Applying Quality by Design Principles to Analytical Methods Associated with OINDPs

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Analytical Methods Working Group

Content

- Background and points to consider
  - The evolving medicines development landscape
  - Analytical QbD - timeline, activities & outcomes so far
- Applying QbD concepts to a specific OINDP method
  - Role of analytical methods in the OINDP development lifecycle
  - Defining the Analytical Target Profile (ATP)
  - Using the ATP to design the analytical method
  - Understanding the impact of method parameters on performance – defining critical parameters
  - Developing a method control strategy, monitoring & continual improvement
- Summary & Future Opportunities
The Evolving Medicines Development Landscape

- Increasing focus on improving both capability and robustness of manufacturing processes by
  - Extensive deployment of lean and six sigma methodologies
  - Increasing adoption of Quality by Design approaches to process and product development (focus on science and risk-based strategies)

- Increased pressure to exploit technical innovation to reduce costs to society

What does this mean for the Analytical Scientist?

- A significantly increased focus on understanding the contribution of the analytical measurement system to the overall process capability.
- A greater recognition of the need to better understand the measurement uncertainty if we are to truly understand our processes.
- Increased pressure to ensure all analytical methods work right first time – every time.
- An increasing need to be able to innovate and continually improve our analytical methods

Can Quality by Design principles be applied to analytical methods?
EFPIA/PhRMA Joint White Paper (PharmTech Feb 2010)

- Describes ideas on how the QbD concepts and tools applied to manufacturing process can be applied to analytical methods, intended as stimulus for further discussion and engagement
- Highlights drivers for change - the evolving regulatory landscape and issues observed with current state
  - Some challenges during validation, transfer and routine operation
  - Challenges for industry in implementing improved methods
- Introduces the concept of the analytical target profile (ATP)
- Highlights potential opportunities presented by using the ATP
- Includes a hypothetical case study to illustrate the concepts, provides a glossary to terms & definitions, proposes next steps

**Timeline, activities and outcomes so far**

- ICHQ2 (A&B)
- ICHQ2 (R1)
- QbD considerations for Analytical Methods, Lilly AAPS (2007)
- Application of QbD to Analytical Methods, GSK PharmTech (2007)
- QbD to USP: Theory & Perspectives (2008)
- QbD Analytical Aspects: Moheb Nasr, FDA (HPLC 2008)
- Method specific papers esp. HPLC (2009)
- Implications & Opportunities of Applying QbD Principles to Analytical Measurements EFPIA/PhRMA PharmTech(2010)
- PhRMA-ATG/FDA Meeting: (2007)
- EFPIA Analytical Design Space Team initiated (2008)
- QbD for analytical methods. JPAG Meeting (Mar 2010)
- APIC Workshop (Oct 2010)
Applying Quality by Design Concepts to Methods

Quality by Design Approach to Drug Development

Critical Material Products & Process Attributes Defined

Define Analytical Target Profile (ATP) & Performance Characteristics /Criteria

Knowledge Management
Analytical Method Operable Design Region
1. Method Design
2. Method Evaluation
3. Method Control Strategy
Continuous Improvement Lifecycle Management

Continuous Improvement in Technology by Site A

Impurity X
Process Control Strategy requires measurement of X over the range from zero to 0.1% with RSD NMT 10% and accuracy (bias) of NMT 0.01% from the reference

EFPIA/PhRMA Example – 1 ATP; 3 methods

Method 1 transferred to Site A (QC Labs - commercial manufacturing of API and DP)

Site A develops/validates with appropriate change control a UPLC method Method 2

Site A develops/validates with appropriate change control a real-time RAMAN measurement – Method 3

Method 2 transferred to site B
EMA Interaction

- EFPIA group developed examples using the proposed concepts
  - Assay (titrimetric), Identification (spectroscopic), Quantification of soluble aggregates.
- A copy of the white paper was submitted, with examples and cover letter, to European Medicines Agency Quality Working Party (QWP) in Nov 2009, feedback received July 2010
- Comments from Quality Working Party were not supportive
  - However, the response also recognised that the development of the concepts are still at an early stage and needed further discussion
- Face to face dialogue has been requested and the EFPIA group are scoping further input to facilitate the discussions and reach a common understanding of the issues

Orally Inhaled & Nasal Drug Products

- Group exploring how Quality by Design principles can be applied to analytical methods intended for use with orally inhaled and nasal drug products
- Group developing a case study to exemplify some of the approaches further and provide an example for inhalation products
The Role of Analytical Methods in OINDP Development

- Analytical Methods support:
  - Product and process selection and optimisation
  - Input raw material and component quality
  - In-process monitoring and control
  - Continued product quality & suitability
  - Monitoring for trends
  - Development of design space

\[ \sigma^2_{\text{total}} = \sigma^2_{\text{batch}} + \sigma^2_{\text{sample}} + \sigma^2_{\text{method}} \]

Applying Quality by Design Concepts to Methods

- Define desired method performance upfront
- Design method to meet target criteria
- Understand impact of method parameters on performance
- Identify and control sources of variability
- Monitor performance to ensure consistent output

Understand the method requirements and develop an Analytical Target Profile (ATP)

Select, develop and validate an analytical method that meets the ATP

Determine any critical analytical method parameters

Understand how these critical parameters will effect the result and develop a strategy to control them

Monitor method performance and continually improve
Defining an Analytical Target Profile

- Start with the Patient (product safety, efficacy & quality)
- Use prior knowledge, regulatory guidance, compendial considerations, voluntary consensus standards
  - Understand what needs to be measured (i.e. which product, material and component properties are critical to process and/or product performance – Critical Quality Attributes)
  - The level of precision and accuracy required to demonstrate that product safety and efficacy requirements are routinely met
  - The discriminating power required to detect any changes that would impact safety and efficacy
- Understand the operating environment for the method, throughout its lifecycle
- Develop an **Analytical Target Profile** (ATP).

Delivered Dose Uniformity

<table>
<thead>
<tr>
<th>Can Number</th>
<th>Beginning</th>
<th>Middle</th>
<th>End</th>
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<tbody>
<tr>
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<tr>
<td>10</td>
<td>✓</td>
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</tr>
</tbody>
</table>

DDU is referenced in Pharmacopoeias & Regulatory Guidance

Define desired method performance upfront
Consideration of Method Operating Environments

- Development Laboratories
- Commercial Quality Control Laboratories
- Contract Research Laboratories

Best way to achieve technology transfer?

Local SOPs

Training/monitoring

Retraining

Data tracking?

Local Availability of laboratory hardware & reagents?

Method cycle time vs shift patterns

Qualification, calibration, inspection and maintenance of equipment

Local environmental conditions & control

Define desired method performance upfront

Consideration of Human Factors


- Analytical task demands range from accuracy in manual skill-based activities to complex knowledge-based activities.

- They are multistage tasks that are manually and cognitively demanding, and are highly repetitive and can be prone to human error.

- A typical analytical method was selected and a hierarchical task flow was developed via observation followed up with interviews.

- Errors associated specific sub-tasks were identified.

- General ergonomic recommendations were made including seating/standing, control of extraneous noise, written checklists/method pro formas, equipment storage and glassware colour coding.

- Specific recommendations for each sub-task also made.

A QbD approach to methods should incorporate ‘Error Proofing’
Analytical Target Profile

"Measure the within canister and throughout delivered dose from a pMDI with a precision of x% RSD and an accuracy of not more than y% bias, over a range A to B mcg per actuation"

<table>
<thead>
<tr>
<th>Analytical Target Profile</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision</td>
<td>± X% label claim</td>
</tr>
<tr>
<td>Accuracy</td>
<td>± Y% label claim</td>
</tr>
<tr>
<td>Range</td>
<td>A-B microgrammes/actuation</td>
</tr>
</tbody>
</table>

Additional assurance that the required ATP criteria can be routinely met:

- Calibration model (for example linearity) meets calibration criteria (for example is linear over specified range)
- Specificity: specific for active ingredient in presence of excipients/impurities
- Robustness assessment under typical operating conditions: impact of small perturbations in critical method factors understood & controlled
- Ruggedness assessment under typical operating conditions: impact of random day to day method factor variation understood & controlled

Define desired method performance upfront

Now need to select, develop and validate an analytical method that meets the ATP

Designing the Analytical Method

- Understanding the ATP
- Device Preparation
- Dose Collection
- API recovery & sample Preparation
- Separation (if required) and Quantification of API

Understanding Technique Capability (Prior Knowledge)

Design method to meet target criteria
Applying additional lean tools to analytical methods can increase the efficiency of the testing process (reduced cycle times, minimisation of raw material usage and optimised use of resources).

Design method to meet target criteria

Determination of Critical Method Factors

- Cause and effect analysis is instructive in identifying the factors that might influence method performance.
- The factors can be grouped according to their influence on the method and the CNX system is a useful classification tool.
  - C: Analytical Method Factors which form part of the method definition and which can be specified at Controllable unique levels (SOPs).
  - N: Analytical Method Noise Factors, unintentional variations that if identified as potentially critical may require ruggedness testing to assess impact.
  - X: Analytical Method Factors which form part of the method definition and which can be varied continuously and if potentially critical may require robustness experimentation to define the method operable design region.

Understand impact of method parameters on performance.
Assessing the Factors that may Influence Performance

Factors that may effect method performance

- Method Factors
- Noise Factors
- Controls
- Experimental

Risk Assessment

Fix parameters where appropriate

Robustness/Ruggedness Experiments

Method Control Strategy

Performance Monitoring

Understand impact of method parameters on performance

Design of Experiments for Experimental Factors

- Assess impact of defined ‘internal’ control & experimental factors
- Design of Experiments and multivariate analysis used to define the method operable design region (MODR)
- DoE approach important to identify any interactions between experimental factors
- Develop control strategy and set out in our method

Understand impact of method parameters on performance
Measurement Systems Analysis of Noise Factors

- ‘External’ Noise factors that influence the ruggedness of the method can be assessed using measurement systems analysis (e.g. gauge R&R)
  - For example, explore analyst, reagent grade, instrument, apparatus

- Study complexity dependant on no of factors/levels studied
- Nested/Crossed designs can be useful
- Perform ANOVA on the output
- Gain knowledge on source & extent of random variability

Dose Collection

Understand impact of method parameters on performance
**Prioritisation Matrix for Dose Collection X Factors**

<table>
<thead>
<tr>
<th>Weighting</th>
<th>7</th>
<th>10</th>
<th>9</th>
<th>8</th>
<th>1</th>
<th>1</th>
<th>Risk Score</th>
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<tbody>
<tr>
<td>Accuracy</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>306</td>
</tr>
<tr>
<td>Repeatability</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>306</td>
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<tr>
<td>Intermediate precision</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>306</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>306</td>
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<tr>
<td>Specificity</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>306</td>
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<tr>
<td>Linearity</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
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<td>Shaking to collect</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>131</td>
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<tr>
<td>Shaking to waste</td>
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<td>3</td>
<td>3</td>
<td>3</td>
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<td>Firing to collect</td>
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<td>1</td>
<td>0</td>
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<td>Firing to waste</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Shaking Technique</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Dose-Collector (Material &amp; Dimensions)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Dose-Collector (Sample Prep)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Dose-Collector (Sample Prep)</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>35</td>
</tr>
</tbody>
</table>

**Understand impact of method parameters on performance**

- 9 = High
- 3 = Medium
- 1 = Low
- 0 = None

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**Comparison of Shaking Profile, Manual vs Automated**

**Manual acceleration data X,Y,Z**
- Sinusoidal arc
- High analyst to analyst variation
- Variable frequency, amplitude
- Sig. y, z parameters
- Variable duration

**Automated Acceleration data x,y,z**
- Shake frequency, velocity and amplitude fixed
- Non sinusoidal, acceleration/deceleration, phases
- Shake duration constant
- Choice of linear, arc or inversion modes

**Identify and control sources of variability**
Standardised Manual Shaking Profile

- Observations of manual shaking technique showed wide variation in technique and total power imparted to the device
- A standardised shaking profile introduced
  - Slow frequency, device moved through 180°
  - Short training video made & used extensively
  - Metronomes used as frequency guides
- In conjunction with training rig, helped to minimise analyst to analyst variability.

![Bar chart showing mean total power across analysts](image)

Comparison of Actuation Mechanism

Automated
- Fixed Down stroke/ hold/ release times
- Constant velocity
- Controlled, distance driven actuation between fixed points

Manual
- Variable force
- Lateral twist movements
- Variable timings

Improved actuation instructions were defined in the method

![Graph comparing automated and manual actuation forces](image)
### Dose Collection Noise Factors FMEA (Excerpt)

<table>
<thead>
<tr>
<th>Category</th>
<th>Specific Factor</th>
<th>Potential Failure Mode</th>
<th>Potential Failure Effects</th>
<th>SEV</th>
<th>Potential Causes</th>
<th>OCC</th>
<th>Current Controls</th>
<th>DET</th>
<th>RPN</th>
<th>Risk = Severity x Occurrence x Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Dilution Techniques</td>
<td>Incorrect use of volumetric glassware</td>
<td>Would impact both accuracy &amp; precision</td>
<td>10</td>
<td>Analyst Error</td>
<td>3</td>
<td>Training</td>
<td>10</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Glassware Cleanliness</td>
<td>Unclean glassware</td>
<td>Carryover from previous analysis - impacts accuracy &amp; precision</td>
<td>10</td>
<td>Ineffective Cleaning</td>
<td>3</td>
<td>Analyst pre-wash and/or machine wash process</td>
<td>6</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Dilution Technique</td>
<td>Uncorrected final volume</td>
<td>Would result in an incorrect result but it would be processed</td>
<td>10</td>
<td>Analyst Error</td>
<td>3</td>
<td>Training, labelling &amp; organisation of the lab</td>
<td>6</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Environment</td>
<td>Ventilation</td>
<td>Variable electrical effects</td>
<td>Could impact accuracy &amp; precision</td>
<td>6</td>
<td>Lack of control</td>
<td>3</td>
<td>Understanding how washstats affect this result &amp; then implementation of necessary controls</td>
<td>6</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Glassware Cleanliness</td>
<td>Unclean glassware</td>
<td>Interference - impacts accuracy, precision &amp; specificity</td>
<td>6</td>
<td>Ineffective Cleaning</td>
<td>3</td>
<td>Analyst wash and/or machine wash process</td>
<td>6</td>
<td>180</td>
<td></td>
</tr>
</tbody>
</table>

**Risk Calculation**

Risk = Severity x Occurrence x Detection

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### Dose Collection Noise Factors - Prioritisation

**Focus on washdown/dilution instructions**

**Need for glassware control procedures**

**Requirement to Investigate electrostatics**

**Identify and control sources of variability**

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**IPAC-RS 2011 Conference**
Develop the Method Control Strategy

- Ensure the method requirements are consistently met via control of the identified critical analytical method factors.
- System suitability checks, instrument performance checks and run qualification procedures may all be used.
- For the manual Delivered Dose Uniformity method, continued training and monitoring is also important.
- Automated Delivered Dose Uniformity method offers controls of specific critical parameters.

Analytical Method Controls

Device Preparation → Dose Collection → API recovery & sample Preparation → Separation (if required) and Quantification of API

Example Control Strategies

User instructions
Storage orientation
Storage conditions & duration

Shaking & Firing parameters for dose collection & between doses

Solvent & solubilisation process parameters

Sampling, Separation parameters & controls, System suitability checks

Design method to meet target criteria

Apparatus Controls

Reference Material Controls
Monitor Method Performance and Continually Improve

- Confirm continued method performance using control charts
- Assessment of analytical method capability expressed as a precision to tolerance ratio, may be instructive.
- Use accumulated knowledge base to assess the impact of any planned or proposed changes including method improvements and technological advances.
- Use the quality management system (see ICH Q10) to manage changes

Finalised Methods

- A comprehensive work programme resulted in an automated delivered dose uniformity method that produces dose profiles that are comparable with those obtained collecting doses as instructed by the patient user instructions.
- Knowledge gained allowed further optimisation of the manual method to also deliver comparable profiles
Summary

- Applying QbD Principles to Analytical Methods should result in;
  - Incorporation of the best scientific practice by linking prior knowledge of techniques and methods to an ATP
  - A mechanistic understanding, based on chemical & physical knowledge, of the factors that influence method performance
  - An investigation of multivariate relationships across method factors
  - An understanding how variation in these method factors affect the analytical result
  - This knowledge will provide
    - An insight on contribution method variability has on the overall product and process variability
    - More focussed method control strategy
    - A thorough understanding of the impact of any planned method changes

- Resulting in better methods in both their operation and outcome

Future Opportunities

- Does the Analytical Target Profile provide a means of proposing more advanced regulatory approaches to method submission and review for orally inhaled and nasal drug products?

- If we fully understand the sources of variability in each of the method ‘modules’ and take steps to control them we can;
  - Use risk based approaches to focus method design and control efforts in the most important areas
  - Propose greater flexibility for the modules that present the least risk or impact on the method outcome
  - This may facilitate continual improvement by making it easier to exploit advances in analytical technology
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