

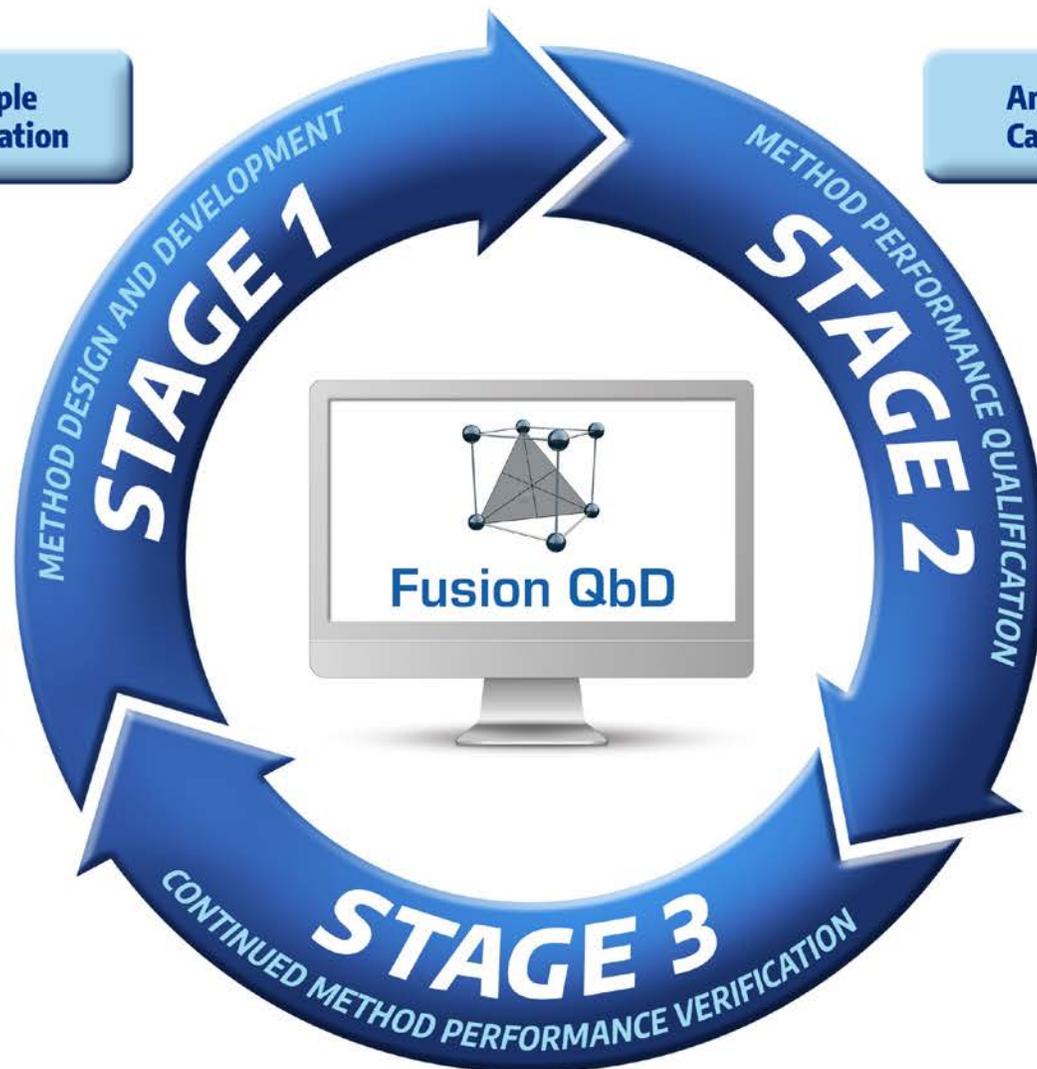


# ***Fusion QbD***

## ***Case Study – Sample Preparation Method Development***

# A Complete Solution for APLM Stages 1 and 2

## FUSION METHOD DEVELOPMENT



## FUSION METHOD VALIDATION



Full Support  
for Part 11  
Compliance



Citrix-Ready  
Certified

## Fusion Process Development

- QbD Formulation and Process Development
- Non-LC Methods Development (e.g. GC, CE, Disso)
- Automated, Audited LC Testing and Data Acquisition  
Standard LC, Time Series, Respiratory

## 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!

Who entered this data – was the data modified?



What Empower Project did this data come from?

Audit Log 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	
29	30	31	1	2		

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

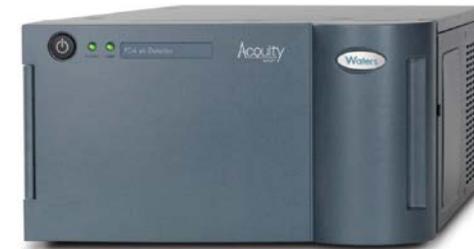
OK Cancel ?



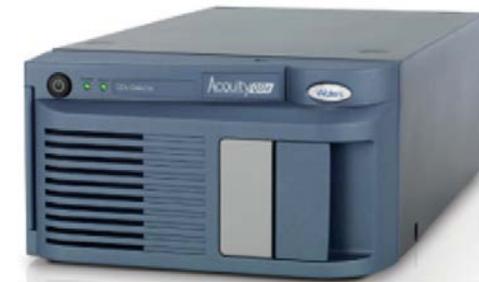
## H-Class UPLC



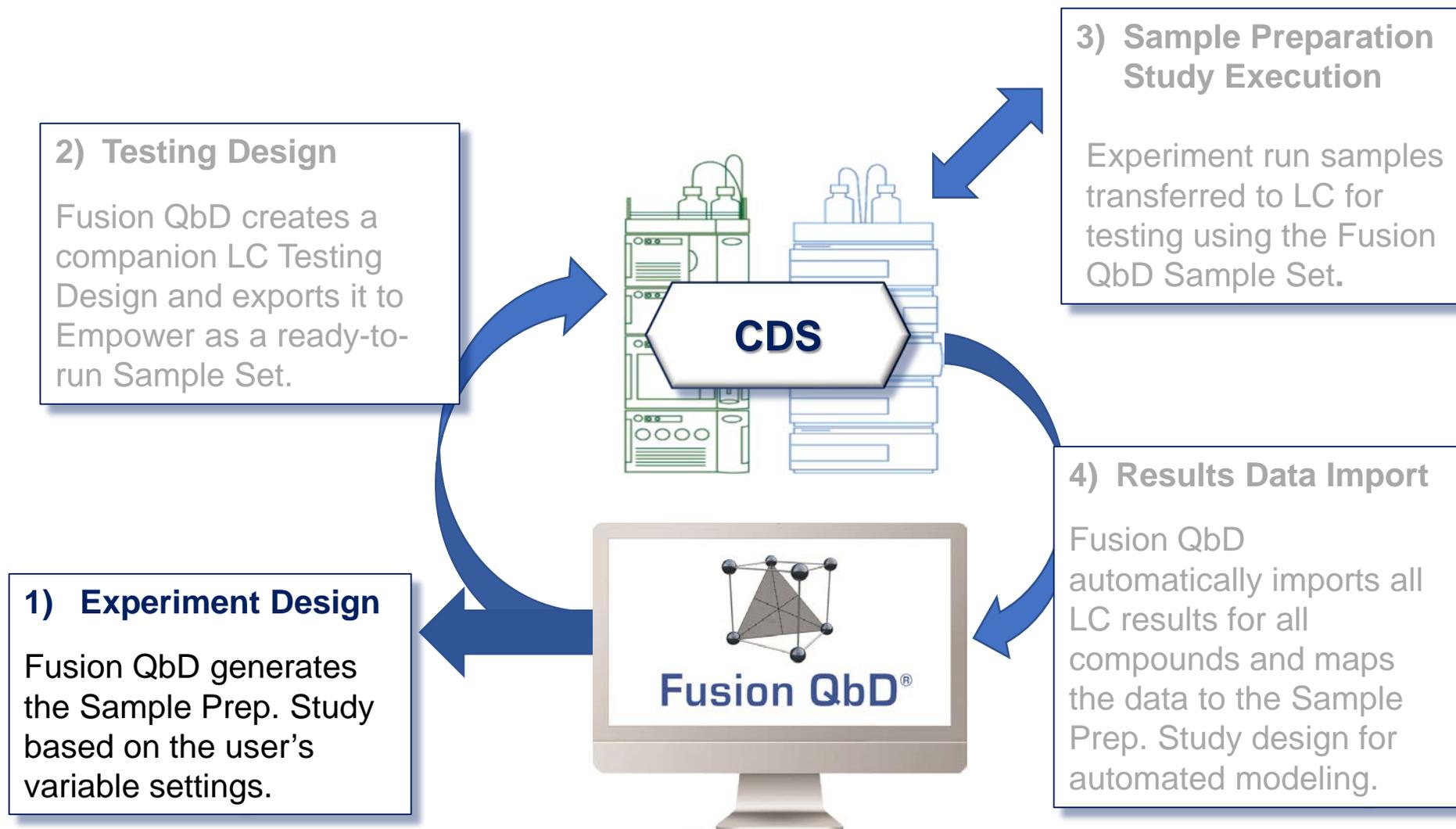
## Acquity PDA



## Acquity QDa



# Sample Preparation Experiment Dataflow



# Flexible Experiment Setup

## Formulation (Mixture) Studies

You specify:

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

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

State

Variable  
 Constant

## 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!

# Completed Experiment Setup Template

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

Validation Status: Your settings are valid.

## Automatically Selects and Generates the Most Defensible and Efficient DOE Design

Name: Administrator  
 Company:  
 Project:  
 Date:



**Experiment Design**

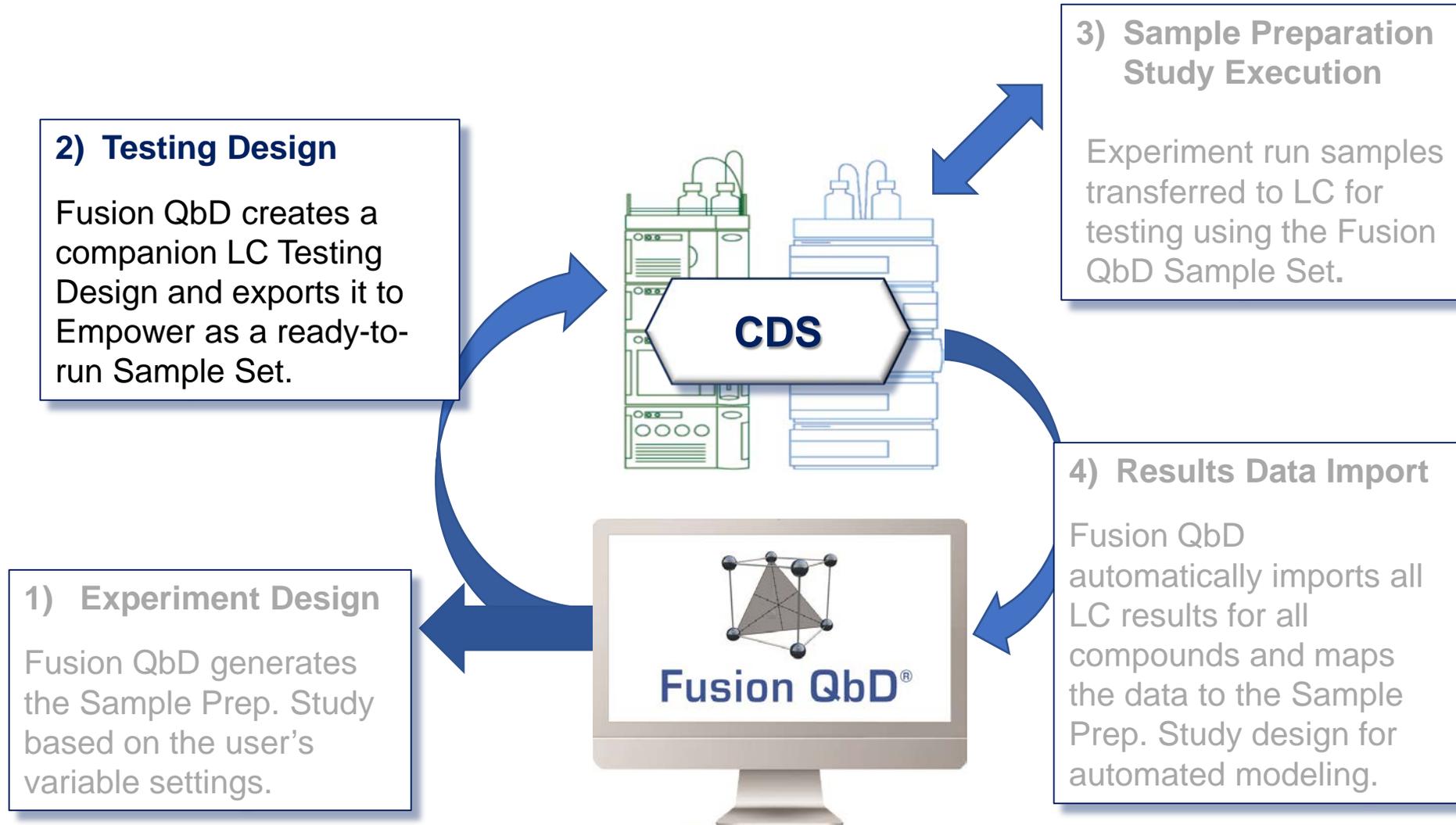
Experiment Design Matrix

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 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 Experiment Dataflow



## Automatically Export Ready-to-Run Testing Design to the CDS

**Export**

Bracketing

Strategy: Bracketing - Overlap

<None Selected>  
 Bracketing - Overlap  
 Bracketing - NonOverlap  
 Grand Average  
 Calibration and Check Standards  
 Multi-level Bracketing - Overlap  
 No. of Injections within Brackets: 5

Bracketing Scheme - first two brackets

```

  1 Std - 1.a
  2
  3
  4 Bracket
  5
  6 Std - 1.b
  7
  8
  9
  10 Bracket
  Std - 1.c
  
```

<< Back    Next >>

Select Project and Method Sets

Select Project

- FIT
- FMD Tutorial - 9\_9\_0
- FMV - A\_L\_R
- Internal Development
- RD1 - Demo Screening Expt
- RD2 - Demo Optimization Expt
- Test
  - FDS\_1\_Named\_Peaks
  - RD2 - Opt - 9\_9\_0 - Named Peak
  - RD2 - Opt - FMD 9\_9\_0
  - RD2\_990\_No\_SS
  - RD2\_990\_No\_SS\_Named\_Peak
  - Screening BOA Confirmation
  - Tip of the Week

Method Set

Acquity\_UPC2  
 ADL\_H\_Class\_AutoBlend\_Plus  
 ADL\_H\_Class\_QDa\_PDA  
 ADL\_H\_Class\_QDa\_PDA\_Fusion  
 Agilent 6890 GC  
 Agilent\_Infinity\_IL\_1  
 Alliance 1  
 Demo Alliance Shutdown Method  
 Demo\_H\_Class Shutdown Method

Enable Shutdown Method

ADL\_H\_Class\_AutoBlend\_Plus  
 ADL\_H\_Class\_QDa\_PDA  
 ADL\_H\_Class\_QDa\_PDA\_Fusion  
 Agilent 6890 GC  
 Agilent\_Infinity\_IL\_1  
 Alliance 1  
 Demo Alliance Shutdown Method  
 Demo\_H\_Class Shutdown Method

User Types (logged in as 'Owner')

Owner

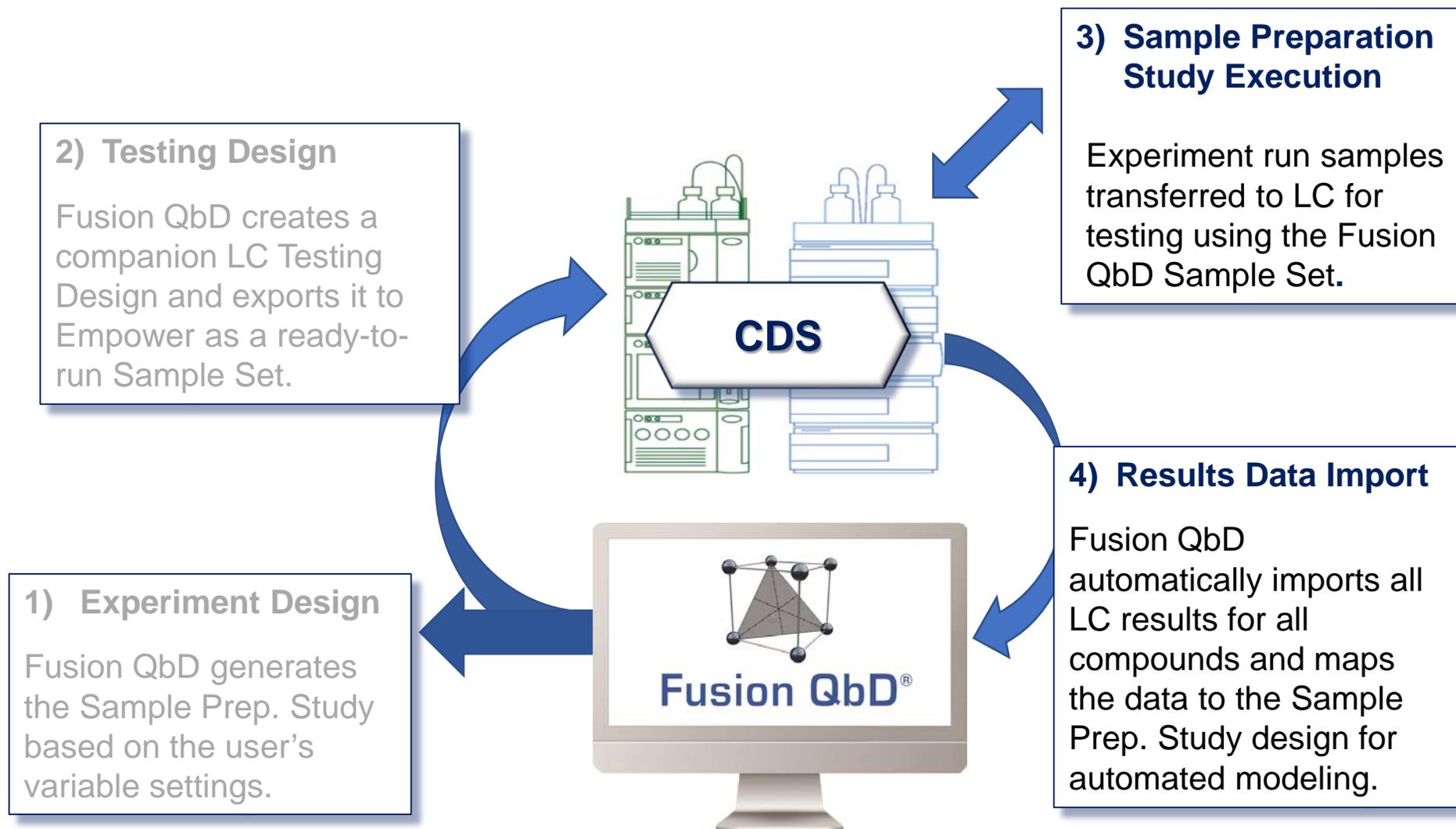
Ready

IMPORTANT: Be sure the selected template method has the correct structure and properties required for the experiment design you are exporting. Refer to the on-line Help for detailed information on these requirements.

<< Back    Next >>    Cancel

**Bi-directional  
 Auditing  
 Assures Data  
 Traceability  
 and Integrity!**

# Sample Preparation Experiment Dataflow



## 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

Select Result Set(s)

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

Select Processed Channel:

Fetch Selected Result Sets: 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

User Types (logged in as 'Owner')

Owner

Ready

Next >> Cancel ?

**Bi-directional  
Auditing  
Assures Data  
Traceability  
and Integrity!**

# Directly Enter Collateral Data

## Directly Enter Non-CDS Generated Results Data

Create/Edit Response Data

Response Name:  Response Units:   Lower Limit  Upper Limit

Add following to empty cells:

	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	

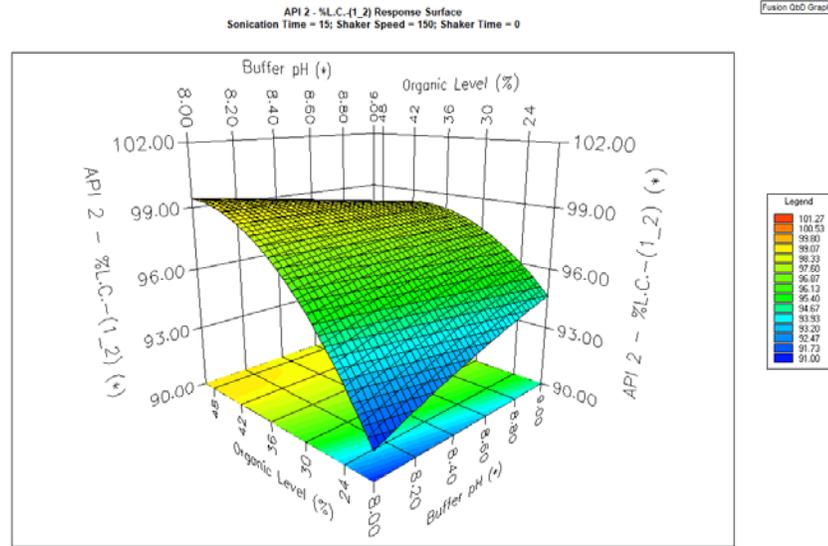
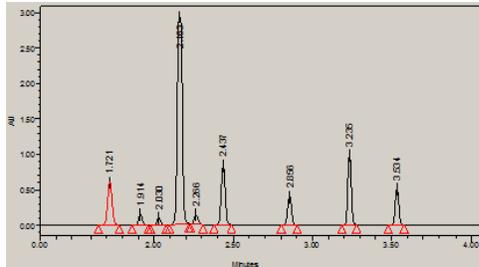
Validation Status: Your settings are valid.

**Full Auditing  
of Entered and  
Edited Data  
Assures Data  
Traceability  
and Integrity!**

# Automated Mode – 1-click Data Modeling

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

Run	Std. Dev.	# of Std. Dev.	Label	Sample Name	Level	Function	Method Set / Report Method	Label Reference	Processing	Run Time (minutes)	Data Start (minutes)	Test No. (minutes)	Column Position	Auto. Autoclave	Sample Vols.	Clones
1						Condition Column	Testfile per 021_017			8.75	0.00	0.00	No Change			
2						Condition Column	Testfile per 021_017			8.75	0.00	0.00	No Change			
3						Equilibrat	Testfile per 021_017			3.00	0.00	7.00	No Change			
4	1	2.0	1	04-001-000	Basic L 1	Inject Samples	Testfile per 021_017	Normal		10.00	0.00	1.00			1.00000	1.00000
5						Condition Column	Testfile per 021_021			8.75	0.00	0.00	No Change			
6						Equilibrat	Testfile per 021_021			3.00	0.00	0.00	No Change			
7	2	2.0	1	04-001-001	1 x 1 x 1	Inject Samples	Testfile per 021_021	Normal		10.00	0.00	1.00			1.00000	1.00000
8						Condition Column	Testfile per 021_022			8.75	0.00	0.00	No Change			
9						Equilibrat	Testfile per 021_022			3.00	0.00	0.00	No Change			
10	2	2.0	1	04-001-002	2 x 1 x 1	Inject Samples	Testfile per 021_022	Normal		10.00	0.00	1.00			1.00000	1.00000
11						Condition Column	Testfile per 021_023			8.75	0.00	0.00	No Change			
12						Condition Column	Testfile per 021_023			8.75	0.00	0.00	No Change			
13						Equilibrat	Testfile per 021_023			3.00	0.00	0.00	No Change			
14	2	2.0	1	04-001-003	3 x 1 x 1	Inject Samples	Testfile per 021_023	Normal		10.00	0.00	1.00			1.00000	1.00000
15						Condition Column	Testfile per 021_024			8.75	0.00	0.00	No Change			
16						Condition Column	Testfile per 021_024			8.75	0.00	0.00	No Change			
17						Equilibrat	Testfile per 021_024			3.00	0.00	0.00	No Change			
18	2	2.0	1	04-001-004	4 x 1 x 1	Inject Samples	Testfile per 021_024	Normal		10.00	0.00	1.00			1.00000	1.00000
19						Condition Column	Testfile per 021_025			8.75	0.00	0.00	No Change			
20						Equilibrat	Testfile per 021_025			3.00	0.00	0.00	No Change			
21	2	2.0	1	04-001-005	5 x 1 x 1	Inject Samples	Testfile per 021_025	Normal		10.00	0.00	1.00			1.00000	1.00000
22						Condition Column	Testfile per 021_026			8.75	0.00	0.00	No Change			
23						Condition Column	Testfile per 021_026			8.75	0.00	0.00	No Change			
24						Equilibrat	Testfile per 021_026			3.00	0.00	0.00	No Change			



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

Linear Effect

Curvature Effect

Interaction Effects

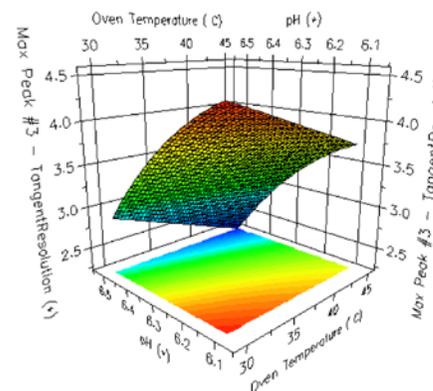
Complex Effect

## Example of a Resolution Model Eqn.

- Peak 3 resolution

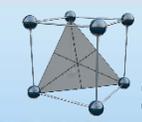
$$R = 3.0607 + 0.4109(\text{GT}) - 0.3367(\text{Temp}) - 0.7772(\text{pH}) - 0.2013(\text{pH})^2$$

## 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



## Regulatory Acceptance of Monte Carlo Simulation Approach

### Monte Carlo Robustness Simulation

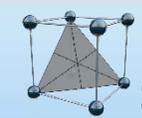
“Statistical treatments (e.g. **Monte Carlo simulations**) can help evaluate the effects of uncertainty.”

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.



## Regulatory Acceptance of Monte Carlo Simulation Approach

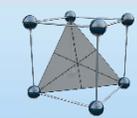
### 3. Process Capability

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



Robustness Simulator
×

**C<sub>p</sub>**  
**C<sub>pk</sub>**  
**C<sub>pm</sub>**  
**C<sub>pkm</sub>**

Use C<sub>pk</sub> 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<sub>pl</sub> is computed when only a lower specification is entered.
- C<sub>pu</sub> is computed when only an upper specification is entered.

**C<sub>pk</sub> – Lower or Upper Specification Limit**

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

**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 (±)	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

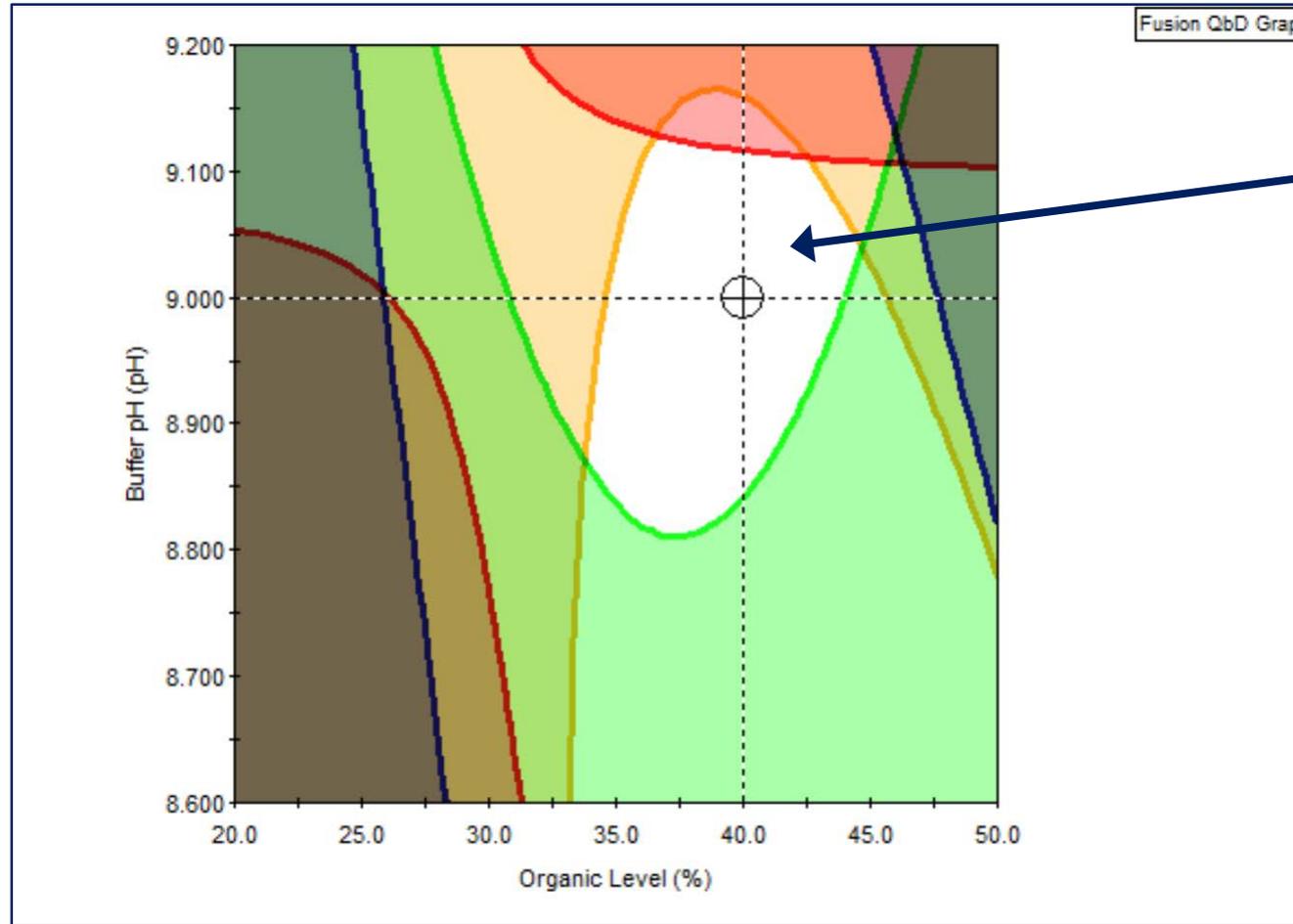
The settings are valid.

**Built-in Robustness Metrics**

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

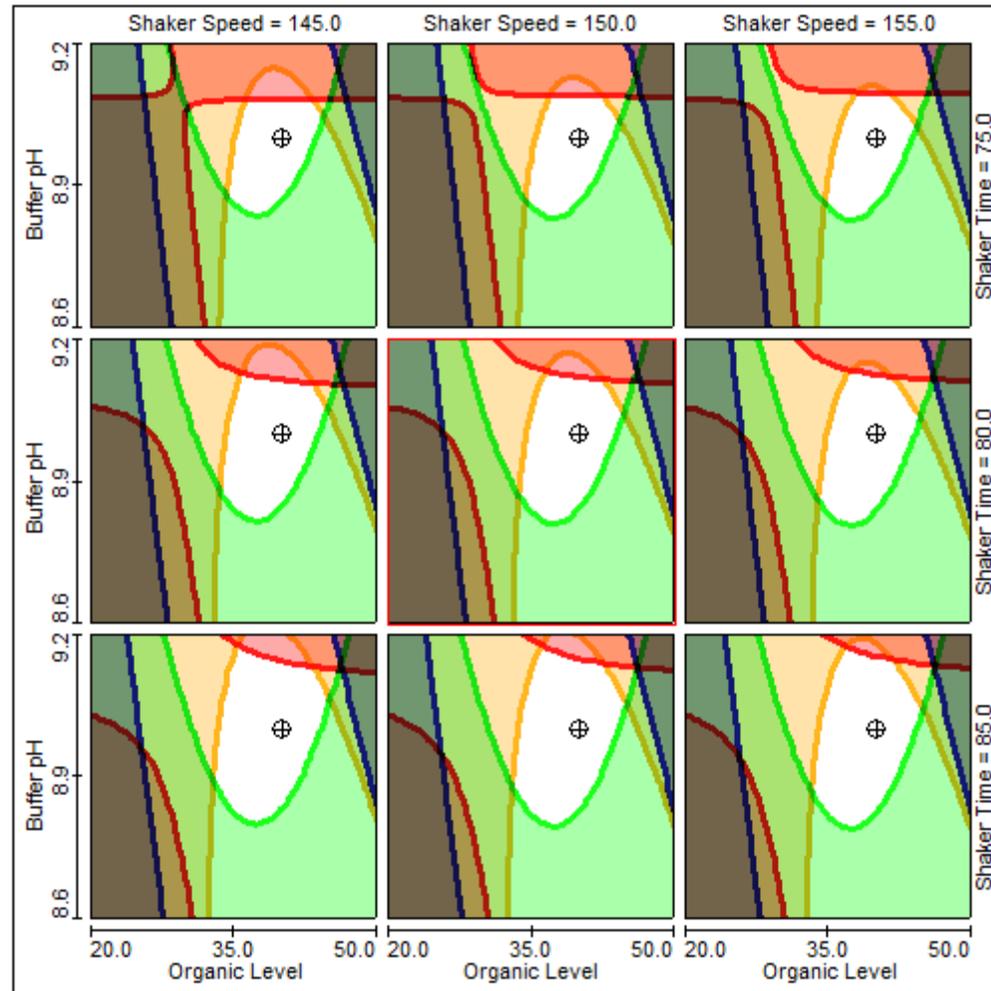
Define edge of failure.

## 2 Study Factors



UNshaded Region  
in the graph is the  
**M**ethod **O**perable  
**D**esign **R**egion  
**(MODR)**

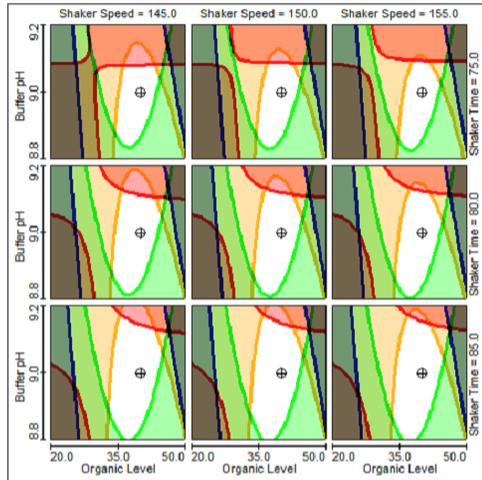
## 4 Study Factors



Name: Administrator  
 Company:  
 Project:  
 Date:



## 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

## Report Output in Multiple Formats

- MS Excel



- MS Word

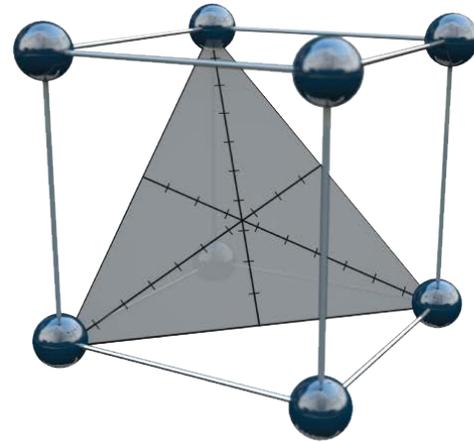


- PDF



- ...

# *End of Presentation*



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