

Sample Preparation Method Development With Fusion QbD[®]



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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

Supported Install Environments

Fusion QbD

Standalone (Workstation)



Network



Citrix Ready Certified

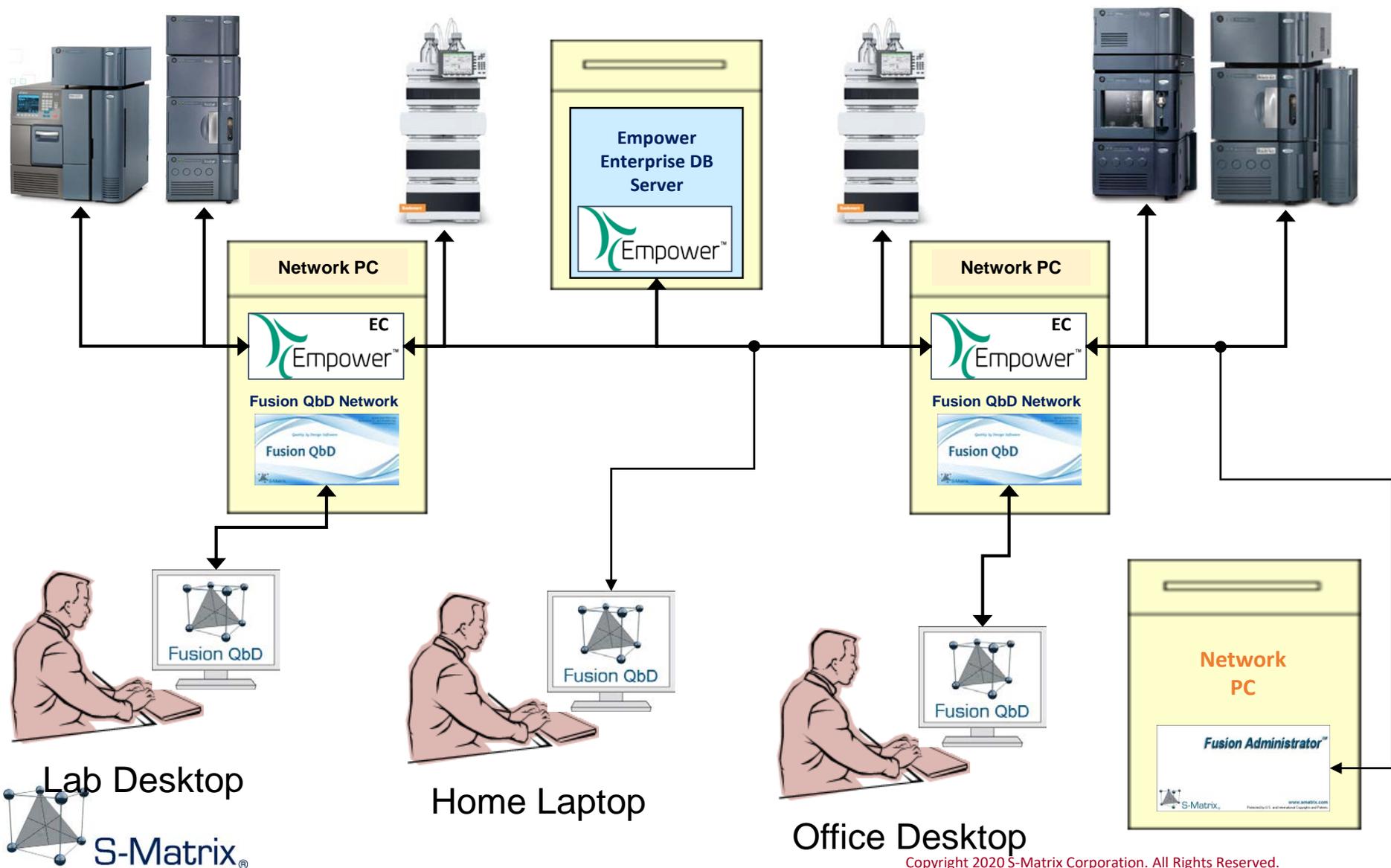


Fully Qualifiable for GxP*



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

Enterprise Installation Example



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)

Why Audit Trail is Important!

What Empower Project did this data come from?



Who entered this data – was the data modified?

Filter Options

Enable

Starting Date:

| March 2020 | | | | | | |
|------------|-----|-----|-----|-----|-----|-----|
| Sun | Mon | Tue | Wed | Thu | Fri | Sat |
| 23 | 24 | 25 | 26 | 27 | 28 | 29 |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| 22 | 23 | 24 | 25 | 26 | 27 | 28 |
| 29 | 30 | 31 | 1 | 2 | 3 | 4 |

Ending Date:

| March 2020 | | | | | | |
|------------|-----|-----|-----|-----|-----|-----|
| Sun | Mon | Tue | Wed | Thu | Fri | Sat |
| 23 | 24 | 25 | 26 | 27 | 28 | 29 |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| 22 | 23 | 24 | 25 | 26 | 27 | 28 |
| 29 | 30 | 31 | 1 | 2 | 3 | 4 |

Users

Enable

Available:

Administrator

Included:

Events

Enable

Available:

- Print Reports
- Experiment Setup
- Enable User Defined Option
- Generate Design
- Export Experiment Design
- Export Testing Design
- Matrix Master Wizard
- Edit Run No. Labels
- Robustness Simulator
- Create Testing Design
- Delete Testing Design
- Response Reductions

Included:

- Import Responses
- Create/Edit Response Data

OK Cancel ?

Flexible Expt. Setup

Experiment Setup

Experiment Type: Screening

Mixture Variable Settings

No. of Mixture Variables: 3

Units: % Mixture Amount: 100.00

| Mixture Variable | State | Lower Bound | Upper Bound |
|--------------------|----------|-------------|-------------|
| Mixture Variable 1 | Variable | 0.00 | 100.00 |
| Mixture Variable 2 | Variable | 0.00 | 100.00 |
| Mixture Variable 3 | Variable | 0.00 | 100.00 |

Process Variable Settings

No. of Process Variables: 1

Split-plot Design (restriction on randomization)

Name: Process Variable 1 Units: * Type: Continuous Lower Bound: -1.0 Upper Bound: 1.0

State: Variable Constant

Type dropdown menu: Continuous, Discrete Numeric, Categorical

Formulation (Mixture) Studies

You specify:

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

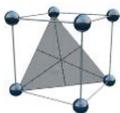
Process (Non-mixture) Studies

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!



Sample Preparation Study – Example Completed Setup Template

| Name | Units | Type | Level Settings | |
|--|-------|------------------|----------------|-----|
| pH | | Discrete Numeric | Level 1 | 2.0 |
| State <input checked="" type="radio"/> Variable <input type="radio"/> Constant | | No. of Levels | Level 2 | 3.0 |
| | | | Level 3 | 4.0 |
| | | | Level 4 | 5.0 |

| Name | Units | Type | Lower Bound | Upper Bound |
|--|-------|------------|-------------|-------------|
| Solvent Amount | % | Continuous | 50 | 100 |
| State <input checked="" type="radio"/> Variable <input type="radio"/> Constant | | | | |

| Name | Units | Type | Lower Bound | Upper Bound |
|--|-------|------------|-------------|-------------|
| Additive | % | Continuous | 0.00 | 0.05 |
| State <input checked="" type="radio"/> Variable <input type="radio"/> Constant | | | | |

| Name | Units | Type | Lower Bound | Upper Bound |
|--|-------|------------|-------------|-------------|
| Stirr time | min | Continuous | 30 | 60 |
| State <input checked="" type="radio"/> Variable <input type="radio"/> Constant | | | | |

| Name | Units | Type | Level Settings | |
|--|-------|---------------|----------------|-----|
| Sonication 5 min | | Categorical | Level 1 | Yes |
| State <input checked="" type="radio"/> Variable <input type="radio"/> Constant | | No. of Levels | Level 2 | No |
| | | | | |

Validation Status: Your settings are valid.

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

Name: Administrator
Company:
Project:
Date:



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



Sample Preparation R&D

Data Flow

2) Testing Design

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

1) Experiment Design

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

Empower

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.

Fusion QbD®

Automatically Import All Required Results Data from CDS

Select a Project and Result Set

Select Project

Find Filter Reset

- Projects
 - Customers
 - Distributors
 - S-Matrix
 - ADL
 - FIT
 - FMD Tutorial - 9_9_0
 - FMV - A_L_R
 - Internal Development
 - Agilent DAD Test
 - FMD - New Tutorial
 - Forced Degradation Study 1
 - PT Dev - Non-Ionizing Peaks
 - RD1 Screening Confirmation
 - RD1_New-1_Traditional-Acquity
 - RD2_Large_Data_Set
 - Replicate Study - PeakTracker
 - RD1 - Demo Screening Expt
 - RD2 - Demo Optimization Expt
 - Test
 - Tip of the Week

User Types (logged in as 'Owner')

Owner

Select Result Set(s)

| Result Set Name | ResultSetID | Date | Sample Set |
|------------------|-------------|--------------------------|----------------|
| RD2 Optimization | 1009 | 2/19/2019 7:23:52 PM EST | RD2 Optimizati |

Fetch Selected Result Sets

Select Processed Channel:

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

Result(s) for Import

| Sample | ResultID | Date | Type | Channel ID |
|--------|----------|----------------------|------|------------|
| 1 | 1422 | 2/19/2019 7:56:43 PM | LC | 1007 |
| 10 | 1378 | 2/19/2019 7:43:08 PM | LC | 1169 |
| 11 | 1380 | 2/19/2019 7:44:13 PM | LC | 1178 |
| 12 | 1382 | 2/19/2019 7:44:53 PM | LC | 1187 |
| 13 | 1384 | 2/19/2019 7:45:20 PM | LC | 1196 |
| 14 | 1386 | 2/19/2019 7:45:47 PM | LC | 1205 |
| 15 | 1388 | 2/19/2019 7:46:04 PM | LC | 1214 |
| 16 | 1225 | 2/19/2019 7:24:36 PM | LC | 1223 |
| 17 | 1390 | 2/19/2019 7:47:44 PM | LC | 1232 |
| 18 | 1392 | 2/19/2019 7:48:06 PM | LC | 1241 |
| 19 | 1394 | 2/19/2019 7:48:42 PM | LC | 1250 |
| 2 | 1364 | 2/19/2019 7:36:34 PM | LC | 1097 |
| 20 | 1396 | 2/19/2019 7:49:11 PM | LC | 1259 |
| 21 | 1398 | 2/19/2019 7:49:28 PM | LC | 1268 |
| 22 | 1400 | 2/19/2019 7:50:01 PM | LC | 1277 |
| 23 | 1402 | 2/19/2019 7:50:33 PM | LC | 1286 |
| 24 | 1404 | 2/19/2019 7:50:59 PM | LC | 1295 |
| 25 | 1406 | 2/19/2019 7:51:48 PM | LC | 1304 |
| 26 | 1408 | 2/19/2019 7:52:15 PM | LC | 1313 |
| 27 | 1410 | 2/19/2019 7:52:46 PM | LC | 1322 |
| 28 | 1412 | 2/19/2019 7:53:02 PM | LC | 1331 |

Ready

Next >> Cancel ?

Directly Enter Non-CDS Generated Results Data

Create/Edit Response Data

Response Name: Response Units: 2 Lower Limit Upper Limit

<= Response <=

| | Run No. | Hardness |
|----|---------|----------|
| 1 | 1 | |
| 2 | 2 | |
| 3 | 3 | |
| 4 | 4 | |
| 5 | 5 | |
| 6 | 6 | |
| 7 | 7 | |
| 8 | 8 | |
| 9 | 9 | |
| 10 | 10 | |
| 11 | 11 | |
| 12 | 12 | |
| 13 | 13 | |
| 14 | 14 | |
| 15 | 15 | |
| 16 | 16 | |
| 17 | 17 | |
| 18 | 18 | |
| 19 | 19 | |
| 20 | 20 | |
| 21 | 21 | |
| 22 | 22 | |

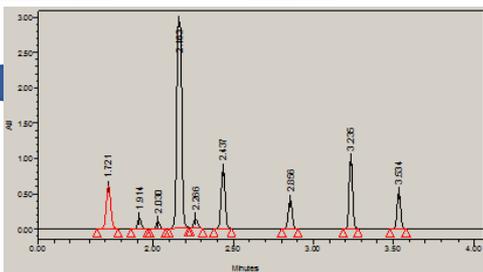
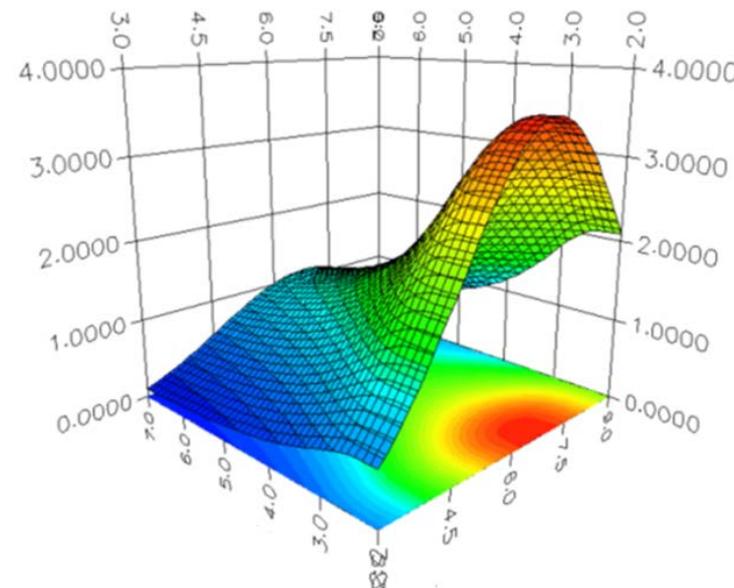
Add following to empty cells:

Validation Status: Your settings are valid.

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)

| Run | 1st Sol. | 2nd Sol. | Label | Temperature | Level | Function | Method Set / Report Method | Label Reference | Processing | Run Time (minutes) | Data Start (minutes) | Peak No. (Sample) | Column Position | Auto Injection | Sample Weight | Order |
|-----|----------|----------|-------------|-------------|-------|----------|----------------------------|-----------------|------------|--------------------|----------------------|-------------------|-----------------|----------------|---------------|---------|
| 1 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 2 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 3 | | | | | | | | | | 9.00 | 0.00 | 1.00 | No Change | | | |
| 4 | 2.0 | 1 | 001-001-000 | Blank-1 | | | | Normal | | 10.00 | 0.00 | 1.00 | No Change | | 8.00000 | 1.00004 |
| 5 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 6 | | | | | | | | | | 9.00 | 0.00 | 0.00 | No Change | | | |
| 7 | 2.0 | 1 | 001-001-001 | 1 x 1 x | | | | Normal | | 10.00 | 0.00 | 1.00 | No Change | | 8.00000 | 1.00004 |
| 8 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 9 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 10 | 2.0 | 1 | 001-001-002 | 2 x 1 x | | | | Normal | | 10.00 | 0.00 | 1.00 | No Change | | 8.00000 | 1.00004 |
| 11 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 12 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 13 | 2.0 | 1 | 001-001-003 | 3 x 1 x | | | | Normal | | 10.00 | 0.00 | 1.00 | No Change | | 8.00000 | 1.00004 |
| 14 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 15 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 16 | 2.0 | 1 | 001-001-004 | 4 x 1 x | | | | Normal | | 10.00 | 0.00 | 1.00 | No Change | | 8.00000 | 1.00004 |
| 17 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 18 | 2.0 | 1 | 001-001-005 | 5 x 1 x | | | | Normal | | 10.00 | 0.00 | 1.00 | No Change | | 8.00000 | 1.00004 |
| 19 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 20 | | | | | | | | | | 8.00 | 0.00 | 0.00 | No Change | | | |
| 21 | 2.0 | 1 | 001-001-006 | 6 x 1 x | | | | Normal | | 10.00 | 0.00 | 1.00 | No Change | | 8.00000 | 1.00004 |
| 22 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 23 | | | | | | | | | | 8.70 | 0.00 | 0.00 | No Change | | | |
| 24 | | | | | | | | | | 9.00 | 0.00 | 0.00 | No Change | | | |



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

Linear Effect

Curvature Effect

Interaction Effects

Complex Effect

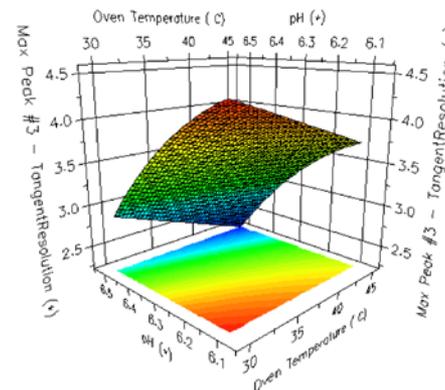
State-of-the-Art Modeling – FDA Accepted

Example of a Resolution Model Eqn.

- Peak 3 resolution

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

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

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.

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 $C_p = C_{pk}$.

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

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

Sample Preparation Method Development with Fusion QbD

Robustness Simulator
✕

C_p
 C_{pk}
 C_{pm}
 C_{pkm}

Use C_{pk} when one of the two cases below applies to the response.

- The response goal is **Maximize**, there is an absolute **Lower** specification limit, and at least some predicted response values **are** near the absolute lower limit.
- The response goal is **Minimize**, there is an absolute **Upper** specification limit, and at least some predicted response values **are** near the absolute upper limit.

Note:

- C_{pl} is computed when only a lower specification is entered.
- C_{pu} is computed when only an upper specification is entered.

C_{pk} – Lower or Upper Specification Limit

$$\hat{C}_{pk} = \min(C_{pl}, C_{pu}) \quad \text{where} \quad C_{pl} = \frac{\bar{x} - LSL}{3\sigma} \quad \text{and} \quad C_{pu} = \frac{USL - \bar{x}}{3\sigma}$$

LSL or USL:
The numerical distance from the mean performance result to the specification limit.

Lower Limit Example

Critical Quality Attribute

Response Settings

Include Additional Error

| Enabled | Response | Robustness Index | Specification Limit Delta (\pm) | LSL |
|-------------------------------------|--------------------|------------------|-------------------------------------|-----|
| <input checked="" type="checkbox"/> | Tablet Hardness... | %RSD | ▼ | |
| <input checked="" type="checkbox"/> | API - % Release... | Cpk | ▼ | |
| <input checked="" type="checkbox"/> | API - % Release... | Cpk | ▼ | |

Select All Select None

The settings are valid.

Cpm
Cpk
Cpkm
Variance
%RSD
1 Std.Dev.
2 Std.Dev.
3 Std.Dev.

Built-in Robustness Metrics

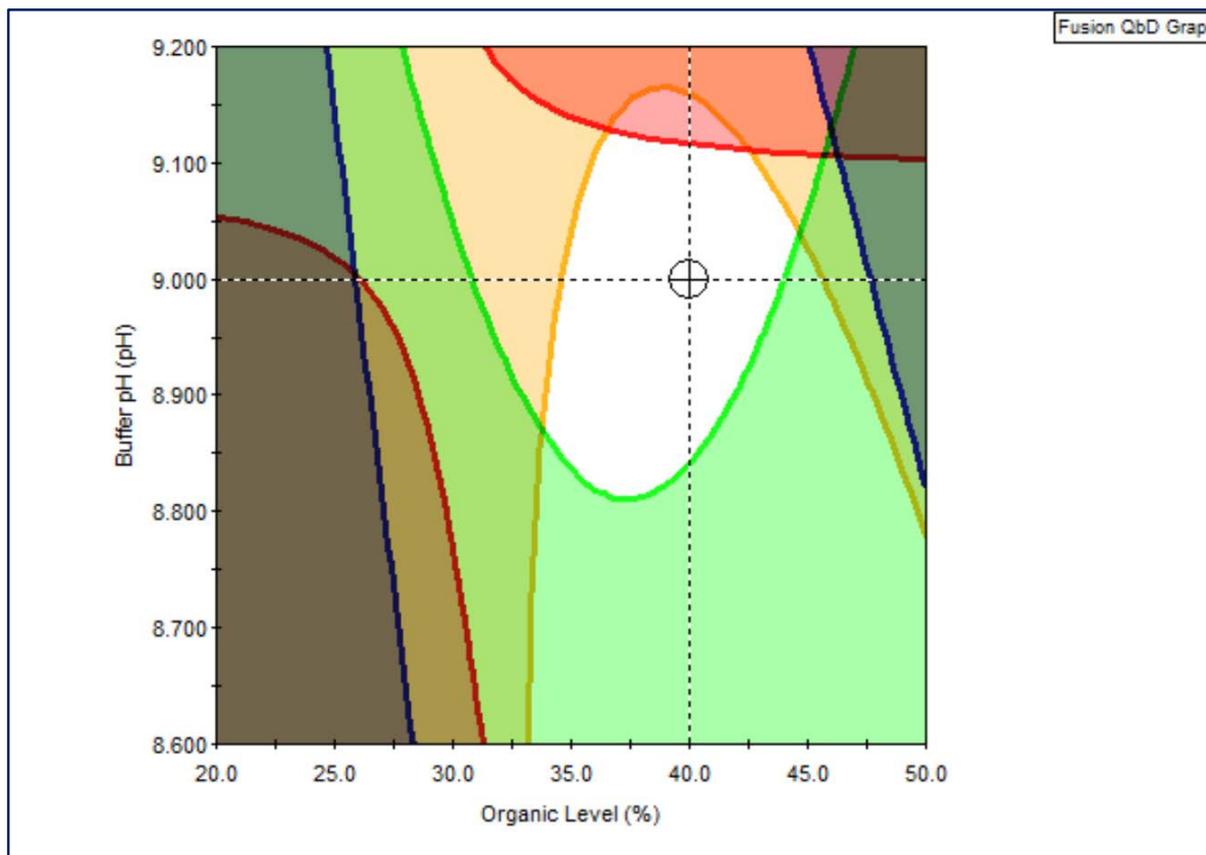
Select correct metric (index) for each response (CQA).

Define edge of failure.

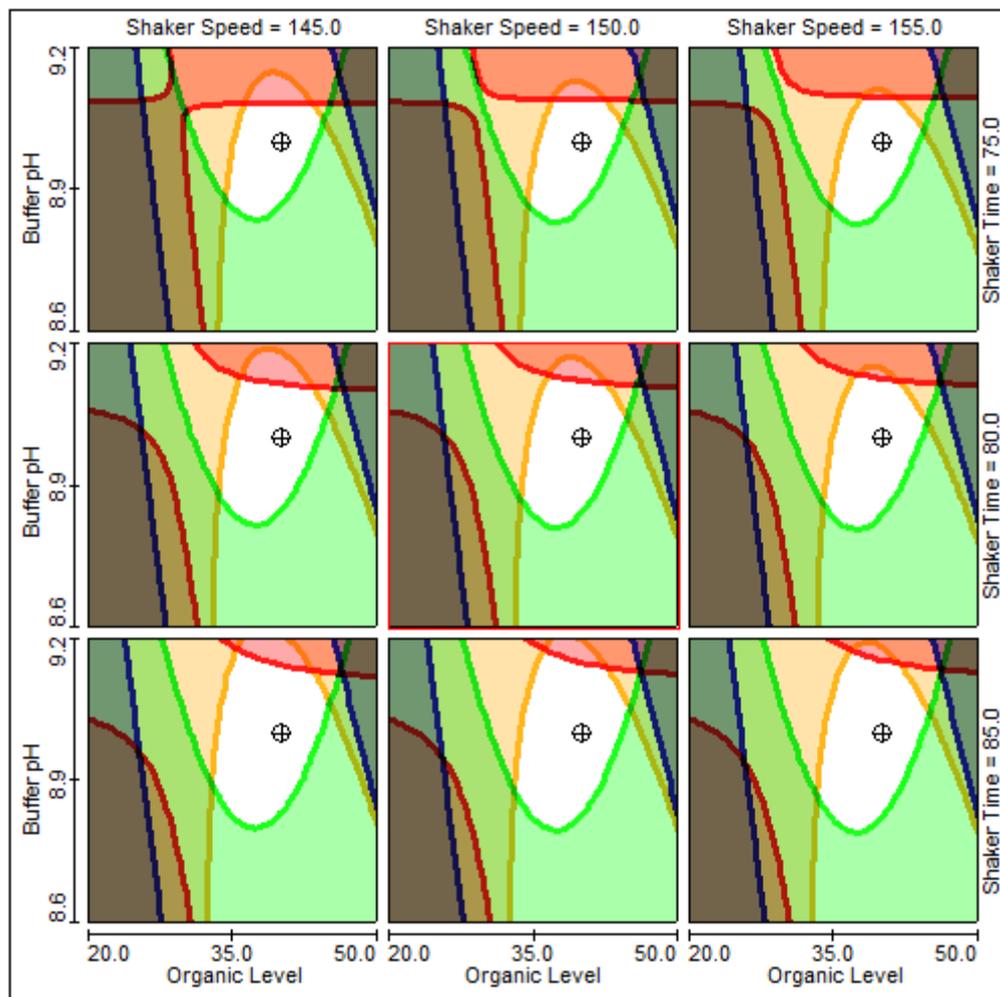
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Graphical Visualization of Robust Design Space – 2 Study Factors



Graphical Visualization of Robust Design Space – 4 Study Factors



Complete QbD Reporting – Output in Multiple Formats

