2019 EASTERN ANALYTICAL SYMPOSIUM & EXPOSITION
ENHANCING ANALYTICAL CHEMISTRY WITH SUSTAINABLE SOLUTIONS
Crowne Plaza Princeton
Conference Center
Plainsboro, NJ
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Integrating and Automating the Use of PDA and MS Data in LC and LC/MS Method Development

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Presentation Outline

1. Introduction to the Fusion QbD® Software Platform
    a. QbD Method Development Experiment Automation
    b. Cross-platform Data Integrity
2. ***PeakTracker*** – UV & MS Spectra Based Peak Tracking
    a. Data Integration for Automated Modeling
    b. Tracking Automation
3. Forced Degradation Study Automation
    a. Peak Tracking in Forced Degradation Studies
    b. Composite Chromatogram Modeling & Visualization

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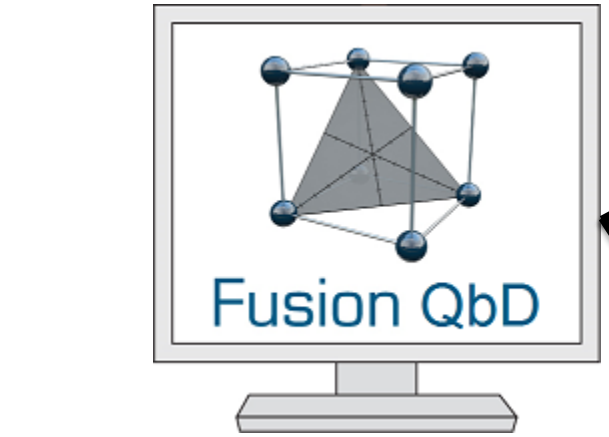
Fusion QbD® – Modular Software Platform



Full QbD Experiment Automation

ChemStation
OpenLAB

Empower™

- **LC Method Development**
- **Analytical Method Validation**
- **Product Development**
  - Formulation & Process Development
  - Non-LC Method Development
- **Respiratory Drug QC Testing**

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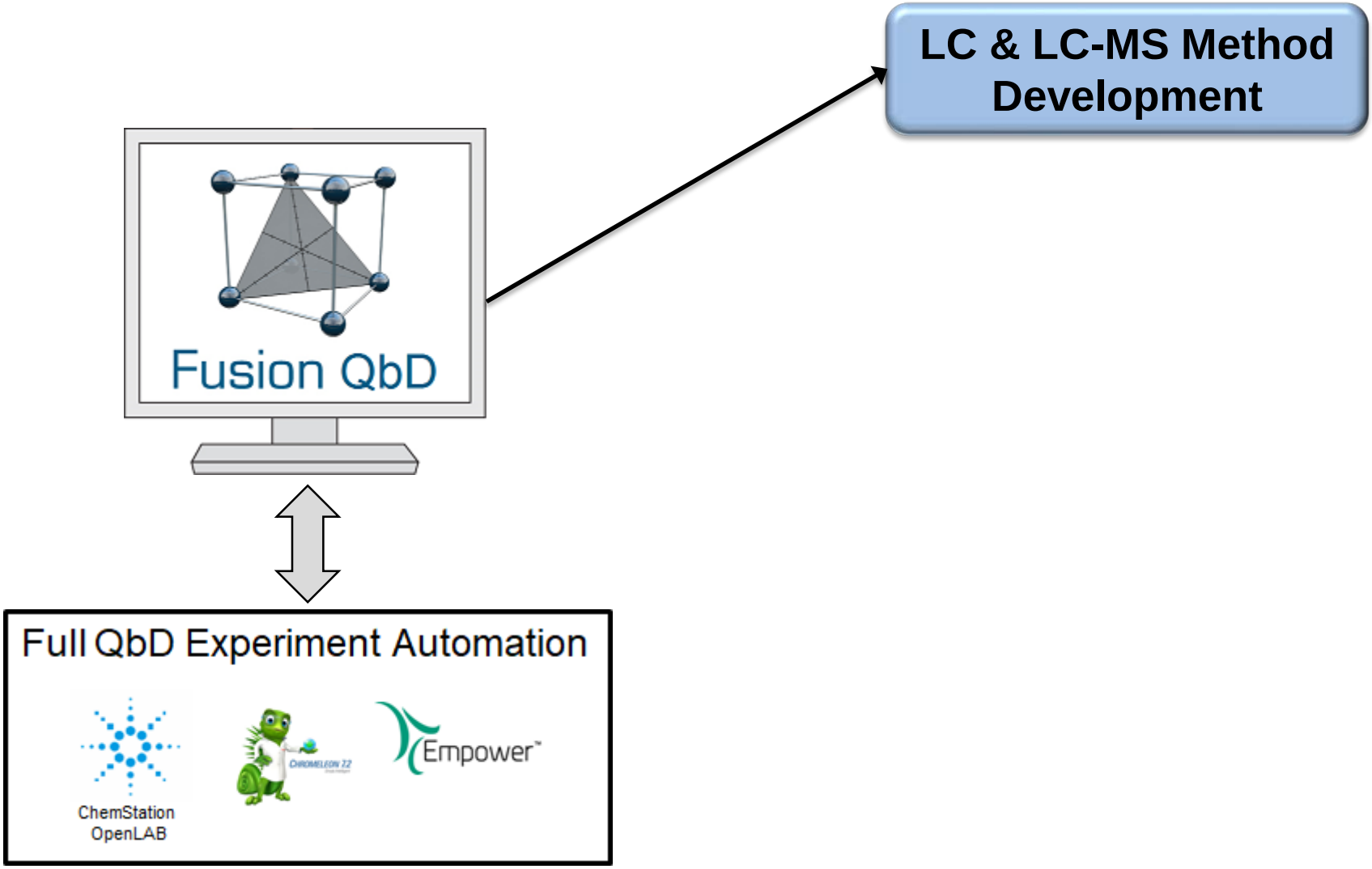
Fusion QbD® – Modular Software Platform



Fusion QbD Automation – Supports All Waters LC Systems

Empower™

- ✓ Solvent Selection Valves
- ✓ Column Switching Valves

Alliance HPLC

Acquity Binary

Acquity H-Class

Acquity Arc

Acquity UPC²

S-Matrix®

Fusion QbD Automation – Supports All Agilent LC Systems

Empower™

CHROMELEON 7.2

ChemStation
OpenLab

- ✓ 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

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Fusion QbD Automation – Supports Thermo LC Systems

- ✓ Solvent Selection Valves
- ✓ Column Switching Valves

UltiMate LCs

Vanquish Horizon And Flex LCs

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Fusion QbD – Supports all Install Environments

Supports all 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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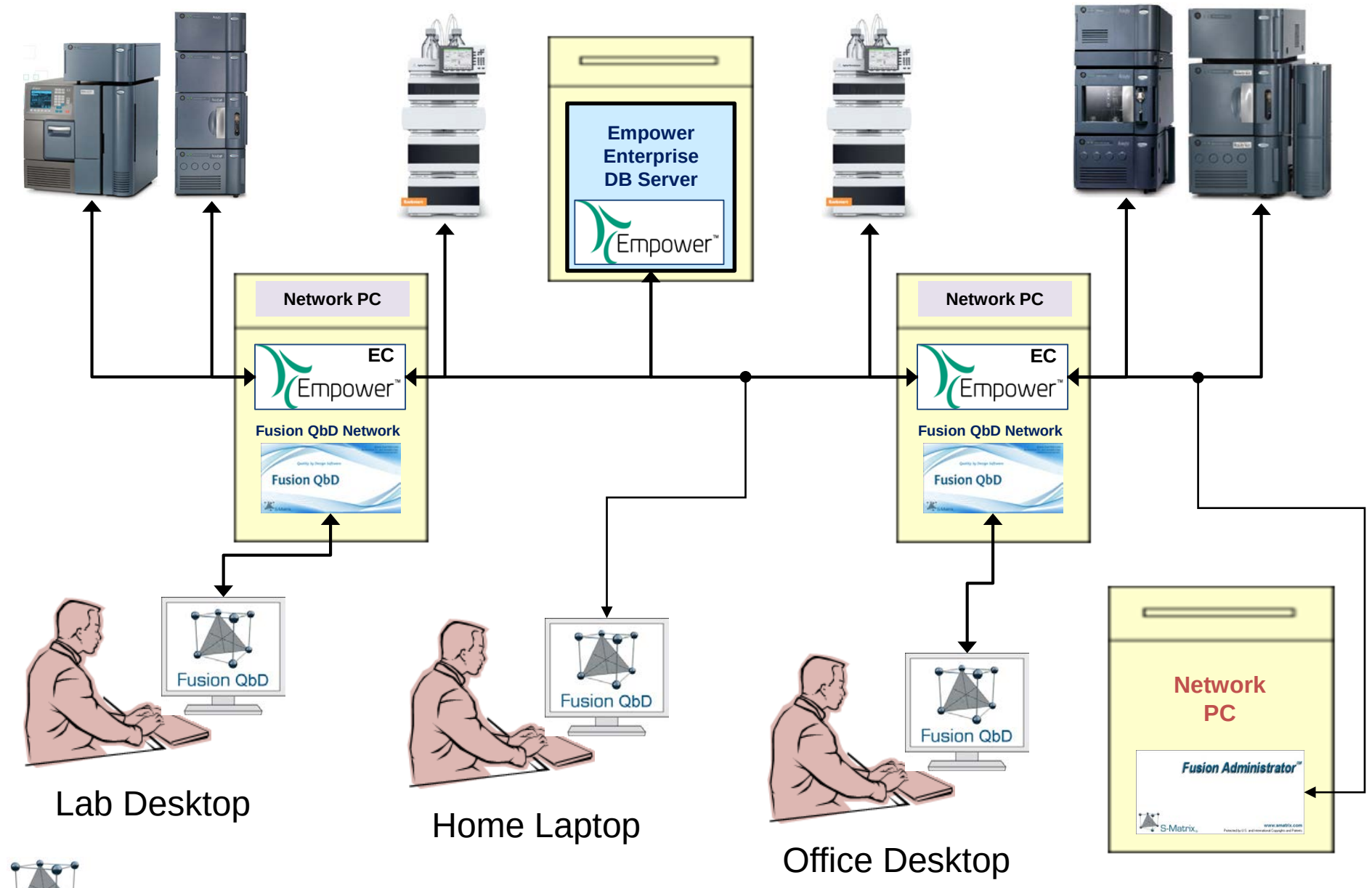
Fusion QbD – Supports all Install Environments



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Supports All These Separation Modes

Reversed Phase

Normal Phase

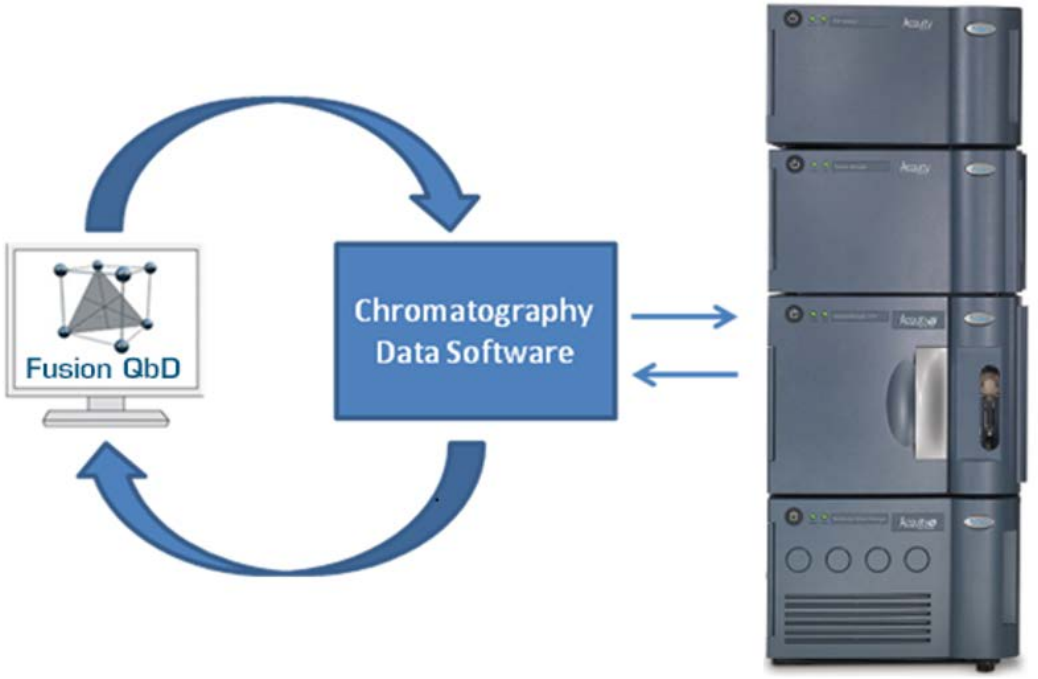
Chiral

HILIC

Ion Exchange

Size Exclusion

SFC



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Fusion QbD – Supports Flexible Experimenting

Enables you to study **any combination** of LC parameters which can **interactively effect** method performance!

- Isocratic Methods
- Gradient Methods
- Any pump program steps – e.g.
  - o Equilibration Time & %
  - o Isocratic Hold Time & %
  - o Gradient Time & Slope
  - o Final Hold Time & %
  - o Re-equilibration Time & %
- Strong Solvent Type
- Mobile Phase Solvent Blend
- Column Temperature
- pH
- Column Type
- Flow Rate
- Injection Volume
- Ionic Strength

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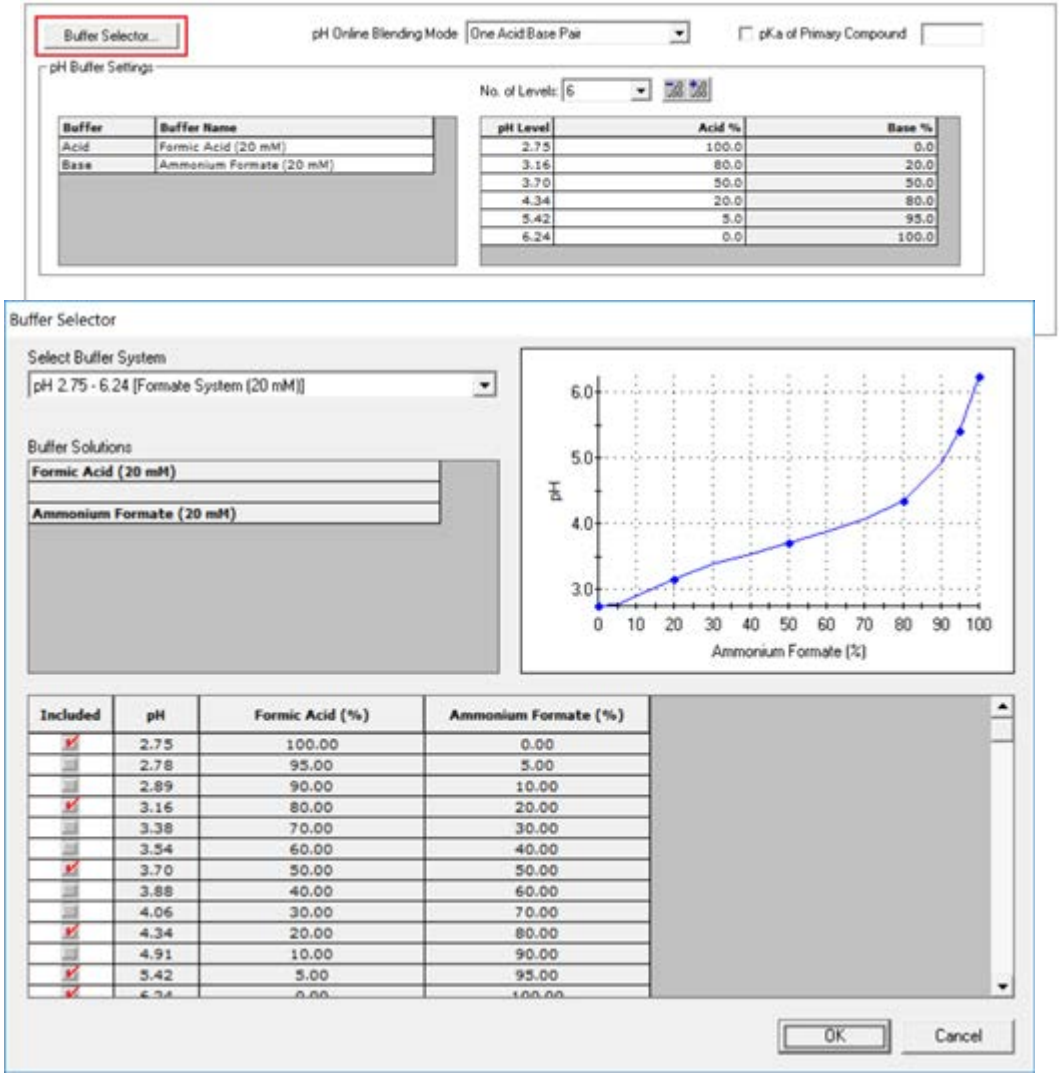
Initial Chemistry Screening – Built In pH Automation



Built in Buffer System Titration Curves

Extremely Precise!

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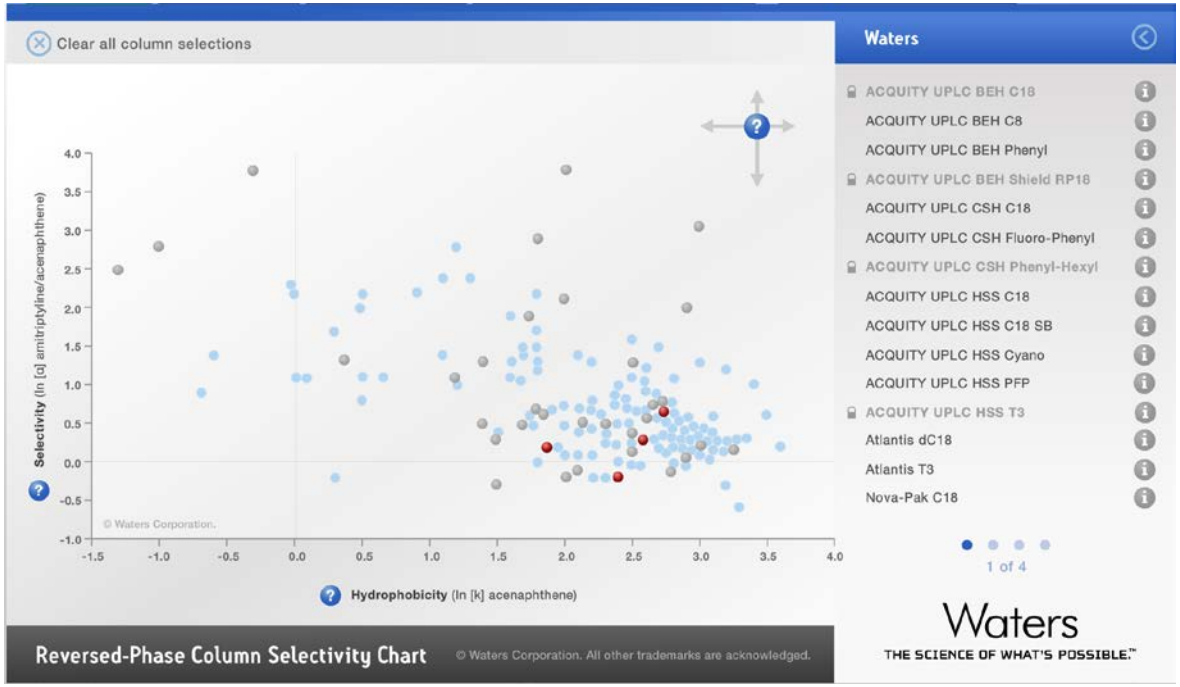
Initial Chemistry Screening – Built In Column Switching Automation



Fusion QbD Automation Supports Column Compartments with Multi-position Valves!

Column Settings

	Name	Valve Position	Condition Column Time	pH Upper Bound
1	BEH C18	Position 1	2.0	14.00
2	BEH Shield RP18	Position 2	2.0	14.00
3	HSS T3	Position 3	2.0	14.00
4	CSH Phenyl Hexyl	Position 4	2.0	14.00

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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.

USP Workshop – Enhanced Approaches for Analytical Procedure Lifecycle: An Alternative to Traditional Validation

(Sept. 24-25, 2018)

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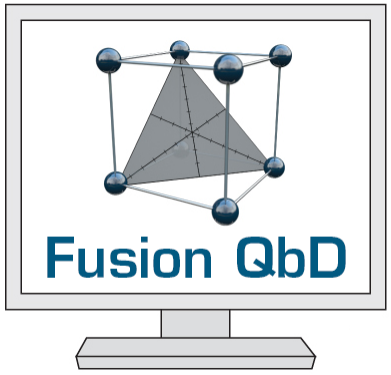
Fusion QbD Automation – Maintains Data Integrity



Generates QbD-aligned DOE Experiment

Automatically Builds Sequence and All Instrument Methods

Chromatography Data Software (CDS)

Text Mix pH in S-Matrix - MD Demo\LC Tutorial - Sample Workup as System/Administrator - Sample Set Method Editor

File Edit View Help

Apply Table Preferences: Sample Set Method

	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			

Eliminate Transcription Errors.
Maintain Data in Audited Environment.

S-Matrix®

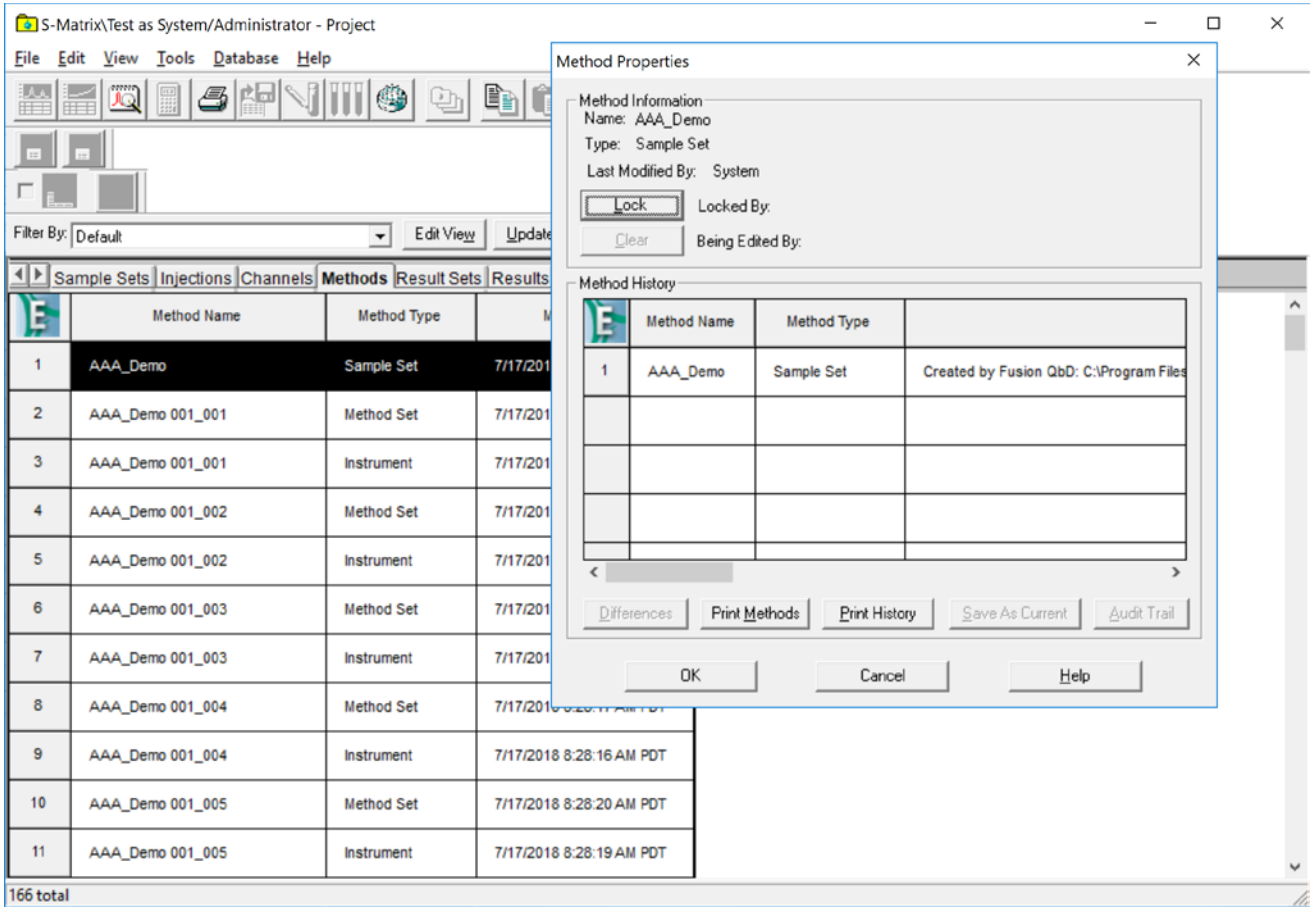
Fusion QbD Automation Supports Full Data Integrity

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

Secure **Workflow** and **Project Management** systems.

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

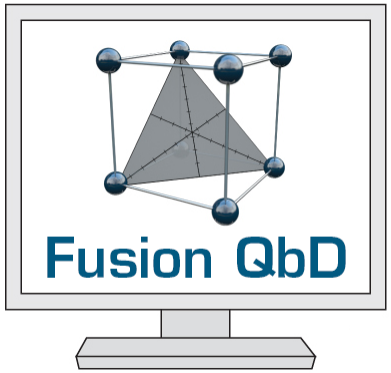
Fusion QbD Automation – Maintains Data Integrity



Audited Data Exchange – Assures Data Integrity

S-Matrix®

Fusion QbD Automation – Maintains Data Integrity

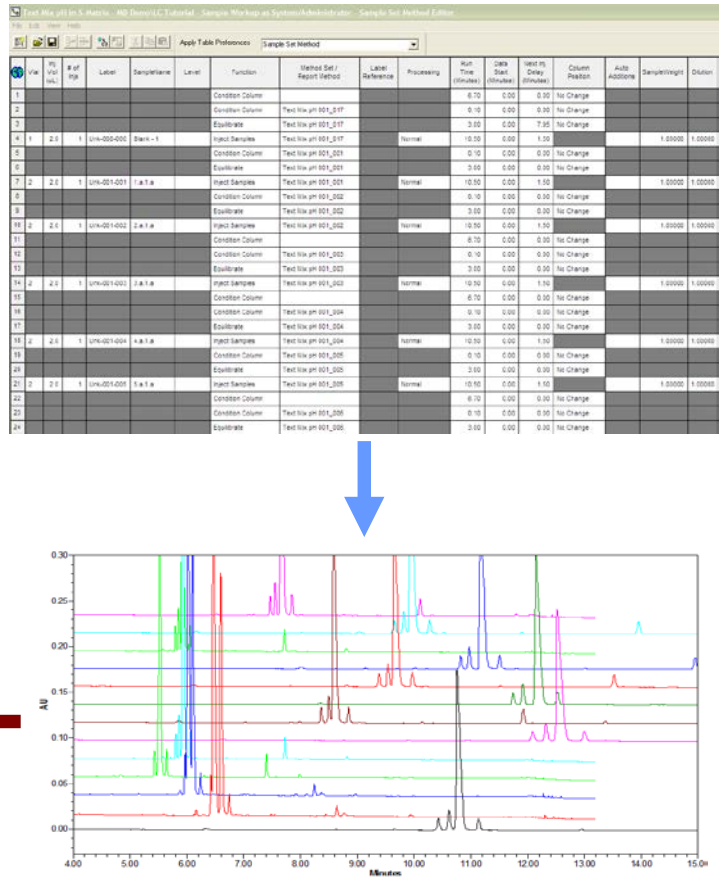


Automatically Retrieves
All Chromatogram
Results Data

Automated analysis, graphing, and reporting.

Report formats:
RTF, DOC, HTML, PDF, XLSX, XML

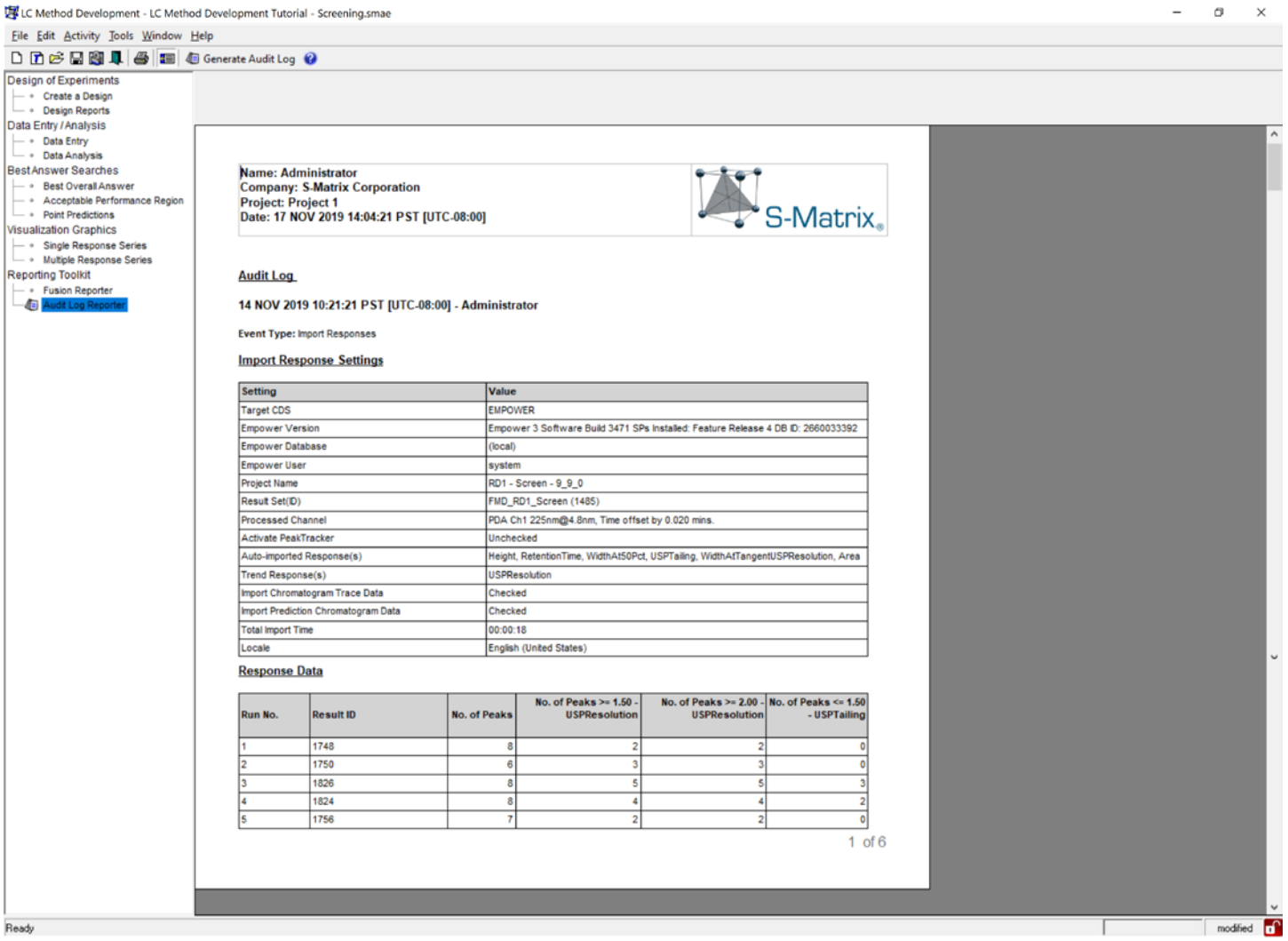
Chromatography Data Software (CDS)



Eliminate Transcription Errors.
Maintain Data in Audited Environment.

S-Matrix®

Fusion QbD Automation – Maintains Data Integrity



Audited Data Exchange – Assures Data Integrity

S-Matrix

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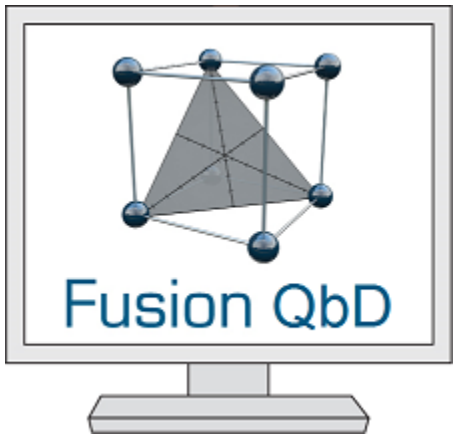
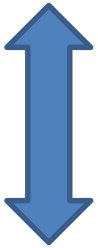
Fusion QbD – *PeakTracker*™





Acquity H-Class With PDA

Acquity QDa Mass Detector

6 Column Capacity

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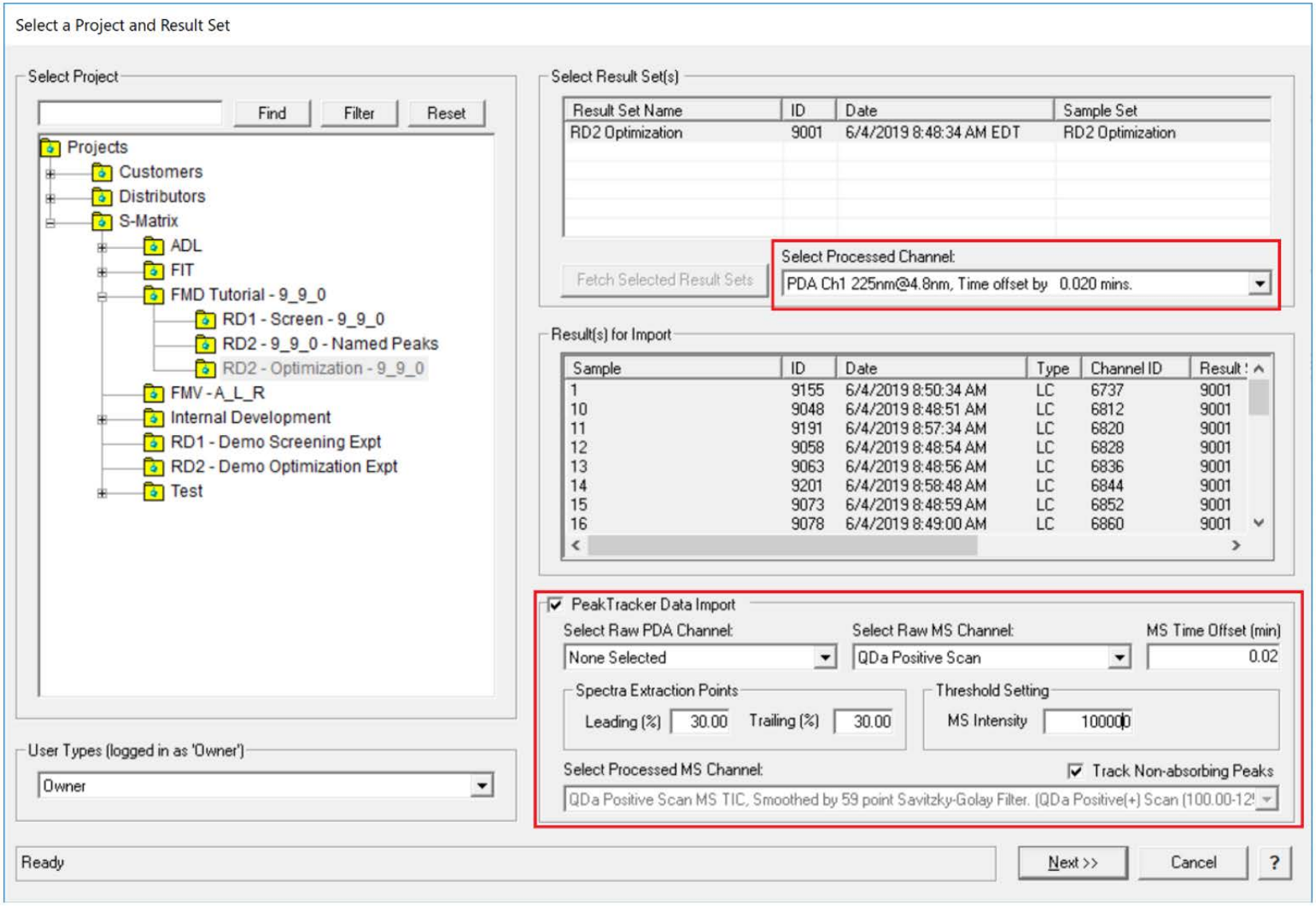
Fusion QbD – Auto-imports UV and MS Spectra Data for Tracking



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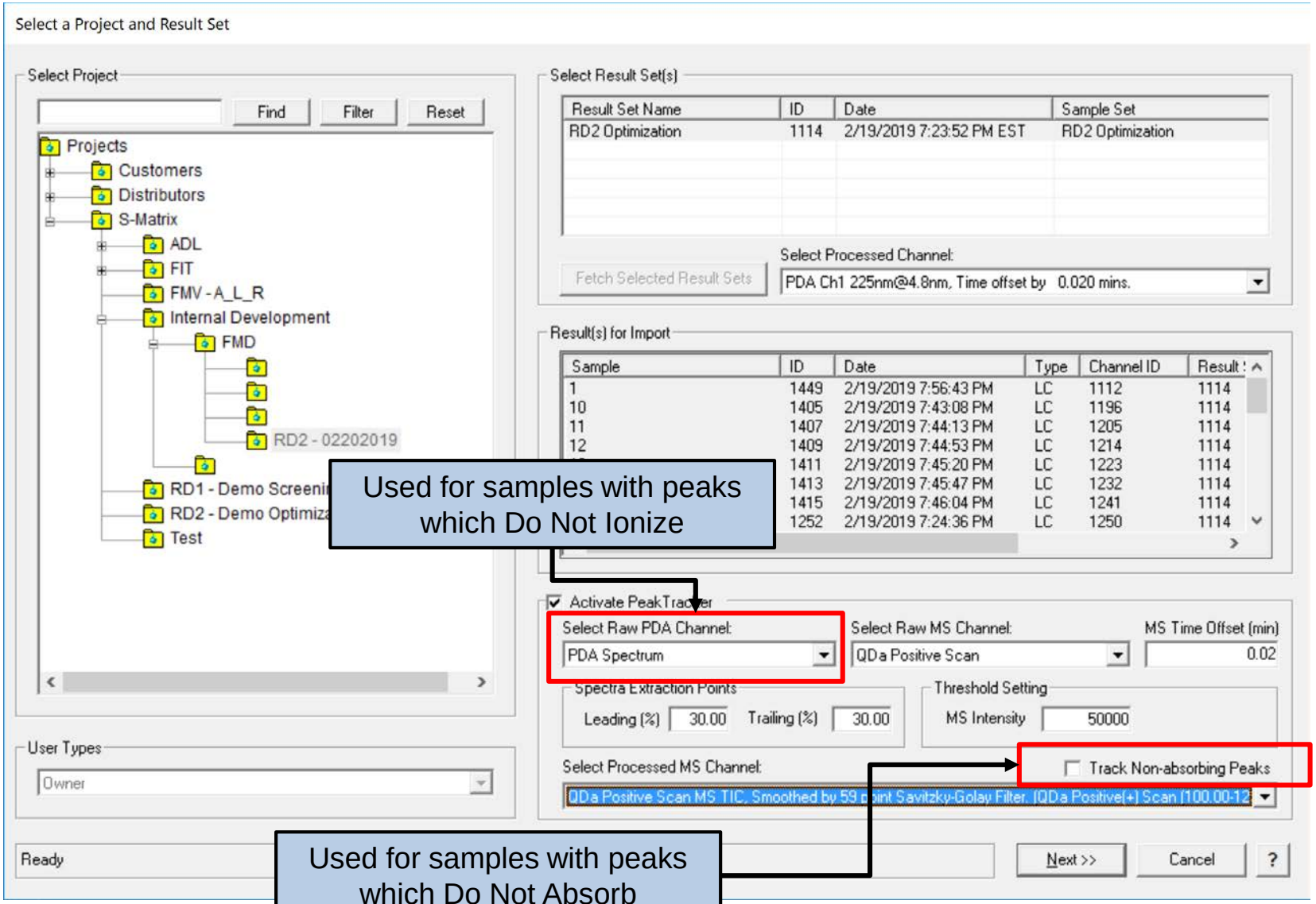
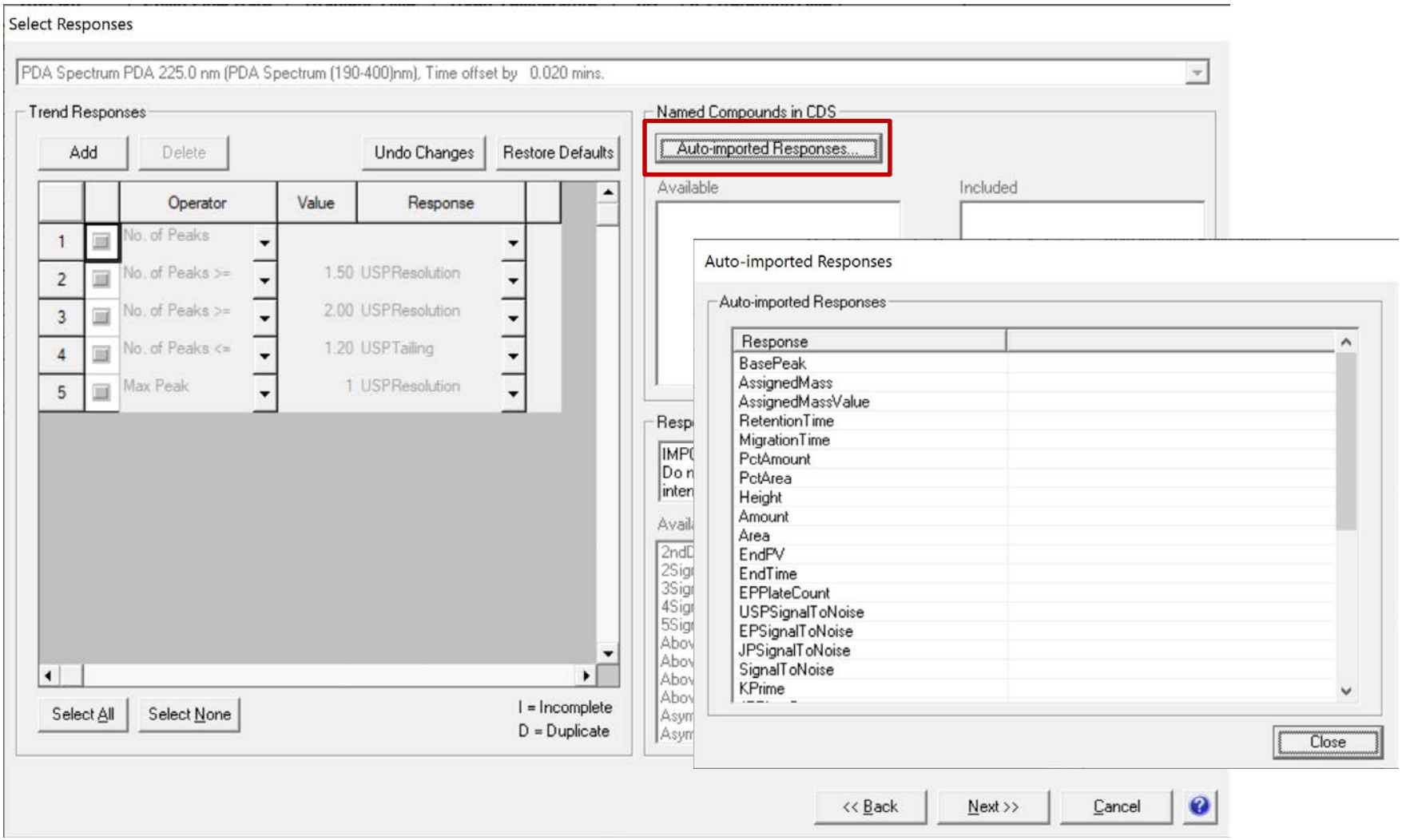
Fusion QbD – Auto-imports UV and MS Spectra Data for Tracking



Fusion QbD – Auto-imports all Results for Modeling, & Simulation



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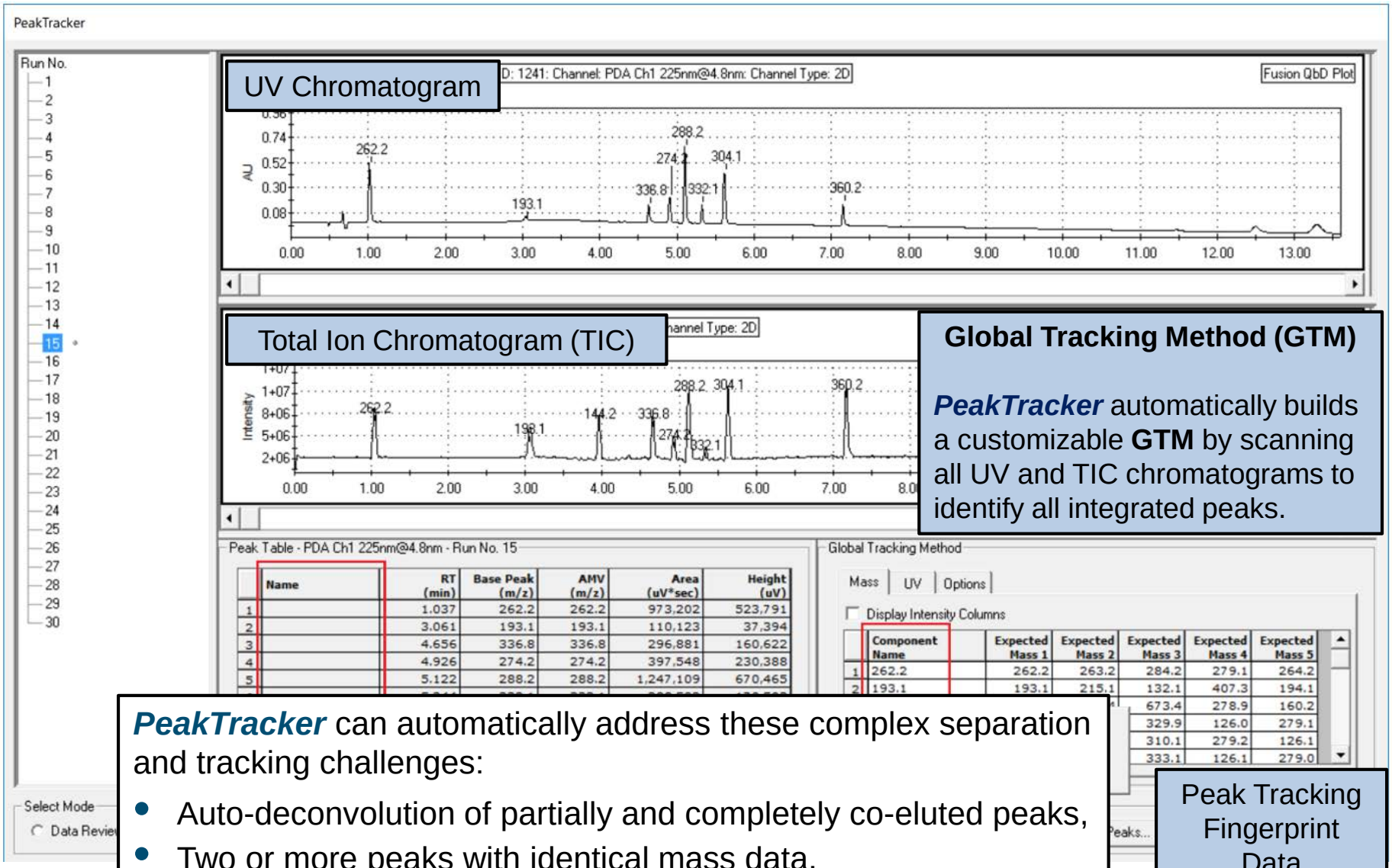
PeakTracker – Displays UV & MS Chromatograms / Auto-builds GTM



Global Tracking Method (GTM)

PeakTracker automatically builds a customizable **GTM** by scanning all UV and TIC chromatograms to identify all integrated peaks.

PeakTracker can automatically address these complex separation and tracking challenges:

- Auto-deconvolution of partially and completely co-eluted peaks,
- Two or more peaks with identical mass data.
- Non-ionizing and non-absorbing compounds.

Peak Tracking Fingerprint Data

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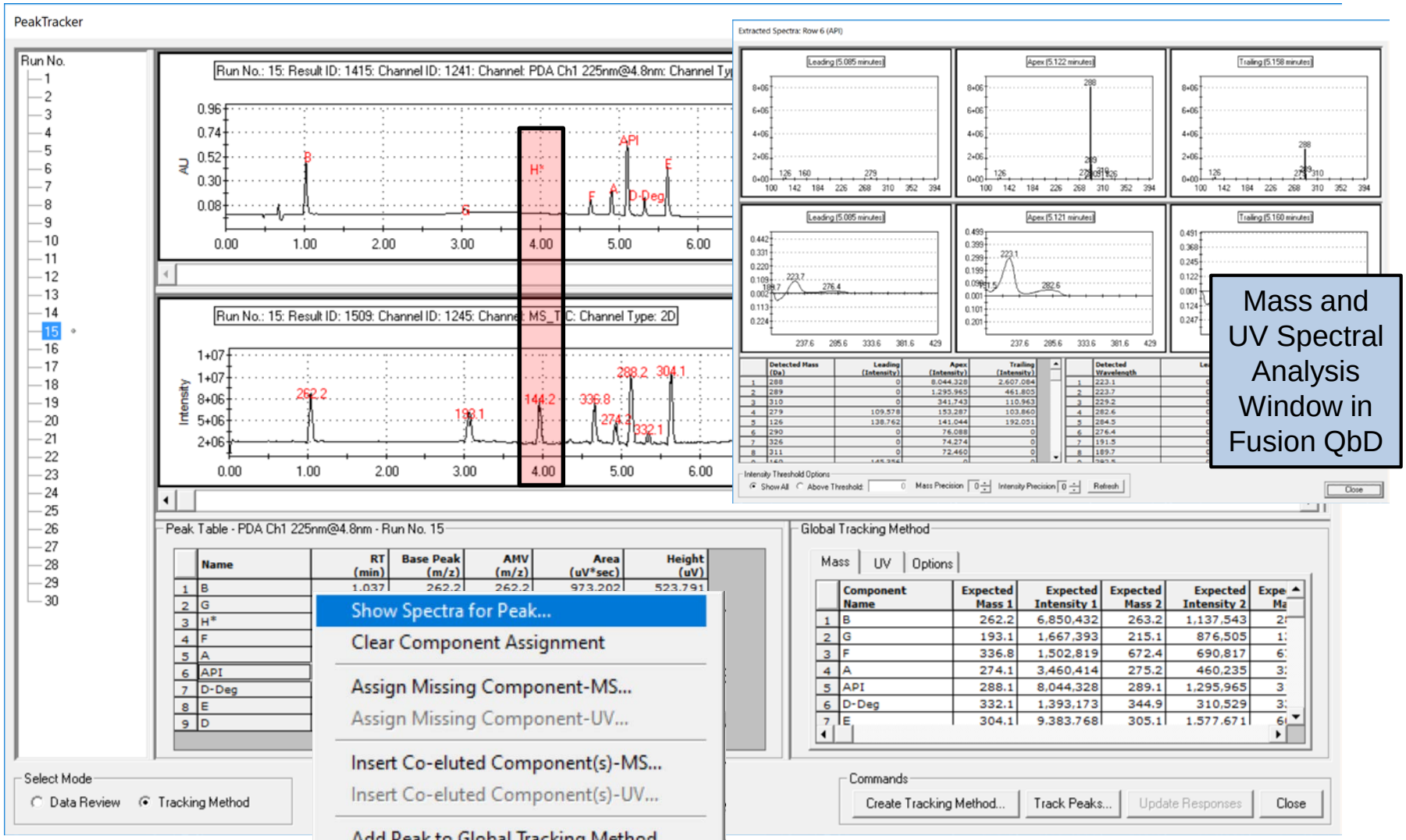
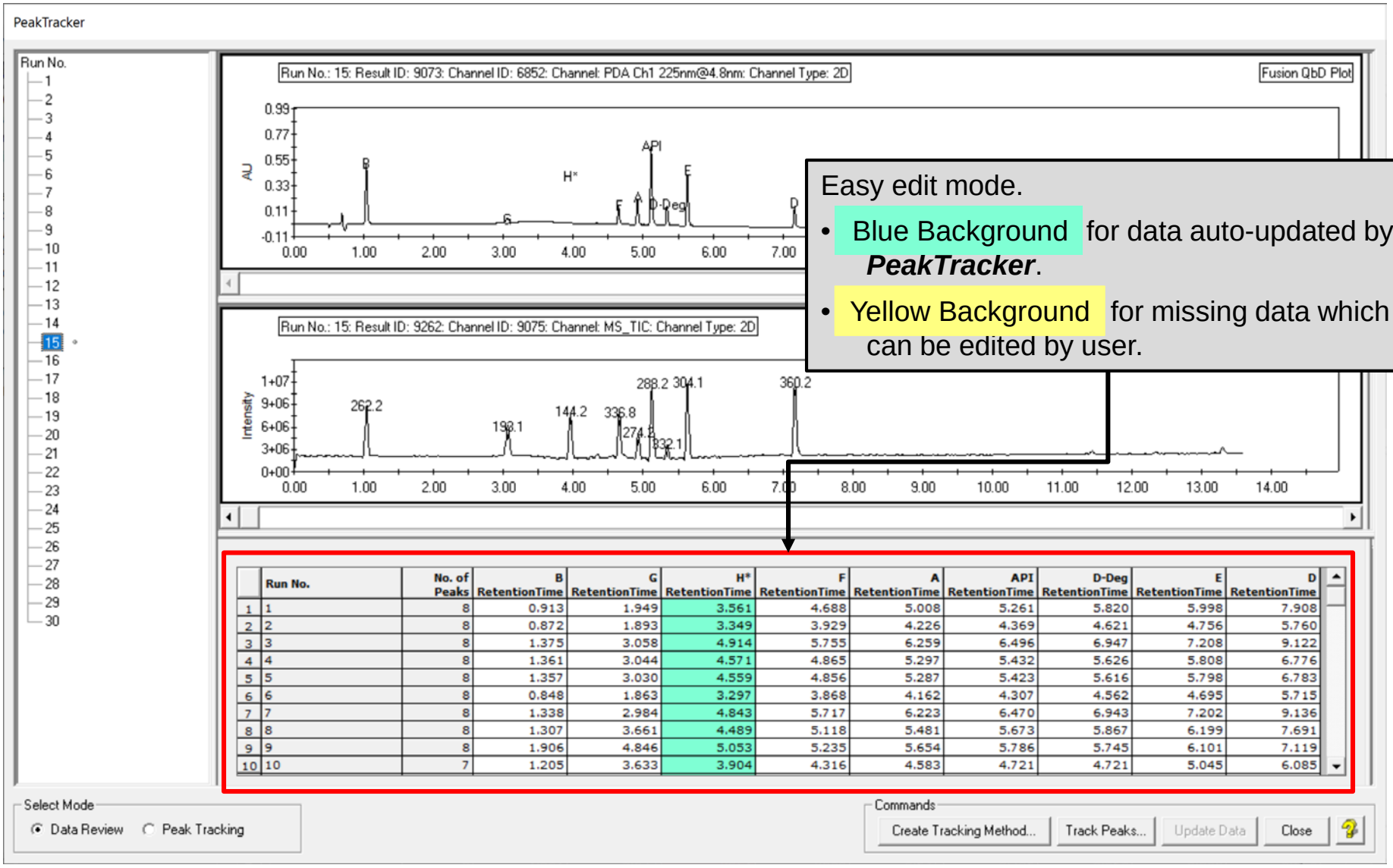
PeakTracker – Displays Tracking Results and Peak Spectra Data



PeakTracker – Instant Preview of Tracking Results



	Run No.	No. of Peaks	B RetentionTime	G RetentionTime	H* RetentionTime	F RetentionTime	A RetentionTime	API RetentionTime	D-Deg RetentionTime	E RetentionTime	D RetentionTime
1	1	8	0.913	1.949	3.561	4.688	5.008	5.261	5.820	5.998	7.908
2	2	8	0.872	1.893	3.349	3.929	4.226	4.369	4.621	4.756	5.760
3	3	8	1.375	3.058	4.914	5.755	6.259	6.496	6.947	7.208	9.122
4	4	8	1.361	3.044	4.571	4.865	5.297	5.432	5.626	5.808	6.776
5	5	8	1.357	3.030	4.559	4.856	5.287	5.423	5.616	5.798	6.783
6	6	8	0.848	1.863	3.297	3.868	4.162	4.307	4.562	4.695	5.715
7	7	8	1.338	2.984	4.843	5.717	6.223	6.470	6.943	7.202	9.136
8	8	8	1.307	3.661	4.489	5.118	5.481	5.673	5.867	6.199	7.691
9	9	8	1.906	4.846	5.053	5.235	5.654	5.786	5.745	6.101	7.119
10	10	7	1.205	3.633	3.904	4.316	4.583	4.721	4.721	5.045	6.085

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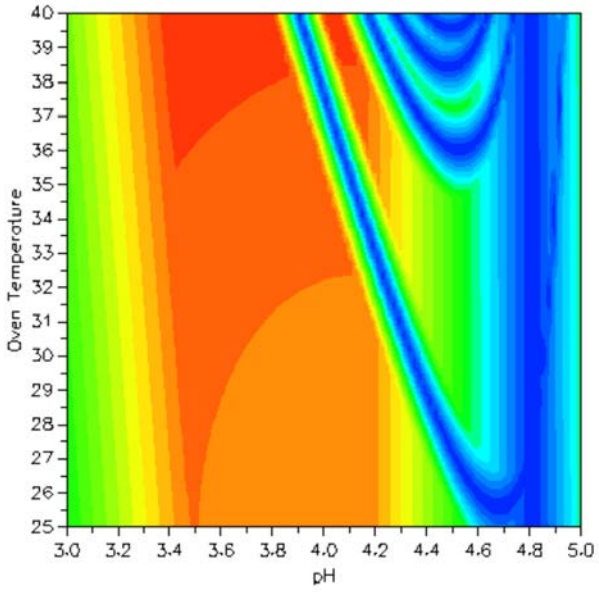
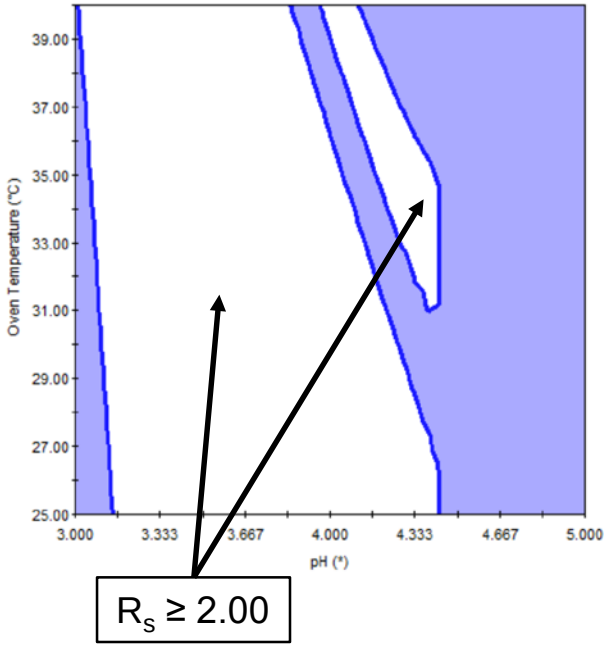
Fusion QbD – *Rs-Map Response*

Fusion QbD now uses its hyper-accurate modeling technologies to predict USP or EP Resolutions for all peaks for any method conditions using standard Resolution equations. Graphical and numerical displays update in real time as you change method conditions.

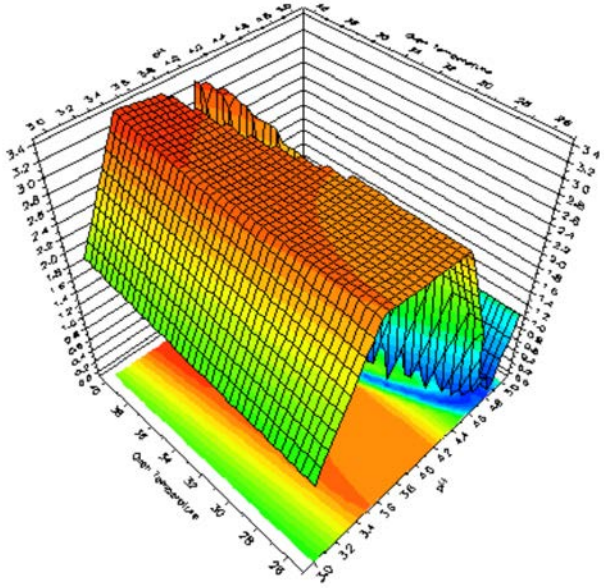
Contour Graph



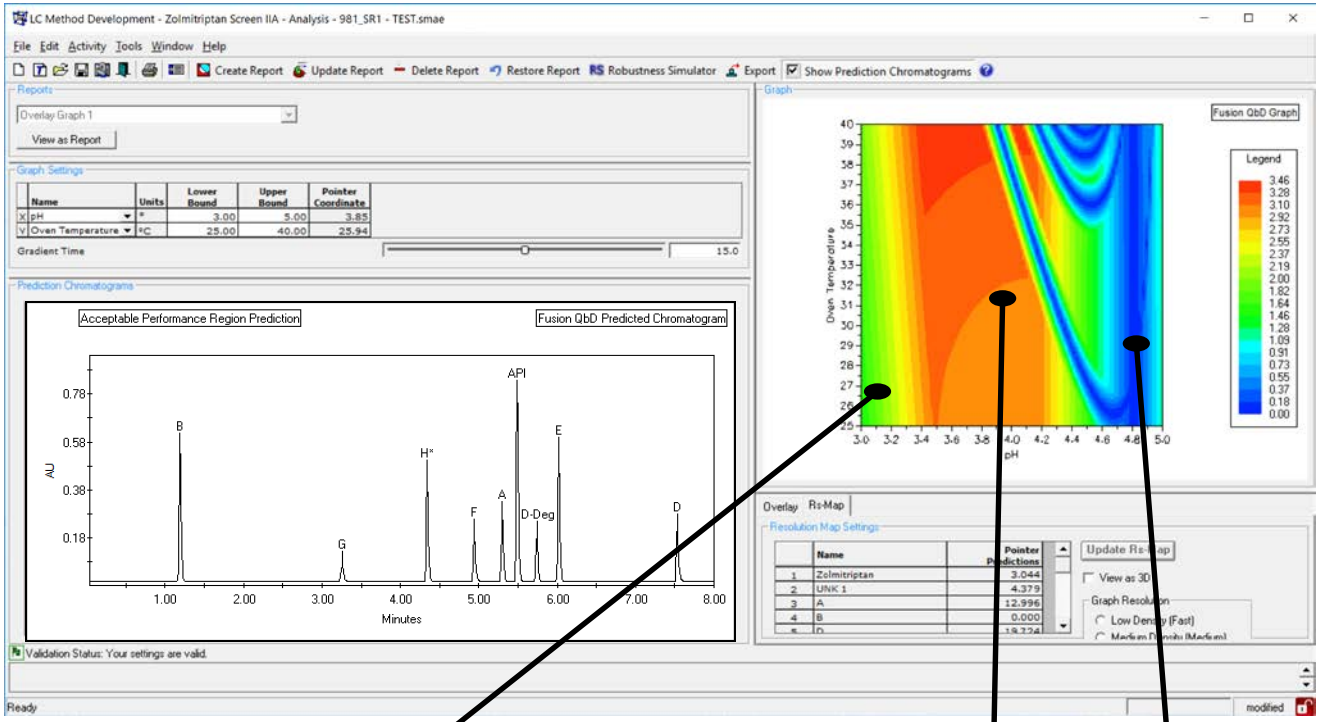
Overlay Graph



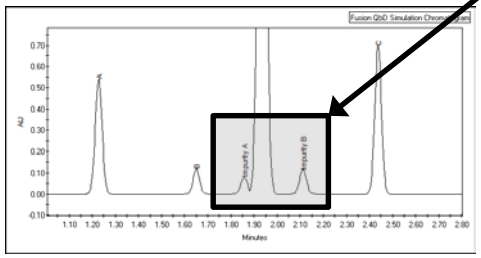
Response Surface Graph



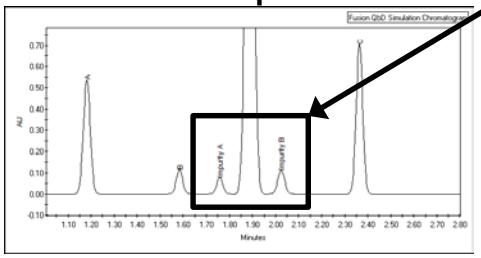
Rs-Map Response



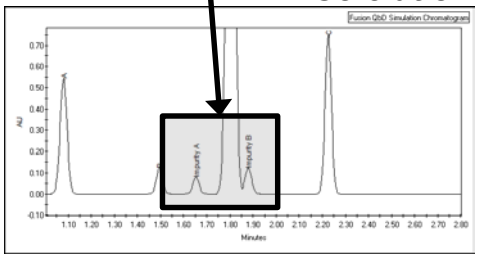
Co-elution



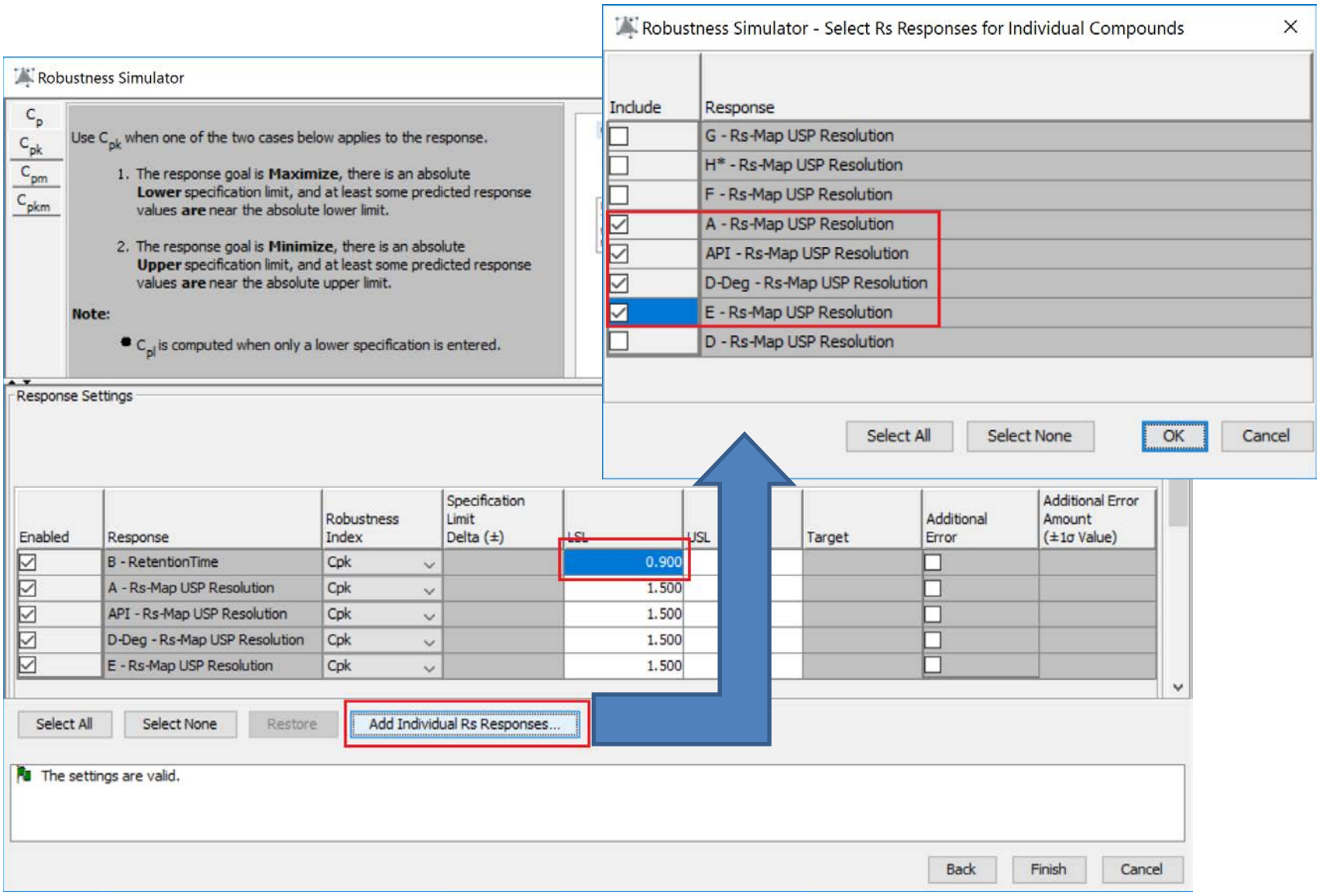
Robust Separation



Co-elution



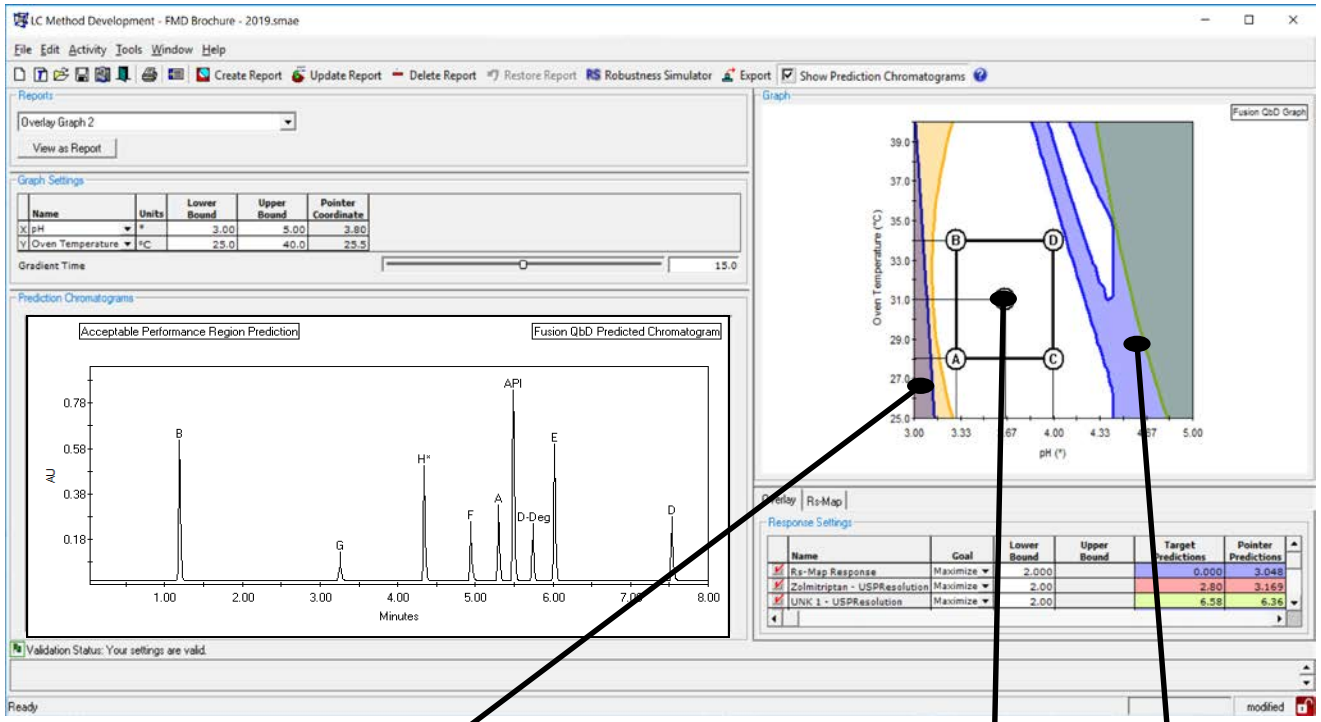
Robust Method Optimization – Robustness Modeling Throughout MODR

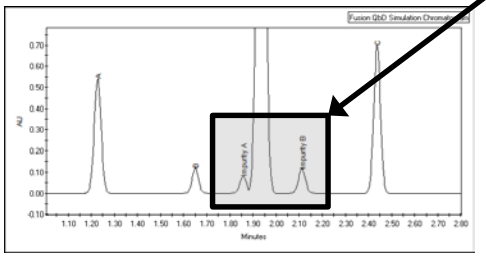


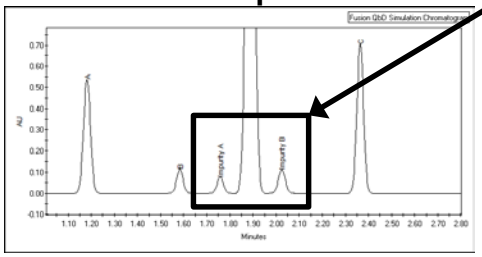
Robustness is calculated for each key performance metric.

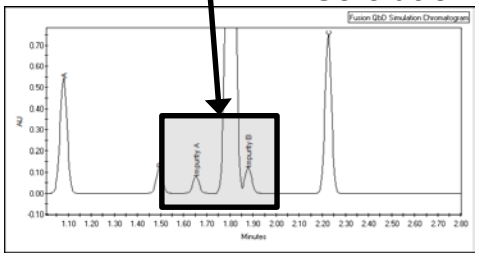
Robust Method Optimization – Robustness Modeled Throughout MODR

- Mean Performance and Robustness Throughout MODR.
- Include Performance Requirements for Critical Peaks and Peak Pairs.









Presentation Outline

1. Introduction to the Fusion QbD® Software Platform
    a. QbD Method Development Experiment Automation
    b. Cross-platform Data Integrity

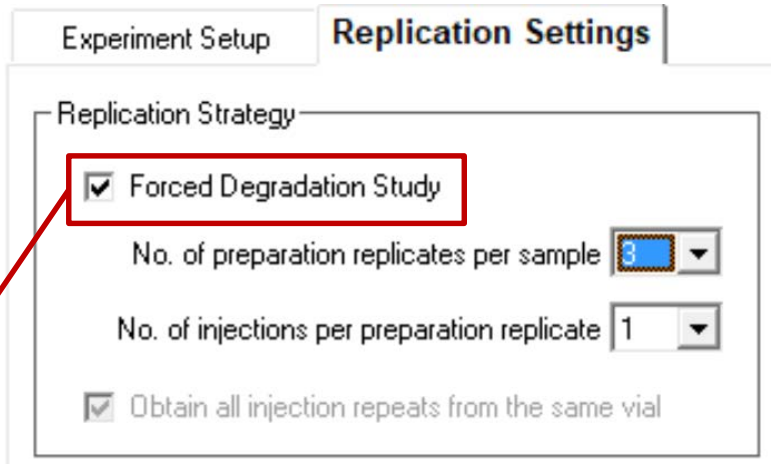
1. PeakTracker – UV & MS Spectra Based Peak Tracking
    a. Data Integration for Automated Modeling
    b. Tracking Automation

2. Forced Degradation Study Automation
    a. Peak Tracking in Forced Degradation Studies
    b. Composite Chromatogram Modeling & Visualization

S-Matrix®

Fusion QbD – *Forced Degradation Studies*

Fusion QbD enables users to set up an experiment execution protocol in which each experiment run will be repeated according to user-specified Replication Strategy which can be any combination of Sample Preparation and/or Injection replicates – with the replicates taken from the same vial or assigned different vials.



S-Matrix has now created a new "Forced Degradation Study" mode to support experiments in which the different Sample Preparation replicates represent different degradation paths such as photo degradation, acid degradation, and peroxide degradation. This activates an entirely new technology which aggregates peak data from the replicates for each run into a "Composite Chromatogram" data set for the run to be used in robust method optimization and prediction chromatogram visualization.

S-Matrix®

Fusion QbD – Forced Degradation Study (FDS) Automation

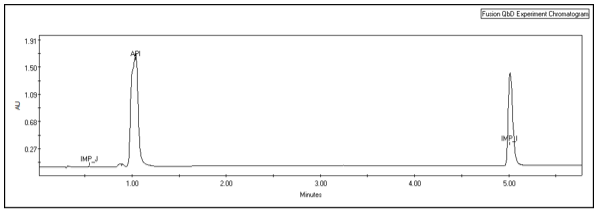
Forced Degradation Studies – Full Automation Support

Experiment Design Matrix

Run No.	Pump Flow Rate (mL/min)	Gradient Time (min)	Oven Temperature (°C)	pH
Condition Column - 1	0.400	2.0	35.0	3.20
1.a	0.300	5.0	35.0	3.20
1.b	0.300	5.0	35.0	3.20
1.c	0.300	5.0	35.0	3.20
2.a	0.500	5.0	35.0	3.20
2.b	0.500	5.0	35.0	3.20
2.c	0.500	5.0	35.0	3.20
3.a	0.300	15.0	35.0	3.20
3.b	0.300	15.0	35.0	3.20
3.c	0.300	15.0	35.0	3.20

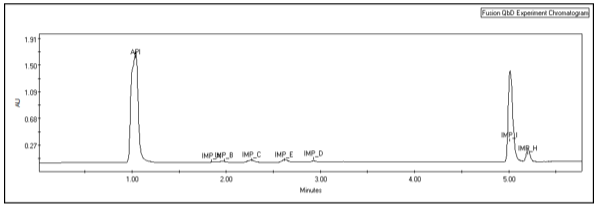
Vial a

Photo Degraded Sample (Vial a)



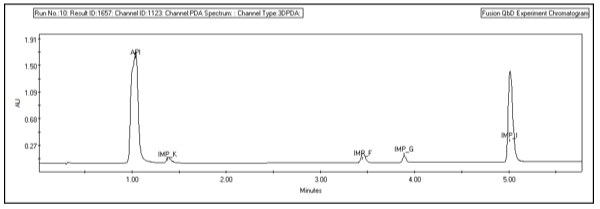
Vial b

Acid Degraded Sample (Vial b)



Vial c

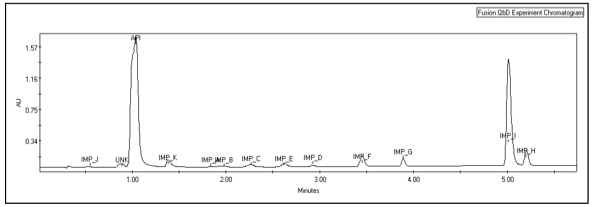
Peroxide Degraded Sample (Vial c)



Full Automation Support

- ✓ Each experiment run is replicated for each degradation path sample.
- ✓ Each peak is tracked in each degradation path sample chromatogram.
- ✓ All peaks from all degradation path sample chromatograms are aggregated into one chromatogram for the run.

Composite Chromatogram – Run 1



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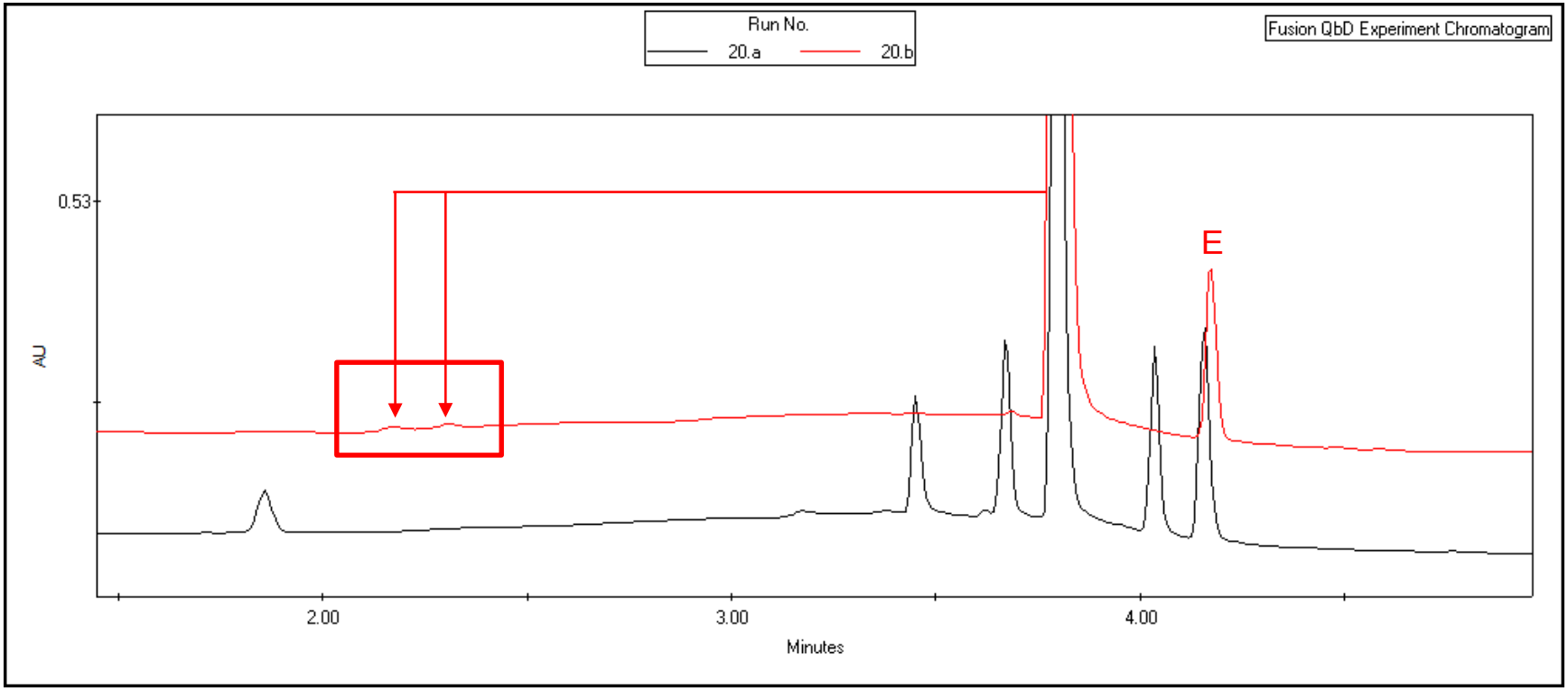
Forced Degradation Study (FDS) – 2 New Degradants Discovered

Black Trace – Undegraded Sample (Note – API material contained Related Compound “E”)

Red Trace – Peroxide Degraded API (generated 2 new degradants)

Chromatogram formatting – zoom, stack, offset, and annotate to get best presentation view.



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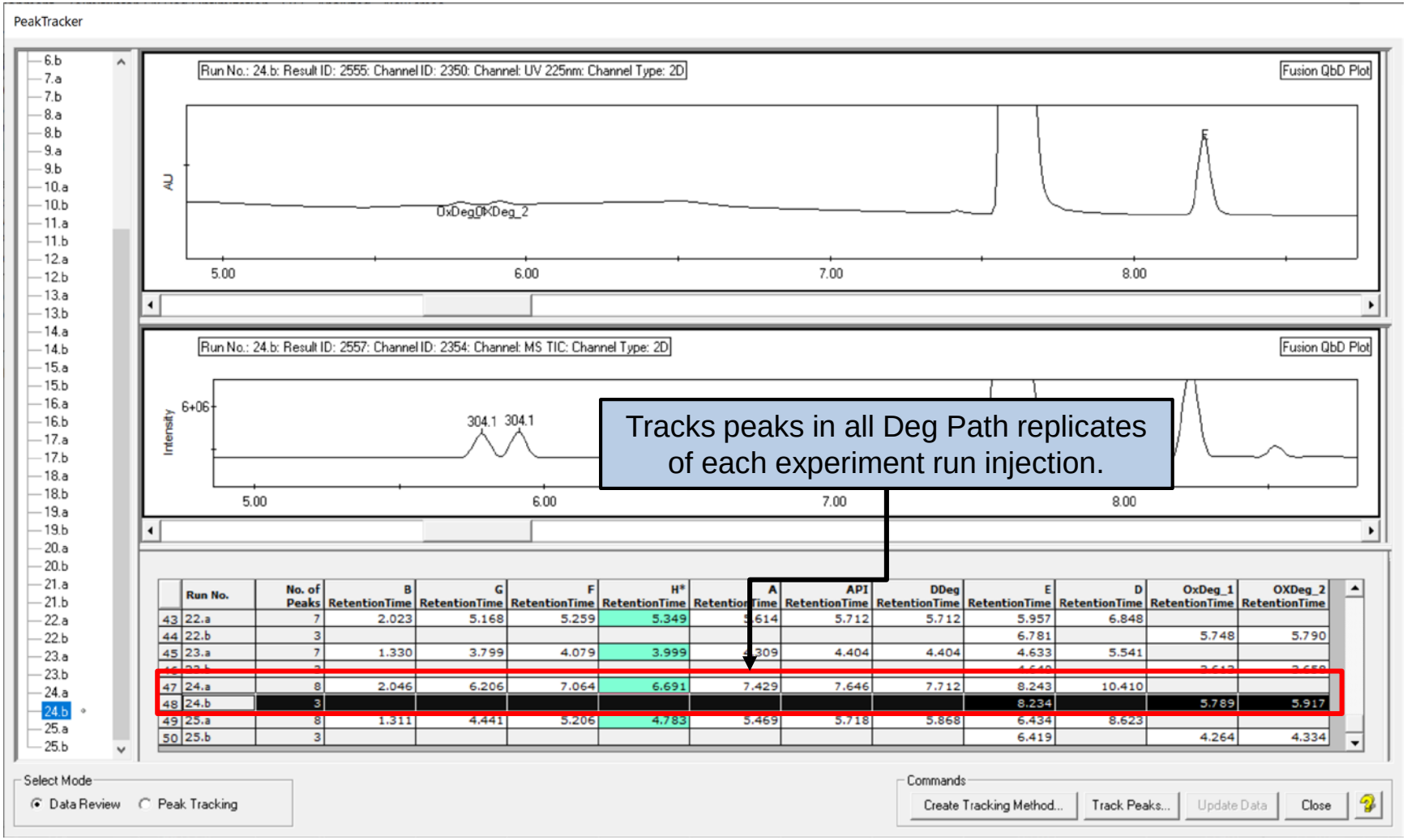
PeakTracker – Instant Preview of Tracking Results



	Run No.	No. of Peaks	B RetentionTime	G RetentionTime	F RetentionTime	H* RetentionTime	A RetentionTime	API RetentionTime	DDeg RetentionTime	E RetentionTime	D RetentionTime	OxDeg_1 RetentionTime	OXDeg_2 RetentionTime
43	22.a	7	2.023	5.168	5.259	5.349	5.614	5.712	5.712	5.957	6.848		
44	22.b	3								6.781		5.748	5.790
45	23.a	7	1.330	3.799	4.079	3.999	4.309	4.404	4.404	4.633	5.541		
47	24.a	8	2.046	6.206	7.064	6.691	7.429	7.646	7.712	8.243	10.410		
48	24.b	3								8.234		5.789	5.917
49	25.a	8	1.311	4.441	5.206	4.783	5.469	5.718	5.868	6.434	8.623		
50	25.b	3								6.419		4.264	4.334

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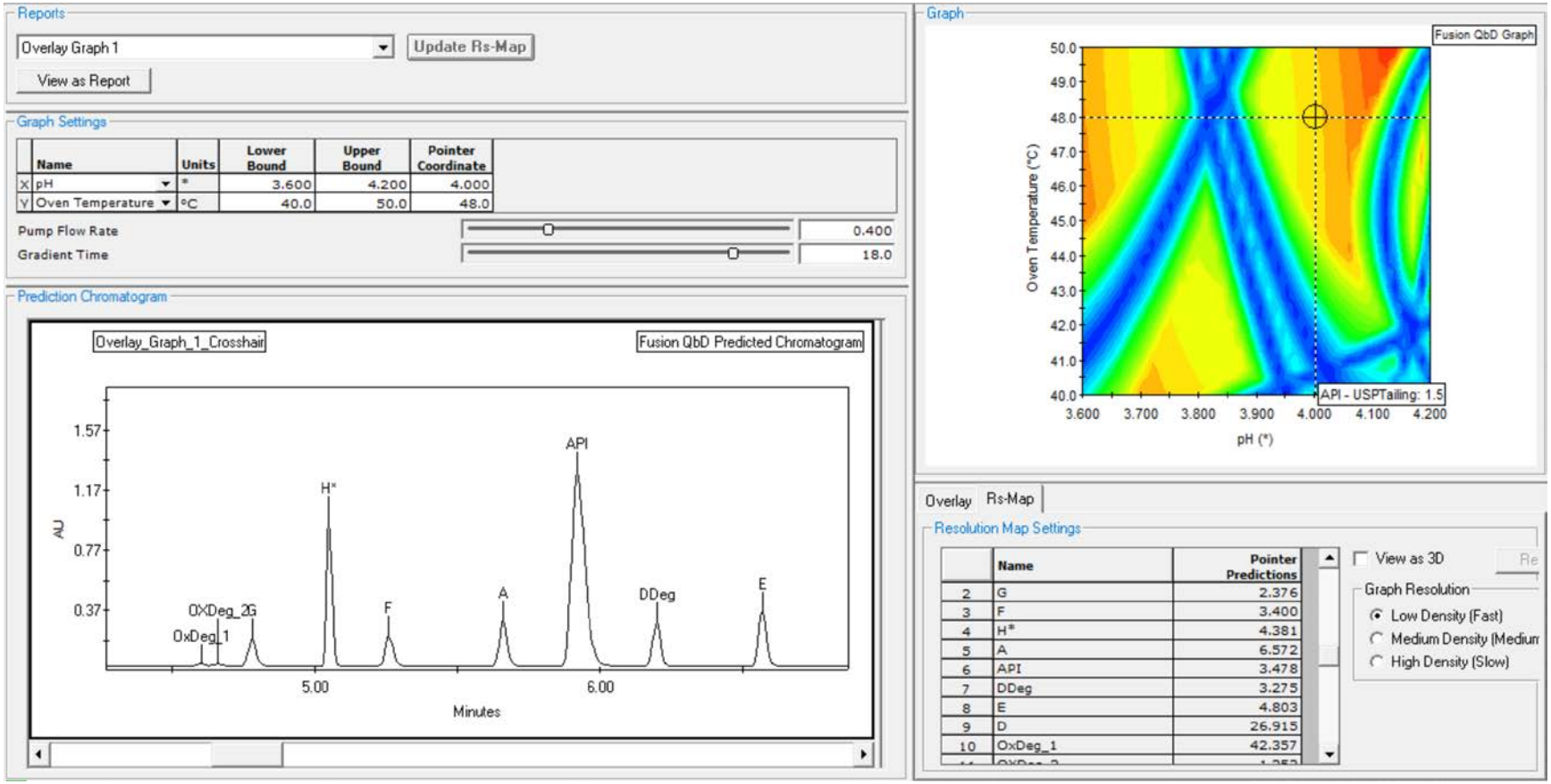
S-Matrix®

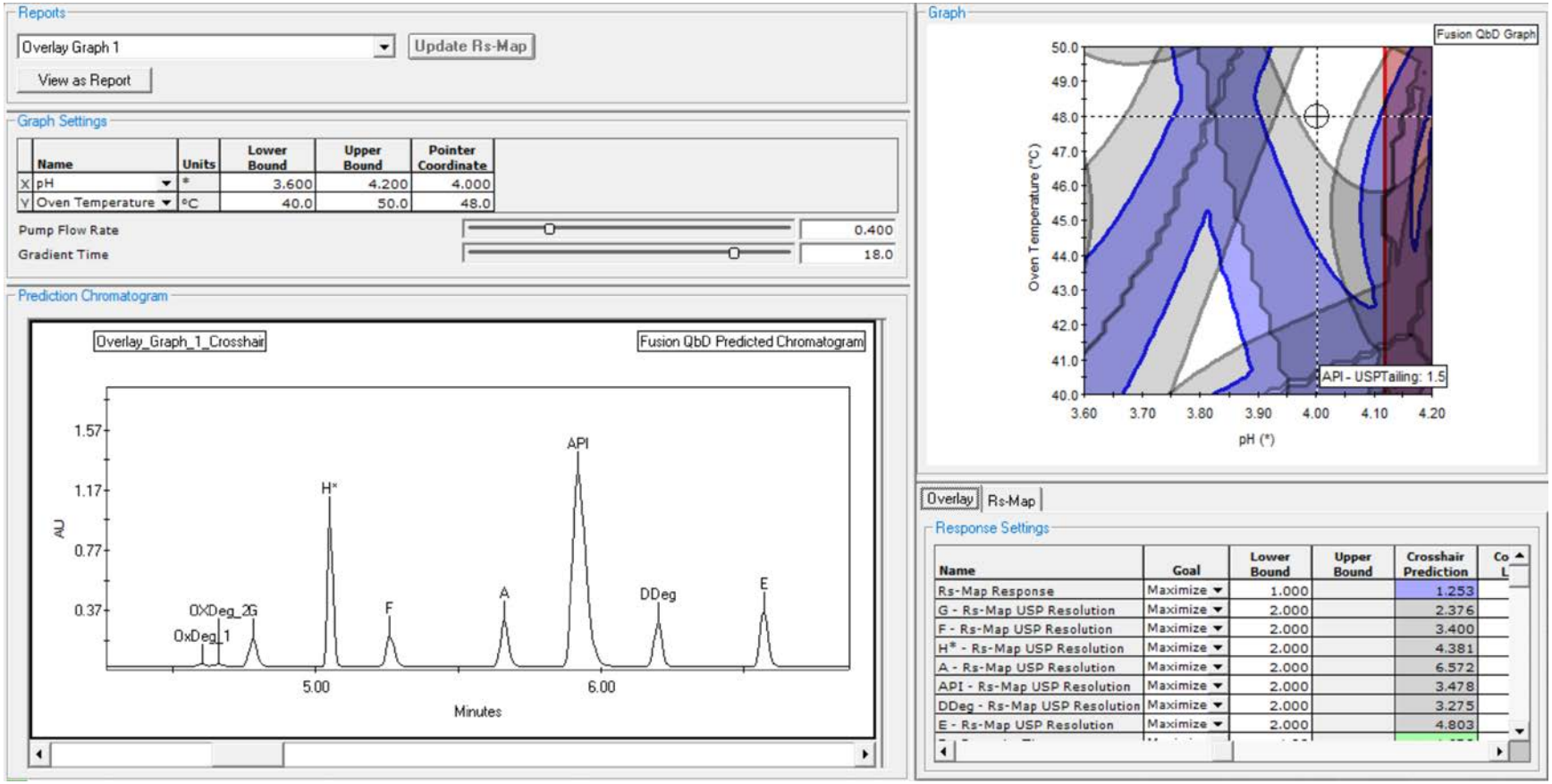
FDS – New Degradants Discovered

Fusion QbD automatically creates a data set of composite chromatograms for peak tracking, modeling, and simulation.



New Degradants Identified – Forced Degradation Study (FDS)

Overlay lets you include mean performance and robustness for any critical performance characteristic across the MODR.



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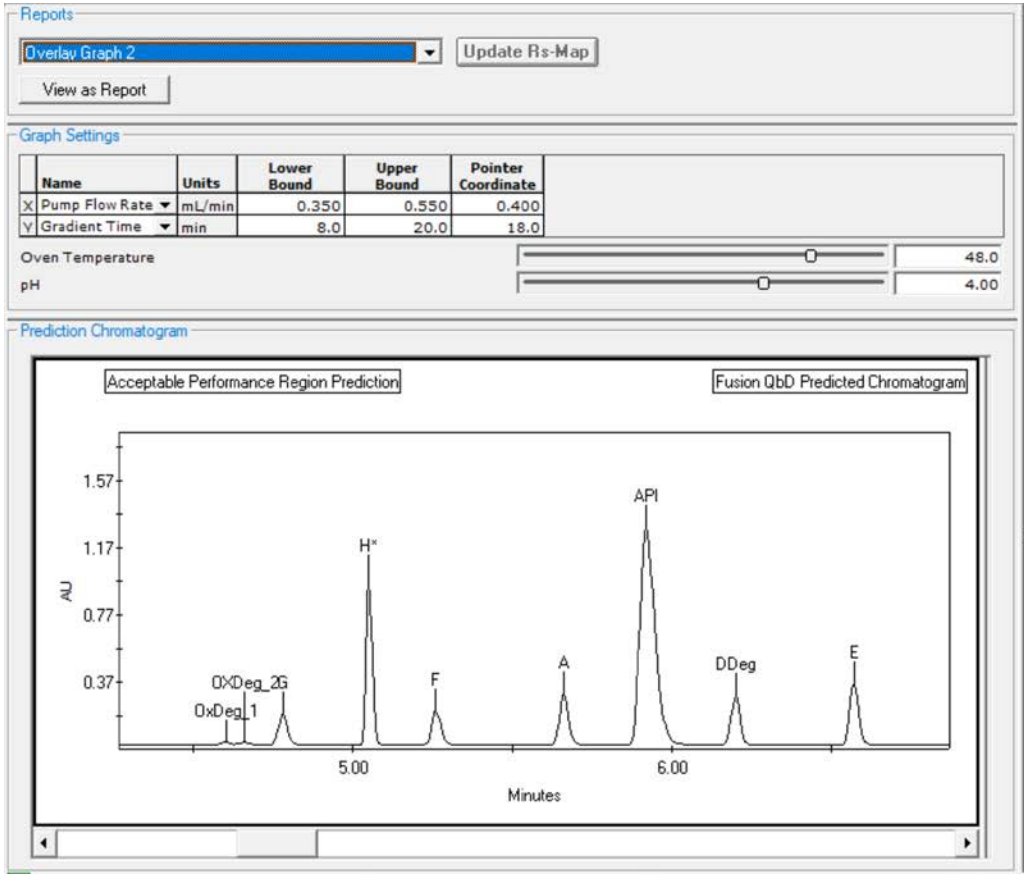
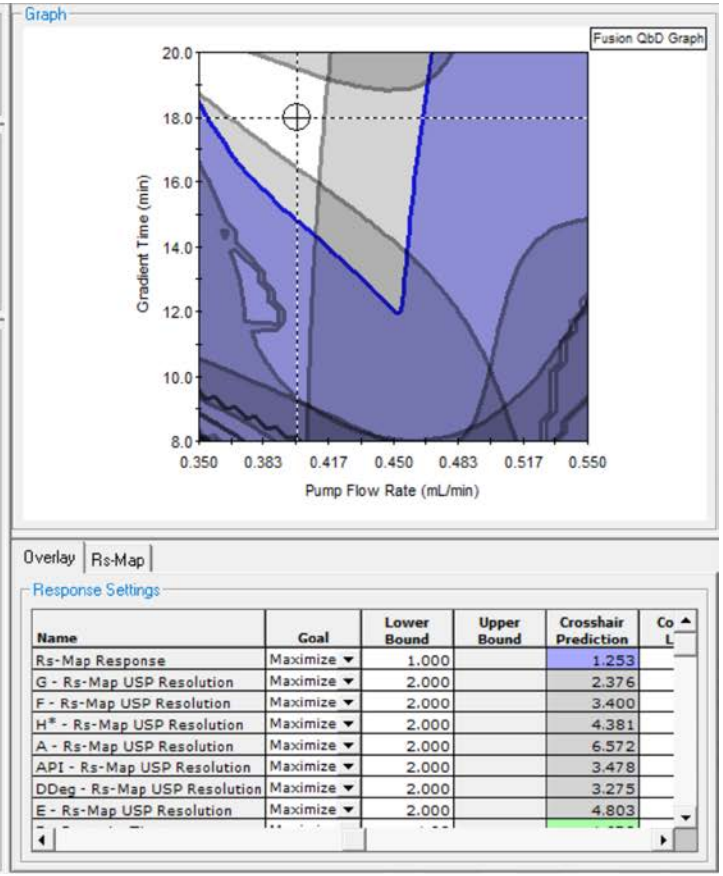
New Degradants Identified – Forced Degradation Study (FDS)

Switch graphed and non-graphed variables – find most robust method overall.





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Fusion QbD – Completely Aligned with ICH Q8(R2)

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.)

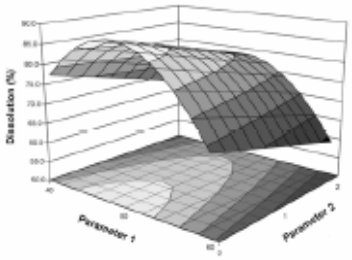

Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

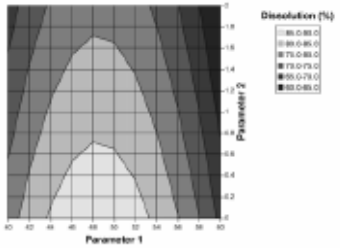

Figure 1b: Contour plot of dissolution from example 1a.

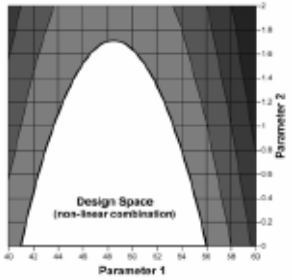

Figure 1c: Design space for granulation parameters, defined by a nonlinear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

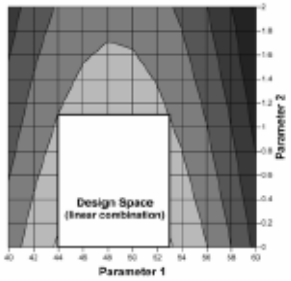

Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

Fusion QbD

Name: Administrator
Company: S-Matrix
Project: Project 1
Date: 08 APR 2018 18:38:09 PDT [UTC-07:00]

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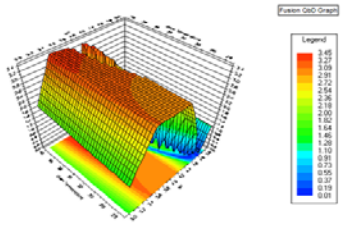
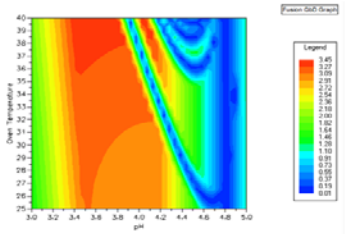
Final Design Space + PARs

Rs-Map Response Surface Graph

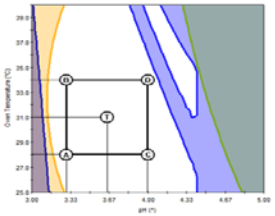


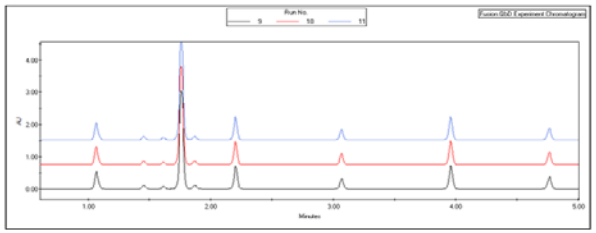
Rs-Map Response Contour Graph



Response	Performance Goal	Color
API – USP Resolution	> 2.00	Red
API – USP Tailing	> 2.00	Blue
Impurity A – USP Resolution	> 2.00	Blue
Impurity B – USP Resolution	> 2.00	Green
API – USP Resolution - Cpk	> 1.33	Orange
Impurity A – USP Resolution - Cpk	> 1.33	Teal
Impurity B – USP Resolution - Cpk	> 1.33	Purple
API – USP Tailing - Cpm	> 1.33	Sky

Multi-Response Overlay with Design Space





1 of 3

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END

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