QbD for robust product

James Pound, IPA Mumbai 2020
Quality

- Patients' safe and efficacious treatment
- Acceptable medicines quality
- GXP
- Public quality standards
- Regulatory assessment
Quality by Design (QbD)

- Systematic approach and predefined objectives
- Product and process understanding and control
- Based on science/data/evidence and risk management
Focus on analytical methods – complexity

Credit: Particle Sciences Technical Brief 2009 Volume 5
Focus on analytical methods – evidence

<table>
<thead>
<tr>
<th>Cite Id</th>
<th>Reference Number</th>
<th>Short Description</th>
<th>Long Description</th>
<th>Frequency</th>
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<tr>
<td>1105</td>
<td>21 CFR 211.22(d)</td>
<td>Procedures not in writing, fully followed</td>
<td>The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***</td>
<td>185</td>
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<td>3603</td>
<td>21 CFR 211.160(b)</td>
<td>Scientifically sound laboratory controls</td>
<td>Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically, ***</td>
<td>124</td>
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Credit: FDA FY 2017 Inspectional Observation Summaries
What is Analytical QbD?

- Analytical Quality by Design (AQbD) takes a structured approach to the development of analytical procedures to ensure they are fit for purpose and consistently deliver results that meet predefined objectives.

- It achieves this through a detailed understanding of all aspects of the analytical methods performance ensuring adequate control and an ability to react to changes which can affect the quality of results.

Global view
MHRA/British Pharmacopoeia project

• Project to investigate the application of AQbD principles to compendial analytical methods.

• In order to fully explore the benefits and potential challenges of implementing AQbD, the development of a pharmacopoeial assay procedure for Atorvastatin tablets was selected as a case study.

• Collaborative - BP, Licensing Division, GMDP Inspectorate, Industry and Therapeutic Goods Administration (TGA) of Australia
MHRA/British Pharmacopoeia project

The project investigated:

• The application of risk based approaches and Design of Experiments (DoEs) to method development and verification, leading to an enhanced understanding of method performance and robustness.

• Different approaches to (pre) define method performance requirements using the concept of an Analytical Target Profile (ATP), to better understand the use and value of this tool as well as to explore its relevance and applicability to compendial methods.
An Analytical Target Profile (ATP) is designed to capture the quality attributes of a reportable value of a method through determining the level of acceptable variability of the method. A suitably designed and applied ATP can be a measure of assurance that an analytical method is fit for purpose throughout its lifecycle; from development, through to validation and into a commercial setting.

(amalgam of thinking from USP, EFPIA and others)

**EXAMPLE:**

The analytical method is capable of quantifying [ACTIVE] in [ACTIVE] Tablets from 70 to 130% of the true value with accuracy and precision of not more than 3.0%, with 95% probability.
Systematic approach

• Critical Method Parameters
  – E.g. Fishbone / Failure Mode Effects Analysis

• Representative Sample Selection
  – E.g. Identification of 5 samples to represent the 100+ marketed Atorvastatin Tablet products

• Design of Experiments
  – Ability to assess all factors using a statistical approach reducing 162 runs to just 24

• Method operable design region (MODR)/analytical design space
Lessons learned

• ATP
  – Confidence in the method – *ensure it is fit for purpose*
  – Variety of approaches/models for ATPs – *no one size fits all*

  – Rationale and justification for statistical analysis - *"Lies, damned lies, and statistics"

  – Demonstration of equivalence – *framework for the use of alternate methods*
Lessons learned

- Enhanced approaches
  - Knowledge transfer - becomes even more important

- Structured risk assessment
  - focus resource on risk

- Multiple formulations - additional complexity
  e.g. In the UK for Metformin Tablets 20,658,987 prescription items/year, 94 products across 33 MAHs

- Design of Experiments – understand where method can fail, streamline resource
Conclusions

- Enhanced risk-based approach to method development and evaluation
  - Improved method understanding
  - Confidence a method will be fit for its intended purpose
  - Focussing resource on risk

- ATP
  - Pre-defined requirements for method – ensure fit for purpose
  - Value for assessing suitability of an alternate method

Taken together, the enhanced risk-based approaches and the ATP concept provide a potential platform for ensuring that the analytical method can continue to evolve throughout its lifecycle
Compendial standards

• Where can the pharmacopoeias add value – specific monographs, general guidance or something else?

• Application – where can we derive most benefit – small molecules, biologics?

Acknowledgement: Adapted from Mark Wiggins, MSD/Merck
Compendial standards

ASSAY

The analytical method must be capable of quantifying ferrocyanide in Ammonial Tablets (0.7% to 1.3%) in a specified time with accuracy and precision of not more than 2.5%, with the procedure of the following solution.

Method understanding/flexibility/added value

- Assay
  - The analytical method must be capable of quantifying ferrocyanide in Ammonial Tablets (0.7% to 1.3%) in a specified time with accuracy and precision of not more than 2.5%, with the procedure of the following solution.
  - The method is flexible and can be adapted to different conditions.
  - Added value: Provides accurate and precise results, improving the quality of the product.

- Status quo
  - Current method: Uses traditional techniques that may not be as accurate or efficient as the proposed method.
  - Flexibility: Limited, as it is not easily adaptable to changes in the product.

- MODR/ADS
  - Methodology: Modern techniques that provide improved accuracy and precision.
  - Added value: Reduces the risk of errors and enhances the overall quality of the product.

- ATP
  - Advanced Technology: Utilizes the latest technology to improve the measurement process.
  - Added value: Ensures the product meets the highest standards of quality and efficiency.
The future


• Consultation response due to be published in early 2020

• Other developments
Thank you

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