Fusion QbD® – Integrated QbD Robustness

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Fusion QbD – Leading the Vision!

2008 – Development of Integrated Robustness

S-Matrix recognized very early the limitations and problems associated with the traditional approach to method validation robustness experimentation, and its inherent likelihood of ***false negative*** outcomes – characterizing a method as robust when it is not.

In response to this problem, S-Matrix integrated QbD robustness modeling and metrics into Fusion QbD according to rigorous statistical principles and industry best practices. This was done in cooperation with several leading international pharmaceutical company customers!

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Fusion QbD – Leading the Vision!

2009: S-Matrix Presentation to the FDA

In 2009 S-Matrix made a major presentation to the FDA demonstrating its integration of QbD robustness modeling and metrics into Fusion QbD.

This presentation was extremely well received!

Fusion QbD – Leading the Vision!

2012+ – FDA Public Presentations

In 2012 the FDA began making public presentations about QbD robustness in analytical method and process development consistent with the robustness methodology and metrics integrated into Fusion QbD.

See the following slides…

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QbD Robustness – Regulatory Statements 2012

Monte Carlo Robustness Simulation

"*Statistical treatments (e.g., **Monte Carlo simulations**) can help evaluate the effects of uncertainty.*"

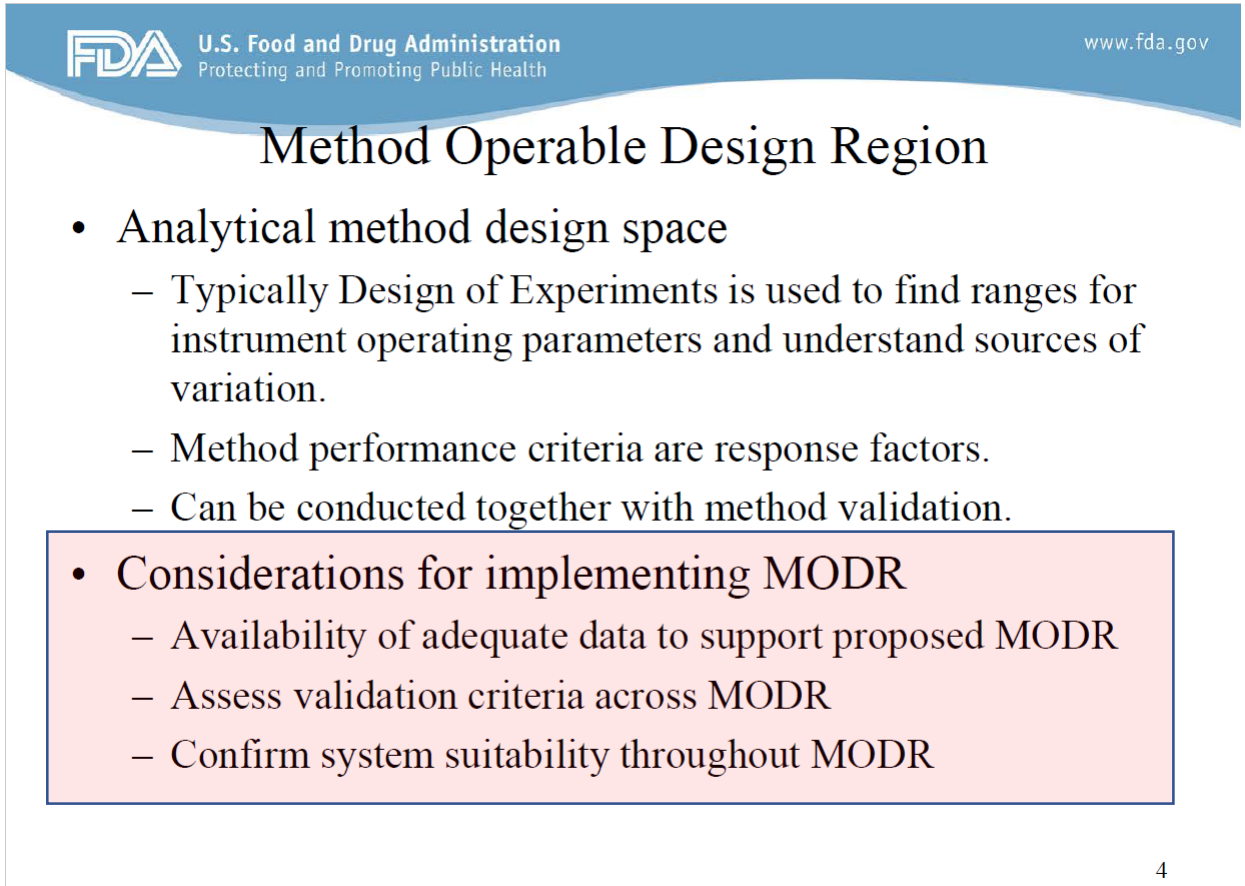
Points to Consider for Design Space – A Regulatory Perspective, Elaine Morefield, Ph.D., 2012 Annual Meeting, AAPS.

Statistical Robustness Metrics

The FDA has stated that accepted process capability indexes such as **C_p, C_{pk}, C_{pm}, and C_{pkm}** are also part of the QbD toolset.

US FDA, Quality by Design: Objectives, Benefits, and Challenges, Lawrence X. Yu, Ph.D., 2012 Annual Meeting, AAPS.

QbD Robustness – Regulatory Statements 2015



John F. Kauffman, Ph.D. and Daniel J. Mans, Ph.D., "*Experimental Design and Modeling to Improve HPLC Method Performance for Small Molecules*", FDA Division of Pharmaceutical Analysis, CASSSCMC Strategy Forum Europe, 2015

System Suitability – Method Variation – Normal Distribution Bell Curve

System Suitability normally has two requirements:

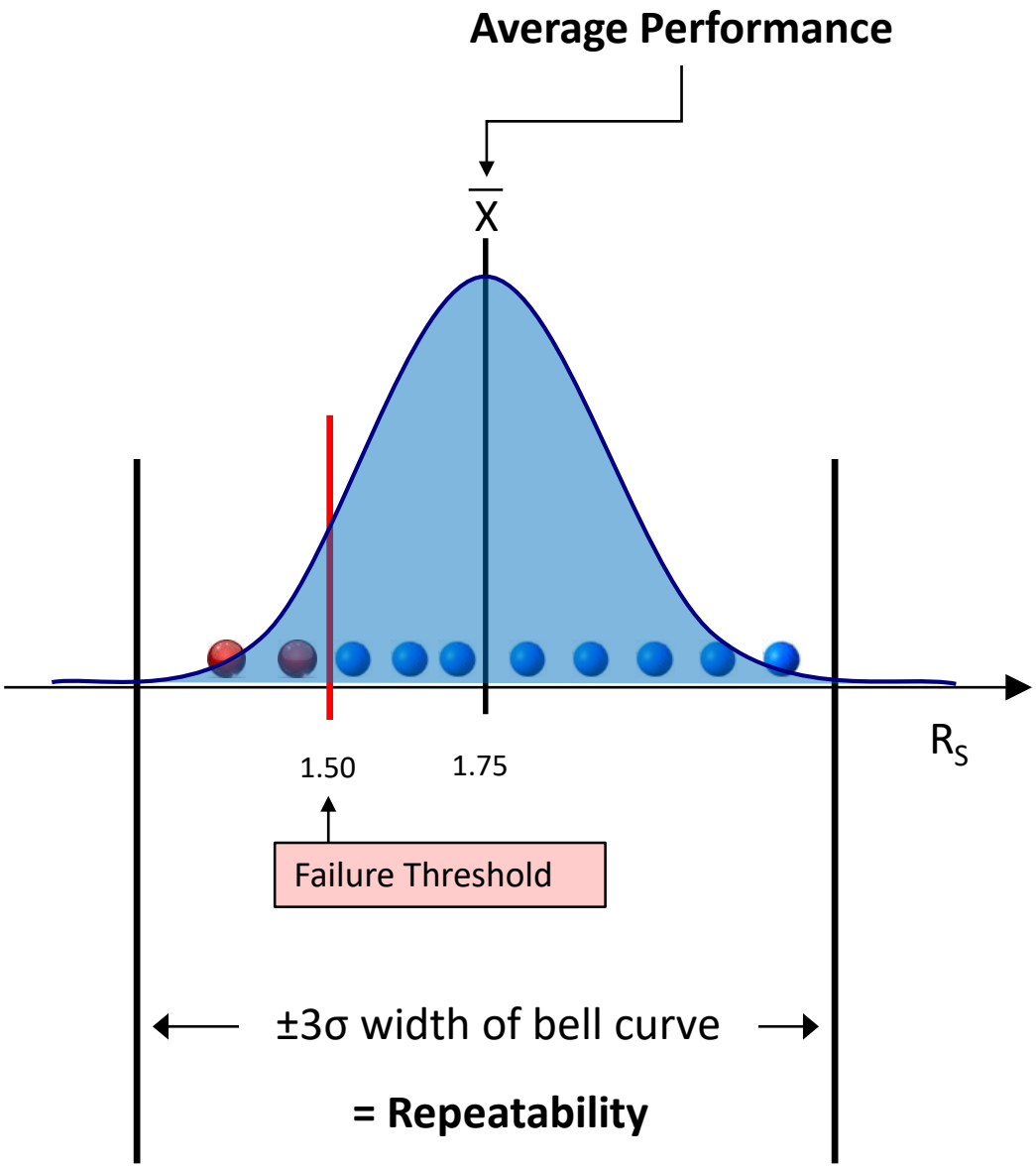
1. Average Performance ($\overline{X}$)

2. Repeatability (% RSD):

   % RSD = [(1.0**σ** / $\overline{X}$)*100%]

   ±3.0**σ** Width =
   Overall Repeatability

Repeatability is a Robustness Specification



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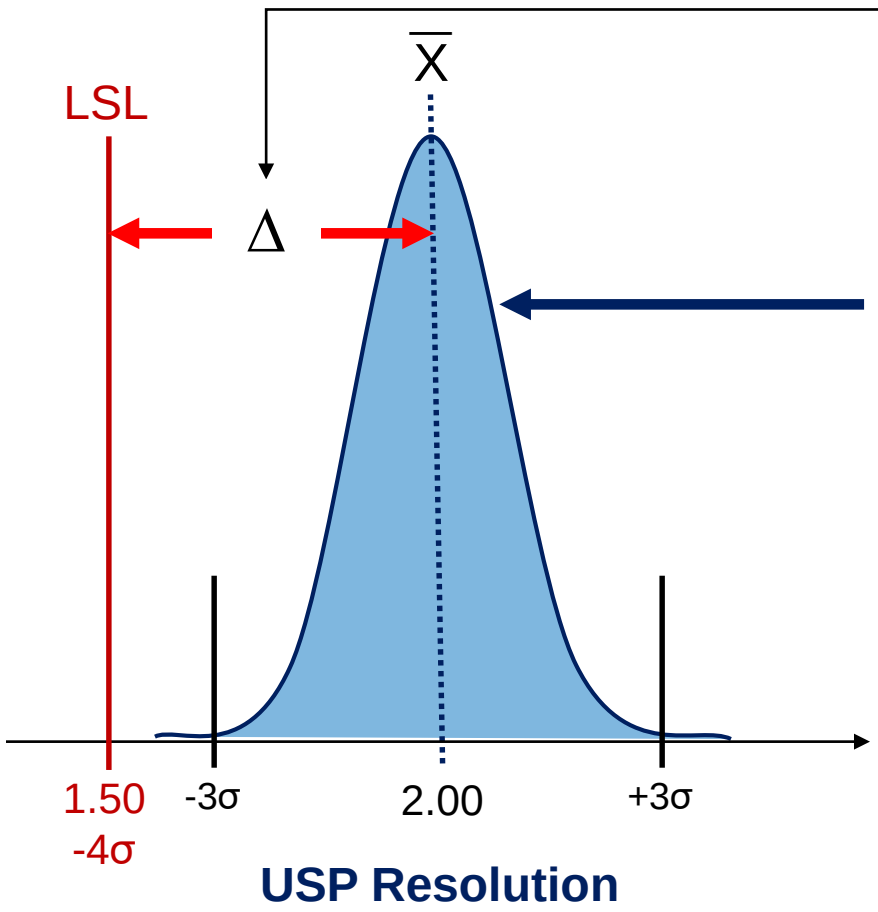
C_{pk} – One-sided Specification Limit

Example: API Resolution

Specification Limit Delta
(± Distance of Mean Response to Edge of Failure)



USP Resolution

Performance Variation Bell Curve:
The numerical distance from the mean performance result to the specification limit.

C_{pk} – **Goal is ≥ 1.33**

Meaning – point of failure is 4σ away from $\overline{X}$

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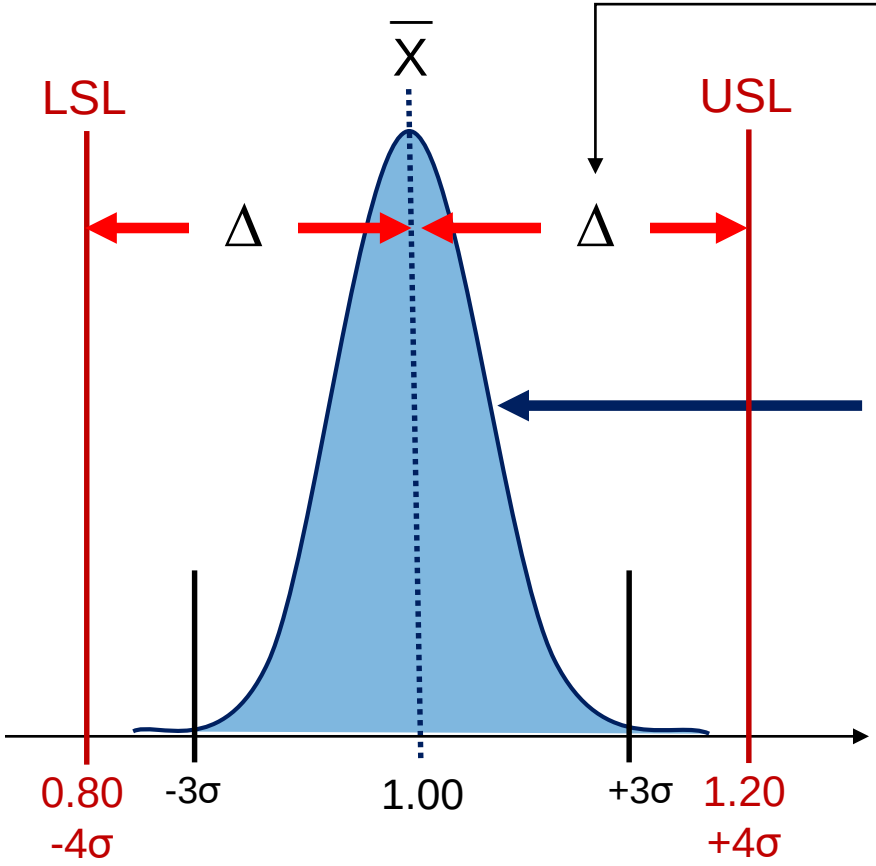
C_{pm} – Target with Two-sided Symmetrical Specification Limits

API Tailing Example:



USP Tailing

Performance Variation Bell Curve:
The numerical distance from the mean performance result to specification limits.

C_{pm} – **Goal is ≥ 1.33**

Meaning – point of failure is 4σ away from $\overline{X}$

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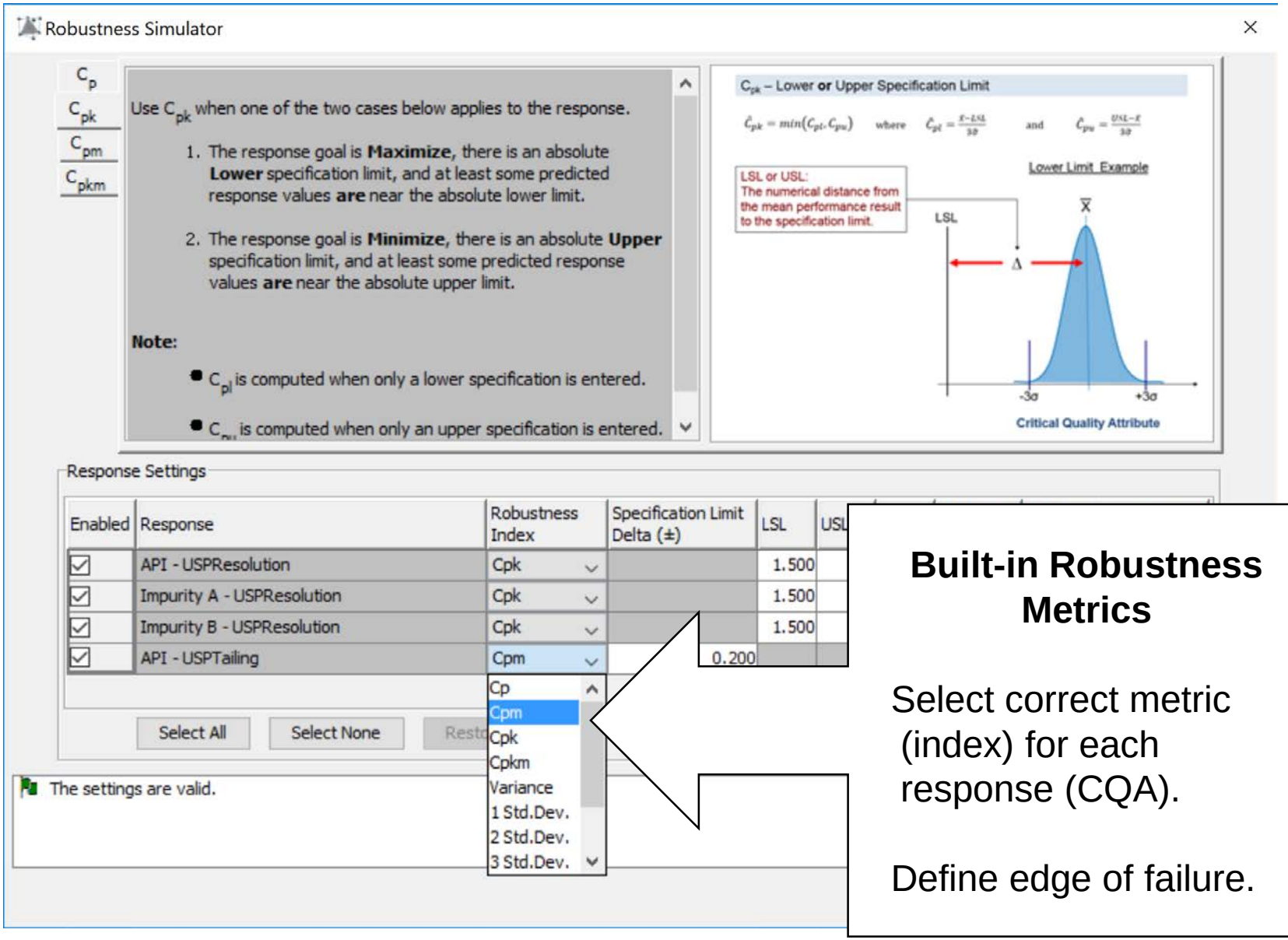
Fusion QbD – Integrated Monte Carlo Robustness



Built-in Robustness Metrics

Select correct metric (index) for each response (CQA).

Define edge of failure.

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Method Robustness versus Mean ($\bar{x}$) Performance

Do all methods within the Preliminary Design Space meet Robustness Requirements?

Reports

Best Overall Answer

Graph Settings

	Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X	Oven Temperature	°C	30.00	40.00	
Y	pH	*	2.60	3.00	

Gradient Time 7.0

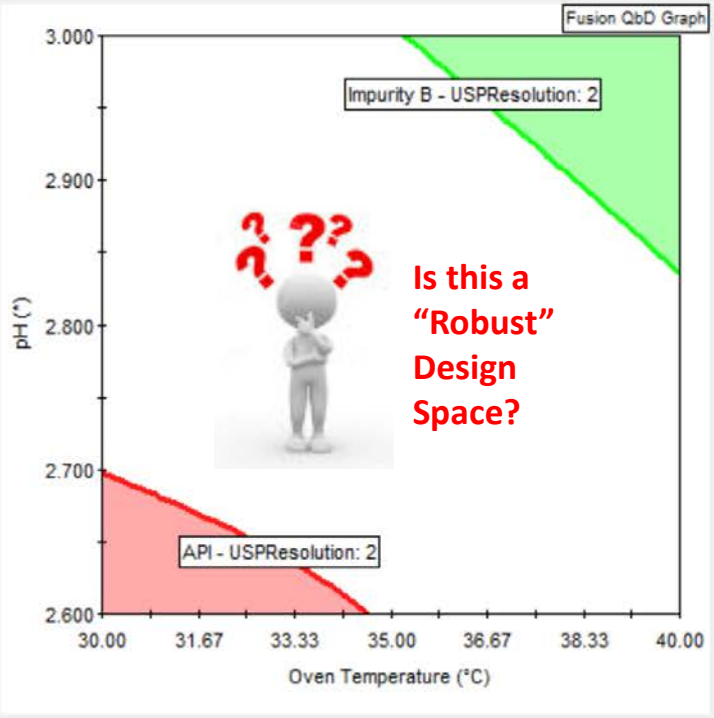
Verification Run Settings

Include Proven Acceptable Ranges (PARs)

Right-click graph to add or remove individual Verification Run points.

Establish Design Space for All CQAs

Graph



Response Settings

	Name	Goal	Lower Bound	Upper Bound	Pointer Predictions	Contour Label	Color
✓	API - USPResolution	Maximize	2.00			✓	Red
✓	Impurity A - USPResolution	Maximize	2.00			✓	Blue
✓	Impurity B - USPResolution	Maximize	2.00			✓	Green
✓	API - USPTailing	Target	0.90	1.10		✓	Orange

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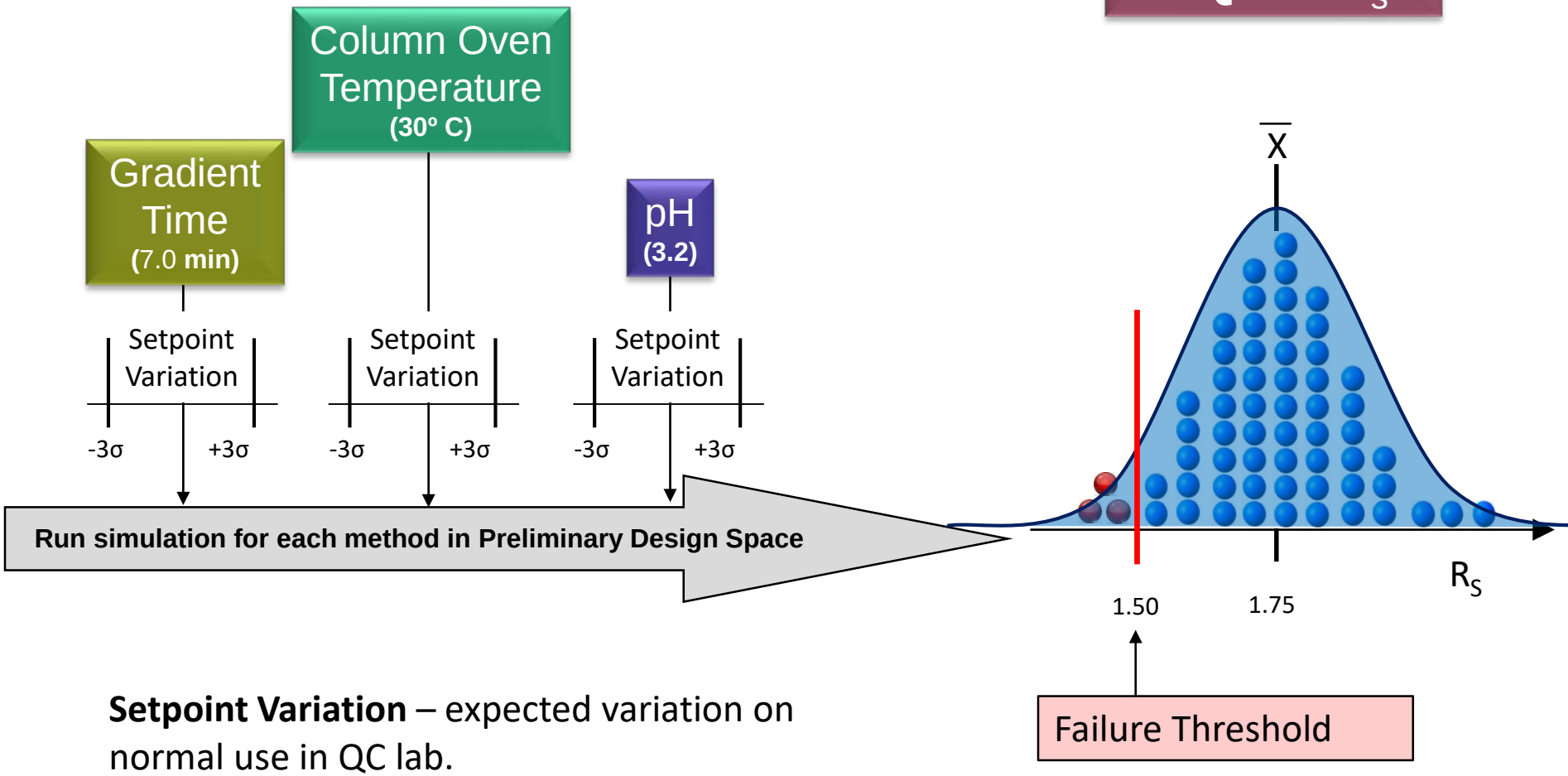
Monte Carlo Simulation – Simulate Many Injections

Example Critical Process Parameters (CPPs)

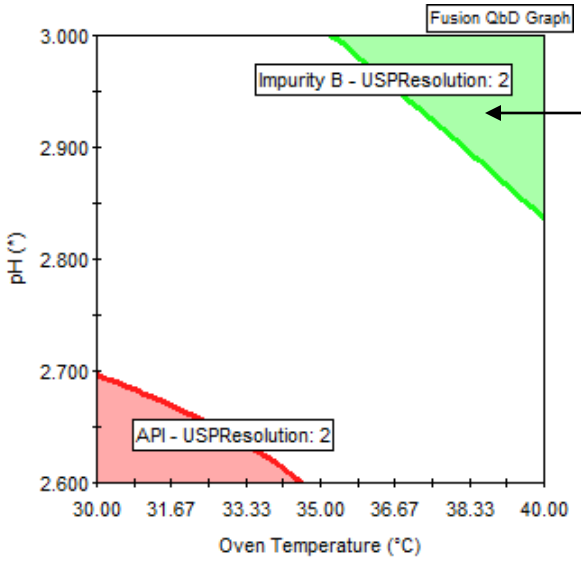
Example CQA – R_s



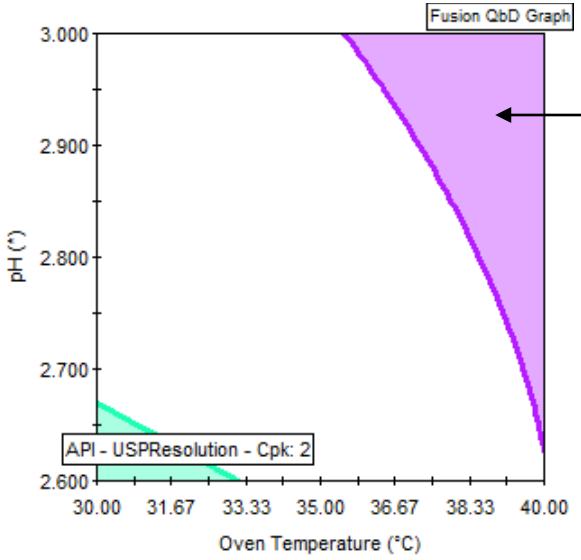
Setpoint Variation – expected variation on normal use in QC lab.

Fusion QbD – Establishes True Robust Design Space

Mean Response – All CQAs

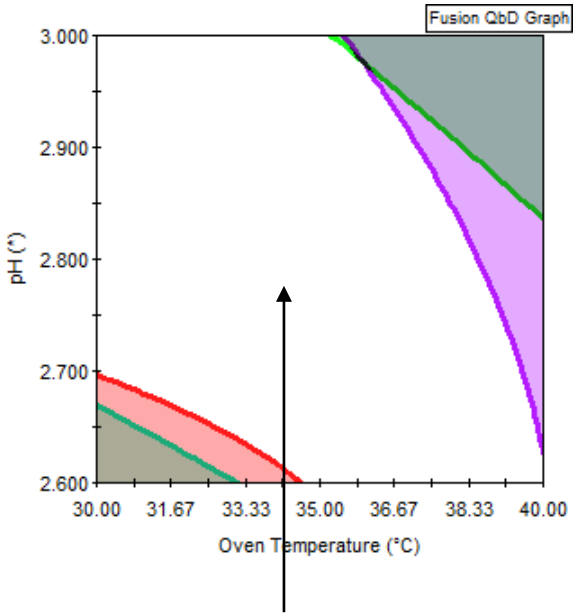


Robustness – All CQAs



Shaded Region – Fails Average Performance

Shaded Region – Fails Robustness



Robust Design Space –

Joint region of acceptable method mean performance and **robustness**.

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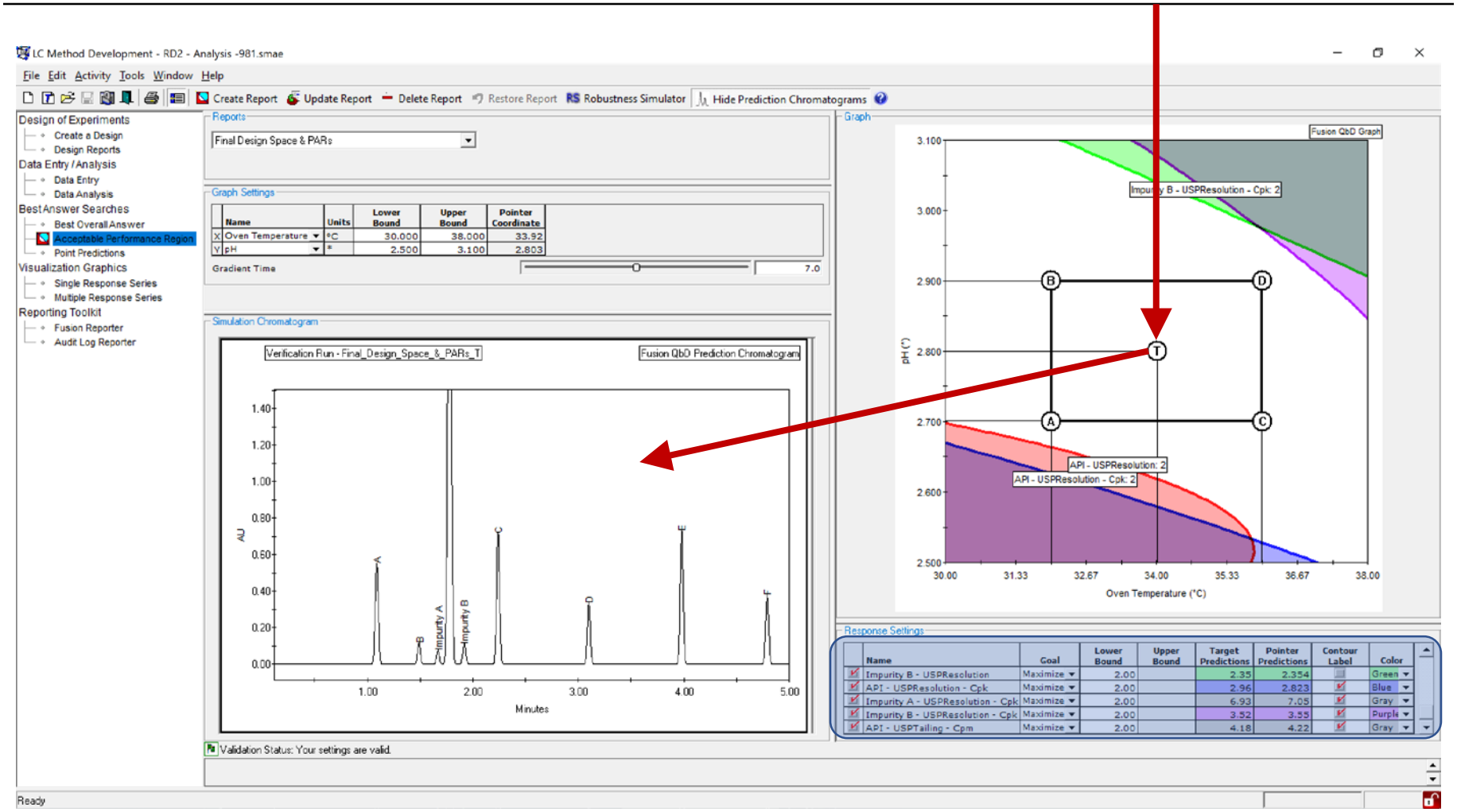
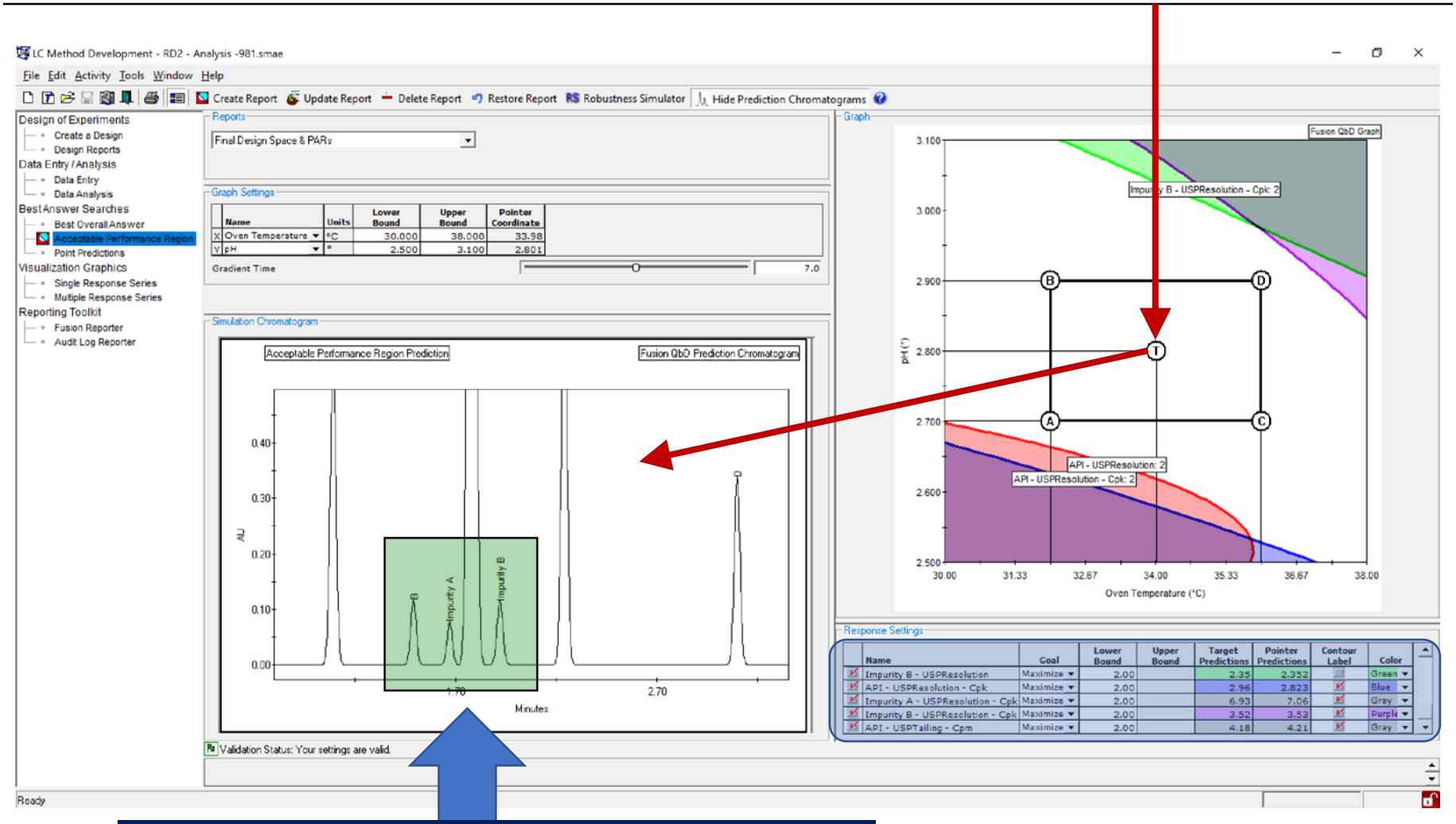
Visualize Final Method and Robust Operating Ranges for All CQAs Across the Entire Design Space – With Predicted Suitability Results and Chromatograms

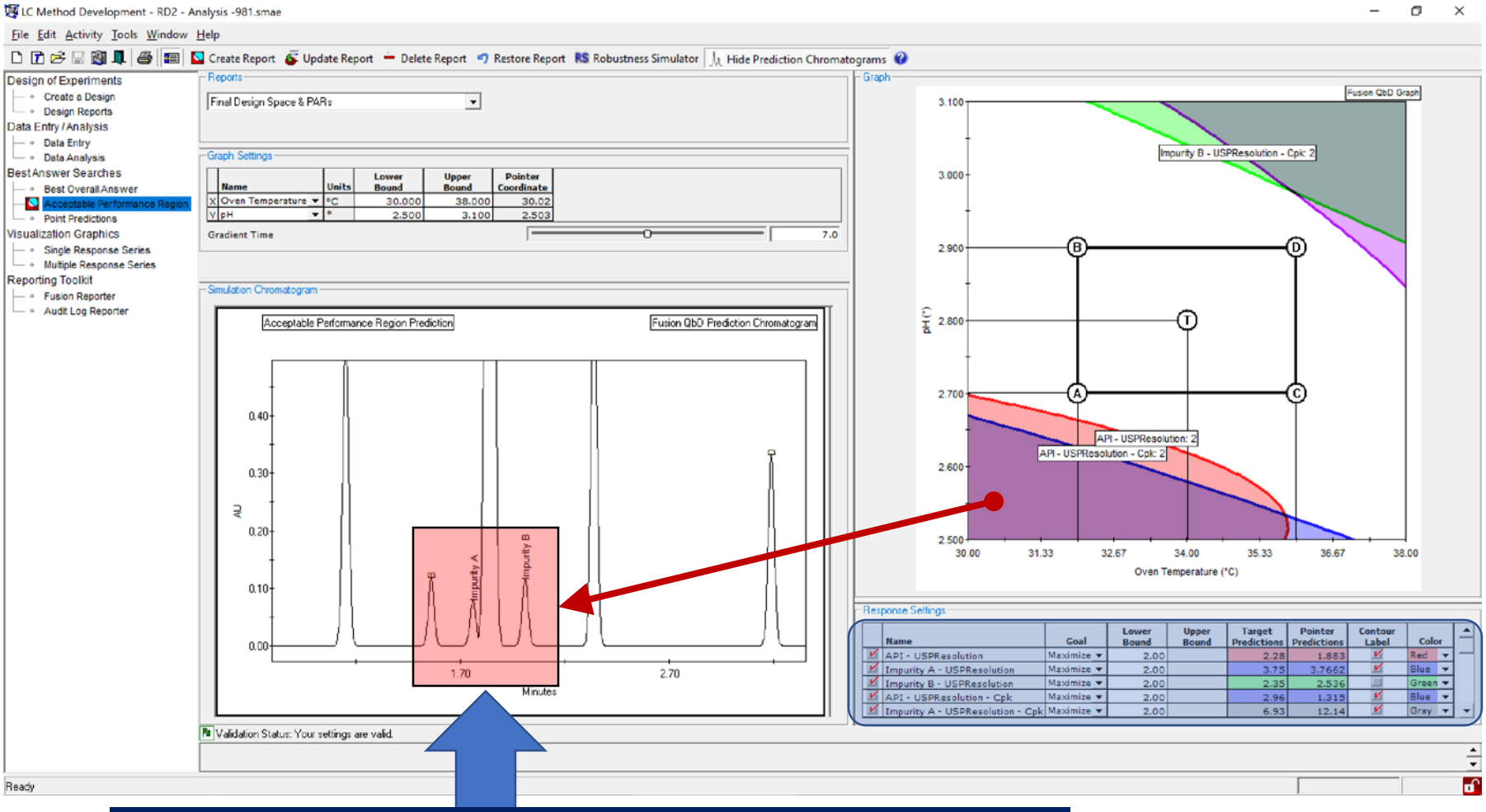


Visualize Final Method and Robust Operating Ranges for All CQAs Across the Entire Design Space – With Predicted Suitability Results and Chromatograms



Zoom in and Format Chromatogram View

Visualize Final Method and Robust Operating Ranges for All CQAs Across the Entire Design Space – With Predicted Suitability Results and Chromatograms



Move Pointer and See how Chromatogram Changes

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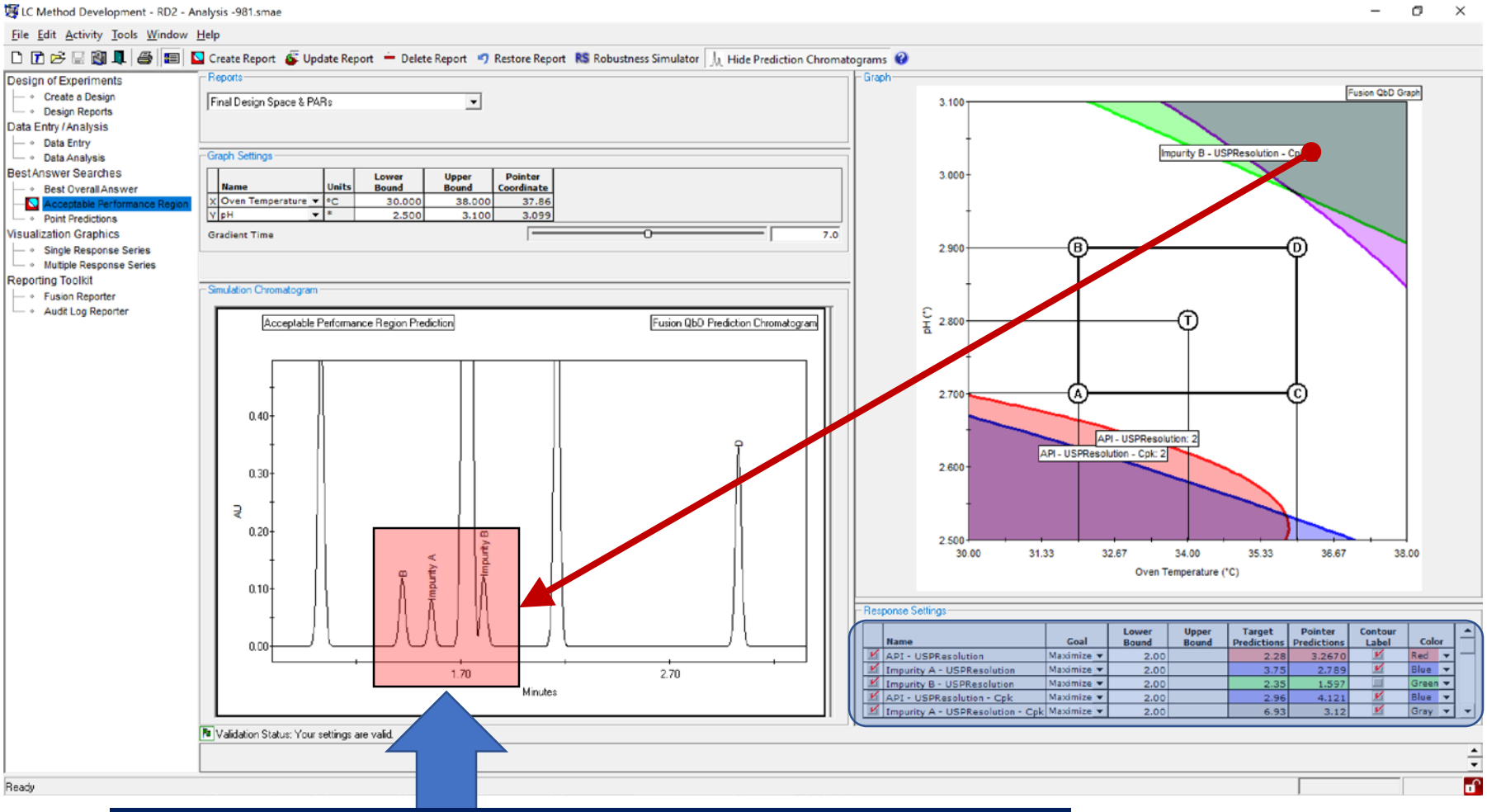
Visualize Final Method and Robust Operating Ranges for All CQAs Across the Entire Design Space – With Predicted Suitability Results and Chromatograms



Move Pointer and See how Chromatogram Changes

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Fusion QbD – Regulatory Guidance Aligned Reporting

ICH Q8(R2) – Page 22

C. Presentations of Design Space

Example 1: Response graphs for dissolution are depicted as a surface plot (Figure 1a) and a contour plot (Figure 1b). Parameters 1 and 2 are factors of a granulation operation that affect the dissolution rate of a tablet (e.g., excipient attribute, water amount, granule size.)

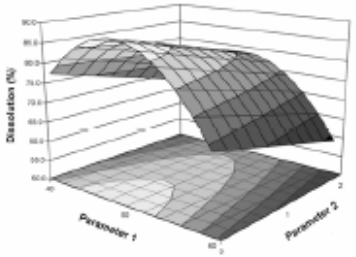

Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

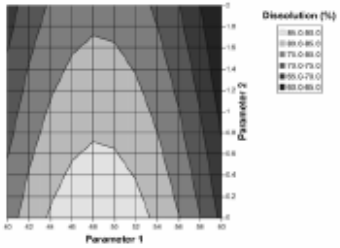

Figure 1b: Contour plot of dissolution from example 1a.

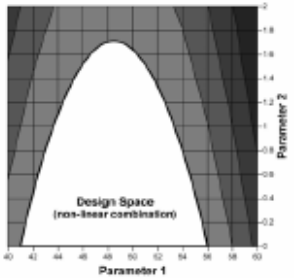

Figure 1c: Design space for granulation parameters, defined by a nonlinear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

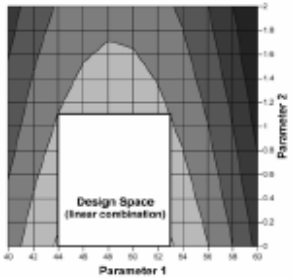

Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

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Name: Administrator
Company: S-Matrix Corporation
Project: Project 1
Date: 25-OCT-2017 22:10:32 PDT [UTC-07:00]

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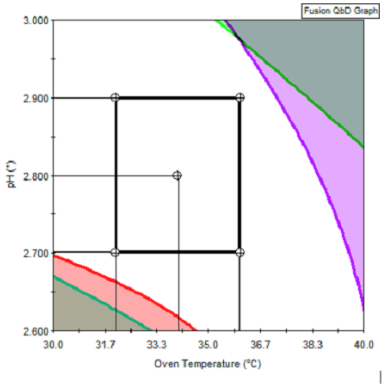
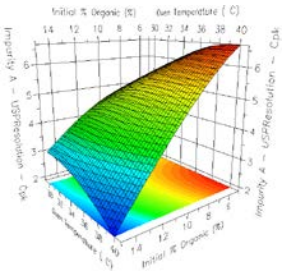
Robust Design Space





Proven Acceptable Range Settings

Axis	Name	Units	Lower Bound	Upper Bound	Centerpoint
X	Oven Temperature	°C	32.0	36.0	34.0
Y	pH	*	2.700	2.900	2.800

Response Variable Goals

Name	Units	Goal	Lower Bound	Upper Bound	Color	Predicted Centerpoint
API-USPResolution	(*)	Maximize	2.00	---	Red	2.25
Impurity A-USPResolution	(*)	Maximize	2.00	---	Blue	3.78
Impurity B-USPResolution	(*)	Maximize	2.00	---	Green	2.35
API-USPTailing	(*)	Target	0.90	1.10	Orange	1.01
API-USPResolution-Cpk	(*)	Maximize	2.00	---	Teal	2.82
Impurity A-USPResolution-Cpk	(*)	Maximize	2.00	---	Blue	7.08
Impurity B-USPResolution-Cpk	(*)	Maximize	2.00	---	Purple	3.56
API-USPTailing-Cpm	(*)	Maximize	2.00	---	Sky	4.20

Graph Variable Settings

Name	Units	Graph Setting	Range/Level(s)
Oven Temperature	(°C)	X Axis Variable	30.0 <= Oven Temperature <= 40.0
pH	(*)	Y Axis Variable	2.600 <= pH <= 3.000

1 of 2

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Fusion QbD – Regulatory Guidance Aligned Reporting

Name: Administrator
Company: S-Matrix
Project: Project 1
Date: March 8, 2016 7:58:12 PM PDT [GMT-07:00]

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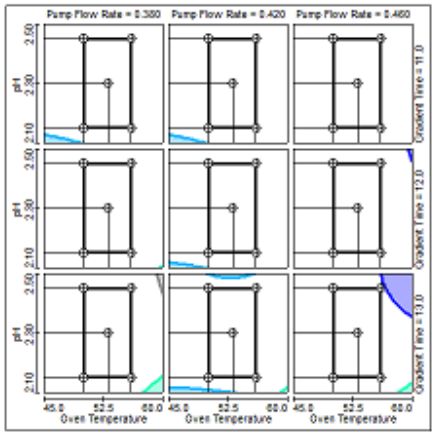
Robust Design Space & PARs



4-factor Robust Design Space and PARs

Operating Space Settings

Axis	Name	Lower Bound	Upper Bound	Centerpoint
X	Oven Temperature	50.0	59.3	59.0
Y	pH	2.15	2.45	2.90

Response Variable Goals

Name	Units	Goal	Lower Bound	Upper Bound	Color
No. of Peaks == 1.2 - USPTailing	(*)	Maximize	7.00	---	Sky
E - USPResolution	(*)	Maximize	2.00	---	Blue
F - USPResolution	(*)	Maximize	2.00	---	Green
J - USPResolution	(*)	Maximize	2.00	---	Orange
K - USPResolution	(*)	Maximize	2.00	---	Red
G - USPTailing	(*)	Target	0.90	1.10	Purple
A - RetensionTime	(*)	Maximize	1.50	---	Lime
G - USPTailing - Cp	(*)	Maximize	1.33	---	Gray
A - RetensionTime - Cp	(*)	Maximize	1.33	---	Gray
E - RetensionTime - Cp	(*)	Maximize	1.33	---	Gray
G - RetensionTime - Cn	(*)	Maximize	1.33	---	Gray

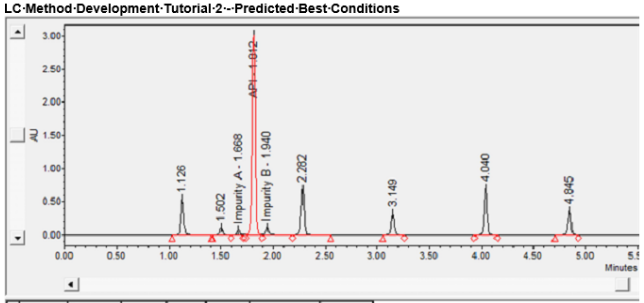
Experiment Variables for Robustness Simulator

Included	Variable Name	Units	Maximum Expected Variation (+/-*3*Sigma Value)
Yes	Gradient Time	min	0.5
Yes	Oven Temperature	°C	2.0
Yes	pH	*	0.10

Responses for Robustness Simulator

Response Name	Robustness Index	Specification Limit Delta (+/-)	LSL	USL	Target	Additional Error	Overall Experimental Error (+/-*3*Sigma Value)
API - USPResolution	Cpk		1.50	---			
Impurity A - USPResolution	Cpk		1.50	---			
Impurity B - USPResolution	Cpk		1.50	---			
API - USPTailing	Cpm	0.20			1.00		

LC Method Development Tutorial 2 - Predicted Best Conditions



	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	USP Resolution	USP Tailing
1		1.126	1124052	8.66	547171		1.19
2		1.502	219379	1.69	115821	7.26	1.07
3	Impurity A	1.668	145624	1.12	76902	3.32	1.07
4	API	1.812	6898993	53.18	3014939	2.75	1.02
5	Impurity B	1.940	254551	1.96	114291	2.33	
6		2.282	1403806	10.82	700581	6.38	0.98
7		3.149	667413	5.14	329419	16.42	0.96
8		4.040	1475656	11.37	713959	16.60	0.97
9		4.845	783934	6.04	373312	14.72	0.96

3D Channels | 2D Channels | Peaks | Fractions

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Fusion QbD – the World is Catching Up!

3. Process Capability

Process capability refers to the performance of the process when it is operating under statistical control. Two capability indices are usually computed: C_p and C_{pk} in a similar way as was described with P_p and P_{pk}. However, C_p measures the **potential** capability in the process, if the process was centred, while C_{pk} measures the actual capability in a process which is off-centre or biased. If a process is centred, then $C_p = C_{pk}$.

$$C_{pk} = \min\left[\frac{U-\bar{\bar{X}}}{3S_w}, \frac{\bar{\bar{X}}-L}{3S_w}\right] \qquad (1.5)$$

The critical thing to note is that whilst the formulae for P_{pk} and C_{pk} look very similar, the standard deviation used to calculate the reference interval for C_{pk} is not S_t but S_w.

S_w is the within batch standard deviation (called the within sub group standard deviation in ISO) not the overall process standard deviation. It is usually estimated from a Shewhart mean and range control chart using the formula

European Compliance Agency, Analytical Quality Control Group, July 2018, Final_r1

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