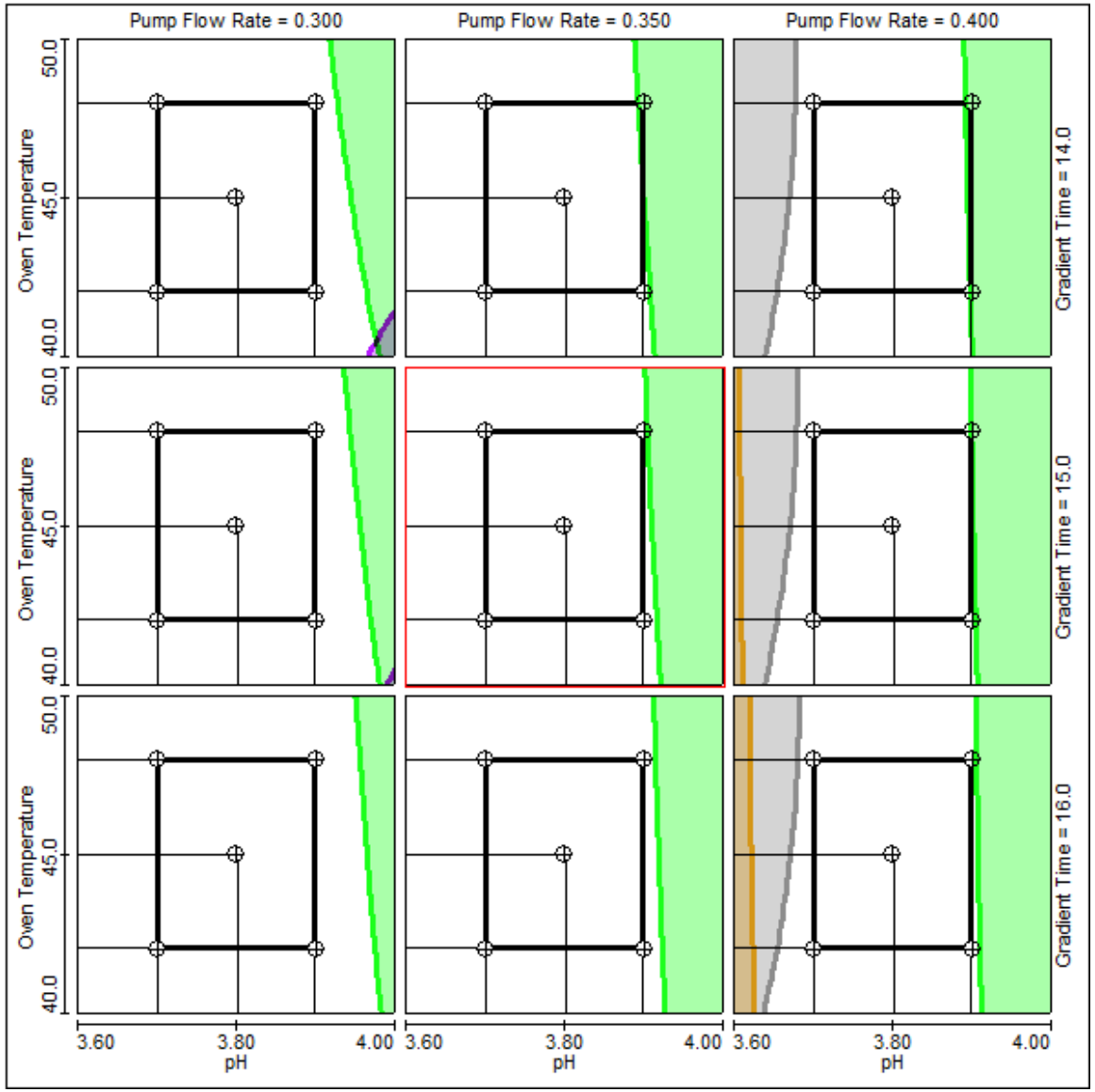
LC System Control Specifications



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

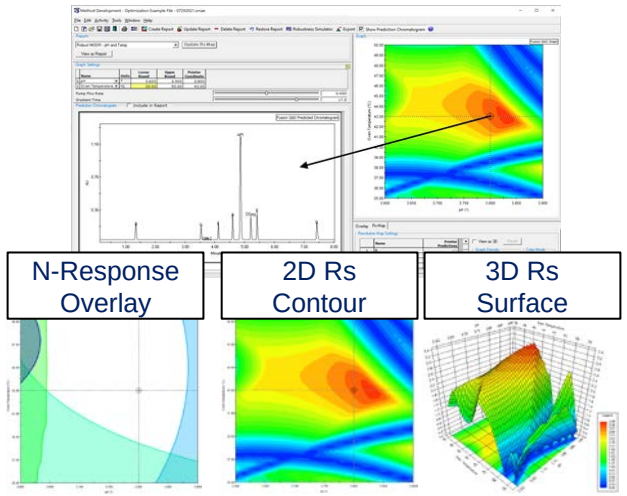
Routine Monitoring – Control Charts



Final LC Method → Replication Strategy Optimization

Robust LC Method Optimization

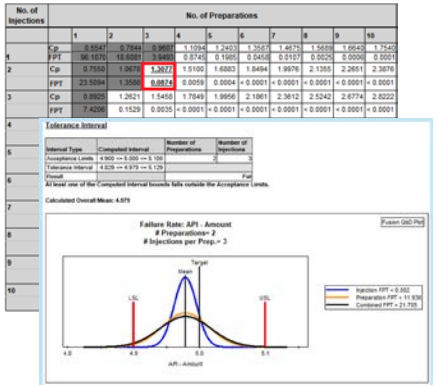
Establish Robust Method Operable Design Region (MODR) for all Critical Analytical Method Attributes.



Replication Strategy Optimization

Define % contributions of Preparation Error and Injection Error to Overall Method Precision (Total Analytical Error).

Select optimal Replication Strategy.



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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.

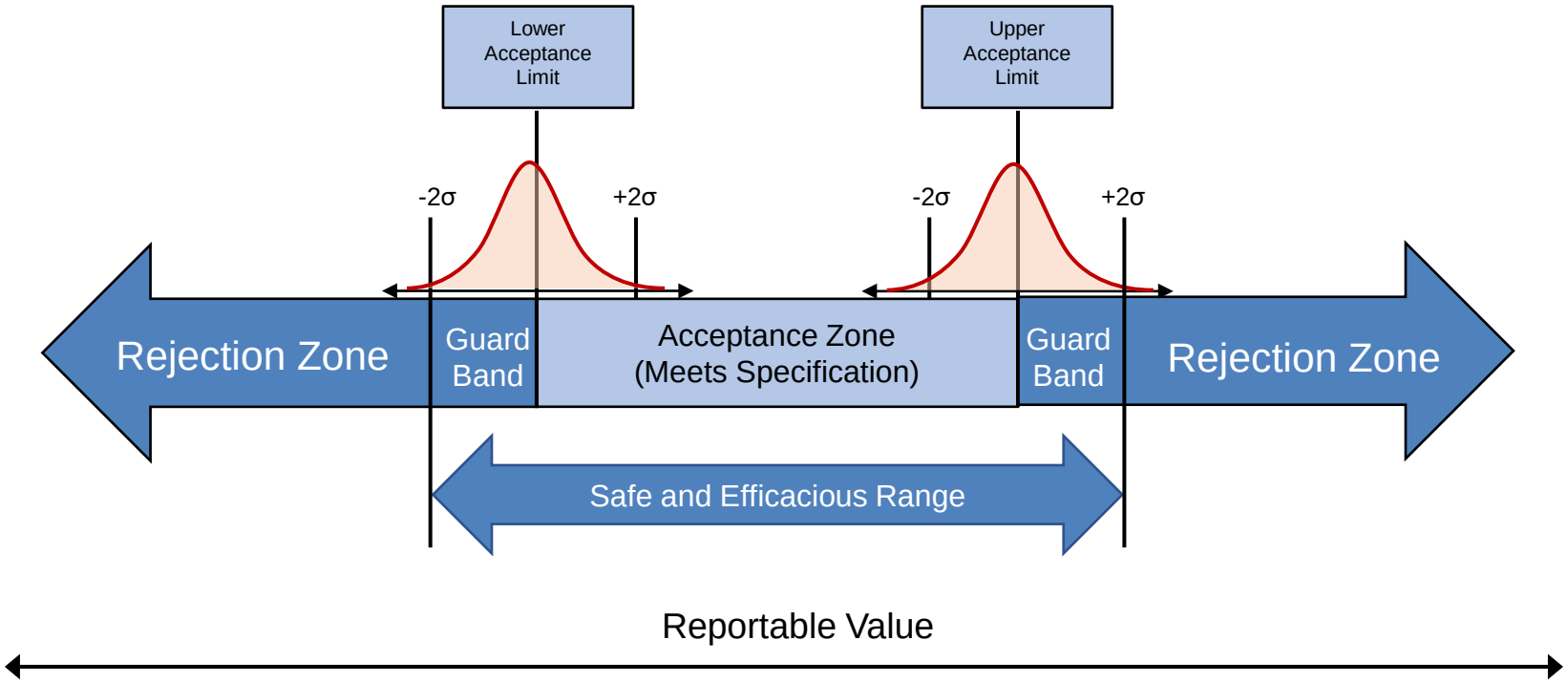
Determining Required Precision (σ_{max})

Tolerance Width = 4.00 (98.0 – 102.0)

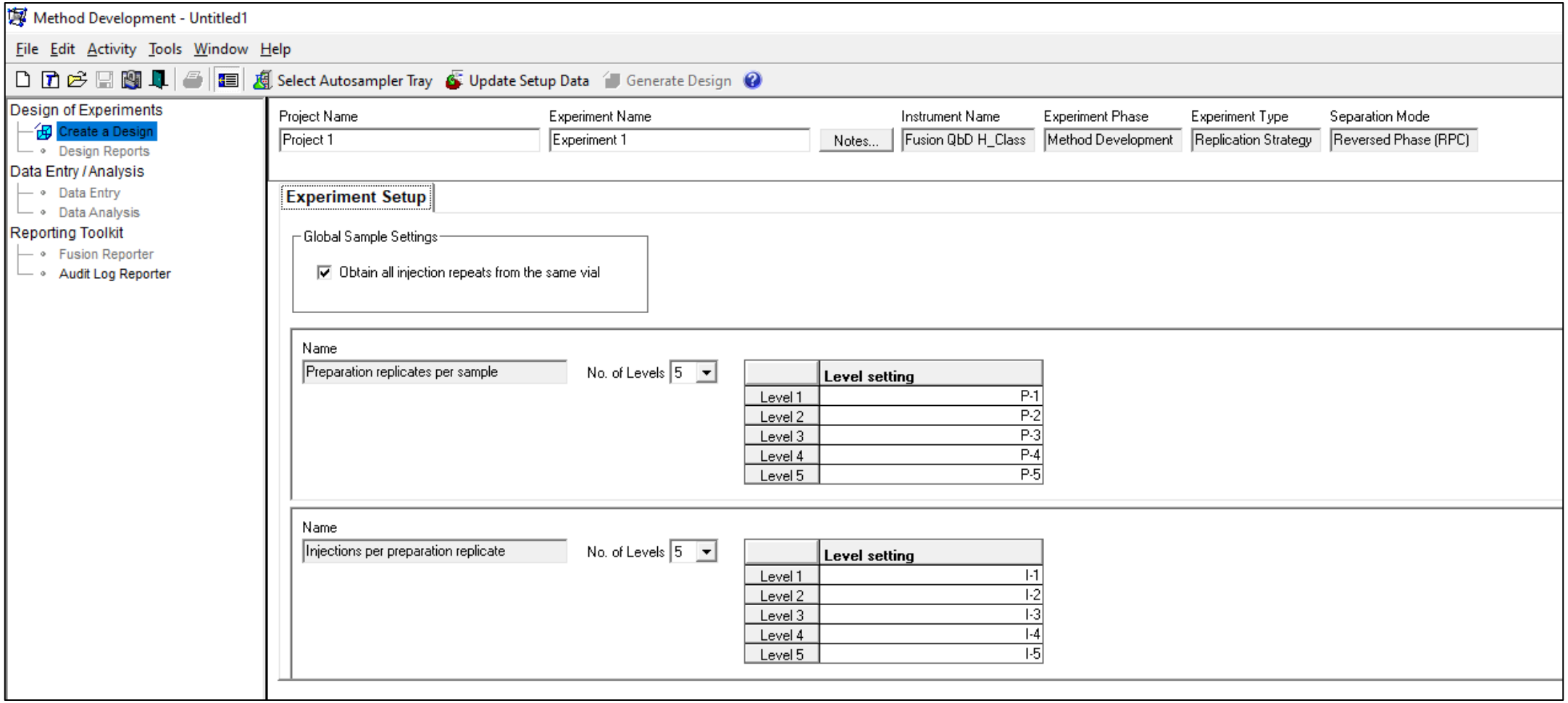
Precision Width = 0.30 x 4.00 = 1.20

Split between LAL and UAL = ±0.60

± 0.60 = ±2σ width for 95% C.I.



Replication Strategy for the Reportable Value



Replication Strategy for the Reportable Value

ANONA

Variable Name	Sum of Squares	Degrees of Freedom	Mean Square	F-ratio	P-value
Sample Preparation	4.05	4	1.01	56.9087	< 0.0001
Injection	0.36	20	0.02		
Overall	4.41	24			

Between Variables Components of Variation

Variable Name	Variance	Standard Deviation	Degrees of Freedom	t-table Value	(+/-) 95% Confidence Limits	Error Contribution (%)
Sample Preparation	0.20	0.45	4	2.7764	1.2	91.79
Injection	0.02	0.13	20	2.0860	0.2	8.21

Interval Test (USP < 1210 >)

Tolerance Interval

Interval Type	Computed Interval	Number of Preparations	Number of Injections per Preparation
Desired Probability %	90.00	2	2
Tolerance Alpha %	10.000		
Target	100.00		
Grand Mean	99.90		
Specification Limits	98.00 <= 100.00 <= 102.00		
Tolerance Interval	98.75 <= 99.90 <= 101.05		
Result	Pass		

Both computed Tolerance Interval bounds are within the defined limits.

±2σ / ±T.I. Results

No. of preparation replicates per sample	2
No. of injections per preparation replicate	2

Statistic	Value
Variance	0.084
±2σ - Target	0.600
±2σ - Calculated	0.580
Standard Deviation	0.289
% RSD	0.29
% CV	0.29

Process Capability - TOST

Cp Failure Rates Reference

Cp	No. of Failures per Thousand	Sigma
0.33	322.174119	1
0.67	44.431189	2
1.00	2.699796	3
1.33	0.066073	4
1.67	0.000544	5
2.00	0.000002	6

No. of Injections		No. of Preparations									
		1	2	3	4	5	6	7	8	9	10
1	±2σ	0.8384	0.5928	0.484	0.4192	0.3749	0.3423	0.3169	0.2964	0.2795	0.2651
	±T.I.	1.4067	0.8614	0.5885	0.556	0.4873	0.4386	0.4019	0.373	0.3495	0.3299
2	±2σ	0.821	**0.5805**	0.474	0.4105	0.3672	0.3352	0.3103	0.2903	0.2737	0.2596
	±T.I.	1.1929	**0.5885**	0.579	0.5166	0.4569	0.4139	0.3811	0.355	0.3336	0.3156
3	±2σ	0.8151	0.5764	0.4706	0.4076	0.3645	0.3328	0.3081	0.2882	0.2717	0.2578
	±T.I.	1.1167	0.579	0.5733	0.5033	0.4467	0.4056	0.3741	0.349	0.3283	0.3109
4	±2σ	0.8121	0.5743	0.4689	0.4061	0.3632	0.3316	0.307	0.2871	0.2707	0.2568
	±T.I.	1.0773	0.5733	0.5695	0.4966	0.4416	0.4015	0.3706	0.3459	0.3256	0.3085
5	±2σ	0.8104	0.573	0.4679	0.4052	0.3624	0.3308	0.3063	0.2865	0.2701	0.2563
	±T.I.	1.0532	0.5695	0.5667	0.4926	0.4385	0.399	0.3685	0.3441	0.324	0.3071
6	±2σ	0.8092	0.5722	0.4672	0.4046	0.3619	0.3304	0.3058	0.2861	0.2697	0.2559
	±T.I.	1.0369	0.5667	0.5647	0.4899	0.4364	0.3973	0.3671	0.3429	0.323	0.3061
7	±2σ	0.8084	0.5716	0.4667	0.4042	0.3615	0.33	0.3055	0.2858	0.2694	0.2556
	±T.I.	1.0253	0.5647	0.5631	0.488	0.435	0.3962	0.3662	0.3421	0.3222	0.3054
8	±2σ	0.8077	0.5711	0.4663	0.4039	0.3612	0.3297	0.3053	0.2856	0.2692	0.2554
	±T.I.	1.0164	0.5631	0.5618	0.4866	0.4339	0.3953	0.3654	0.3414	0.3216	0.3049
9	±2σ	0.8072	0.5708	0.466	0.4036	0.361	0.3295	0.3051	0.2854	0.2691	0.2553
	±T.I.	1.0095	0.5618	0.556	0.4854	0.433	0.3946	0.3648	0.3409	0.3212	0.3045
10	±2σ	0.8068	0.5705	0.4658	0.4034	0.3608	0.3294	0.3049	0.2852	0.2689	0.2551
	±T.I.	1.004	0.5166	0.5166	0.4845	0.4323	0.394	0.3644	0.3405	0.3208	0.3042

Final LC Method → Sample Prep Method Optimization

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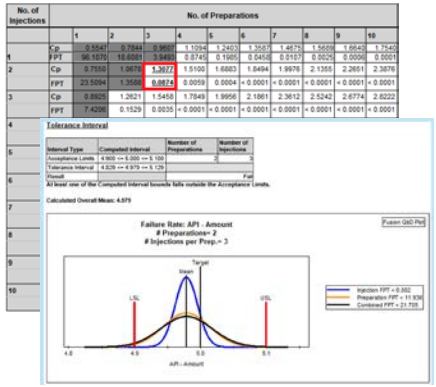
Replication Strategy Optimization

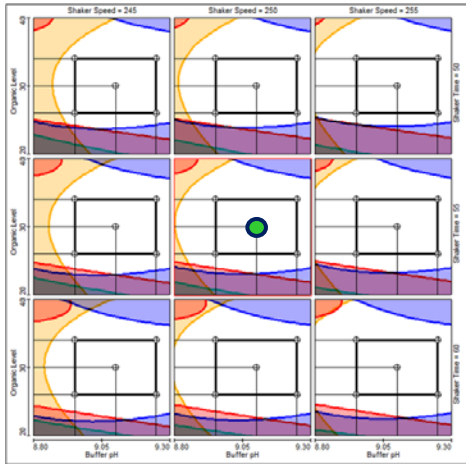
Define % contributions of Preparation Error and Injection Error to Overall Method Precision (Total Analytical Error).

Select optimal Replication Strategy.



Sample Preparation Method Optimization

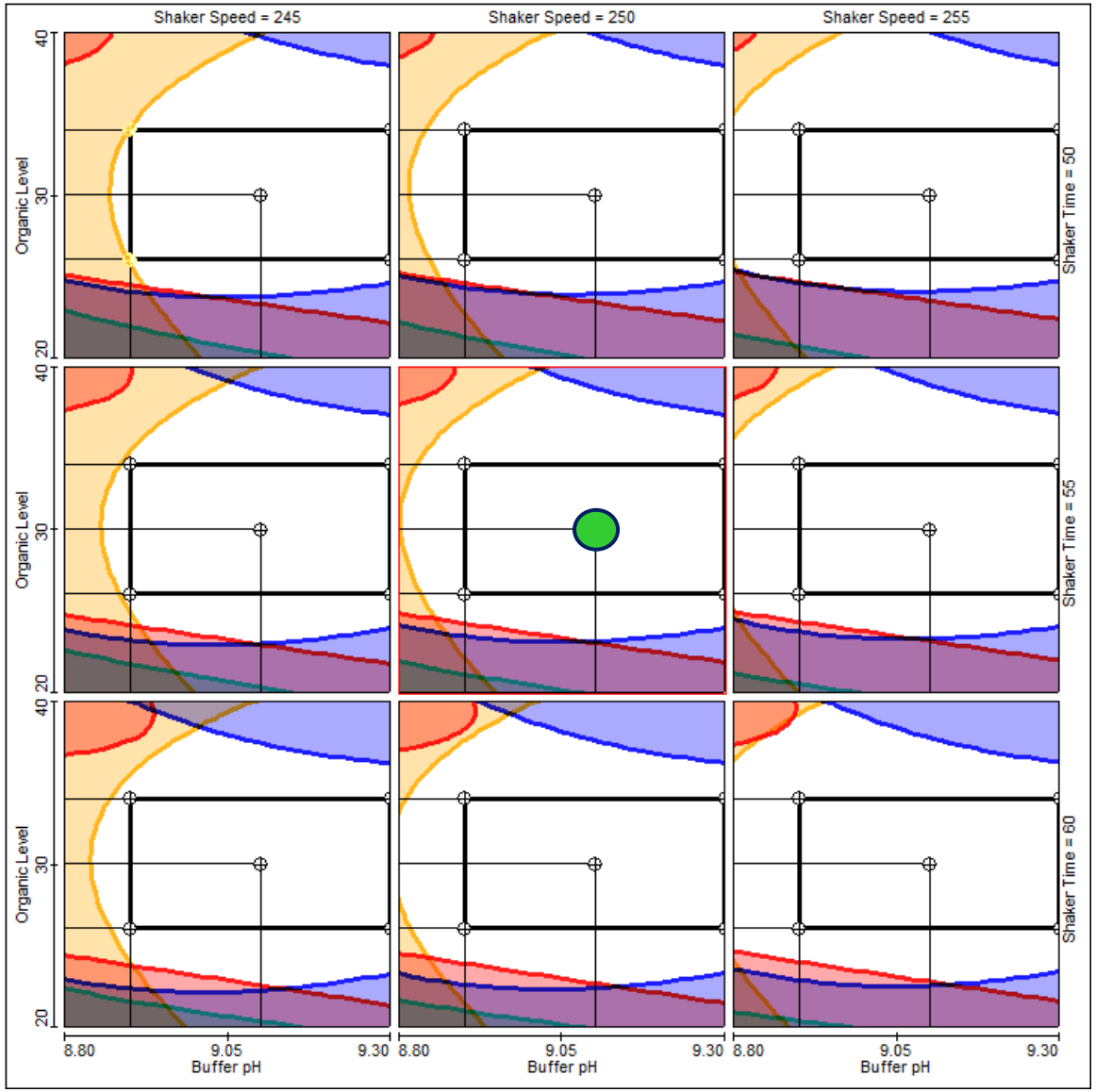
Sample Preparation Optimization reduces the amount of the TAE contributed by the current Sample Preparation Method.



Analytical Control Strategy (ACS)

Enabled	Experiment Variable	Units	Maximum Expected Variation (±3σ Value)
☑	Buffer pH	*	0.15
☑	Organic Level	%	2
☐	Sonication Time	min	0
☑	Shaker Speed	rpm	5
☑	Shaker Time	min	2

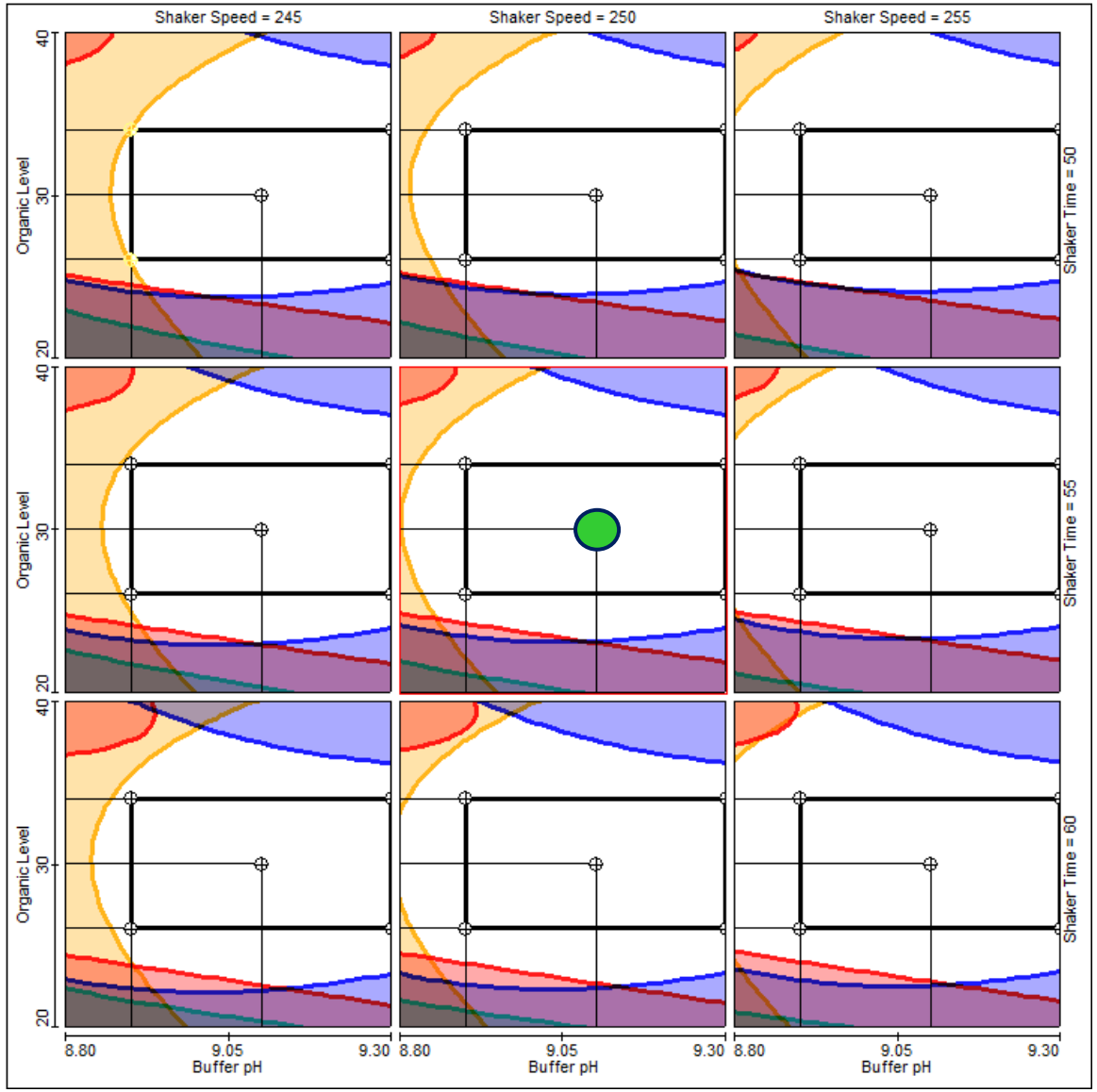
Prep Factor Operating/Control Specs



Analytical Control Strategy (ACS)

	Name	Units	Goal	Lower Bound	Upper Bound	Color
☑	API 1 - %L.C.-(1_1)	*	Target	96.50	98.50	Blue
☑	API 2 - %L.C.-(1_2)	*	Target	97.50	99.50	Red
☑	API 1 - %L.C.-(1_1) - Cpm		Maximize	1.33		Orange
☑	API 2 - %L.C.-(1_2) - Cpm		Maximize	1.33		Teal

Routine Monitoring – Control Charts



The Business Case

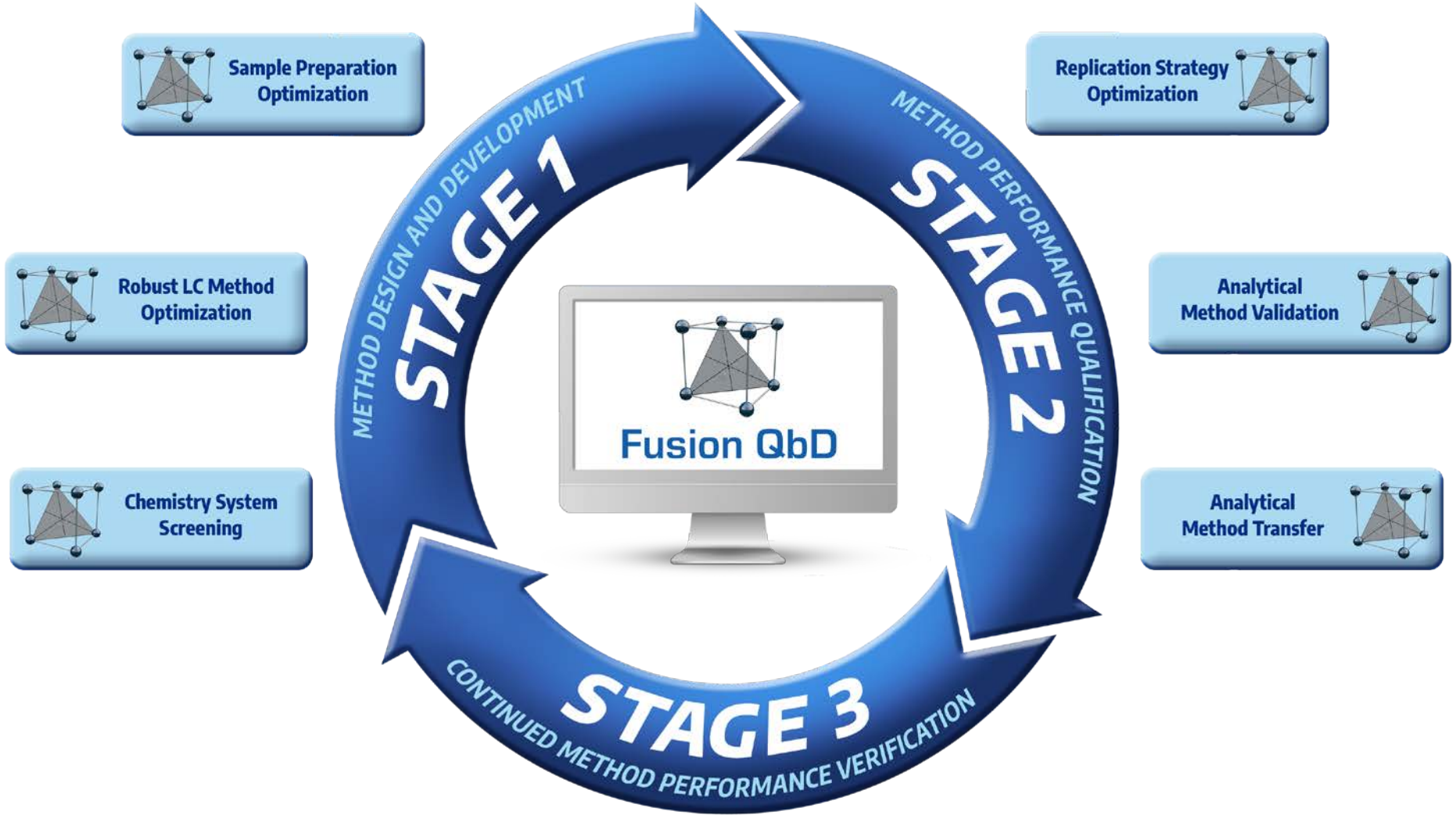
Why am I doing this?

Development of a fit-for purpose robust method makes good business sense for three important reasons.

1. Minimizes the possibility that the method will fail on validation and/or transfer.
2. Minimizes or eliminates out-of-specification results, and therefore OOS investigations.
3. Most importantly, it provides accurate, precise, unbiased results which support both good business decisions and successful regulatory review.

S-Matrix

THANK YOU!



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