Sample Preparation Method Development With Fusion QbD®

S-Matrix Corporation
1594 Myrtle Avenue
Eureka, CA 95501
USA
Phone: 707-441-0404
URL: www.smatrix.com

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Fusion Product Development (FPD)

Full Support for Part 11 Compliance

Citrix-Ready Certified

PRODUCT DEVELOPMENT

- QbD Formulation & Process Development
- Non-LC Method Development (e.g. CE, Disso)
- Automated LC Testing & Data Acquisition:
  Standard LC / Time Series / Respiratory

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Sample Preparation Method Development with Fusion QbD

Supported Install Environments	Fusion QbD
Standalone (Workstation)	✓
Network	✓
Citrix Ready Certified	✓
Fully Qualifiable for GxP*	✓

* - Fusion QbD is operating in the GxP environments of international pharmaceutical companies worldwide.

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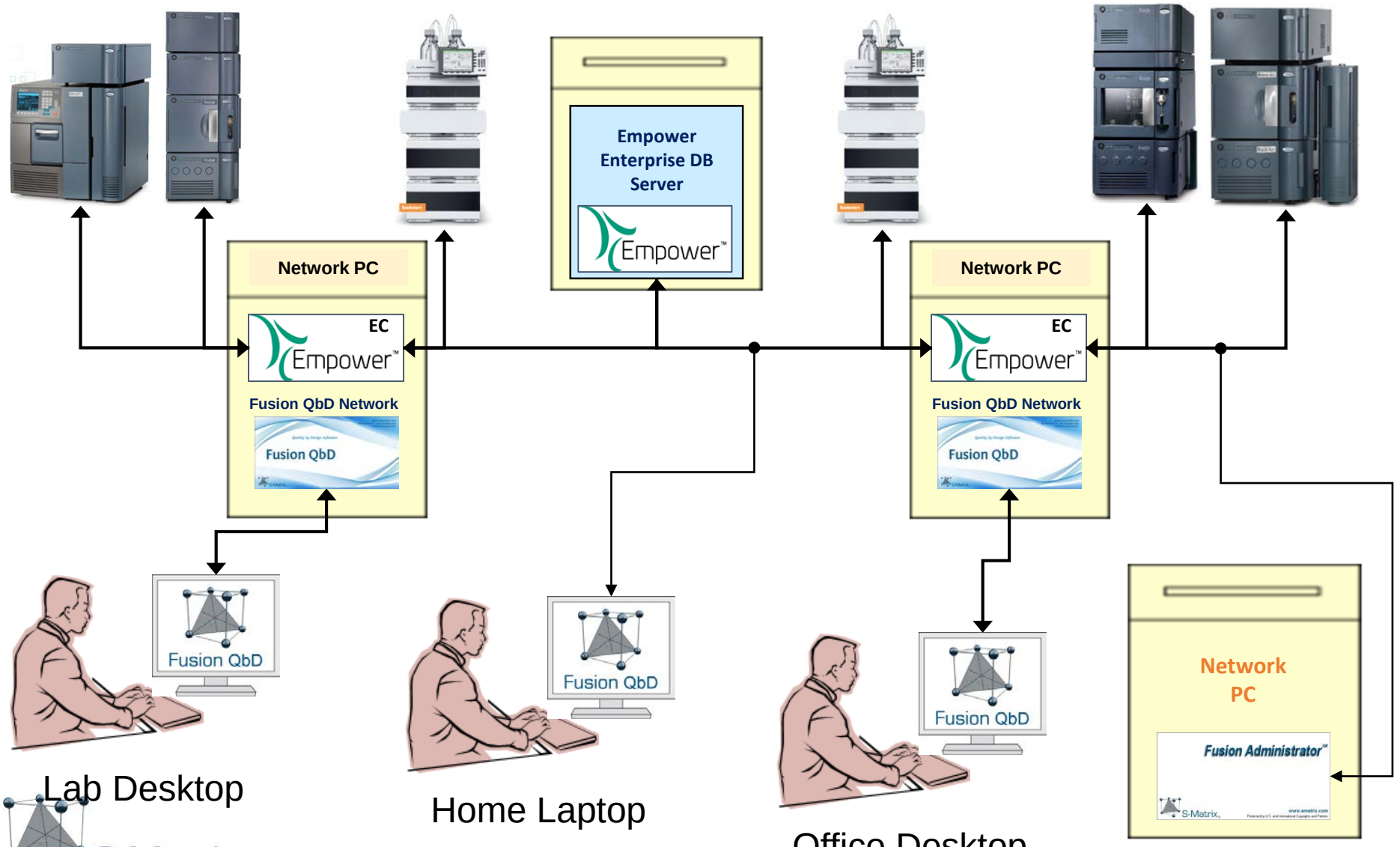
Enterprise Installation Example



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Why Compliance is Important!

FDA Statement* –

As long as the **data integrity** associated with the method development work matches what would be done in a formal Validation Robustness effort, then the results are acceptable.

Same Regulatory Expectation for Claims of Formulation and Process Robustness

*** – USP Workshop – Enhanced Approaches for Analytical Procedure Lifecycle: An Alternative to Traditional Validation (Sept. 24-25, 2018)**

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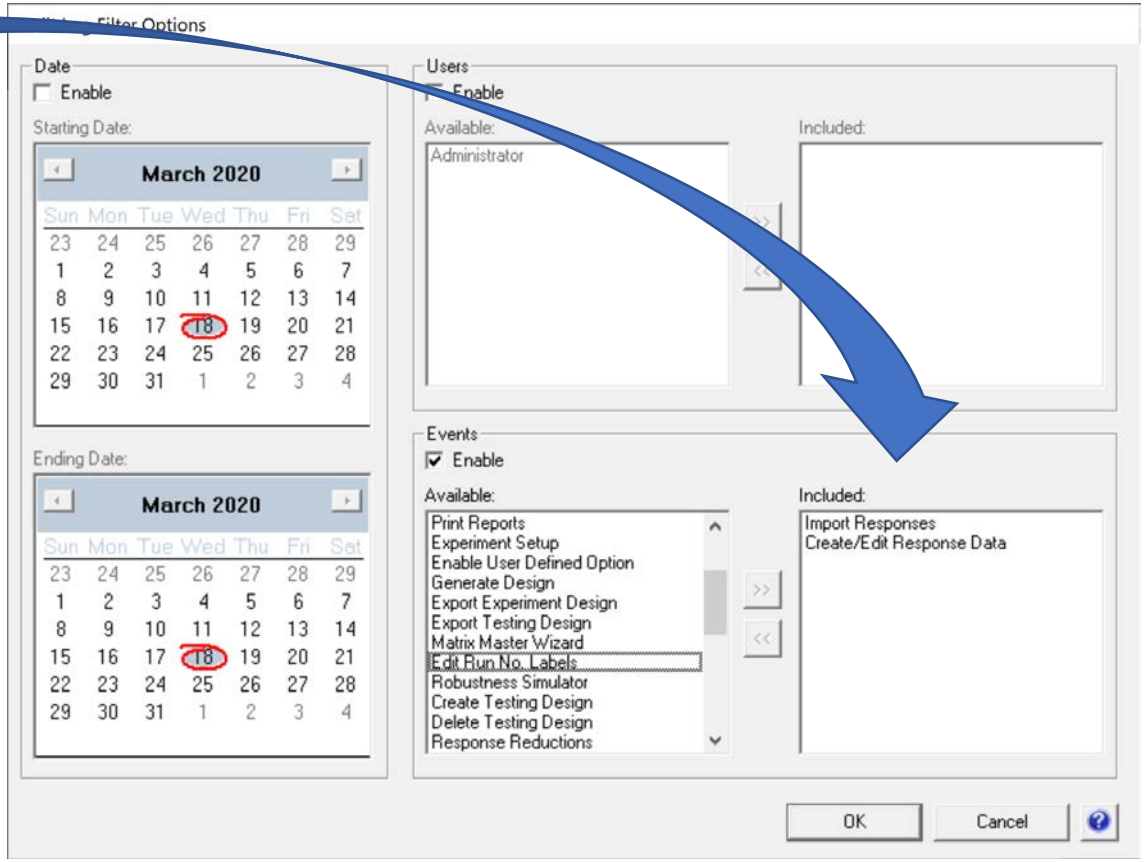
Why Audit Trail is Important!

What Empower Project did this data come from?

Who entered this data – was the data modified?



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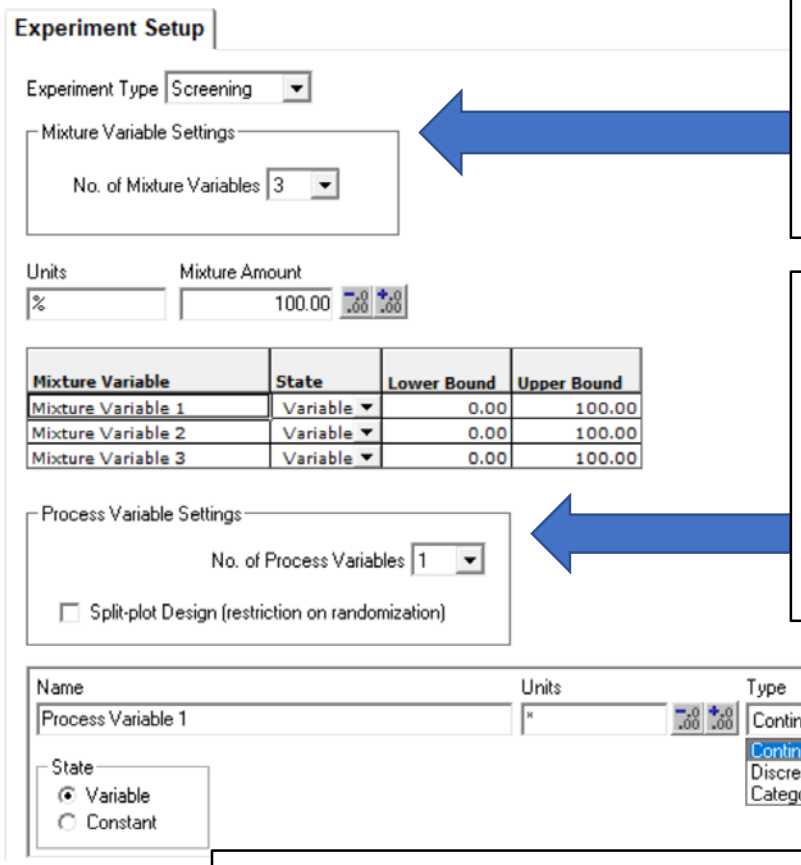
Flexible Expt. Setup



Formulation (Mixture) Studies

You specify:

- Number of Mixture Components
- Component Study Ranges
- Total Sample Amount and Units

Process (Non-mixture) Studies

You specify:

- Number of Study Factors
- Type of Each Factor
- Study Ranges or Levels

Combined Mixture-Process Studies

Enable you to characterize interactions between the two!

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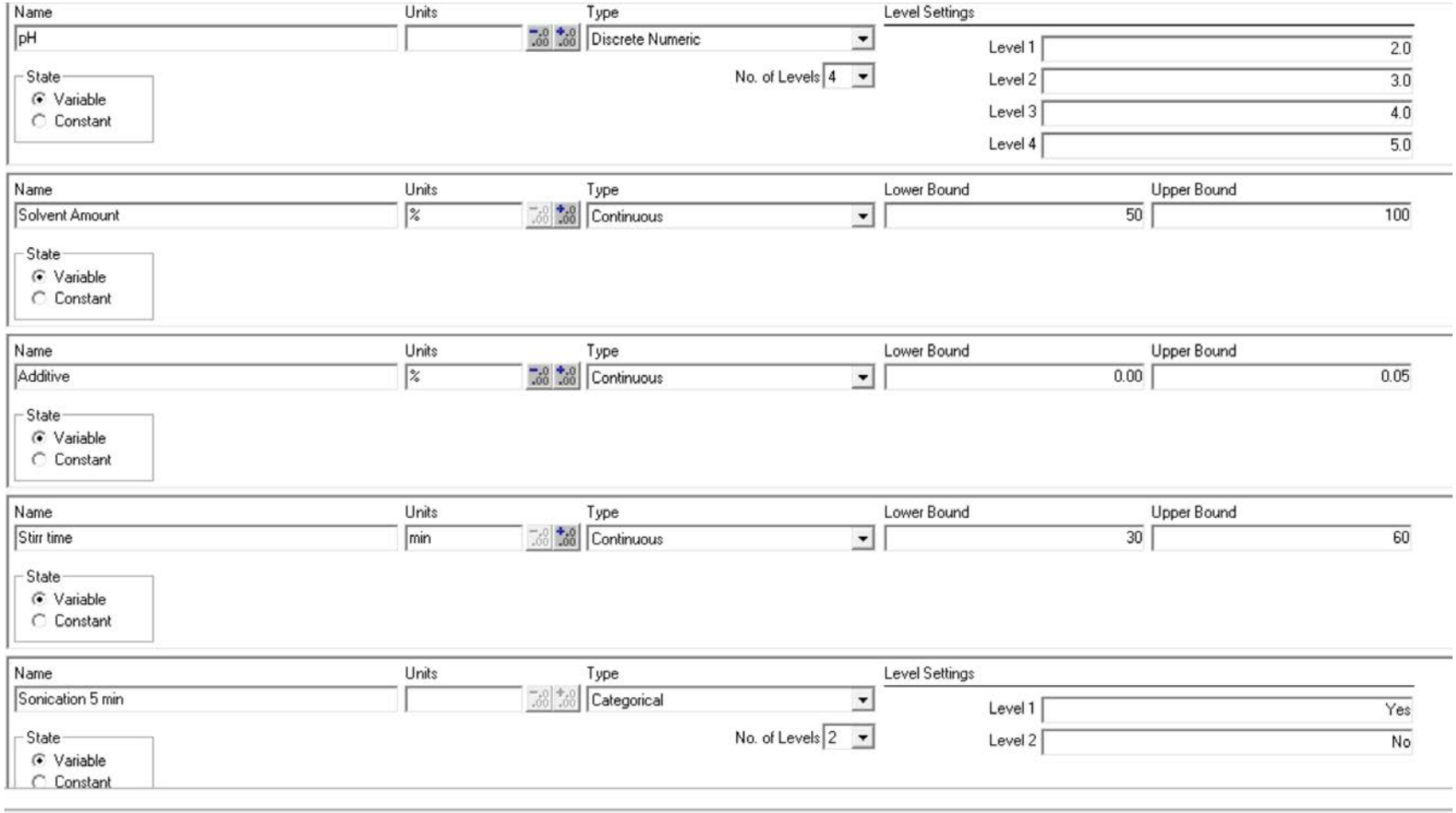
Sample Preparation Study – Example Completed Setup Template



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Automated Mode – 1-click selects the design for you!

Name: Administrator
Company:
Project:
Date:

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Experiment Design

Experiment Design Matrix

Run No.	pH	Solvent Amount (%)	Additive (%)	Stirr time (min)	Sonication 5 min
1	5.0	100	0.00	60	No
2	5.0	75	0.05	60	Yes
3	3.0	50	0.05	30	No
4	2.0	100	0.05	60	No
5	5.0	100	0.05	60	Yes
6	3.0	75	0.03	45	No
7	5.0	50	0.05	60	No
8	2.0	100	0.00	30	No
9	5.0	50	0.00	30	No
10	3.0	75	0.03	45	No
11	2.0	50	0.00	60	No
12	2.0	50	0.05	60	Yes

Fusion QbD 1-click Design Logic Accounts for:

- **Stage of the Work**
  (Screening or Optimization)
- **Number of Variables**
- **Types of Variables**
  Continuous Numeric
  Discrete Numeric
  – # of defined levels
  Categorical (Non-numeric)
  – # of defined levels

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Sample Preparation R&D

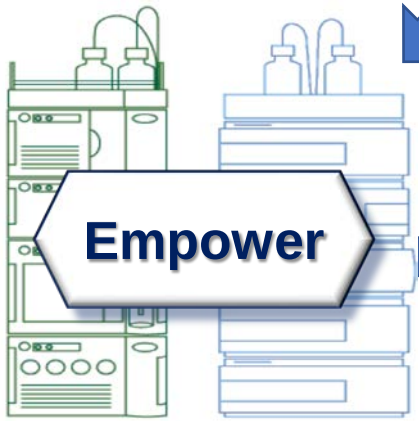
Data Flow

1) Experiment Design

Fusion QbD generates the Sample Prep. Study based on the user's variable settings.

2) Testing Design

Fusion QbD creates a companion LC Testing Design and exports it to Empower as a ready-to-run Sample Set.



3) Sample Preparation Study Execution

Experiment run samples transferred to LC for testing using the Fusion QbD Sample Set.

4) Results Data Import

Fusion QbD automatically imports all LC results for all compounds and maps the data to the Sample Prep. Study design for automated modeling.

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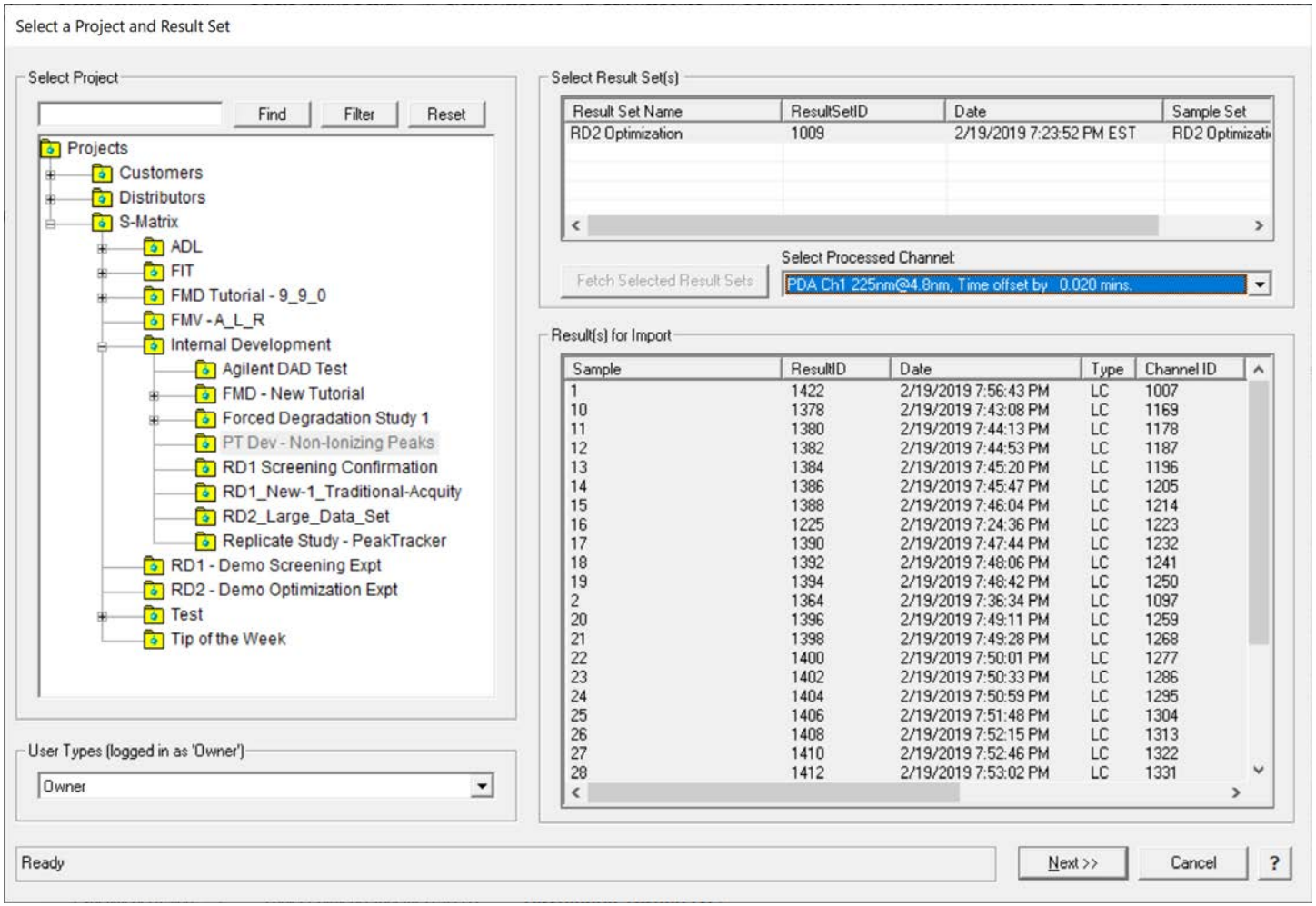
Automatically Import All Required Results Data from CDS



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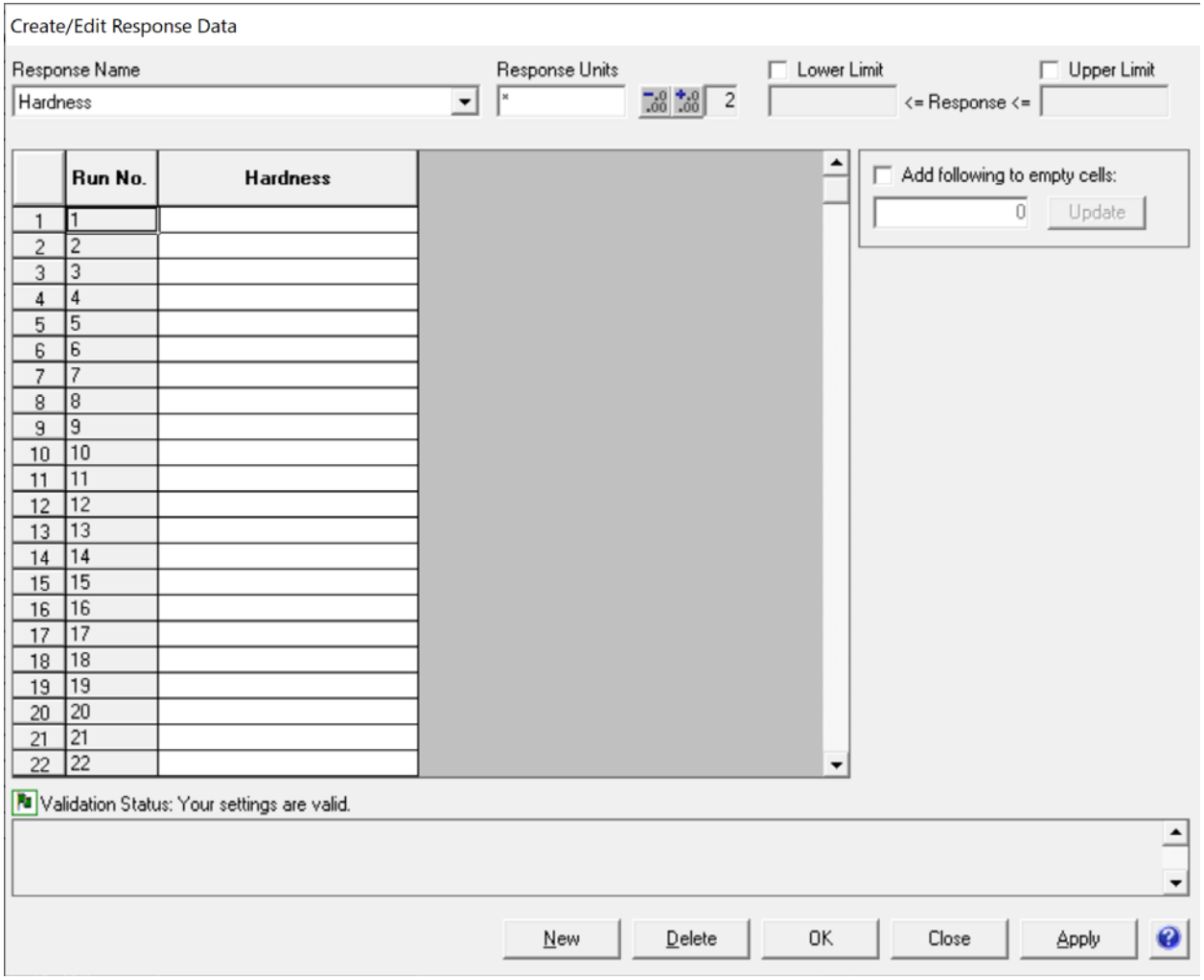
Directly Enter Non-CDS Generated Results Data



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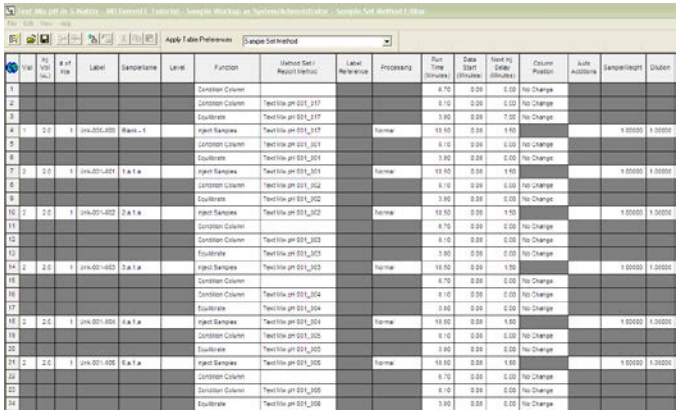
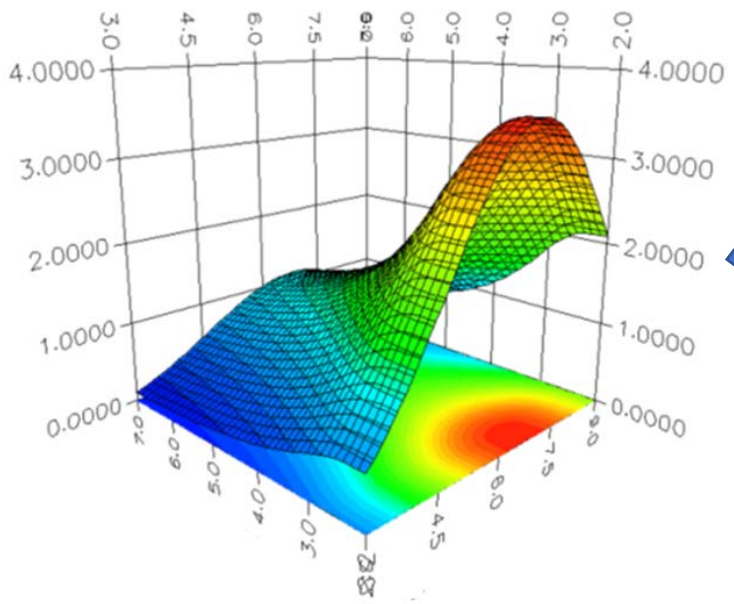
Sample Preparation Method Development with Fusion QbD

Multivariate DOE Study – goal is characterizing all significant effects of the study parameters on all Critical Quality Attributes (CQAs)





$$CQA = 9.3 + 4.2(Sol.) - 5.4(Add.)^2 + 12.7(Add*Stir\Delta t) + 1.3(Sol.*Stir\Delta t) + 1.6[(\Delta pH)^2(Add.)] + \ldots$$

Linear Effect	Curvature Effect	Interaction Effects	Complex Effect

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State-of-the-Art Modeling – FDA Accepted

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Example of a Resolution Model Eqn.

- Peak 3 resolution

$$R = 3.0607 + 0.4109(GT) - 0.3367(Temp) - 0.7772(pH) - 0.2013(pH)^2$$

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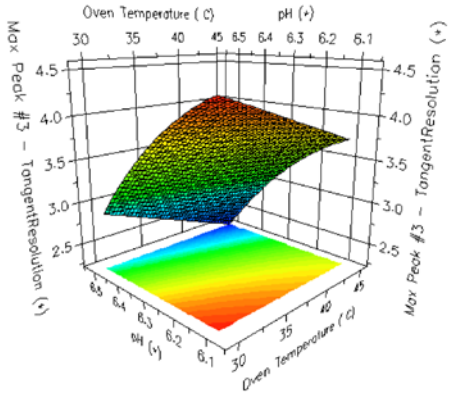
Protecting and Promoting Public Health
www.fda.gov

Example of a Resolution Model Eqn. Predicted Response



✓ Regulatory Acceptance of Fusion QbD

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, CASSS CMC Strategy Forum Europe 2015

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QbD Robustness – Regulatory Statements

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.

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QbD Robustness – Regulatory Statements

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

ECA _AQCG_ SOP 03_APLM_v1.0_July 2018_Final_r1 Page 78 of 80

Analytical Procedure Lifecycle Management

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

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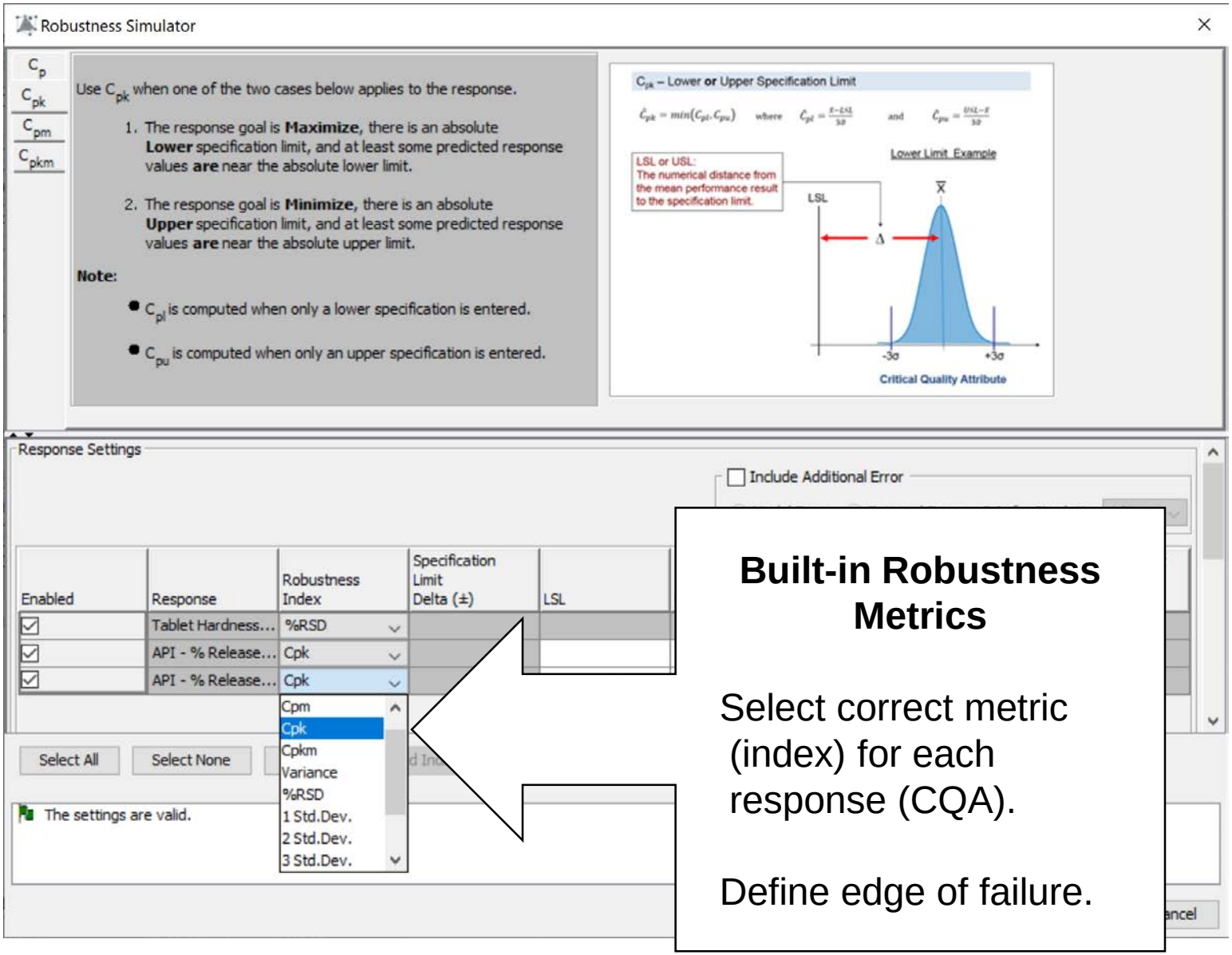
Sample Preparation Method Development with Fusion QbD



Built-in Robustness Metrics

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

Define edge of failure.

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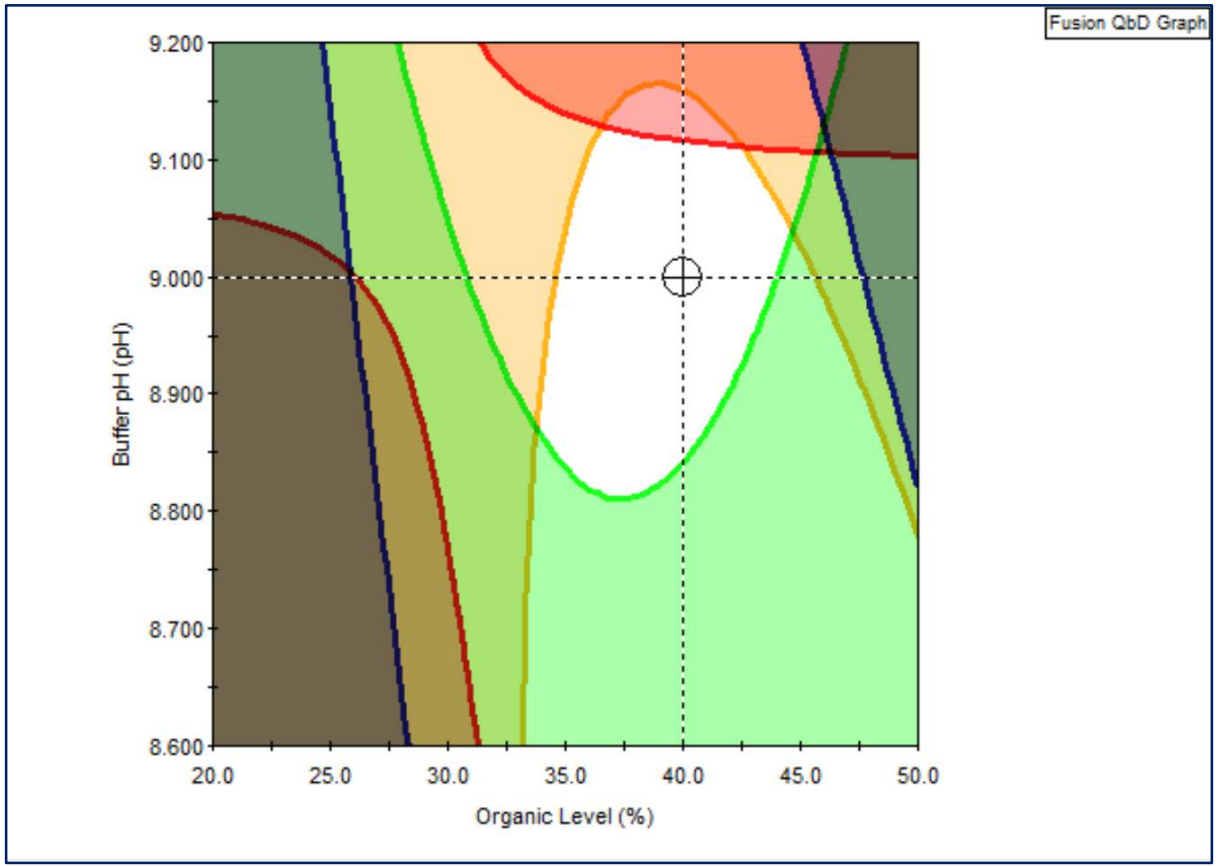
Graphical Visualization of Robust Design Space – 2 Study Factors



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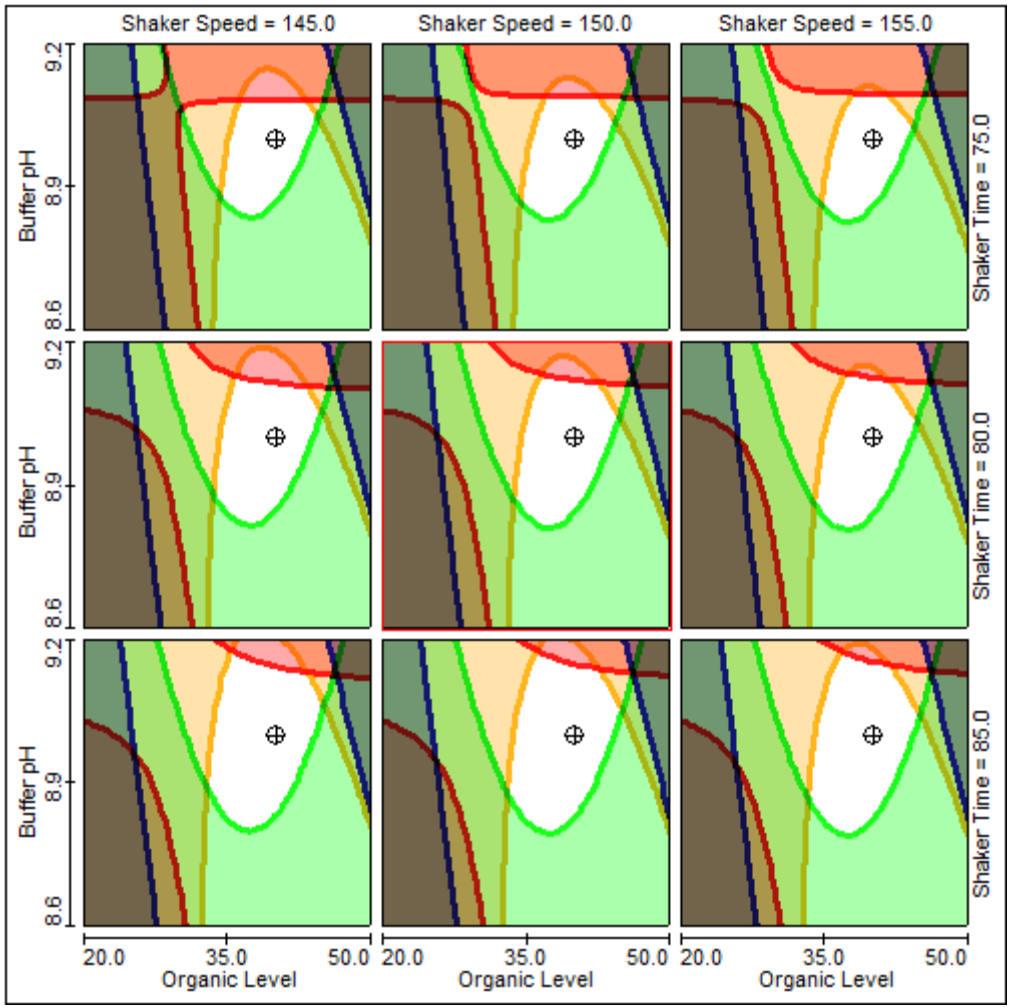
Graphical Visualization of Robust Design Space – 4 Study Factors



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Complete QbD Reporting – Output in Multiple Formats

Name: Administrator
Company:
Project:
Date:

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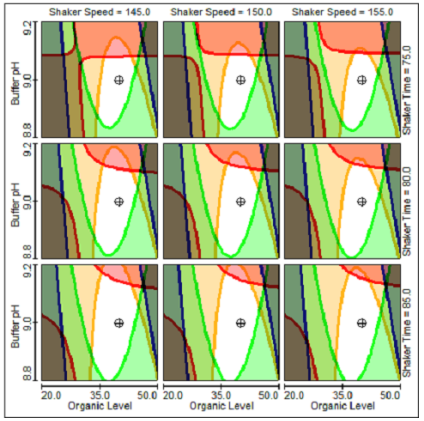
Robustness Trellis



Response Variable Goals

Name	Units	Goal	Color	Lower Bound	Upper Bound
Response 1 - Mean	*	Maximize	Red	97.5	
Response 2 - Mean	%	Maximize	Blue	99.0	
Response 1 – Robustness Cpm		Maximize	Green	1.33	
Response 2 – Robustness Cpm		Maximize	Orange	1.00	

Trellis Variable Settings

Series	Variable Name	Units	Low	Middle	High
Horizontal	Shaker Speed	rpm	145.0	150.0	155.0
Vertical	Shaker Time	min	75.0	80.0	85.0

1 of 2

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