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Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS):Through Enhanced Science and Risk-Based Approaches Changes to Analytical Equipment/ Instrumentation that are Deemed Equivalent

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Industry One-Voice-of-Quality (1VQ) Solutions

Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches

Changes to Analytical Equipment/Instrumentation that are Deemed Equivalent

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Abstract

Post-approval changes are inevitable and necessary throughout the lifecycle of pharmaceutical products to implement new knowledge, maintain a state of control, and drive continual improvement.
This One-Voice-of-Quality (1VQ) position paper is part of a series of industry case studies intended to demonstrate the standard application of the principles outlined in the publication "*Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches Industry; One-Voice-of-Quality (1VQ) Solutions*" in *PDA Journal of Pharmaceutical Science and Technology*, 2020 [1].

Furthermore, this 1VQ position paper provides a practical application of the concepts described in ICH Q9, *Quality Risk Management* [2], ICH Q10, *Pharmaceutical Quality System* [3], and ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* [4] to changes to analytical equipment/instrumentation that are deemed to be equivalent.
This paper describes changes to analytical equipment that are considered 'like for like' or equivalent. The conclusion drawn from this case study is that such changes present a low risk, and therefore can be downgraded from a prior-approval, and managed only within the company's PQS.

KEYWORDS

CMC, Chemistry Manufacturing and Control, Regulatory, Post-approval Change, PAC, ICH Q9, Quality Risk Management, QRM, ICH Q10, Pharmaceutical Quality System, PQS, ICH Q12, Lifecycle Management, Change Control, Regulatory Considerations, Regulatory Flexibility, Science and Risk-based Approach, One-Voice-Of-Quality, Analytical Equipment/Instrumentation

BACKGROUND AND CONTEXT

ICH Q10, *Pharmaceutical Quality System*, Annex 1 describes potential opportunities to enhance science and risk-based regulatory approaches to PACs as follows: When a company can *"demonstrate effective PQS and product and process understanding"* this is an opportunity to *"optimize science and risk-based PAC processes to maximize benefits from innovation and continual improvement"* [3]. Current regulatory mechanisms and guidance for PACs do not consider the company's latest product and process knowledge when determining the type of filing required to implement the change. Further, the application of ICH Q9, *Quality Risk Management,* or the effectiveness of the company's PQS to manage PACs is not considered during the assessment of individual PACs or during inspections. Demonstrating a detailed understanding, effective implementation, and compliance with ICH Q10, will allow companies to overcome barriers to continual improvement and innovation. Additionally, it will help reduce drug shortages in the global environment by allowing faster implementation of PACs and reducing the PAC burden on both industry and regulators.

This specific example of changes to analytical equipment/instrumentation that are deemed to be equivalent demonstrates the application of the principles outlined in ICH Q9, Q10, Q12 irrespective of current national or regional reporting category, and concludes that such

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changes can be managed within the PQS only without any regulatory submissions. It is acknowledged that different companies might be handling this example differently and may not need to pursue a regulatory downgrade for this PAC. However, companies that file this as a prior approval change, may use this position paper as a starting basis and modify scope and relevant considerations for their specific need and in accordance with their company's PQS requirements.

This PAC example and the 1VQ work in general is sponsored by the Chief Quality Officer's from more than 20 pharmaceutical companies [5].

DESCRIPTION OF CURRENT STATE FOR MANAGING CHANGES TO ANALYTICAL EQUIPMENT/INSTRUMENTATION

Changes to analytical equipment/instrumentation are needed for a variety of reasons, e.g. the instrument is no longer supported by a vendor or the instrument is outdated and no longer able to be fixed, replacement parts are unavailable, a newer or better replacement is available, software has been updated etc.

For analytical methods, and associated equipment/instruments/parts, software names and versions, specific equipment names, brand and model number etc. may be detailed along with the associated operating parameters relevant for that equipment/instrument/part within the registrations. Often an allowance is included for an 'equivalent' equipment/instrument/part in the registration which provides the appropriate regulatory flexibility for these types of changes. However, there are instances, where the term "equivalent' may not be included and this often creates an unnecessary need for health authority approvals for these registration changes. This in turn delays proactive and timely implementation of necessary analytical instrumentation changes which can be managed under a robust PQS. A consequence of such delays is unnecessary and avoidable method or equipment failures, errors, deviations or out of specification investigations that can result in testing and product release delays.

This position paper describes how ICH Q10 and Q12 can provide the basis for regulatory relief for certain 'like for like' changes in analytical equipment/instrumentation that present no risk to product quality and/or patient safety and minimal regulatory risk. In some cases, these types of changes can improve reliability of product supply to the patient and product

quality. e.g. increase data integrity and cyber security, better sensitivity of the method and the reduction in human error.

SCOPE

The position paper applies science and risk-based concepts from ICH Q9, Q10 and Q12 to the following types of analytical equipment changes so that such changes can be implemented proactively utilizing the framework of an effective PQS, and without extensive regulatory burden:

- Retirement, de-commissioning or replacement of 'like for like' [1] laboratory equipment/ instruments (offline, at-line, in-line, laboratory computer) and parts. Examples include change from one equipment model or equipment part to another where the manufacturer will no longer be manufacturing that model or part.
- Installation of new laboratory equipment/instruments or parts that are 'like for like' which includes the use of automation when there is no change in the fundamental principle of manual vs. automation techniques (i.e. moving from a manual to automated lab operation is considered a 'like for like' change where the automation mimics the core manual process, there is no change in the fundamental controls in executing a method, and equivalence has been demonstrated between the manual and automated operation).

INDUSTRY 1VQ POSTION FOR MANAGING ANALYTICAL CHANGES TO EQUIPMENT/INSTRUMENTATION

ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* provides regulatory flexibility in post-approval changes to the product or its manufacturing process based on latest product and process knowledge, sound-scientific and risk-based approaches [4].

[1] The term 'Like for like' applies where its replacement, retirement or decommissioning does not cause any change in analytical methodology, method principles, method parameters and method validation as defined by ICH Q2(R1), analytical specifications, or system suitability, and/or where full method re-validation is not required, and equivalency has been demonstrated.

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Leveraging the principles in ICH Q9, Q10 and Q12, regulatory discretion will be used for 'like for like' changes to analytical equipment/instrumentation, where the change can be managed solely within the PQS as long as the change assessment and/or equivalency data conclude that the change does not impact product quality and/or patient safety. Instrumentation change types should be considered Non-Regulatory Impacting if there are no changes in analytical methodology, method principles, method parameters and method validation as defined by ICH Q2(R1), *Validation of Analytical Procedures: Text and Methodology* [6], analytical specifications, or system suitability, and method re-validation is not required.

The pharmaceutical industry's position is that such changes should not need to be assessed as regulatory impacting, simply because the M3 dossier has additional equipment details (e.g. part numbers, brand name, model or version numbers), or has not specifically stated an allowance for 'equivalent' equipment/instrumentation. There is no regulatory requirement to register detailed instrument settings and operating information, model number, instrument name, etc.; therefore, it is not considered appropriate to update the dossier with similar detail. These details can be removed or revised to include the term "equivalent" in future updates to the dossier.

This will facilitate timely upgrades and replacement of outdated or aging analytical equipment, reducing related errors, issues, delays in testing and release of product ultimately ensuring reliable supply. In addition, it will contribute towards meeting the ICH Q10 objectives of achieving product realization, establishing and maintaining a state of control, and continual improvement.

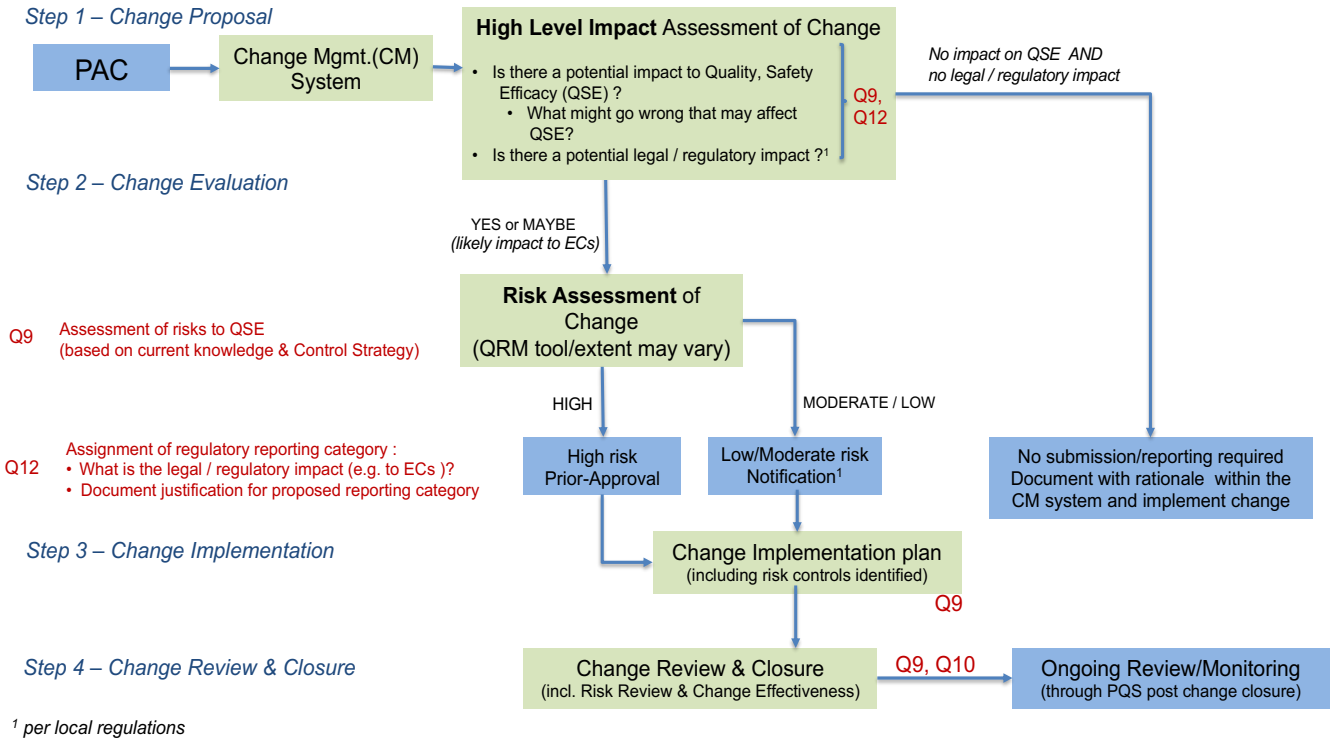
As part of a company's change control process, a science and risk-based approach with appropriate justification will be documented when evaluating changes in the analytical instrumentation that are deemed to be 'like for like', regardless of the detailed equipment information filed.

STANDARD RISK-BASED APPROACH

Figure 1 below [1] describes the risk-based approach for assessment of a PAC to 'like for like' analytical equipment/instrumentation. Application of this risk-based assessment and

supporting equivalency data, should demonstrate that at a minimum, the change does not increase the risk to product quality, efficacy and/or patient safety.

Figure 1: Risk-based Assessment of PACs and Determination of Regulatory Reporting Category



When a 'like for like' PAC to analytical equipment/instrumentation is proposed and entered into the change management system, the potential Quality, Safety Efficacy (QSE) and legal/regulatory impact of the change should be considered including current control strategies. The impact assessment indicates that

- there is no change in analytical methodology, method principles, method parameters and method validation as defined by ICH Q2 (R2), analytical specifications, or system suitability
- there is no need for method re-validation
- there is no impact to product QSE

As the initial impact assessment concluded that there is no potential impact associated with the change, no further quality risk assessment is required. There may be a change needed to the specific equipment details in the dossier, but none of these impact product QSE. Therefore, an update to the dossier can be bundled with a future change, and a filing does

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not need to be submitted solely for this analytical equipment change. Such a change along with the supporting equivalency assessment and revisions to relevant procedures, can be managed solely within the company's PQS and implemented immediately without the need for a regulatory submission. Change implementation, review and closure should be performed according to the change management process. After implementation of the change, any unintended consequences introduced as a result of the change should be evaluated, documented and handled adequately through effectiveness verification mechanisms.

DEMONSTRATING EFFECTIVE MANAGEMENT OF A 'LIKE FOR LIKE' ANALYTICAL EQUIPMENT CHANGE WITHIN THE PQS

The following risk control elements have been considered and documented within the PQS for ensuring effective management of a 'like for like' change to analytical equipment/instrumentation:

- No change in analytical methodology
- No change in method principles and/or method parameters
- No change in approved method validation and no need for method re-validation
- No change in approved analytical specifications, or system suitability
- IQ/OQ/PQ is adequately performed and documented
- Equivalency between current and new equipment is demonstrated and documented
- Relevant test and equipment (e.g. maintenance) procedures are revised for the new analytical equipment as part of the change implementation.

The PIC/S Recommendation Paper on *How to Evaluate/Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Managemen*t" [7] provides a practical checklist tool that can be used by the company to evaluate the effectiveness of its risk-based change management process.

CONCLUSION

This 1VQ position paper provides a standard and enhanced risk-based approach within the framework of an effective PQS, that can be utilized by any company to gain regulatory flexibility, reduce the burden and global complexity, and enable faster implementation of 'like for like' changes to analytical equipment/instrumentation, without increasing risk to the patient and/or product quality, safety and efficacy. More specifically, no regulatory prior approval will be pursued based on the premise that appropriate 'analytical' due diligence' has been completed and documented in the PQS. This would include such elements such as instrument appropriately IQ/OQ/PQ under the company's PQS, use of the same technology e.g. HPLC to HPLC, equivalent data generated during PQ, and that no revalidation or re-qualification of method is required.

The benefits of practical application of the principles of ICH Q9, Q10 and Q12 as described in this document are:

1. Continual improvement with timely (weeks or months vs years) implementation of many PACs
2. Enhancing product availability and mitigating potential drug shortages
3. Focusing regulatory resources on PACs that may have a potential to impact product quality as it relates to safety and efficacy
4. Reducing the regulatory approval burden for medium and low risk changes
5. Faster implementation of analytical equipment upgrades

About One-Voice-Of-Quality

Many post-approval changes require regulatory agency approval by individual countries before implementation. Because of the global regulatory complexity, individual post-approval changes (PACs) usually take years for full worldwide approval even when they reduce patient risk, improve compliance, or enhance the manufacturing process or test methods.

Senior Quality leaders (Chief Quality Officers and Heads of Quality) from more than 20 global pharmaceutical companies are speaking with "One-Voice-Of-Quality" (1VQ) to advocate for an effective management of specific PACs that currently are handled as a prior-approval change in some countries, but where a standard science and risk-based approach

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concludes that these should be downgraded to a notification or handled only in the Pharmaceutical Quality System (PQS). This benefit would be a reduction of the implementation timeline from years to months with no increased risk to patient safety.

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Conflict of Interest Statement

The authors declare no conflict of interest related to the content of the article.

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