PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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Concept Note on a Document prepared by the PIC/S QRM Expert Circle on

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

Note by the PIC/S QRM Expert Circle Coordinating Committee, reviewed by the SCEC and SCT

Introduction

One of the goals of the Expert Circle, as set out in its current mandate, concerns the development of new guidance documents on QRM, the review and updating of existing PIC/S guidance documents on QRM, and contributing to related international standards and documents on QRM. Another goal concerns the development and provision of advanced QRM training courses for GMP inspectors. (Ref. Goals 3 and 1 in the current mandate of the Expert Circle in document PS/W 19/2017.)

In light of these and other goals of the Expert Circle, the future activities of the Expert Circle were discussed at a meeting of the Expert Circle in Taipei in September 2018. That meeting was held immediately after an advanced QRM training course for GMP inspectors that was run by the Expert Circle that same week in Taipei. In relation to the goal to develop new QRM-related guidance documents, the Expert Circle focused on the topic of effectiveness of the pharmaceutical quality system (PQS) in relation to risk-based change management. This was considered a natural progression of the Expert Circle's existing QRM training activities, which for several years had included risk-based change management as a topic in all of its advanced QRM training courses.

Guidance for GMP Inspectors on evaluating the effectiveness of the PQS in relation to risk-based change management was considered important, given the requirements of the PIC/S GMP Guide in these areas (see below). This specific topic had not been dealt with extensively in the existing training materials of the QRM Expert Circle up until then, but it has become a topic of high relevance at this time, given the pending agreement of ICH Q12, for which PQS effectiveness in relation to risk-based change management is a core concept.

The PIC/S GMP Guide requires companies to demonstrate the effectiveness of their PQS, and it requires the application of QRM principles to change control activities. In this regard, Chapter 1 of the PIC/S GMP Guide states the following:

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

Annex 15 states:

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

At the QRM Expert Circle meeting in Taipei, an industry representative who had considerable past involvement in the area of risk-based change management contributed to the discussions. The Expert Circle decided that the topic of PQS effectiveness in relation to risk-based change management was relevant to its mandate for developing QRM-related guidance and advanced training courses, and it was agreed that the Expert Circle would consider developing guidance on the topic.

Following agreement within the Coordinating Committee of the Expert Circle on February 20th 2019, the topic (PQS effectiveness in relation to risk-based change management) was developed in more detail at the April 8th 2019 face-to-face meeting of the Committee in Dublin. The output of that meeting, and taking into account the earlier work that had taken place at the Taipei meeting in September 2018, was a brief document on the topic of PQS effectiveness in relation to risk-based change management. It is proposed that this document be a *PIC/S Recommendation*.

Details of the Document on *How to Evaluate / Demonstrate PQS Effectiveness for Risk-based Change Management*

The document provides practical guidance for GMP inspectors when seeking to evaluate the effectiveness of a company's PQS in relation to risk-based change management. It is important to note that the document does not suggest or create any new GMP expectations or requirements.

The document covers all relevant steps in the change management process – from change proposal, change assessment, change planning & implementation, through to change review and effectiveness checks, and it indicates within each step the aspects that render the PQS to be effective in that area. The 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, 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.

The Expert Circle considers that the application by a pharmaceutical company of the above will provide evidence of the effectiveness of the PQS at that company in relation to risk-based change management. This is important in the context of the aforementioned PIC/S GMP requirements, and it is also important in the context of ICH Q10 (see next section). If such a risk-based change management system were in place within a 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.

Anticipated Benefits of the Document

The document will deliver benefits in several ways. For the QRM Expert Circle, for example, it can serve as the basis for the development of practical training materials and case studies for GMP inspectors in relation to inspecting the effectiveness of the PQS with regard to risk-based change management activities. In addition, the principles set out in the document could be used to assist in updating the current PIC/S QRM Aide Memoire, to delineate a risk-based approach for inspecting change management programmes.

The document will help inspectors better understand what risk-based change management means at a practical level, and how it might be demonstrated by pharmaceutical companies. This is of practical relevance to GMP inspectors, because, as noted above, the PIC/S GMP Guide requires companies to demonstrate the effectiveness of their PQS, and change management is expected to be a major component of the PQS. In addition, the PIC/S GMP Guide requires companies to use risk-based approaches to the management of changes. Therefore, PQS effectiveness and risk-based change management go hand-in-hand and indeed, they complement each other.

There are additional benefits from having guidance in this area also. ICH Q10 sets out the potential for risk-based regulatory oversight for companies which demonstrate that an effective PQS is in place. ICH Q10 indicates that, if the principles and concepts of ICH Q8, Q9 & Q10 are adopted, and if the effectiveness of the PQS is <u>demonstrated</u>, then there may be opportunities for some form of risk-based regulatory oversight from regulators to promote lifecycle continual improvements. This concept was also a cornerstone principle behind FDA's 21st Century GMP initiative, published in 2002.

However, despite ICH Q10 being in place for over 10 years now, the above vision of ongoing continual improvement has probably not been realised to a meaningful extent. The PIC/S QRM Expert Circle, being well-placed to focus on the QRM concepts of the GMPs and of ICH Q10, is seeking to train GMP inspectors on what a good risk-based change management system can look like within the PQS, and how to assess the level of effectiveness of the PQS in this area. The document developed here will form the basis of the training for Inspectors that the Expert Circle will develop in this area.

Next Steps for the Document

It is respectfully requested that this document be reviewed by the SCEC, the SCT and the PIC/S Committee, with a view to agreeing to its publication via the PIC/S website. It is suggested that the document be a PIC/S Recommendation.

The QRM Expert Circle considers that the document would serve as useful guidance for GMP inspectors on evaluating the effectiveness of a company's PQS in the context of risk-based change management. This will likely become especially important when inspecting a company that is seeking regulatory relief for change management as envisaged by ICH Q10 and ICH Q12. The document provides clear and practical guidance that meets current expectations, and which the industry could use within their companies to demonstrate an effective PQS in context of risk-based change management.

It is proposed that the document would carry a statement that the input of industry representatives was taken into account during its development.

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