Examples of Applying Quality by Design Principles to Analytical Methods

Kimber Barnett, PhD
Pfizer Inc, Analytical Research and Development
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Why QbD for analytical?

- Enhanced method understanding and robustness
  - understand, reduce and control sources of variability
- Method aligned with processes
  - better understanding and control of method variability enables better understanding and control of process variability
- Facilitates continuous improvement
  - performance criteria is independent of analytical technique
Define Objectives (Method Design) → Method Selection (Method Design) → Develop Method Understanding → Develop MODR & Control Strategy → Knowledge Management

- Analytical Target Profile
- Develop MODR and Control Strategy (Risk Mitigation)
- Perform Experimental Strategy
- Risk Assessment Prioritize Experiments
- Quality Risk Assessment Identify and Prioritize Method Parameters
- ID Experiments Understand CQA = f(CPP)
Method Performance and the ATP


“The objective of a “good” analytical procedure is to be able to quantify as accurately as possible each of the unknown quantities that the laboratory will have to determine.

In other words, what the analyst is seeking is that the difference between the “measured value” and the “true value”, is as low as possible or at least lower than an acceptable limit.”

ICH Q2 does not recommend setting criteria for the total error of the method.

–Sources of error are treated separately
  • Method Precision
  • Method Bias
Graphical Representation of Traditional Method Validation Criteria

- At boundaries: no trade-off between method bias and precision
- It is possible to accept a method with both high bias and high precision
- Does not consider TOTAL method variability

Criteria: Bias: NMT 3.0%  Precision: NMT 2.0%
Analytical Target Profile

• ATP describes method performance criteria
  – based on a probability of result being within a given range from the “true value”

Example ATP for Drug Product Assay
The procedure must be able to accurately quantify [drug] in film coated tablets over the range of 70 – 130% of the nominal concentration with accuracy, precision such that measurements fall within ±3.0% of the true value with 95% probability.
Graphical Representation of the Analytical Target Profile

ATP plot: measurement ± 3.0% of the true value with 95% probability
USP: ATPs and Performance Based Monographs

• Approach is consistent with USP performance based monographs.
Why Accuracy and Precision are in the ATP: Types of Data Associated with Analytical Procedures

- Accuracy and Precision

Method Performance Data:
- Method Range
- Specificity/Peak Resolution
- Linearity
- Limit of Detection
- Stability in Solution
- Instrument Repeatability

*Modified from a slide presented by Oliver Groche, Pittcon 2013 | 18-Mar-2013 | Analytical Change Control*
Technique Selection - Considerations

• HPLC, SFC, GC, NIR, Raman, etc.?
  – Desired method performance
    • Physical and chemical properties of analytes
      – volatility, solubility, stability, detect-ability
  – Typical accuracy & precision achieved by the techniques
  – Sample matrix
  – Sensitivity
  – Linear Range
  – Instrumentation and expertise at the testing lab
  – On-line vs. off-line
  – Method cycle time
  – etc.
Risk Assessment

Overview of typical quality risk management process (from ICH Q9)

Risk Identification

- Identify Method Factors that may affect method performance
  Examples (HPLC method): Column Temperature, Flow Rate, Mixing accuracy, etc.

Risk Analysis

Estimate risk associated with method factors.
Example Tools: Cause & Effect Matrix, FMEA, Ishikawa Diagram, etc.
Method Operable Design Region

- A description of the multidimensional combinations and interaction of method parameters that have been demonstrated to meet measurement system requirements.
- A region over which changes to target method conditions (Normal Operating Conditions) can be made without risk to method performance.
Case Study
Drug Substance Assay
Method Evaluation and Verification
Drug Substance specification: of 98.0-102.0%

- **Assay:** The procedure must be able to accurately quantify the drug substance over a range of 80% to 120% of the nominal concentration with accuracy and precision such that measurements fall within $\pm 2.0\%$ of the true value with at least a 95% probability.
Method Conditions

Starting conditions developed via comprehensive screening using predictive software and risk assessments.

Chromatogram of KPSS

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>% A</th>
<th>% B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>0.9</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>38</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>38.1</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>45</td>
<td>97</td>
<td>3</td>
</tr>
</tbody>
</table>

A single method was developed for both Assay and Impurities testing.
Risk Assessments – Assay and Purity Method

- Risk assessments were performed to identify parameters for further study.

<table>
<thead>
<tr>
<th>Name</th>
<th>Method Set Point</th>
<th>C, N, X</th>
<th>Experimental Strategy</th>
<th>Risk (H,M,L)</th>
<th>Expt. Range (low, high)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffer Strength</td>
<td>0.05%</td>
<td>X</td>
<td>DoE-1 &amp;2</td>
<td>H</td>
<td>0.02, 0.08</td>
</tr>
<tr>
<td>Flow Rate</td>
<td>0.4 mL/min</td>
<td>X</td>
<td>DoE-1 &amp;2</td>
<td>H</td>
<td>0.35, 0.45</td>
</tr>
<tr>
<td>Gradient Parameters</td>
<td></td>
<td>X</td>
<td>DoE-1 &amp;2</td>
<td>H</td>
<td>@14min (20, 26%) @31min (45, 55%)</td>
</tr>
<tr>
<td>Column Temperature</td>
<td>55 C</td>
<td>X</td>
<td>DoE-1 &amp;2</td>
<td>H</td>
<td>48, 58</td>
</tr>
<tr>
<td>Binary Solvent Manager Configuration</td>
<td>Not Directly Specified</td>
<td>X</td>
<td>DoE-3</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>Mobile Phase Preheat Temperature</td>
<td></td>
<td>X</td>
<td>DoE-3</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>Pump Type (Low vs. High Pressure)</td>
<td>Not Directly Specified</td>
<td>X</td>
<td>DoE-3</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>Column History</td>
<td></td>
<td>X</td>
<td>OFAT</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>Column Lifetime</td>
<td></td>
<td>X</td>
<td>OFAT</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>Etc...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Method Evaluation and Verification Strategy

- **Two phases:**
  - **Screening DoEs** – Evaluation of method performance across a range of method parameters
    - Identify/confirm regions of optimal performance
  - **Verification DoE** – ATP verification
    - A subset of method conditions with highest risk for method performance as determined by screening DoEs
Screening Design (DoE1)

- ½ fractional factorial split-plot \((2^{5-1})\) design with blocking experiments with levels of perchloric acid.
  - more difficult to change from run to run (long equilibration times)
- Replicates at the set condition and randomly chosen conditions
  - estimate the whole-plot error, lack of fit and within plot error.
  - 26 runs in total: 16 replicates for split-plot ½ fractional factorial design + 10 replicates at 5 conditions.
- Data collected (combined assay/purity method):
  - **Resolution** Target: \((Rs) \geq 1.5\) between impurities and \(Rs \geq 2.0\) between impurities and drug substance
  - **Impurity Area\%** Target: For peaks > 0.15\% the accuracy \(\pm 15\%\), for peaks \(\leq 0.15\%\) the accuracy must be \(\pm 20\%\) versus the center point average.
  - **Signal to Noise** at 0.1\%. No target; Identify regions with optimum sensitivity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Set Point</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Perchloric Acid</td>
<td>0.05%</td>
<td>0.02 – 0.08</td>
</tr>
<tr>
<td>Flow Rate</td>
<td>0.4</td>
<td>0.35 – 0.45</td>
</tr>
<tr>
<td>Temperature</td>
<td>55</td>
<td>50 – 60</td>
</tr>
<tr>
<td>Start % B</td>
<td>3</td>
<td>2-5</td>
</tr>
<tr>
<td>Ending % B</td>
<td>50%</td>
<td>45 - 55</td>
</tr>
</tbody>
</table>
Screening DoE1: Resolution

• Resolution was the limiting attribute.
• Nine resolutions were measured and divided into two groups
  – Group 1: all conditions met resolution criteria
  – Group 2: some conditions did not meet resolution criteria
The perchloric acid concentration is most dominant. Resolution increases with increasing perchloric acid concentration.

Arrow points in the direction of increasing resolution.
2nd Screening DoE (DoE2) and Proposed MODR

- Proposed MODR ranges were tightened based on DoE1
- DoE2 was performed to verify resolution over the tightened ranges
- 12 runs in total = split-plot half fractional factorial design on 4 pars (8) + 4 replicates at standard condition.

DoE2 showed satisfactory results.

Proposed MODR

The proposed method operable design region correspond to ranges confirmed by the 2nd screening DoE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Set Point</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Perchloric Acid</td>
<td>0.05%</td>
<td>0.03 – 0.07</td>
</tr>
<tr>
<td>Temperature</td>
<td>55°C</td>
<td>50 - 60</td>
</tr>
<tr>
<td>Flow Rate</td>
<td>0.4 ml/min</td>
<td>0.35 – 0.42</td>
</tr>
<tr>
<td>Start %B</td>
<td>3%</td>
<td>2 – 4</td>
</tr>
<tr>
<td>End %B</td>
<td>50%</td>
<td>47 – 55</td>
</tr>
</tbody>
</table>
Part II
ATP Verification
ATP Verification Design Strategy - Assay

• **Regions of higher risk were chosen for ATP verification**
  – Interaction between %Perchloric*EndB% was detected for peak height.
    • 2x2 factorial study for Perchloric concentration and EndB%
  – Temperature was not significant, therefore it was fixed at the set point
  – Flow Rate and StartB% had negative linear effects with the poorest performance predicted at high flow rate and high StartB%.
    • flow rate and StartB% were fixed at the high end (worst case)
• Two replicates were included at the set point (Run 1 and Run 6)
• Prepared 3 samples each at 80, 100 and 120% of nominal concentration

<table>
<thead>
<tr>
<th>Run</th>
<th>Buffer</th>
<th>Temp (C)</th>
<th>Flowrate (ml/min)</th>
<th>StartB(%)</th>
<th>EndB(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>55</td>
<td>0.4</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>0.03</td>
<td>55</td>
<td>0.42</td>
<td>4</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>0.03</td>
<td>55</td>
<td>0.42</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>0.07</td>
<td>55</td>
<td>0.42</td>
<td>4</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>0.07</td>
<td>55</td>
<td>0.42</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>55</td>
<td>0.4</td>
<td>3</td>
<td>50</td>
</tr>
</tbody>
</table>
Assay ATP Verification: Accuracy vs. Precision

- Observed high σ values for runs #3 and #5 in the 100% (middle) recovery analysis.
- Also observed a negative bias when assayed vs STD A.
  - STD A and STD B match passed criteria, but was on the high side.
  - Recalculated vs Average of STD A and B
• Using Average STD A and STD B decreased the negative bias.

• Higher than expected $\sigma$ value for the 100% (middle plot) values for #3 and #5. (Examination of the chromatogram indicates that #3 is likely a failed injection.)

• Further analysis was performed to determine causes of variability.
Standard Preparation Variability Study

- 6 Standards prepared, 6 independent injections on 2 UPLC’s

- In this study, the major variability came from injection precision not from Standard preparations.

- Injection precision was about 0.3% RSD, so acceptable.

- Further studied ways to improve Injection precision:
  - Decreased solution concentration
  - Increased injection volume (to potentially reduce injection variability)
  - Also considering increasing the number of sample replicates to further improve overall precision.
Bracketing with Duplicate Standards

1. Precision was acceptable

2. Use of 2 bracketting standards (STD A and STD B) implemented to reduce potential for bias in assay results. See method below.

<table>
<thead>
<tr>
<th>CHROMATOGRAPHIC PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>After initial system suitability has been demonstrated, inject prepared test samples bracketed by an injection of STD 1 and STD 2. Make no more than six injections between bracketing STD 1 and STD 2 injections.</td>
</tr>
<tr>
<td>A recommended run sequence for Assay/Purity/Identity is:</td>
</tr>
<tr>
<td>Blanks</td>
</tr>
<tr>
<td>LOQ (6 Injections)</td>
</tr>
<tr>
<td>STD 1 (6 Injections)</td>
</tr>
<tr>
<td>STD 2</td>
</tr>
<tr>
<td>Samples</td>
</tr>
<tr>
<td>STD 1</td>
</tr>
<tr>
<td>STD 2</td>
</tr>
</tbody>
</table>

For each standard and sample injection, measure the retention time and area of all peaks of interest.
## Summary of Method Understanding

<table>
<thead>
<tr>
<th>Method Parameter</th>
<th>Effect on Resolution</th>
<th>Effect on Sensitivity</th>
<th>Initial MODR modified based on Screening DoEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Perchloric Acid</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Flow Rate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Initial Organic %B</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Final Organic %B</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Temperature</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

The method is robust at the set point and slight variations that occur as part of typical usage should not significantly affect accuracy and precision of the data.

During ATP verification, the main contributor to precision was found to be standard variability. Therefore an additional replicate was added.
Final Thoughts

- AQbD concepts and tools are being applied in support of our method development efforts
  - Practices continue to evolve and be refined as we gain more experience
- ATPs presented here are based on the probability of a measurement being within a given difference from the “true value”
  - Direct link to the decision to be made with the data
- Analytical QbD is an evolving concept
- Presently no regulatory or industry guidances for AQbD; the dialog continues……