

***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)

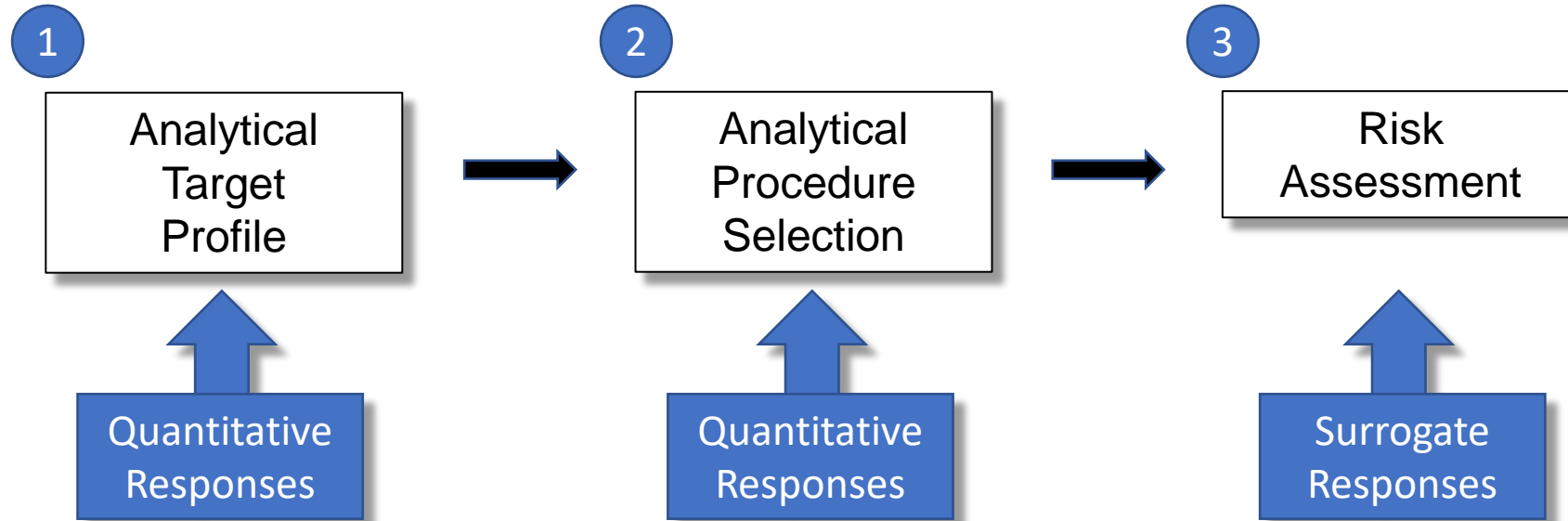
- a. Establishing a true, multi-dimensional, robust MODR.
- b. Capturing the Analytical Control Strategy knowledge required for APLM Stage 3.

3. Replication Strategy Optimization

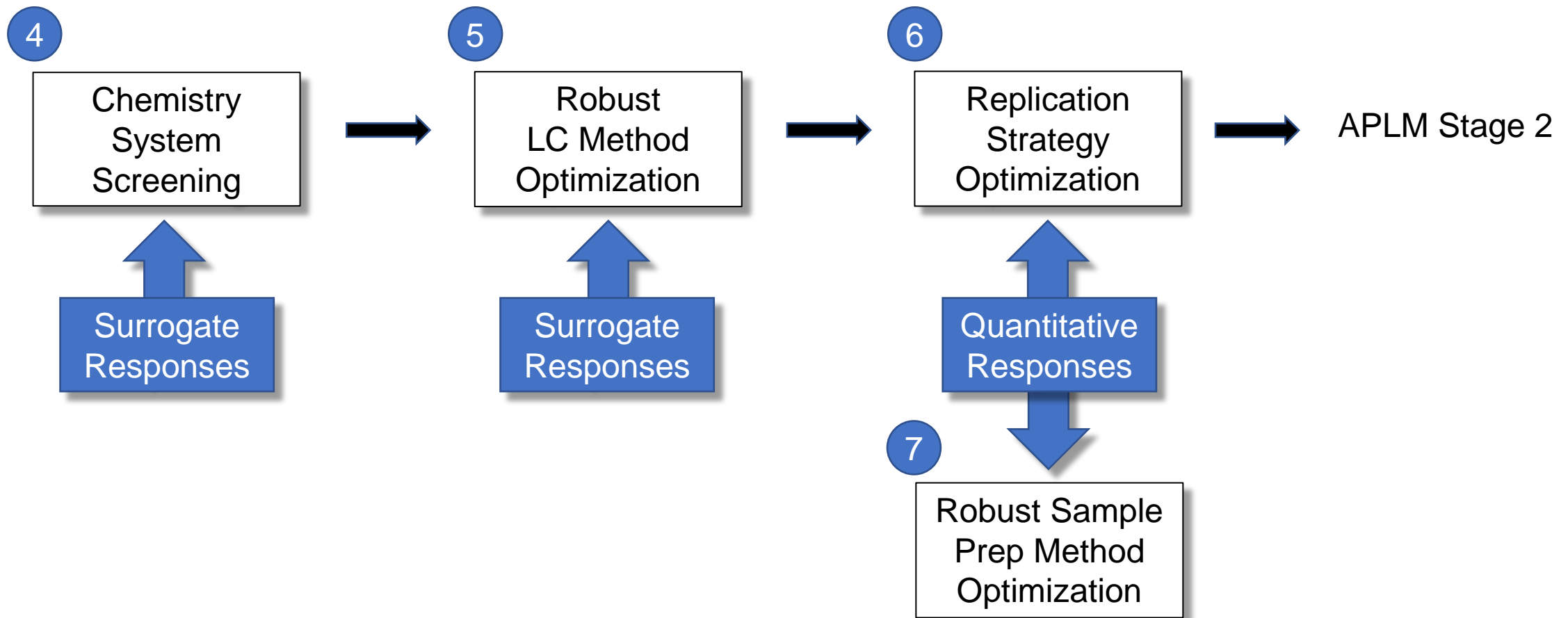
Identifying the most efficient strategy for generating Reportable Values (a.k.a. Reportable Results) which meet ATP Performance Requirements.

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

APLM Stage 1 Workflow



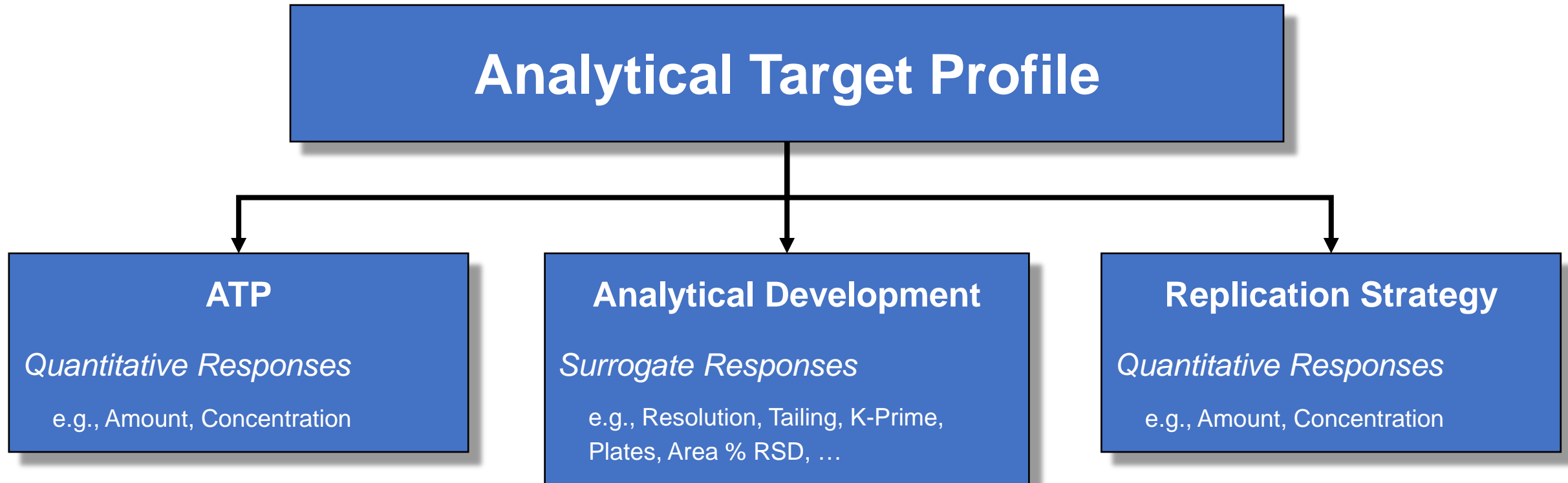
APLM Stage 1 Workflow - Continued



7

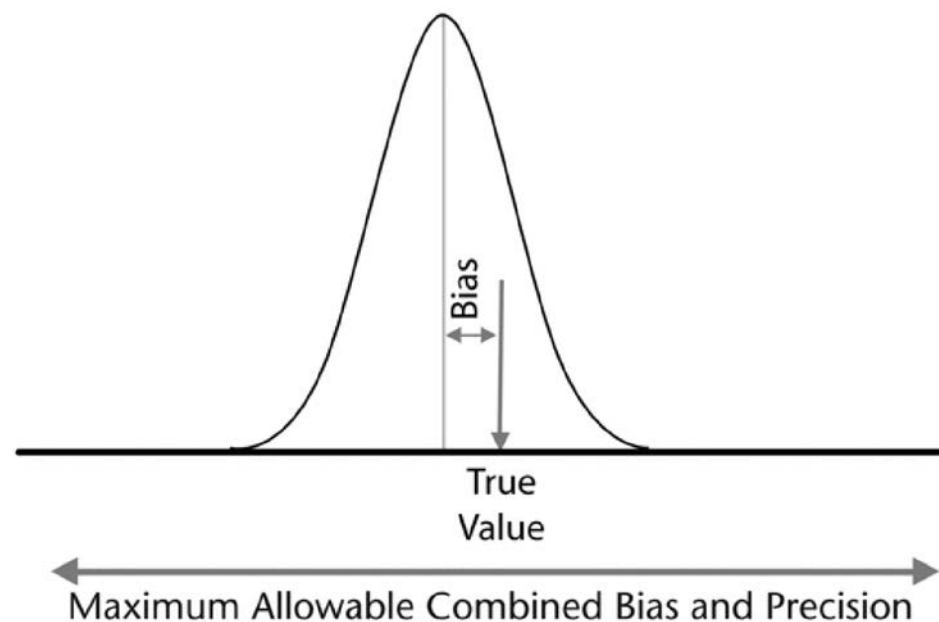
Run a Sample Preparation Optimization study when the minimum Replication Strategy required to meet the method precision requirements in the ATP is not feasible, and Sample Prep is the major source of error.

ATP as a Bridge



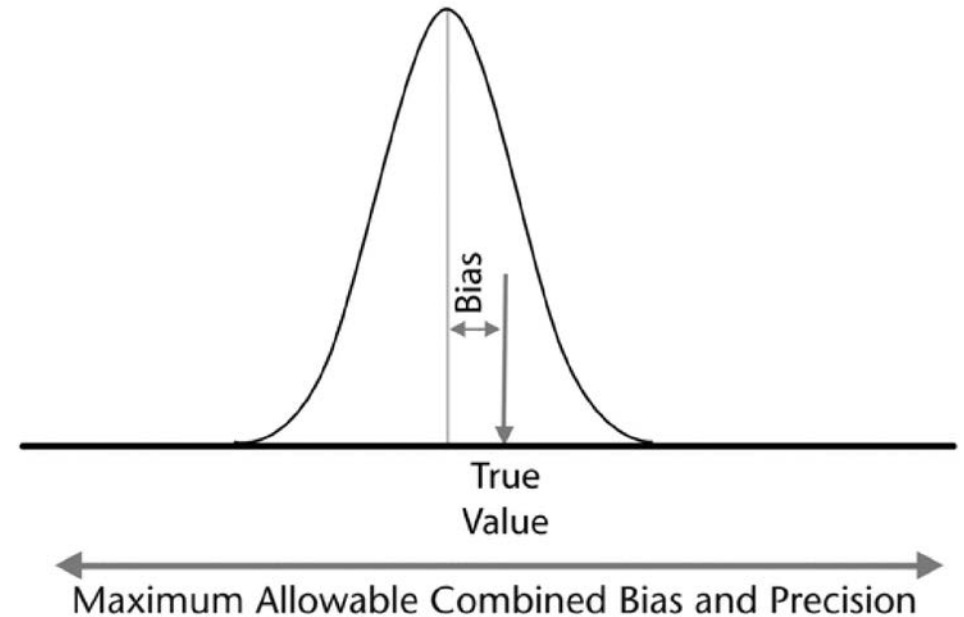
Analytical Target Profile (USP <1220>)

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 \pm [C%].



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.



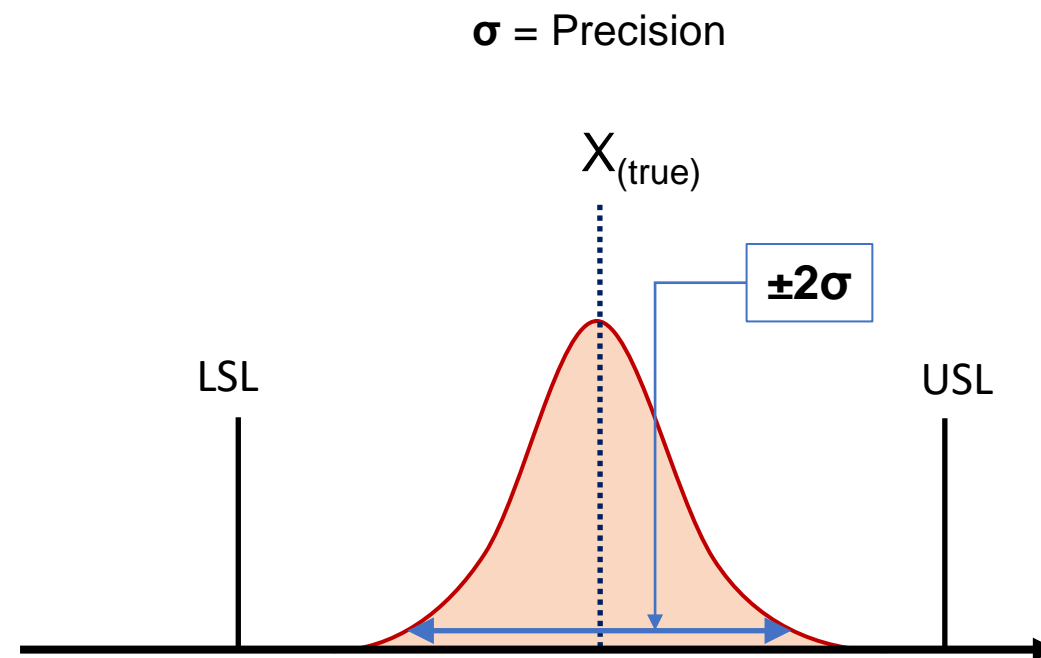
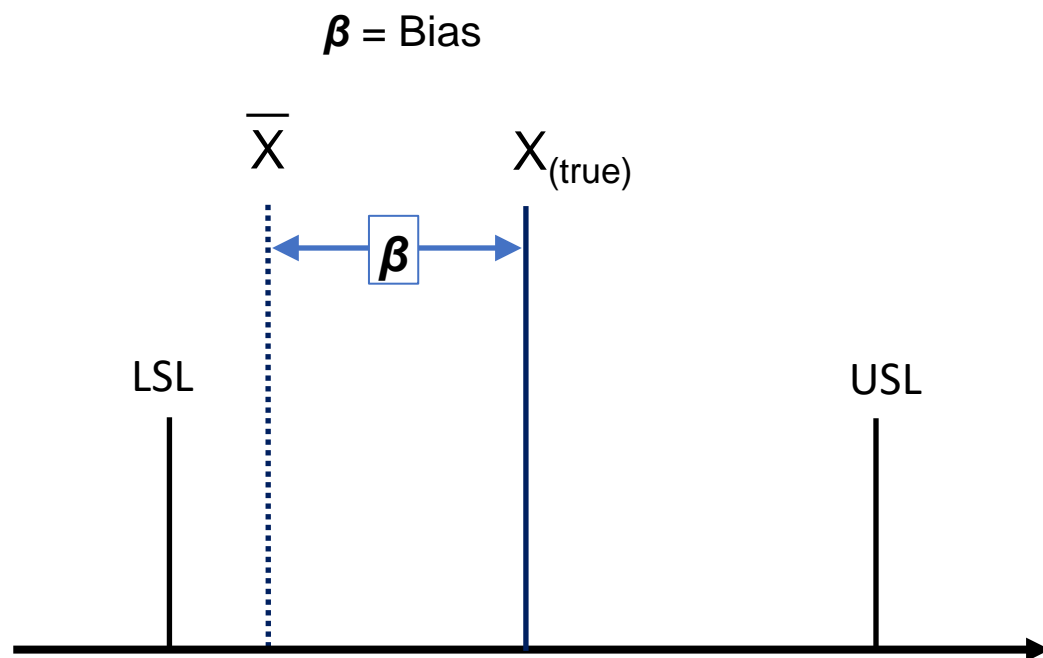
Two Critical Considerations:

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.

3. ACCURACY AND PRECISION

3.2 Combined Validation of Accuracy and Precision

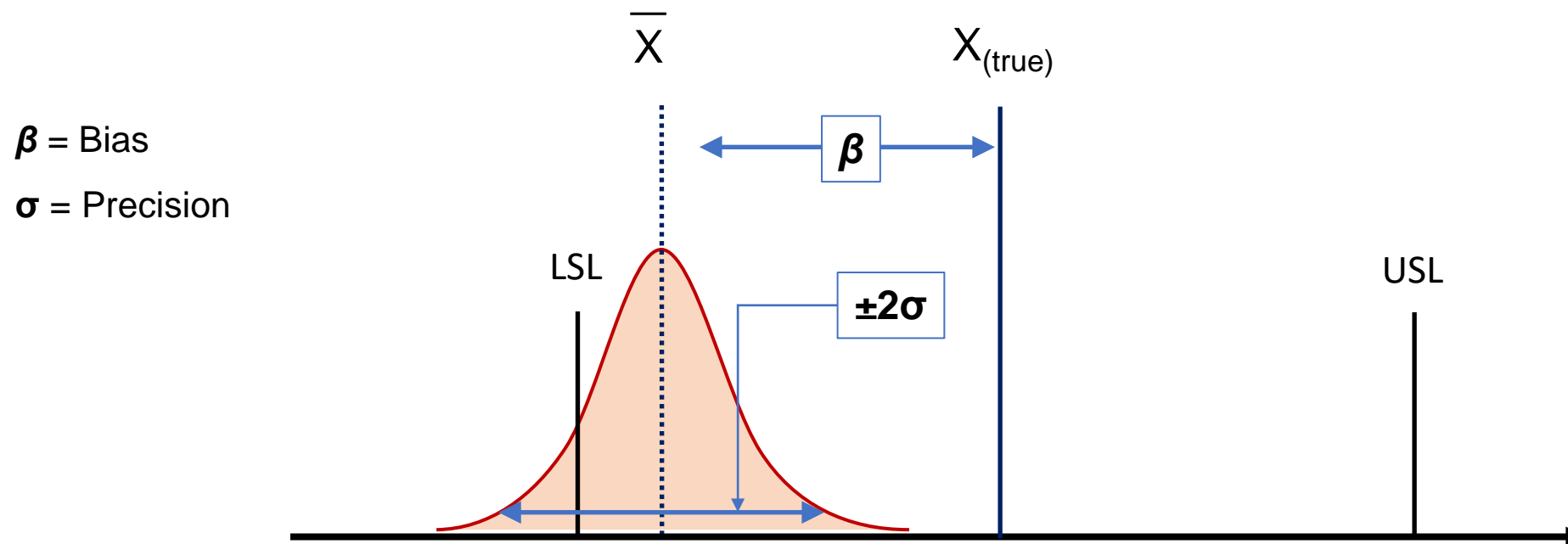
An underperforming method can pass System Suitability for the Critical Method Attribute being evaluated when Accuracy (β – bias) and Precision (σ – precision) **are assessed separately = High Risk Approach.**



3. ACCURACY AND PRECISION

3.2 Combined Validation of Accuracy and Precision

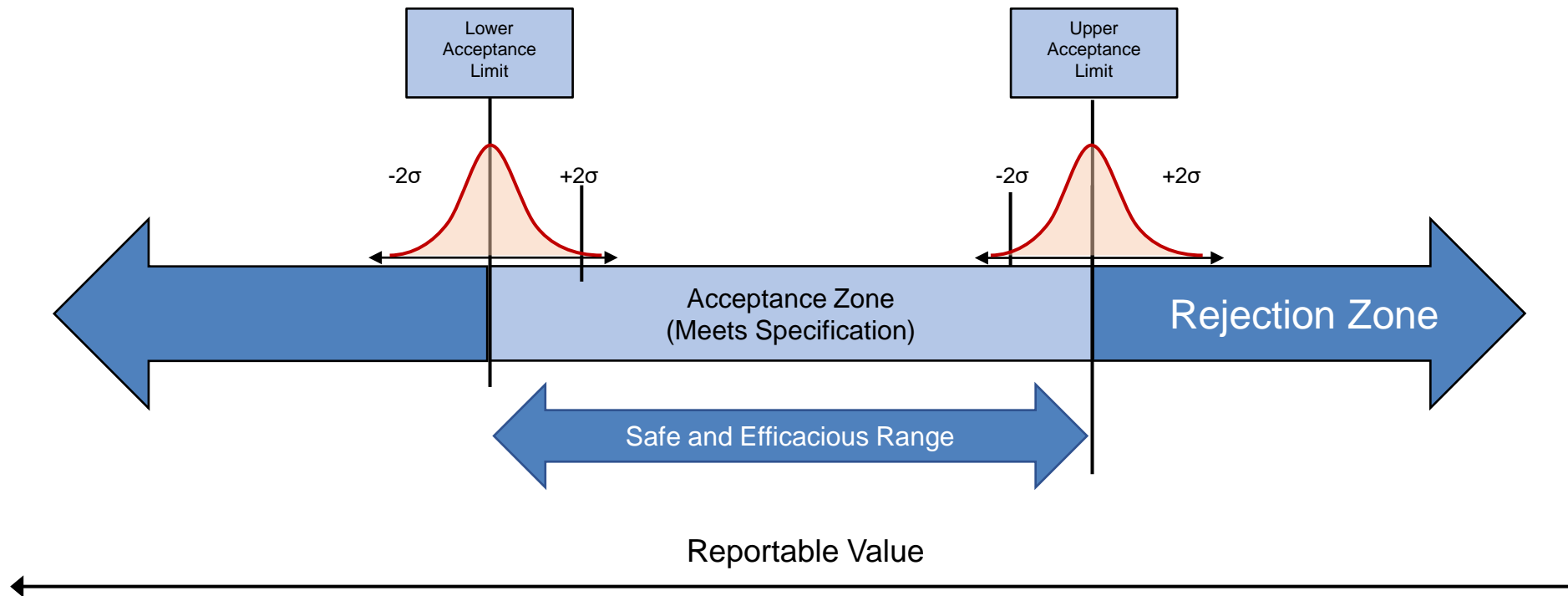
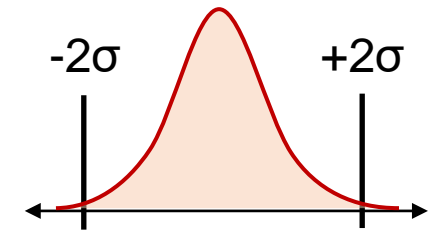
As the illustration below shows – the method does not have acceptable System Suitability performance for the Critical Quality Attribute (CQA) being tested when both Accuracy (β – bias estimation) and Precision (σ – variation estimation) are assessed together = Low Risk Approach.



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”.

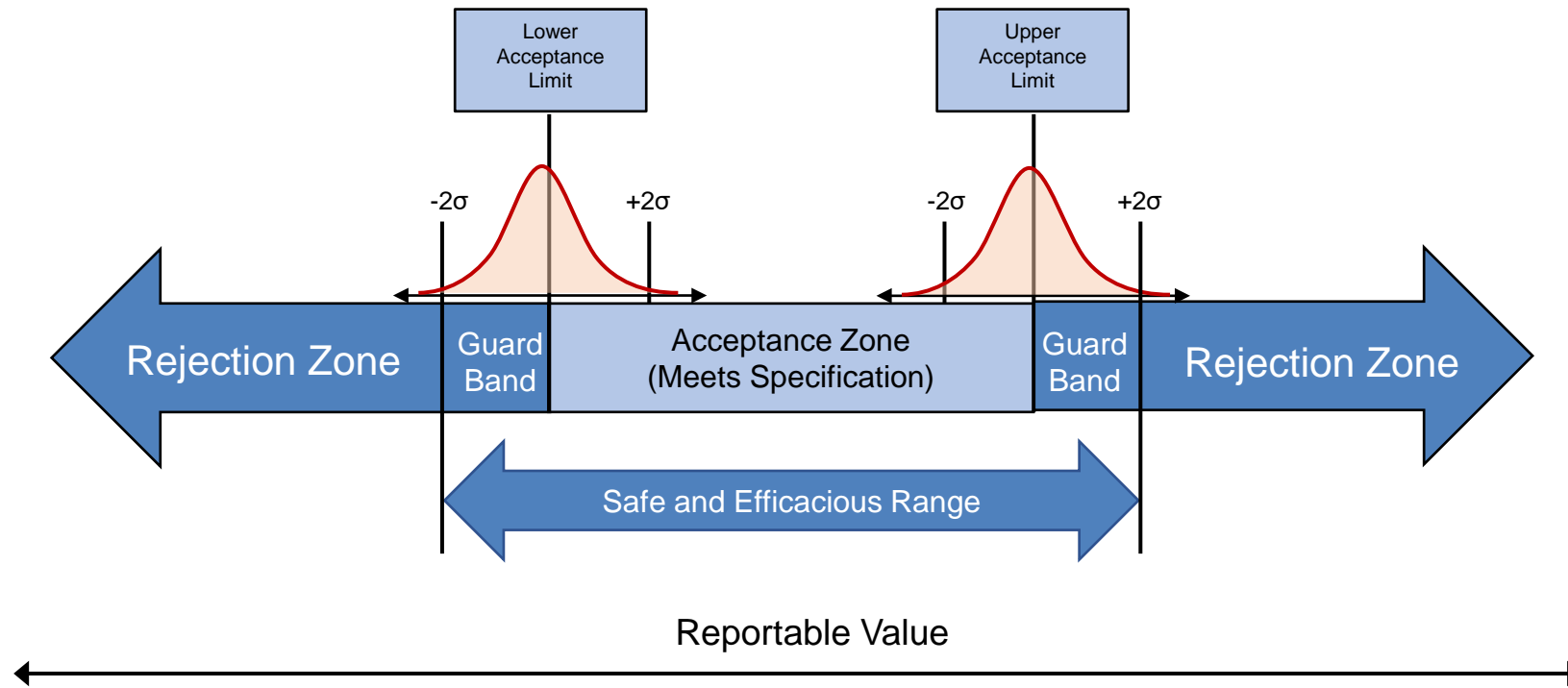
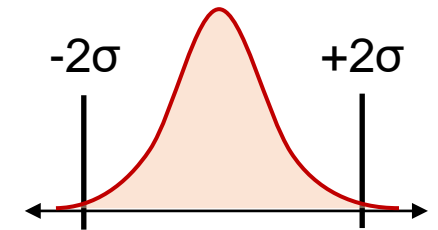
Total Analytical Error Distribution



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.

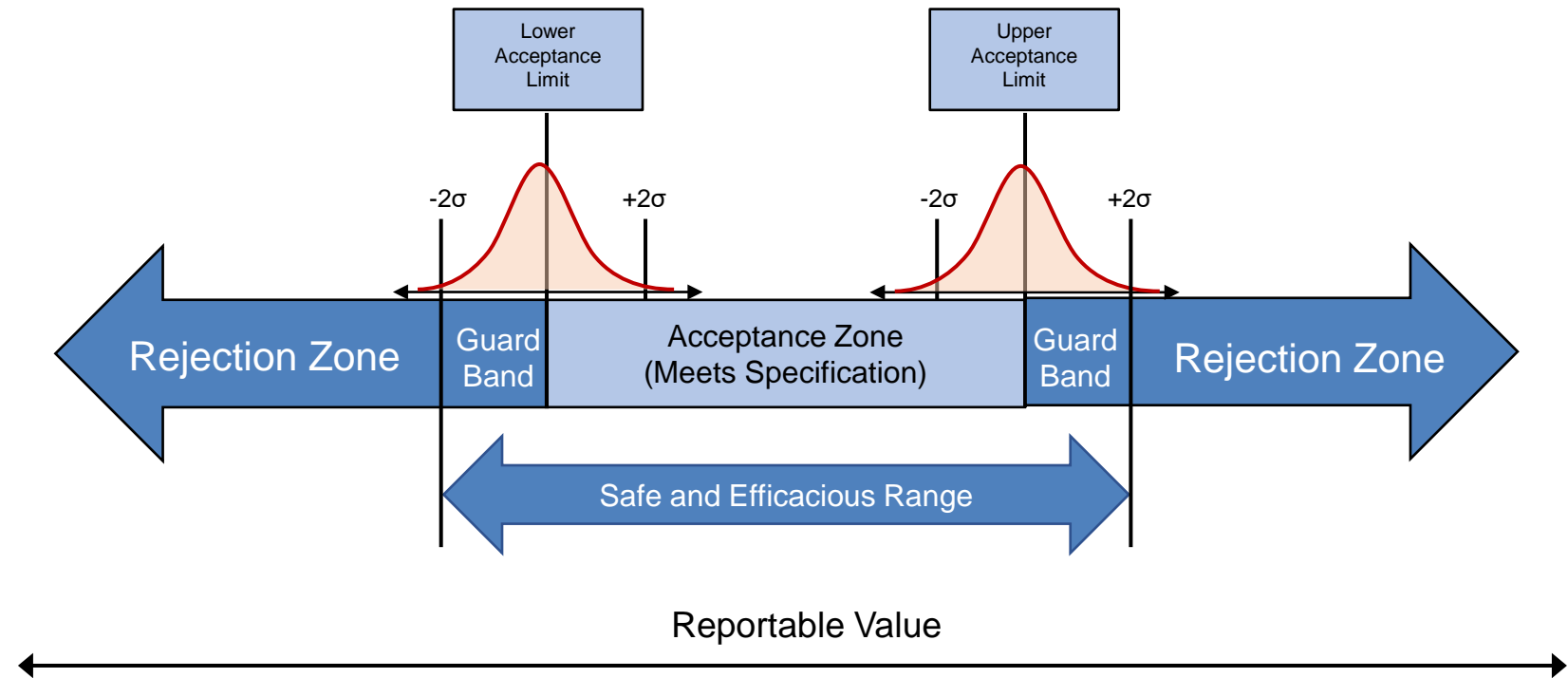
Determining Required Precision (σ_{\max})

Tolerance Width = 4.00 (98.0 – 102.0)

Precision Width = $0.30 \times 4.00 = 1.20$

Split between LAL and UAL = ± 0.60

$\pm 0.60 = \pm 2\sigma$ width for 95% C.I.



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

Selected Analytical Procedure = UHPLC:

Combined Bias and Precision Allowance Becomes the ATP Quantitation

Performance Metric:

- Robust Method Optimization
- Replication Strategy Optimization

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

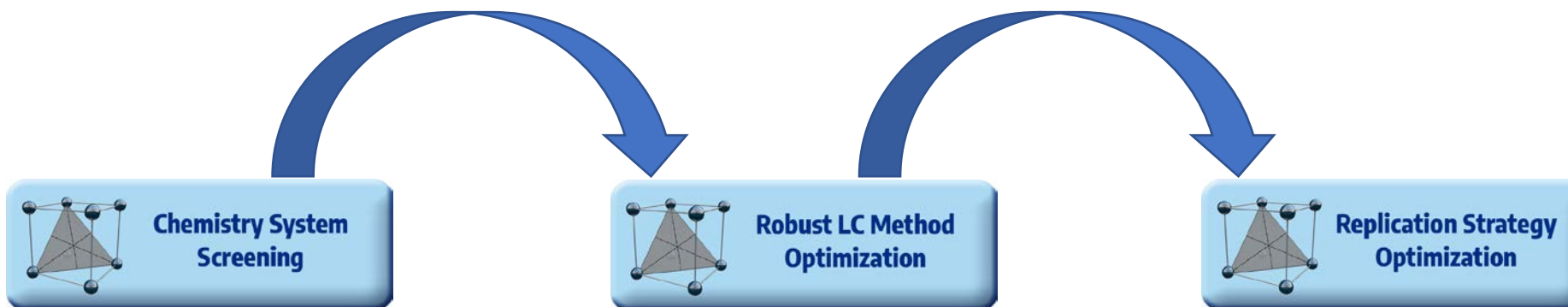
C = Controlled Factor, N = Noise Factor, X = eXperimental Factor (S = Screening, O = Optimization)

Impact Severity

Low = 1
Medium = 3
High = 5

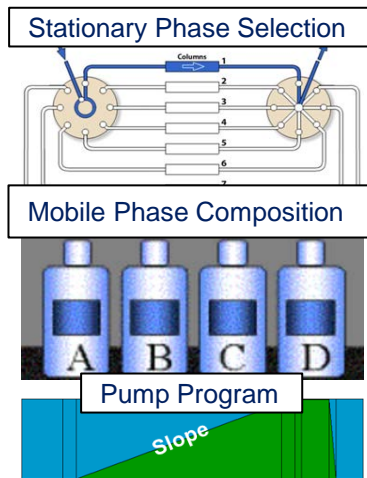
Full Experiment Automation with the CDS.

Full 21 CFR 11 Compliance with Bi-directional Audit Trail



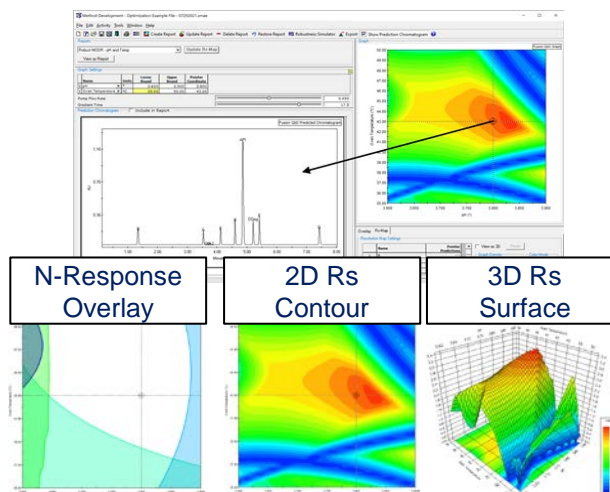
Chemistry System Screening

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



Robust LC Method Optimization

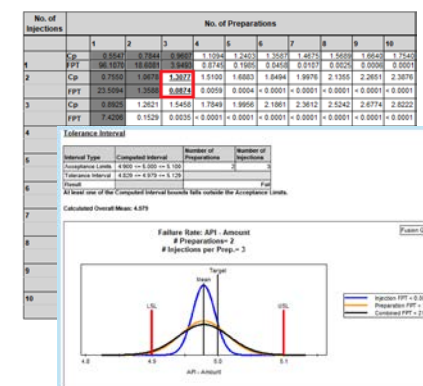
Establish Robust Method Operable Design Region (MODR) for all Critical Analytical Method Attributes.



Replication Strategy Optimization

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

Select optimal Replication Strategy.



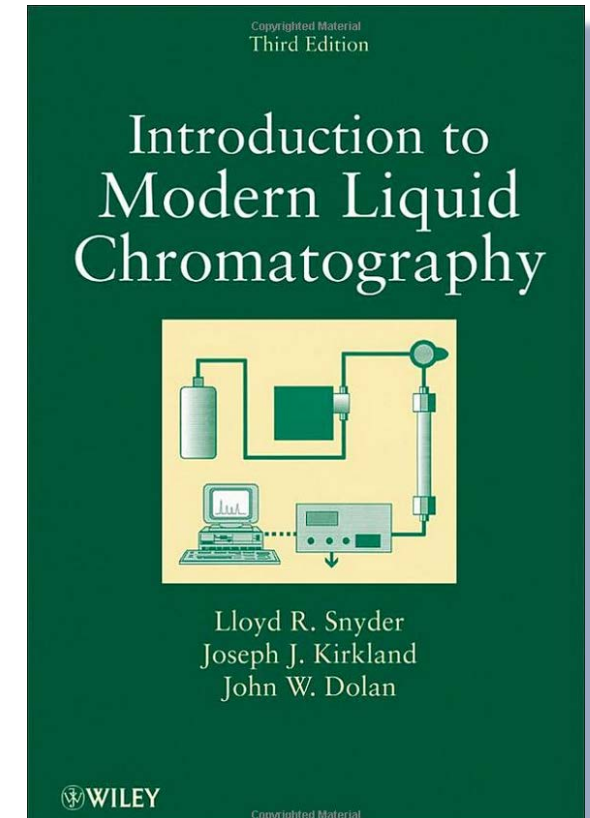


Chemistry System
Screening

“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)

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

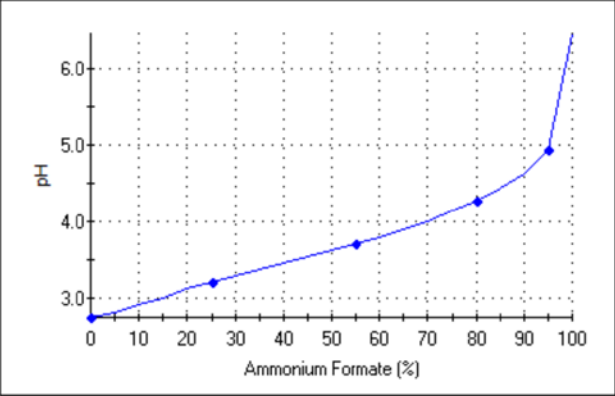
Select One of the Built-in Buffer Systems or Enter Your Own

Buffer Selector

Select Buffer System
pH 2.74 - 6.45 [Formate System (20 mM)]

Buffer Solutions

- Formic Acid (20 mM) - pH 2.74
- Ammonium Formate (20 mM) - pH 6.45



No. of Levels: 5

Buffer	Buffer Name	pH Level
Acid	Formic Acid (20 mM)	2.73
Base	Ammonium Formate (20 mM)	3.20
		3.69
		4.27
		4.93

	Included	pH	Formic Acid (%)	Ammonium Formate (%)
1	<input checked="" type="checkbox"/>	2.74	100.00	0.00
2	<input type="checkbox"/>	2.80	95.00	5.00
3	<input type="checkbox"/>	2.91	90.00	
4	<input type="checkbox"/>	3.00	85.00	
5	<input type="checkbox"/>	3.11	80.00	
6	<input checked="" type="checkbox"/>	3.20	75.00	
7	<input type="checkbox"/>	3.29	70.00	
8	<input type="checkbox"/>	3.37	65.00	
9	<input type="checkbox"/>	3.45	60.00	
10	<input type="checkbox"/>	3.53		
11	<input type="checkbox"/>	3.61		
12	<input checked="" type="checkbox"/>	3.69		
13	<input type="checkbox"/>	3.78		
14	<input type="checkbox"/>	3.88		

Select All Select None OK Cancel

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: Time Precision

	No.	Step Name	Time State	Time - Lower Bound	Time - Upper Bound	% Strong Solvent
<input checked="" type="checkbox"/>	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	---	---
<input checked="" type="checkbox"/>	6	Column Wash	Constant ▼	4.00	---	99.0
	7	Ramp Down from Wash	Constant	0.50	---	---
<input checked="" type="checkbox"/>	8	Re-equilibration	Constant ▼	3.00	---	5.0

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

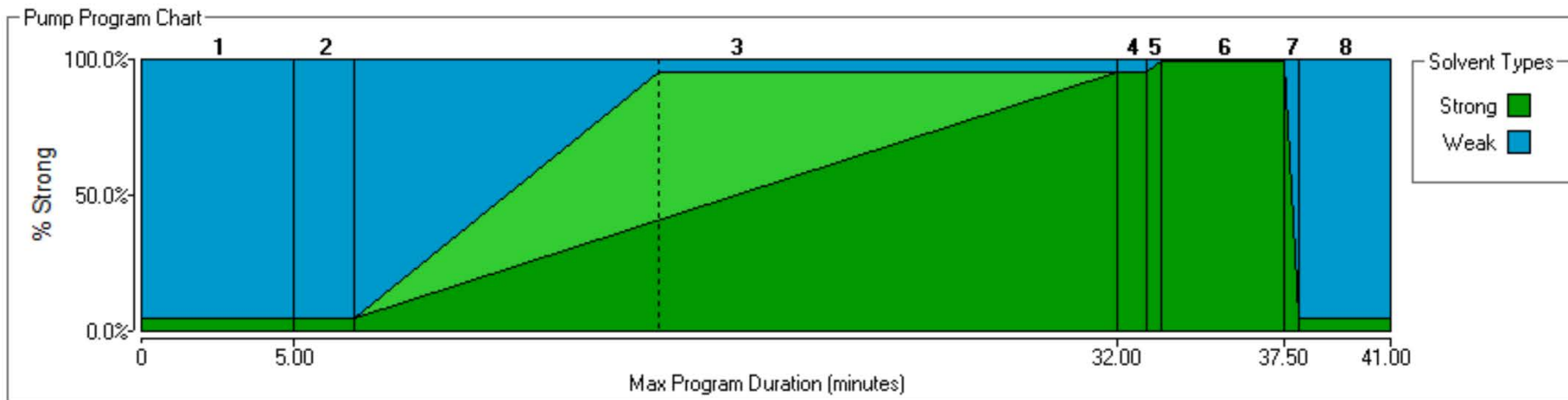
Gradient Study Factor: Gradient Time

Setting Mode
 Time
 Slope

Gradient

No. of Levels

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



Experiment Setup – Column Type

Name
Column Type

State
 Variable
 Constant

No. of Columns 4

Column Settings					
	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.

Select Responses

PDA Ch1 225nm@4.8nm, Time offset by 0.020 mins.

Trend Responses Named Compounds in CDS

Add Delete Undo Changes Rest

	<input type="checkbox"/>	Operator	Value	Response
1	<input checked="" type="checkbox"/>	No. of Peaks		
2	<input checked="" type="checkbox"/>	No. of Peaks >=	1.50	USPResolution
3	<input checked="" type="checkbox"/>	No. of Peaks >=	2.00	USPResolution
4	<input checked="" type="checkbox"/>	No. of Peaks <=	1.20	USPTailing
5	<input checked="" type="checkbox"/>	Max Peak	1	USPResolution
6	<input checked="" type="checkbox"/>	Max Peak	1	USPTailing

Select All Select None

I = Incomplete
D = Duplicate

Auto-imported Responses... << Back Next >> Cancel ?

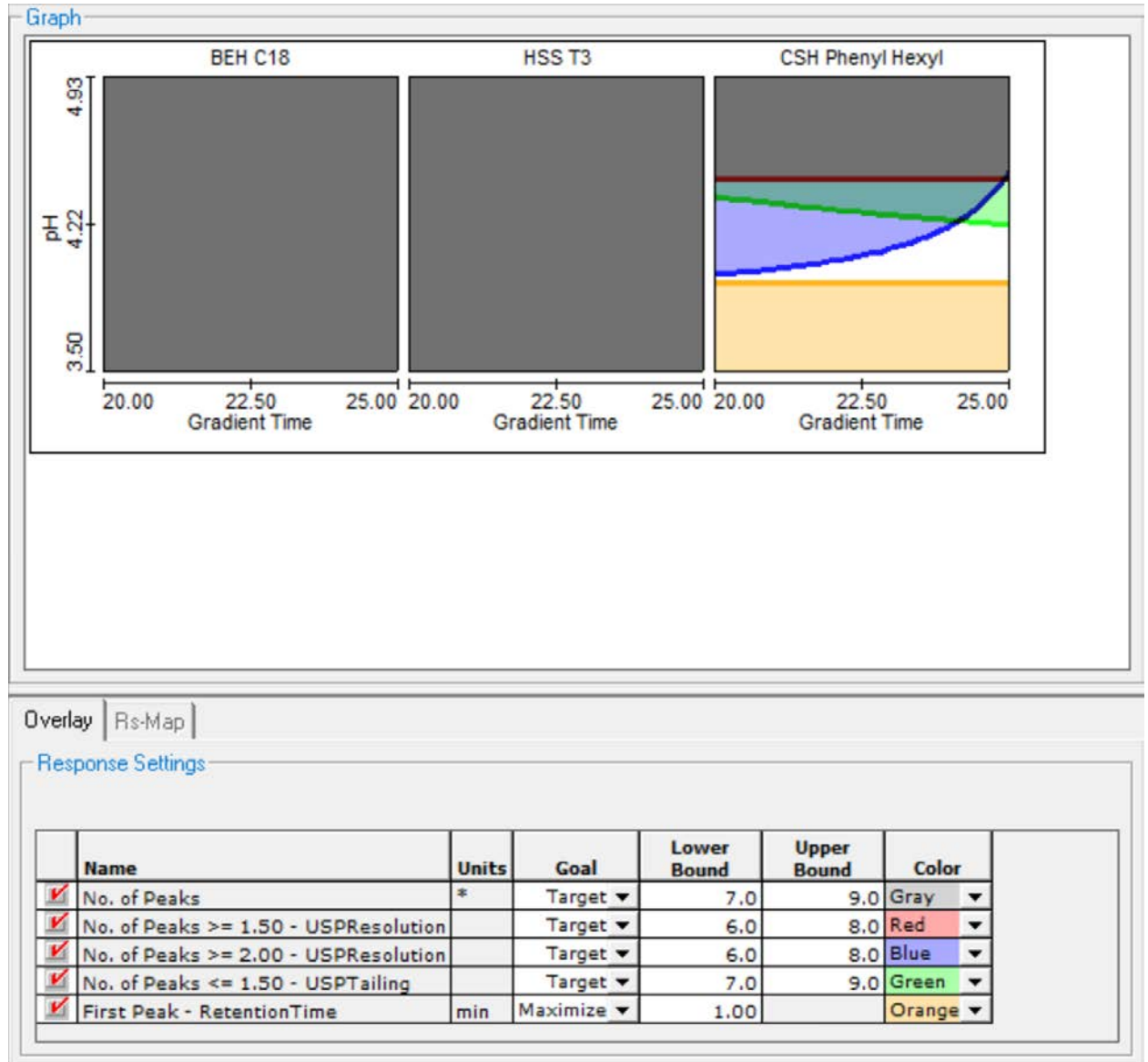
Trend Responses Support a Chromatographer's Screening Goals

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)!

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.



1e1p

Create Report Update Report Delete Report Restore Report RS Robustness Simulator Show Prediction Chromatogram

Reports

Best Overall Answer APR 1

View as Report

Graph Settings

Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X Gradient Time	min	20.00	25.00	24.00
Y pH	°	2.73	4.93	3.90

Column Type CSH Phenyl Hexyl

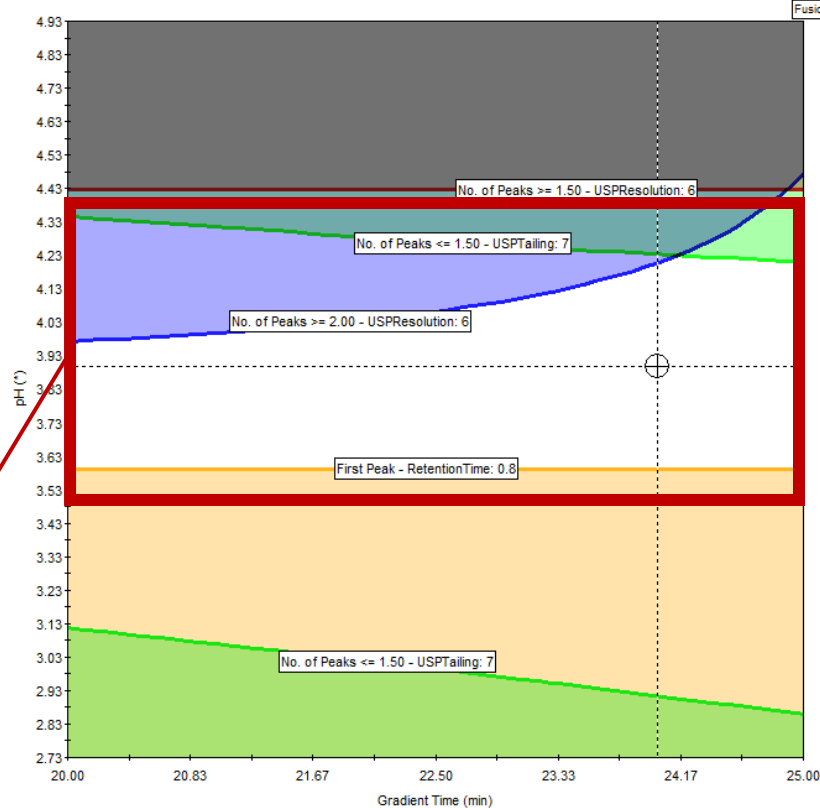
Optimization – CSH Phenyl-Hexyl Column

Verification Run Settings

Include Verification F None

Rectangle Identifies the pH and t_G Study Ranges to use in an Optimization Experiment with the Shield RP18 Column

Graph

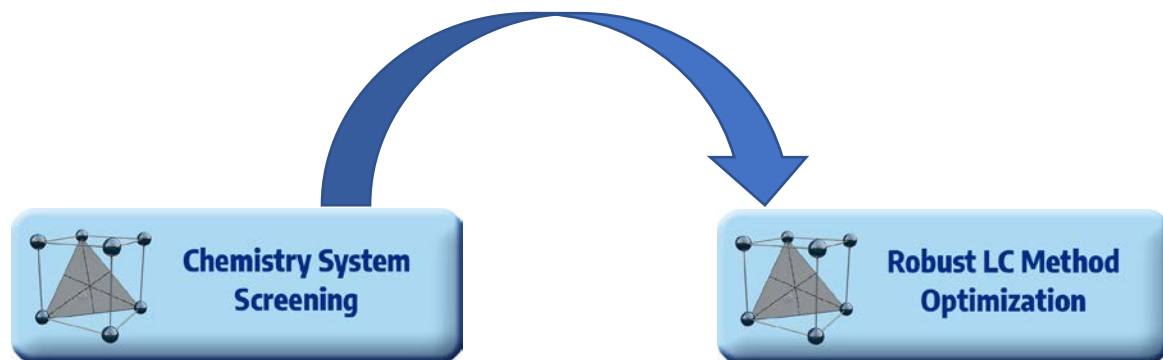


Fusion QoD Graph

Graph showing pH (°) vs Gradient Time (min) with optimization contours. A red rectangle highlights the study region for pH and t_G optimization.

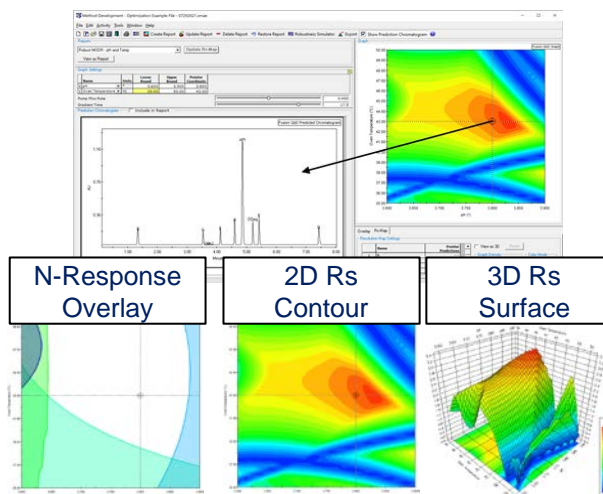
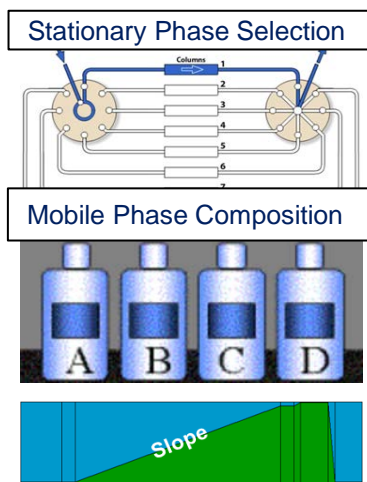
Response Settings

Name	Units	Goal	Lower Bound	Upper Bound	Crosshair Prediction	Contour Label	Color
No. of Peaks	*	Target	7.0	9.0	7.78		Gray
No. of Peaks >= 1.50 - USPResolution		Target	6.0	8.0	6.28		Red
No. of Peaks >= 2.00 - USPResolution		Target	6.0	8.0	6.07		Blue
No. of Peaks <= 1.50 - USPTailing		Target	7.0	9.0	8.01		Green
First Peak - RetentionTime	min	Maximize	0.80		0.982		Orange



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

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



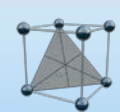
Full Experiment Automation with the CDS.

Full 21 CFR 11 Compliance with Bi-directional Audit Trail

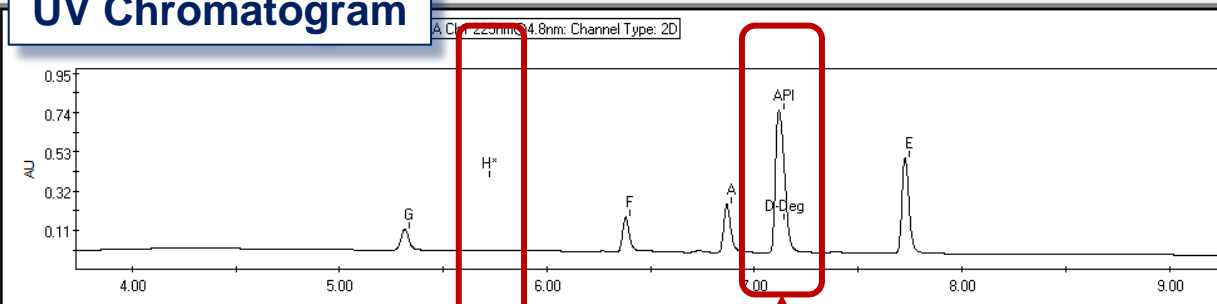


Method Parameter	Study Range
Pump Flow Rate (mL/min)	0.30 – 0.50
Column Oven Temperature (°C)	25.0 – 45.0
Gradient Time (min)*	20.0 – 25.0
pH	3.50 – 4.30
Column Type	CSH Phenyl-Hexyl

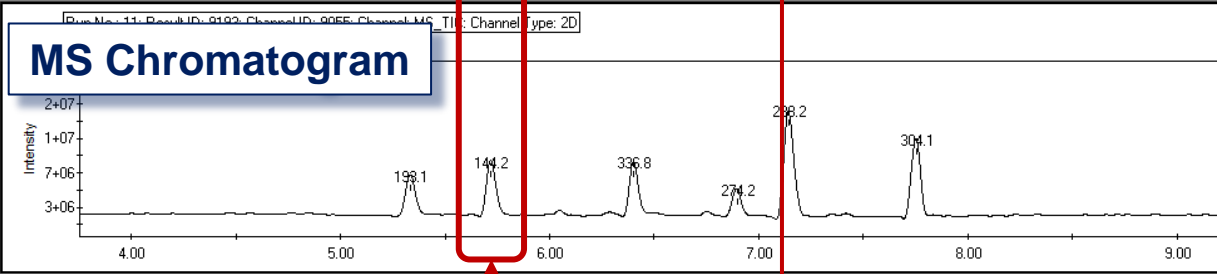
Light green background color indicates result obtained from screening study.



UV Chromatogram



MS Chromatogram



Peak Table - PDA Ch1 225nm@4.8nm - Run No. 11

Name	RT (min)	Base Peak (m/z)	Height (uV)	Area
1 B	1.916	262.2	524,998	1,508,961
2 G	5.336	193.1	113,225	3,8630
3 H*	5.720	144.2	403,264	20,57,007
4 F	6.400	336.8	185,768	4,7,804
5 A	6.889	274.2	260,696	6,1,066
6 API	7.139	288.2	774,666	2,37,701
7 D-Deg	7.139	170.503	170,503	
8 E	7.747	304.1	522,540	1,27,677
9 D	9.748	360.2	212,243	59,618

Global Tracking Method (GTM): Generated from run 15

Mass UV Filters Auto-name Peaks in GTM

Display Intensity Columns

Run #	Component Name	RT	Area	Expected Mass 1	Expected Mass 2	Expected Mass 3	Expected Mass 4	Expected Mass 5
1	15 B	1.037	973,202.2	262.3	263.2	279.1	160.3	126.1
2	15 G	3.061	110,123.2	193.1	215.1	132.1	279.1	194.1
3	15* H*	3.958	17,435,187.9	144.2	190.2	145.3	126.0	191
4	15 F	4.656	296,880.8	336.8	672.4	673.5	279.3	
5	15 A	4.926	397,548.5	274.2	275.2	279.0	296.2	126
6	15 API	5.122	1,247,108.7	288.1	289.1	126.0	160.3	310
7	15 D-Deg	5.844	200,691.0	300.2	344.0	126.0	279.1	303
8	15 E	5.633	809,240.9	304.1	305.2	326.1	607.5	279
9	15 D	7.171	332,729.9	360.2	361.2	279.1	126.0	160

UV and MS Spectra Analysis Dialog

Extracted Spectra: Row 7 (7)

Detected Mass (Da)	Leading (Intensity)	Apex (Intensity)	Trailing (Intensity)
1 661	4,201,244	13,400,470	598,699
2 663	2,442,044	10,676,912	493,867
3 662	1,339,995	3,645,166	0
4 665	856,023	2,571,824	47,855
5 683	270,540	825,603	0
6 684	289,782	365,052	3,800
7 460	95,431	176,563	11,209
8 685	56,250	170,395	31,053

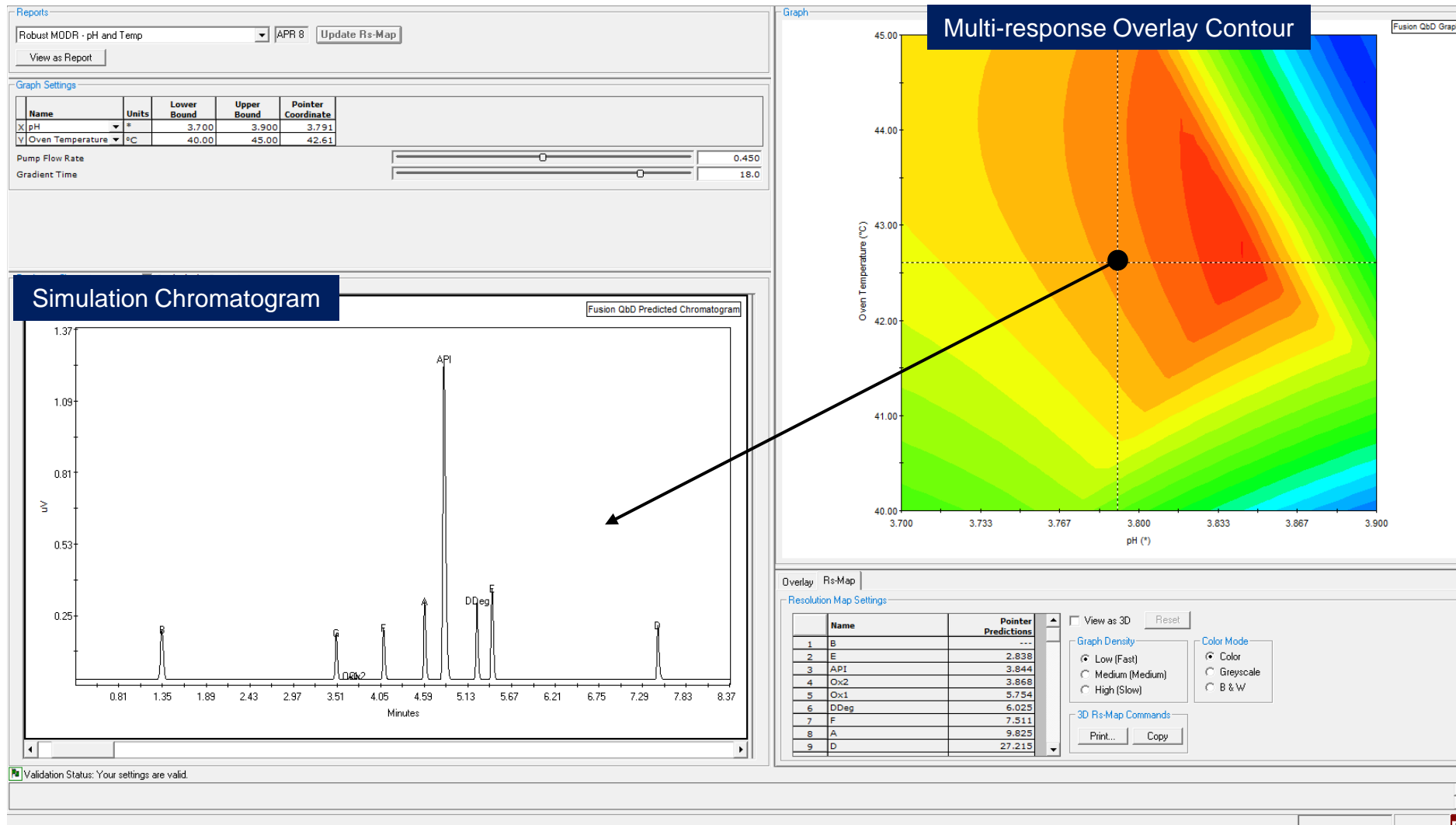
Automatic Peak Deconvolution

Virtual Integration of Non-absorbing Peaks

Select Mode
 Data Review Peak Tracking

Commands
 Create Tracking Method Track Peaks... Apply Tracking Changes Close

Traditional Resolution Map – 2D



Resolution Map – 3D

Reports

Robust MODR - pH and Temp | APR 8 | Update Rs-Map

View as Report

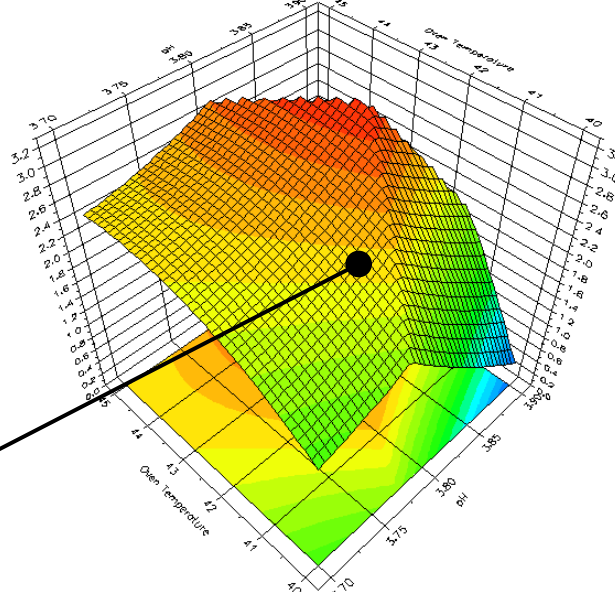
Graph Settings

Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X pH	°	3.700	3.900	3.791
Y Oven Temperature	°C	40.00	45.00	42.61

Pump Flow Rate: 0.450
Gradient Time: 18.0

Graph

Multi-response Overlay Contour

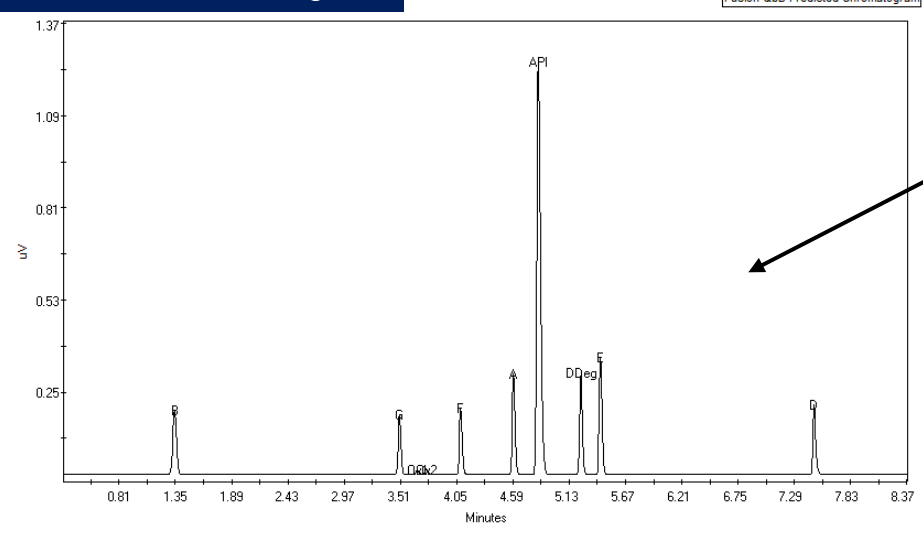


Legend

3.29
3.12
2.95
2.78
2.60
2.43
2.26
2.09
1.91
1.74
1.40
1.23
1.05
0.88
0.71
0.36
0.19
0.02

Simulation Chromatogram

Fusion QbD Predicted Chromatogram



Validation Status: Your settings are valid.

Overlay Rs-Map

Resolution Map Settings

Name	Pointer Predictions
1 B	---
2 E	2.838
3 API	3.844
4 Ox2	3.868
5 Ox1	5.754
6 DDeg	6.025
7 F	7.511
8 A	9.825
9 D	27.215

View as 3D | Reset

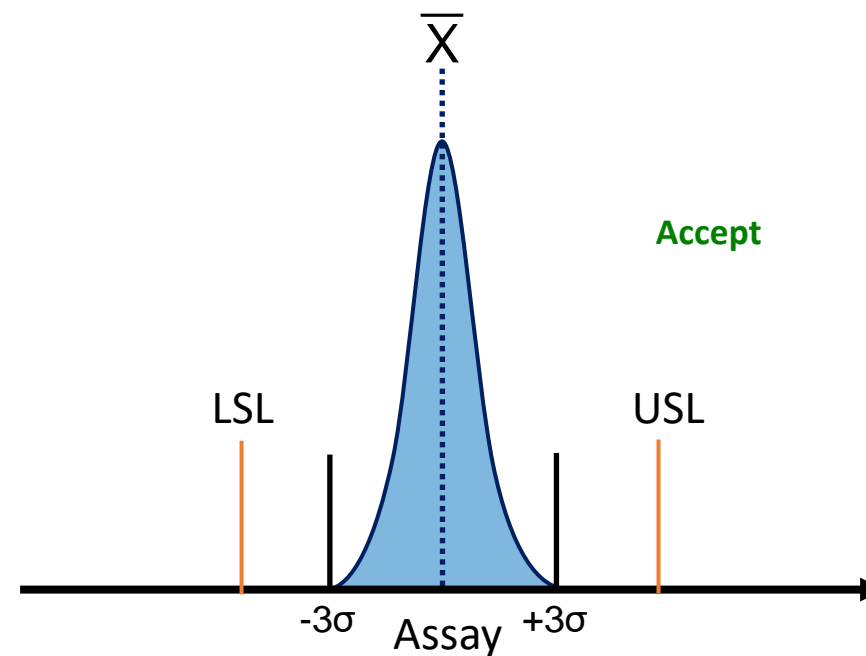
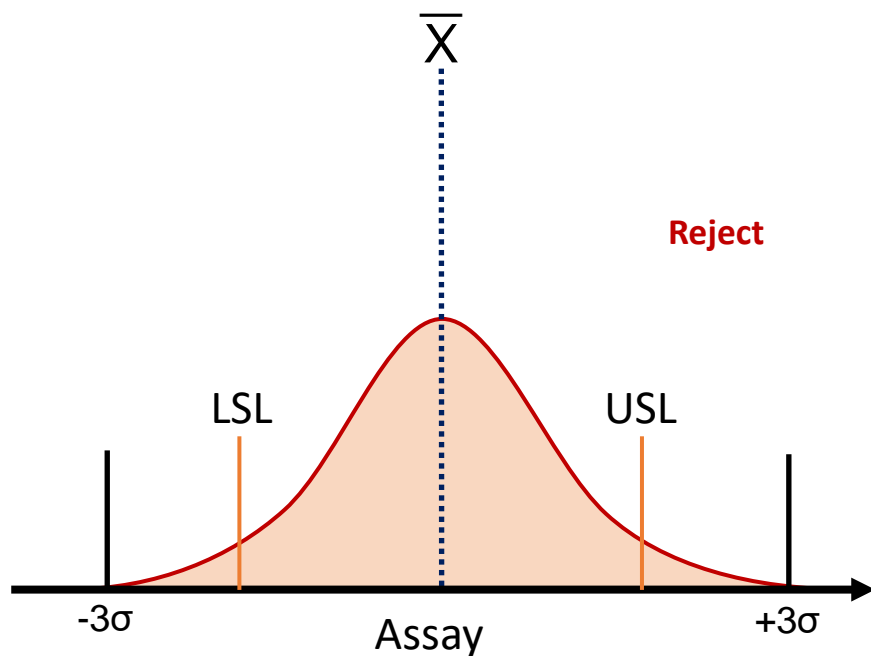
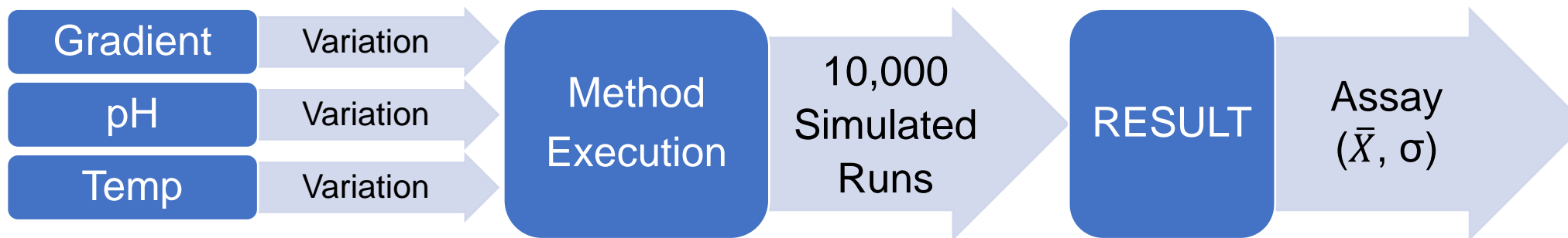
Graph Density
 Low (Fast)
 Medium (Medium)
 High (Slow)

Color Mode
 Color
 Greyscale
 B & W

3D Rs-Map Commands
 Print... Copy

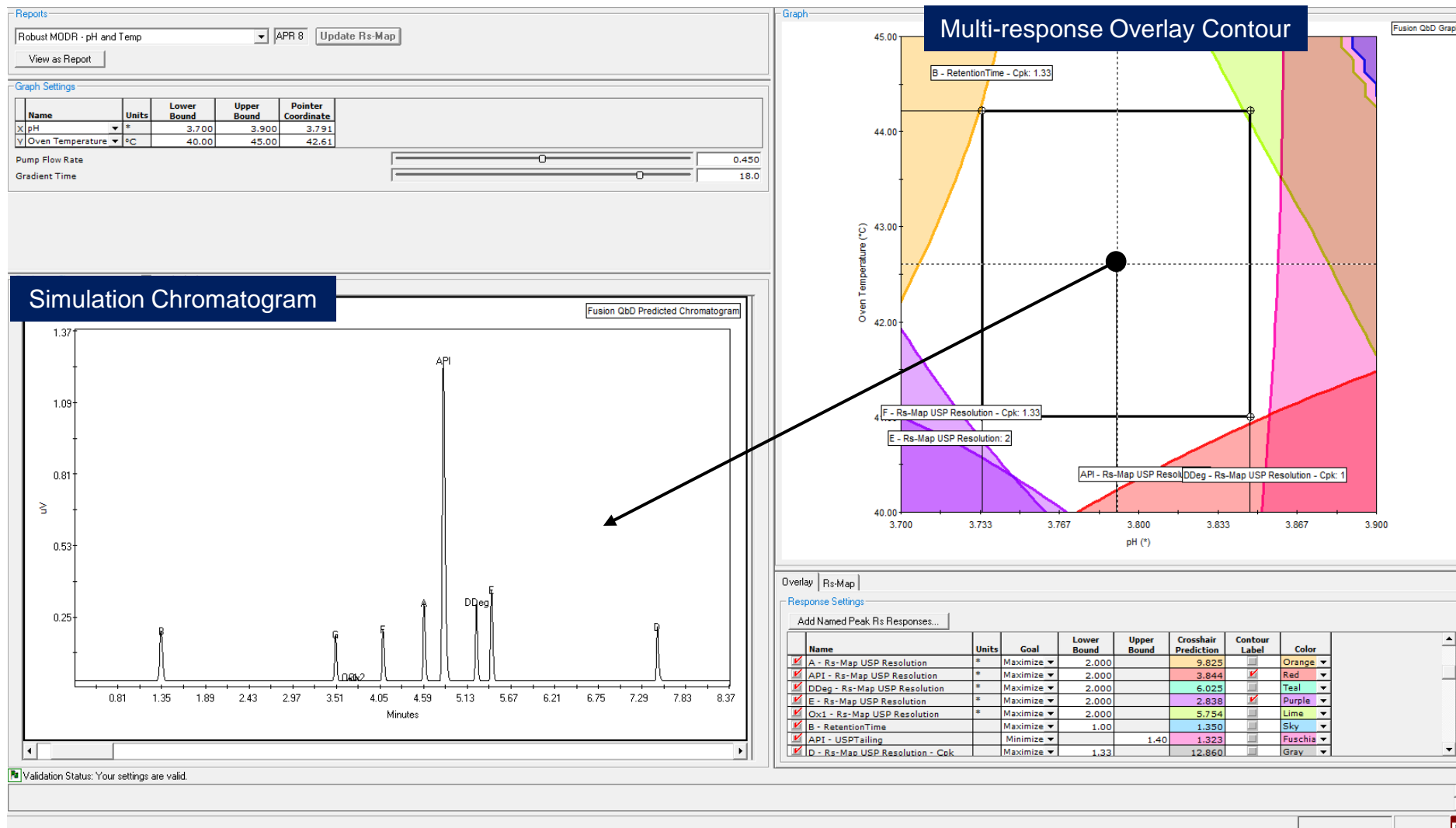
Monte Carlo Robustness Simulation

Example Study Parameters –
Expected Variation on Transfer



Mean Performance and Robustness:

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

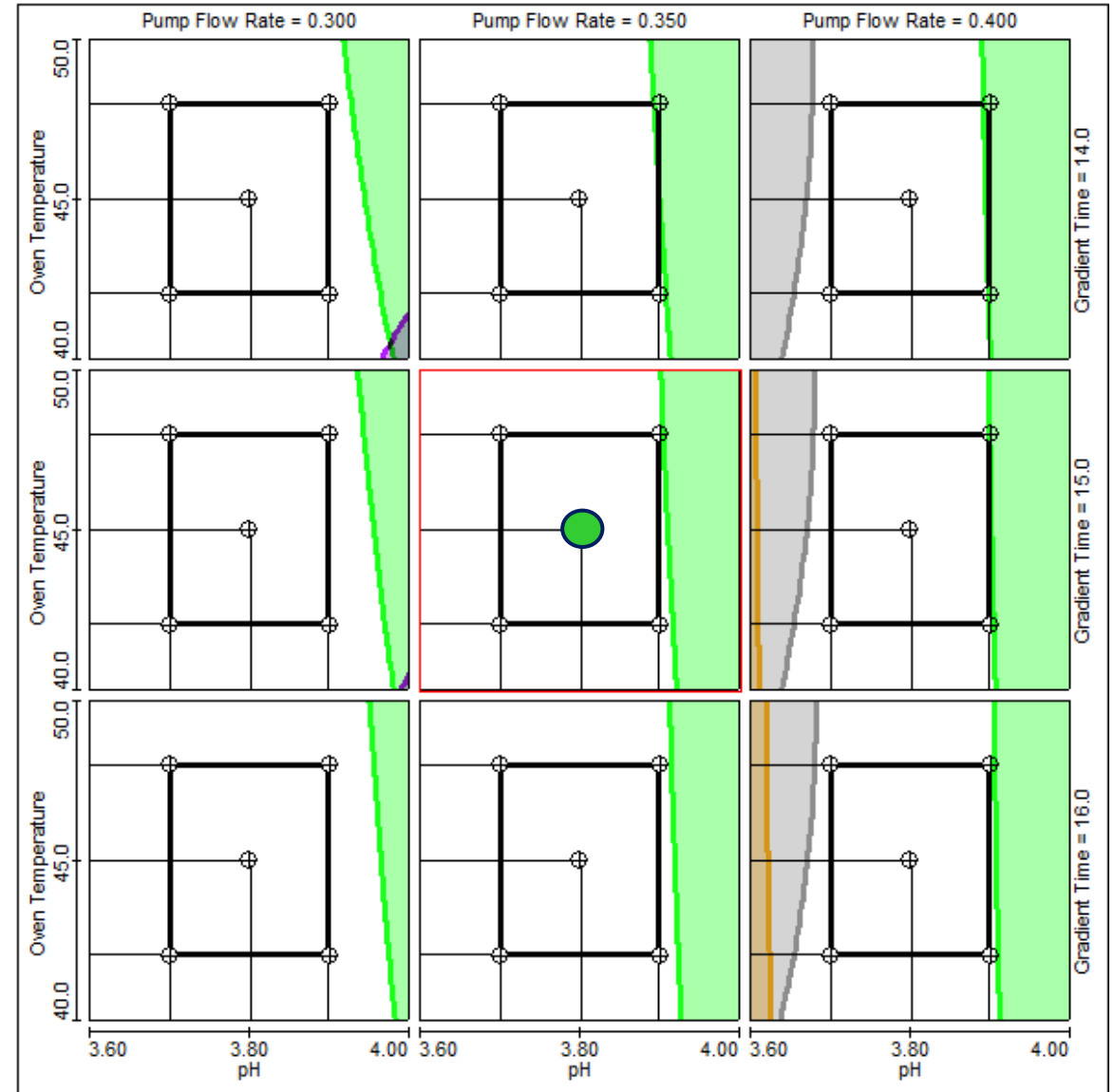


User Settable Expected Variation Ranges

Variable Settings			
Enabled	Experiment Variable	Units	Maximum Expected Variation ($\pm 3\sigma$ Value)
<input checked="" type="checkbox"/>	Pump Flow Rate	mL/min	0.020
<input checked="" type="checkbox"/>	Oven Temperature	°C	3.0
<input checked="" type="checkbox"/>	pH	*	0.15
<input checked="" type="checkbox"/>	Mobile Phase Composition (MPC)*	%	2.0

* - MPC variation is composition (blend) variation due to pump precision limits. A commonly used $\pm 3\sigma$ value = $\pm 2.0\%$.
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.



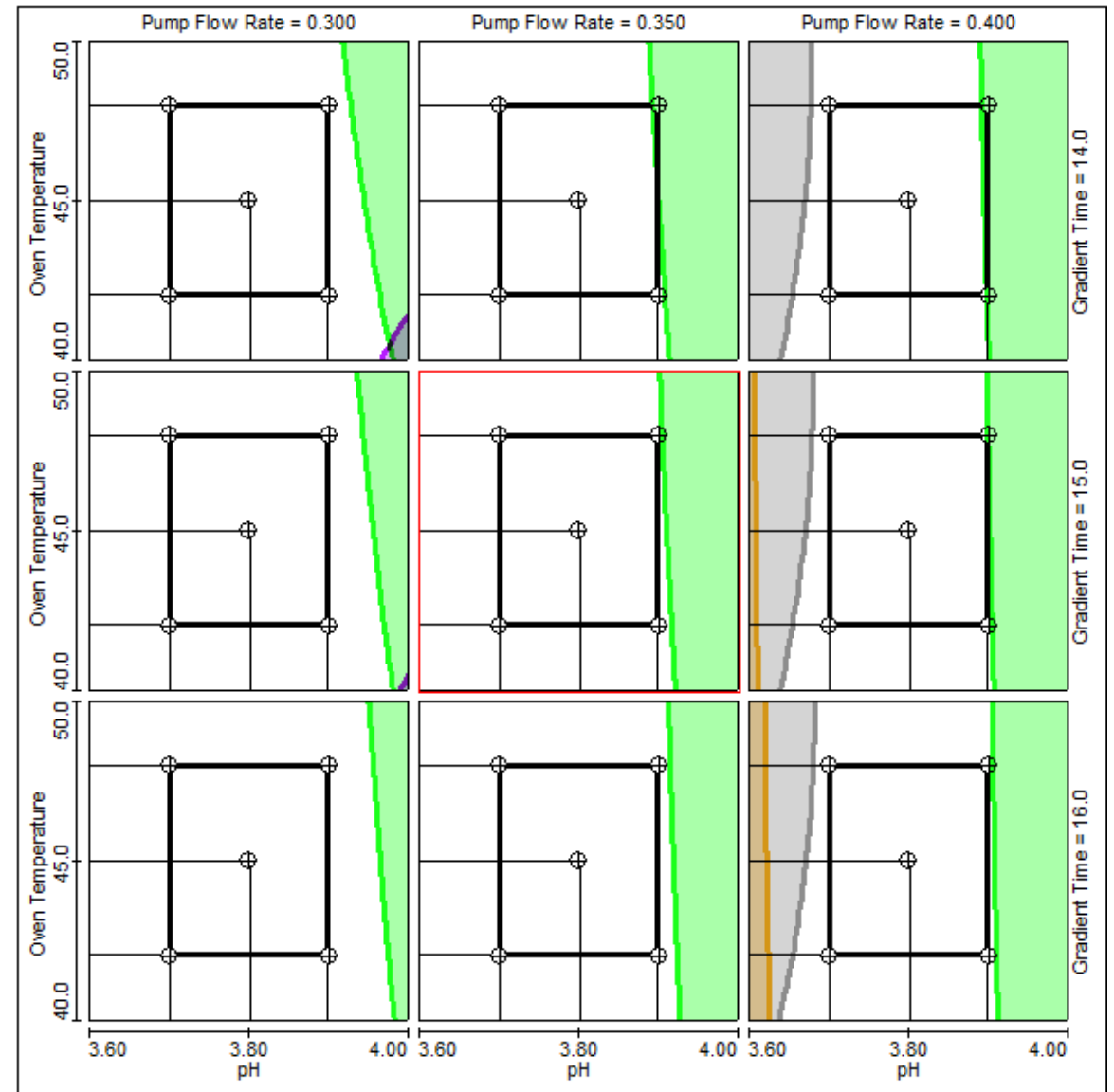
Analytical Control Strategy (ACS)

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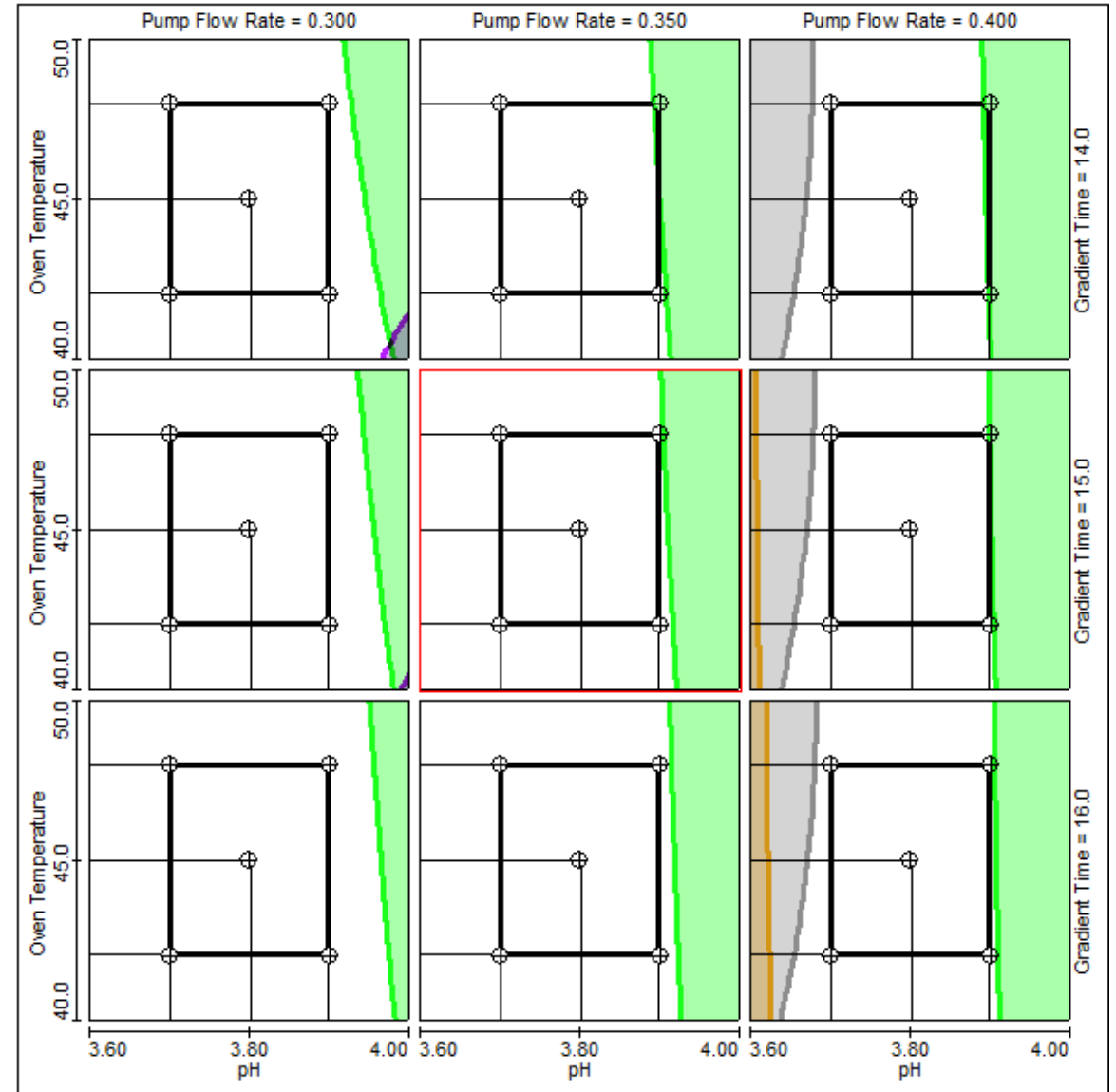
LC System Control Specifications



	Name	Units	Goal	Lower Bound	Upper Bound	Color
<input checked="" type="checkbox"/>	A - ResolutionW50	*	Maximize	2.000		Red
<input checked="" type="checkbox"/>	API - ResolutionW50	*	Maximize	2.000		Blue
<input checked="" type="checkbox"/>	D-Deg - ResolutionW50	*	Maximize	2.000		Green
<input checked="" type="checkbox"/>	E - ResolutionW50	*	Maximize	2.000		Orange
<input checked="" type="checkbox"/>	B - RetentionTime		Maximize	1.00		Gray
<input checked="" type="checkbox"/>	API - USPTailing		Minimize		1.50	Purple
<input checked="" type="checkbox"/>	B - RetentionTime - Cpk	*	Maximize	1.330		Gray
<input checked="" type="checkbox"/>	API - USPTailing - Cpk	*	Maximize	1.330		Purple
<input checked="" type="checkbox"/>	A - ResolutionW50 - Cpk	*	Maximize	1.330		Red
<input checked="" type="checkbox"/>	API - ResolutionW50 - Cpk	*	Maximize	1.330		Blue
<input checked="" type="checkbox"/>	D-Deg - ResolutionW50 - Cpk	*	Maximize	1.330		Green
<input checked="" type="checkbox"/>	E - ResolutionW50 - Cpk	*	Maximize	1.330		Orange

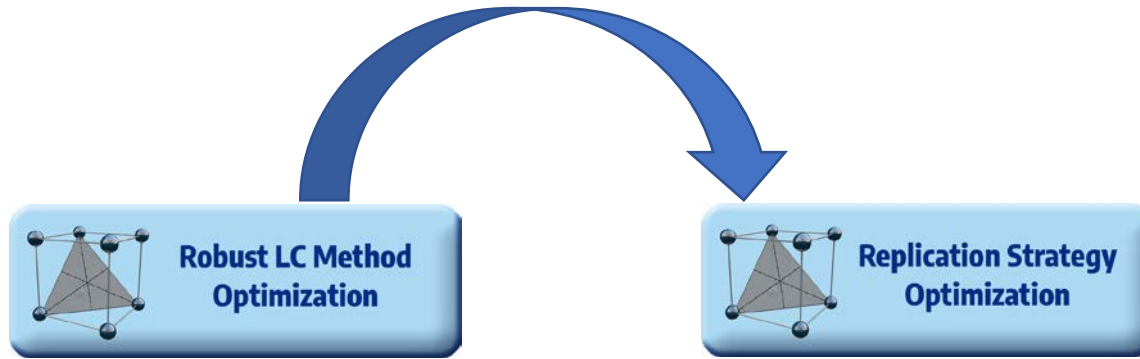


Routine Monitoring – Control Charts



Full Experiment Automation with the CDS.

Full 21 CFR 11 Compliance with Bi-directional Audit Trail



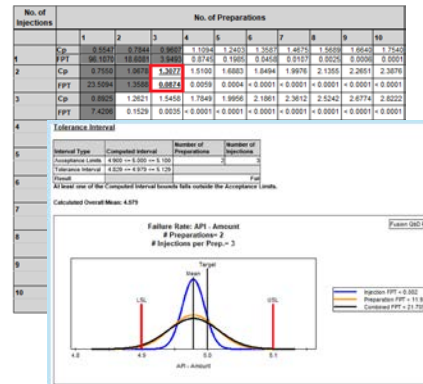
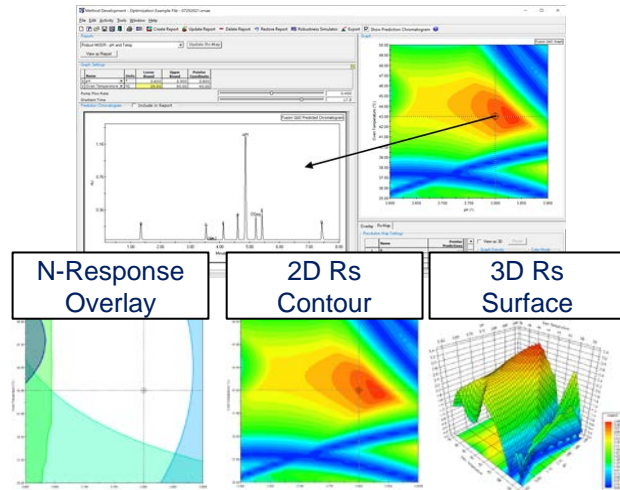
Robust LC Method Optimization

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.



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.

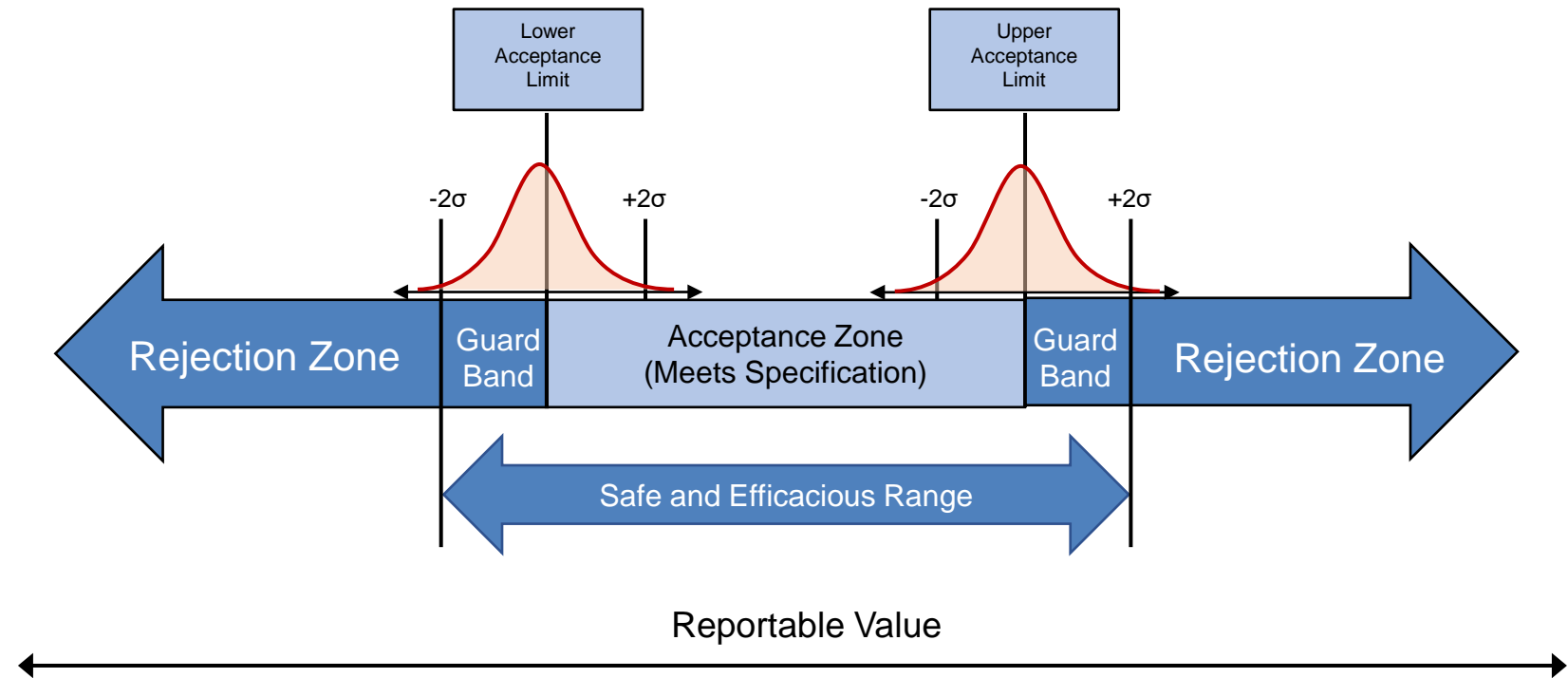
Determining Required Precision (σ_{\max})

Tolerance Width = 4.00 (98.0 – 102.0)

Precision Width = $0.30 \times 4.00 = 1.20$

Split between LAL and UAL = ± 0.60

$\pm 0.60 = \pm 2\sigma$ width for 95% C.I.



Method Development - Untitled1

File Edit Activity Tools Window Help

Select Autosampler Tray Update Setup Data Generate Design ?

Design of Experiments

- Create a Design
- Design Reports

Data Entry / Analysis

- Data Entry
- Data Analysis

Reporting Toolkit

- Fusion Reporter
- Audit Log Reporter

Project Name: Project 1 Experiment Name: Experiment 1 Instrument Name: Fusion QbD H_Class Experiment Phase: Method Development Experiment Type: Replication Strategy Separation Mode: Reversed Phase (RPC)

Experiment Setup

Global Sample Settings

Obtain all injection repeats from the same vial

Name: Preparation replicates per sample No. of Levels: 5

	Level setting
Level 1	P-1
Level 2	P-2
Level 3	P-3
Level 4	P-4
Level 5	P-5

Name: Injections per preparation replicate No. of Levels: 5

	Level setting
Level 1	I-1
Level 2	I-2
Level 3	I-3
Level 4	I-4
Level 5	I-5

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

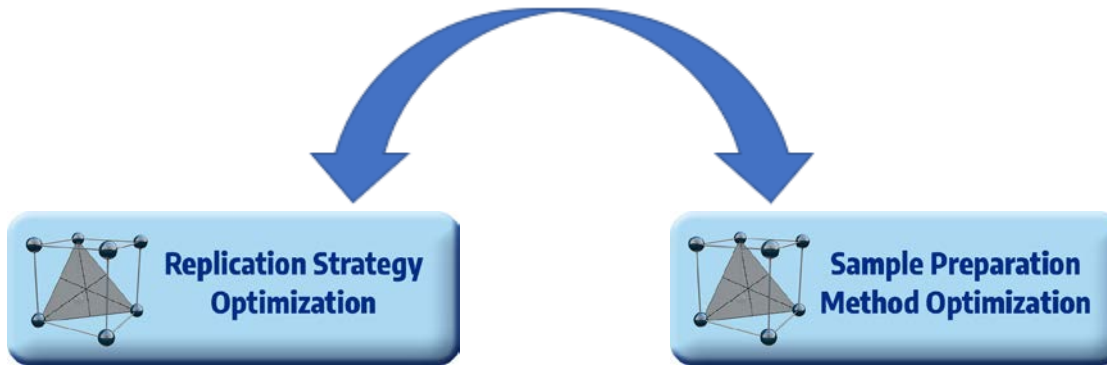
Cp Failure Rates Reference

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

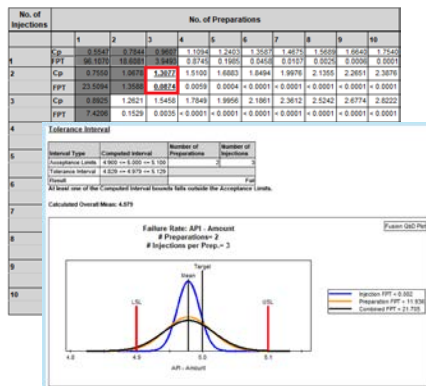
Full Experiment Automation with the CDS.

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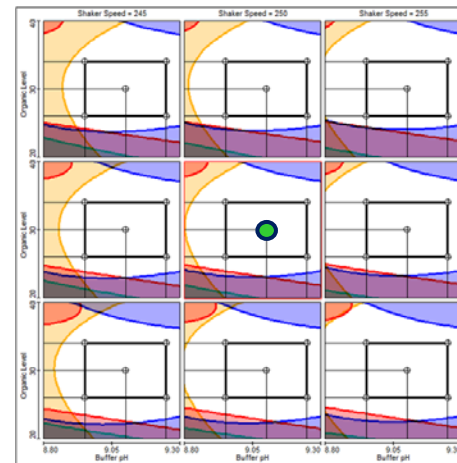


Define % contributions of Preparation Error and Injection Error to Overall Method Precision (Total Analytical Error).

Select optimal Replication Strategy.



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

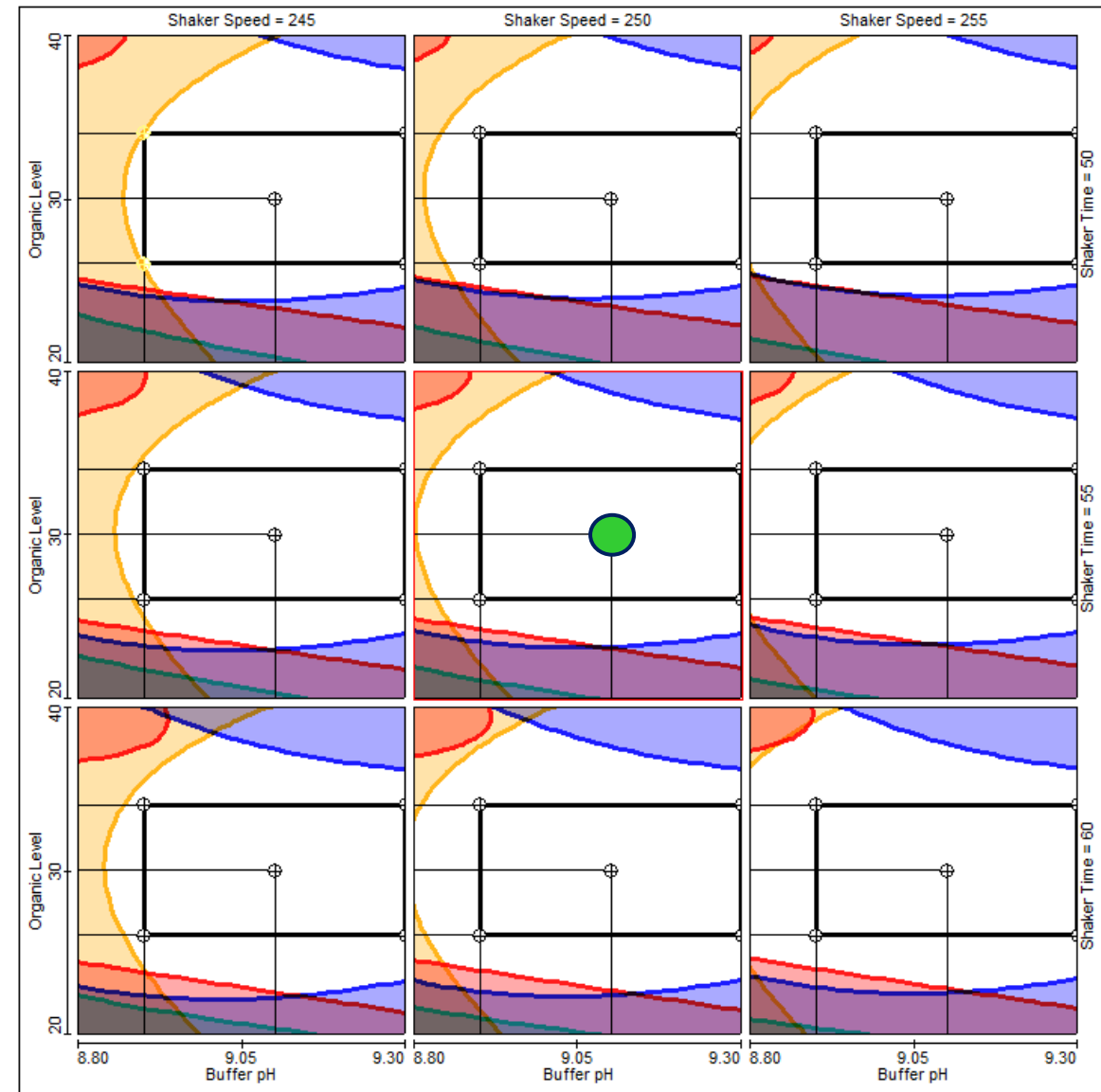


Analytical Control Strategy (ACS)

Enabled	Experiment Variable	Units	Maximum Expected Variation ($\pm 3\sigma$ Value)
<input checked="" type="checkbox"/>	Buffer pH	*	0.15
<input checked="" type="checkbox"/>	Organic Level	%	2
<input type="checkbox"/>	Sonication Time	min	0
<input checked="" type="checkbox"/>	Shaker Speed	rpm	5
<input checked="" type="checkbox"/>	Shaker Time	min	2



Prep Factor Operating/Control Specs

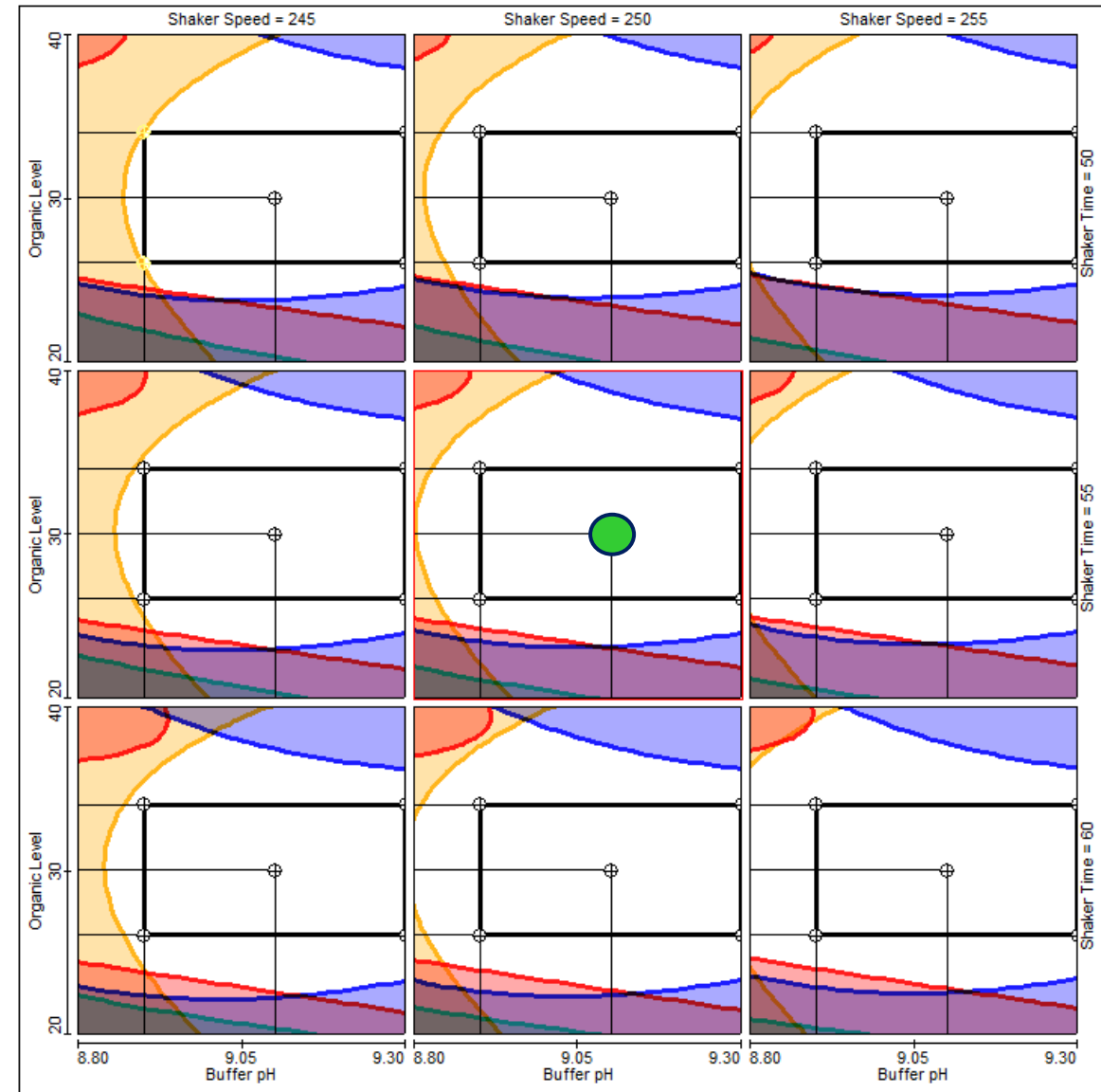


Analytical Control Strategy (ACS)

	Name	Units	Goal	Lower Bound	Upper Bound	Color
<input checked="" type="checkbox"/>	API 1 - %L.C.-(1_1)	*	Target ▼	96.50	98.50	Blue ▼
<input checked="" type="checkbox"/>	API 2 - %L.C.-(1_2)	*	Target ▼	97.50	99.50	Red ▼
<input checked="" type="checkbox"/>	API 1 - %L.C.-(1_1) - Cpm		Maximize ▼	1.33		Orange ▼
<input checked="" type="checkbox"/>	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.

