Case Study – Dissolution Method Development
A Complete Solution for APLM Stages 1 and 2

**Stage 1:**
- Robust Method Optimization
- Chemistry System Screening

**Stage 2:**
- Analytical Capability
- Method Validation
- Method Transfer

**Stage 3:**
- Continued Method Performance Verification

**Fusion QbD**

**Fusion Method Development**

**Fusion Method Validation**
Fusion Process Development

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

FDA Statement* –
As long as the data integrity associated with the method development work matches what would be done in a formal Validation Robustness effort, then the results are acceptable.

Same Regulatory Expectation for Claims of Formulation and Process Robustness

* – USP Workshop – Enhanced Approaches for Analytical Procedure Lifecycle: An Alternative to Traditional Validation
(Sept. 24-25, 2018)
Why Audit Trail is Important!

- Who entered this data – was the data modified?
- What Empower Project did this data come from?
1) Experiment Design – e.g.
   • Process – e.g.
     o Time, Temp, Speed, …
   • Chemistry – e.g.
     o Buffer ΔC, pH, …

2) Testing Designs
   • Descriptive Statistics
   • Time Series

3) Time Series Testing
   Dissolution (% Rel. vs Time)

4) Results Data Import
   • All LC Results for all Compounds
   • Tablet testing results
     • f1 and f2
     • % Released and Time X
     • More …
Flexible Experiment Setup

Formulation (Mixture) Studies
You specify:
- Number of Mixture Components
- Component Study Ranges
- Total Sample Amount and Units

Process (Non-mixture) Studies
You specify:
- Number of Study Factors
- Type of Each Factor
- Study Ranges or Levels

Combined Mixture-Process Studies
Enable you to characterize interactions between the two!
Complete Flexible Experiment Setup Template

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<th>Type</th>
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<th>Upper Bound</th>
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</table>
Automatically Selects and Generates the Most Defensible and Efficient DOE Design

Built-in Design Logic Accounts for:

- Stage of the Work (Screening or Optimization)
- Number of Variables
- Types of Variables
  - Numeric or Categorical
  - # of Defined Levels
Automatically incorporates your standard injection strategy into the exported sequences.
1) Experiment Design – e.g.
   • Process – e.g.
     o Time, Temp, Speed, …
   • Chemistry – e.g.
     o Buffer ΔC, pH, …

2) Testing Designs
   • Time Series

3) Time Series Testing
   • Dissolution (% Rel. vs Time)

4) Results Data Import
   • All LC Results for all Compounds
   • Tablet testing results
     • f1 and f2
     • % Released and Time X
     • More …
Time Series – Multiple Time Point Tests per Run

E.g., Dissolution Testing

Time Series – Instant Testing Protocol
Supports:

- Uniform or variable time-point testing protocols
- Multiple sample preparation repeats
- Multiple test repeats at each time point
- Internal test standard data
Re-usable Testing Design Template

The template is automatically replicated to support CDS auto-import of all your desired results for all compounds.
1) Experiment Design – e.g.
   - Process – e.g.
     - Time, Temp, Speed, …
   - Chemistry – e.g.
     - Buffer ΔC, pH, …

2) Testing Designs
   - Time Series

3) Time Series Testing
   - Dissolution (% Rel. vs Time)

4) Results Data Import
   - All LC Results for all Compounds
   - Tablet testing results
     - f1 and f2
     - % Released and Time X
     - More …
Automatically Export Ready-to-Run Testing Design to the CDS

Automated File-less Data Transfer

Bi-directional Auditing Assures Data Traceability and Integrity!
Dissolution Experiment Dataflow

1) Experiment Design – e.g.
   - Process – e.g.
     - Time, Temp, Speed, …
   - Chemistry – e.g.
     - Buffer $\Delta C$, pH, …

2) Testing Designs
   - Time Series

CDS

3) Time Series Testing

Dissolution (% Rel. vs Time)

4) Results Data Import
   - All LC Results for all Compounds
   - Tablet testing results
     - f1 and f2
     - % Released and Time X
     - More …
Automatically Import All Required Results Data from CDS

Bi-directional Auditing Assures Data Traceability and Integrity!
Automatically Generates Average Response Curves (Profiles) from Individual Test Repeats for each Run. For example, results from multiple dissolution vessels.
Coordinated Response Reductions:

- Handles test repeat data
- Computes average profiles
- Computes $f_1$ & $f_2$ curve fit metrics
- Computes sensitive Weibull curve fit metrics
- Computes additional profile response metrics
Multivariate DOE Study – goal is characterizing all significant effects of the study parameters on all Critical Quality Attributes (CQAs)

CQA = 9.3 + 4.2(pH) – 5.4(Surf.)² + 12.7(pH*Surf.) + 1.3(Vol.*Speed) + 1.6[(∆pH)²(Surf.)] + ...

Linear Effect  Pure Curvature Effect  Interaction Effects  Complex Effect
Example of a Resolution Model Eqn.

- Peak 3 resolution
  \[ R = 3.0607 + 0.4109(GT) - 0.3367(Temp) - 0.7772(pH) - 0.2013(pH)^2 \]

✓ Regulatory Acceptance of Fusion QbD

Regulatory Acceptance of Monte Carlo Simulation Approach

Monte Carlo Robustness Simulation

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

Points to Consider for Design Space – A Regulatory Perspective, Elaine Morefield, Ph.D., 2012 Annual Meeting, AAPS.

Statistical Robustness Metrics

The FDA has stated that accepted process capability indexes such as $C_p$, $C_{pk}$, $C_{pm}$, and $C_{pkm}$ are also part of the QbD toolset.

US FDA, Quality by Design: Objectives, Benefits, and Challenges, Lawrence X. Yu, Ph.D., 2012 Annual Meeting, AAPS.
3. Process Capability

Process capability refers to the performance of the process when it is operating under statistical control. Two capability indices are usually computed: $C_p$ and $C_{pk}$ in a similar way as was described with $P_p$ and $P_{pk}$. However, $C_p$ measures the potential capability in the process, if the process was centred, while $C_{pk}$ measures the actual capability in a process which is off-centre or biased. If a process is centred, then $C_p = C_{pk}$.

$$C_{pk} = \min \left[ \frac{U - \bar{X}}{3S_w}, \frac{\bar{X} - L}{3S_w} \right]$$  \hspace{1cm} (1.5)

The critical thing to note is that whilst the formulae for $P_{pk}$ and $C_{pk}$ look very similar, the standard deviation used to calculate the reference interval for $C_{pk}$ is not $S_i$ but $S_w$.

$S_w$ is the within batch standard deviation (called the within subgroup standard deviation in ISO) not the overall process standard deviation. It is usually estimated from a Shewhart mean and range control chart using the formula...
Fusion QbD – Integrated Monte Carlo Robustness

Built-in Robustness Metrics

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

Define edge of failure.
Below is the **Final Robust Design Space** in which methods meet or exceed all critical mean performance and robustness goals simultaneously.
MODR Trellis Graph – 4 Study Factors

Unshaded Region in the graphs in combination with the Lower & Upper Bounds Of the Trellis Factors represent the 4-Factor Method Operable Design Region (MODR).

Rectangle represents the independently adjustable ranges of Buffer pH and Organic Level within the MODR.
Complete QbD Reporting

Report Output in Multiple Formats

- MS Excel
- MS Word
- PDF
- …
End of Presentation

S-Matrix

www.smatrix.com