Integrating and Automating the Use of PDA and MS Data in LC and LC/MS Method Development

Fusion QbD

Quality by Design Software System

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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
Presentation Outline

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Fusion QbD® – Modular Software Platform

LC Method Development

Analytical Method Validation

Product Development
- Formulation & Process Development
- Non-LC Method Development

Respiratory Drug QC Testing

Full QbD Experiment Automation

Fusion QbD

Fusion QbD® – Modular Software Platform

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Fusion QbD® – Modular Software Platform

LC & LC-MS Method Development

Fusion QbD

Full QbD Experiment Automation

ChemStation
OpenLAB

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Fusion QbD Automation – Supports All Waters LC Systems

- Alliance HPLC
- Acquity Binary
- Acquity H-Class
- Acquity Arc
- Acquity UPC²

- Solvent Selection Valves
- Column Switching Valves
Fusion QbD Automation – Supports All Agilent LC Systems

- Agilent 1100s
- Agilent 1200 Infinity Series
- Agilent 1260 Infinity II Series
- Agilent 1290 Infinity Series
- Agilent 1290 Infinity II Series

Solvent Selection Valves
Column Switching Valves
Fusion QbD Automation – Supports Thermo LC Systems

- Solvent Selection Valves
- Column Switching Valves

**UltiMate LCs**

**Vanquish Horizon And Flex LCs**
## Fusion QbD – Supports all Install Environments

<table>
<thead>
<tr>
<th>Supports all Install Environments</th>
<th>Fusion QbD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standalone (Workstation)</td>
<td>✔</td>
</tr>
<tr>
<td>Network</td>
<td>✔</td>
</tr>
<tr>
<td>Citrix Ready Certified</td>
<td>✔</td>
</tr>
<tr>
<td>Fully Qualifiable for GxP*</td>
<td>✔</td>
</tr>
</tbody>
</table>

* - Fusion QbD is operating in the GxP environments of international pharmaceutical companies worldwide.
Fusion QbD – Supports all Install Environments
Fusion QbD – Supports a wide Variety of Separation Modes

Supports All These Separation Modes

Reversed Phase
Normal Phase
Chiral
HILIC
Ion Exchange
Size Exclusion
SFC
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.
  - Equilibration Time & %
  - Isocratic Hold Time & %
  - Gradient Time & Slope
  - Final Hold Time & %
  - Re-equilibration Time & %
- Strong Solvent Type
- Mobile Phase Solvent Blend
- Column Temperature
- pH
- Column Type
- Flow Rate
- Injection Volume
- Ionic Strength
Initial Chemistry Screening – Built In pH Automation

Built in Buffer System Titration Curves

Extremely Precise!
Initial Chemistry Screening – Built In Column Switching Automation

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

Reversed-Phase Column Selectivity Chart

Column Settings

<table>
<thead>
<tr>
<th>Name</th>
<th>Valve Position</th>
<th>Condition Column Time</th>
<th>pH Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BEH C18</td>
<td>Position 1</td>
<td>2.0</td>
<td>14.00</td>
</tr>
<tr>
<td>2 BEH Shield RP18</td>
<td>Position 2</td>
<td>2.0</td>
<td>14.00</td>
</tr>
<tr>
<td>3 HSS T3</td>
<td>Position 3</td>
<td>2.0</td>
<td>14.00</td>
</tr>
<tr>
<td>4 CSH Phenyl Hexyl</td>
<td>Position 4</td>
<td>2.0</td>
<td>14.00</td>
</tr>
</tbody>
</table>
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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)
Fusion QbD Automation – Maintains Data Integrity

Generates QbD-aligned DOE Experiment

Automatically Builds Sequence and All Instrument Methods

Chromatography Data Software (CDS)

Eliminate Transcription Errors. Maintain Data in Audited Environment.
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.
Audited Data Exchange – Assures Data Integrity
Automated analysis, graphing, and reporting.

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

Eliminate Transcription Errors. Maintain Data in Audited Environment.
Fusion QbD Automation – Maintains Data Integrity

Audited Data Exchange – Assures Data Integrity
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Fusion QbD – PeakTracker™

Fusion QbD

Acquity H-Class With PDA

Acquity QDa Mass Detector

6 Column Capacity

Empower™
Fusion QbD – Auto-imports UV and MS Spectra Data for Tracking
Used for samples with peaks which Do Not Ionize

Used for samples with peaks which Do Not Absorb
Fusion QbD – Auto-imports all Results for Modeling, & Simulation

Select Responses

PDA Spectrum PDA 225.0 nm (PDA Spectrum (190-400) nm). Time offset by 0.020 mins.

<table>
<thead>
<tr>
<th>Operator</th>
<th>Value</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Peaks</td>
<td></td>
<td>1.50 USPResolution</td>
</tr>
<tr>
<td>No. of Peaks &gt;</td>
<td>2.00 USPResolution</td>
<td></td>
</tr>
<tr>
<td>No. of Peaks &lt;=</td>
<td>1.20 USPResolution</td>
<td></td>
</tr>
<tr>
<td>Max Peak</td>
<td>1 USPResolution</td>
<td></td>
</tr>
</tbody>
</table>

Named Compounds in CDS

<table>
<thead>
<tr>
<th>Available</th>
<th>Included</th>
</tr>
</thead>
</table>

Auto-imported Responses

<table>
<thead>
<tr>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>BasePeak</td>
</tr>
<tr>
<td>AssignedMass</td>
</tr>
<tr>
<td>AssignedMassValue</td>
</tr>
<tr>
<td>RetentionTime</td>
</tr>
<tr>
<td>MigrationTime</td>
</tr>
<tr>
<td>PctAmount</td>
</tr>
<tr>
<td>PctArea</td>
</tr>
<tr>
<td>Height</td>
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<tr>
<td>Amount</td>
</tr>
<tr>
<td>Area</td>
</tr>
<tr>
<td>EndPV</td>
</tr>
<tr>
<td>endTime</td>
</tr>
<tr>
<td>EPPlateCount</td>
</tr>
<tr>
<td>USPSignalToNoise</td>
</tr>
<tr>
<td>EPSignalToNoise</td>
</tr>
<tr>
<td>JPSignalToNoise</td>
</tr>
<tr>
<td>SignalToNoise</td>
</tr>
<tr>
<td>KPrime</td>
</tr>
</tbody>
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**PeakTracker** – Displays UV & MS Chromatograms / Auto-builds GTM

**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.

**Global Tracking Method (GTM)**

**PeakTracker** automatically builds a customizable **GTM** by scanning all UV and TIC chromatograms to identify all integrated peaks.
Mass and UV Spectral Analysis Window in Fusion QbD

Flexible Tracking Editor
PeakTracker – Instant Preview of Tracking Results

- Blue Background for data auto-updated by PeakTracker.
- Yellow Background for missing data which can be edited by user.
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.

Rs ≥ 2.00
Rs-Map Response

Co-elution

Robust Separation

Co-elution
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.
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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.
Fusion QbD – Forced Degradation Study (FDS) Automation

**Forced Degradation Studies** – Full Automation Support

<table>
<thead>
<tr>
<th>Experiment Design Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run No.</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>1.a</td>
</tr>
<tr>
<td>1.b</td>
</tr>
<tr>
<td>1.c</td>
</tr>
<tr>
<td>2.a</td>
</tr>
<tr>
<td>2.b</td>
</tr>
<tr>
<td>2.c</td>
</tr>
<tr>
<td>3.a</td>
</tr>
<tr>
<td>3.b</td>
</tr>
<tr>
<td>3.c</td>
</tr>
</tbody>
</table>

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.

Photo Degraded Sample (Vial a)

Acid Degraded Sample (Vial b)

Peroxide Degraded Sample (Vial c)

Composite Chromatogram – Run 1
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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Run No.  
  20.a  20.b

Fusion QbD Experiment Chromatogram
Tracks peaks in all Deg Path replicates of each experiment run injection.
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FDS – New Degradants Discovered

Fusion QbD automatically creates a data set of composite chromatograms for peak tracking, modeling, and simulation.
Overlay lets you include mean performance and robustness for any critical performance characteristic across the MODR.
New Degradants Identified – Forced Degradation Study (FDS)

Switch graphed and non-graphed variables – find most robust method overall.
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%).
THANK YOU!

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