Development of the Self Inspection Programme to Assist Demonstrating PQS Effecetiveness

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Abstract

Demonstration of an effective pharmaceutical quality system (PQS) is a regulatory requirement and is essential if pharmaceutical companies are to achieve the flexible regulatory approaches envisioned by ICH Quality guidelines, the most recent being for post-approval changes as per ICH Q12. While self-inspection has the potential to be a useful tool in achieving this demonstration, the evidence suggests that it is currently under-utilised. Therefore, a research study was performed with the aim of determining how self-inspection might be used to demonstrate the effectiveness of the PQS, the findings of which are outlined in this paper.

The research methodologies employed to achieve the research aim included a literature review of the regulatory requirements and guidelines associated with self-inspection and PQS effectiveness and other literature associated with these topics, along with a review of the output of brainstorming studies performed by MSc. Peer Focus Groups at Technological University (TU) Dublin. Finally, three Subject Matter Expert interviews were conducted.

Based on the research findings, a roadmap for taking a QRM approach to the self-inspection process was developed, which when applied may demonstrate the effectiveness of the PQS from a Quality Risk Management (QRM) perspective. A checklist was also generated for performing an internal audit of the self-inspection process to verify its effectiveness. Additionally, a self-inspection checklist was generated for each element of the PQS as per ICH Q10:

1. Process Performance and Product Quality Monitoring
2. Change Management
3. Corrective and Preventive Action
4. Management Review

1. Introduction

An effective pharmaceutical quality system (PQS) is an essential part of any pharmaceutical company's operations, underpinning all activities that take place at a site. In spite of the fact that regulators have been proposing the concept of *regulatory relief* by demonstrating the effectiveness of the PQS for many years now, there is little evidence (Greene *et al.*, 2019) that companies proactively approach regulators to consider applying for such relief as

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envisioned in ICH Q10 (Pharmaceutical Quality System) (ICH, 2008), and more recently ICH Q12 (Technical and regulatory considerations for pharmaceutical product lifecycle management) (ICH, 2019). One wonders if the reluctance to apply for regulatory relief is a result of the lack of clarity on how to demonstrate the effectiveness of the PQS.

To address this, Dr Kevin O'Donnell from the Irish Health Products Regulatory Authority (HPRA) presented a potential model for demonstrating the effectiveness of the PQS from a Quality Risk Management (QRM) perspective (Greene *et al.*, 2019). The model is based on 'successful integration of QRM with the four key elements of the PQS' as per ICH Q10: Process Performance and Product Quality Monitoring (PPPQM), Change Management, Corrective and Preventive Action (CAPA) and Management Review; together with the demonstration of the application of the two principles of Quality Risk Management (QRM) as per ICH Q9: that the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and that the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk. This model presented by O'Donnell is reproduced in Figure 1.
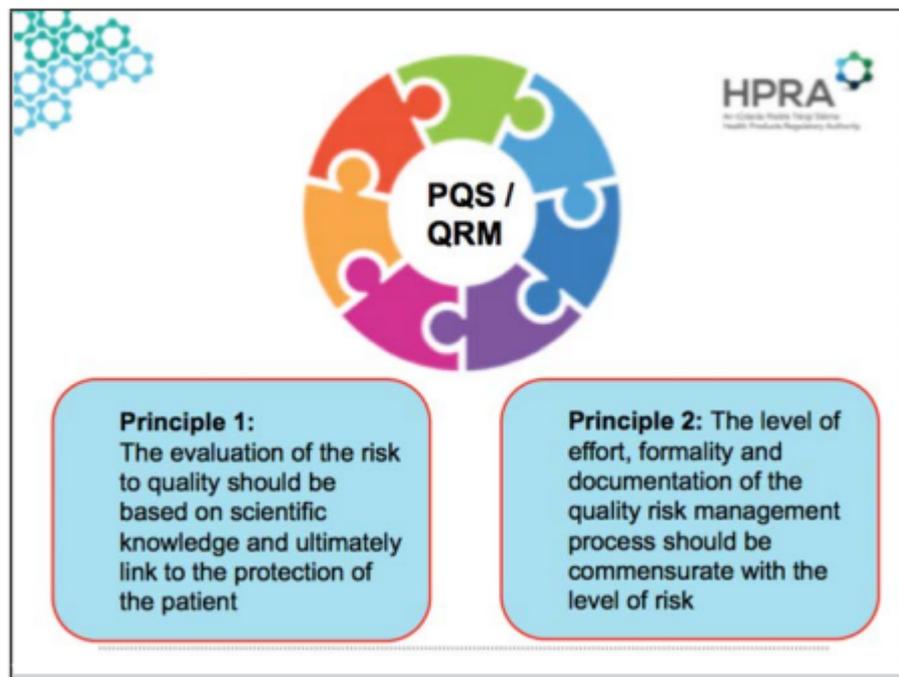

Figure 1: A visual representation of a model for demonstrating PQS effectiveness from the perspective of QRM as presented by O'Donnell (Greene et al., 2019).

In the opinion of the authors, a key process for a company in demonstrating PQS effectiveness is the existence of an effective self-inspection programme as described in Chapter 9 of *EudraLex Volume 4* (European Commission, 2019).

A research study into Self Inspection in 2019 reviewed the deficiencies found during HPRA inspections, from 2013 to 2017, revealing that in almost one fifth of inspections carried out during the period in which self-inspection was reviewed, a deficiency relating to self-inspections was found (O'Mahony 2019). The majority of these deficiencies were categorised under 'QRM' and 'Procedure', with 'Management Commitment' not far behind, suggesting that there are insufficient risk-based processes for self-inspections in place in those companies.

Furthermore, O'Donnell first highlighted self-inspection as an area for improvement in 2008 (O'Donnell, 2008), and repeated this again in 2010 (Poska, 2010). O'Donnell suggests that self-inspection programmes were not delivering the value that they were capable of giving, with obvious deficiencies being found in regulatory inspections that should have been identified in an internal audit. Perhaps the lack of improvement seen in the area of self-inspection may be due to the level of resources committed to the process by management being too low, a suggestion which is supported by the evidence presented by O'Mahony.

This paper explores approaches companies could take to better utilise self-inspection in demonstrating PQS effectiveness through a research study which involved:

- A literature review of the current regulations, guidelines and related peer reviewed papers.
- A review of brainstorming studies performed by MSc Peer Focus Groups at Technological (TU) Dublin.
- Subject Matter Expert (SME) interviews to gain insight into current opinions on the research topic from a regulatory and industry perspective.

This study was carried out between June and November 2020 as part of the Masters of Science programme in Pharmaceutical Quality Assurance at Technological University (TU) Dublin. The outputs of the study were as follows:

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1. A 'roadmap' or process outline for an effective self-inspection process

2. A checklist for the internal audit of a self-inspection programme

3. A checklist for an internal audit of the four PQS elements as per ICH Q10.

The roadmap and checklists can be used by companies to assist in the development of their self-inspection programme to aid in demonstrating the effectiveness of the PQS.

2. Literature Review

A literature review was carried out to determine current regulatory requirements, best practices and enablers for self-inspection, and for the demonstration of PQS effectiveness.

2.1 Regulatory Requirements

EU GMP requirements

Looking first at the EU GMP requirements, it was found that while the PQS is cited throughout most chapters of the European Union (EU) Good Manufacturing Practices (GMPs), Chapter 1 deals exclusively with the core elements of the PQS which includes the requirement for implementing, documenting and monitoring the effectiveness of the PQS (European Commission, 2019). Amongst other requirements in the chapter, it specifically states that:

> *"A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that there is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System".*

However, Chapter 9 Self-Inspection does not describe in any detail a process that could be used to appraise the effectiveness and applicability of the PQS. In fact, the most notable finding of this review is the significant lack of detail in Chapter 9. It consists of only 4 paragraphs; an introductory sentence and three listed requirements: self-inspections should

be scheduled according to a programme, conducted in an independent manner, documented, and the purpose of which is to ensure compliance with GMP and quality assurance principles.   There is no explicit reference to PQS, QRM or continuous improvement in the chapter.

US GMP Requirements

Turning now to the US GMP requirements, it was found that there is no direct reference to quality system effectiveness, internal audits or self-inspection in the US Food & Drug Administration (FDA) requirements CFR 210 and 211 (FDA, 2019a; FDA, 2019b). However, FDA's guidance document entitled '*Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*' does detail the requirement for maintaining a 'robust' quality system, along with the requirement to conduct internal audits stating:

> "*A quality systems approach calls for audits to be conducted at planned intervals to evaluate effective implementation and maintenance of the quality system and to determine if processes and products meet established parameters and specifications.*"(FDA, 2006)

While some of the detail is similar to that found in Chapter 9 of *EudraLex Volume 4*, the paragraph on internal audits is more extensive and incorporates the consideration of risk management. For example, it is explicitly stated that the audit schedule must be based on the 'relative risks' of the quality system activities, along with 'the results of previous audits and corrective actions'.

2.2 Best Practices for Self-Inspection

While the regulatory details for self-inspection were found to be scarce, a review of the literature was carried out in an attempt to identify any best practices reported. The key findings from this review of best practices in relation to self-inspection can be summarised as follows:

- The programme must be designed to meet the needs of the company (Tsvetanova, 2014; O'Mahony, 2019).

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- A risk-based approach to self-inspection planning should be taken (EMA, 2010; Coetzee and Lubbe, 2014; Sandle, 2016; Nikityuk *et al.,* 2019).

- The scope of the audit must be challenged. It should not just be about ensuring compliance to procedures but also challenging the content of those procedures (Poska, 2010). Further, it should be ensured that the PQS is integrated into each process by focusing on ICH Q10 content in audits (Macuvele, Eich and Ritz, 2019).

- A process-based approach should be taken where audits are focused on the processes within the PQS rather than on individual structural units, i.e. they are conducted as process audits rather than functional audits (Nikityuk *et al.*, 2019).

- Auditor training and competency should be a priority (Poska, 2010; Karamavrova, 2018; Qiu *et al.*, 2018; O'Mahony, 2019).

- Those who perform or manage a process should be involved in the internal audit to ensure a transfer of knowledge (Shanley, 2020b).

- Audit findings should be trended, particularly for root causes of non-conformities, to identify risks or recurring trends that may require further investigation (Shanley, 2020a).

- Self-inspection should be used as an enabler for improvement (Howell, 2015).

- Management commitment is needed to ensure follow up of audit actions (Venkatesh and Puranik, 2018; Hanskamp-Sebregts *et al.*, 2020).

The literature review highlighted the lack of guidance in the regulatory requirements and identified several best factors for self-inspection, however there was no real information found on how to demonstrate the effectiveness of the PQS so further research was carried out on this, through Focus group reviews, and SME interviews.

3. Peer Focus Group Review

A study was conducted to identify examples of industry best practices for 'Demonstrating Effectiveness of the PQS from the perspective of QRM', as per the model presented by O'Donnell, by two Pharmaceutical MSc. classes in TU Dublin. These studies were performed by six peer focus groups of eight part-time MSc. students made up of a combination of 'Pharmaceutical Quality Assurance and Regulation' and 'Pharmaceutical

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Validation Technology ' course members during the period of October – December 2019. All students involved in these studies were employed in pharmaceutical and related sectors at the time of the studies.

An intensive review of the output of these focus group studies was performed by the author, to identify best practices amongst the participating members companies and highlight areas that could be emphasised in the self-inspection process with respect to demonstrating PQS effectiveness. This review gave the authors access to case studies from a number of different companies and sectors of the pharmaceutical and medical device industry, giving a good reach within the context of the research topic.

The findings from the focus group review initiated the development of '*Internal Audit Checklis*ts', which were built upon following the learnings from the literature review and SME interviews described in the next section.

4. SME Interviews

Three interviews were carried out during the autumn of 2020, two with GMP Inspectors from the HPRA both with a particular interest in this topic, and one with a senior GMP consultant. The purpose of the interviews was to explore the SME's views on the following topics:

- The current situation with respect to Self-Inspection
- Key essentials for effective Self-Inspection
- Possible opportunities to reframe Self-Inspection such that it contributes to a company demonstrating the effectives of its PQS
- How to present Self-Inspection findings to regulators
- The use of metrics relating to Self-Inspection

4.1 Current situation

All three interview candidates agreed that there has been little change in self-inspection since it was first highlighted as an area for improvement by O'Donnell in 2008. To date, self-inspection has been about compliance, not about adding value to a company. The regulator's approach to self-inspection was cited as a possible reason for this lack of improvement by each interview candidate. Regulators spend little time on self-inspection, it is not even examined in some audits. Where it is reviewed, it is seen as low-risk and is a cursory check for a procedure, schedule and schedule adherence. Additionally, a significant contributor to the status of self-inspection programmes in

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industry relates to the lack of detail and change to Chapter 9 of the EU GMPs, as identified in the literature review.

A theme that emerged from the study is that: *when there is no obvious value placed on Self-Inspection by the regulators, little value will be put in it by the companies themselves.*

4.2 Self-inspection essentials identified during the SME interviews

Relationship between the auditor and auditees

It must be reinforced to the auditees that the purpose of the internal audit is not to catch someone out, but instead is an opportunity for risk identification and improvement. There needs to be open, collaborative sharing between auditors and auditees.

Management commitment

Management focus tends to be concentrated on six sigma, Operational Excellence (OpEx), and similar projects, with little value placed on improvements that could be gained from having a well-functioning self-inspection system. It would be of benefit if management could refocus on programmes such as self-inspection which may improve quality, and subsequently reduce corrective costs, i.e. the more hidden costs of poor or 'non'-quality. This could start by dedicating a responsible person at Management level for overseeing self-inspection. Management support and seniority is also required to ensure implementation of significant audit findings, for example, repeated deviations or out of specification results highlighted during the Self-Inspection process may indicate a need to redesign or implement a new process.

Auditor competency

The auditor must have knowledge and expertise in the area being audited to get any value from self-inspection. Currently internal auditors are often junior roles in the company, this is a potential issue as they may not yet have the level of expertise required to properly challenge procedures. As processes become increasingly complex and automated, it will only become harder for companies to adequately inspect themselves. Using experts from sister sites may be beneficial to overcome this challenge. Finally, if the internal audit is to have a focus on risk identification and measuring risk reduction, retraining of auditors may be required.

4.3 How to reframe self-inspection?

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For the programme to have value, it must move away from simply validating compliance to procedures and needs to be refocused. The following proposals were made by the interview candidates:

- Reframe self-inspection as an opportunity for risk identification and improvement.
- Re-emphasise self-inspection as a cost-reduction programme by capturing trends and deficiencies that could later lead to non-conformances in regulatory inspections, or recalls.
- Take a more competency-based approach. Area or process owners could be asked to self-assess and benchmark their own processes. Subsequently, self-inspection could be used collaboratively to identify improvement opportunities.

4.4 What to present to the regulator?

While it is not common practice to present self-inspection findings and reports to the regulator, all three interview candidates discussed the paradigm shift with the incoming of ICH Q12 and how the approach from all sides may need to change soon.

In terms of what could be presented to a regulator, the following was discussed:

- Demonstration that the self-inspection programme is less focused on deficiencies and more about identifying opportunities for continuous improvement and using it as a risk identification tool, which would in turn trigger the risk management process. Additionally, the risk register, risk assessments, and similar PQS documents, should show that audit findings were considered. Evidence for such is not seen at present.
- A sense of management commitment could be imparted through proactive presenting of metrics boards, meaningful improvement projects, and management review. It was noted by both GMP inspectors that it is rare that a company is proactive in presenting visual management boards. This was also addressed with the GMP consultant who suggested that there is little tangible value for companies to do such an activity.
- Presenting an auditor competency or training programme if a value-adding one is in place.

4.5 Use of metrics

Metrics can be valuable but only if they are appropriate for what they are measuring – often this is not the case. Three high level metrics as an outcome of self-inspection were proposed; degree of risk reduction, level of continuous improvement, and outcome of regulatory inspections. However, it was noted that the outcome of regulatory inspections is currently considered an unfair metric as

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internal audits do not come close to the level of rigor and resources applied for external audits. For example, holistic analysis of data tends not to be performed during internal audits, however this is the approach that regulators would take. Further, having a patient centric focus throughout an internal audit would serve to align the approaches taken to internal and external audits, by ensuring decisions are always linked to the protection of the patient. 'Outcome of regulatory inspections', and other benchmarking exercises, will only be appropriate as the gap closes between internal and external audits.

5. The Development of a Self-Inspection Roadmap

The research findings from the literature review, Peer Focus Group review, and SME interviews were amalgamated to develop a process outline, or 'roadmap' for a self-inspection process that if implemented may serve to demonstrate PQS effectiveness. An outline of the self-inspection roadmap is provided in Figure 2, the steps of which are discussed in this section. In addition, 5 checklists were generated from the research findings that could be used for an internal audit of the self-inspection process itself and the 4 PQS elements as per ICH Q10. These checklists are presented in an appendix to this paper. The main intention of the roadmap and checklists is to ensure that QRM and management commitment are embedded throughout the self-inspection and the PQS processes. It is important to note that the structure and content of a self-inspection process at a facility is dependent on its own activities.

5.1 Outline of the Roadmap

The roadmap is presented in six steps as follows:

1. Assign a Responsible Person
2. Define the processes to be audited
3. Define the programme
4. Define the schedule
5. Perform the audit
6. Audit outcomes
7. Assess Effectiveness

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Step 1: Assign a Responsible Person

A dedicated *'responsible person'* from the quality unit should be assigned to oversee and drive the entire self-inspection process. This person should be of suitable seniority and at management level within the company. Top management should give that person the freedom to evolve and improve the process. It must be ensured that the responsible person has appropriate training, qualification and understanding of the requirements for self-inspection to be effective.

The responsible person should oversee a cross-functional team of internal auditors and assign auditors to individual audits based on their competencies. Those performing the audit should be independent of the process being audited where possible, while still having the required competency to adequately perform a value-adding audit. If the auditors have an understanding of the process they will be equipped to challenge the procedures that are being audited. If there is a gap in competency requirements, consideration should be given to the use of external experts or experts from sister sites within the organisation.

Step 2: Define the processes to be audited

The processes to include in the self-inspection programme must be determined. While the items listed in Chapter 9 of the EU GMPs need to be included in some capacity, organisations should consider expanding the scope of processes to be audited. For example, the four elements of the PQS should also be included, suggested checklists for which are provided in the Appendix to this paper. Additionally, other examples to consider for inclusion are supplier qualification and management, data integrity, process design and development, performance of mock recalls, and interactions between outsourced activities and the marketing authorisation holder. Ultimately, the processes to be audited will be dependent on the structure of the organisation.

A number of documents may aid in this step. SOPs or similar procedural and/or policy documents are likely already available for many or all processes, and this will be a good starting point. Additionally, process maps and process flow diagrams may already be

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available for manufacturing processes and some utilities. While outside the scope of the self-inspection process, an additional prerequisite that may be beneficial is to generate process maps of the processes to be audited as per ISO 9001:2015 (ISO, 2015). These maps should demonstrate the inputs and outputs, the steps of the process, interactions with other processes, resources and responsibilities, and methods of measuring and monitoring for control and effectiveness of the process. In particular, this type of exercise should demonstrate where systems or processes are complex and tightly coupled.

Step 3: Define the programme

All processes identified in Step 2 should be considered in the self-inspection programme and then be categorised and prioritised for self-inspection based on their associated risk. A suggested method to consider when defining the programme is:

a. Gather all useful data from activities *already* performed at the site. Documentation to be used includes risk assessments, risk register, management review reports, previous audit findings (Internal and external), and Product Quality Reviews (PQRs). The documents detailed in Step 1 may also be useful.

b. Evaluate the risk.

A risk ranking system may be used. Holistically review the gathered data to evaluate the inherent or intrinsic risk (based on process complexity and criticality) and the variable or compliance risk (based on previous audit findings). Process complexity should include supply chain complexity and the extent of outsourced activities.

Other risk factors may be considered such as personnel changes, new process introductions, new process changes, recurring deviations/trends, regulatory updates, delay in implementing previous audit finding CAPA and time since last inspection.

c. Define the scope and frequency for self-inspections of each process identified in Step 2.

This should be based on the risk evaluation and be an iterative process. Self-inspection is an iterative process and thus the programme must be frequently

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reviewed and updated based on new information gleaned from the other elements of the PQS.

Step 4: Define the schedule

The schedule should be generated from Step 3 'Define the programme' above, detailing the internal audits to be performed in the schedule period. A suggested method to consider when defining the schedule is:

a. Define the resources required, along with objectives, scope and criteria for each individual audit based on the risk evaluation in Step 3.

b. Further define the scope using risk assessments already performed. Specific elements of the process that are considered to have an inherently 'high' risk associated with them and their control measures, or those with a high level of residual risk, may be included. Conversely, depending on the risk, it may not be necessary to audit all steps or control points within a process.   For example, elements of the process that are lower risk or are considered to be in a demonstrated state of control (through PQRs, continuous process verification, PPPQM, risk assessments etc.) may be suitable for exclusion.

c. Include the four elements of the PQS and how the process interacts with them in the audit scope. This ensures that the PQS is considered in all audits performed, providing sufficient evidence that the PQS is effective. Appropriate elements of the PQS checklists are given in the Appendix to this paper.

Step 5: Perform the audit

Only objective evidence should be considered and relied upon for satisfying the audit criteria. All audit findings should be documented with reference to the objective evidence

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supporting those findings.   While ensuring compliance to regulations and procedures is a requirement, other factors to consider are as follows:.

a. Focus on identifying risks and potential opportunities for improvement.

This may also include ensuring there are procedures in place in the event of something going wrong, or if a potential hazard occurs in the process.

b. Take a collaborative approach.

It is vital that those closest to the process are interviewed and consulted as part of the audit process, to capture the tacit knowledge that may otherwise be missed. This type of collaborative approach provides an opportunity to identify strengths and weaknesses in the process from those who are a part of it, and should be maintained during assessment and follow-up of the audit outcomes too. Simple questions that could be asked are 'what would you like to change about the procedure or process?' and 'what do you think is/is not working?'. These types of open questions allow a flow of information and reassure the auditee that the purpose of the audit is not to catch them out.

c. Take a holistic approach

Audits should not just be performed vertically, lateral thinking should be employed, i.e. it should be considered how one process may influence another and ensure that these linkages are reviewed.   It may be appropriate to consider the Plan -Do –Check-Act cycle approach to the process during the audit.

d. An opportunity to assess QRM

This may be in the form of verifying risk control measures are effective (e.g. process is in a statistical state of control), or through risk review to verify appropriateness of the residual risk decisions made (e.g. no new deviations raised, CAPA review etc.). In addition, it should be considered whether the risk decisions made were based on scientific knowledge and had a patient centric focus.

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Step 6: Audit outcomes

The output of the internal audit should become inputs to the other elements of the PQS. Audit findings and recommendations should also consider the impact that they may have on other processes within the organisation. Suggested actions to consider are:.

a. Immediately following the audit, the risk evaluation performed during Step 3, 'Define the programme' should be assessed and updated if required. It may also be beneficial to document whether management support was demonstrated throughout the audit through the provision of required resources.

b. CAPAs raised

If non-conformances are identified, they should be assigned a level of criticality in order to establish how they should be managed, the extent and magnitude of the non-conformity should be commensurate with the investigation and correction and/or prevention. This criticality determination should include risk assessment in which risk to patient safety and product quality is considered.   The non-conformances should be entered into the deviation management/CAPA system and investigated for root cause.

Some audit findings may be recommendations for improvements. Of particular importance could be to recommend reviewing processes that are found to be complex and tightly-coupled to determine if they can be simplified. As mentioned, a collaborative approach with the owners of the process or area being audited is again important during these steps.

c. Risk review

If new risks are identified, risk review should be performed for the process and new control measures implemented if necessary.   The risk register should be updated as required based on the audit findings.

d. Management review

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The audit findings should be an input into the management review process. The internal audit report should provide key information on the status of a process that can then help to determine where attention should be placed in management review.

<u>Step 7: Assess Effectiveness</u>

A number of Key Performance Indicators (KPIs) may be reviewed that indicate the self-inspection programme is operating effectively and these are given in Figure 2. An internal audit of the self-inspection process itself should also be undertaken to appraise its effectiveness. A proposed checklist for performing such an internal audit is found in the Appendix of this paper.

6. Development of Internal Audit Checklists

A series of 5 Checklists were developed, the purpose of which were to provide a basis of questions to be considered by the auditor during the internal audit that, when checked, should contribute to the demonstration of PQS effectiveness, particularly from a QRM perspective. Some notes and additional questions are given under each checklist item to aid the auditor. However, the checklists are not intended to be totally prescriptive, nor used in isolation. The checklists may also be useful in aiding a company in identifying gaps between the current state of their own processes and a more desired state.
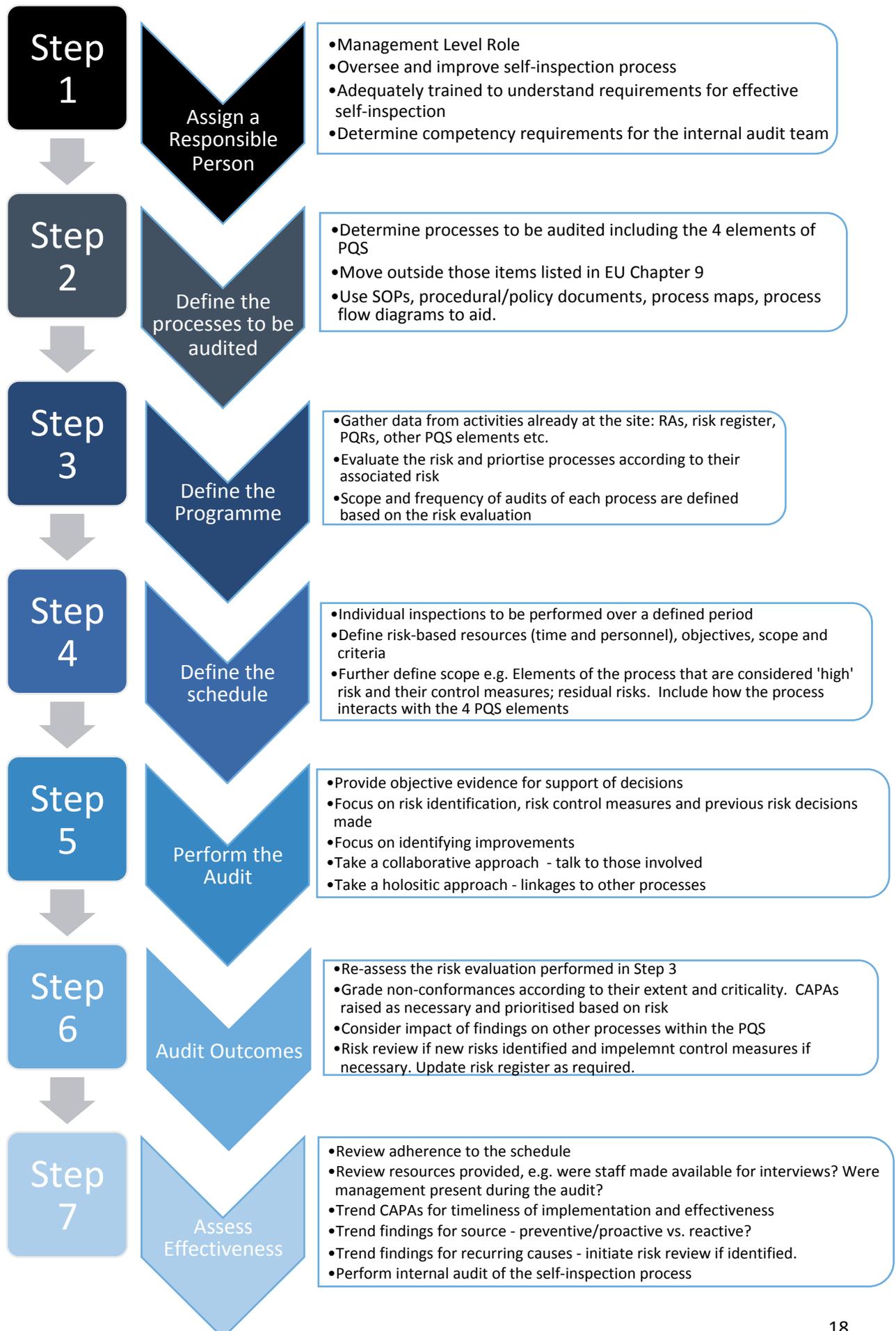
The questions outlined in the checklists were considered to ensure that they were not just 'tick-the-box' exercises. While it is important to ensure that there are documented procedures in place, there must also be consideration of the content of those procedures. A review of decisions made should be performed, whether that be as an acceptance of the residual risk in a risk assessment, stating that a process is in a state of control following a PQR, a prioritisation of a CAPA implementation, or the decision not to implement a change proposal, to name a few. While it is not specifically itemised in the checklists, reviewing decisions in this way is both a good QRM and KM review exercise. The auditors are assessing whether the decisions taken were appropriate and effective, based on objective evidence. The capturing and review of these decisions

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in the audit report should aid in demonstrating QRM and KM effectiveness, and in turn PQS effectiveness, at the site.

The importance of management commitment was repeatedly identified throughout the research. Therefore, this was also a consideration in building the checklists. Management behaviours, quality culture, application of resources, risk-based decision making, provision of training, and continuous improvement focuses are present throughout the checklists to give an overview of the management commitment to the PQS and its enablers at the site.

Finally, while some suggestions for metrics and monitoring are given in the checklist, it is advised that companies develop metrics and KPIs appropriate to their own quality systems and quality objectives. One note to be made, however, is a negative attitude towards strict time-related metrics was found in the literature review, the Peer Focus group review, and the SME interviews, specifically having 30 day close out times for CAPA investigations, for example. These types of metrics may drive insufficient investigation and lack of identification of true root causes, thus causing recurrence in the long run. An alternative approach may be to monitor the time CAPAs, investigations, change management action plans, etc. are open to ensure schedule adherence and re-application of resources based on the risk to product quality and patient safety. This would be a more beneficial demonstration of an effective PQS than an early close out of a root cause investigation, in the authors' opinion.

Figure 2: Suggested outline of the self-inspection process

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Step 1

Assign a Responsible Person

- Management Level Role
- Oversee and improve self-inspection process
- Adequately trained to understand requirements for effective self-inspection
- Determine competency requirements for the internal audit team

Step 2

Define the processes to be audited

- Determine processes to be audited including the 4 elements of PQS
- Move outside those items listed in EU Chapter 9
- Use SOPs, procedural/policy documents, process maps, process flow diagrams to aid.

Step 3

Define the Programme

- Gather data from activities already at the site: RAs, risk register, PQRs, other PQS elements etc.
- Evaluate the risk and priortise processes according to their associated risk
- Scope and frequency of audits of each process are defined based on the risk evaluation

Step 4

Define the schedule

- Individual inspections to be performed over a defined period
- Define risk-based resources (time and personnel), objectives, scope and criteria
- Further define scope e.g. Elements of the process that are considered 'high' risk and their control measures; residual risks. Include how the process interacts with the 4 PQS elements

Step 5

Perform the Audit

- Provide objective evidence for support of decisions
- Focus on risk identification, risk control measures and previous risk decisions made
- Focus on identifying improvements
- Take a collaborative approach - talk to those involved
- Take a holositic approach - linkages to other processes

Step 6

Audit Outcomes

- Re-assess the risk evaluation performed in Step 3
- Grade non-conformances according to their extent and criticality. CAPAs raised as necessary and prioritised based on risk
- Consider impact of findings on other processes within the PQS
- Risk review if new risks identified and impelemnt control measures if necessary. Update risk register as required.

Step 7

Assess Effectiveness

- Review adherence to the schedule
- Review resources provided, e.g. were staff made available for interviews? Were management present during the audit?
- Trend CAPAs for timeliness of implementation and effectiveness
- Trend findings for source - preventive/proactive vs. reactive?
- Trend findings for recurring causes - initiate risk review if identified.
- Perform internal audit of the self-inspection process

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7. Conclusion

The research study and literature review identified that the content of internal audit reports are not typically looked at by regulatory authorities during inspection (FDA, 2006; EMA, 2010). Furthermore, there is currently little time spent on reviewing the self-inspection process during regulatory inspections, due to other areas taking priority. Thus, relying on presenting internal audit reports to the regulator to demonstrate PQS effectiveness is not currently a suitable approach.

Two key areas which could help address the lack of emphasis on Self-Inspection are suggested as follows:

- Management Commitment
- Regulators' focus

It was identified that an overall sense of *management commitment* to the self-inspection programme, and continuous improvement in general, may serve as an alternative and more realistic approach to demonstrating PQS effectiveness through self-inspection.

The importance of management commitment cannot be underestimated. Senior management set the tone for the quality culture of an organisation, along with implementing and providing the landscape for adhering to the quality policy. Therefore, success of the self-inspection programme, risk-based decision making and an effective PQS is entirely underpinned by management commitment and management review. Indeed, Self-inspection cannot be a useful tool in the demonstration of PQS effectiveness without management commitment. This should not just be seen as important for regulatory compliance, but rather should be viewed as a business opportunity to improve the organisation.

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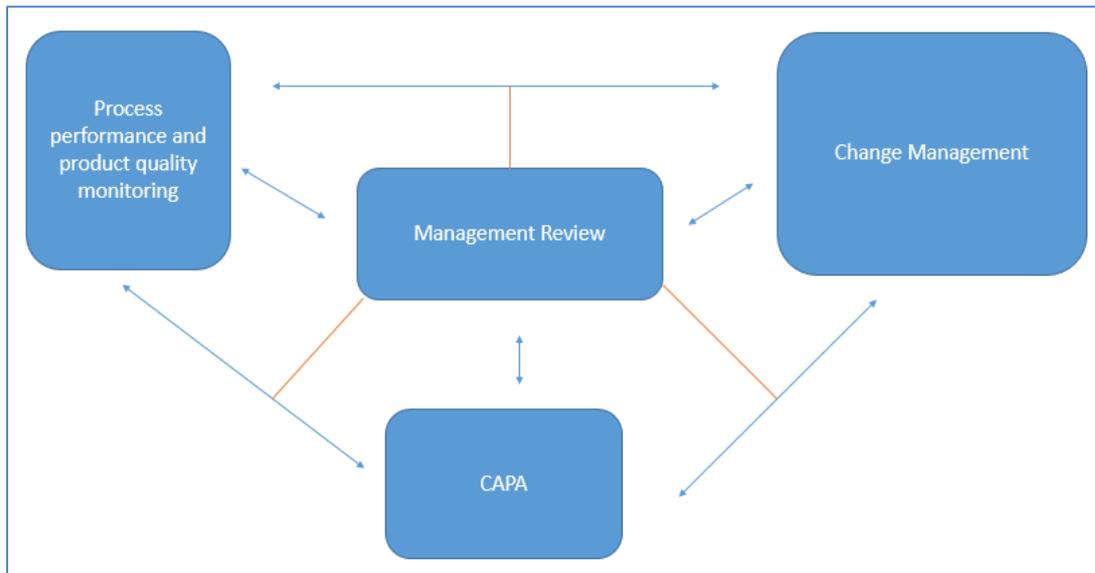
Figure 3: The four elements of the PQS are intrinsically linked with one another, with management review enabling these linkages through decision making and resource allocation.

In addition to management commitment another interesting paradox presented itself in the study, that of _regulators' focus_; while it was identified that they did want self-inspection to add value, typically it is found that the focus is on compliance during regulatory inspections. Despite desiring improvement, it was found that regulatory authorities do not currently put a strong focus on self-inspection. This is evidenced by the lack of update to Chapter 9 of _EudraLex Volume 4_, and the interviews conducted. Naturally, when resources are limited, pharmaceutical companies will focus on those activities that add value or are seen to be requirements, whereas when it comes to activities such as self-inspection they may only perform enough to achieve compliance as this is all the regulator looks for.

However, it could be argued that pharmaceutical companies should take a more proactive approach in improving their self-inspection programmes and demonstrating this to health authorities. But in practice, this is only going to be worthwhile if there is a beneficial outcome.   While there are paradigm changes coming, particularly with ICH Q12 and research conducted by Ramnarine _et al._ (Ramnarine _et al._, 2020), the reality of reduced regulatory oversight or regulatory flexibility has not yet been reached. This is not only going to take a shift in the behaviour and approach by pharmaceutical companies, but also requires a shift in regulatory approaches. Updating and repositioning self-inspection may be a worthwhile starting point for this shift, beginning with updating Chapter 9 of the EudraLex, as proposed by O'Mahony (O'Mahony, 2019).

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Final Thoughts

To achieve the objectives envisioned by ICH Q8, Q9, Q10 and Q12, an effective pharmaceutical quality system is essential. The two enablers of the PQS according to ICH Q10 are QRM and KM. It is the researcher's belief that along with QRM and KM, self-inspection could be positioned as a third enabler of the PQS, if utilised correctly.
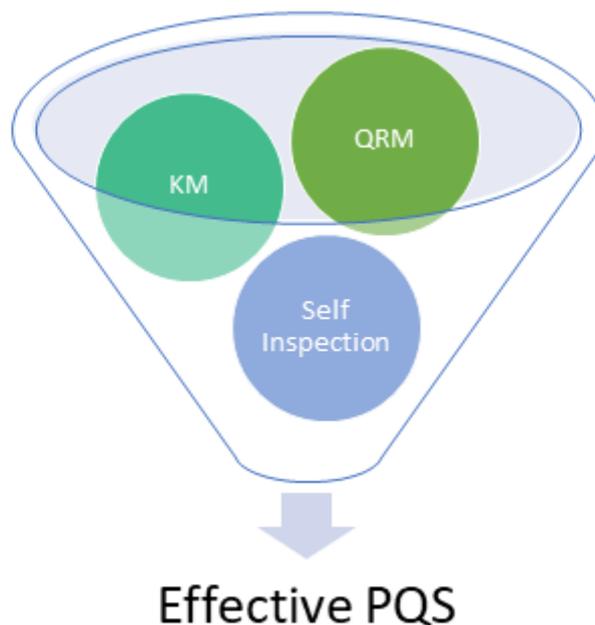
Figure 4: QRM, KM and Self-Inspection are enablers of an effective PQS.

Demonstrating PQS effectiveness is a challenge for pharmaceutical companies. However, it may not be as challenging as they think. Companies continuously gather information about their quality systems through various means, the next step is capturing that information. Product Quality Reviews, for example, tell a significant story about the PQS, if appropriate data analysis is performed. Self-inspection should also be seen as a tool that could aid in this information capture. It can be reframed as a tool for risk identification, risk review, and an opportunity for continuous improvement.

The research presented in this paper aimed to determine how self-inspection could be better utilised in demonstrating PQS effectiveness. A QRM approach to developing the self-inspection process was proposed, along with checklists for the four PQS elements and the self-inspection process itself. These, when used in conjunction with one another and adapted to suit the size and complexity of the organisation, could be useful in

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demonstrating that QRM is embedded across all processes within the PQS, and that emphasis is placed on continuous improvement. Together, this should serve to show regulators that the PQS is effective and may contribute towards achieving the ultimate goal of regulatory relief. However, the success of such an approach depends on management commitment. Management underpin the quality culture at the site, with management behaviour influencing employee behaviour at all levels. Without management buy-in and support of PQS activities, the objectives of the ICH Quality guidelines will be very difficult to realise.

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Appendix

1. Self-Inspection Checklist

Is there a documented procedure? Does it include (at least) the following: • Responsibilities - senior and departmental level management responsibilities, designation of a coordinator/programme manager/facilitator? • Requirements for internal auditor competencies and training policy? • Objectives of the self-inspection programme? • Risk-based planning requirements of the programme and schedule (with suggested inputs as per Step 3 of roadmap)? • Defining criticality of non-conformances (e.g. critical, major, minor/other or low, medium, high)? • Highlights that risk review must form part of the self-inspection process (regardless of what area/process is being audited)?
Has a self-inspection programme been established? • Are all processes within the PQS considered? (may not all be included in the schedule but should be considered). • Has the programme been established based on QRM principles, i.e. processes prioritised and scope and frequency defined based on risk evaluation? • Are the decisions made documented and evidence provided for rationale behind decisions? • Are objectives defined? • Is it continuously monitored for adherence and status presented to management? Risk-based updates supported by management if needed? • Is it updated based on new information from the other elements of the PQS and as an outcome of audit findings? • Have any changes been risk-assessed and justified?
Has a self-inspection schedule been established? As above for self-inspection programme. • Is the objective, scope and criteria defined for each audit? Does the scope consider specific risks and the PQS elements? • Are the resources required for each audit defined and based on risk?
Is the effectiveness of the self-inspection programme verified? • Through an audit, continuous review for adherence to schedule, tracking of CAPAs, monitoring of external audit findings, metrics such as audit completion (i.e. completed on time), number of CAPAs raised (non-conformances and recommendations). • Any actions as a result of the audit should be monitored for status (open, overdue, effectiveness monitoring, closed), number of days open. • Programme could be deemed effective if a reduction in deviations etc. is seen, along with adherence to schedule, number of open actions reduced, number of CAPAs raised during audit period reduced (but should have a nuance here to ensure that proactive recommendations are promoted).
Was risk and the PQS considered in all self-inspections performed? • Was review of relevant risk assessments carried out during the inspection? • Were new risks identified in the audit? If yes, did this trigger the QRM process to implement new control measures if required?

- Are risk decisions reviewed for effectiveness and appropriateness?
- Are risk mitigations assessed to determine effectiveness in reducing the risk?
- Are risk related activities reviewed to ensure that decisions were based on scientific knowledge and linked to the protection of the patient?

Together, these may demonstrate that QRM principles are applied to the processes being audited.

- Were the relevant elements of the PQS considered in the inspection?
- Was KM and data integrity considered?

Did the outputs of the self-inspections include update to risk assessment, if required?

- Was risk review performed based on the audit findings?
- Was the risk register updated?
- Was the initial risk evaluation performed during programme and schedule planning reassessed for appropriateness and updated if required?

Are continuous improvement opportunities identified during internal audits?

Are recommendations made based on evidence of negative trends to prevent the occurrence of a non-conformance/deviation?

Is management commitment demonstrated?

- Are the audit findings reviewed by management?
- Is there evidence that self-inspection is an input to management review?
- Are adequate resources allocated to the self-inspection programme (from both an auditor and an auditee perspective), i.e management buy-in at all levels?
- Was the audit schedule adhered to?
- Were CAPAs implemented and prioritised based on risk?
- Were previous inspection findings corrected?
- Is the audit programme/procedure updated based on the outcomes of effectiveness check/management review/other PQS elements?

Are the persons performing the inspections adequately trained?

- Do they have process knowledge/understanding of the area being audited? (Employees from sister sites could be utilised)
- Are they independent of the area being audited (as far as reasonably possible)?
- Is there a lead auditor assigned to each inspection?
- Are their training competencies regularly assessed and continuous professional development encouraged?
- Are they trained in QRM activities?

Are the audit findings entered into the CAPA system and investigated for root cause?

- Are non-conformities graded based on risk?(e.g. risk to product quality, process performance and in turn patient safety).
- Are audit findings and action plans prioritised based on risk?
- Are impacts to other processes assessed?

Can refer to CAPA checklist for further guidance on how they should be managed.

- Are findings trended by root cause to identify a deficiency in the overall PQS, e.g. training, documentation (lack of) etc?
- If negative trends are seen, does this trigger risk review?

Has each process been determined to be effective as a result of the audit, based on objective evidence?

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- If not, has re-audit been considered following completion of CAPAs?
  - This would then demonstrate that while that particular process may have an issue, the PQS is effective in terms of identifying a high risk area, mitigating risk with CAPAs, and assessing the effectiveness through a re-audit.
- Was the assessment at the end of the audit valid?

Possible metrics for assessment:
- Schedule adherence/number of audits performed vs. number planned
- % continuous improvement/proactive actions vs. reactive actions
- Non-conformances identified in external audits (if appropriate)
- Number of new risks identified (this may be useful for trending purpose to infer whether there is a lack of control in the process)

2: Process Performance and Product Quality Monitoring Checklist

Is there a documented procedure for process performance and product quality monitoring? • May not be a specific procedure but is it a feature of the quality policy? • Are control strategies documented?
Is there a documented procedure for the performance of Product Quality Reviews?
How often are PQRs carried out? If annually, are there other review processes that occur more frequently? E.g. Daily, Weekly, Monthly management of trends and performance.
What is captured/reviewed in the PQR? For example, stability data, complaints, recalls, deviations, lot acceptance rate, rejected batches, CAPAs and their effectiveness, qualification status of systems, outsourced activities, change controls, review of marketing authorisations/variations that have been submitted, validation activities, supplier reliability, risk assessments/risk register.
How is that data treated in the PQR? Is it analysed to demonstrate process robustness and capability? • Is a holistic approach to data analysis and trending taken following the accumulation of the data? For example, if stability issues are seen in the review, are other factors such as changes made to the process assessed as a contributory factor? • Are trends monitored over time and compared to the previous review period?
Does risk review form part of the PQR process (at every stage)? PQRs should be seen as a risk review tool. • Is the risk register consulted during PQR? Are the following items examined: • Were risk acceptance decisions made during the review period appropriate? • Was the level of effort and formality commensurate with the level of risk? • Is the level of residual risk still valid? Has it been reduced or increased? If risk level has remained the same or reduced, have continuous improvement opportunities been identified?
What are the outputs of PQRs? • Is it stated that the process is (or is not) in a validated state of control? Is that decision valid based on the objective evidence provided in the PQR? • Do the outputs have a positive impact on the process/product? • Are actions taken preventive? • Has risk been considered in the decisions taken? Has the risk decision been documented? • Is the control strategy updated, if required? Are changes are made to ensure that CPPs are continuously in a state of control, subsequently maintaining the CQAs of the product? • Have revalidation and changes in CPV requirements been considered? • Is management commitment demonstrated through management review and allocation of resources? • Have risk assessments been updated with a review of the residual risk, if necessary?
Are trends frequently monitored for variation? • Is statistical process control employed, i.e. Cpk and Cp with limits defined? Or Pp and Ppk

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if the process is not currently in a state of control?
- Are alert limits set to ensure that processing veering out of control are captured before action levels are reached?
- Are the frequency and limits captured in a CPV plan/control strategy?
- How are adverse trends treated?
- Is common vs. special cause variation considered?
- Are they investigated for root cause?
- Are CAPAs raised and subsequently risk-assessed? (see CAPA checklist for details)

Is there daily/weekly management of trends?
- Are there demonstrated feedforward and feedback mechanisms based on trends monitored and decisions made?
- Procedures for escalation where necessary and risk-based resources allocated if required?
- Are decisions made captured in real-time (including data/reasons supporting that decision)? Through a simple form, also 'lessons learned' and 'after-action review' type documents.
- Are visual management tools utilised?

Is the control strategy a living process, i.e. is it continuously updated based on the data and knowledge generated throughout the product lifecycle?
For example from risk review, trend analysis, deviation management, CAPAs, management review, self-inspection findings, external audit findings, literature review for identifying best practice.

Is there a culture of continuous improvement?
- Are there procedures to allow staff at all levels to make suggestions for improvement?
- Is continuous improvement demonstrated? (e.g. through increase of lot acceptance rate, reduction of complaints/recalls/deviations, increased process capability, a measure of risk reduction).
- Plan, Do, Check, Act employed?
- DMAIC process employed?

Metrics that may indicate operational stability
- Lot acceptance rate/number of rejected batches /frequency or degree of meeting the quality standard in manufacturing
- Number of recalls
- Number of customer complaints
- Number of deviations or OOS results
- Time from manufacture to lot release
- Process capability indices
- % of Proactive vs reactive actions taken

Has QbD approach been used for product development?
- Has the QTPP been defined?
- For legacy products, have they been reviewed to ensure that the process is understood and QTPP is identified, even where QbD may not have been employed? Are more controls in place for such legacy products?
- Are all the sources of variability identified and documented?
- For legacy products, does the process performance and product quality monitoring system allow for the updating and review of specifications? Introduction of new

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technologies?

Are emerging technologies considered during process performance and product quality monitoring for new and legacy products?
- Are emerging technologies considered during product development?
- Is PAT employed and part of the control strategy?
- If new technologies are to be installed into the process, are they risk assessed for suitability?
- Is a gap analysis (including risk assessment) performed between the current process and the 'state of the art'?

Was QbD used in developing the control strategy?
- Focus on in-process real-time controls vs. end-product verification?
- Is the risk to patient and product quality considered for each step in the control strategy?
- Are the different process parameters and their controls risk assessed to determine a spectrum of importance? Or at least defined as critical, key and non-key. (Can aid in indicating where focus should be in internal audit)

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3: Change Management Checklist

Is there a documented standardised procedure for change management?

Does it contain requirements for the following:

- Documentation requirements of each stage of the process?
- Risk based approach to be taken to proposals, evaluation, planning and implementation?
- Requirements for review and effectiveness check following closure?
- Personnel who should be involved in each stage of the process?
- Decision nodes highlighted?
- Possible sources/triggers/inputs that will initiate a change? These may include CAPA, Management review, Audit findings, results of PPPQM and trend monitoring, complaints, etc.
- Process for documenting and communicating lessons learned from the change process for improvements?

Are all change proposals documented?

- Are the triggers for the change and the related evidence documented?
- Are the objectives, scope and expected outcomes/benefits included?
- Is the acceptance/rejection of the change proposal documented?
- Has pre-defined acceptance criteria been documented?

Are the change proposals impact assessed on the basis of risk?

- Has a risk assessment been performed to determine the level of rigor, effort and documentation required for the change? Specifically, validation and testing requirements. The impact on the validated state should be included here, including impact to critical process parameters and critical quality attributes.
- Has a risk vs. benefit analysis been performed? Do the benefits outweigh the risk, or at least no change in risk level foreseen?
- Have the impacts and risks of the proposal on other processes and products been considered?
- Have the impacts on the same product/process in other sites/regulatory regions been assessed? Is there a plan for cross-site implementation?
- Has an impact assessment for regulatory filing requirements been performed?

Are risk decisions based on scientific data, i.e. current process and product knowledge?

- Is supporting documentation available?
- Were emerging technologies and 'state of the art' considered during the assessment process for possible implementation?
- Are cross functional teams utilised with SMEs from different impacted areas?

Are change proposals and plans reviewed and approved by the relevant/key stakeholders?

- Is the risk decision documented based on the outcome of the impact/risk assessment?
- Are changes reviewed by Validation even if it has been established that the 'validated state is not impacted'?
- If the change is rejected, is the risk of this decision considered?

Are changes categorised based on the risk assessment?

- Does the risk level determine the categorisation and prioritisation of the change?
- Are implementation timelines considered based on risk?

Are open changes monitored continuously ensuring a state of control is maintained?
- Is it ensured timelines are being met?
- Are action plans generated if it is seen that timelines are not being met?
- Are visual management boards utilised to track the status of the open change?
- Are open changes reprioritised depending on the risk associated with them?

These factors demonstrate management commitment.

Do change plans consider the risk and risk control?
- Are risks that may be temporarily introduced during the process considered?
- Are interim controls put in place to mitigate those risks?
- Is monitoring for new risks performed throughout the implementation of the plan?

Are change plans adhered to?
- If not, are deviations justified and risk-assessed in terms of risk to process control/product quality?
- Have the relevant regulatory filings been completed on time?
- Have the relevant risk control measures been implemented on time?
- Have relevant risk assessments been reviewed and updated?

Were the outcomes set out at the start of the process met?
- Specific conditions and acceptance criteria defined?
- Was all criteria met and remained unchanged? If changed, was it adequately justified and risk-assessed?
- Were residual risks assessed and managed to acceptable levels through successful implementation of risk controls?
- If objectives not achieved, was management review carried out with CAPA action plans and 'lessons learned' documented?

Is quantitative data used to determine the implemented change plan outcomes have been achieved and effectiveness of change verified? i.e. science and knowledge based decisions.

Tools used may include CPV, statistical process control indices such as CpK/PpK, reduction in non-conformances/deviations/complaints
- Has a degree of risk reduction been achieved?
- Is there ongoing monitoring performed? (the rigor of which should have been stated during the change process)

Residual risk and unintended consequences considered?
- Is this performed throughout the change process, not just a once off activity?
- If there are residual risks, are these controlled and managed?
- If there are unintended consequences, have they been assessed with adequate controls put in place, if necessary?

Is there a live risk register in use?

Are key risks captured, managed and tracked for implemented and pending PACs, prior to the effectiveness check?

Have relevant risk assessments been updated post-change?

Are relevant processes and strategies updated based on the updated risk assessments?

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If a change is introduced on a product/process at multiple locations, has it been ensured that there is consistency in its introduction across all sites? Is the PQS integrated across multiple sites? (there could be specific site level access as required). Also relevant for outsourced activities - communication between MAH and the contract acceptor is essential.
Potential Metrics for Assessment: • Rate of project's deviation from schedule time, i.e. schedule adherence • % of PACs managed within the PQS without requiring prior approval vs. total PACs • Actual vs. planned resources given to changes • % of changes based on reactive vs. proactive triggers • % changes that actually lead to risk reduction

4: Corrective and Preventive Action Checklist

Is there a standardised procedure and is it followed?
Does the procedure contain the following requirements:
- Cross functional review of initial deviation/identified problem/adverse trend.
- Clear indication of when a CAPA should/should not be raised.
- Clear instructions for evaluation and classification in terms of severity and impact, with QRM principles employed?
- Does the severity determine the resolution and level of investigation required, i.e. demonstrating that the level of effort is commensurate with the level of risk
- Root cause analysis process to be followed, including tools that may be used (e.g. 5 Why's, Cause and Effect diagrams, 6M).
- Review of CAPA proposal and risk assessment to ensure it does not introduce new risk
- CAPA implementation
- CAPA review for effectiveness

Problem statement evaluation based on risk
- Problem statement clearly states the occurrence (requirement, evidence, deficiency) and extent of that occurrence?
- Does the procedure for evaluation of the severity and impact include a review of previous occurrences of the deviation and their CAPAs?
- Does it include risk review?
- Is a risk assessment employed in the determination of the criticality and classification?

Are investigations clearly documented?
Are they performed cross functionally? Or at least reviewed cross functionally?
Increases process and product understanding, demonstrates good KM as gets inputs from all key stakeholders.
- Is there a diversity of opinion when performing root cause investigations?
- Are the findings challenged, with a high level of scientific rigor applied? i.e. is there evidence that root cause analysis based on objective evidence and actual data, rather than subjective opinion?
- Were the tools used appropriate and effective?

Is analysis performed horizontally and not just vertically?
- Have similar products/processes been considered that may also be impacted by the deviation/CAPA?
- Have other lots of same product been considered for impact?

Are root causes adequately defined, coded and trended ?
- Not just documented as 'other'?
- Is it possible to track the root causes to identify trends/repeats?
- Are repeated issues with a certain process step/department/product line highlighted?
- Are root causes reviewed to highlight systemic issues that may be occurring across multiple processes?
- Is recurrence assessed for similar deviations in different processes?

How many root causes are attributable to human error?
To be avoided where possible.
- Is reclassification of human error considered?

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- Is there over reliance on 'retraining' as a CAPA?

Is risk assessment part of the CAPA procedure?
- Are risk documents reviewed and updated?
- Where risk decisions are made, are they based on scientific data and is subjectivity controlled?
- Are previous risk decisions considered during investigation and analysed for appropriateness and effectiveness?

Are CAPAs categorised, filtered and prioritised according to risk?
- Examples:
  - If there are limited resources, is risk assessment used to characterise and prioritise the CAPAs and assign resources to those of higher risk ratings?
  - Is the deviation going to result in drug shortage?
  - Is it something that will likely require a long term project that isn't immediately required but could be incorporated into continuous improvement? (This shouldn't be seen as an opportunity to ignore or avoid implementing CAPAs.)
- To demonstrate effectiveness, it should be shown that resources are applied accordingly but that deviations are still being managed within reasonable timeframes. For self-inspection of the CAPA process this will form an essential part of the review.
- Management commitment may be demonstrated through review of open CAPAs and assigning resources based on risk.

Are all open CAPAs regularly reviewed?
- Are the investigations and implementation of actions assessed for timeliness for monitoring and assessment purposes in the context of risk?
- Are actions taken following the review of open investigations and CAPAs if they are deemed high risk?
- Is there a procedure for escalating where necessary?
- Are high-risk CAPAs presented to management for review to give an indication of the overall risk level of the company?

Is there a process for reviewing the effectiveness of the CAPA?
- Are the timelines selected for review appropriate? Criteria may include number of batches rather than a fixed time point.
- Has it been ensured that the CAPA has not resulted in an adverse event?
- Has there been a differentiation between adverse event vs. a non-effective action?
- Has the effectiveness check been carried out on the root cause/CAPA, rather than a check for recurrence of the original problem statement?
- Has risk assessment and risk review been performed in the effectiveness check?
  - For example, has the severity or frequency of the risk identified in the initial evaluation been reduced to acceptable levels following implementation?
  - Have no unexpected risks been introduced?
  - Has the CAPA lead to risk mitigation?
- Has justification been provided for the effectiveness evaluation?
- If deemed not effective, are they reopened and more rigorous investigation applied?

Are CAPAs linked to the other elements of the PQS?
- Have CAPAs been triggered through internal and external audit findings, complaints, rejections, recalls, deviations, PPPQM trends, risk review?

• Are CAPAs considered during PPPQM, Change Management, Management review?
Personnel • Are personnel adequately trained in root cause analysis and QRM principles? • Are personnel adequately trained in awareness of human heuristics? • Are they trained and empowered to recognise and raise deviations or adverse trends that may lead to deviations? • Are there established procedures for communication of deviations/adverse trends?   o For example, the use of a decision tree with relevant reporting structures? If yes, this demonstrates a good culture of quality and management commitment. • Are the key stakeholders involved in analysis/decision making/approval?
Is the CAPA procedure reviewed by management for appropriateness and effectiveness? • Does it enable continuous improvement of the process?   o Demonstrated via a change in PPPQM, introduction of new/emerging technologies, reduction in deviations/recalls/complaints, increased statistical process control. These factors may also be assessed in the effectiveness check of the CAPA. • Is it updated following review, if required?
Potential metrics for assessment • Number of deviations raised • Level of risk reduction, e.g. reduction in frequency of occurrence. • How many deficiencies of each type? (critical, major, minor/low, medium, high) • Are strict time related metrics avoided unless based on risk to product quality/patient safety? • Ratio of proactive improvements versus reactive actions raised in the CAPA system?

5: Management Review Checklist

Are management review decisions/outcomes documented?   • Could a summary report be generated for presentation to an external auditor?   • Is a statement made regarding the compliance of the site to regulatory requirements?   • Is a statement made regarding the quality and risk profile at the site?   • Is there objective evidence provided to support these statements/decisions made?
Is there a Quality Policy in place?   • Is a quality plan generated with objectives set?   • Are the quality objectives clearly defined and supported by management, e.g. through resource allocation/training/communication?   • Are they effectively communicated to all business levels?   • Are they assessed at management review and updated accordingly?
Is there a QRM policy or procedure in place?   • Is it updated as an output of management review? Does it drive continuous improvement?   • Is there a QRM manager or similar role?   • Are roles, responsibilities and competencies defined?   • Does it include clear risk ranking/rating instructions? (this may be process dependent, so at least it should be shown there is provision for risk assessment and evaluation in all PQS procedures).
Quality Risk Profile   • Is a risk register in place? Is it reviewed by management?   • Is a review of trends/indicators that may indicate risks to quality/compliance performed?   • Is this an input into the management review procedure?   • Is the extent of risk reduction assessed?   • Is a risk vs. benefit analysis performed?   • Is the site's overall risk level considered?   • Are open 'high' risks prioritised and escalated?   • Is it verified that risk management plans are appropriate?
Are QRM activities adequately resourced with trained staff?   Is this as an output of the management review procedure?
Self-inspection programme implemented to confirm application of QRM principles and processes?   • Is it adequately resourced and resources applied on a risk-basis?   • Adequate training and competency assured by management?   • Are results inputted into management review and actions taken if necessary?   • Is it being completed according to the schedule?   • Are CAPAs reviewed by management for completion and timeliness?
Are the following included as inputs to management review? (Non-exhaustive list)   • PQRs/other PPPQM trends (e.g. deviations, customer complaints, stability data)   • Open CAPAs and changes   • Audit findings (external and internal)   • New/changes regulatory filings

- Updates to regulatory requirements
- Supplier audits/assessments
- Outsourced activities

PQRs
- Are the PQRs completed on time?
- Does risk review form part of the PQR? Are risk decisions considered for effectiveness and appropriateness?
- Are resources allocated for holistic analysis of data and trends?
- Are resources allocated if PQR indicates the state of control is not being maintained or veering out of control?
- Are resources allocated for continuous improvement activities?
- Is it confirmed that the control strategy is adequately implemented?
- Are decisions taken to update the control strategy based on information gleaned from the PQR?

Are trends monitored for system failures?
- Is continuous monitoring of trends performed to highlight issues that may lead to deviations/non-conformances, and in turn drug shortages?
- Do management review for recurrent trends in inspection findings/root causes that may indicate a process/system moving out of a state of control?
- If negative trends are found, are they actioned upon with follow through?

Outsourced activities
- Are all contract organisations audited and approved?
- Are the activities and assessments considered in the management review?

Is management commitment and review integrated throughout the organisation?
- Do more frequent, local reviews take place, if applicable to the size of the site/organisation?
- Demonstrated feedback mechanisms to senior management?
- Is each system and subsystem within the PQS reviewed?
- Management review meetings attended by all stakeholders?
- Knowledge capture of 'on the floor' decisions made?
- Are visual management boards utilised? E.g. for continuous improvement projects, 5S, open changes, open CAPAs etc.

Does management review procedure/management behaviours influence a culture of quality?
- Are management applying QRM procedures to management review and escalation of action plans, where necessary?
- Are decisions based on risk to quality, not just risk to business?
- Is an output of review to apply resources and training to higher-risk areas?
- Are management committed to QRM? (e.g. through self-inspection, allocation of resources)
- Is the creation of further risk considered when making decisions?
- Are proactive decisions made that facilitate continuous improvement/control of negative trends?
- Are regular communication sessions held?
- Are GEMBA walks performed?

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Is the effectiveness of CAPAs/Post-approval changes monitored by management? • If determined that the change/CAPA has not been effective, is a CAPA action plan raised? • Are lessons learned documented for future changes/CAPAs?
Are open changes and CAPAs regularly reviewed? • Changes may be trended based on source, e.g. KM, QRM, PPPQMS, CAPA etc. • If objectives have not been met for changes, is a CAPA action plan raised? Are lessons learned documented for future changes/CAPAs? • If timelines for implementation of change plans/CAPAs are not being met, are they re-prioritised based on risk to product quality and patient safety?
Potential metric for assessment: • Number of external inspection observations not identified through self-inspection • Rate of reactive vs proactive decisions made • % of effective risk mitigations • % of quality objectives met