



**PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME**

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2 Appendices
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RECOMMENDATION

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

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1. Document History

Adoption by Committee of PI 054-1	[Date]
Entry into force of PI 054-1	[Date]

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 accord with the considerations that are already typical and commonly applied in a change control process; they do not introduce any new GMP requirement.

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. 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, where risk assessments adequately assess potential risks and benefits of changes to product quality, safety and efficacy, and where those risk assessments assess the potential risks and benefits to other products, processes and systems.
- The categorisation 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.
- 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 the application by a pharmaceutical company of the guidance set out in Section 5 below will provide evidence of the effectiveness of the PQS at that company in relation to risk-based change management. If such a risk-based change management system were in place within the company's 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. This is important not only in the context of the aforementioned PIC/S GMP requirements, it is also important in the context of ICH Q10, which sets out the potential for risk-based regulatory oversight for companies which demonstrate that 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, which is currently under development at ICH in relation to post-approval change management.

- 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.

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

- The trigger(s) for changes and the related evidence are clearly documented. Common lifecycle factors that trigger change include:
 - upgrades to equipment or facilities
 - improvements in raw materials
 - improvements in manufacturing performance and consistency (to reduce variability, improve yield, etc.)
 - enhancements in manufacturing capacity
 - corrections of quality issues
 - addressing signals from the PQS such as deviations, complaints/adverse events, corrective action and preventative action (CAPA), product quality review, operational review metrics, management review, new regulations, compliance gaps
 - implementing innovation or continual improvement initiatives.
- The objectives, scope, expected outcomes and anticipated benefits of the proposed change are documented.
- The potential impacts of the proposed change to other products, processes, systems or sites are assessed and rationales are documented.
- Relevant experts and stakeholders (e.g., various subject matter experts (SMEs), specific departments) are involved in change proposal development and approval.
- The potential impacts to pending/approved filings and regulatory commitments are addressed.
- The system ensures that changes are proposed in a timely manner, that proposed changes are formally evaluated, and that a decision to accept or reject the proposal is documented. For rejected change proposals, the system ensures that the rationales for those rejections are documented, and that continued risks are adequately managed.

5.2. Change Risk Assessments:

Changes typically have an impact assessment performed within the change control system. However, an impact assessment is often not as comprehensive as a risk assessment for the proposed change. Impact assessments often assign categorization to proposed changes, and determine their filing impact, etc., but they do not always fully address what might go wrong with the proposed change. They also often do not address what might be improved, in the context of current product and process knowledge, the control strategy, and the product lifecycle.

Therefore, a structured risk assessment for the change should be performed, and where possible, changes should reduce product quality risks and/or patient safety hazards. At a minimum, the change should not increase these risks beyond current levels and it would not be expected to increase process variability.

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

- The level of rigor, 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, systems.
- Risk assessments identify and document 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.
- Change categorizations 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.
- Data to support the change, as well as acceptance criteria and change effectiveness criteria, are pre-defined in change planning. These may include continuous process verification (CPV) and statistical assessments, (e.g. CpK/PpK) etc., to aid with the quantitative assessment of risk control.
- 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) 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 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 (e.g. annual reporting must include all changes of relevance to filings).

5.4. **Change Review and Effectiveness:**

Prior to change closure:

- Changes meet their intended objectives and pre-defined effectiveness criteria. Any deviations from those criteria are adequately assessed, accepted and managed/justified. 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 evaluated, documented, accepted and handled adequately, 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 post-effectiveness assessments. New product/process knowledge resulting from those risk assessments are captured in the appropriate Quality and Operations documents (e.g. SOPs, Reports, Product Control Strategy documents, etc.)
- Changes are monitored via ongoing monitoring systems to ensure maintenance of a state of control, and lessons learned are captured and shared/communicated.

5.5. Conclusion

The application of 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.

Note: The input of industry representatives was taken into account 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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