ICMRA PQKM Workshop Summary Report

Date: 1 November 2023

Executive Summary

On 20 July 2023, the International Coalition of Medicines Regulatory Authorities (ICMRA) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) hosted a one-day joint virtual public workshop[1] on the development of a global Pharmaceutical Quality Knowledge Management (PQKM) capability. The workshop highlighted the progress made in developing approaches for enhanced global collaboration in medicines regulation since the ICMRA workshop on enabling manufacturing capacity in the COVID-19 pandemic, which was held in July 2021.

The ICMRA PQKM project aims to leverage collective resources and information sharing on pharmaceutical quality between regulatory agencies. This will be achieved through the alignment of regulatory requirements for data submissions and regulatory assessments as well as inspections in the post-approval setting. In turn, this will help to significantly reduce the need for multiple separate submissions from sponsors, avoid duplicative assessments and on-site inspections, and facilitate assessment and inspection reliance. As part of this project, ICMRA is overseeing two pilot programmes on collaborative assessments of post-approval changes and hybrid inspections.

The workshop was launched with introductory remarks provided by Emer Cooke of the European Medicines Agency (EMA) and Chair of ICMRA, followed by opening comments from Greg Perry for IFPMA. During the workshop, both industry and regulators shared feedback on their experiences with the ongoing pilots, highlighting the successes and the challenges. Participants explored barriers to involvement in the pilots, as well as practical solutions to those barriers. Panellists also discussed future direction and planning for the PQKM project, including what they believed to be the enormous potential of the project.

The report that follows provides a summary of some of the key content presented and discussed during the workshop, including an ICMRA overview of the PQKM work and plans to date, and an industry perspective on this work. It also provides an overview of the two joint regulator-industry panel discussions which took place focusing on the post-approval change (PAC) collaborative assessment pilot work and the Collaborative Hybrid Inspections Pilot (CHIP), and the experience and learnings from both.

Background to the ICMRA PQKM project and progress to date

Lorraine Nolan of the Health Products Regulatory Authority (HPRA) provided a background and vision for the ICMRA PQKM capability and project to date. Figure 1 provides a timeline of events leading up to the formation of the PQKM working group in September of 2021. Dr. Nolan described ICMRA's vision for a global PQKM capability outlined in the June 2021 paper which included the following goals:

- Enhance regulatory reliance, agility, effectiveness, and efficiency

[1] The workshop was jointly organised by ICMRA and IFPMA, including ICH, IPRP, PIC/S, ABPI, BIO, DCVMN, EFPIA, IGBA, JPMA, Medicines Australia, PhRMA, and Vaccines Europe.

- Harmonise data submissions, regulatory expectations, assessments, and inspections
- Accelerate global availability of quality medicines

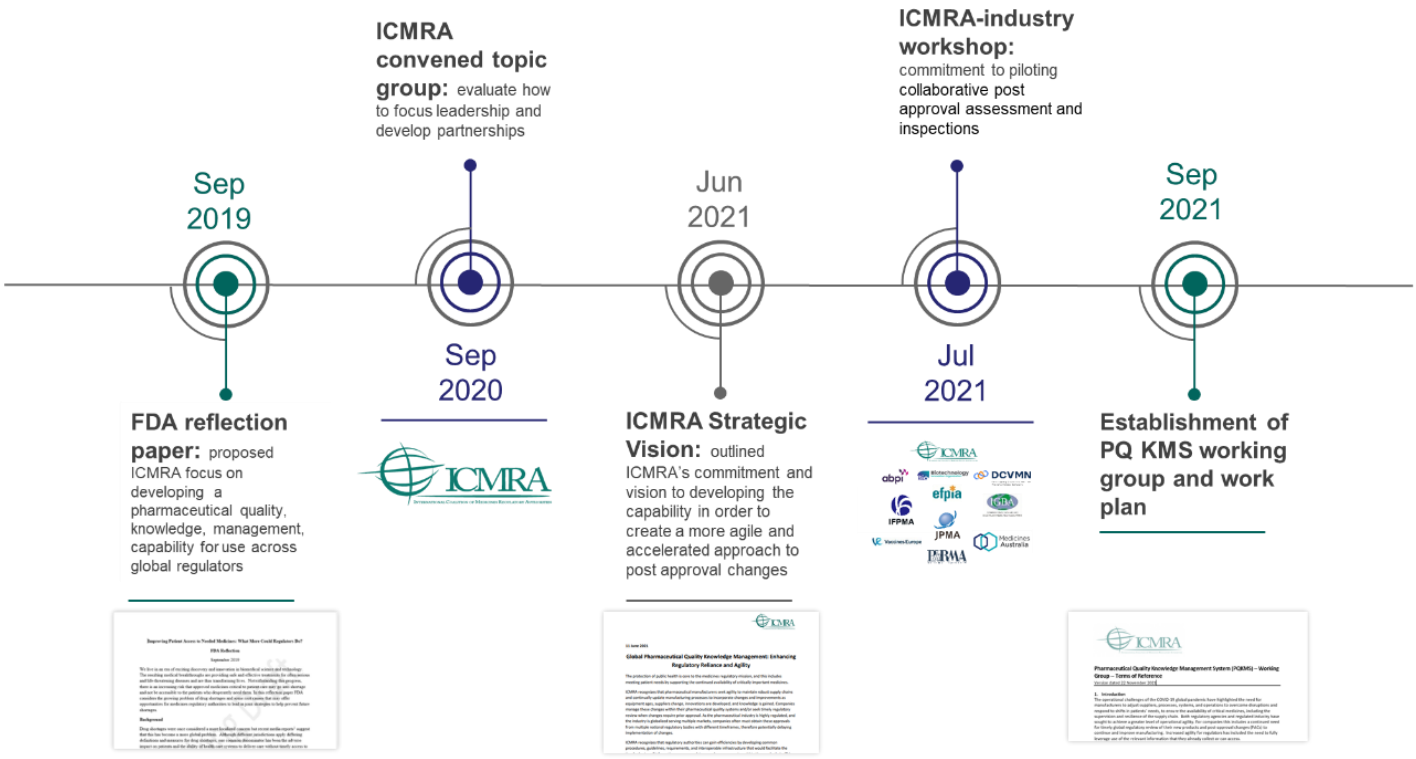

Figure 1: Timeline of events that led to a PQ KMS working group

Dr. Nolan described the structure and function of the PQKM working group under ICMRA. Figure 2 provides a diagram of the working group's structure and initiatives. The PQKM working group reports to the ICMRA Executive Committee. Under the working group are three subgroups that work on four initiatives which include: developing two pharmaceutical quality-related regulatory collaboration pilots; consideration of the need for unique identifiers for key PQKM data elements; requirements for a future secure shared technology platform; development of the ICMRA-ICH-IPRP-PIC/S joint reflection paper; and compilation of these organizations' related work plans. It is also noted that the development of the envisioned PQKM capability involves strategic collaboration of ICMRA with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the International Pharmaceutical Regulators Programme (IPRP), and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

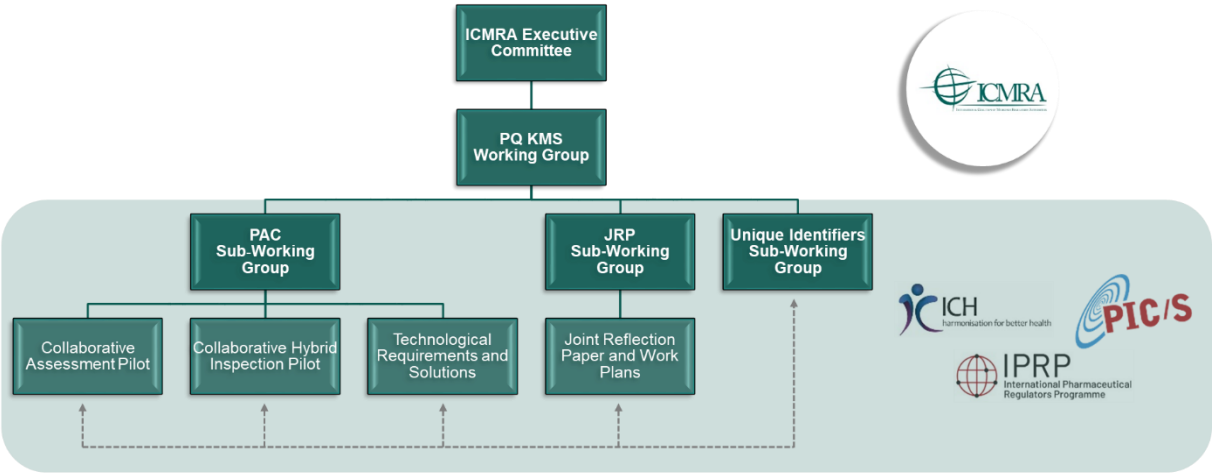

Figure 2: Structure of the PQ KMS Working Group under ICMRA. The dotted line represents the linkage across the subgroups in developing the deliverables.

Regarding the deliverables, Dr. Nolan described key achievements to date which include the commencement of two pilot programs and publication of a joint ICMRA-ICH-IPRP-PIC/s reflection paper. The joint reflection paper (JRP) describes a joint commitment of the participating organizations to develop PQKM capability and infrastructure. The JRP subgroup is developing a combined work plan that aligns with the example commitments outlined in Figure 3.

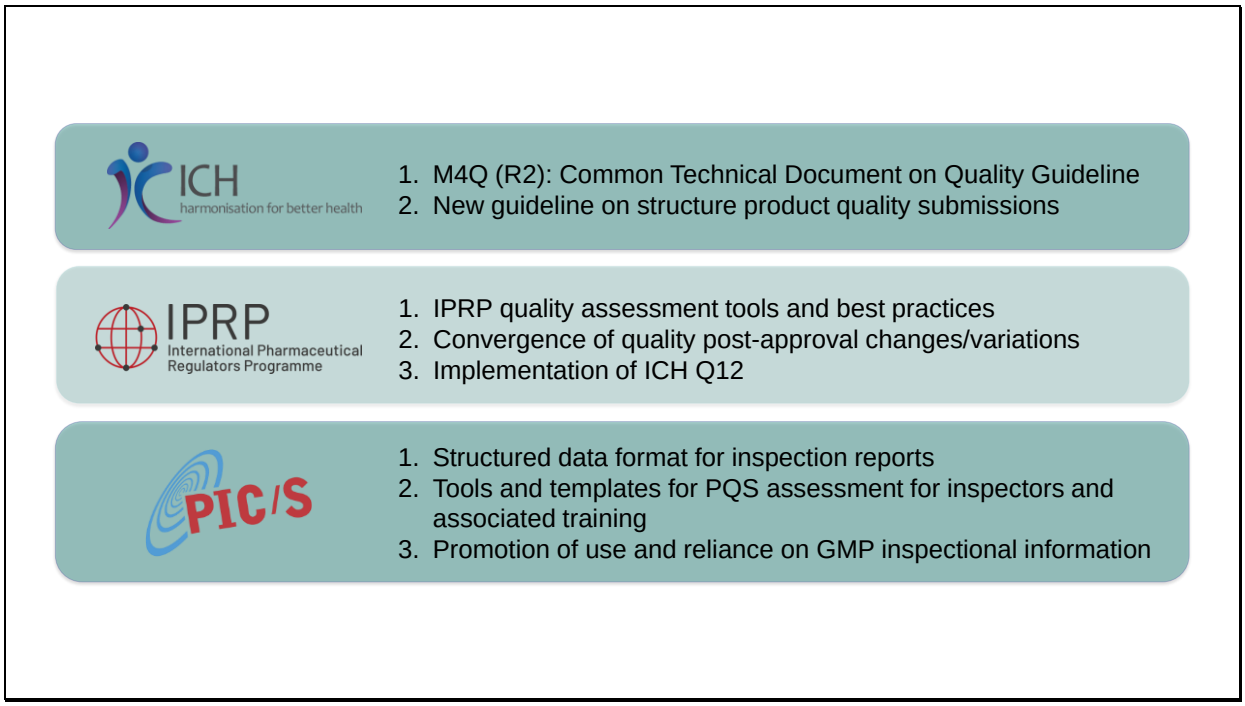

Figure 3: Examples of work commitments from ICH, IPRP and PIC/s that contribute to the development of a PQ KM capability.

Industry's perspective on ICMRA's Global Strategy & Pilots for PQKM

Ginny Beakes-Read provided IFPMA's perspective on the PQKM project and industry engagement to date related to the ongoing PQKM pilots, referencing the timeline shown in Figure 4 to reflect how the COVID-19 pandemic had influenced interest in this area.

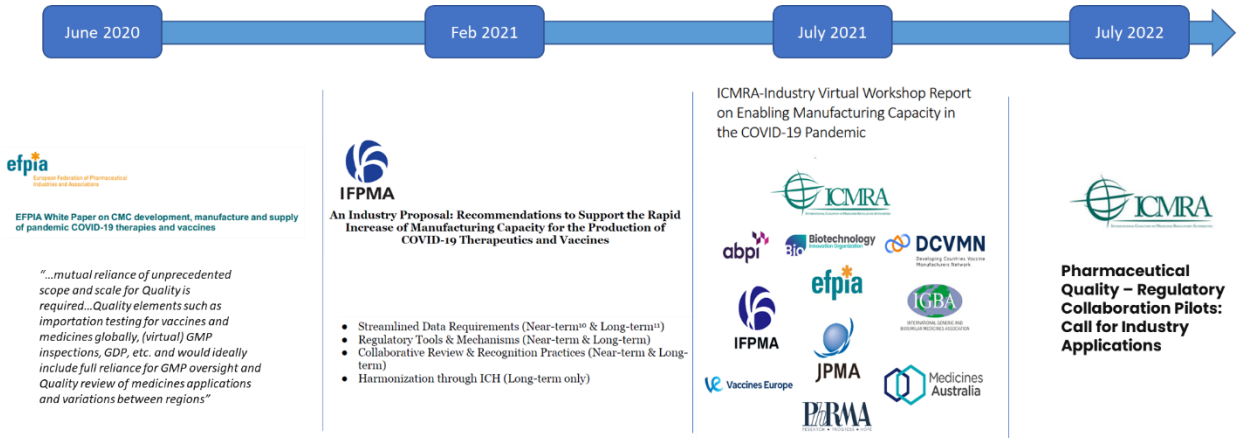

Figure 4: Timeline of events post-COVID-19 pandemic onset that led to industry's participation in ICMRA PQ KMS pilots

Overall, Ms. Beakes-Read indicated that IFPMA strongly supported ICMRA's PQKM global strategy and pilots. They considered that the collaboration pilots could have many potential benefits including, in their view, the potential for streamlined regulatory assessments by increasing mutual understanding through enhanced regulatory convergence and reliance. She conveyed that highlighting the potential outcomes of pilots by sharing successes and challenges could incentivize further industry participation. She presented a summary of industry members' experiences and recommendations for improvements for the CMC/PAC collaborative assessment pilot as shown below in Table 1.

Table 1: Industry Experiences and Potential Improvements for PAC Pilot

Experience	**Potential Areas for Improvement**
• Many companies have considered the pilot programs • >10 applicants for the PAC pilot • Positive experiences with application process and submission • Welcomed critical assurances that there will be no delays • Interested in extension of pilot	• Platform for shared assessment • What are the timelines for submission and review when multiple regulators are involved • Industry would like to better understand the role of observer regulators • Scope is limited (PACMPs, types of therapeutic products) • Limited number of regulators closely involved

The presented summary of industry members' experiences and recommendations for improvements thus far for the CHIP pilot is provided in Table 2.

Table 2: Industry Experiences and Potential Improvements for CHIP

Experience	Potential Areas for Improvement
• Many companies have considered the pilot programs • Limited applicants to-date for the CHIP • Positive experiences with application process and submission • Welcomed critical assurances that there will be no delays • Interested in extension of the pilot	• Different focus of regulators (e.g., new facility vs. pre-approval inspection) • Lack of real experience – company concerns that process would multiply queries, not reduce them • Challenges of scheduling to accommodate all parties and manufacture • Timelines and potential to impact critical supply plans • Scope is limited (new facilities, types of therapeutic products); could expand to new manufacturing platforms that are not related to a specific product/change

Finally, based on the limited experience to date, IFPMA offered suggestions for further enhancing these pilots including continuation of the pilot programs and consideration to expand the product scope (e.g., to include vaccines and non-critical-need); exploration of enhanced cloud-based IT platform to allow more efficient data exchange; inclusion of additional regulator authorities; including the goal of reliance as appropriate, and broader implementation of ICH Q12 life cycle management tools.

Collaborative Assessment of Post-Approval Change Management Protocols ICMRA collaborative assessment Pilot status and experience and Panel I Discussion

To set the scene for Panel 1 discussion, Evangelos Kotzagiorgis of EMA provided a brief overview of the ongoing pilot looking at collaborative assessment of post-approval change management protocols (PACMPs). The presentation began with background on the pilots citing the ICMRA-Industry workshop in July 2021 which indicated the need for the following:

- A joint effort to expand availability of COVID-19 therapeutics and vaccines by increasing manufacturing capacity
- More convergence on CMC aspects between regions to allow faster supply of critical medicines to patients
- Overcoming logistical challenges created by the pandemic through use of hybrid inspections

The presentation next reviewed the scope of the pilots which include focus on specific therapeutic areas and product types for an anticipated duration of 1-1.5 years.

Table 3: Scope of PAC Pilot

Therapeutic Area	Product Types
• Products intended for the treatment of patients with COVID-19, or changes necessitated by COVID-19, e.g., supply chain changes • Breakthrough/ PRIME/ Sakigake/ similar-eligible products • Products deemed medically necessary/critical medicine.	• Therapeutics, including small molecules and biologicals • Vaccines are excluded from the pilot (however, they may be considered in the future if the pilot is extended).

Dr. Kotzagiorgis also explained the aim of the PAC pilot which includes the following:

- Develop a framework, which provides a platform for multiple regulatory agencies to participate in a collaborative assessment of post-approval chemistry, manufacturing and controls (CMC) changes including PACMPs
- Deliver a single list of questions to the applicant wherever possible, however a stated goal of the pilot is to identify misalignments, differences, and potential areas for further convergence or harmonization across regions (i.e., predictability)
- Regulators to work towards a common approach to the application assessment and decision making.
- Develop best practices in the quality assessment of CMC PACs and share learnings to build further collaborations in assessment

Lastly, Dr. Kotzagiorgis provided the current status of the pilot. The call to industry for proposals had been open since June 2022 and since then, there had been 12 proposals submitted with four selected. At the time of the workshop, one application was still under evaluation, one ongoing and under assignment, and one had been completed. The completed pilot case lasted 120 days and included PACMPs for drug substance / drug product / quality control site transfer for a biological molecule with EMA as the Lead authority, the U.S. Food and Drug Administration (FDA) participating in PACMP assessment, and Pharmaceuticals and Medical Devices Agency (PMDA) observing. From this completed pilot, best practices are under development to improve in subsequent pilot cases.

Overall, the first pilot case showed a strong commitment and collaboration from all parties and despite resource intensity was considered successful in achieving a harmonized outcome and providing valuable lessons for future assessments. Positive uptake by regulators and positive feedback from Industry was also observed, ultimately leading to the decision to expand the number of applications in the pilot.

Panel 1: Collaborative Assessment Pilot

The first panel consisted of a group of regulators and industry members [see Annex 1] who actively participated in the Collaborative Assessment of PACMPs Pilot. Pilot members from EMA, PMDA, and FDA represented regulator perspectives along with industry pilot participants from Roche, AstraZeneca, Amgen, MSD, and Merk/EMD Serono. The discussion was structured around three topics and panelist perspectives on a series of questions related to: design and selection process, sharing experiences, and learnings for the future.

Design and Selection Process

What is the pilot aiming to achieve?

Regulators highlighted that the ultimate importance of this effort is to benefit patients by providing them with access to reliable medicines through simultaneous approvals in different regions. This need came to light during the COVID-19 pandemic and regulators saw PACs as a focus area for this pilot effort. The pilot provides an opportunity for multiple regulators to work together, learn from each other, and in the future, develop reliable mechanisms and approaches for regulators. Because regulators were able to coordinate in advance to consolidate and prioritize a final set of questions, the pilot provided more efficient and consolidated opportunities for regulators to ask questions from sponsors. This pilot thus offered an opportunity to streamline communications with a sponsor during the assessment. Regulators shared their mutual satisfaction with the ability to coordinate with each other, keep to timelines, and hold successful exchanges with sponsors throughout this new pilot process.

Is there a need for manufacturing agility?

Industry shared that manufacturing agility is needed for supply chain resilience and balancing supply networks within companies and contract manufacturing organizations (CMOs). From their perspective, current challenges with long approval timelines for implementing changes globally prove a substantial obstacle to improving manufacturing agility and resilience. Although the challenges of PACs for global supplies existed before COVID-19, the effects of the pandemic on pharmaceutical supplies and manufacturing are still being felt. From the industry panelists' perspective, the ability to prevent drug shortages is assisted by harmonization and globalization of PAC review process, timings, and outcomes. The pilot thus presents the theoretical potential to reduce a 5-year global approval timeframe per change to 3-6 months. This efficiency and positive impact for patient medicine supplies deserves everyone's attention and focus. In response to questions about aspects of the pilot design they found uncertain or particular aspirations for the pilot based on their experiences, industry expressed excitement regarding the involvement of multiple regulators but some uncertainty about the systems that would be used for secure information sharing. They nonetheless saw value in this opportunity to enhance understanding and acceptance of PACMPs by ICMRA member agencies as a way that would lead to greater harmonization.

Sharing Experiences

What are the pilot's greatest successes, challenges, and learnings so far?

In their experience thus far, regulators reported being able to develop a harmonized process to coordinate and to reach a single agreed outcome and considered this a real success. Their harmonized implementation included putting together tools to "scale up and scale out" the pilot, work together through shared timelines, and develop standardized templates. While there have been positive engagements and collaboration between regulators and industry, these pilots have nonetheless had to overcome several logistical, administrative, and technical challenges. For example, regulators do not have a pre-existing global collaborative assessment process. As a result, authorities needed to be flexible to reach agreement on a single submission assessment timeline that would meet all the different regional regulatory timelines for action at the same time. The assessment team noted working through the collaboration pilot required more time when compared to traditional assessments. Additional meetings were needed to discuss the assessment and identify regional requirements, collating them into a single information request for the sponsor. Regulators participating in the pilot had to manage meetings across

different time zones, consider the differences between regulatory review processes, and reach agreement on sharing of documents amongst each other. They also experienced challenges due to not having a globally shared secure platform with appropriate access for all regulators.

To address these technological challenges, the pilot working group put together a separate technology platform working group comprised of experts from FDA, EMA, and PMDA. In the short term, they have recommended regulators work through Microsoft Teams to support their pilot needs to collaborate across regulatory members. The technology working group is documenting the current process (e.g., assessment timeline with milestones) that will allow regulators to better understand their technology needs, especially as the program becomes more mature. For the long-term goals of the pilot, the tech working group is working to develop a solution that accounts for the complexity of working across legal and regulatory jurisdictions while meeting their data and system security needs. This work group has given regulators the ability to better understand the appropriate governance over a potential technology solution and provided suggestions on how to finance and procure additional technology capabilities.

What have you found to be the most helpful things that companies have done in partnering and interacting on this pilot?

Regulators shared that the success of this pilot is based on the ability for industry and regulators to rely on and trust each other. Everyone understands the concerns companies may have about participating in a pilot involving collaborative review by multiple regulators and the potential for increased questions and delay. Regulators consider that having a common goal related to patient access can enable productive work in partnership. Working together should thus be seen as a shared responsibility between both parties. Regulators on the panel urged companies to reach out and continue asking questions so the pilot team can surface and address new challenges and identify areas of opportunity and learning. So far, regulators expressed their satisfaction with industry's willingness to participate and communicate transparently about their questions and concerns. Regulators emphasized that they are committed to the success of the pilot and will continue to work together as partners in facing new obstacles.

What motivated your company to apply, or not apply, to participate in the pilot?

Industry panelists noted that their companies had consulted internally to determine if they had a product that met the pilot's criteria. In these discussions, companies noted they were motivated to apply for several reasons, including the unprecedented opportunity to collaborate and interact with regulators, test the joint review and approval at the same time from FDA/EMA, and address a consolidated list of questions. Others mentioned the opportunity to promote the harmonization of quality dossier assessment and standards across different regulatory authorities. Some companies shared that due to the timeframe of the pilot (expected to be 1-1.5 years), the choice of the products and eligible PACMP changes could be quite limited.

What were the major questions or considerations for your company [near-term and longer-term] when thinking about applying?

Some of the key questions companies considered internally included:

- How would review work across different legal, IT and process/timing, work across multiple agencies?
- Would agencies with no legal framework for PACMPs be included in the pilot?

- Will participating in the pilot affect timelines and potentially delay approvals for supply-critical changes, particularly for COVID-19 products?
- What's the role and impact for observing regulators in the pilot?
- How can Industry help to encourage the participation of ICMRA member authorities in this pilot?

What were some of your key learnings from your experience?
Industry panelists shared experience to date from their company's perspective. For example, one company shared that their application submission enabled early engagement with ICMRA regulators who were open to discuss and support their selected countries for the submission. This offered the company an opportunity to engage and address local expectations (e.g., pre-meeting, translation, etc.) and seek clarity on how to submit their application to observer agencies. The company shared that this pilot process worked best when planning early, especially where multiple agencies were involved. This included having strong project management support throughout the whole process to assist with: local clinical research associates' engagement on pre-submission meeting, confidentiality forms, additional M1 content, aligned submission calendar, translation, and other considerations.

Another company shared that their experience was smooth, included predictable timelines, and allowed for open and collaborative dialogue with regulators. This dialogue was the most valuable part of their experience. Some key learnings included that the participating regulators are eager to make this pilot work, learn from the experience, align on most topics, and be willing to point out differences in opinion. Overall, the pilot did not add significant additional work and benefited directly from same-day approval. The logistics in the pilot are a continuing challenge. To get to the ultimate goal of global convergence and reliance in the long-term, Roche Genentech encouraged other industry members to actively participate in these important ICMRA pilots.

Learnings for the Future

How do you envision this pilot evolving over time?
Noting the significant investment of time and work required for real-time collaborative review, regulators shared that it would be impossible to expand this type of collaborative assessment to all applications. However, regulators believe that this type of collaborative assessment should really focus on a common or global regulatory process that offers maximum benefits to all regulators as well as industry. Regulators also considered that this pilot could have a great future impact on how regulators and industry work together to implement and promote innovative approaches or technologies. In pilot to date, regulators have already seen great opportunities for convergence and an opening to develop a common approach for innovative manufacturing technologies. Through these pilot efforts, there has also been a continued focus on securing drug supply, especially for critical medicines. In combination with the development of the necessary infrastructure tools mentioned before, the scaling up of this pilot in the future should help remove some of the current administrative burdens to inspection and assessment processes. This pilot is taking a step-by-step approach to learning, starting with PACMPs, making necessary adjustments, and eventually extending to other areas, facilitated by anticipated implementation of new technology and standardized tools.

How do you envision expanding the engagement of this pilot with more regulators? And what are some of the benefits of this expanded engagement?
Panelists thought this pilot could potentially develop a toolbox to identify where joint work is beneficial through collaborative assessments or hybrid inspection and define areas where more direct reliance would work best. By increasing the number of observers for a pilot inspection/assessment, the pilot could offer more opportunities for regulators to share and learn from each other, and in the long run, support a more harmonized approach across regulators. A suggestion for the future of the pilot would be to have industry members think strategically about what regulators they would like to include in the pilot inspection or assessment for their product, either as participating members or observers. If industry could strategically include an expanded list of regulators in either capacity this would enable greater impact for the pilots.

Another pilot challenge is related to secure information sharing and a regulatory workspace. Are you envisioning other ways that this might be addressed more formally and sustainably in the future?
The pilot technology working group believes that the technology exists to support this type of secure information sharing that provides access to both regulators and industry. However, regulators consider that the platform support needs to encompass more than just technology, and must also address questions on the eventual governance, financing, and security of such a system. The proposed approach needs to address all these areas to ensure there is alignment across regulators and the support of industry. Eventually, regulators see the need for a new kind of tool or platform that would allow for regulators to work through a single system that provides a seamless opportunity for regulators to efficiently manage documents and sponsor authorizations permitting all participating authorities to share information among themselves.

What are some areas where you think it would make sense to consider focusing on the future?
Industry members shared they would like the future of the pilot to:

- Expand to cover other products beyond those for unmet medical need, to minimize potential impact on supply chain and deliver “practice/experience” for companies and regulators.
- Expand scope to include other modalities such as vaccines.
- Develop a global regulatory process and implement collaborative tools to facilitate the management of interagency and industry interactions.
- Include more participating countries in the collaborative assessment (including ICMRA, ICH and non-ICH members) and expansion of confidentiality agreements.
- Expand beyond the use of PACMP to facilitate alignment between the agencies on some routine PACs.
- Acceptance of PACMPs use in more countries (expansion)

What are some good targets of opportunity where industry can actively partner to help achieve the most success and progress?
Industry panelists shared that they are willing to support the development of a single dossier and platform, expand to other PACs (not just PACMPs), the development of a detailed guidance on the process (submission and review), and continue to collaborate in all areas to establish workable and efficient processes.

Some regulators and some in industry have discussed the value of companies moving to a single format for a quality dossier for each product to enable regulatory reliance. What are your thoughts about these concepts for the future? If attractive, what are some important steps on the path to get there?

For industry panelists, the idea of a single global quality dossier was considered attractive and as noted through previous efforts, there would be clear benefits in terms of progress toward achieving the "Holy Grail" of harmonization. For industry, there needs to be a willingness to change and adopt digitalization of regulatory submissions. Industry and regulators should work to fully embrace the concepts of structured data, fast healthcare interoperability resources (FHIR) standards, and a common platform for data exchange to enable parallel submission and reviews, plus accelerate updates and change management.

As an example, Roche has been moving towards a single dossier and there are benefits in reducing approval timelines, fewer questions during review and increased use of reliance.

From the industry perspective some important steps to get there include:

- Common understanding across regulatory authorities that supportive information is not binding
- Assurance that requests from regulators for Q&A (e.g., from EMA and FDA) will support reliance and faster approvals
- More regulators open to piloting reliance
- Fewer region-specific requirements

Collaborative Hybrid Inspection Pilot (CHIP) — Collective Vision and Achievements to Date Paving the Way Forward and Panel 2 Discussion

To set the scene for the Panel 2 discussion, Stelios Tsinontides from FDA provided an overview of the ongoing CHIP. The CHIP has been open for industry submissions since June 2022 and has received three proposals. Two of these proposals have been accepted and are proceeding while the third has been withdrawn. CHIP is still open for new proposals from industry for future work.

Lessons learned from CHIP engagements to date were presented and included the following:

- Positive and productive collaborations among regulators and sponsors
- Significant effort to align regulatory approach to inspections from regulators requested to participate and timelines
- Significant effort to clarify CHIP expectations, regulatory limitations to the sponsor
  - Existence of Mutual Recognition Agreements and Confidentiality Agreements
- Need for enhanced IT platform capabilities for efficient and secure collaborations

Feedback on CHIP from industry was combined with the lessons learned to create follow-up actions for future CHIP work. The table below highlights these concerns and consequential responses.

Table 4: Industry Feedback and Follow-Up Items for CHIP

Industry Feedback	CHIP Imminent Follow-Up Actions

• CHIP viewed as risky
  ○ Concern that outcome will be "sum of all" duration and observations
• Limited scope; Small molecule pre-approval inspections and biologics pre-license inspections
  ○ Expand to vaccines and surveillance
• Sponsor's limiting factors
  ○ Business priorities
  ○ Availability of on-site resources
  ○ Limited safety stock on medically necessary products
	• Issue an Expectations for Chip Participants document for participating regulators and industry
	• Clarify expectations for industry in hosting a collaborative hybrid inspection
	  ○ No longer than an inspection by a single regulatory authority
	  ○ Onsite regulator serves as the single voice for participating regulators (see last paragraph of this section for more information)
	  ○ Aim to deliver single inspection outcome
	  ○ Highlight CHIP benefits (more information following this table)
	• Clarify anticipated CHIP timelines (see table 5)

Dr. Tsinontides highlighted the perceived benefits of participating in the CHIP which included the opportunity to receive a compliance agreement from multiple regulators with only a single inspection, ultimately minimizing effort, cost, and time to achieve multiple approvals. Next, there is the possibility to receive a single list of information requests, comments, and questions from multiple regulators at once, which will allow for increased efficiency in regulatory submissions, resulting in a more robust and resilient corrective and preventive action (CAPA) plan. Lastly, CHIP participation will provide an opportunity to contribute towards building an inspection framework that will serve as a foundation for future global convergence and reliance efforts.

Further to the perceived benefits, Dr. Tsinontides clarified the role of the on-site lead inspector. The on-site lead inspector is responsible for coordinating the scope of coverage with facility and remote teams by obtaining site information prior to inspection, planning observation activities, liaising with on-site facility personnel, coordinating remote set-up with facility, providing feedback to remote team on which activities to observe, and overseeing on-site and virtual engagement with the facility.

The presentation concluded with a review of the anticipated timeline, shown in table 5, and expectations beyond CHIP. At the conclusion of each pilot case, the participating regulators and company will provide feedback and performance data will be evaluated. After three to five cases, the outcomes are anticipated to be summarized in a report to ICMRA in the second half of 2024.

Table 5: CHIP Anticipated Timelines

Activity	Timeline (calendar days)
Pre-inspection planning between regulatory authorities	30 - 60 days before the start of the inspection
Communication with the facility to test IT and communication capabilities	7-14 days prior to the inspection
Start of the inspection	0
Close out meeting to provide the firm with a consolidated list of observations	5 - 8 days after initiating the inspection
Regulatory authorities receive CAPAs	30 days after close out meeting
Engagement with facility to clarify CAPA plan(s), if necessary	10 days after receipt of CAPAs from the facility
Preliminary inspection report reviewed by the regulatory authorities	60 days after inspection
Final inspection report(s) sent by regulatory authorities (GMP certificate or equivalent issued/ or statement of GMP Non- Compliance, if applicable) to facility	90 days after inspection

Panel 2: Collaborative Hybrid Inspection Pilot

The Panel 2 participants included representatives from ICMRA regulatory authorities and industry [See Annex 1] with the discussion structured around the initial drivers for the CHIP, and experiences and learnings to date.

Reflecting on the drivers and goals for the CHIP, the regulators noted that the COVID-19 pandemic highlighted existing inefficiencies in the global supply chain for medicines as well as regulation. Regulators agreed that the core motivation for the CHIP was patient safety, and the need to accelerate availability, and ensure continuous supply of medicines for patients. The CHIP also complements existing priorities for regulators, including establishing a global network of inspectorates working to agreed standards and enabling biomanufacturing capacity. The CHIP leverages the use of existing technologies and virtual inspection methods and in doing so can support stronger international collaboration among regulators and maximize limited inspection resources. These are key steps to help move closer to the goal of increased trust, mutual recognition, and reliance.

In addition to highlighting inefficiencies, the COVID-19 pandemic had a major impact on inspections, removing the possibility for onsite inspections. This necessitated an agile response from regulators and industry to develop and test tools to avoid delays to regulatory approvals. Panelists spoke to experience gained during the COVID-19 pandemic of conducting hybrid inspections and noted the advantages of this approach to inspections in supporting collaboration and increasing regulatory efficiencies. Regulators also noted the significant benefit of a single inspection report accepted by multiple regulators, a key outcome of the CHIP.

Sharing experiences

Industry panelists were invited to share their perspectives on their engagement with the CHIP. They were also asked to provide feedback on the content proposed for the “Expectations for CHIP participants”

document summarized in the presentation by Dr. Tsinontides prior to the panel discussion, and whether they believed it would be a helpful resource for companies considering participation in the pilot.

Industry explained that the decision to be involved in the CHIP was not a straightforward one. There were clear motivators to support involvement, not least the huge potential to improve access to, and availability of, medicines for patients globally. Equally, there were concerns arising from operational uncertainties regarding the hybrid inspection process itself. Specific concerns highlighted by panelists included the perceived potential for misalignment among participating regulatory authorities in the form of differing priorities, queries, and observations. Industry's hesitancies stemmed predominantly from concern that involvement in the CHIP could result in delays in the inspection process. There were worries that such delays could potentially impact manufacturing timelines, with subsequent implications for the pace at which critical medicines eligible for inclusion in the pilot could be made available for patients who needed them.

Industry representatives spoke highly of their interaction with regulators in all exchanges and engagements throughout the CHIP to date. The regulatory teams involved were described as having been responsive, collaborative, flexible, and adaptive. Through their interactions, regulators provided clarity on many matters, allayed concerns, and offered flexibility to overcome potential barriers. Reassurances were provided that participation in the pilot would not result in delays to the inspection process. In turn, industry panelists were able to offer insights into some of the difficulties faced in planning for and facilitating a hybrid inspection. For example, panelists spoke of complexities in coordinating timing of inspections in the face of changing manufacturing plans. The open discussions between industry and regulators created understanding and trust and were considered to have been highly valuable for all parties involved.

In relation to the "Expectations for CHIP participants" document, industry panelists noted that the document addressed many of the questions and concerns held prior to engaging with the pilot. Contributors agreed that as more experience is gained, all such resources and updates providing details of the specificities of the hybrid inspection process would act as very useful tools for any companies considering participation in the CHIP.

At this point in the panel, regulatory panelists were asked to comment on some of the key learnings to date from their experience with the CHIP, including any challenges they had encountered during the pilot. Regulators noted that, at the time of the workshop, experience with the CHIP was limited. Therefore, the challenges faced had predominantly related to the planning of, and preparing for, hybrid inspections. One example presented involved discussions regarding production schedules. In certain jurisdictions, there is a requirement that production is ongoing at the time of inspection. This meant that plans were put in place to ensure the timing of the hybrid inspection aligned with the relevant production schedule. As a result, this had not been an impediment to the hybrid inspection, but rather an example of how regulators and industry had worked together to anticipate and prevent problems arising through careful planning.

Hybrid inspections require a greater level of coordination in comparison to traditional inspections, given complexities such as virtual participation and differing time zones. For this reason, the role of Coordinating Officer was introduced in the context of the CHIP. The role of the Coordinating Officer is to provide logistical support and ensure smooth planning and information sharing between the manufacturing facility, the onsite inspection team, and the virtual inspectorates. It was highlighted that the CHIP application form had been designed to encourage the applicant to consider their preparedness for the

practicalities of the inspection process. This included considerations around information sharing, technological supports, and language requirements.

On the subject of sharing confidential information, regulators noted that many regulators already have Mutual Recognition Agreements or Memorandums of Understanding in place, which allow for the sharing of proprietary information. These are legal requirements that must be respected, and their impact is taken into account when planning for hybrid inspections. The implementation plan for the CHIP, which is available on the ICMRA website, includes provisions to ensure that confidentiality is maintained throughout the pilot.

When asked if there were plans for new tools or technology to support the CHIP, regulators confirmed that consideration was being given to the development of appropriate technological solutions. Such solutions would need to support sharing and exchange of information, while catering to the security and confidentiality requirements of all pilot participants. Regulators envisaged that an exciting opportunity presented by the CHIP was the potential to explore and determine the specific requirements of a technological platform and how it might operate.

As a final point when reflecting on experience from the CHIP, regulators spoke to the fact that many of the inspectorates involved are already members of PIC/S. This meant that there were pre-existing agreements in place, confidence in inspectors' capabilities, and a high degree of mutual understanding and trust. This also presented the benefit of allowing participating inspectorates to draw on guidance and standards developed by PIC/S.

Learnings for the future

In the final part of Panel 2, contributors from industry and regulatory authorities were given an opportunity to briefly outline how they envisioned the pilot evolving.

Regulators started by reiterating that the CHIP was still at an early stage, and an initial focus would be to continue gaining experience with additional hybrid inspections, involving additional regulatory authorities. This in turn would allow regulators to identify areas of differences in inspection approaches and make recommendations on how to bridge those gaps. ICMRA regulators had a shared goal with organizations such as PIC/S and IPRP to develop a global framework for facility assessment to enable collaboration and reliance. Such a framework would include a standardized approach to inspection that is thorough and timely, standardized training and certification for inspectors, and standardized inspection reports.

Industry panelists echoed the importance of continuing the pilot and gaining further experience, as they believed this to be the correct approach to bring about important change. Industry expressed their desire for consideration to be given to expanding the scope of the pilot and explore the potential to introduce other types of inspections.

Finally, panelists remarked that there was a lot to be done, and a lot to be learned, but they were excited to pave the way for more recognition and convergence, and ultimately chart a new way of working to the benefit of regulators, industry, and patients.

Conclusions

This milestone ICMRA-Industry workshop provided an opportunity for an exchange of views between regulators and the pharmaceutical industry on the progress and development of the two ICMRA PQKM Collaborative Pilots. To date, the experiences of the pilots have furthered the goals of developing global PQKM capabilities by optimizing the design and approach of collaborative interactions. These pilots have provided evidence to the ability of regulators and industry partners to collaboratively develop efforts to enhance regulatory reliance, agility, effectiveness, and efficiency, and pushed forward globally harmonized data submissions, expectations, assessments, and inspections.

The pilots so far have uncovered technical and regulatory barriers that limit the use of regulatory flexibilities. In so doing, they have also identified effective mechanisms, regulatory approaches, and technological solutions to help increase regulatory reliance. These ICMRA pilots continue to provide opportunities for further collaboration, alignment, and harmonization that will enable a more efficient and effective global regulatory approach.

It is a shared hope that this workshop will serve as a catalyst for further collaboration between regulatory agencies and industry partners, and that such collaboration will lead to greater convergence and further efficiencies in global CMC assessment and inspection activities.

Annex 1: ICMRA Industry Workshop Agenda

ICMRA-industry virtual workshop on
Development of a Pharmaceutical Quality Knowledge Management System
Thursday, July 20, 2023
7:00 – 10:00 ET | 13:00 – 16:00 CET
AGENDA

7:00 – 7:05 **ICMRA welcoming remarks**
Emer Cooke, EMA and Chair ICMRA

7:05 – 7:10 **Industry welcoming remarks**
Greg Perry, IFPMA

7:10 – 7:25 **ICMRA presentation**
"Background to the ICMRA Pharmaceutical Quality Knowledge Management System project and progress to date"
Lorraine Nolan, HPRA
Description: In this session, regulators will provide an overview of the background to the ICMRA PQ KMS project, in addition to updates on progress made to date, ongoing work packages, and future plans.

7:25 – 7:35 **Industry presentation**
"Industry's perspective on ICMRA's Global Strategy & Pilots for PQ KMS"
Ginny Beakes-Read, Amgen (IFPMA)
Description: In this presentation, industry will provide their perspective on topics relevant to the PQ KMS project and will speak to their engagement with, and involvement in, the ongoing PQ KMS pilots.

7:40 – 7:45 **Introduction to Panel 1**
Evangelos Kotzagiorgis, EMA
Description: A brief presentation will provide an overview of the ongoing pilot looking at collaborative assessment of post-approval change management protocols (PACMPs).

7:45 – 8:45 **Panel 1: Pilot of collaborative assessment of post-approval change management protocol**
Co-moderated by Mónica Perea-Vélez, GSK (Vaccines Europe), and Theresa Mullin, FDA

Panellists: Regulators	***Panellists: Industry***
Larry Lee, FDA	*Christine Wu, Roche*
Yasuhiro Kishioka, PMDA	*Diane Wilkinson, AstraZeneca*
Evdokia Korakianiti, EMA	*Nina Cauchon, Amgen*
Susan Polifko, FDA	*Sylvie Meillerais, MSD*
Ranjit Thomas, FDA	*Wan-Li Liao, Merck/ EMD Serono*

Description: Panellists will discuss their experiences with the collaborative assessment pilot, looking at the benefits, challenges and learnings gained through participation in the pilot to date. Panellists will also look at potential barriers to participation, and explore practical solutions to those barriers, along with next steps for the pilot and plans to support sustainable and achievable implementation of collaborative assessment of post-approval changes.

8:40 – 8:45 **Introduction to Panel 2**
Stelios Tsinontides, FDA
Description: A brief presentation providing an overview of the ongoing collaborative hybrid inspection pilot (CHIP).

8:45 – 9:45 **Panel 2: Collaborative hybrid inspection pilot**
Co-moderated by Nick Cappuccino, IGBA, and Theresa Mullin, FDA

Panellists: Regulators	***Panellists: Industry***
Stelios Tsinontides, FDA	*Fabian Welte, Roche*
Brendan Cuddy, EMA	*Tim Watson, Gilead*
Magda Joseph, Health Canada	*Matt Popkin, GSK*
Christian Schärer, Swissmedic	

Description: Panellists will discuss their experiences with the collaborative hybrid inspection pilot, looking at the learnings gained through participation in the pilot to date, and discussing how best to carry out such inspections, including the associated practical considerations. Panellists will also explore potential and anticipated next steps for the CHIP.

9:45 – 9:50 **Industry concluding remarks**
Ginny Beakes-Read, Amgen (IFPMA)

9:50 – 9:55 **ICMRA concluding remarks**
Lorraine Nolan, HPRA