A Regulatory Pharmaceutical Quality Knowledge Management System (PQ KMS) to Enhance the Availability of Quality Medicines

ICMRA-ICH-PIC/S-IPRP Joint Reflection Paper

Background and Rationale

Changes to pharmaceutical manufacturing processes, technological innovations, and altered supply chains are just some examples of the many issues requiring operational agility that affect the availability of medicines required to meet patient needs. Whether pursuing continuing improvement in manufacturing a novel therapeutic based on post approval experience, or routine updates to operations, equipment, suppliers, and other post approval changes (PACs) later in a product life cycle, manufacturers are expected to proactively manage pharmaceutical quality using existing frameworks outlined in the internationally harmonized guidelines. Specifically, this includes ICH Q10 Pharmaceutical Quality System[1], building on the guidance in ICH Q8 Pharmaceutical Development[2], while applying the principles in ICH Q9 Quality Risk Management[3], and utilizing the enablers and tools outlined in the ICH Q12 guideline on Lifecycle Management[4].

While companies manage these PACs within their pharmaceutical quality systems (PQS), the current operating environment requires prior approval by the regulatory authority of each region and country individually. For a product to be globally available to patients, this can translate to numerous and often duplicative regulatory review processes and time frames. This presents regulatory complexity that can significantly constrain manufacturer agility in addressing challenges such as supply chain disruptions, or the need to significantly scale up production to meet urgent needs for critical therapies in multiple regions that could directly impact on the supply of critical medicines.

Importantly, regulatory agencies also seek greater levels of agility to better respond to a dynamic operating environment with rapidly evolving technology, increasing public health challenges and patient needs, ensuring pharmaceutical access while maintaining public confidence and operating with often very limited staffing and other resources. The need for agility has been highlighted in the recognized importance of inspection reliance, for example, as expressed in the ICMRA developed and PIC/S published Guidance on GMP Inspection Reliance[5]. Enabling inspection reliance, sharing of inspection information, and communicating on the maturity of a PQS will become increasingly important with the implementation of the ICH Q12 guideline.

To further enhance regulatory effectiveness and efficiency, there is growing support for pursuing a practical approach to better leverage resources and information among regulators to reduce regulatory complexity. Ultimately, this approach would require that regulators in all participating regions adopt the same requirements for the formats and data expectations in regulatory submissions and apply the same standards in regulatory review, assessment and inspection. Importantly, this would also require that sponsors submit the same quality dossier for

the same product in all regions (i.e., same formulation, facilities, etc.). In addition to facilitating information exchange and greater reliance on assessments performed by global regulatory authorities over time, submission of the same dossier to participating regulators would also help obviate legal concerns regarding the sharing of confidential information.

Harmonization work to align data submissions, expectations, assessments and inspection are essential to support the development of a regulatory PQ KMS needed to leverage collective resources and information sharing between regulatory agencies. This will help facilitate inspection reliance; significantly reduce or eliminate the need for multiple separate submissions from sponsors; and help to avoid duplicative assessments, often performed in parallel, relating to Chemistry, Manufacturing and Controls (CMC)-related PACs and enhance the availability of quality medicines.

1. Introduction

This joint Reflection Paper (RP) outlines the coordinated multi-stakeholder approach to harmonization work required to support the development of a regulatory PQ KMS. The harmonization work proposed will contribute to efficiency gains envisioned by the International Coalition of Medicines Regulatory Authorities (ICMRA)[6] , by supporting greater regulatory reliance[*7], agility, and the appropriate, timely and effective sharing of information concerning the state of manufacturers' pharmaceutical quality and risk management capabilities between global regulatory agencies.

Specifically, the envisaged PQ KMS aims at strengthening international collaboration to support global development, manufacture, and supply of pharmaceutical and biological /biotechnological medicinal products. The PQ KMS will enable further collaboration and reliance in the field of inspections and more convergence among regulators regarding regulatory evaluation of pharmaceutical quality information. Together, this will facilitate manufacturing agility, addition of new manufacturing sites, and strengthen the resilience of global supply chains. A key enabler for delivering the full benefits of a PQ KMS is an enhanced product and process knowledge coupled by a mature on-site PQS.

ICMRA is providing the global leadership and strategic vision to advance this work through the PQ KMS Working Group[8] tasked with facilitating the coordination of efforts undertaken by existing and highly experienced international regulatory harmonization and information-sharing bodies. This includes the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), International Pharmaceutical Regulators Programme (IPRP), and Pharmaceutical Inspection Co-operation Scheme (PIC/S).

In addition, input from other key stakeholders such industry and other relevant technical groups will be sought. It is imperative that key stakeholders work in close cooperation toward a shared vision of enhancing pharmaceutical quality knowledge management, amongst regulators, through the establishment of a regulatory PQ KMS, and facilitating industry agility in quality

[*] The current RP utilizes the WHO definition of "regulatory reliance" as the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision

management with the ultimate goal of achieving timely access to safe, effective, high-quality medicines and assuring public health.

The significant long-term benefits of establishing a PQ KMS would include:

- Rapid integration and analyses of quality information that will support efficient and enhanced risk-based and targeted oversight of manufacturers. This is enabled by transitioning to harmonized structured and standardized electronic formats for key regulatory information, including use of unique product and facility identifiers and a commonly agreed data standard for information exchange.
- Improved, consistent and expedited regulatory authority decision making facilitated by the secure sharing of confidential and non-confidential information among regulatory authorities about all critical aspects of pharmaceutical manufacturing, quality and risk management capabilities, in addition to pharmaceutical manufacturing facilities, contributed by, and accessible to, authorized users from multiple participating regulatory authorities in a secure knowledge management system.
- Developing a framework that might, in time, support the possibility for simultaneous filing of common data sets within a marketing authorization application (MAA) and related PACs to all regulatory authorities currently using common technical document (CTD) standard formats, e.g., including improved capabilities for both industry and regulators in management of PACs, and ultimately reduce regulatory burden.
- More extensive reliance among regulators facilitated by work to harmonize specific data expectations for sponsors and standards for review among regulators, so that regulators can be assured of the comparability of the assessments and related determinations of other regulatory authorities.
- Similarly, more extensive reliance among regulators on the supervision of manufacturing facilities will be enabled through specification of structured data formats for inspection reports.
- The development of a comprehensive set of tools to evaluate PQS effectiveness for risk-based PACs would enable inspectorates to evaluate the effectiveness of a manufacturers PQS under a harmonized framework and to communicate this information to assessors to facilitate product lifecycle management (cf. ICH Q12).

Industry stakeholders will need to ensure control and product knowledge to benefit from the PQ KMS concept. The ultimate enabler to develop a regulatory PQ KMS is an enhanced product and process knowledge. Such knowledge, when coupled with a manufacturer's mature on-site PQS, would allow the full benefit of the PQ KMS framework. Moreover, the establishment of a regulatory PQ KMS would further support the global implementation of existing technical and regulatory guidance concerning mature on-site PQS and pharmaceutical product lifecycle management as outlined in ICH Q10[1] and ICH Q12[4], respectively.

This joint RP is focused on specific next steps that can be taken by ICMRA, ICH, PIC/S and IPRP, respectively, concerning the planning, coordination, and communication needed between organizations to build a global PQ KMS capability.

2. Proposed Areas of Harmonization Work

The following section provides a high-level overview of harmonization work each organization intends to complete to support the development of a PQ KMS. Although technical experts from respective organizations will have to progress certain areas of work within their remit, regular engagement with ICMRA will ensure alignment on the overall strategic direction. Moreover, a collaborative approach that builds on work already completed or ongoing is required to develop the use of unique identifiers. In this instance, ICH, IPRP, PIC/S and ICMRA, in collaboration with industry, will progress the necessary harmonization work to complete the development, adoption, operation, governance and maintenance of internationally harmonized unique identifiers related to pharmaceuticals.

ICH – Data Elements and Standards

ICH works to ensure that safe, effective, and high-quality medicines are developed, registered and maintained in the most resource-efficient manner through the development of ICH Guidelines. ICH Working Groups composed of regulatory and industry experts develop the guidelines, which are adopted by the regulatory members in the ICH Assembly.

The work proposed for ICH is primarily focused on further specification or clarification of harmonization required for data elements and data standards submitted in the quality modules of the CTD. The proposed approach to work is intended to complement efforts already ongoing (leveraging existing data formats) or completed in this space to avoid any unnecessary duplication of effort and to ensure work is completed in an effective and efficient manner.

Specifically, work is focused on establishing the data formats and standards to support regulatory submissions. The work currently under way in the ICH M4Q(R2) Expert Working Group (EWG) will largely serve to address this opportunity. The M4Q(R2)[9] is anticipated to include, among other matters, a complete renovation of the quality-related components in the CTD to accommodate PACs, emerging concepts like data analytics, and advanced manufacturing to better facilitate review. Following the work on M4Q(R2), ICH plans further work on structured product quality submissions e.g., standards for submitting CMC information in structured formats.

ICH will further advance PQ KMS capabilities and support PQS assessments for PACs through harmonization of data elements and data standards that are in scope for submission via the quality modules of the CTD. Submission of the same standardized application or quality dossier to multiple regulators will greatly facilitate information sharing between regulators, enable collaborative assessments, more convergence and ultimately increased reliance among those regulators in PAC assessment and outcomes.

IPRP – Alignment of Regulatory Assessment and Expectations

IPRP is a forum for regulators to exchange information on issues of mutual interest and enable regulatory cooperation. It currently comprises several working groups, with the Quality

Working Group (QWG)[*] and the Identification of Medicinal Products (IDMP) Working Group[†] central to progressing the harmonization work proposed in the current joint RP. Specifically, work proposed within IPRP aims to examine and align standards of quality assessment approaches and documentation requirements for greater convergence, and ultimately reliance, between regulators.

As a standing regulator-only working group, the IPRP QWG serves as a forum in which quality-related issues can be discussed confidentially, including important emerging quality-related issues that arise. In turn, this facilitates the implementation of ICH guidelines and, in a reciprocal manner, with the QWG also identifying topics that are suitable for broader discussions within the ICH environment, when necessary.

The work proposed to be undertaken in IPRP will focus on convergence of the regulatory expectations among participating regulators regarding quality assessments for new applications and in relation to PACs – considering (or based on) the harmonized technical guidelines available. The QWG seeks to increase the efficiency and effectiveness of drug substance and drug product review processes by developing and making common quality-assessment tools available to medicine regulators. This includes, but is not limited to, developing a lexicon of quality terms, common active substance master file (ASMF) /drug master file (DMF) submission forms, and common quality assessment report templates. Moreover, IPRP will help to reduce differences in the interpretation of quality issues between regulators by developing training tools and guidance documents for quality assessors.

On reducing the overall regulatory burden and enhancing convergence, an additional issue that can be progressed by IPRP is the area of PACs. The QWG could analyze the current situation and work on a common science-and risk-based framework to facilitate convergence, collaborative assessments, and ultimately, more reliance on assessment of PACs over time. These efforts would be facilitated by the ICH work on harmonization of requirements for data to be submitted in the quality modules of the CTD.

PIC/S – Inspections

The PIC/S is a non-binding, informal co-operative arrangement between participating regulatory authorities primarily in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use. PIC/S aims at harmonizing inspection procedures worldwide by developing common standards in the field of GMP and by providing training opportunities to Inspectors. Current work of PIC/S on harmonizing inspections, inspection report templates, and establishing unique facility identifiers will contribute to the PQ KMS implementing a risk-based focus.

The proposed work of PIC/S is to focus on inspection related elements with particular attention to PQS. This paper has noted the importance of regulatory assessment of PQS effectiveness in the context of regulatory review of PACs. Although there are aspects of review and assessment of PACs that involve both the expertise of inspectorates and pharmaceutical

[*] https://www.iprp.global/working-group/quality
[†] https://www.iprp.global/working-group/identification-medicinal-products

quality assessors, the inspectorates and leadership of PIC/S are anticipated to be critical in the development of some key aspects of a global PQ KMS capability.

The harmonization work that PIC/S will consider includes, but is not limited to:

- Identification of key facility attributes already/being submitted in market applications to be captured in structured electronic form (anticipating a future virtual repository of facility information).
- Specification of a structured data format for inspection reports (to facilitate regulatory reliance and risk/analysis-based oversight).
- Further tools and templates for PQS assessment for inspectors.
- Development and publication of related PIC/S Inspectorates Academy (PIA) training modules.
- Promoting use and reliance on GMP inspectional information provided by PIC/S authorities.

PIC/S will consider and pursue opportunities to enhance approaches and tools for evaluation of other key elements that ensure the operation of an effective PQS. The development of a comprehensive set of tools, in collaboration with other key stakeholders, to evaluate PQS effectiveness for risk-based PACs would enable all inspectorates to evaluate the effectiveness of the full PQS under a harmonized framework. This would serve as a practical means to achieve further sharing of intelligence on the current state of industry and knowledge among inspectorates and made available to assessors about the health of the PQSs in regulated companies and to support ongoing oversight of product lifecycle management.

Cross-Organizational Collaboration – Unique Identifiers

Regulators currently have limited ability to make maximum use of information already collected. Although some authorities use national or regional identifiers, a common and inter-operable set of unique identifiers for manufacturing facilities, pharmaceutical products, substances (in line with ISO IDMP 11238), marketing applications, and/or marketing application holders are not currently available. It is also necessary to adopt common standards by using internationally agreed terminologies (e.g., MedDRA). Considerable work has already been done to develop unique identifiers, including, but not limited to the work of the International Organization for Standardization for the Identification of Medicinal Products (ISO-IDMP) and coding conventions for some of these elements in addition to the publication of Unique Facility Identifiers (UFI) by PIC/S.

The ICMRA PQ KMS working group proposes to establish a new sub-working group that will consider the status of current standards, their implementation, the potential need for new standards and outline approaches for the development, adoption, operation, governance, and maintenance of internationally harmonized unique identifiers related to pharmaceuticals building on work already completed to date. This follow-on work undertaken by the new ICMRA PQ KMS sub-working group will engage relevant technical experts considering from ongoing efforts such as the ICH M2 Electronic Standards Working Group, ICH QDG (Quality Discussion Group), the IPRP IDMP Working Group, the PIC/S Working Group on UFI, as well as other relevant sources of expertise, e.g., WHO.

3. Coordination of PQ KMS-Related Work Streams

The ICMRA PQ KMS working group can provide the cross-organization coordination for the different work streams undertaken respectively with the ICMRA PQ KMS group, and in ICH, PIC/S and IPRP (referred to below as the four organizations). Each organization will commit to develop a multi-year workplan guided by the concepts outlined in the current paper. Each workplan will identify the specific harmonization or convergence topics/projects that the respective organizations will undertake in a coordinated and prioritized manner and focus on work to be initiated in the next 5 years.

- For each identified topic the organization will identify the expected starting period (e.g., Q1, Q2, Q3 or Q4 in CY2023-CY2027), and similarly indicate the target period for completion.
- The four organizations will cooperate in joint planning for harmonized implementation of topics with shared responsibility (e.g., implementation of unique identifiers for facilities, clarifying and expanding on how inspectional findings and other measures of the health of the PQS influence regulatory flexibility in terms of PACs, etc.).
- The ICMRA PQ KMS working group can provide a template to facilitate the four organizations' workplan development and later combining the separate workplans into a joint view and common roadmap. A combined workplan will enable further refinement of the prioritization and sequencing of how work should proceed within each organization.
- The ICMRA PQ KMS working group will provide update reports for ICMRA Plenary meetings, and propose topics for Summit meetings as appropriate, in addition to regular engagement with ICH, PIC/S and IPRP, as required, during scheduled PQ KMS working group meetings.
- The PQ KMS working group sets the aspiration to conduct a public meeting at least once per year with industry and other external stakeholders to present and discuss the work under way, review future plans, and gather stakeholder input. This could be in conjunction with international conferences organized by non-for-profit organizations.
- Together, the four organizations will conduct an annual review, led by the PQ KMS working group, to reflect on and incorporate stakeholder input, as appropriate, and gather any updates to the workplans based on the experience and progress to date.

4. Future Considerations and Challenges

Supporting Technology Platform for Virtual Repository

While it is beyond the scope of the current joint RP to define specific technological solutions to the envisaged PQ KMS before harmonization work is undertaken, a technology and platform strategy will be developed to examine options to progress the sustained delivery of a PQ KMS capability. Any virtual repository would need to ensure, for instance, secure and controlled authorized access to information and regulatory assessments to maintain confidentiality agreements and trade secrets, information security and protection from cyber threats, an ability

to leverage current technologies to interface with existing regulatory authority and sponsor/ market authorization holder systems. Any future strategy will also address the need for longer-term governance, financing, personal data protection and data integrity of a suitable technology platform, and its desired evolution, as well as the nearer term development and standup and ongoing operational performance of the virtual information repository.

Legal and Regulatory Considerations

There are at least two areas of potential regional variation that will need to be further explored and analyzed as part of the work to advance and shape the longer-term roadmap. For instance, some of the information proposed for inclusion in a virtual secure repository will contain commercially confidential data or trade secrets with disclosure subject to strict statutory and/or regulatory requirements in different regions. Other regional legal and regulatory requirements related to information storage and access require attention. Further analysis of these issues and proposed options or solutions will be included in the technology and platform strategy. For example, current regional legal and regulatory requirements for PAC submissions vary and pose limitations in the degree to which regulators can achieve harmonization in their submission requirements and related assessments for the purposes of convergence. Harmonization work performed by specific bodies (e.g., IPRP) will require analysis, discussion, and planning for future convergence to ultimately facilitate reliance of regulatory assessment of PACs over time.

5. Capability-Piloting Strategy

Pilot testing a knowledge management system capability extending regulatory information sharing and collaboration—through more narrowly defined cases involving CMC or PAC review for specific products, sponsors, and set of participating regulators--will serve multiple goals in progressing development of the PQ KMS capability. These include:

- Identifying and communicating areas where convergence of regulatory assessment and inspection works well and where there is divergence.
- Further characterizing what might be elements of the essential minimum set of technology platform needs to support assessments, and the areas where current legal parameters may present barriers that could over time be addressed.
- Providing industry with experience submitting and assessing the same CMC information for the same product and manufacturing facilities to multiple regulators for near-simultaneous review and potential approval in multiple regions.
- Identifying types of products where “early wins” are likely to be most achievable.
- Increasing confidence among both regulatory authorities and industry regarding the PQ KMS capabilities that could be operationalized and how to approach regulatory collaboration to achieve the greatest success.

The ICMRA PQ KMS Working Group is also overseeing such pilot efforts following the 2021 ICMRA-Industry workshop on enhancing manufacturing capacity for COVID-19 therapeutics and vaccines[10]. The two pilot efforts are focused respectively on collaborative CMC PAC assessments and collaborative hybrid inspections[11]. Current and potentially new pilot projects will serve as a

starting point for future international regulatory convergence that will ultimately be supported by the PQ KMS capability.

6. Stakeholder outreach and engagement strategy

The proposed global PQ KMS capability is anticipated to have far-reaching benefits for regulators and industry. Therefore, it will be important to engage all relevant external stakeholders to realize a PQ KMS capability and associated benefits. Regular opportunities for stakeholder outreach and engagement are anticipated through the planning of public workshops and/or additional public stakeholder sessions to occur on the margins of the annual ICMRA Plenary sessions. Moreover, ICMRA and the regulatory organizations contributing to the PQ KMS capability may also wish to engage in targeted communications with specific communities or other relevant stakeholders interested in the harmonization or convergence work being undertaken by their organization. Such engagement plans should be built into the respective multi-year workplans of each organization.

Conclusion

This joint RP outlines the shared vision and ambition of leading international regulatory convergence and harmonization organizations to advance the development of a global PQ KMS with the ultimate goal of enhancing the availability of quality medicines. It provides high-level framing for the work that would be undertaken respectively, and in some cases jointly, in ICH, PIC/S, ICMRA and IPRP requiring coordination of those efforts over time to enhance synergy and avoid any duplication of work. This will be accomplished through continued cooperation, regular engagement and information sharing related to the progress of work and lessons learned across organizations and in combination with key stakeholders.

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