Part 2: Regulatory Matters

2.1 Demonstrating the Effectiveness of the Pharmaceutical Quality System from a Quality Risk Management Perspective

Kevin O Donnell, Market Compliance Manager HPRA

Introduction

As regulators with the Health Products Regulatory Authority (HPRA) my colleagues and I deal with various problem issues that result in quality defects and recalls of medicines every year. Indeed, in 2018 we investigated approximately 1050 reports of quality defects, and these resulted in 204 recalls of medicines in Ireland. Each of these issues presented risks to patients (and sometimes to animals, in the case of veterinary medicines) which were unintended and unanticipated, and this called into doubt whether the manufacturing processes had truly been validated with QRM principles in mind, as required by the GMPs.

The quality defects area is of relevance to my talk today, because it directly relates to the effectiveness of the manufacturer's pharmaceutical quality system in terms of quality risk management. Truly effective pharmaceutical quality systems from a risk perspective can be expected to provide a high degree of assurance that the batches released by that manufacturer will not present risks to patients and animals via the presence of quality defects in those batches.

ICH Q10 – Annex 1

Reflecting on ICH Q10, published in 2008, which describes the ICH model for the Pharmaceutical Quality System (1), is a good place to begin. In the last decade since its publication ICH Q10 has been widely discussed by the Industry. However, while the document itself is well known, there is little evidence that Annex 1, which describes *Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches*, has been considered to any meaningful extent.

Table 1 opposite is presented in Annex 1 of ICH Q10.

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 Q1O).	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.

Table 1

The first scenario described in the table is that, when companies just comply with the GMPs, there is little opportunity for those companies to access regulatory relief from regulators. However, when companies apply the principles and concepts outlined in ICH Q8 (Pharmaceutical Development) (2), ICH Q9 (Quality Risk Management) (3) and ICH Q10 (Pharmaceutical Quality System), there are opportunities open to them in relation to science and risk-based regulatory approaches, which constitute various forms of regulatory relief, such as reduced frequency and scope risk-based inspections, innovative approaches to process validation, and flexibility in relation to post-approval change management.

A key to this relief is demonstrating the effectiveness of the Pharmaceutical Quality System, as outlined in the ICH Q10 annex. But in my experience, this key aspect of ICH Q10 appears to be poorly understood and not discussed very often.

As regulators, we apply the concepts outlined in ICH Q10 within our agencies, as demonstrated by the following 3 examples:

Example 1: In relation to GMP inspection planning:

Many regulatory agencies, including the HPRA, apply QRM principles and tools when planning GMP inspections. Formal risk ratings are applied to sites that help inform the frequencies of inspections and their scope. At the HPRA, these ratings are derived from the application of a customised version of a PIC/S risk-based GMP inspection planning tool (4, 5) which the HPRA was heavily involved in developing together with inspectors from other agencies. This tool allows for science-based risk ratings to be applied to manufacturing sites – it considers complexity, criticality and compliance-related risk factors when risk assessing sites, and the result is both increased and reduced frequency inspections, as well as a risk-based inspection scope being developed for the next inspection at each site.

Example 2: In relation to risk-based surveillance testing by medicines agencies and Official Medicines Control Laboratories (OMCLs):

Customised and science-based QRM tools have been developed to support the design and execution of risk-based independent surveillance activities performed by competent authorities and their OMCLs. This is where companies and products that score high in risk are more likely to be subjected to surveillance work than others.

Example 3: In relation to the assessment of Marketing Authorisations and their related applications by Competent Authorities:

Risk-based approaches are also applied by assessors when assessing Marketing Authorisation applications, and customised QRM tools have been developed for this work.

Time for Reflection…

While the examples above demonstrate three quite different applications of science and risk-based approaches, it is interesting to note that they have all been regulator-driven, and indeed, regulator initiated. We are generally not seeing companies approach regulators with data which make a case for being granted regulatory relief in these or other areas. It would be interesting to know how many pharmaceutical companies have demonstrated sufficient effectiveness in their Pharmaceutical Quality System to the degree where their regulators have agreed to give them some form of regulatory relief based on science and risk? While data are not readily available on this, it is, from my own experience, likely to be few in number.

It seems that most individual companies do not proactively make the case for receiving risk-based regulatory oversight from their regulators to any meaningful extent, and perhaps there is a lack of proactive initiatives in the area by the industry generally. While regulators do need to be somewhat conservative by nature when it comes to risk, there are opportunities for the industry, via ICH Q8, Q9 and Q10, to access more risk-based approaches by regulators, when the effectiveness of their pharmaceutical quality systems has been demonstrated.

It is timely to discuss this at this time, given the pending finalisation of the ICH Q12 guideline entitled '**Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management**" (6). This guideline is anticipated to be finalised in 2019.

ICH Q12 & Post-approval Change Management

A large part of ICH Q12 focusses on post-approval CMC change management, and it sets out new ways to manage post-approval changes based on established conditions and risk considerations. It places a strong emphasis on the need for an effective pharmaceutical quality system to be in place, and it lists various principles of change management that will need to be complied with in order to access the regulatory flexibility that is envisioned.

It also discusses the role that knowledge management has in relation to triggering post-approval changes that may or may not require prior approval by regulators, and the connection between Knowledge Management and Change Management is presented in a diagram that is reproduced below in **Figure 1**.

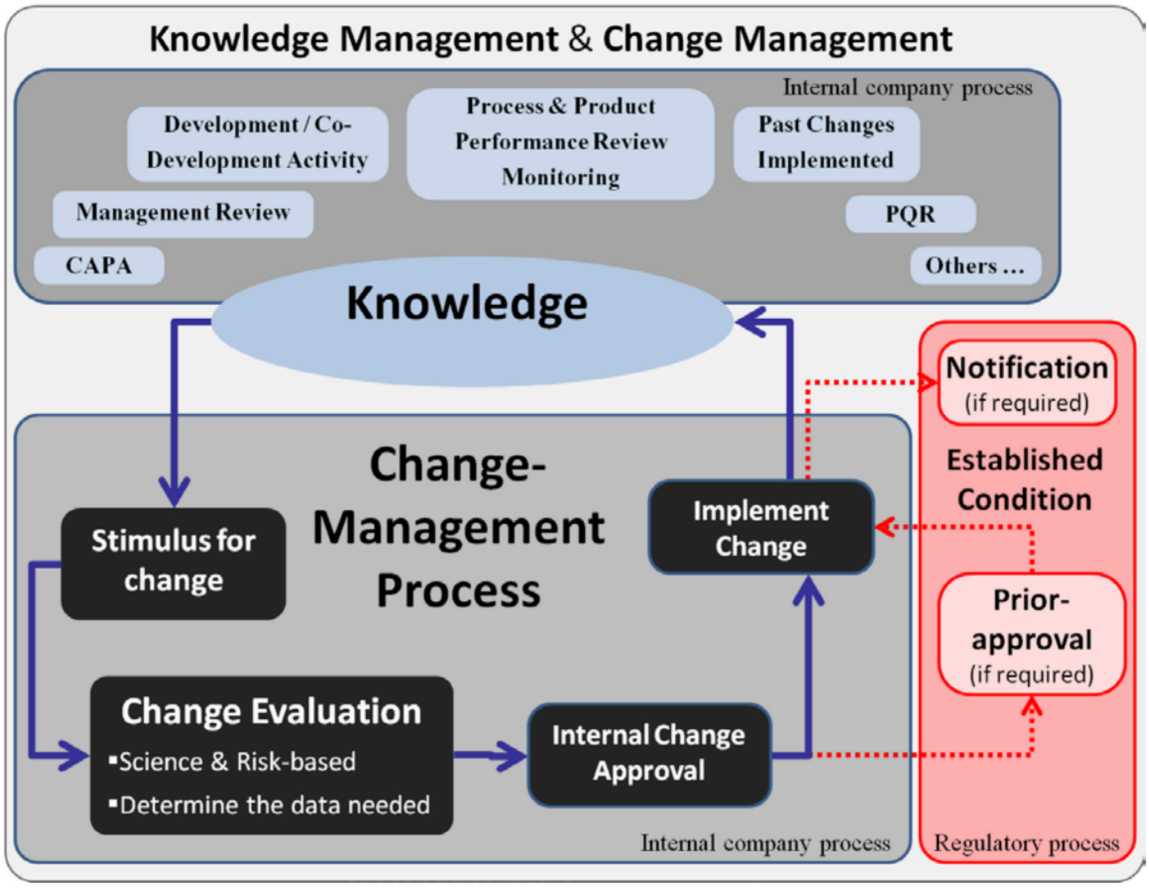

Figure 1

Focusing on the pink section of this diagram on the righthand side, the vision of ICH Q12 is that companies may be allowed to make certain CMC changes with reduced regulatory oversight when they meet certain pre-conditions, and demonstrating the effectiveness of the PQS is one such condition. This all can be linked back to Appendix 1 of ICH Q10, the premise of which is that, where a company applies the principles and concepts of ICH Q8(R1), ICH Q9 and ICH Q10 and demonstrates the effectiveness of its PQS, it may be eligible for some degree of regulatory relief, including relief in relation to post-approval change management.

Demonstrating effective PQS

It is important to note, however, that demonstrating the effectiveness of the PQS is not just an ICH Q10 concept; it is also a core expectation of the EU GMPs (7). The following are relevant extracts from Chapter 1 of the EU GMP guide, which sets out the expectations in relation to the PQS.

- **Principle**: To achieve this quality objective reliably 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**: While some aspects of [the PQS] can be company-wide and others site-specific, the effectiveness of the system is normally demonstrated at the site level.
- **Section 1.4:** A PQS appropriate for the manufacture of medicinal products should ensure:
  xvii) There is a process for self-inspection and/or quality audit, which regularly appraises the ***effectiveness*** *and applicability of the PQS.*
- **Section 1.5**: Senior management has the ultimate responsibility to ensure an effective PQS is in place…

This emphasis in the GMPs on demonstrating that an effective PQS is in place leads one to consider how this may be achieved at a practical level. There is currently little guidance available on this, and the HPRA is interested in exploring this topic. At a simplistic level, one might wonder if it involves some of the following activities:

- *Is it about displaying satisfactory CAPA and other metrics data on a chart in a corridor in a manufacturing plant? (Such charts are now very common in many manufacturing sites.)*
- *Is it about signing off Management Review reports that conclude that everything is in control?*
- *Is it about when all PQRs conclude that the processes are operating consistently?*
- *Is it when there is a low level of non-compliance detected via Self Inspections?*
- *Is it about Corporate Audits resulting in good site ratings?*
- *Is it when no Critical or Major deficiencies were issued at the last regulatory inspection?*
- *Or is it simply about a having a GMP Cert?*

I think that demonstrating the effectiveness of the PQS is more complex than simply doing the above activities. In order to tackle this problem, the HPRA has decided to focus attention on just a sub-set of PQS effectiveness for now, and this relates to PQS effectiveness from the perspective of quality risk management.

Demonstrating PQS Effectiveness from a QRM Perspective

This is a useful approach to take, because so much of the GMPs now rely on effective QRM activities. This is evidenced by the fact that over the last 10 years or so, the EU GMP guide (7) has been significantly revised to incorporate QRM principles and references to risk assessment in several chapters and annexes, such as Chapters 1, 3, 5 and 8, and Annexes 1, 2, 11, 15, 16 and 17.) For example, Annex 15, on Qualification and Validation, now states:

> *'A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes.'*

> *'The way in which risk assessments are used to support qualification and validation activates should be clearly documented.'*

In addition, it is anticipated that the successful implementation of ICH Q12 will rely heavily on QRM, and the current draft carries this wording:

> *'An effective change management system is one that ...requires a science and data-based risk assessment and risk-categorisation of the proposed change, including the management of risk in the event the proposed changed is not implemented.'*

When trying to understand what PQS effectiveness means from the perspective of QRM, one might consider the following:

- Does it mean that all potential quality-related risks posed to patients and animals are rendered low, via risk control or mitigation?
- Does it mean that the QRM activities at a site are seen to be working correctly?
- Does it mean that a site's risk registers show only green risks?
- Might it mean that the objectives of all QRM activities are consistently met? (*What are the typical objectives of QRM activities at sites?*).

Clearly, there is more to do in this area if we are to truly understand how PQS effectiveness might be demonstrated from the perspective of QRM. And in response to this, the HPRA has developed a model that might serve as a starting point or further work in this area. This is described below.

A Potential Model for Demonstrating PQS Effectiveness from a QRM Perspective

In order to develop an approach for *demonstrating PQS effectiveness* from a QRM perspective, the following is one suggested model that may serve as the basis for future work in this area. It is designed around the principles and guidance of ICH Q9 and Q10, and it is based on three key components:

- *The successful integration of QRM with the four key elements of the PQS as set out in ICH Q10:*
  - » *Process Performance and Product Quality Monitoring Performance*
  - » *Change Management*
  - » *Corrective and Preventative Action (CAPA)*
  - » *Management Review of Process Performance and Product Quality*
  - » *The first principle of QRM as per ICH Q9*
  - » *The second principle of QRM as per ICH Q9*

The model can be visualised as shown in **Figure 2** below:

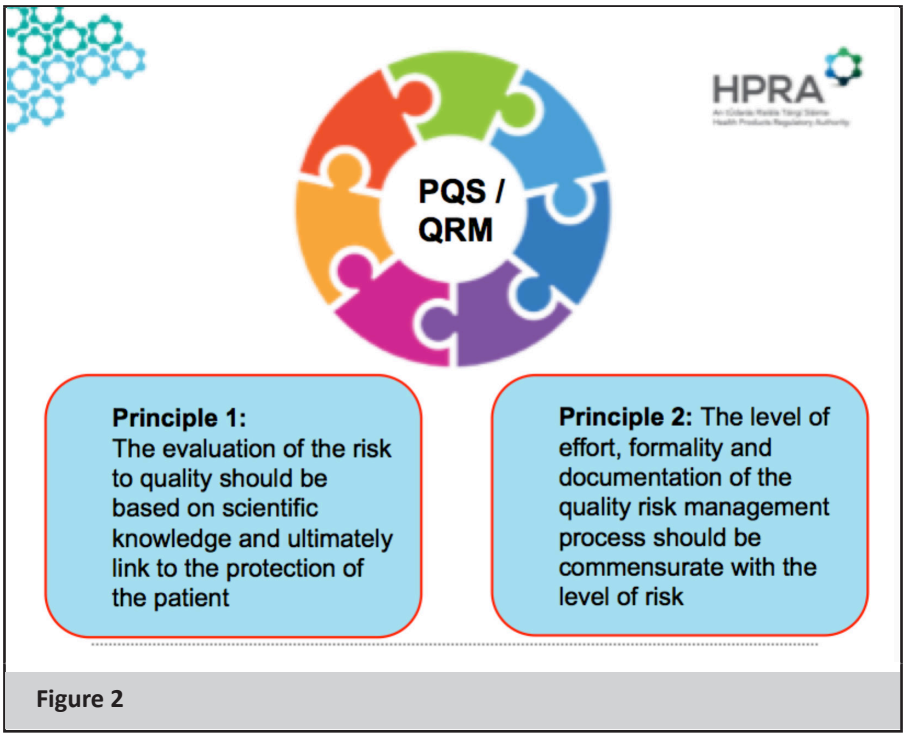

Figure 2

A Potential Model for Demonstrating Pharmaceutical Quality System Effectiveness from a QRM perspective

Reflecting the concepts and principles of ICH Q9 and ICH Q10

The Pharmaceutical Quality System (PQS) can be considered effective from a Quality Risk Management (QRM) perspective when one can show the following:

1. QRM is integrated across the four key elements of the PQS as per ICH Q10

The Process Performance and Product Quality Monitoring Performance System: for example;

- The control strategy has been informed by an understanding of process and other risks to Critical Quality Attributes (CQAs), and it can be directly expressed in terms of risk control.
- Risk assessment and risk control activities have informed the design of Qualification and Validation protocols.
- The system generates verifiable data that demonstrates the state of control at any point in time as well as indicating areas for improvement to reduce variability.
- The monitoring system provides empirical evidence that the risks of producing out-of-specification / defective / non-compliant batches are under adequate control.

The Change Management System: for example;

- All Change Controls deliver demonstrated risk reductions or they ensure there is no increased risk to product quality.
- When using QRM to evaluate proposed changes, the level of testing performed during and after the change control is commensurate with the level of risk.
- The system drives innovation and continual improvement which lead to reduced risks.

The Corrective and Preventative Action (CAPA) System: for example;

- There is a high degree of assurance that CAPAs deliver the required level of risk reduction with respect to the root causes and consequences of deviations, complaints, non-compliances, audit findings, and other issues.
- The system emphasises CAPAs that focus on prevention rather than detection.

The Management Review of Process Performance and Product Quality element: for example;

- Management Reviews lead to improvements in manufacturing processes and products, resulting in risk reductions.
- They lead to the provision of training and/or a realignment of resources where required, resulting in adequate risk control and in the necessary QRM competencies being in place.

- They lead to the capture and dissemination of process and product knowledge, facilitating more robust risk assessments.
- The Management Review system verifies that the four elements of QRM as per ICH Q9 (Risk Assessment, Risk Control, Risk Communication and Risk Review) are in operation to the required standard and that they feed into decision making.
- The self-inspection programme is designed taking process complexity, criticality and risk into account and it generates data that confirms that the state of control is maintained.

2. *Scientific knowledge is applied in all risk assessments*

- Risk Assessment tools or approaches result in the scientific measurement (or at least reliable estimation) of risks, both before and after risk mitigation.
- The role that GMP controls have with respect to the probability of occurrence, severity and detection of hazards / negative events is documented (when these three factors are rated or considered during risk assessment and risk control exercises).
- The factors that can lead to subjectivity and uncertainty (e.g. human heuristics) in the outputs from risk assessments are addressed by science-based countermeasures.
- Risk control strategies are predominantly based on prevention rather than detection.

3. *The evaluation of risk to product quality ultimately leads to patient protection*

- Meaningful risk reduction is achieved for patients as a result of risk assessment and control activities that relate to product quality.
- One can measure (or estimate) product quality risk levels and residual risk levels as they relate to patients.

4. *The level of effort is always commensurate with the level of risk*

- ***Question***: How can companies demonstrate that the level of effort which was applied was sufficient?
- Is it about the degree of rigour applied during a risk assessment?
- Is it about reflecting complexity? The more complex the subject matter, the more rigorous the risk assessment needs to be?

(Note: This part warrants further research work.)

5. The level of documentation is always commensurate with the level of risk

- ***Question***: How can this be demonstrated?
- In a complex manufacturing process that is under a good state of control, the risks of producing a defective and harmful batch may be low, so is a low level of documentation of QRM activities sufficient here?

(Note: This part warrants further research work.)

6. The level of formality is always commensurate with the level of risk

- Question: What is formality in QRM?
- Is this about using tools (or not using tools)?
- Is it about how much rigour is applied?

(Note: This part warrants further research work.)

Conclusion

The model presented in this paper is intended as a starting point for discussion and dialogue on how to demonstrate the effectiveness of a site's PQS from a QRM perspective. While the model is relatively simple in structure, it has been designed around the concepts and guidance of ICH Q9 and ICH Q10, and it incorporates a number of key areas of importance, including the following:

- Proactive approaches to QRM (e.g. Change Management, Qualification & Validation activities, etc.)
- Reactive approaches to QRM (e.g. CAPA activities)
- Product-related monitoring activities
- Process-related monitoring activities
- Management activities
- The need for good science
- Effort, Formality and Documentation-related considerations
- And importantly, patient protection.

It is hoped that this model may serve as the basis for additional work in this area over the next year or two, so that practical solutions may be developed by the pharmaceutical industry as individual sites may seek to demonstrate the effectiveness of their PQS in relation to QRM.

In relation to the question of how can companies get to the stage where they are able to access the regulatory flexibility foreseen by Annex 1 in ICH Q10, perhaps this model may serve as a useful place starting point.

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