ICMRA-industry virtual workshop Development of a Pharmaceutical Quality Knowledge Management System

Thursday, July 20, 2023

ICMRA

INTERNATIONAL COALITION OF MEDICINES REGULATORY AUTHORITIES

Background to the ICMRA Pharmaceutical Quality Knowledge Management System project and progress to date

ICMRA-industry virtual workshop on development of a PQ KMS

20 July 2023

Dr Lorraine Nolan

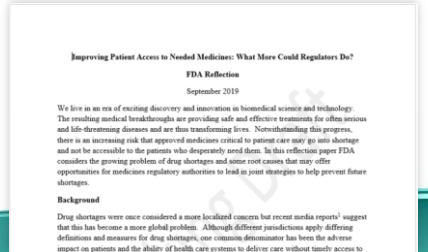
Chief Executive

Health Products Regulatory Authority

Background to the PQ KMS project

Sep 2019

FDA reflection paper



Improving Patient Access to Needed Medicines: What More Could Regulators Do?

FDA Reflection

September 2019

We live in an era of exciting discovery and innovation in biomedical science and technology. The resulting medical breakthroughs are providing safe and effective treatments for often serious and life-threatening diseases and are thus transforming lives. Notwithstanding this progress, there is an increasing risk that approved medicines critical to patient care may go into shortage and not be accessible to the patients who desperately need them. In this reflection paper FDA considers the growing problem of drug shortages and some root causes that may offer opportunities for medicines regulatory authorities to lead in joint strategies to help prevent future shortages.

Background

Drug shortages were once considered a more localized concern but recent media reports[1] suggest that this has become a more global problem. Although different jurisdictions apply differing definitions and measures for drug shortages, one common denominator has been the adverse impact on patients and the ability of health care systems to deliver care without timely access to

Sep 2020

ICMRA convened topic group

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International Coalition of Medicines Regulatory Authorities

Jun 2021

ICMRA Strategic Vision

ICMRA

11 June 2021

Global Pharmaceutical Quality Knowledge Management: Enhancing Regulatory Reliance and Agility

The protection of public health is core to the medicines regulatory mission, and this includes meeting patient needs by supporting the continued availability of critically important medicines.

ICMRA recognizes that pharmaceutical manufacturers seek agility to maintain robust supply chains and continually update manufacturing processes to incorporate changes and improvements as equipment ages, suppliers change, innovations are developed, and knowledge is gained. Companies manage these changes within their pharmaceutical quality systems and/or seek timely regulatory review when changes require prior approval. As the pharmaceutical industry is highly regulated, and the industry is globalized serving multiple markets, companies often must obtain these approvals from multiple national regulatory bodies with different timeframes, therefore potentially delaying implementation of changes.

ICMRA recognizes that regulatory authorities can gain efficiencies by developing common procedures, guidelines, requirements, and interoperable infrastructure that would facilitate the

Jul 2021

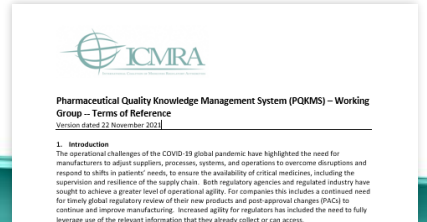
ICMRA-industry workshop

ICMRA

abpi · Biotechnology Innovation Organization · DCVMN · efpia · IGBA · IFPMA · JPMA · Vaccines Europe · PhRMA · Medicines Australia

Sep 2021

Establishment of PQ KMS working group



ICMRA

Pharmaceutical Quality Knowledge Management System (PQKMS) – Working Group – Terms of Reference

Version dated 22 November 2021

1. Introduction

The operational challenges of the COVID-19 global pandemic have highlighted the need for manufacturers to adjust suppliers, processes, systems, and operations to overcome disruptions and respond to shifts in patients' needs, to ensure the availability of critical medicines, including the supervision and resilience of the supply chain. Both regulatory agencies and regulated industry have sought to achieve a greater level of operational agility. For companies this includes a continued need for timely global regulatory review of their new products and post-approval changes (PACs) to continue and improve manufacturing. Increased agility for regulators has included the need to fully leverage use of the relevant information that they already collect or can access.

ICMRA vision for a global PQ KM capability

Aims

- Enhance **regulatory reliance** and **agility**
- Enhance regulatory **effectiveness** and **efficiency**
- **Harmonise** data submissions, expectations, assessments, and inspections
- Enhance availability of **quality medicines**

11 June 2021

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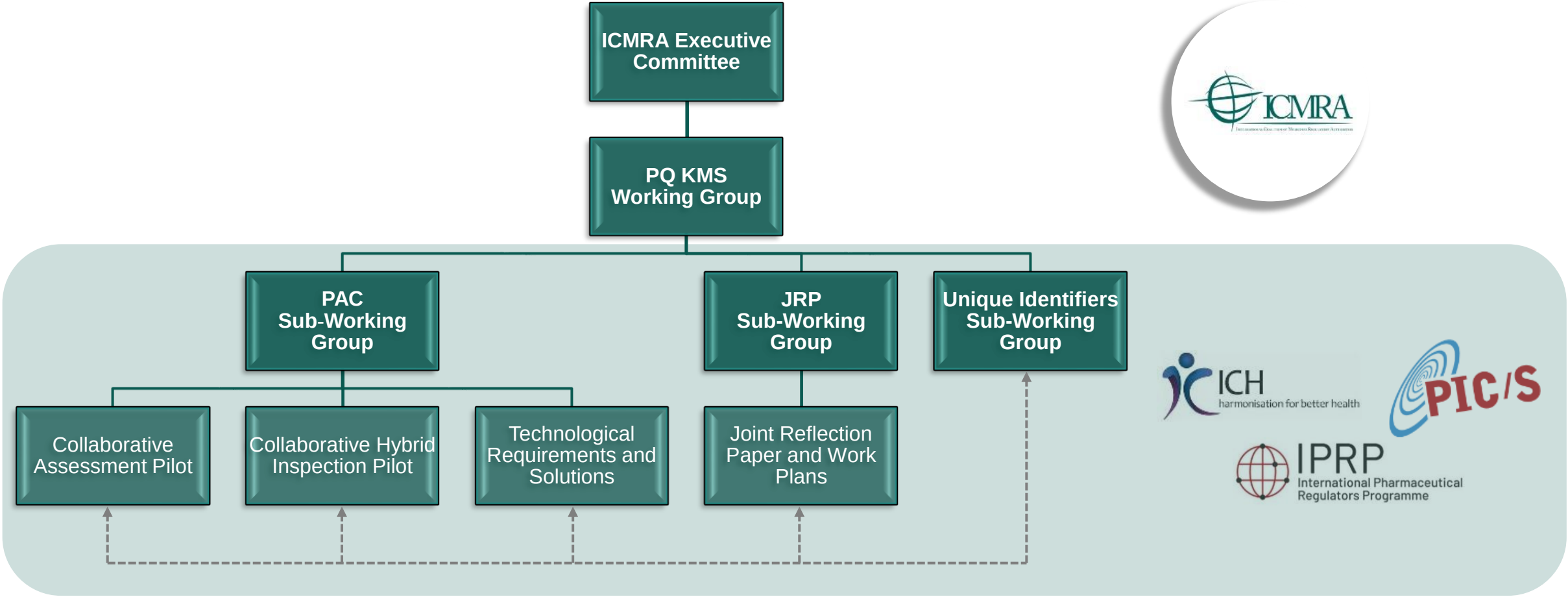
ICMRA recognizes that regulatory authorities can gain efficiencies by developing common procedures, guidelines, requirements, and interoperable infrastructure that would facilitate the timely sharing of information among regulators on changes occurring within the supply chain. This may include reliance on the assessments of other regulators reviewing those changes. ICMRA considers that this could lead to more timely availability of medicinal products for patients by shortening approval timelines.

A Coordinated Pharmaceutical Quality Knowledge Management Strategy

ICMRA supports the prioritization of efforts to strategically work to further leverage the information, expertise and knowledge among ICMRA member authorities. This includes establishing a collective Pharmaceutical Quality Knowledge Management capability to ensure timely and complete information and assessments about the state of pharmaceutical quality management and risk management capabilities. The envisioned capability would provide for:

- Transitioning to harmonized structured and standardized electronic formats using unique facility identifiers for appropriate regulatory information to enable rapid analyses of quality information to support enhanced risk-based and targeted oversight of manufacturers.
- Secure sharing of information about pharmaceutical manufacturing facilities, which can be contributed to, and accessible by, multiple participating regulators.
- Developing a framework that might, in time, support full harmonization of data elements submitted in the quality modules of the common technical document. This could pave the way for sponsors to make simultaneous submissions within a marketing authorization application to all associated regulatory authorities and provide improved capabilities for both industry and regulators in management of post-approval changes (PAC).

PQ KMS Working Group



Achievements to date

Commencement of two pilot programmes

PQKMS Collaborative Pilot Information and Application Forms

Following the July 2021 ICMRA-Industry virtual workshop on enabling manufacturing capacity in the COVID-19 pandemic, ICMRA is commencing two pilot programs focusing on i) collaborative assessment with initial focus on chemistry, manufacturing, and control (CMC) post-approval changes and ii) collaborative hybrid inspections. The overall aim of these pilots is to improve manufacturing capacity for production of critical medicines and facilitate collaborative assessments and inspections by multiple regulatory authorities (see links for further information).

Call for Applications to PQ Pilots

Application Form for Collaborative Assessment

Application Form for Collaborative Hybrid Inspection

Overview of Collaborative Assessment

Overall Plan for Collaborative Assessment

Overview of Hybrid Inspection

Overall Plan for Hybrid Inspection

Publication of a Joint Reflection Paper

Version Dated: 21 July 2022

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

Development of JRP-cited work plans

ICH harmonisation for better health

1. M4Q (R2): Common Technical Document on Quality Guideline
2. New guideline on structure product quality submissions

IPRP International Pharmaceutical Regulators Programme

1. IPRP quality assessment tools and best practices
2. Convergence of quality post-approval changes/variations
3. Implementation of ICH Q12

PIC/S

1. Structured data format for inspection reports
2. Tools and templates for PQS assessment for inspectors and associated training
3. Promotion of use and reliance on GMP inspectional information

Ongoing and future work

Continue to gain further experience with the pilots

Collaborative Pilot Update

16 December 2022

Background

In July 2022, ICMRA initiated two pilot programs focusing on i) collaborative assessment of chemistry, manufacturing, and control (CMC) related post-approval changes (PACs) and ii) collaborative hybrid inspections to inform CMC assessment. In addition to maximising resources and facilitating more effective and efficient reviews, the overarching goal of each collaborative pilot is the identification of misalignments, differences, and potential areas for alignment or harmonization in assessment and inspection activities across participating regulatory regions in the context of manufacturing lifecycle management. A better understanding of areas of potential alignment and difference is an important first step to harmonising specific CMC- and inspection-related regulatory procedures to facilitate the timely implementation of appropriate regulatory actions across different regions. In the interests of transparency and openness, ICMRA will provide regular updates on the status of each collaborative pilot and include further information on the types of applications received and selected for each pilot to help industry take advantage of this opportunity to participate.

Development of a reflection paper on technological solutions to support a PQ KMS

Exploring the potential use of unique identifiers in a PQ KMS

Scan the QR code for further information or visit:
https://www.icmra.info/drupal/en/strategicinitatives/pqkms

IFPMA

Industry's perspective on ICMRA's Global Strategy & Pilots for PQ KMS

Presented by Ginny Beakes-Read, Amgen (IFPMA)

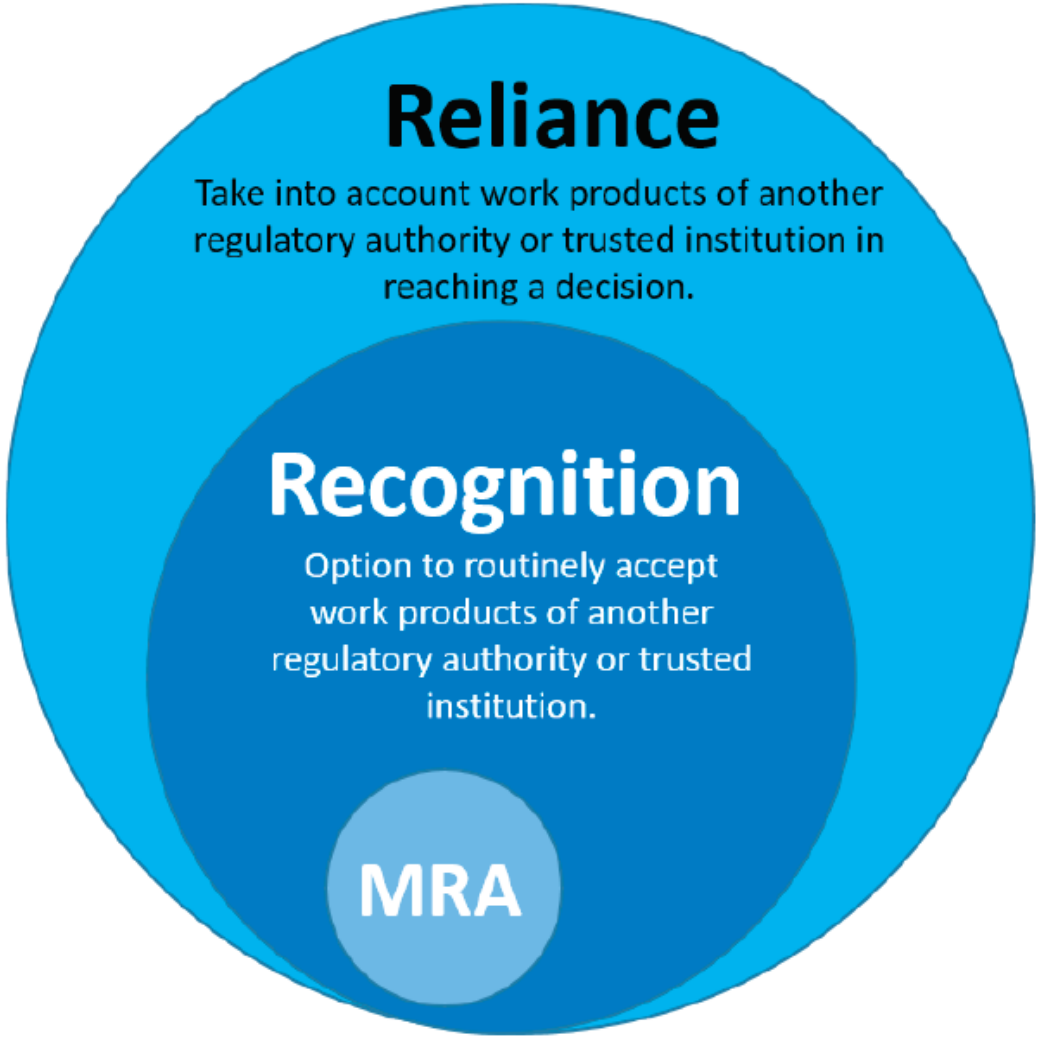
On behalf of: ABPI, BIO, DCVMN, EFPIA, IFPMA, IGBA, JPMA, Medicines Australia, PhRMA, Vaccines Europe

20 July 2023

Overview – General Considerations

- → **Overall strong support for ICMRA PQ KMS global strategy and pilots**
- → **Pilots have many potential benefits, including advancing approaches that could support regulatory reliance when appropriate**
- → **Highlighting potential outcomes of pilots, and sharing successes and challenges, can incentivize industry participation**
- → **Support continued implementation of ICH Q12 guideline, and principles related to regulatory flexibilities and convergence**
- → **Adoption of Unique Facility Identifiers (UFI), that build on existing standards, can support reliance and other initiatives**
  - Potential to help address issue of product “sameness” that is critical to establish trust needed for reliance and convergence
  - Industry looks forward to hearing more about UFI proposals and to providing input
- → **Support development of structured data sets for inspections, along with other systems and tools for collaboration**

Opportunities for National Regulatory Authorities (NRAs) **beyond Collaboration**



Source: Regulating Medicines in a Globalized World: The Need for Increased Reliance Among Regulators

Pilots can help address challenges in Regulatory Reliance implementation journey

- **Philosophical - mindset**
  - Trust and experience are barriers to uptake by NRAs
  - Change management is needed to drive adoption and implementation
  - Predictability

- **Pragmatic**
  - Guidelines often do not have clear requirements
  - Additional regulatory documents often required
  - Different legal and regulatory pathways, including protections for confidential information

Reflection: COVID-19 as the Catalyst

June 2020 → Feb 2021 → July 2021 → July 2022

efpia
European Federation of Pharmaceutical Industries and Associations

EFPIA White Paper on CMC development, manufacture and supply of pandemic COVID-19 therapies and vaccines

"...mutual reliance of unprecedented scope and scale for Quality is required...Quality elements such as importation testing for vaccines and medicines globally, (virtual) GMP inspections, GDP, etc. and would ideally include full reliance for GMP oversight and Quality review of medicines applications and variations between regions"

IFPMA

An Industry Proposal: Recommendations to Support the Rapid Increase of Manufacturing Capacity for the Production of COVID-19 Therapeutics and Vaccines

- Streamlined Data Requirements (Near-term[10] & Long-term[11])
- Regulatory Tools & Mechanisms (Near-term & Long-term)
- Collaborative Review & Recognition Practices (Near-term & Long-term)
- Harmonization through ICH (Long-term only)

ICMRA-Industry Virtual Workshop Report on Enabling Manufacturing Capacity in the COVID-19 Pandemic

ICMRA
abpi
Biotechnology Innovation Organization
DCVMN Developing Countries Vaccine Manufacturers Network
efpia
IFPMA
IGBA International Generic and Biosimilar Medicines Association
JPMA
Vaccines Europe
Medicines Australia
PhRMA Research • Progress • Hope

ICMRA

Pharmaceutical Quality – Regulatory Collaboration Pilots: Call for Industry Applications

Experience and Potential Improvements: PAC pilot

Experience

- → Many companies have considered the pilot programs
- → >10 applicants for the PAC pilot
- → Positive experiences with application process and submission
- → Welcome critical assurances that there will be no delays
- → Interest in extension of pilot

Potential Areas for Improvement

- → Platform for shared assessment
- → Timelines for submission and review when multiple NRAs are involved
- → Understanding role of observer NRAs
- → Scope is limited (PACMPs, types of therapeutic products)
- → Limited number of NRAs closely involved

Experience and Potential Improvements: CHIP pilot

Experience

- → Many companies have considered the pilot programs
- → Limited applicants to-date for the CHIP pilot
- → Positive experiences with application process and submission
- → Welcome critical assurances that there will be no delays
- → Interest in extension of the pilot

Potential Areas for Improvement

- → Different focus of NRAs (e.g., new facility vs. PAI)
- → 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

Recommendations

- → Continue the pilot programs and **expand product scope**
  - → Include vaccines
  - → Allow changes not linked to critical medical need/COVID-19
  - → Surveillance inspections for pilots (with MRAs still the expected norm in practice)
- → Explore enhanced **cloud-based IT platform** to allow more efficient data exchange
- → Include **additional NRAs** once learnings are embedded, consistent with data confidentiality protections
- → Include goal of **increased reliance**, as appropriate
  - → Consider success of GMP MRAs, and how to improve utility globally
  - → Enhanced reliance on one NRA assessment for PACMPs
- → Consider broader **implementation of lifecycle management tools** (ICH Q12)

Opportunities for the Future

- Overall shortened approval timelines, supporting availability of critically important medicines

- Streamlined regulatory assessments by increasing mutual understanding and ongoing dialogue opportunities

- Enhanced regulatory convergence and reliance

"Path forward to optimize PACs management and facilitate continuous supply of medicines and vaccines of high quality worldwide." Therapeutic Innovation & Regulatory Science. *2023;57:7-11.*

IFPMA

Thank you!

On behalf of: ABPI, BIO, DCVMN, EFPIA, IFPMA, IGBA, JPMA, Medicines Australia, PHRMA, Vaccines Europe

Introduction to Panel 1

Evangelos Kotzagiorgis, EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ICMRA collaborative assessment Pilot status and experience - EMA

ICMRA
International Coalition of Medicines Regulatory Authorities

- ICMRA – Industry workshop - July 2023

Presented by
Evangelos Kotzagiorgis
Pharmaceutical Quality Senior Specialist
Quality and Safety of Medicines Department
European Medicines Agency

Background

ICMRA PQ KMS

ICMRA-Industry workshop in July 2021 highlighted the need for :

- 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
- overcome travel logistical challenges created by the pandemic through use of hybrid inspections.

and motivated the planning of two collaboration pilots.

Background

ICMRA Pilots - Scope

Therapeutic area

1. Products intended for the treatment of patients with COVID-19, or changes necessitated by COVID-19, e.g. supply chain changes

Vaccines are excluded (may be considered in the future if pilot extended)

2. Breakthrough/ PRIME/ Sakigake, etc. products
3. Products deemed medically necessary/critical medicine.

Product types

- 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).

27 July 2023

Anticipated duration of pilot 1-1.5 years

Background

Aim of the ICMRA Collaborative Assessment Pilot:

- Develop a framework, which provides a platform for **multiple** regulatory **agencies** to participate in a **collaborative assessment** of post-approval CMC changes including post-approval change management protocols (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->**predictability**
- Regulators to work towards a common approach to the application assessment and decision making.
- Develop **best practices** in the quality assessment of CMC post-approval changes and share learnings to build **further collaborations** in assessment

Status

PACMP collaborative assessment pilot

- Call to industry is open since June 2022
- 12 proposals submitted
- 4 were selected - 1 under evaluation
- 1 ongoing under assessment
- 1 completed

1st Pilot summary

- PACMPs for DS/DP/QC site transfer for a biological molecule
- EMA (Lead), FDA (Participating) and PMDA (Observing)
- Received January 2023
- 3 rounds of RfSIs
- 120 days
- Completed successfully May 2023

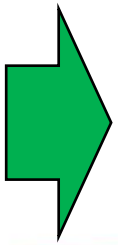
Experience 1st Pilot

- No specific international procedure/pathway. Regional procedures should be respected.
- Timetable with a “hard” start and end date (plus regional deadlines), but very flexible in-between.
- No specific AR templates.
- Templates were developed to facilitate the interactions among assessors.
- Lessons learnt - Best practices being developed.

1st Pilot observations

- Strong commitment of all parties
- Good collaborative spirit, goal oriented
- Informative, constructive discussions
- Procedural flexibility - resource intensive as it is
- Successful in achieving harmonised outcome
- Successful in providing valuable lessons
- Positive uptake by regulators - positive feedback from Industry

decision to **expand the number of applications** in the pilot **!**



Introduction to Panel 2

Stelios Tsinontides, FDA

ICMRA-Industry virtual workshop on Development of a Pharmaceutical Quality Knowledge Management System

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

20 July 2023

Main Workshop Goals from July 2021

- Opportunity for an **exchange of views between regulators and the pharmaceutical industry** on the regulatory flexibilities introduced to enhance the manufacturing capacity of COVID-19 products
- **Identification of key enablers and bottlenecks** limiting the use of regulatory flexibilities, in addition to the most effective mechanisms that enabled increased manufacturing capacity
- Workshop will serve as a **catalyst…leading to greater convergence and further efficiencies** in global chemistry, manufacturing, and control (CMC) assessment and inspection activities

https://www.icmra.info/drupal/sites/default/files/2021-10/covid-19_manufacturing_capacity_ws_report.pdf

ICMRA-Industry Virtual Workshop Report on Enabling Manufacturing Capacity in the COVID-19 Pandemic

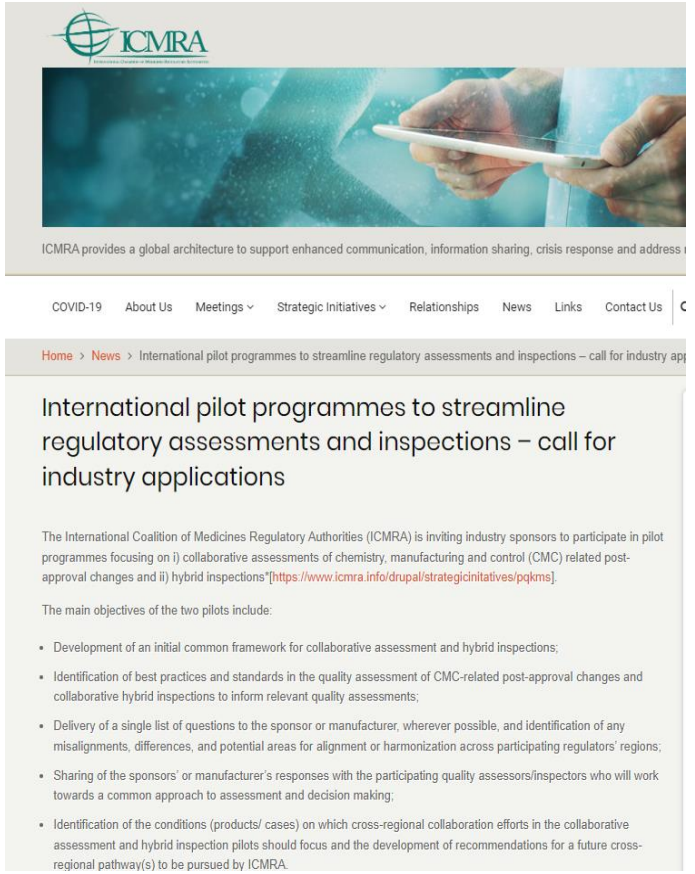
ICMRA Vision

- **Advance international regulatory effort through strategic partnership** among regulatory agencies and industry to facilitate faster access and continuous supply of high-quality medicines to patients across regions

- **Enable convergence on CMC aspects between regions** to allow faster supply of critical medicines to patients via
  - Collaborative Quality Assessment and
  - Collaborative Hybrid Inspection

Collaborative Hybrid Inspection Pilot (CHIP)

- Open call to Industry since June 2022
- **Three** proposals submitted for CHIP
  - ✓ Planned to accept three proposals
  - ✓ **Two proposals accepted & proceeding**
  - ✓ **One proposal withdrawn**
- The first collaborative hybrid inspection expected to happen in 2H2023 and second one in early 2024
- CHIP is OPEN to new proposals



Lessons from CHIP Engagements

- Positive and productive collaborations among Regulators and Sponsors
- Significant effort to align reg. approach to inspections from RAs requested to participate & timelines
- Significant effort to clarify CHIP expectations, RAs limitations to Sponsor
  - Existence of MRAs and Confidentiality Agreements
- Need Enhanced IT Platform Capabilities for Efficient and Secure Collaborations

Feedback From Industry

- CHIP still highly risky proposition
  - Outcome being “sum of all” duration & observations
- Limited scope; Small Molecule PAI & Biologics PLIs
  - Expand to Vaccines and Surveillance
- Sponsor’s Limiting Factors
  - Business Priorities
  - Availability of on-site resources
  - Limited safety stock on medically necessary products

CHIP Imminent Follow-Up Actions

- Issue a Clarification Document for Participating RAs and Industry

- Clarify expectations for industry in hosting a collaborative hybrid inspection
  - Not longer than an inspection by a single RA
  - Onsite RA serves as the single voice for participating RAs
  - Aim to deliver single inspection outcome

- Highlight CHIP benefits

- Clarify Anticipated CHIP Timelines

CHIP Participant Expectation Highlights

Benefits to Participation

- An opportunity to reach agreement from multiple RAs on the compliance of a site with a single inspection
  - Minimizes effort, cost and time to achieve multiple approvals

- A possibility to receive a single list of information requests, comments, questions from multiple RAs, which will allow for increased efficiency in regulatory submissions
  - Results in a more robust & resilient CAPA Plan

- An opportunity to contribute toward building an inspection framework which will serve as foundation for future international & global convergence/reliance efforts e.g., by PIC/S

CHIP Participant Expectation Highlights

On-Site Lead Inspector Role – One Quality Voice

Will coordinate scope of coverage with facility and remote team by

- Obtaining site information prior to inspection
- Planning activities to be observed, liaising with on-site facility personnel
- Coordinating remote set-up with facility & providing feedback to remote team on which activities to observe
- Overseeing on-site and virtual engagement with facility

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
RAs receive CAPAs	30 days after close-out meeting
Engagement with facility to clarify CAPA plan(s), if necessary	10 days post receipt of CAPAs from the facility
Preliminary inspection report reviewed by the RAs	60 days post inspection
Final inspection report(s) sent by RAs (GMP certificate or equivalent issued/ or statement of GMP Non- Compliance, if applicable) to facility	90 days post inspection

What to Expect Beyond the CHIP Pilot

- At the conclusion of each pilot case, participating RAs and Industry will provide feedback – ongoing thru 1H2024
- Responses will be assembled, and performance data will be evaluated – ongoing thru 1H2024
- After the completion of the pilots with evaluation of 3-5 cases in each, outcomes will be summarized in a report to ICMRA – 2H2024
  - Challenges
  - Recommendations on how to operationalize

ICMRA PAC & Pilot Organizing RAs