A Risk-Based Approach To Process Validation: Stages 1-3 Implementation

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Presentation Outline

I. Introduction
II. GSK Risk Based Approach to PV Implementation
III. Area of Focus – Stage 3
IV. Case Study
V. Building PV Competency – Capability Build
VI. Conclusion
**Product Lifecycle Management (PLM)**

Product Lifecycle Management is GSK’s interpretation of the regulatory guidance for Process Validation. PLM provides a framework that is key to ensuring the consistent and robust commercial products.

It ties together the critical quality concepts of risk assessment, control strategy, validation, monitoring and change control to enable us to detect drift in product performance.
PLM has been integrated into our QMS.

QMS provides the guidance on the end-to-end process of PLM. It also provides the assurance that PLM is aligned with industry standards.
Risk Based Approach Key to Effective Implementation

- **Balanced & paced** approach to implementation based on agreed risk tolerances
- Clarity on what constitutes an ‘At Risk’ product which will require focused investigation and remediation
- **Shifts resources** from ‘number crunching’ to focused fixes
- Ensures inclusions of other quality attributes and links PPR outputs
- **Links all stages** of the Process Validation lifecycle
- Provides **specific instructions, tools and templates** to escalate and remediate issues

Risk Based Approach – Key Outputs

1. Establish “At Risk CQA’s” that require further investigation & remediation efforts as an organizational priority
   - What Do We Need To Fix First?

2. Establish minimum CQA, CPP & CMA SPC & Ppk review frequencies for “At Risk CQA's” vs. marginal CQA’s vs. target CQA’s.
   - Where Can I Ease Up Versus Apply More Focus?

3. Establish risk triggers (tolerances) for PPR-related product quality indicators (i.e. complaints, batch rejections, deviations).
   - How Does This Relate To Other PPR-related Product Quality Risks?
**New Product vs. Legacy PV Implementation Approach**

**1-2-3 Approach**
- TRA confirms CQAs & CPPs
- Document and implement control strategy
- Implement CPV

**3-1-2 Approach**
- Implement CPV & document current Control Strategy
- Conduct TRA (change control)
  - Various triggers
- Confirm/Refine Product Control Strategy

**AREA OF FOCUS**
STAGE 3 – CONTINUED PROCESS VERIFICATION IMPLEMENTATION
Background on CPV Implementation - *Regulatory Expectations*

  
  "Production data should be collected to evaluate process stability and capability."

  "If properly carried out, these efforts can identify variability in the process and/or signal potential process improvements."

  "We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability."

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**Continued Process Verification - Learnings**

Avoid using data and statistics like a drunk uses a lamppost – more for support than illumination.

<table>
<thead>
<tr>
<th>CPV Should Not Be</th>
<th>CPV Should Be</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primarily focused on Process Control only, tracking and chasing of run rule breakages</td>
<td>Based on independent and important measures of process control (control charting) AND process capability</td>
</tr>
<tr>
<td>Trending CQAs to satisfy the compliance requirements only – no real process understanding</td>
<td>Risk-based in order to prioritize those high risk processes (i.e. low Ppk, deviations,)</td>
</tr>
<tr>
<td>Focused on manufacturing process only</td>
<td>Incorporating the assessment of the Measurement System</td>
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**Continued Process Verification – High Level Process Flow**

- **Capability analysis** should be used to **prioritise** those processes/products most at risk. This should be undertaken before deciding on the rate at which CQAs and CPPs should be trended.

- The state of a process (both its stability and capability) should be used as a guide to what improvement strategy to adopt.

**Use statistical control charts to monitor processes**

- Collect data, clean it and import into Statistical Analysis Tool.
- Confirm the CQAs and CPPs that are to be included in the CPV programme.
- Prioritise all CQAs and CPPs for improvement.
- Use one (or a combination) of the following statistical tools to understand and reduce variation: statistical control chart, graphs, MSA, DOE, regression analysis, t-tests, F-test and ANOVA.
- Establish Alert Limits
- Process Capability (Risk) Assessment.
- Implement and confirm improvements.
- Sustain improvements.

**CASE STUDY**
Case Study – Oral Solid Dose Product

- Low dose product – 0.5 mg strength
- Recent batches displayed OOS for Assay at the end of shelf life (36 Months, 25°C/60%RH. Initial low Assay at release stage i.e. 94%
- Shelf life reduced to 18 months based on data after the failure; Spec limit tighten with immediate effect from 92.5-107.5% to 95-105% to avoid stability failure
- Low Ppk for Assay on recent batches - 0.41

<table>
<thead>
<tr>
<th>Quality Improvement Plan Perform.</th>
<th>Driver</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Non Robust Products resulting in poor Quality metrics (deviations, stability failures) and/or Out of Stock scenario.</td>
</tr>
<tr>
<td>To Improve Assay Ppk from 0.41 to &gt; 0.70</td>
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</table>

Case Study – Oral Solid Dose Product

C: Change control completed for 1) modified analytical method and 2) BMR/MFR or starch compensations 3) Updated PCS

C: 1) Product performance monitoring 2) PCS Confirmation Exercise (regular) 3) Fortnightly product performance meeting

D: Identify Target Problem Area and Define Scope – Define Problem Statement: Improve Assay Ppk from 0.41 to > 0.70

M/A: MSA of assay test (UV and HPLC); data trending of attributes and parameters affecting assay, process capability assessment to identify special causes of variability

A: Conduct Operational TRA

1. Implementation of reduction of starch compensation less than 5% in MFR and BMR
2. Method transfer for improved method for API extraction (efficiency)
3. Update to Product Control Strategy
4. Temporary change control to confirm root cause(s)
5. Analyst training
Case Study – Oral Solid Dose Product

- Assay PpK improved from 0.40 to 1.05
- Reduced risk of stock-out due to Assay failure
- Equivalent of 3 additional batches (6 MM tablets) will be available to patients yearly
- Increased process robustness and analyst confidence in running analytical method
## PLM Competency Framework

### Core Module

<table>
<thead>
<tr>
<th>Core Module</th>
<th>Competency Level</th>
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<tbody>
<tr>
<td><strong>Aware</strong></td>
<td><strong>Developing</strong></td>
</tr>
<tr>
<td><strong>Product Lifecycle Management, Stage 1 (Process Design)</strong></td>
<td></td>
</tr>
<tr>
<td>Technical Risk assessment / Product Control Strategy (TRA / PCS)</td>
<td>Technical Director</td>
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<tr>
<td><strong>Product Lifecycle Management Stage 2 (Process Qualification)</strong></td>
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<tr>
<td>Process Validation</td>
<td>Technical Director</td>
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<tr>
<td>Sampling plans (AQL/LQL, acceptance sampling)</td>
<td>Technical Director</td>
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<td></td>
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<tr>
<td><strong>Product Lifecycle Management, Stage 3 (Continued Process Verification)</strong></td>
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<tr>
<td>Data Trending and Periodic Process Review (PPR)</td>
<td>Technical Director</td>
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<td></td>
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<tr>
<td>Material Risk Assessment (MRA) - as part of Change Control</td>
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Each of the core module will have its own competency profile

Role competency level for core modules may vary depending on job accountability

**TRA Target: Awareness all, 1 x L1 Practitioner (Proficient) per site, 1 x L2 Mentor (expert) per supply chain/region**

**MRA Target: Awareness all, 1 x L1 Practitioner (Proficient) per site, 1 x L2 Mentor (expert) per supply chain/region**
CONCLUSIONS

Lessons Learned

1. Clear Quality Management System (QMS) framework in place
2. Decision tree for application of risk based approach to establish clear priorities
3. Accessible tools and templates that enable consistent implementation
4. Competency framework to ensure Technical and Quality staff are on ‘same page’
5. Differentiated approach for Legacy versus New Products
6. Mechanism for continuous sharing across the organization