

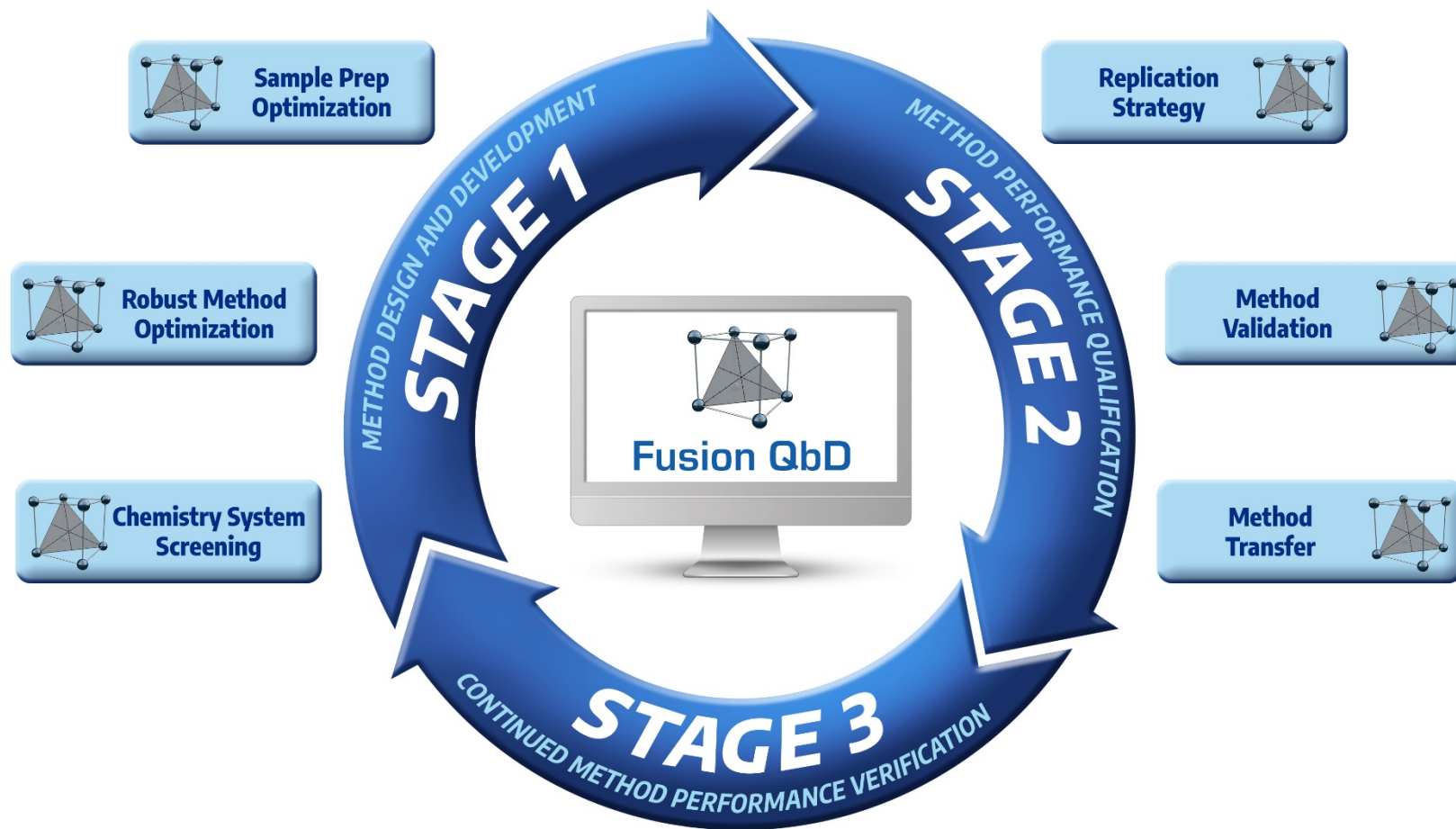


Fusion QbD

***Advanced QbD Software for
Analytical Method Validation
and Transfer***

A Complete Solution for APLM Stages 1 and 2

Analytical Procedure Lifecycle Management Workflow



A Complete Solution for APLM Stage 2



METHOD VALIDATION MODULE

- Full Validation Experiment Suite
- Instant Analysis and Reporting
- Advanced Method Transfer Support
- Meets all Regulatory Requirements

All the Critical QbD Capabilities You Need

Critical QbD Capability

FMV

Supports All Install Environments (Citrix Certified)



Full 21 CFR Part 11 Compliance Support



Complete Method Validation Experiment Suite



Simple Experiment Workflows



Full LC Experiment Automation



USP 1210> Tolerance and Prediction Interval Metrics



- Replication Strategy and TMU
- Accuracy and Repeatability
- Analytical Method Transfer

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Install Environment

FMV

Standalone (Workstation)



Network (Enterprise)



Citrix Ready Certified

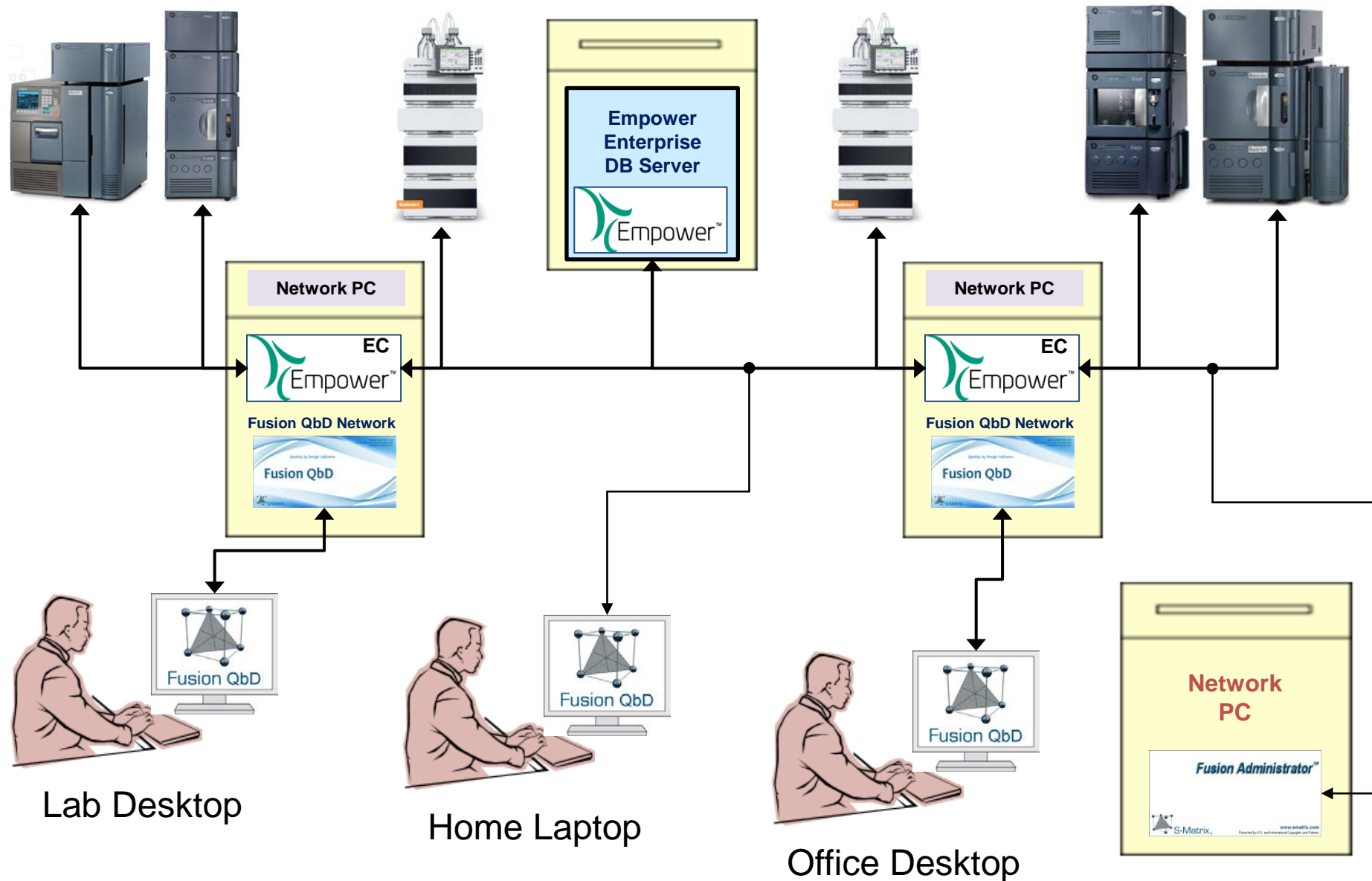


Fully Qualifiable for GXP Environments*



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

Example Network Deployment



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Full Support for 21 CFR 11 Compliance

FMV

Full integration of all e-record and all e-signature features and functions required to support full 21 CFR 11 compliance.



Integrated Workflow Management and Secure Project Management Systems.



Full audit trail, including bi-directional auditing of all data exchanges with the CDS.



Why Audit Trail is Important!

Where did this data come from?
Empower Project?
Results Set?
Chromatograms?



Who imported this data – was the data modified?

Audit Log Filter Options

Date

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 ?

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Critical QbD Capability

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Full LC Experiment Automation



USP 1210> Tolerance and Prediction Interval Metrics



- Replication Strategy and TMU
- Accuracy and Repeatability
- Analytical Method Transfer

- Analytical Capability*
 - Specificity
 - Filter Validation
 - Sample Solution Stability
 - Accuracy*
 - Linearity & Range
 - Repeatability*
 - Accuracy / Linearity / Repeatability*
[Combined as per ICH Q2(R1)]
 - LOQ*, LOD*
 - Intermediate Precision and Reproducibility
 - Validation Robustness – LC
 - Validation Robustness – Non-LC
[e.g. Sample Preparation, Dissolution]
 - Method Transfer Study Support*
- * – integration of USP <1210> Tolerance & Prediction Intervals]

All the Critical QbD Capabilities You Need

Critical QbD Capability

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Full LC Experiment Automation



USP 1210> Tolerance and Prediction Interval Metrics



- Replication Strategy and TMU
- Accuracy and Repeatability
- Analytical Method Transfer

Example: Accuracy / Linearity / Repeatability – Combined Experiment

Create New Work File

Project

Select Project: Audit Logging Enabled

Project Name:

Instrument

Instrument Type: LC
Data System: Waters Empower
Pump Module: Quaternary


Sample Compound Type

Small Molecule Large Molecule

Experiment Phase

Experiment Type

- Analytical Capability
- Specificity
- Accuracy
- Linearity and Range
- Repeatability
- Accuracy, Linearity, Repeatability**
- Robustness
- Robustness Non-LC



1. Simple Experiment Setup Template

Create and Maintain Templates.
Control Use with E-Review and E-Approve Loops.

Experiment Setup | Sampling Plan

Include LOQ / LOD

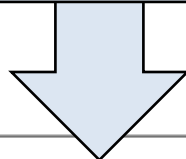
- Limit of Quantitation
- Limit of Detection

Assay Type: Potency (Drug Content)

Global Compound Settings

- No. of Compounds: 2
- No. of Levels per Compound: 5
- 100% Std. Level: Level 3

Define Acceptance Criteria for each Key Result for each Compound.



Compound Name	Units	Level Settings	Validation - Acceptance Criteria
Compound 1	%	Level 1: 80 Level 2: 90 Level 3: 100 Level 4: 110 Level 5: 120	<input type="checkbox"/> Accuracy (% Bias <) <input type="text" value=""/> <input type="text" value=""/> <input type="text" value=""/> <input type="checkbox"/> Linearity (% Bias <) <input type="text" value=""/> <input type="text" value=""/> <input type="text" value=""/> <input type="checkbox"/> Repeatability (% RSD <=) <input type="text" value=""/> <input type="text" value=""/> <input type="text" value=""/> <input checked="" type="checkbox"/> Linearity (Regression r >=) 0.999 <input type="text" value=""/> <input type="text" value=""/> <input type="text" value=""/>
Compound 2	%	Level 1: 80 Level 2: 90 Level 3: 100 Level 4: 110 Level 5: 120	<input type="checkbox"/> Accuracy (% Bias <) <input type="text" value=""/> <input type="text" value=""/> <input type="text" value=""/> <input type="checkbox"/> Linearity (% Bias <) <input type="text" value=""/> <input type="text" value=""/> <input type="text" value=""/> <input type="checkbox"/> Repeatability (% RSD <=) <input type="text" value=""/> <input type="text" value=""/> <input type="text" value=""/> <input checked="" type="checkbox"/> Linearity (Regression r >=) 0.999 <input type="text" value=""/> <input type="text" value=""/> <input type="text" value=""/>

2. Standards Setup Options

Standards Setup

Standards Strategy
 Calibration and Check Standards
 <None Selected>
 Bracketing - NonOverlap
 Grand Average
 Calibration and Check Standards
 Multi-level Bracketing - Overlap

No. of Repeat Injections per Level 1

Check Standards Scheme
 No. of Standards per Group 1
 No. of Injections Between Groups 5

Experiment Design

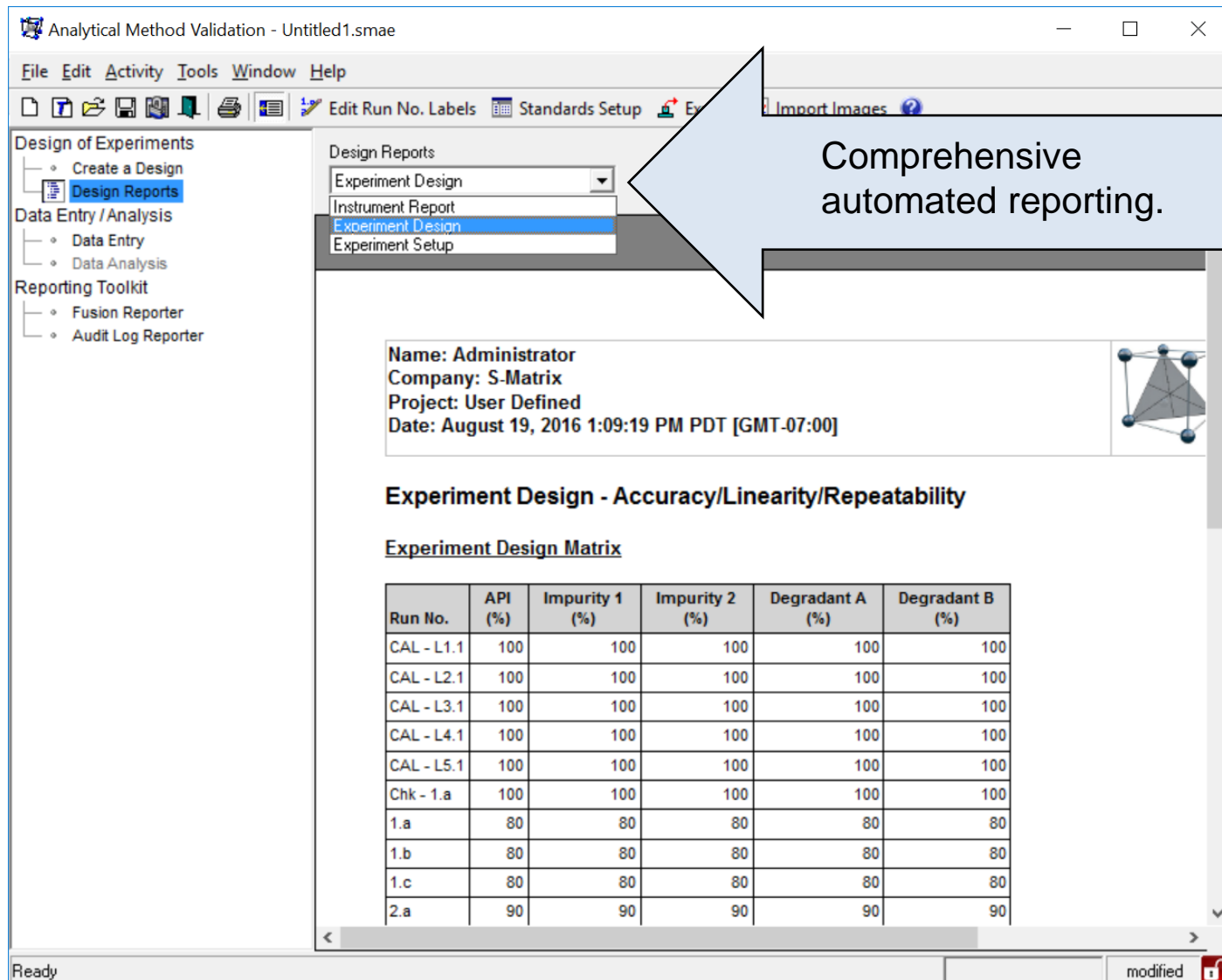
	Run No.	API	Impurity 1	Impurity 2	Degradant A	Degradant B
1	CAL - L1.1	---	---	---	---	---
2	CAL - L2.1	---	---	---	---	---
3	CAL - L3.1	---	---	---	---	---
4	CAL - L4.1	---	---	---	---	---
5	CAL - L5.1	---	---	---	---	---
6	Chk - 1.a	100	100	100	100	100
7	1.a	80	80	80	80	80
8	1.b	80	80	80	80	80
9	1.c	80	80	80	80	80
10	1.d	80	80	80	80	80
11	1.e	80	80	80	80	80
12	Chk - 1.b	100	100	100	100	100
13	2.a	90	90	90	90	90

Validation Status: Your settings are valid.

Clear Reset Next >> Cancel ?

Flexible setup of the required Standards Strategies.

3. Auto-generated Experiment Design



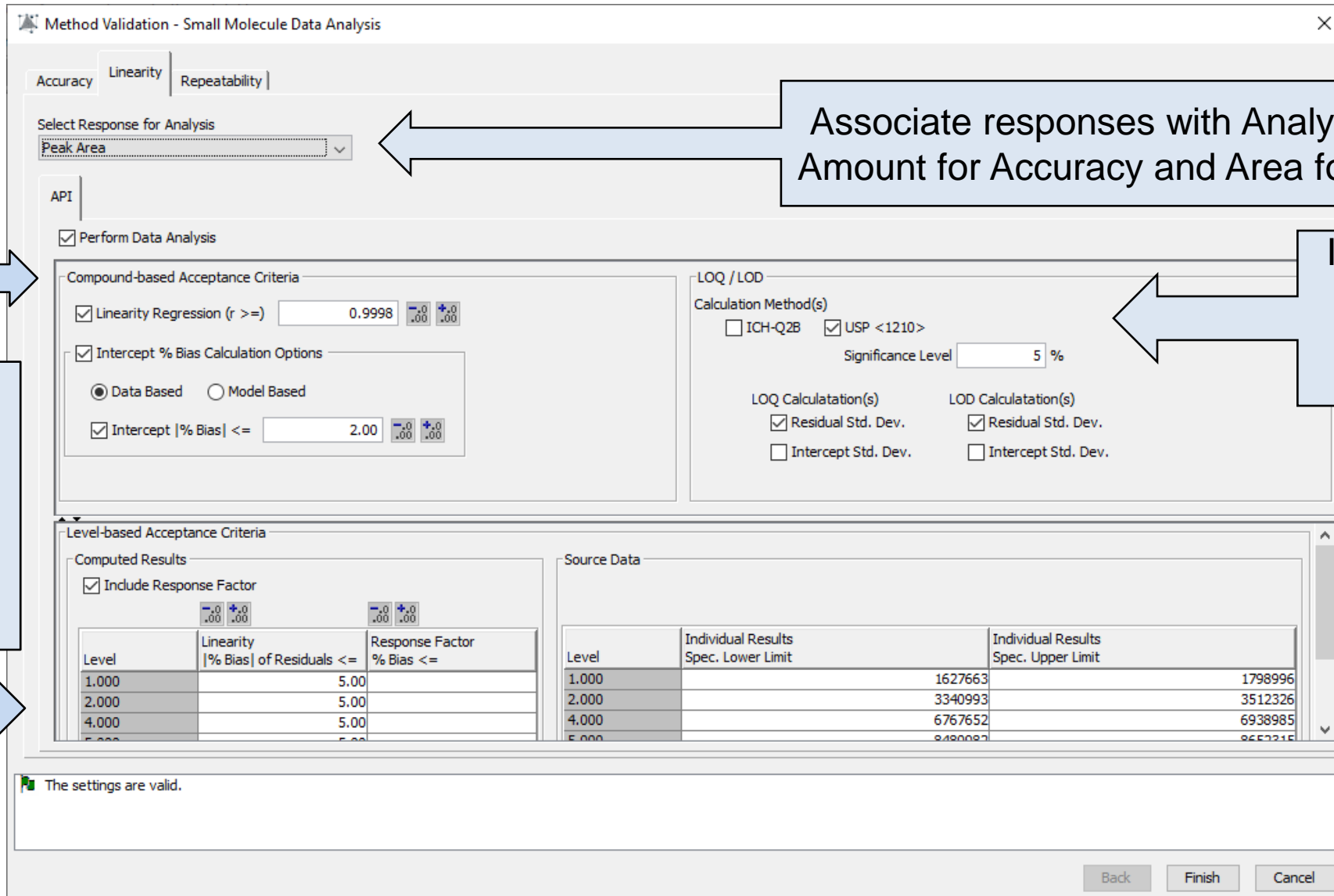
Name: Administrator
Company: S-Matrix
Project: User Defined
Date: August 19, 2016 1:09:19 PM PDT [GMT-07:00]

Experiment Design - Accuracy/Linearity/Repeatability

Experiment Design Matrix

Run No.	API (%)	Impurity 1 (%)	Impurity 2 (%)	Degradant A (%)	Degradant B (%)
CAL - L1.1	100	100	100	100	100
CAL - L2.1	100	100	100	100	100
CAL - L3.1	100	100	100	100	100
CAL - L4.1	100	100	100	100	100
CAL - L5.1	100	100	100	100	100
Chk - 1.a	100	100	100	100	100
1.a	80	80	80	80	80
1.b	80	80	80	80	80
1.c	80	80	80	80	80
2.a	90	90	90	90	90

4. Analysis Wizard for CDS Imported Results



Method Validation - Small Molecule Data Analysis

Accuracy | **Linearity** | Repeatability

Select Response for Analysis
Peak Area

API

Perform Data Analysis

Compound-based Acceptance Criteria

Linearity Regression ($r \geq$)

Intercept % Bias Calculation Options

Data Based Model Based

Intercept |% Bias| \leq

LOQ / LOD

Calculation Method(s)

ICH-Q2B USP <1210>

Significance Level %

LOQ Calculation(s)

Residual Std. Dev. Intercept Std. Dev.

LOD Calculation(s)

Residual Std. Dev. Intercept Std. Dev.

Level-based Acceptance Criteria

Computed Results

Include Response Factor

Level	Linearity % Bias of Residuals \leq	Response Factor % Bias \leq
1.000	5.00	
2.000	5.00	
4.000	5.00	
5.000	5.00	

Source Data

Level	Individual Results Spec. Lower Limit	Individual Results Spec. Upper Limit
1.000	1627663	1798996
2.000	3340993	3512326
4.000	6767652	6938985
5.000	8480023	8652315

The settings are valid.

Back Finish Cancel


Associate responses with Analyses – e.g. Amount for Accuracy and Area for Linearity

Include LOQ and LOD and select Calculation Method(s)

Set Global and Level-specific Acceptance Criteria, including Spec Limits for Data

5. Instant Analysis, Graphing, and Reporting

Name: Administrator
Company: S-Matrix Corporation
Project: Project 1
Date: October 13, 2012 8:51:17 PM PDT [GMT-07:00]

 S-Matrix®

Linearity and Range Report: API - Amount (mg)

Linearity and Range Data Table

Run No.	Target API (mg)	Actual Amount (mg)	API - Amount
1a	1.000	1.003	1.001
1b	1.000	1.01	1.002
1c	1.000	1.013	1.013
2a	2.000	1.995	2.009
2b	2.000	1.99	2.009
2c	2.000	2.004	2.018
3a	4.000	3.998	4.118
3b	4.000	4	4.087
3c	4.000	3.997	4.089
4a	6.000	6.005	6.107
4b	6.000	6.002	6.084
4c	6.000	6.008	6.082
5a	6.000	6.004	6.03
5b	6.000	6.003	6.028
5c	6.000	6.007	6.007

General Regression Statistics Table

Regression Statistic Name	Statistic Value	Pass / Fail
r	0.9997	Pass
R Square	0.9993	---
Adj. R Square	0.9993	---
Residual Sum of Squares	0.00229	---
Standard Error (s)	0.05082	---
±95% C.I.	0.11001	---
Intercept Bias	2.49	---
Observations	15	---

Acceptance Criterion - Regression r: > 0.9990

Regression ANOVA Statistics Table

Source of Variation	Sum of Squares	Degree of Freedom	Mean Square	F-Statistic	P-Value
Regression	19.82199	1	19.82199	19.2132299	0.0001
Residual	0.00229	14	0.000163571	---	---
Total	19.82428	15	---	---	---

Regression Coefficient Table

Variable Name	Coefficient Value	Coefficient Standard Error	Coefficient t-Statistic	P-Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Intercept	0.12532	0.02475	4.9420	0.0004	0.04222	0.14759
API	0.88221	0.00708	124.8118	0.0001	0.84769	0.89693

Natural Variable Model
API - Amount (pred) = 0.12532 + (0.88221 x API)

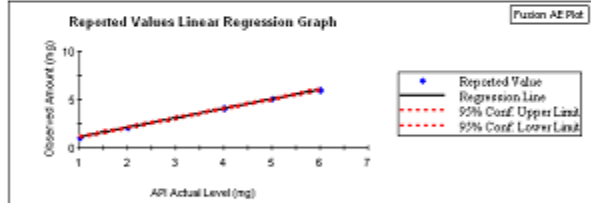
Range
1.003 ≤ API ≤ 6.997

Residuals Table

Actual API - Amount (mg)	Predicted API - Amount	Observed API - Amount	Residuals	% Bias of Residuals	% Bias Pass / Fail
1.003	1.11148	1.001	-0.00018	-0.04	Fail
1.01	1.11927	1.043	-0.09627	-9.60	Fail
1.013	1.12039	1.109	-0.01139	-1.71	Pass
1.992	2.04443	2.108	0.01917	0.94	Pass
1.99	2.04191	2.098	0.01709	0.84	Pass
2.004	2.04598	2.008	-0.04768	-2.34	Fail
2.998	4.0421	4.118	0.09178	1.22	Pass
4	4.05817	4.097	0.03883	0.97	Pass
3.997	4.05503	4.099	0.04378	1.10	Pass
2.002	2.04490	2.107	0.06270	1.21	Pass
4.992	4.05552	5.084	0.99048	1.01	Pass
2.008	2.05004	2.092	0.01478	0.73	Pass
6.004	6.02629	6.990	-0.09629	-1.61	Pass
6.003	6.02732	6.998	-0.07122	-1.19	Pass
6.997	6.02142	6.007	-0.01492	-0.24	Pass

Acceptance Criterion: (% Bias) < 2% for each concentration tested.

Reported Values Linear Regression Graph



Reported Values Linear Residuals Plot



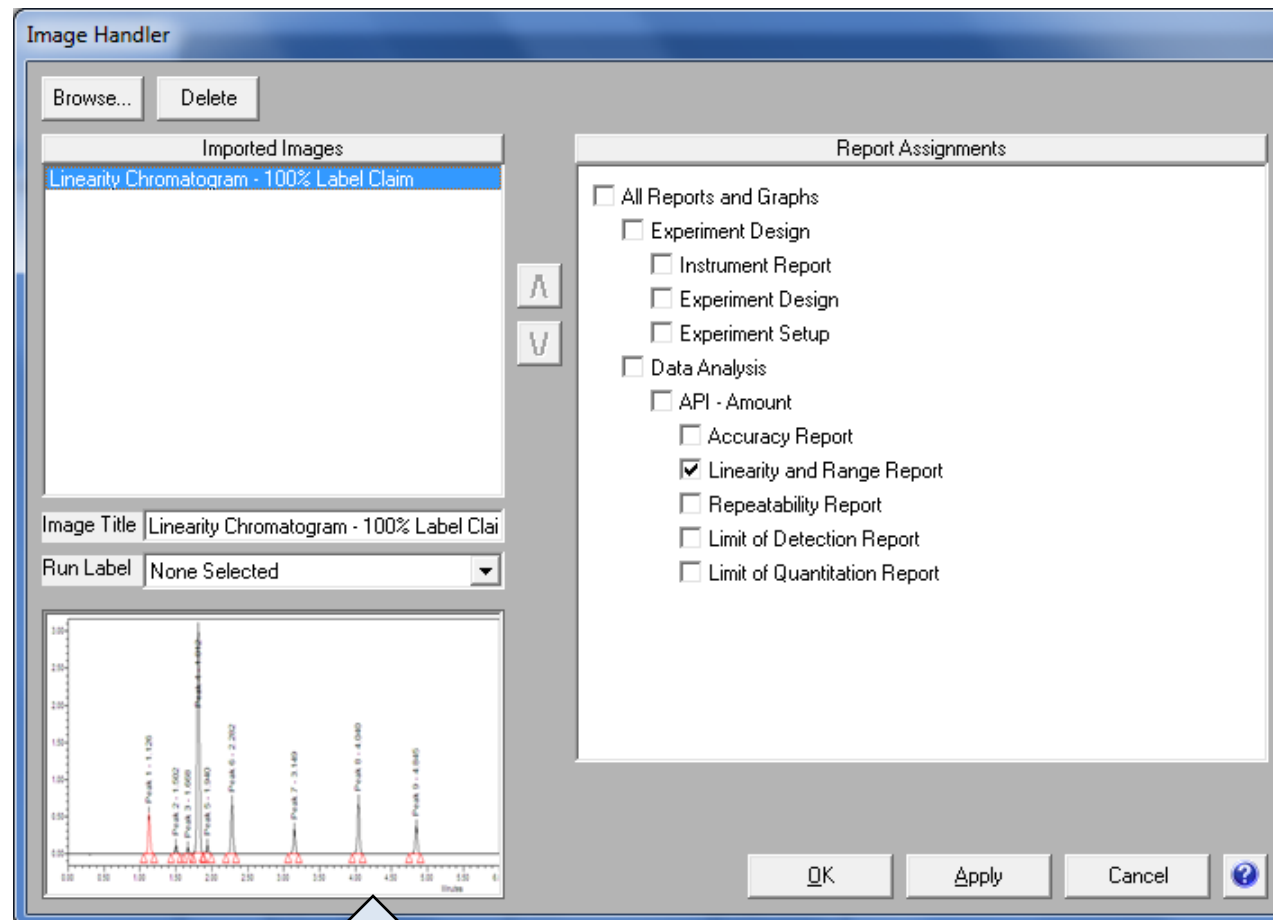
Fusion QbD instantly creates formal reports with all required tables and graphs.

5. Instant Analysis, Graphing, and Reporting

ICH Q2(R1):

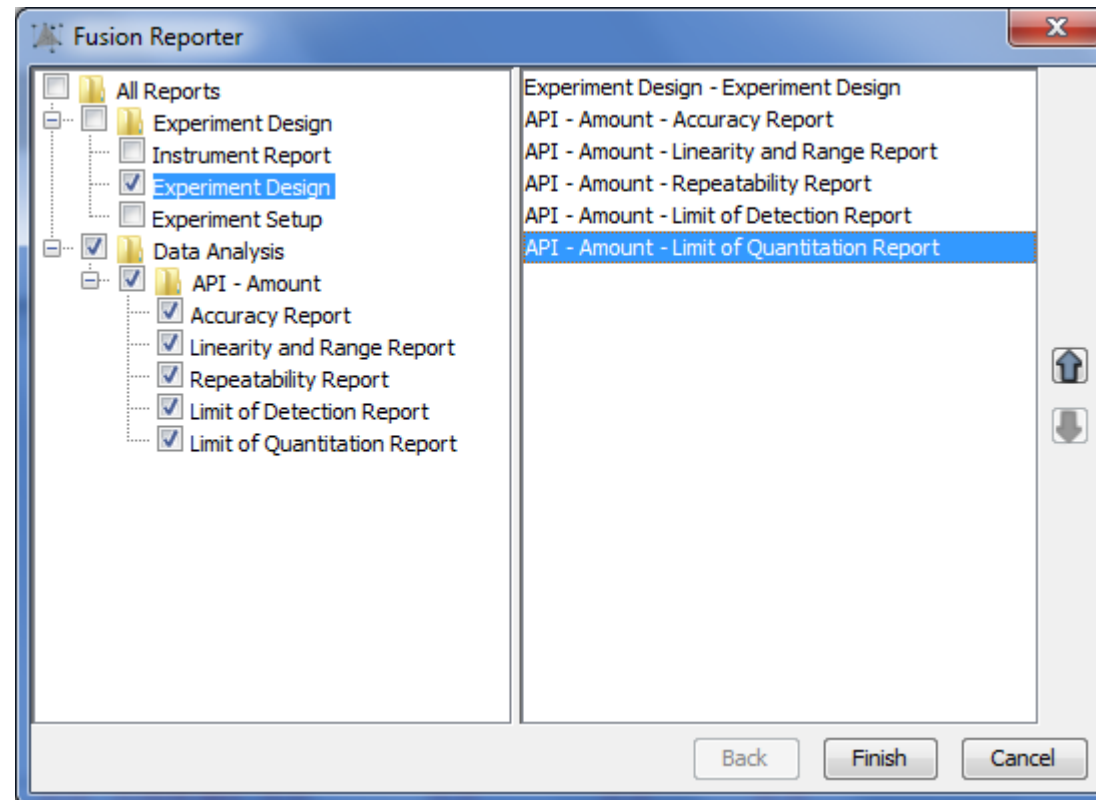
For chromatographic procedures, representative chromatograms should be used to demonstrate specificity, and individual components should be appropriately labeled.

If DL is determined based on visual evaluation or based on signal-to-noise ratio, the presentation of the relevant chromatograms is considered acceptable for justification.



Reports can be augmented with images of relevant chromatograms.

5. Instant Analysis, Graphing, and Reporting



Reports meet all output format requirements:

.TXT / .RTF / .DOC / .PDF / .HTML / XLSX

All the Critical QbD Capabilities You Need

Critical QbD Capability

FMV

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Full 21 CFR Part 11 Compliance Support



Complete Method Validation Experiment Suite



Simple Experiment Workflows



Full LC Experiment Automation



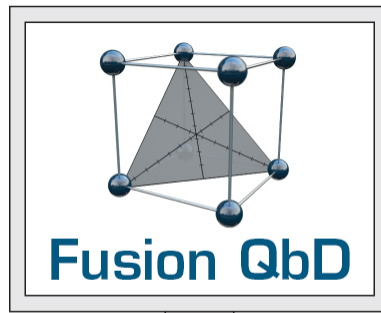
USP 1210> Tolerance and Prediction Interval Metrics



- Replication Strategy and TMU
- Accuracy and Repeatability
- Analytical Method Transfer

Automated Experiment Workflow

Steps 1 and 2



Generates Selected
Validation Experiment

Automatically Builds
Sequence with
Standards Protocol and
Assigns Method

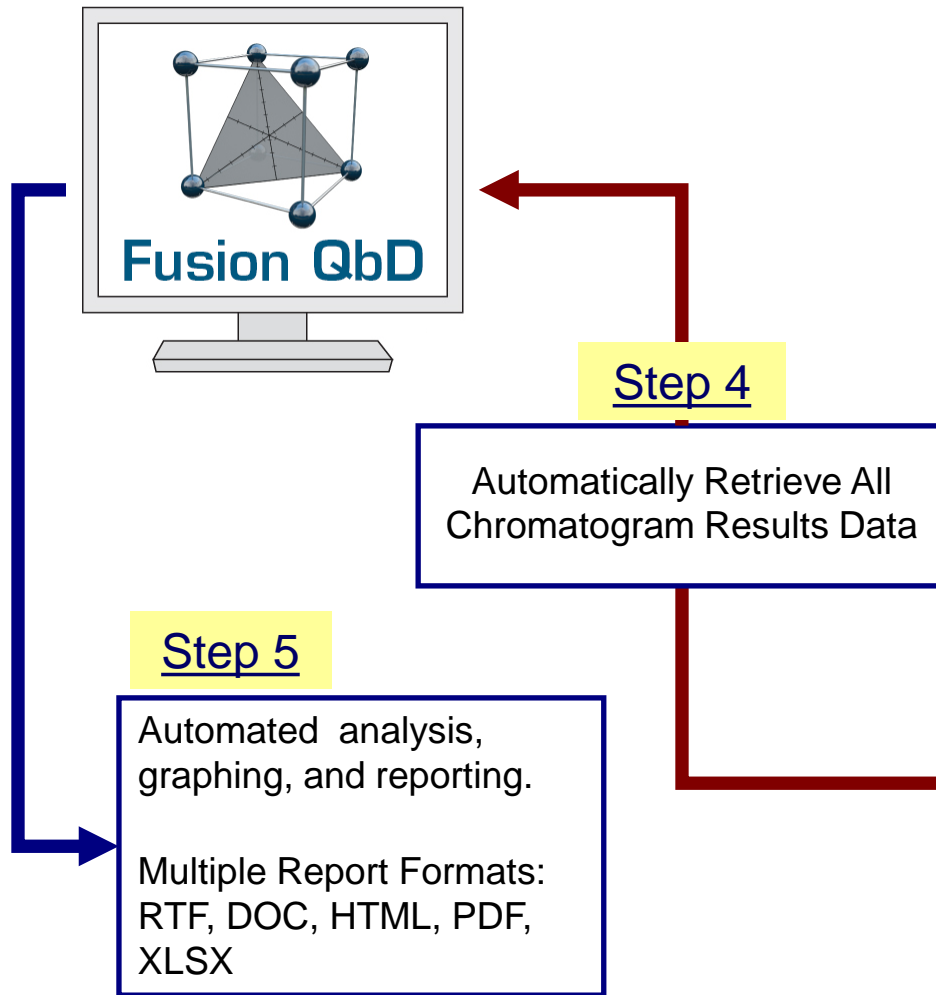
Step 3

Chromatography Data Software (CDS)

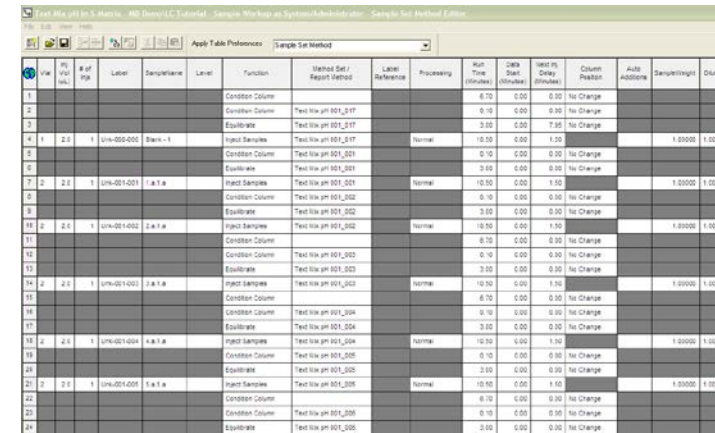
Vial	Inj Vol (uL)	# of Injs	Label	SampleName	Level	Function	Method Set / Report Method	Label Reference	Processing	Run Time (Minutes)	Data Start (Minutes)	Next Inj. Delay (Minutes)	Column Position	Auto Additions	SampleWeight	Dilution
1						Condition Column				6.70	0.00	0.00	No Change			
2						Condition Column	Text Mix pH 001_017			0.10	0.00	0.00	No Change			
3						Equilibrate	Text Mix pH 001_017			3.00	0.00	7.95	No Change			
4	1	2.0	1	Unk-000-000	Blank - 1	Inject Samples	Text Mix pH 001_017		Normal	10.50	0.00	1.50			1.00000	1.00000
5						Condition Column	Text Mix pH 001_001			0.10	0.00	0.00	No Change			
6						Equilibrate	Text Mix pH 001_001			3.00	0.00	0.00	No Change			
7	2	2.0	1	Unk-001-001	1.a.1.a	Inject Samples	Text Mix pH 001_001		Normal	10.50	0.00	1.50			1.00000	1.00000
8						Condition Column	Text Mix pH 001_002			0.10	0.00	0.00	No Change			
9						Equilibrate	Text Mix pH 001_002			3.00	0.00	0.00	No Change			
10	2	2.0	1	Unk-001-002	2.a.1.a	Inject Samples	Text Mix pH 001_002		Normal	10.50	0.00	1.50			1.00000	1.00000
11						Condition Column				6.70	0.00	0.00	No Change			
12						Condition Column	Text Mix pH 001_003			0.10	0.00	0.00	No Change			
13						Equilibrate	Text Mix pH 001_003			3.00	0.00	0.00	No Change			
14	2	2.0	1	Unk-001-003	3.a.1.a	Inject Samples	Text Mix pH 001_003		Normal	10.50	0.00	1.50			1.00000	1.00000
15						Condition Column				6.70	0.00	0.00	No Change			
16						Condition Column	Text Mix pH 001_004			0.10	0.00	0.00	No Change			
17						Equilibrate	Text Mix pH 001_004			3.00	0.00	0.00	No Change			
18	2	2.0	1	Unk-001-004	4.a.1.a	Inject Samples	Text Mix pH 001_004		Normal	10.50	0.00	1.50			1.00000	1.00000
19						Condition Column	Text Mix pH 001_005			0.10	0.00	0.00	No Change			
20						Equilibrate	Text Mix pH 001_005			3.00	0.00	0.00	No Change			
21	2	2.0	1	Unk-001-005	5.a.1.a	Inject Samples	Text Mix pH 001_005		Normal	10.50	0.00	1.50			1.00000	1.00000
22						Condition Column				6.70	0.00	0.00	No Change			
23						Condition Column	Text Mix pH 001_006			0.10	0.00	0.00	No Change			
24						Equilibrate	Text Mix pH 001_006			3.00	0.00	0.00	No Change			

Automated, Audited Data Exchange
Preserves Data Integrity

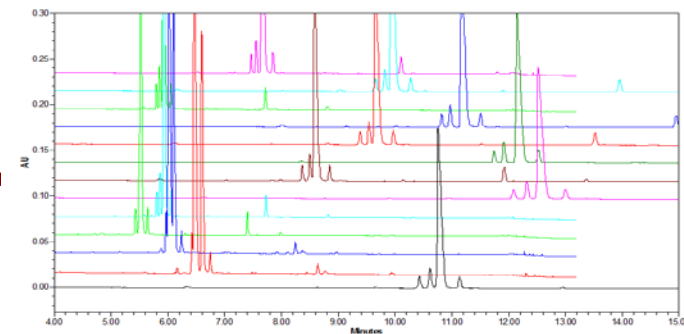
Automated Experiment Workflow



Chromatography Data Software (CDS)



Run No	Vial No	# of Pkts	Label	Sample Name	Level	Function	Method Set / Report Defect	Label Reference	Processing	Run Time (Minutes)	Data Start (Minutes)	Inject MS Delay (Minutes)	Column Position	Auto Adjusts	Sample Weight	Date
1						Condition Column				8.70	0.00	0.00	No Change			
2						Condition Column	Test file pH 01_017			8.70	0.00	0.00	No Change			
3						Equilibrat	Test file pH 01_017			3.00	0.00	7.00	No Change			
4	1	2.0	1	UW-005-000	Blank - 1	Inject Samples	Test file pH 01_017		Normal	10.00	0.00	1.00			1.00000	1.00000
5						Condition Column	Test file pH 01_021			8.70	0.00	0.00	No Change			
6						Equilibrat	Test file pH 01_021			3.00	0.00	0.00	No Change			
7	2	2.0	1	UW-001-001	1 a 1 a	Inject Samples	Test file pH 01_021		Normal	10.00	0.00	1.00			1.00000	1.00000
8						Condition Column	Test file pH 01_022			8.70	0.00	0.00	No Change			
9						Equilibrat	Test file pH 01_022			3.00	0.00	0.00	No Change			
10	2	2.0	1	UW-001-002	2 a 1 a	Inject Samples	Test file pH 01_022		Normal	10.00	0.00	1.00			1.00000	1.00000
11						Condition Column	Test file pH 01_023			8.70	0.00	0.00	No Change			
12						Equilibrat	Test file pH 01_023			3.00	0.00	0.00	No Change			
13	2	2.0	1	UW-001-003	3 a 1 a	Inject Samples	Test file pH 01_023		Normal	10.00	0.00	1.00			1.00000	1.00000
14						Condition Column	Test file pH 01_023			8.70	0.00	0.00	No Change			
15						Equilibrat	Test file pH 01_024			3.00	0.00	0.00	No Change			
16	2	2.0	1	UW-001-004	4 a 1 a	Inject Samples	Test file pH 01_024		Normal	10.00	0.00	1.00			1.00000	1.00000
17						Condition Column	Test file pH 01_025			8.70	0.00	0.00	No Change			
18						Equilibrat	Test file pH 01_025			3.00	0.00	0.00	No Change			
19	2	2.0	1	UW-001-005	5 a 1 a	Inject Samples	Test file pH 01_025		Normal	10.00	0.00	1.00			1.00000	1.00000
20						Condition Column	Test file pH 01_026			8.70	0.00	0.00	No Change			
21						Equilibrat	Test file pH 01_026			3.00	0.00	0.00	No Change			



Automated, Audited Data Exchange Preserves Data Integrity



- ✓ Solvent Selection Valves
- ✓ Column Switching Valves

Alliance HPLC



Acquity Binary



Acquity H-Class



Acquity Arc



Acquity UPC²





OpenLab –
ChemStation
Edition



Solvent Selection Valves



Column Switching Valves

Agilent 1100s
And 1200s



Agilent 1260
Infinity Series



Agilent 1260
Infinity II Series



Agilent 1290
Infinity Series



Agilent 1290
Infinity II Series





- ✓ Solvent Selection Valves
- ✓ Column Switching Valves

UltiMate LCs



Vanquish Horizon And Flex LCs



All the Critical QbD Capabilities You Need

Critical QbD Capability

FMV

Supports All Install Environments (Citrix Certified)



Full 21 CFR Part 11 Compliance Support



Complete Method Validation Experiment Suite



Simple Experiment Workflows



Full LC Experiment Automation



USP 1210> Tolerance and Prediction Interval Metrics



- **Replication Strategy and TMU**
- **Accuracy and Repeatability**
- **Analytical Method Transfer**

2. CONSIDERATIONS PRIOR TO VALIDATION

How many individual determinations will compose the reportable value, and how will they be aggregated?

- To answer this question, it is necessary to understand the contributors to the procedure variance and the ultimate purpose of the procedure.

Estimation of variance components during pre-validation provides useful information for making this decision.

All the Critical QbD Capabilities You Need

Critical QbD Capability

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- Accuracy and Repeatability
- Analytical Method Transfer

Replication Strategy Experiment

Define your Target (known value), Acceptance Limits, desired FPT upper limit, and your Proposed Replication Strategy. You can also set your required LoC for the determination.

Method Validation - Analytical Capability Analysis Setup ✕

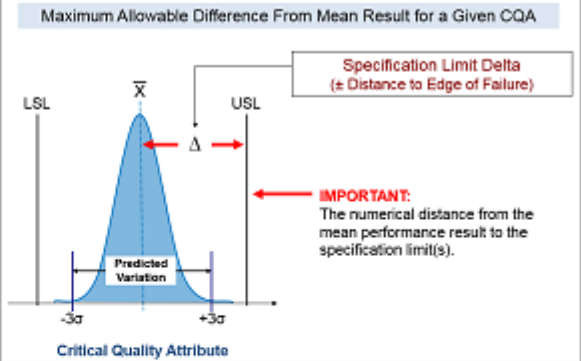
Acceptance Limits(±)
The +/- distance from the target.

Number of Preparations
Number of proposed preparation replicates for method validation. Used as the basis for calculating the Failure Rate graph and the Tolerance/Prediction Interval.

Number of Injections
Number of proposed injection replicates for method validation. Used as the basis for calculating the Failure Rate graph and the Tolerance/Prediction Interval.

Number of Failures per Thousand

Maximum Allowable Difference From Mean Result for a Given CQA



Critical Quality Attribute

Enabled	Responses	Target Value	Acceptance Limits (±)	Number of Failures per Thousand	Number of Preparations	Number of Injections	Interval Type	Desired Probability %	Tolerance Alpha %
<input checked="" type="checkbox"/>	API - Amount	5.000	0.100	3.000000	2	3	<input checked="" type="checkbox"/> Tolerance	95.00	5.000

Select All Select None

✔ The settings are valid.

Back Finish Cancel

Replication Strategy Experiment

Fusion QbD reports the Components of Variation and the Corresponding % Contributions to method precision.

Analytical Capability Report: API - Amount (*)

ANOVA

Variable Name	Sum of Squares	Degrees of Freedom	Mean Square	F-ratio	P-value
Sample Preparation	0.055	4	0.014	7.9681	0.0005
Injection	0.035	20	0.002		
Overall	0.090	24			

Sample Preparation Bias

Sample Preparation Level	Mean Bias	Mean Bias Std. Dev.	Mean Bias DoF	Mean Bias t-statistic	P-value
P-1	-0.096	0.019	20	-5.169	0.0000
P-2	0.030	0.019	20	1.603	0.0623
P-3	-0.033	0.019	20	-1.778	0.0453
P-4	-0.035	0.019	20	-1.904	0.0357
P-5	0.028	0.019	20	1.530	0.0709

Between Variables Components of Variation

Variable Name	Variance	Standard Deviation	Degrees of Freedom	t-table Value	(+/-) 95% Confidence Limits	Error Contribution (%)
Sample Preparation	0.002	0.049	4	2.7764	0.13	58.22
Injection	0.002	0.042	20	2.0860	0.08	41.78

Fusion QbD also reports the Analytical Capability and Failures Per Thousand Results for any Proposed Replication Scheme.

Cp/Failures per Thousand Results

Observed Result:
Cp = 0.8623
No. of Failures per Thousand = 9.7873

No. of Injections		No. of Preparations									
		1	2	3	4	5	6	7	8	9	10
1	Cp	0.5179	0.7324	0.8970	1.0358	1.1580	1.2686	1.3702	1.4648	1.5537	1.6377
	FPT	120.2620	28.0042	7.1229	1.8877	0.5125	0.1414	0.0395	0.0111	0.0031	0.0009
2	Cp	0.5823	0.8234	1.0085	1.1645	1.3020	1.4262	1.5405	1.6469	1.7468	1.8413
	FPT	80.6734	13.4986	2.4820	0.4766	0.0939	0.0188	0.0038	0.0008	0.0002	0.0000
3	Cp	0.6091	0.8623	1.0561	1.2194	1.3634	1.4935	1.6132	1.7245	1.8291	1.9281
	FPT	67.3784	9.6873	1.5340	0.2539	0.0431	0.0074	0.0013	0.0002	0.0000	0.0000
4	Cp	0.6250	0.8839	1.0825	1.2500	1.3975	1.5309	1.6535	1.7677	1.8749	1.9764
	FPT	60.8013	8.0120	1.1643	0.1769	0.0276	0.0044	0.0007	0.0001	0.0000	0.0000
5	Cp	0.6347	0.8976	1.0993	1.2694	1.4193	1.5547	1.6793	1.7952	1.9041	2.0071
	FPT	56.8940	7.0847	0.9736	0.1400	0.0206	0.0031	0.0005	0.0001	0.0000	0.0000
6	Cp	0.6415	0.9072	1.1110	1.2829	1.4343	1.5712	1.6971	1.8143	1.9244	2.0284
	FPT	54.3100	6.4996	0.8589	0.1187	0.0169	0.0024	0.0004	0.0001	0.0000	0.0000
7	Cp	0.6464	0.9142	1.1196	1.2928	1.4454	1.5834	1.7102	1.8283	1.9392	2.0441
	FPT	52.4759	6.0982	0.7828	0.1051	0.0145	0.0020	0.0003	0.0000	0.0000	0.0000
8	Cp	0.6502	0.9195	1.1262	1.3004	1.4539	1.5926	1.7202	1.8390	1.9506	2.0561
	FPT	51.1074	5.8062	0.7288	0.0957	0.0129	0.0018	0.0002	0.0000	0.0000	0.0000
9	Cp	0.6532	0.9237	1.1314	1.3064	1.4606	1.6000	1.7289	1.8475	1.9596	2.0656
	FPT	50.0000	5.6000	0.6800	0.0900	0.0120	0.0015	0.0001	0.0000	0.0000	0.0000

Replication Strategy Experiment

Fusion QbD also reports:

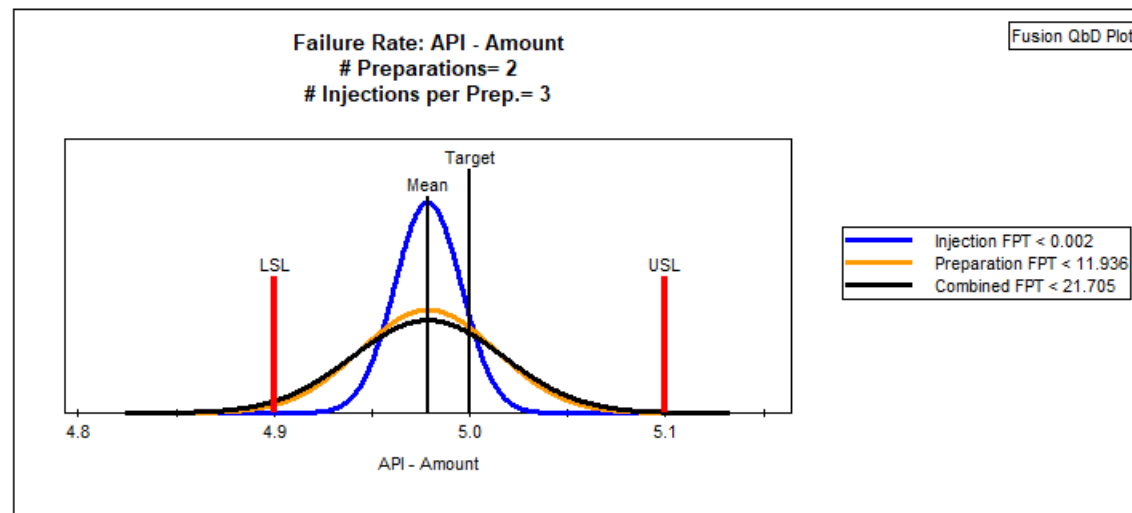
- The USP <1210> Tolerance or Prediction Interval – the Actual Measurement Uncertainty Corresponding to your Specified Replication Strategy.
- The Target Measurement Uncertainty (TMU) Set by your Defined Acceptance Limits.
- The Pass/Fail Test Results.

Tolerance Interval

Interval Type	Computed Interval	Number of Preparations	Number of Injections
Acceptance Limits	4.900 <= 5.000 <= 5.100	2	3
Tolerance Interval	4.829 <= 4.979 <= 5.129		
Result			Fail

At least one of the Computed Interval bounds falls outside the Acceptance Limits.

Calculated Overall Mean: 4.979



All the Critical QbD Capabilities You Need

Critical QbD Capability

FMV

Supports All Install Environments (Citrix Certified)



Full 21 CFR Part 11 Compliance Support



Complete Method Validation Experiment Suite



Simple Experiment Workflows



Full LC Experiment Automation



USP 1210> Tolerance and Prediction Interval Metrics

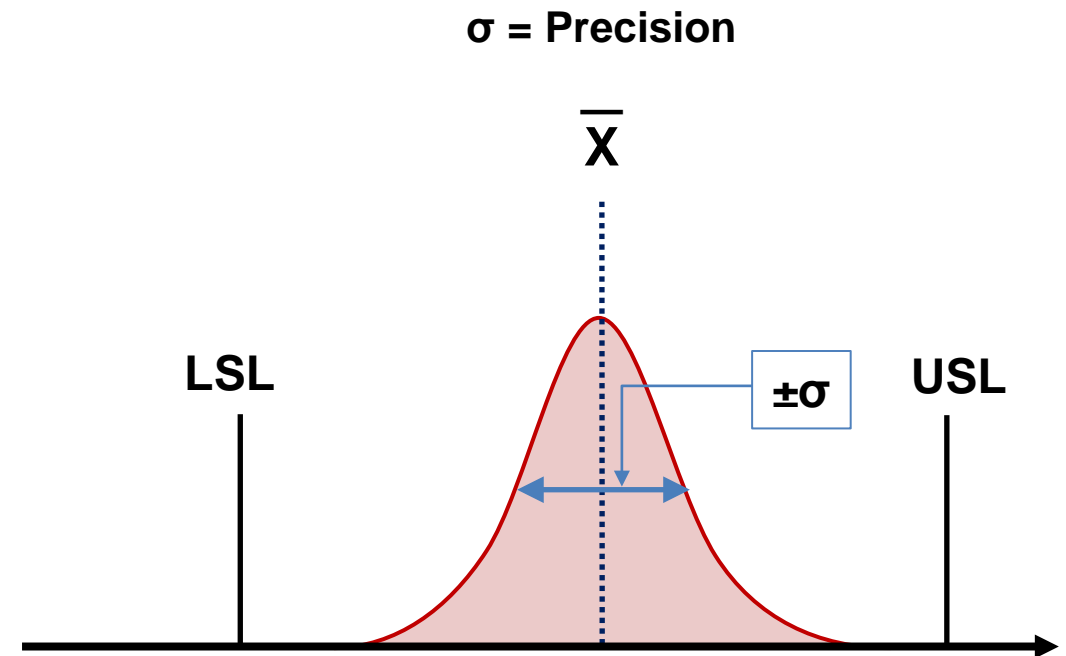
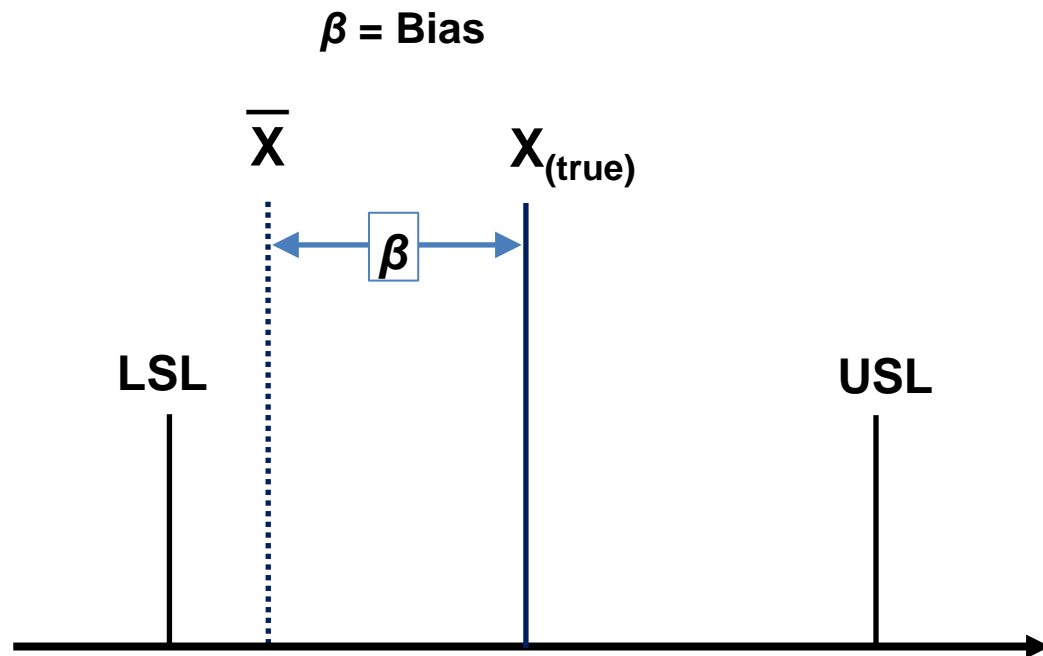


- Replication Strategy and TMU
- **Accuracy and Repeatability**
- Analytical Method Transfer

3. ACCURACY AND PRECISION

3.2 Combined Validation of Accuracy and Precision

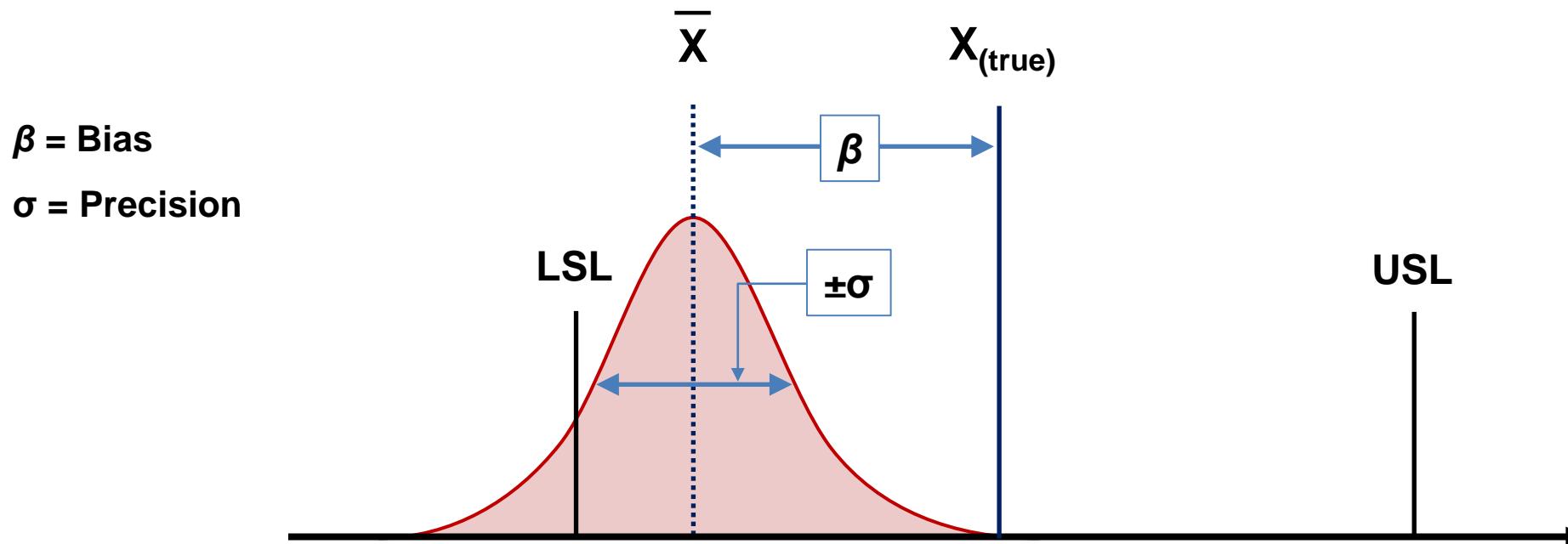
The illustration below shows that the method will pass System Suitability performance for the Critical Quality Attribute (CQA) being tested SST when Accuracy (β – bias estimate) and Precision (σ – variation estimate) are assessed independently (= High Risk Approach).



3. ACCURACY AND PRECISION

3.2 Combined Validation of Accuracy and Precision

However, 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).**



<1210> Metrics – Accuracy & Repeatability

Define your Acceptance Limits and required LOC for the determination.

Method Validation - Small Molecule Data Analysis

Accuracy | Linearity | Repeatability

Select Response for Analysis
Amount

API

Perform Data Analysis

Response Treatment
 % Recovered (Relative) Difference from Mean (Absolute)


Compound-based Acceptance Criteria
 Tolerance / Prediction Interval
 Interval Type
 Tolerance Prediction

Name	Value	Unit
Acceptance Limit <=	0.10	mg
Desired Probability	95.00	%
Tolerance Alpha	5.00	%

Level-based Acceptance Criteria

Level	Accuracy [% Bias] <=
1.000	15.00
2.000	10.00

Level	Individual Results Spec. Lower Limit	Individual Results Spec. Upper Limit
1.000	0.900	1.100
2.000	1.800	2.200

 The settings are valid.

Back Finish Cancel

<1210> Metrics – Accuracy & Repeatability

Fusion QbD Automatically Generates All Analysis Results and Graphs for Accuracy, Linearity, and Repeatability. Fusion QbD also reports the <1210> Tolerance or Prediction Analysis Results.

Tolerance Interval

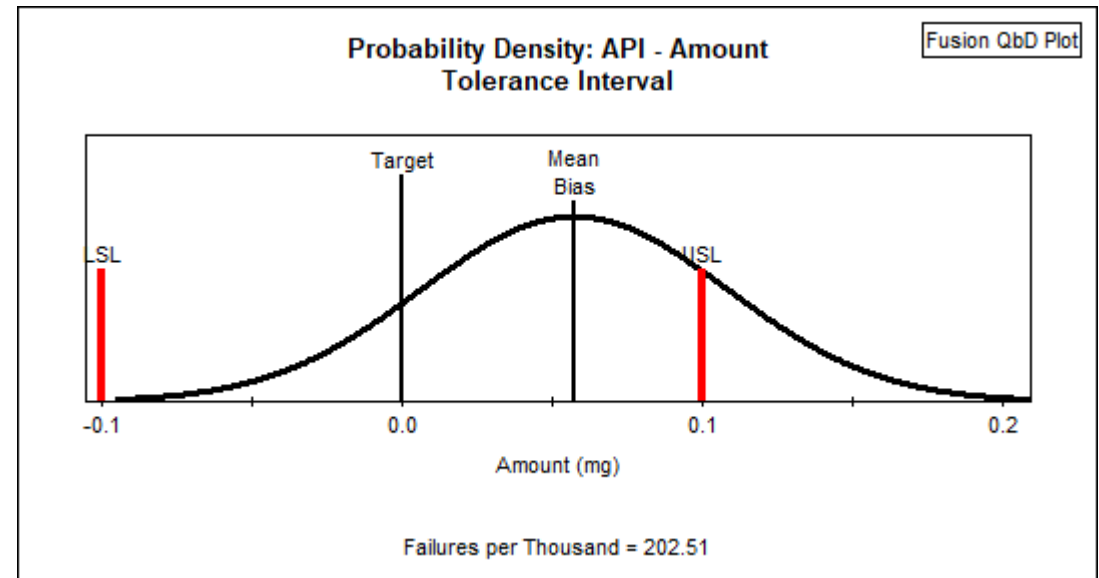
Name	Value
Acceptance Limits	-0.10 <= Target <= 0.10
Computed Interval	-0.04 <= Mean <= 0.16
Result	Fail

[Difference From Mean: Target = 0.00, Mean (Pooled) = 0.059]

At least one of the Computed Interval bounds falls outside the Specification Interval bounds.

Replicate Group Error Statistics

Replicate Group	Group Run No.	Observed Value	Group Std. Dev.	F-Ratio	P-Values
1	1.a	0.018	0.027	0.7366	0.5086
	1.b	0.072			
	1.c	0.051			
2	2.a	0.111	0.038	1.7550	0.2334
	2.b	0.109			
	2.c	0.044			
3	3.a	0.120	0.012	0.1267	0.8827
	3.b	0.097			
	3.c	0.102			
4	4.a	0.102	0.024	0.5602	0.5920
	4.b	0.092			
	4.c	0.056			
5	5.a	-0.074	0.043	2.5143	0.1422
	5.b	-0.047			
	5.c	0.010			



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USP 1210> Tolerance and Prediction Interval Metrics



- Analytical Capability
- Accuracy and Repeatability
- **Analytical Method Transfer**

Comparative Testing

Comparative testing requires the analysis of a predetermined number of samples of the same lot by both the sending and the receiving units. Other approaches may be valid, e.g., if the receiving unit meets a predetermined acceptance criterion for the recovery of an impurity in a spiked product. Such analysis is based on a preapproved transfer protocol that stipulates the details of the procedure, the samples that will be used, **and the predetermined acceptance criteria, including acceptable variability**. Meeting the predetermined acceptance criteria is necessary to assure that the receiving unit is qualified to run the procedure.

Analytical Method Transfer Example

Transferring Lab



Fusion QbD
Sequence
Execution

Chromatography
Data Software

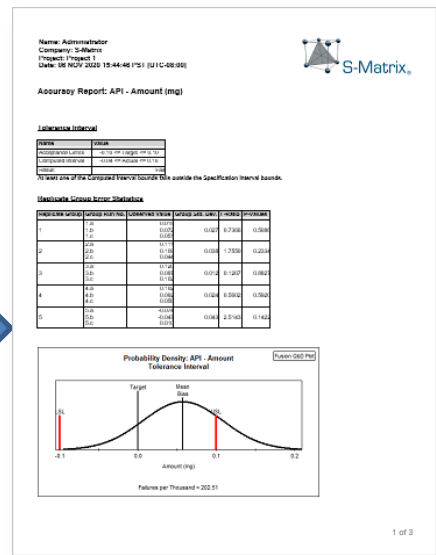
ALR
Design



Fusion QbD
Sequence
Execution

Chromatogram
Results Data

Receiving Lab



Accuracy
Linearity
Repeatability
Tolerance or
Prediction Interval
Pass/Fail Results

1. Fusion QbD – Exports experiment to the CDS
As Ready-to Run sequence, methods, standards
2. Sequence is run at both labs.
3. Fusion QbD – Imports results for instant and complete analysis and reporting.

Key Benefits of FMV

1. Consistency – Workflow and Reporting.

Work is standardized – done the same way every time. Reporting is standardized, complete, easy to communicate.

2. Simplicity

Tremendous ease of use. Very brief learning curve. Clearly defined templatable workflows with built-in workflow management.

3. Speed (Productivity)

Automation and simplified workflows dramatically increase productivity. Review process is minimized and simplified.

4. Regulatory Alignment and Completeness

All required validation experiment types are supported. Reporting meets regulatory requirements. Reports can be attached to Project specific narrative documents.

5. Platform Independence

Support for Empower, ChemStation, and Chromeleon means that the standardized workflows and reporting can be easily extended to users of other platforms at other sites or other companies (e.g. CMOs).

6. Customer Support

Our support is top-rated worldwide. S-Matrix and our local distributors have a multi-year history of proven ability to meet all our customer's support needs.

End of Presentation

Analytical Procedure Lifecycle Management Workflow

