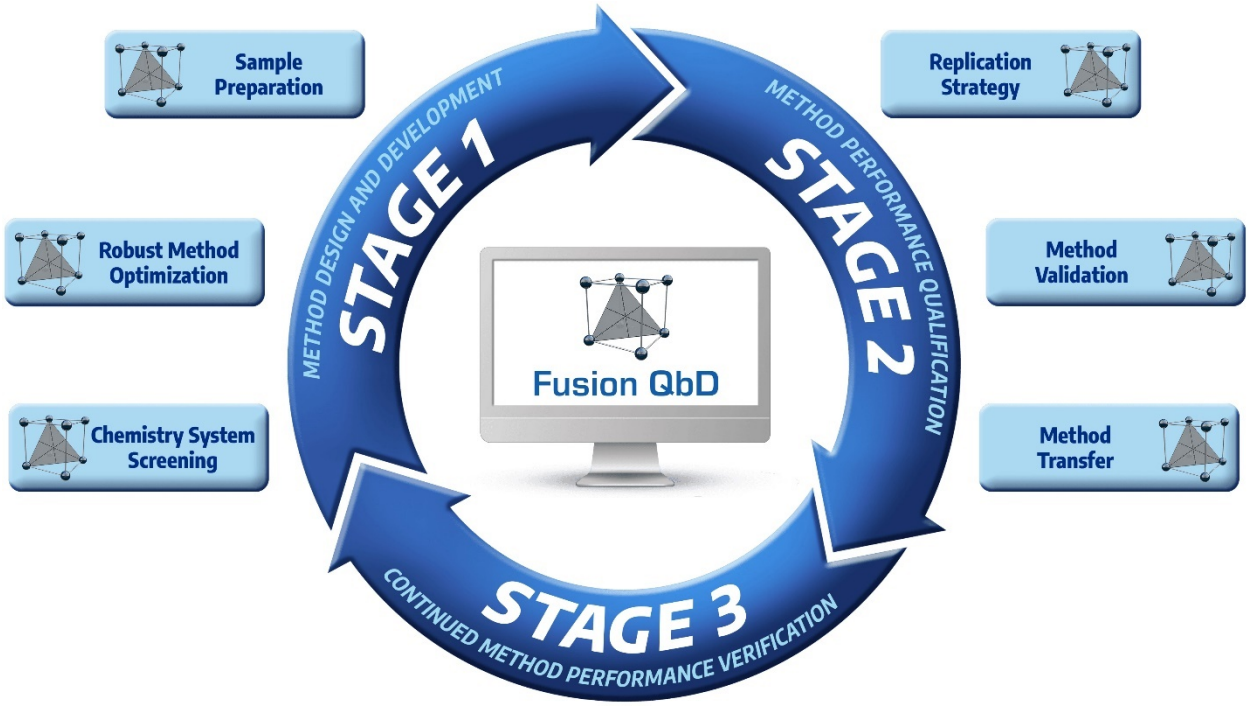
FUSION QBD

QUALITY BY DESIGN SOFTWARE

NEW FEATURES – VERSION 9.9.2



S–Matrix Corporation
www.smatrix.com

Contents

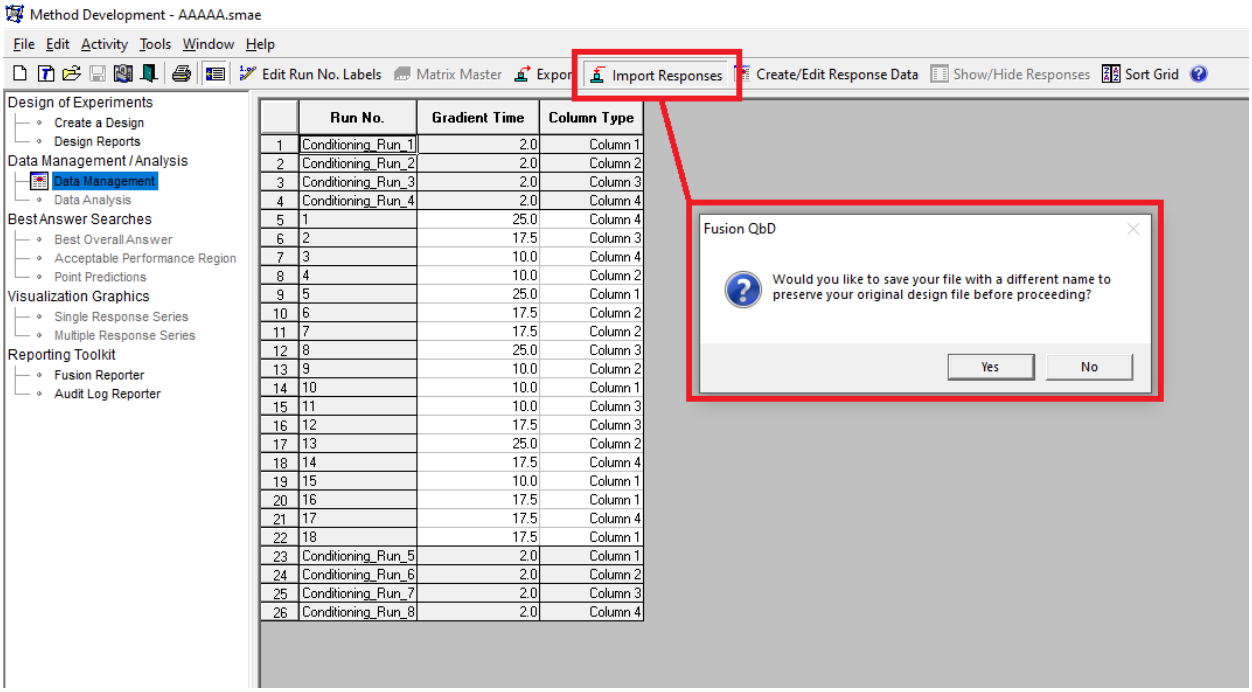
New Features – General – 9.9.2

Instrument Drivers/Configurations – Increased Data Integrity

Fusion Administrator application (FA) instrument and device drivers, and instrument configurations for Named Instrument Systems generated in Fusion Administrator, are now integrated within an encrypted FA database for greater security and integrity. This data security enhancement eliminates the possibility of driver/configuration corruption and facilitates the FA database Backup and Restore operations.

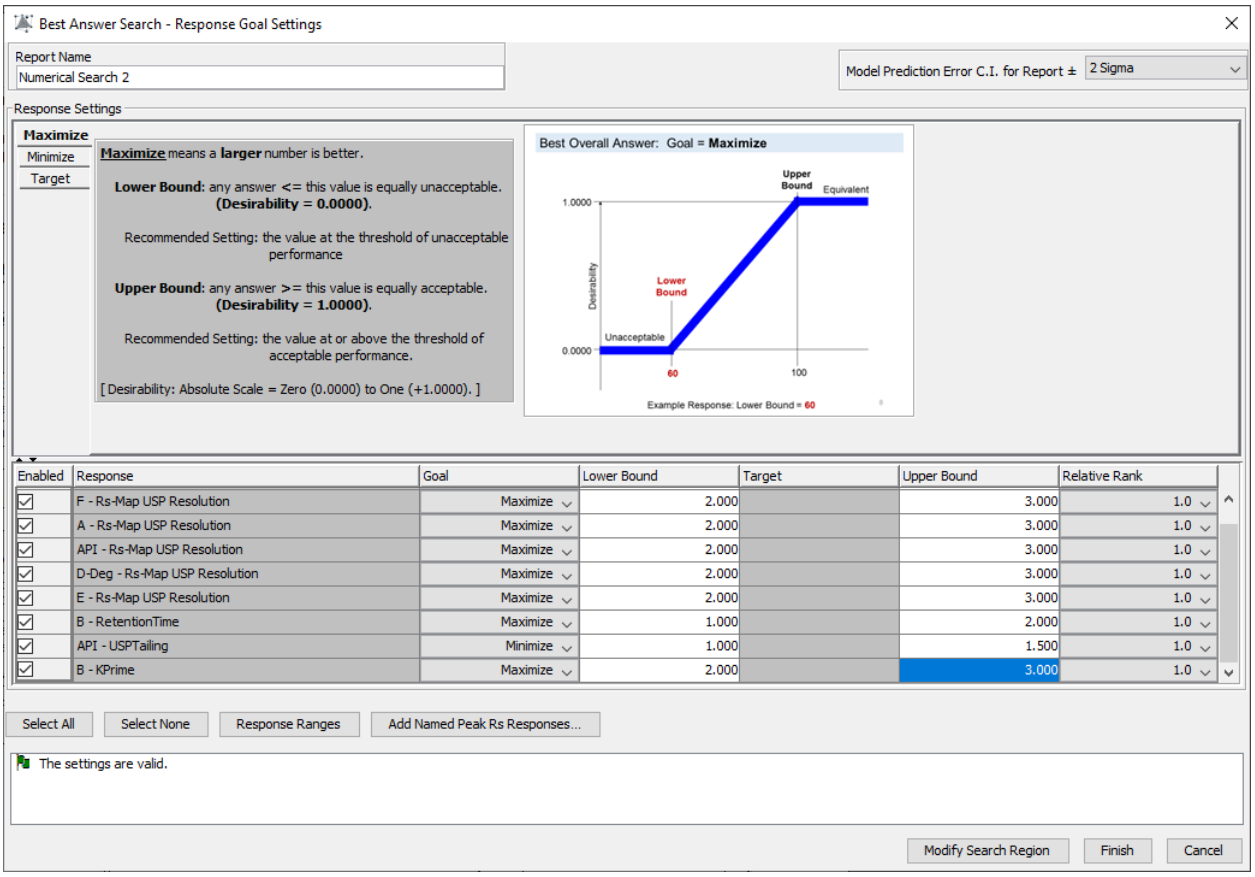
Response Data Import – Rename File Support

Initiating the Import Responses operation now prompts the user to rename the file prior to proceeding with data import. This enables the user to preserve the original design file in case the user wishes to start over after importing results, analyzing data, etc. S-Matrix implemented this feature in response to a large number of support inquiries over the years in which the user wanted to know how to return to a "clean slate" starting point but no longer had access to their original design file.



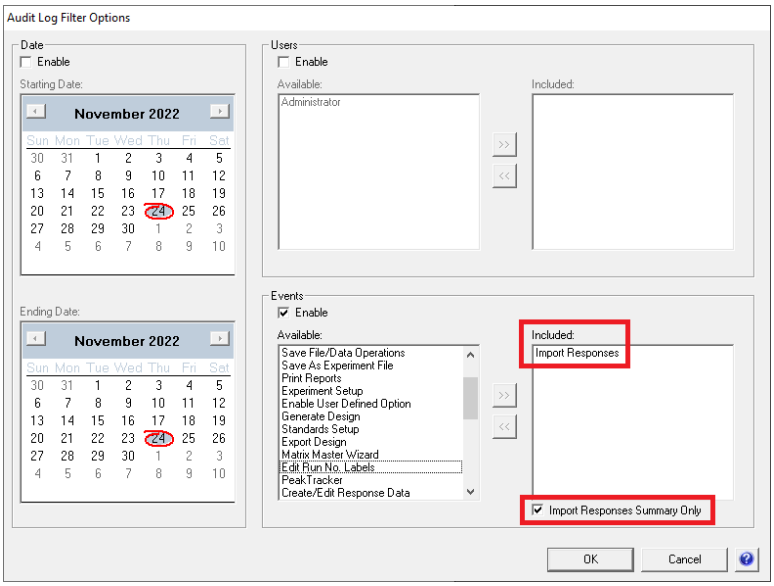
Best Overall Answer Math Engine – Efficiency Enhancement

The mathematics underlying the Best Overall Answer (BOA) search routine has been upgraded to accelerate the search operation. A more efficient integrated search operation has now replaced the three-search-cycle operation in previous releases. As a result, users will now typically experience a 3x–5-x increase in speed associated with each search. For example, a search which previously took three minutes should now take a maximum of one minute.



Audit Log Report – Import Responses Summary

Report generation can require a significant amount of time in cases in which the user has imported a large amount of response data. This is especially true in cases in which the imported results include MS spectra data imported to support PeakTracker. Therefore, as shown in the top image below, the Audit Log Report wizard now includes an “Import Responses Summary Only” checkbox option which is enabled when the user includes the Import Responses auditable operation. When the checkbox is checked, the Audit Log Report will only contain the metadata associated with the Import Responses operation and not all the imported response data.



Audit Log

20 JUN 2021 10:13:51 PDT [UTC-07:00] - Administrator

Event Type: Import Responses

Import Response Settings

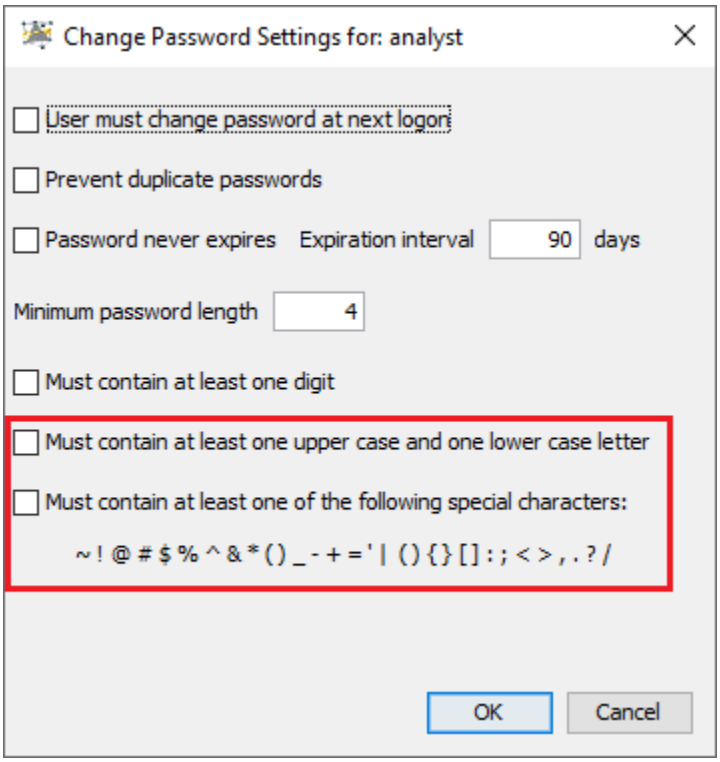
Setting	Value
Target CDS	EMPOWER
Empower Version	Empower 3 Software Build 3471 SPs Installed: Service Release 3 DB ID: 2484307300
Empower Database	(local)
Empower User	system
Project Name	RD2 - Optimization - 9_9_0
Result Set(ID)	RD2 Optimization (9001)
Processed Channel	PDA Ch1 225nm@4.8nm, Time offset by 0.020 mins.
Activate PeakTracker	Checked
Raw PDA Channel	Unchecked
Raw MS Channel	QDa Positive Scan
MS Time Offset(min)	0.02
MS Intensity Threshold	100000
Processed MS Channel	QDa Positive Scan MS TIC, Smoothed by 59 point Savitzky-Golay Filter. (QDa Positive(+) Scan (100.00-1250.00)Da, Centroid, CV=15)
Track Non-absorbing Peaks	Checked
Auto-imported Response(s)	Height, RetentionTime, WidthAt50Pct, USPTailing, WidthAtTangentUSPResolution, Area
Import Chromatogram Trace Data	Checked
Import Prediction Chromatogram Data	Checked
Total Import Time	00:06:42
Locale	English (United States)

User Access Passwords – Complexity Enhancements

The following password requirement setting options have been added to the current requirement that the password "Must contain at least one digit" to enhance password complexity:

- Must contain at least one upper case and one lower case letter
- Must contain at least one of the following special characters:

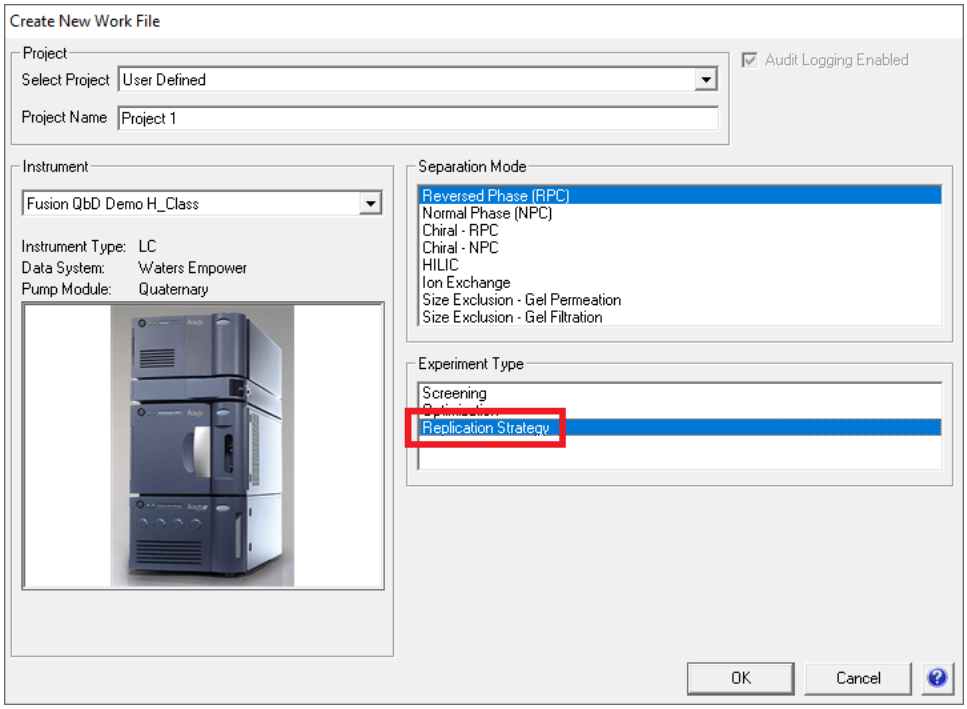
  ~ ! @ # $ % ^ & * ( ) _ - + = ` | \ ( ) { } [ ] : ; < > , . ? /



Replication Strategy Experiment

Replication Strategy is described in the new ICH Q14 and USP <1220> guidances on Analytical Procedure Lifecycle Management (APLM). The optimal **Replication Strategy** for the method is determined during development and becomes part of the final method SOP.

The Fusion Method Development application module (FMD) now includes a **Replication Strategy** experiment. A **Replication Strategy** is a combination of Sample Preparation and Sample Injection repeats (***preparation x injection***). The result obtained from averaging these repeated measures is the **Reportable Value** (or Reportable Result) for each critical method performance characteristic.

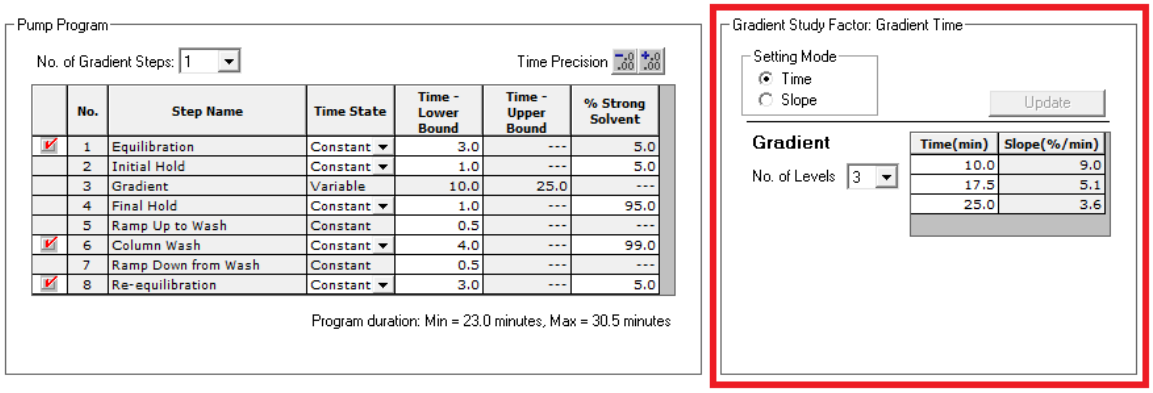


The **Replication Strategy** experiment in FMD has the following capabilities:

- Quantifies the relative contribution of Sample Preparation error and Sample Injection error to the Total Analytical Error (TAE), which includes both accuracy (bias) and precision limits.
- Incorporates the USP <1210> Interval metric calculations which combine accuracy and precision into a single criterion which can be used to simultaneously evaluate both accuracy and precision for each measured critical method performance characteristic.
- Determines the TAE and the specified USP <1210> Interval metric associated with all replication strategies from 1x1 to 10x10.
- Identifies all replication strategies which generate reportable values meeting the method precision requirement specified in your Analytical Target Profile (ATP) for each critical method performance characteristic.

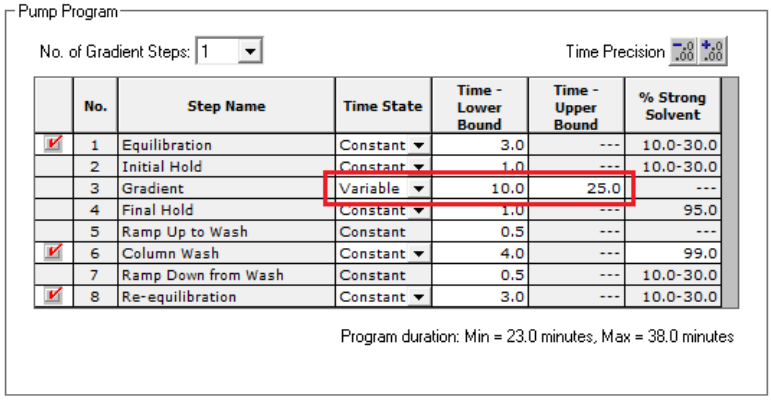
Gradient Time Settings Control

The Experiment Setup activity within FMD now has a flexible settings control for the Gradient Time study factor. Users can now specify the exact number of levels which should be included in the experiment design. Users can also enter the target levels as either slope or time. The control will automatically convert user-entered slope levels as the corresponding time levels which will be used in design generation.

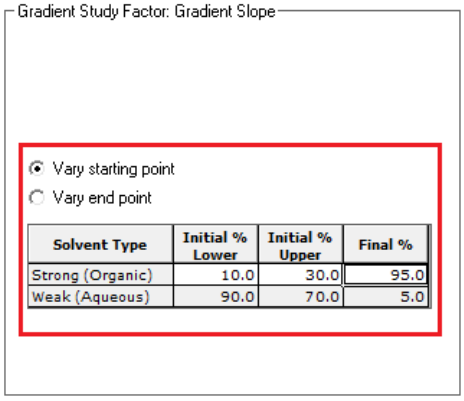


Combining Gradient Time and Gradient Slope

As shown in the images below, Fusion QbD now enables the user to create method development and robustness studies which include both Gradient Time and Gradient Slope study factors. In the case of the Gradient Slope study factor, the user can specify varying the starting point or the endpoint % strong solvent. Studies have shown that these factors can have strong interaction effects on shape and selectivity. Therefore, in many cases combining them in a study can provide important method development results.

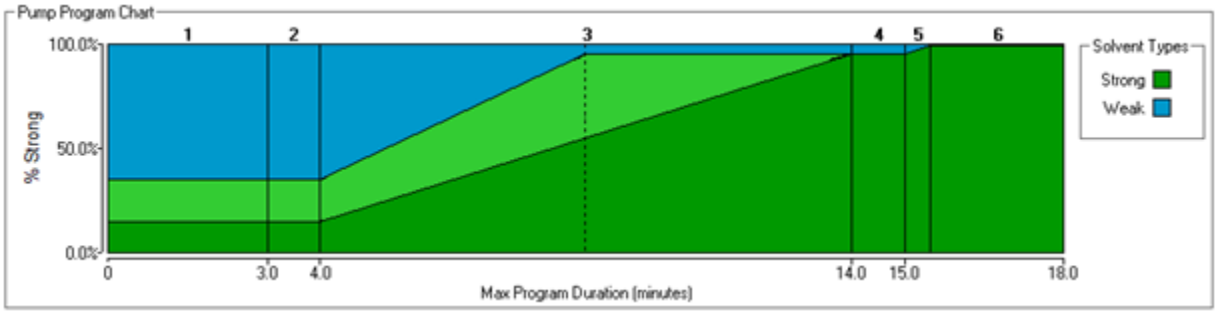


	No.	Step Name	Time State	Time - Lower Bound	Time - Upper Bound	% Strong Solvent
☑	1	Equilibration	Constant	3.0	---	10.0-30.0
	2	Initial Hold	Constant	1.0	---	10.0-30.0
	3	Gradient	Variable	10.0	25.0	---
	4	Final Hold	Constant	1.0	---	95.0
	5	Ramp Up to Wash	Constant	0.5	---	---
☑	6	Column Wash	Constant	4.0	---	99.0
	7	Ramp Down from Wash	Constant	0.5	---	10.0-30.0
☑	8	Re-equilibration	Constant	3.0	---	10.0-30.0

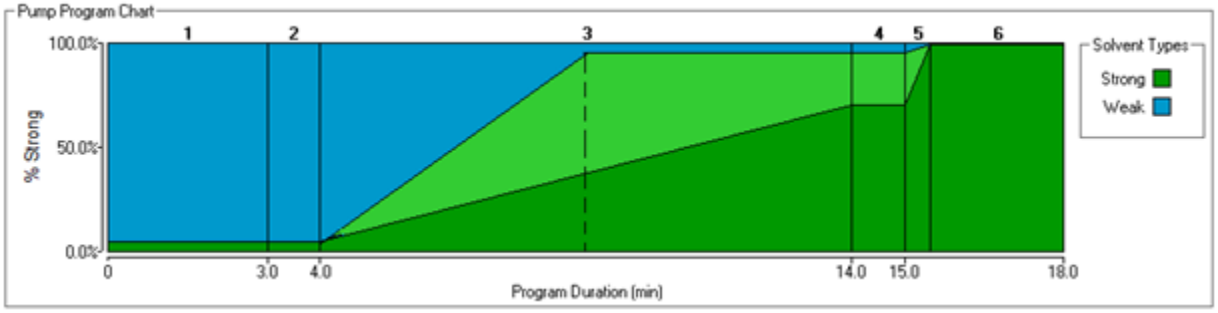


Solvent Type	Initial % Lower	Initial % Upper	Final %
Strong (Organic)	10.0	30.0	95.0
Weak (Aqueous)	90.0	70.0	5.0

Gradient Time + Gradient Slope – Vary Starting Point % Strong Solvent



Gradient Time + Gradient Slope – Vary End Point % Strong Solvent



PeakTracker – New Features

Global Tracking Method Optimization

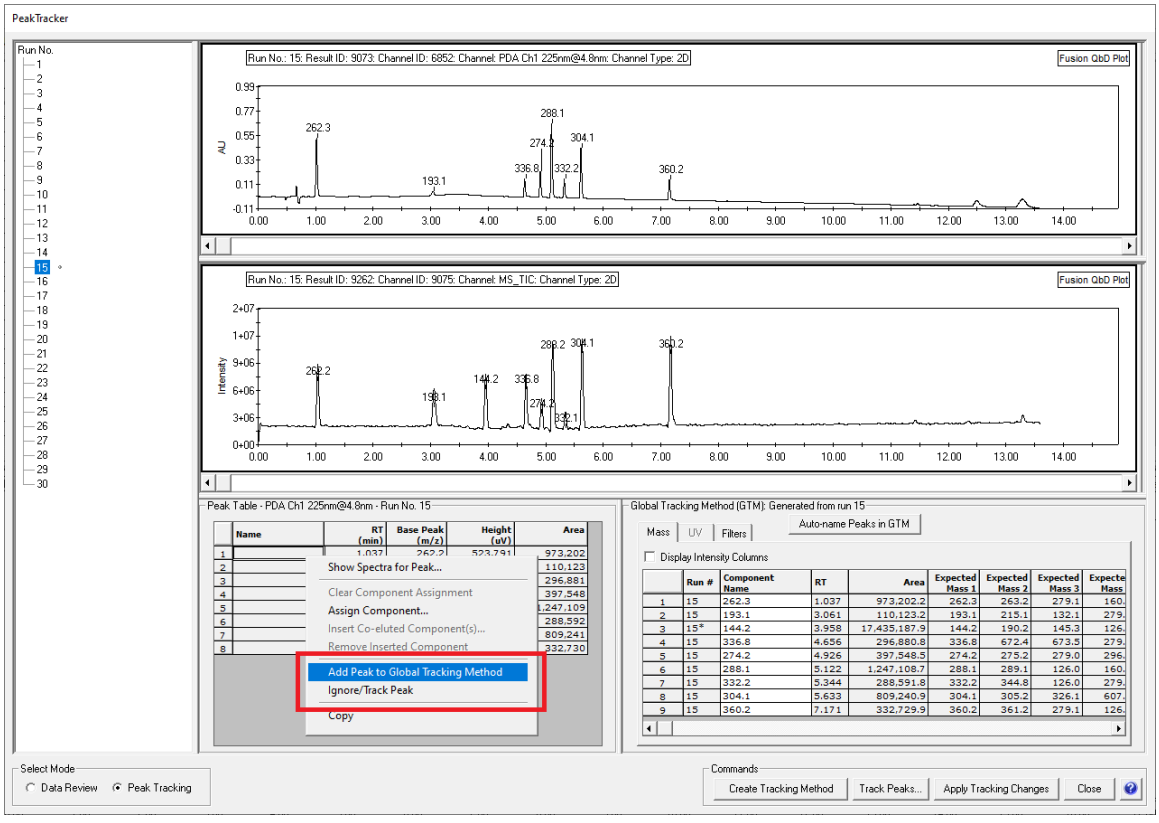
Two new simple operations have been added to the PeakTracker popup menu to optimize the Global Tracking Method (GTM) used in peak tracking:

- Add Peak to Global Tracking Method

  This option is used when a peak is not visible in the chromatogram on which the GTM is based – for example due to peak co-elution, but which is at least partially separated in another run, and so visible in the run. In this case users can select this option to add the peak to the GTM. This option assures that all sample peaks are included in the GTM prior to tracking.

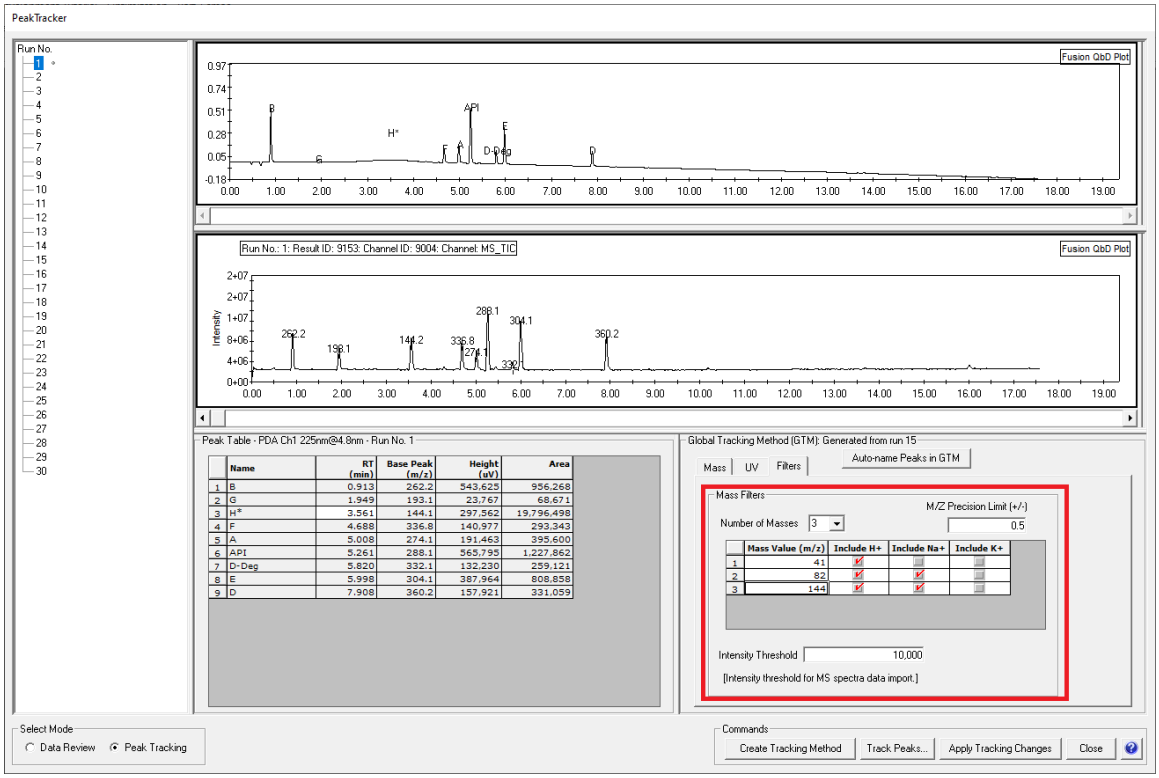
- Ignore/Track Peak

  This option is used when the chromatogram for the run on which the GTM is based contains an integrated peak which the user does not want to track. In this case the user can exclude the peak from the GTM prior to tracking. Alternatively, if a peak was incorrectly excluded, then the option can toggle to include the previously excluded peak, in which case the peak will again be present in the GTM.



m/z Filtering for Baseline & Interfering Compounds

Filters can now be added to PeakTracker to eliminate specific m/z values from the imported mass spectra data used for peak tracking. Filter values can be entered for extraneous (background noise) compounds such as mobile phase solvents and their associated adducts which may compromise the mass spectra of compounds of interest, especially in the case of small peaks with low mass signal. The filters enable you to specify the expected compound mass and the possible presence of three common ions: H^+, Na^+, and K^+. PeakTracker will automatically eliminate these masses from the mass spectra data for the Global Tracking Method compounds prior to tracking.



Tracking Algorithm Enhancements

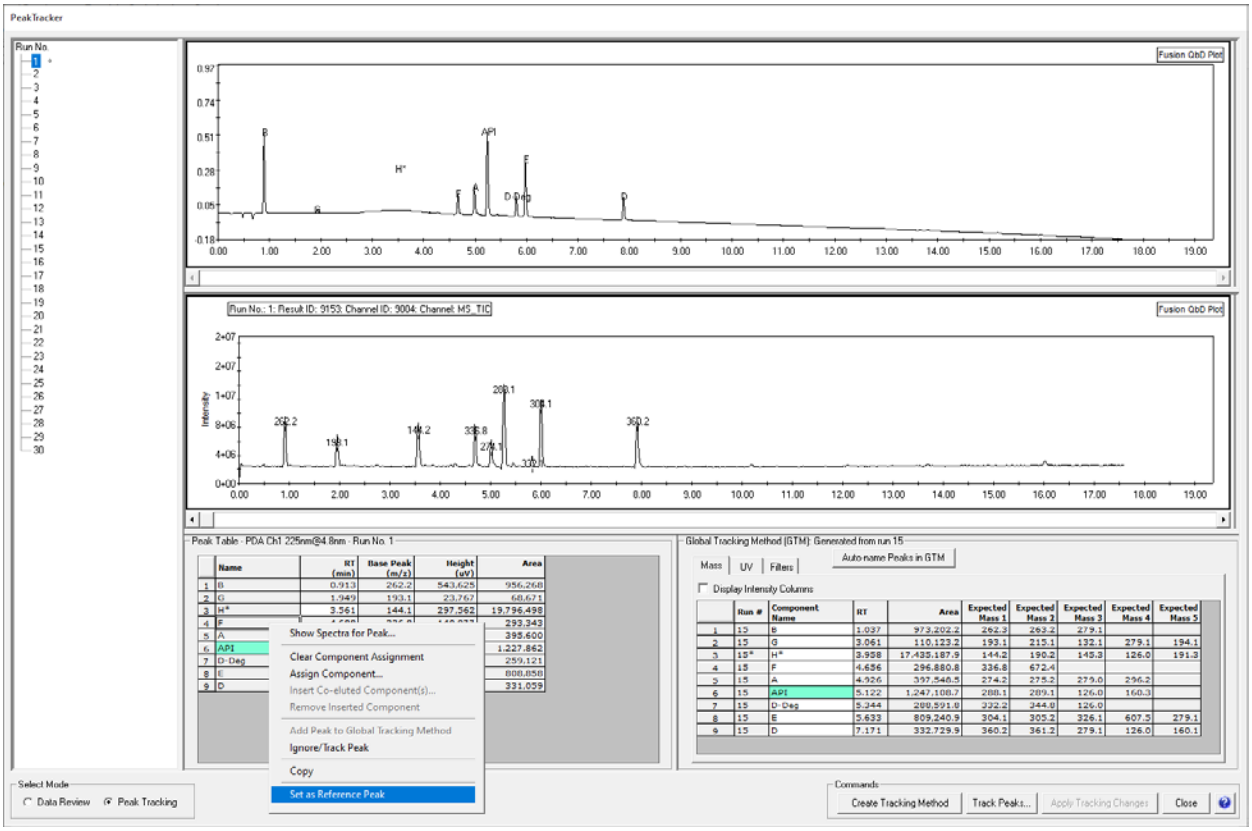
S-Matrix has developed powerful advancements to its peak tracking algorithms which support the following cases:

- Peak results data do not include MS spectra data.
- One or more sample compounds do not ionize.
- Forced Degradation Studies.
- Peptide Mapping studies.

Reference Peak Designation

In cases such as Peptide Mapping studies there is normally no single, large API peak present in the sample. In such cases it is best if the user can spike the sample with a ‘Reference Peak’ prior to running the experiment. The spiked peak should 1) be substantially larger than all other peaks, and 2) elute in a region of the chromatogram which results in it being always well separated from all other sample compounds. When this is not possible, PeakTracker now enables the user to define an alternate ‘Reference Peak’ to support corrections needed to the tracking for individual chromatograms.

As shown in the image below, the initial tracking operation has defined the API component as the ‘Reference Peak’ – as indicated by the blue background in the corresponding ‘Component Name’ cell within the Global Tracking Method (GTM) grid. However, a new “Set as Reference Peak” function has been added to the popup menu in the ‘Peak Table’ panel whenever a peak other than the current reference peak has the focus. This enables the user to easily designate another peak as the ‘Reference Peak’ and automatically retrack the peaks in the current run.

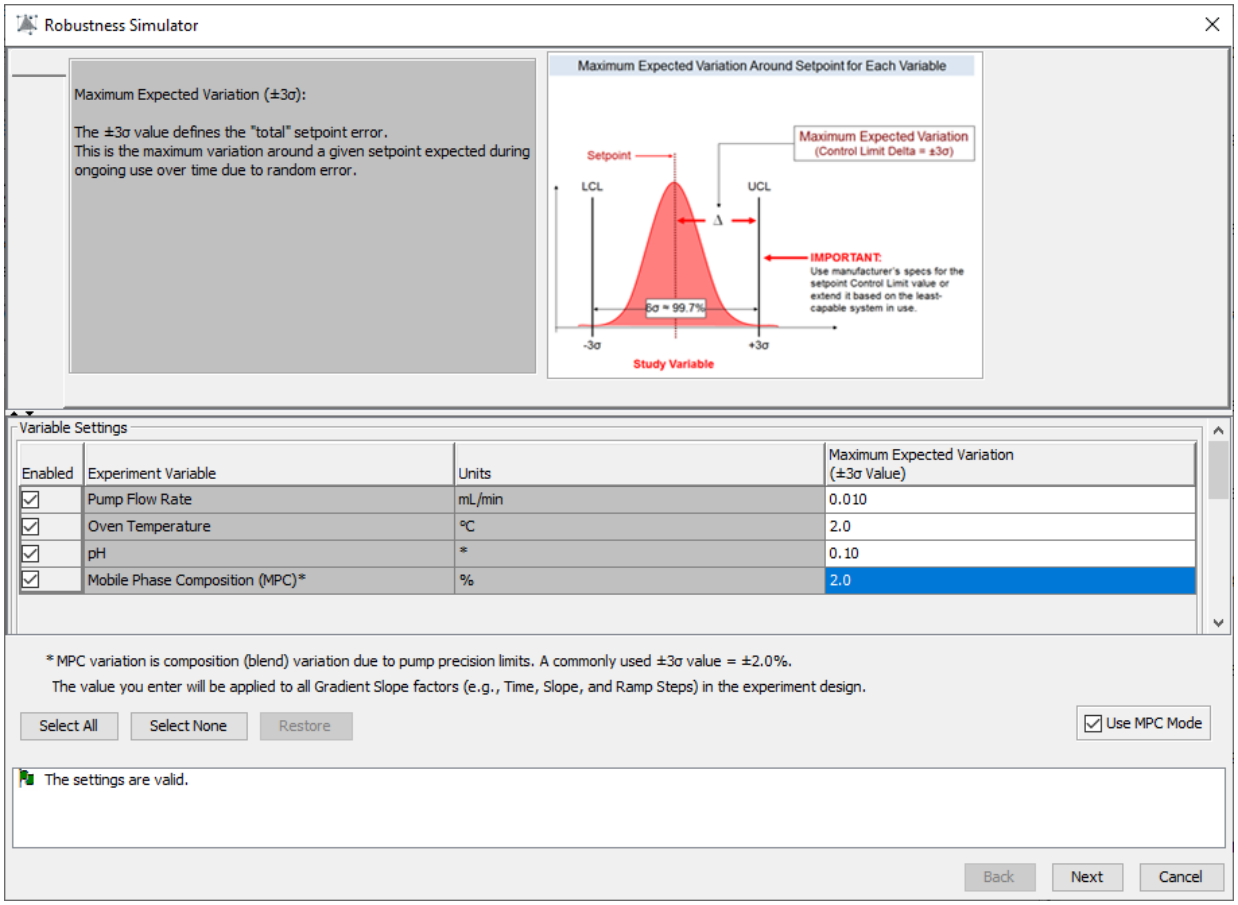


Robustness Simulator – New Features

Mobile Phase Composition (MPC) Variation

Gradient slope variation during method execution is an expression of moment-to-moment Mobile Phase Composition (MPC) variation due to pump precision limits. Gradient Time and Gradient Slope study factors both affect the slope of the gradient. For example, Gradient Time varies the time at constant initial and final % strong solvent. The different time level settings therefore directly equal changes in slope. And Gradient Slope directly varies either the starting point % or endpoint % strong solvent. Therefore, MPC variation is the correct input into robustness simulation to represent slope variation occurring during method execution for Gradient Time and Gradient Slope study factors included in an experiment design.

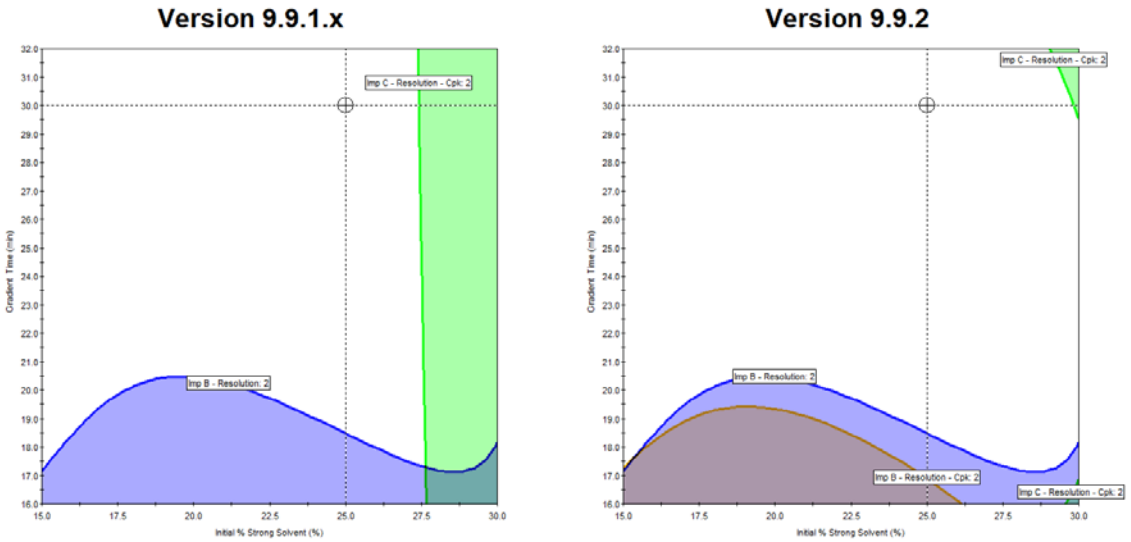
Users have always been able to directly input the desired MPC variation, for example ±2.0%, into the Robustness Simulator wizard for each Gradient Slope study factor. However, prior to Version 9.9.2 the user was required to carry out a 2-step calculation procedure for each Gradient Time study factor to convert the desired MPC variation setting into the corresponding time variation for input into the wizard. As shown in the image below, with Version 9.9.2 users can now directly input the desired MPC variation as a single global entry into the Robustness Simulator wizard. For Gradient Time study factors the software will automatically convert the desired MPC variation setting into the corresponding time variation for the simulation and then associate the single input with each Gradient Time and Gradient Slope study factor in the design.



Modeling Advancement – Resolution Robustness

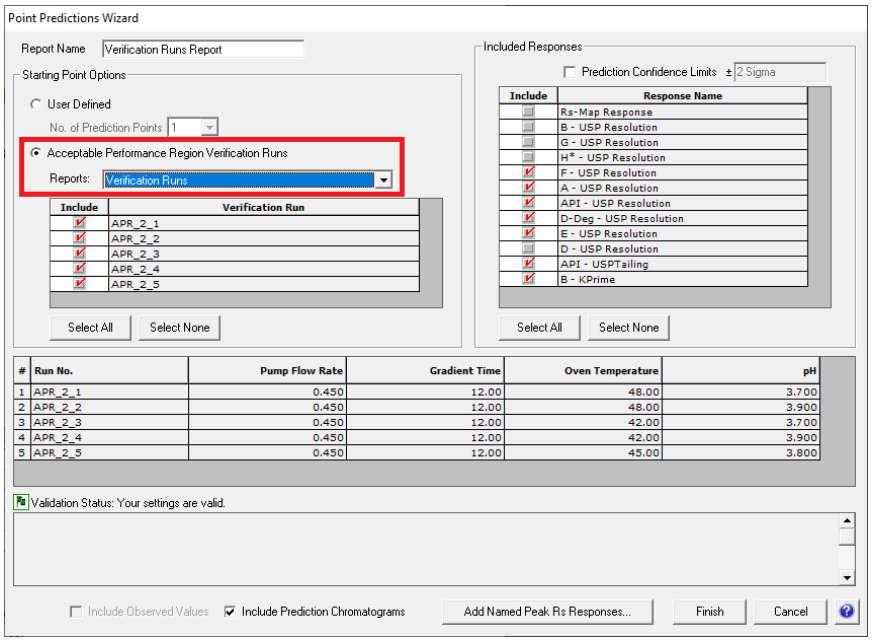
S-Matrix has adapted its hyper-precise resolution modeling capabilities to its Robustness Simulator for robustness simulation of the Rs-Map Resolution response and of individual peak resolutions. This has resulted in a powerful advancement to the precision associated with resolution robustness predictions – especially in experimental regions corresponding to methods which yield results close to edges of failure for one or more peak resolutions.

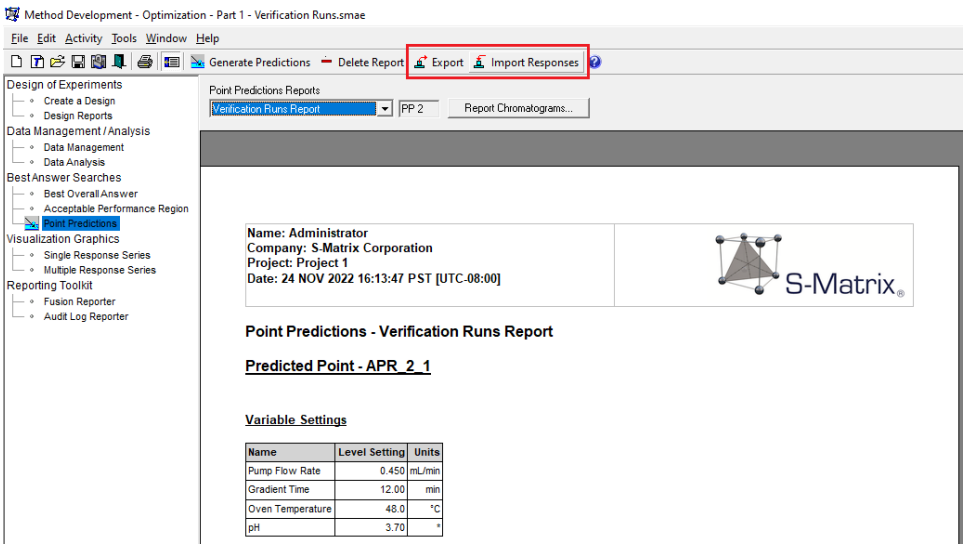
The two graphs below show the mean (average) resolution and the corresponding resolution robustness of two critical peak pairs (B–A and C–E) obtained from Version 9.9.1.x (left graph) and from Version 9.9.2 (right graph). In both graphs the resolution performance requirement for each critical pair was set to a mean (average) resolution of ≥2.00 and a minimum acceptable resolution threshold for individual injections of ≥1.50. A comparison of the two graphs shows that Version 9.9.1.x (left graph) over predicted the resolution robustness of the B–A peak pair at the lower end of the Gradient Time study range (no orange shaded region). This is evidenced by the fact that the orange robustness failure region for the B–A peak pair, which is present in the right graph, is more closely aligned with the corresponding mean performance failure region (blue shaded region). The two graphs also show that Version 9.9.1.x under-predicted the resolution robustness of the C–E peak pair at the upper end of the Initial % Strong Solvent study range. This is evidenced by the large robustness performance failure region for the C–E peak pair in the left graph (green shaded region) and reinforced by the fact that the mean resolution of the C–E peak pair is >2.00 throughout the graphed region (no red shaded regions in either gpah).



Verification Runs – Full Automation and Reporting Support

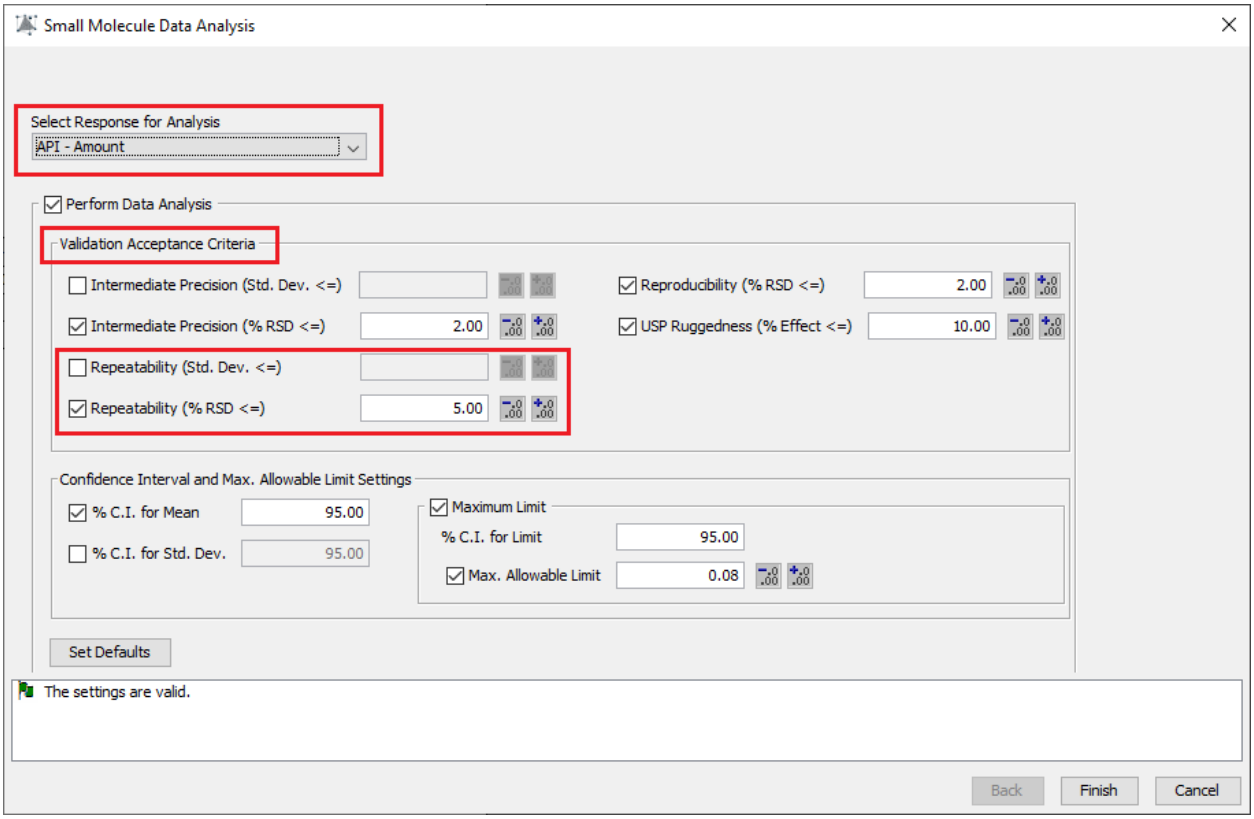
Fusion QbD now provides full closed-loop CDS automation and reporting support for experiment verification runs. As shown in the top image below, users can now select an Acceptable Performance Region report containing verification runs and generate a report containing predicted results and graphs for these runs. Users can then export them directly to the CDS as a ready-to-run sequence and methods. As shown in the bottom image below, when the user runs the sequence and processes the chromatograms in the CDS, Fusion QbD can then import the verification run chromatograms and data and integrate them into the report.





Intermediate Precision and Reproducibility (IP&R) Advancements

Prior to Version 9.9.2, the Validation Acceptance Criteria (VAC) settings for IP&R experiments were located on the main Experiment Setup display, and these settings were global – meaning the same settings were used for all compounds. As shown in the image below, the analysis wizard now contains the VAC settings, and the settings are now compound specific – meaning that users can now set independent VAC criteria for each compound included in the analysis.



In addition, as shown in the image above, the IP&R analysis wizard now also contains Repeatability VAC settings. When the user enters VAC values, Fusion QbD automatically performs a full Repeatability analysis, and the report will contain the Repeatability analysis results within the Intermediate Precision and Repeatability Results table shown below.

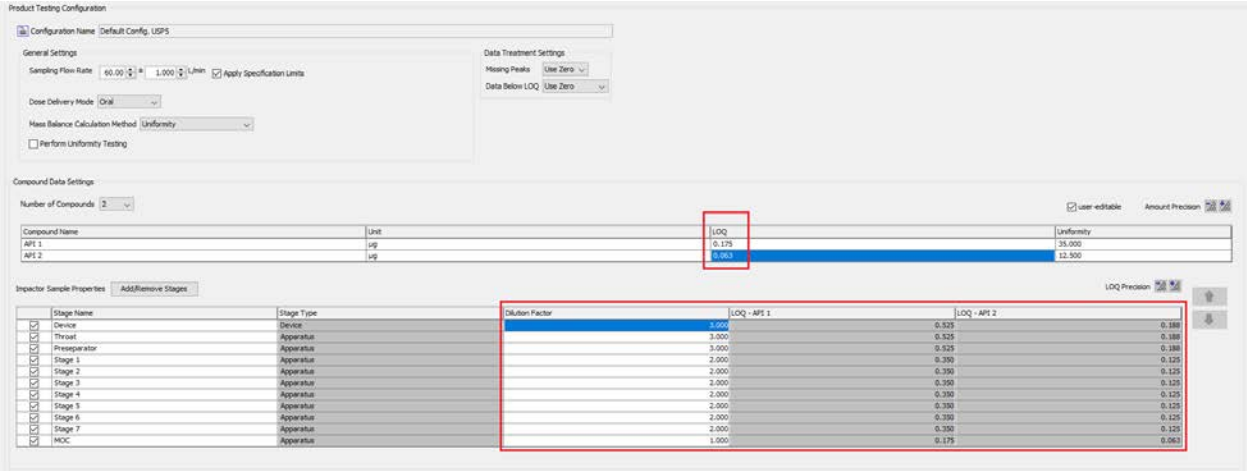
Intermediate Precision and Repeatability Results

Name	Value	Pass/Fail
Intermediate Precision Variance	0.003	
Intermediate Precision Std. Dev.	0.054	---
Intermediate Precision Upper 95% C.I.	0.078	
Intermediate Precision Lower 95% C.I.	0.042	
Intermediate Precision % RSD	1.06	Pass
Repeatability Variance	0.001	
Repeatability Std. Dev.	0.027	---
Repeatability Upper 95% C.I.	0.045	
Repeatability Lower 95% C.I.	0.019	
Repeatability % RSD	0.52	Pass

Acceptance Criterion: Intermediate Precision % RSD <= 2
Acceptance Criterion: Repeatability % RSD <= 5

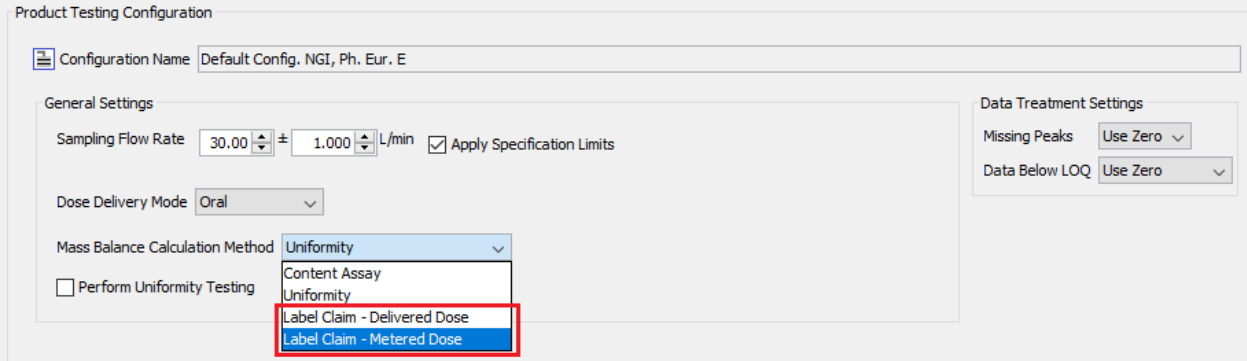
Product Testing Configuration – Automated LOQ Calculations

Prior to Version 9.9.2, users had to manually calculate the individual apparatus stage LOQ values for each compound manually and enter the values into the LOQ column within the "Impactor Sample Properties" grid. Now Fusion Inhaler Testing will automatically calculate the individual apparatus stage LOQ values for each compound based on 1) the Compound LOQ value, and 2) "Dilution Factor" value associated with the stage.



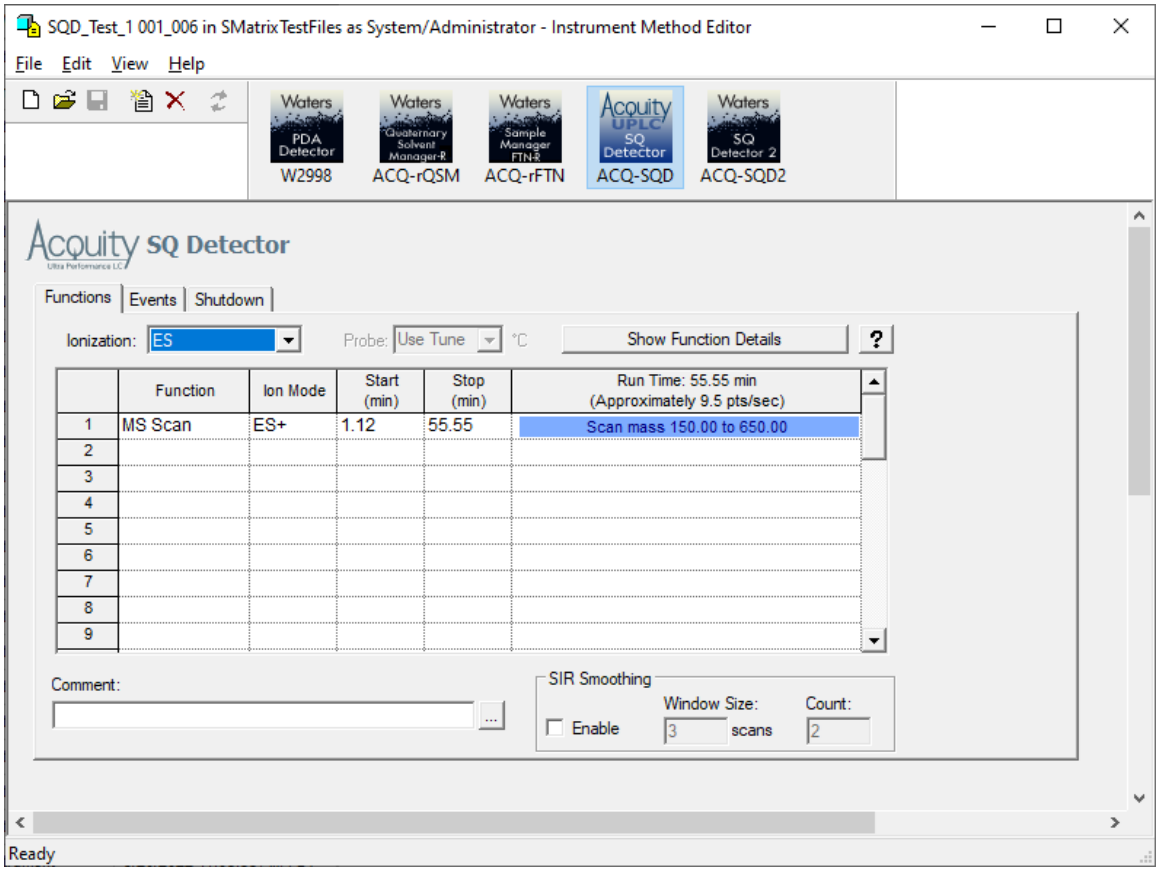
New Mass Balance Calculation Method Options

In Version 9.9.2 the main Product Testing Configuration setup display contains two new mass balance calculation options: **Label Claim – Metered Dose** and **Label Claim – Delivered Dose**. Fusion Inhaler Testing calculations and reporting operations now include support for these new mass balance calculation options.



Empower CDS – SQD and SQD2 Support

Fusion QbD now automatically updates the "**Start**" and "**Stop**" time settings in the Functions tab grid within Empower instrument methods for both the **SQD** and **SQD2** Mass Detectors supported by Empower to those required by the individual experiment runs based on the pump program settings within Experiment Setup. This assures that MS detection is activated, and coordinated with UV detection, to support MS spectra based peak tracking in Fusion QbD.



Chromeleon CDS – External Solvent Selection Valve Support

Fusion QbD now supports the flexible configuration (2-position to 15-position) solvent selection valve drive (Dionex-Ext-SSV). As shown in the image below, users can now easily configure the specific valve configuration on their LC system within Fusion Administrator.