Real World Application of QbD Principles to Development of Dry Powder Inhaled products

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GlaxoSmithKline
Agenda

1. Background

2. Clear definition of product requirements (QTPP)

3. Use of Risk Assessment to drive development

4. Develop Scientific Understanding of Product and Manufacturing Process
   • Exemplified with examples

5. Control Strategy

6. Lessons learnt
Content of this presentation is based on the application of science and risk based principles to Dry Powder inhalation products within GlaxoSmithKline

- Based on development experience from the GSK product portfolio over the past ~10 years and ICH Q8,9,10 guidance
  - Including novel NCEs and Container Closure System (Inhaler and Pack)
- The experience of more than 20 Market Authorisations submitted over the last 2 years
  - Including multiple interactions with regulatory authorities during review process
- Approval of several applications throughout the world (including USA, EU, Japan, Canada)
• Is the critical starting point for any product development and is a clear and complete description of the intended goal (drug product requirements)

• QTPP provided a concise summary of the product and the quality standards which needed to be achieved. It includes:
  – Clear description of the product requirements
  – The disease – therefore likely dose range
  – Patient and disease focused - Device/handling considerations
  – Focus on safety and efficacy of the product

• These are aligned with the requirements of ICH Q8

• QTPP also ensures cross discipline engagement
Inhaled Dry Powder product QTPP
Partial example

Develop a dry powder inhalation product for once daily administration in adults for the treatment of asthma and COPD. The product will contain 1 months supply and have suitable stability for global distribution and supply.

Potential Drug Product CQA

- Emitted Dose
- Drug related impurities
- Aerodynamic Particle size distribution

Target Profile

- Target dose >80% of nominal content
- Achieve regulatory standards globally for content uniformity
- ICH requirements achieved for related impurities and genotoxins. Degradation products minimised (total <3%)
- Similar performance to existing medium airflow resistance approved products

Continued....
Risk Assessment process

• Risk assessment was at the core of the development
  – Used to drive the direction and structure of the experimental programme and the
documentation in the regulatory files
  – Was the ‘Story Board’ to explain that scientific understanding underpinning the
Control strategy

• Based on:
  – ICH Q9 guidance and prior GSK knowledge
  – Scientific and engineering principals
  – Experimental evidence derived from development programme

• Example of tools utilised;

<table>
<thead>
<tr>
<th>Risk Identification</th>
<th>Input-Process-Output diagrams, Process definition diagrams, Rich picture/mechanism maps, Fishbone, GEMBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Analysis</td>
<td>FMEA</td>
</tr>
<tr>
<td>Risk Evaluation</td>
<td>Pareto analysis</td>
</tr>
</tbody>
</table>
Risk Assessment process
Risk based development

• Risk assessment at core of development

[Diagram showing severity, detection, occurrence, risk score (RPN), criticality, CQAs & CPPs, and key]

Key:
- Risk Assessment
- Control Strategy
### Risk Assessment

**Worked example**

**Starting point of assessing a drug homogeneity risk**

<table>
<thead>
<tr>
<th>Potential failure mode</th>
<th>DP CQAs Affected</th>
<th>Potential effect of failure</th>
<th>Potential cause of failure</th>
<th>Sev</th>
<th>Occ</th>
<th>Det</th>
<th>RPN</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of atypical drug rich powder blend</td>
<td>Content Uniformity of Emitted Dose</td>
<td>Fail Content Uniformity of Emitted Dose on batch release testing</td>
<td>Presence of API agglomerates within powder blend formulation</td>
<td>7</td>
<td>1</td>
<td>10</td>
<td>70</td>
<td>Scored based on prior experience with equipment with similar formulation and testing strategy</td>
</tr>
</tbody>
</table>

- **Blending last mixing step, therefore direct link to Emitted Dose uniformity**
- **High score as off-line end product test applied**
- **Low score due to prior experience with similar formulation and equipment**
- **Medium level risk therefore homogeneity assessed as part of development studies**
Developing Scientific Understanding

Principles and approach

- **Early risk assessment**
- **Gather experimental evidence (Scoping studies)**
- **Develop deeper scientific understanding**
- **Re-assess risks**
- **Define Controls**
- **Confirm Effectiveness of Controls**
- **Validate Product**
- **Control Strategy**

**Develop deeper scientific understanding**
- Typically multifactorial DoEs studies
- Targeted studies based on risks assessment
- Studies may be a mixture of univariate and multivariate studies

**Re-assess risks**
- To confirm all risks controlled to an acceptable level

**Define Controls**
- Aggregate data across multiple studies to confirm findings of targeted studies
- Confirm findings are consistence with scientific understanding and/or with other related products
- Start process monitoring and trend analysis
Developing Scientific Understanding
Example 1 – Blend homogeneity

- **Initial Risk assessment**
  - Initial risk assessment based on prior knowledge (Slide 8)

- **Clinical batch manufacture**
  - 3 incidents of high drug content found
  - Risk assessment revised

- **Experimental Investigation (6 months)**
  - Increased level of sampling (‘000 per batch) – Stats based
  - Sieve studies
  - Blender parameter optimisation studies

- **Process re-design (6 months)**
  - Blending process was modified,
  - Control Strategy updated

- **Process confirmation (6 months)**
  - Increase level of sampling for extended period to demonstrate robustness of process modification - More than 25,000 assays (460 samples/batch x ~40 batches)

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**Drug Content Uniformity**

**Initial Process**

**Modified Process**
Developing Scientific Understanding
Example 2 – Change of 2<sup>ry</sup> Pack

• Pack change
  – 2<sup>ry</sup> pack provides moisture protection during shelf-life of product
  – Pack design changes made during pivotal clinical studies to improve pack performance
    • Changed from foil laminate flow wrap pack to foil laminate tray with lid
  – How?
    • Conducted risk assessment to identify key areas for investigation
    • Built deep scientific understanding of the properties of pack (CQAs) and effect on Drug Product CQAs
  – Introduced change and verified with additional expt’s studies
    • Moisture vapour transmission rate (MVTR)
    • Stress testing
    • Formal stability studies
Developing Scientific Understanding
Example 2 - Change of 2nd Pack

Risk assessment
- Identified key areas of risk for pack change based on the desired attributes of the pack (moisture protection, mechanical robustness, easy of opening by patients)

Developed Scientific understanding
- Developed knowledge of moisture sensitivity of the formulation
- Developed & validated math model for pack RH
- Used model to establish acceptable pack MVTR
- Used MVTR knowledge to identify pack options

Design Selection
- Used stress testing (temp, RH and pressure) to compare options
- Performed simulated and real transportation and handling studies

Design Verification
- Demonstrated consistent Pack %RH on long term stability studies

Validation of pack RH model

Effect of MVTR on Predicted Pack RH

MVTR for various pack options
Scientific product understanding and appropriateness of the control strategy confirmed in two parts:

- Multivariate regression analysis of aggregated data sets (see below)
- Re-enforcement of effectiveness of identified CQAs and CPPs
- Product performance confirmed during life cycle validation studies

Regression coefficients and significance

<table>
<thead>
<tr>
<th>Product attributes &amp; process parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression coefficients and significance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model error</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regression based on all attributes and parameters (48)</strong></td>
</tr>
<tr>
<td><strong>Regression based on only identified CQAs &amp; CPPs</strong></td>
</tr>
<tr>
<td><strong>APSD mean estimation error (as % nominal)</strong></td>
</tr>
<tr>
<td><strong>Batches</strong></td>
</tr>
<tr>
<td><strong>Determinations</strong></td>
</tr>
</tbody>
</table>

Color key:
- Process parameter
- Input drug attributes
- Process 1 sensors
- Intermediate 1 attributes
- Excipient attributes
- Process 2 sensors
- Intermediate 2 attributes
- Intermediate 3 attributes
## Control Strategy

**Summary representation for 2 drug product CQAs**

<table>
<thead>
<tr>
<th>Input materials</th>
<th>Blending</th>
<th>Filling</th>
<th>Assembly</th>
<th>Packing</th>
<th>Specification test</th>
<th>Drug product CQA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug-related impurities</strong></td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td><strong>Drug-related impurities</strong></td>
</tr>
<tr>
<td>• Drug-related impurities</td>
<td></td>
<td></td>
<td></td>
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</tbody>
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<table>
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<tr>
<th>Aerodynamic particle size distribution of the emitted dose</th>
<th>![x]</th>
<th>![x]</th>
<th>![x]</th>
<th>![x]</th>
<th>![x]</th>
<th>Aerodynamic particle size distribution of the emitted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug PSD&lt;br&gt;• Excipient PSD&lt;br&gt;• Desiccant ERH</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
</tr>
<tr>
<td>• Blister fill weight&lt;br&gt;• Blister sealing parameters</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
</tr>
<tr>
<td>• Air flow geometry&lt;br&gt;• Secondary pack integrity</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
<td>![x]</td>
</tr>
<tr>
<td>• Aerodynamic particle size distribution</td>
<td>![x]</td>
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<td>![x]</td>
<td>![x]</td>
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</tr>
</tbody>
</table>

**Key:**

- **Red text – CQA**: There are CPPs and/or CQAs in this unit operation which impact the drug product CQA or specification testing is performed.
- **Blue text- CPP**: The drug product CQA is not impacted by parameters or attributes in this unit operation.
Lessons Learnt

• QTPP critical in having a clear, aligned understanding of the product being developed
  – What features, what standards, patient requirements, commercial considerations

• Integrated development of whole product required (Formulation, Inhaler and Pack)

• Risk assessment critical to ensure focus on the most important aspects (safety and efficacy)

• Rigorous alignment required in Control Strategy between input materials, process controls and finished product specifications (Drug Product CQAs)
Lessons Learnt

- Early and regular regulatory agency interaction invaluable, especially in areas such as specification setting and change management

- Product and process change underpinned by risk assessment and detailed scientific understanding

- Specifications set on relevant data using appropriate statistical tools to derive commercial relevant limits

- The inclusion of an appropriate level of scientific and experimental details in the marketing application enables agencies to better understand the product and can actually reduce the number of questions during review

- Use the ICH-aligned terminology (not company specific descriptors)
Thank you