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PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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RECOMMENDATION

How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management

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Editor: PIC/S Secretariat

e-mail: info@picscheme.org
web site: https://www.picscheme.org

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1. Document History

Adoption by Committee of PI 054-1	30 June 2021
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2. Introduction

2.1. This document provides practical guidance for GMP inspectors when seeking to evaluate the effectiveness of a company's pharmaceutical quality system (PQS) in relation to risk-based change management. It covers all relevant steps in the change management process – change proposal, change assessment, change planning and implementation, change review and effectiveness checks. It indicates within each step the aspects that render the PQS to be effective in that area.

2.2. Note: These aspects are in accordance with the considerations that are already typical and commonly applied in a change management process; they do not introduce any new GMP requirement.

2.3. Other useful guidance for GMP Inspectors in relation to change management is provided in the PIC/S Aide Memoire on QRM Implementation.

3. Purpose

3.1. The purpose of this document is to provide guidance on evaluating and demonstrating the effectiveness of a PQS in relation to risk-based change management as are governed by the PIC/S GMP Guide. This is in recognition of the fact that the PIC/S GMP Guide requires companies to demonstrate the effectiveness of their PQS and to apply quality risk management (QRM) principles to change control activities.

3.2. It is useful to note that Chapter 1 of the PIC/S GMP Guide states the following in relation to PQS effectiveness and planned changes:

- Principle: '…there must be 'a comprehensively designed and correctly implemented PQS incorporating GMP and QRM. It should be fully documented and its effectiveness monitored'.
- Section 1.3 ...'the effectiveness of the system is normally demonstrated at the site level'.
- Section 1.5 'Senior management has the ultimate responsibility to ensure an effective PQS is in place...'
- Section 1.4 (xii) Arrangements [should be] in place 'for the prospective evaluation of planned changes and their approval prior to implementation…'

3.3. In relation to change management, Annex 15 of the PIC/S GMP Guide states:

- Section 11.1. 'The control of change is an important part of knowledge management and should be handled within the pharmaceutical quality system.'
- Section 11.4. 'Quality risk management should be used to evaluate planned changes… and to plan for any necessary process validation, verification or requalification efforts.'
- Section 11.7. '…an evaluation of the effectiveness of change should be carried out…'

3.4. The guidance in Section 5 of this document addresses the following points:

- The key elements that could be included in risk-based change proposals.
- The assessment by the pharmaceutical manufacturer of change proposals from a risk perspective, where:
    - the level of rigor, effort and documentation is commensurate with the level of risk,
    - the risk assessments adequately evaluate the potential risks and benefits of changes to product quality, safety and efficacy, and
    - those risk assessments consider the potential risks and benefits to other products, processes and systems.
- The classification by the pharmaceutical manufacturer of changes based on the level of risk.
- The role of change planning and implementation, where the outcomes of risk assessments and the assigned risk levels drive change planning, prioritisation, implementation, and their timelines. (Note: this section also addresses situations where proposed changes are not implemented.)
- Change review and effectiveness assessments at the pharmaceutical manufacturer, in terms of whether changes meet their intended objectives and pre-defined effectiveness criteria, where residual risks are assessed and managed to acceptable levels, and where changes are monitored via ongoing monitoring systems to ensure maintenance of a state of control.

3.5. It is considered that application by a pharmaceutical manufacturer (including quality control laboratories) of the guidance set out in Section 5 below will provide evidence of the effectiveness of their PQS in relation to risk-based change management. If such a risk-based change management system were in place within the PQS, it should lead to the timely management of risks to product quality and patient safety, as well as better quality and manufacturing performance, continual improvement and innovation.

3.6. Effective change management is important not only in the context of the aforementioned PIC/S GMP requirements, but also in the context of ICH Q10, which sets out the potential for risk-based regulatory oversight for companies that demonstrate an effective PQS is in place (see Appendix 1). This guidance may also be useful in supporting implementation of the principles and concepts in the ICH Q12 guideline where mature risk-based change management within an effective PQS is considered foundational to enable greater regulatory flexibility in reporting of post-approval changes.

3.7. Further information on the background to this Recommendation and the anticipated benefits of this guidance are provided in PIC/S Concept Note PS/INF 88/2019, which is available at https://picscheme.org/en/publications

4. Scope

4.1. This document applies to GMP inspections of manufacturers of medicinal products and active pharmaceutical ingredients.

5. Guidance on evaluating and/or demonstrating the effectiveness of a PQS in relation to risk-based change management –

the checklist below is a tool that can be used for this evaluation.

It may be useful for manufacturers to use the checklist as a guide to help define their internal change management procedures and practices.

5.1. Change Proposals - Determination of when a change is needed:

The following are key points to consider:

- The trigger(s) for changes and the related evidence are clearly documented. Common lifecycle factors that trigger change include, but are not limited to:
  - new product introductions
  - upgrades to equipment or facilities, including computerised systems, or changes intended to enhance upstream detectability (e.g. integrated monitoring/testing)
  - changes in raw materials/packaging materials or in their suppliers
  - changes in analytical test methods

- changes to improve manufacturing performance and consistency (to reduce variability, etc.)
- changes to enhance manufacturing capacity
- corrections of quality issues
- addressing signals from the PQS such as those from deviations, complaints/adverse events, compliance gaps, corrective actions and preventative actions (CAPAs), product quality reviews, performance indicators, management reviews,
- new or updated regulations, guidance documents, policies, procedures, etc.
- implementing innovation or continual improvement initiatives (including lean initiatives to eliminate waste).

- The change management system ensures that changes are proposed in a timely manner, proposed changes are formally evaluated, and a decision to accept or reject the proposal is documented. For rejected/voided change proposals, particularly those that relate to mitigation of a quality/safety/efficacy/compliance hazard, the system ensures that the rationales for those decisions are documented and well justified, and that continued risks are adequately managed.
- The objectives, scope, expected outcomes and anticipated benefits of the proposed change are documented.
- The potential impacts of the proposed change on other products, processes, systems or sites are objectively assessed and adequately documented.
- The potential impacts of the proposed change on other change proposals that may be ongoing at the same time are assessed, and there is appropriate management of risks due to the collective effect of multiple change proposals.
- Relevant subject matter experts and appropriate internal/external stakeholders (e.g. contract givers, quality assurance, other relevant departments) are involved in change proposal development and approval.
- The potential impacts to pending/approved filings and regulatory commitments are addressed.

5.2. **Change Risk Assessments:**

Change Management procedures often require a risk-based classification (e.g. critical, major, minor) to be assigned to proposed changes as well as an impact assessment to be performed. The latter routinely determines the potential impacts of the proposed change on various items, such as product quality, documentation, cleaning, maintenance, regulatory compliance, etc. In some cases, especially for simple and minor/low risk changes, an impact assessment is sufficient to document the risk-based rationale for a change without the use of more formal risk-assessment tools or approaches.

More formal risk assessments should be applied to change proposals, which represent more complex or significant (e.g. major, critical) changes. Such risk assessments should more substantially address what might go wrong with the

proposed change, as well as the potential impact of the change in the context of current process knowledge and the product/facility lifecycle.

Where possible, changes should reduce product quality risks and/or patient safety hazards to an acceptable level. At a minimum, changes should maintain or improve product quality and/or patient safety, and should not increase process variability.

The Change Management system ensures that appropriate science and knowledge-based risk assessments are performed and documented for changes, considering the points below:

- The level of formality, effort (e.g. testing, validation, review) and documentation is commensurate with the level of risk.
- Risk assessments adequately assess the potential risks and benefits of changes to product quality, safety and efficacy.
- Risk assessments adequately assess potential risks and benefits to other products, processes, and systems.
- Risk assessments identify and document both current and needed risk controls.
- Changes and their risks are assessed using current product and process knowledge. Appropriate data and information are used (or generated, if needed) to support such risk assessments.
- Classifications (and any pre-defined approaches that are used for assigning such classifications) are appropriate and based on the level of risk.

5.3. **Change Planning and Implementation:**

- The outcomes of risk assessments and the assigned risk levels drive change planning, prioritisation, implementation, and their timelines.
- The data needed to demonstrate effective implementation of the change, as well as the acceptance criteria and change effectiveness criteria, are pre-defined in change planning. These may include provisions such as intensified sampling, continuous process verification (CPV) and statistical assessments (e.g. CpK/PpK) to aid with the quantitative assessment of risk control.
- Potential risks with the current state (until changes are implemented) and any risks that might be temporarily introduced during the change process are adequately assessed.
- Interim controls (short-term measures), as needed, are identified and implemented in a timely manner to monitor/mitigate risks associated with the current situation (until change implementation).
- Identified risk control measures are adequately implemented in a timely manner.
- The change management system ensures that approval to proceed with change implementation is documented.

- Relevant risk assessments are reviewed and are updated after the implementation of changes.
- Relevant and timely updates are made to regulatory filings, when appropriate, in accordance with the relevant requirements.
- The change management system triggers any required communications with Marketing Authorisation Holders or other parties in relation to changes made.

5.4. **Change Review and Effectiveness:**

Prior to change closure:

- Changes meet their intended objectives and pre-defined acceptance and effectiveness criteria. Any deviations from those criteria are adequately assessed, managed, and justified, or follow-up measures are identified. Whenever possible, quantitative data are leveraged to objectively determine change effectiveness (e.g. statistical confidence and coverage).
- As part of the quality risk management activities, residual risks are assessed and managed to acceptable levels, and appropriate adaptations of procedures and controls are implemented.
- Any unintended consequences or risks introduced as a result of changes are adequately evaluated, documented, mitigated or accepted, and are subject to a pre-defined monitoring timeframe.

Prior to or after change closure:

- Any post-implementation actions needed (including those for deviations from pre-defined acceptance criteria and/or CAPAs) are identified and adequately completed.
- Relevant risk assessments are updated following effectiveness assessments. New product/process knowledge resulting from those risk assessments and from the related change management activity are captured in the appropriate Quality and Operations documents (e.g. SOPs, Reports, Product Control Strategy documents.)
- Changes are monitored via ongoing monitoring systems to ensure maintenance of a state of control, and lessons learned are captured and shared/communicated. (Note: Activities such as Management Review, Annual Product Quality Review, Continuous Process Verification, Deviation Management and Complaint Monitoring can be useful in this regard.)

5.5. Conclusion

The adherence to the above guidance should provide sufficient evidence of an effective science and risk-based change management system. It should drive risk reduction, where possible, to ensure better quality performance, manufacturing performance, continual improvement and innovation, through adequate and timely management of product quality and patient safety risks. Maturity in change management may support maximal benefits from the regulatory flexibilities discussed in ICH Q12.

Note: The input of industry representatives was considered by the PIC/S Expert Circle on QRM during the development of this document.

6. Revision History

Date	Version Number	Reasons for revision

Appendices

Appendix 1: Extract from ICH Q10:

Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches

Scenario	**Potential Opportunity**
1. Comply with GMPs	Compliance – status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g. ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk-based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g. ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g. ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk-based approaches for regulatory inspections; • facilitate science based pharmaceutical quality assessment; • optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.

Appendix 2: List of Abbreviations

PQS	Pharmaceutical Quality System
QRM	Quality Risk Management
CAPA	Corrective Action and Preventative Action
SME	Subject Matter Expert
CPV	Continuous Process Verification
CpK	Process Capability Index
PpK	Process Performance Index