ICMRA PQKMS pilots – the Roche experience

CASSS CMC Strategy Forum Japan – Tokyo, Dec 4th, 2023

Markus Goese, Head EU CMC Regulatory Policy
F. Hoffmann-La Roche Ltd
Basel/ Switzerland

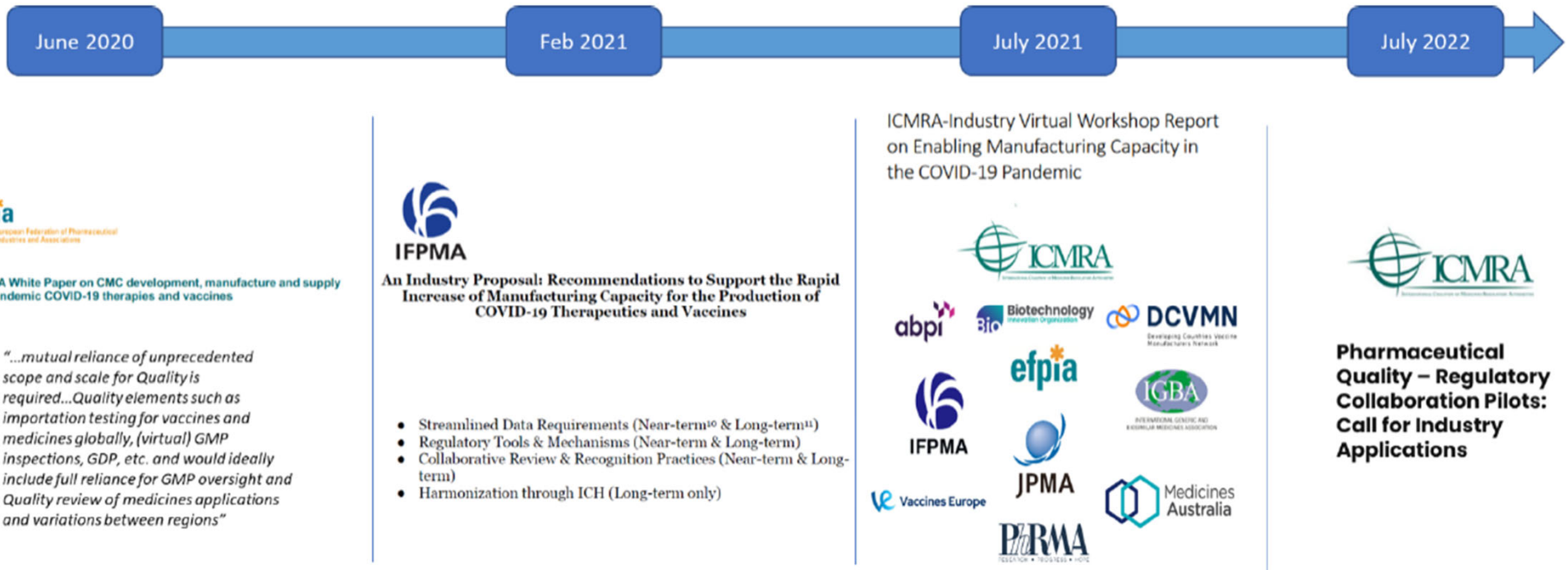
Table of contents

Table of Contents

1. Background – Covid-19 & July 2021 ICMRA Stakeholder workshop

Background: The pandemic catalyst

Reflection: COVID-19 as the Catalyst



Slide from "Industry's perspective on ICMRA's Global Strategy & Pilots for PQ KMS"--Presented by Ginny Beakes-Read, Amgen (IFPMA), 20 July 2023

Background: July 2021 ICMRA Stakeholder workshop

- During the COVID-19 pandemic, the International Coalition of Medicines Regulatory Authorities (ICMRA) was acting as a forum to support strategic coordination and international cooperation among global medicine regulatory authorities.

- The aim of these activities was to expedite and streamline the development, authorisation and availability of COVID-19 treatments and vaccines worldwide.

- ICMRA members also work towards increasing the efficiency and effectiveness of regulatory processes and decision-making.

- A key event in support of these activities was the July 7, 2021 joint (virtual) stakeholder workshop with industry on *"Enabling Manufacturing Capacity in the COVID-19 Pandemic"* (more detailed information in back-ups)

2. ICMRA PQ-KMS & Pilot Programs

Next steps: Pharmaceutical Quality Knowledge Management System (PQKMS) - Collaborative ICMRA pilots launched in June 2022

Pharmaceutical Quality Knowledge Management System (PQKMS)

The International Coalition of Medicines Regulatory Authorities (ICMRA) has developed a joint statement on the establishment of a pharmaceutical quality knowledge management system, which could help to better inform both public and industry stakeholders on the coalition's efforts to improve global regulatory harmonisation and alignment.

Regulatory authorities can gain efficiencies by developing common procedures, guidelines, requirements, and interoperable infrastructure that would facilitate the timely sharing of information on changes occurring within the supply chain of medicines. This may include reliance on the assessments of other regulators but could lead to more timely availability of medicines for patients by shortening approval timelines.

Following an initial period of consultation with the broader ICMRA membership, the ICMRA Executive Committee formally established a PQ KMS Working-Group with specific responsibility for advancing efforts needed to develop a PQ KMS capability.

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.

Collaborative ICMRA Pilots

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 considering that the development, manufacture, and supply of medicines is global
- The ICMRA workshop highlighted the need for more convergence on CMC aspects between regions to allow faster supply of critical medicines to patients and the need to overcome travel logistic challenges through use of hybrid inspections.

1. PACMP Assessment Pilot

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)
- ✓ The applicants' responses will be shared between the participating quality assessors, who will work towards a common approach to the application assessment and decision making.
- ✓ The intention is to 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
- ✓ Develop best practices in the quality assessment of CMC post-approval changes and share learnings
- ✓ Identify the conditions (products/ cases) where cross-regional collaboration assessment efforts should focus and make recommendations to ICMRA for a future cross-regional CMC collaborative assessment pathway, which may include development, initial approval and major lifecycle evaluations and make proposals to ICH for standards and guidance development

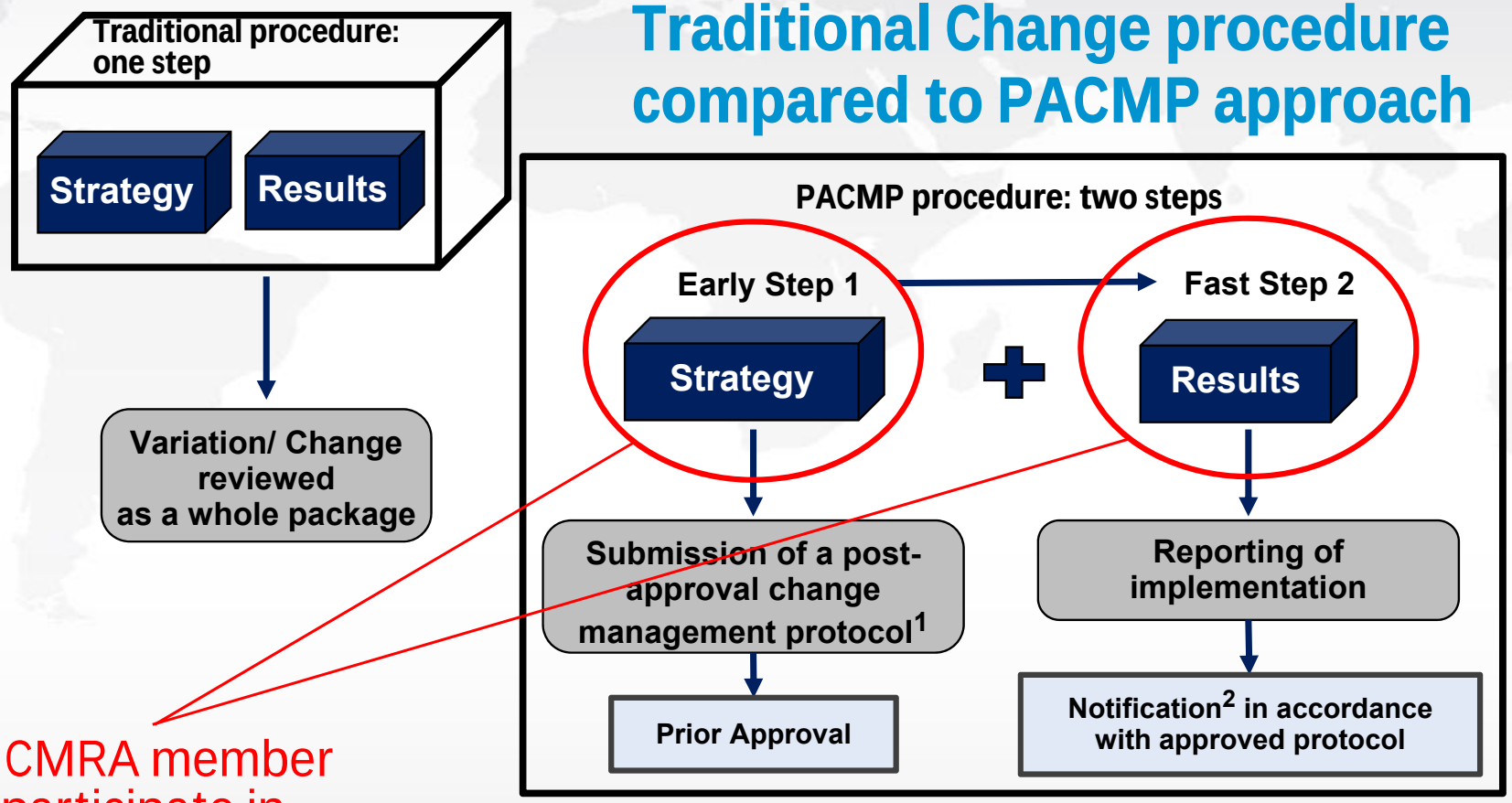
1. PACMP Assessment Pilot

Regulatory Submission Considerations for the collaborative assessment pilot

- The proposal should be based on a planned CMC post-approval change(s).
- Products that are distributed under an emergency use mechanism and not a marketing application should not be considered
- The product(s) involved should be intended for the treatment of patients with COVID-19, breakthrough/PRIME products, or medically necessary.
- The changes should be intended to be submitted to multiple regions
- The changes should involve an area where differences in regulatory approaches may occur.
- A common dataset should be provided to all participating agencies.
- There should be no restrictions on sharing data among the regulatory agencies participating in the pilot.
- There should be agreement to publicly share some high-level data and results of the collaborative assessment.
- Industry representatives are willing to participate in a virtual discussion meeting to have open dialogues with regulators from multiple regions on technical and regulatory issues related to their applications.

Recap: ICH Q12 Module 4 - PACMP

Traditional Change procedure compared to PACMP approach



Multiple ICMRA member agencies participate in collaborative assessment pilot

1: PACMP may be submitted with the original MAA or subsequently as a standalone submission

2: approval by the regulatory authority may be required prior to implementation

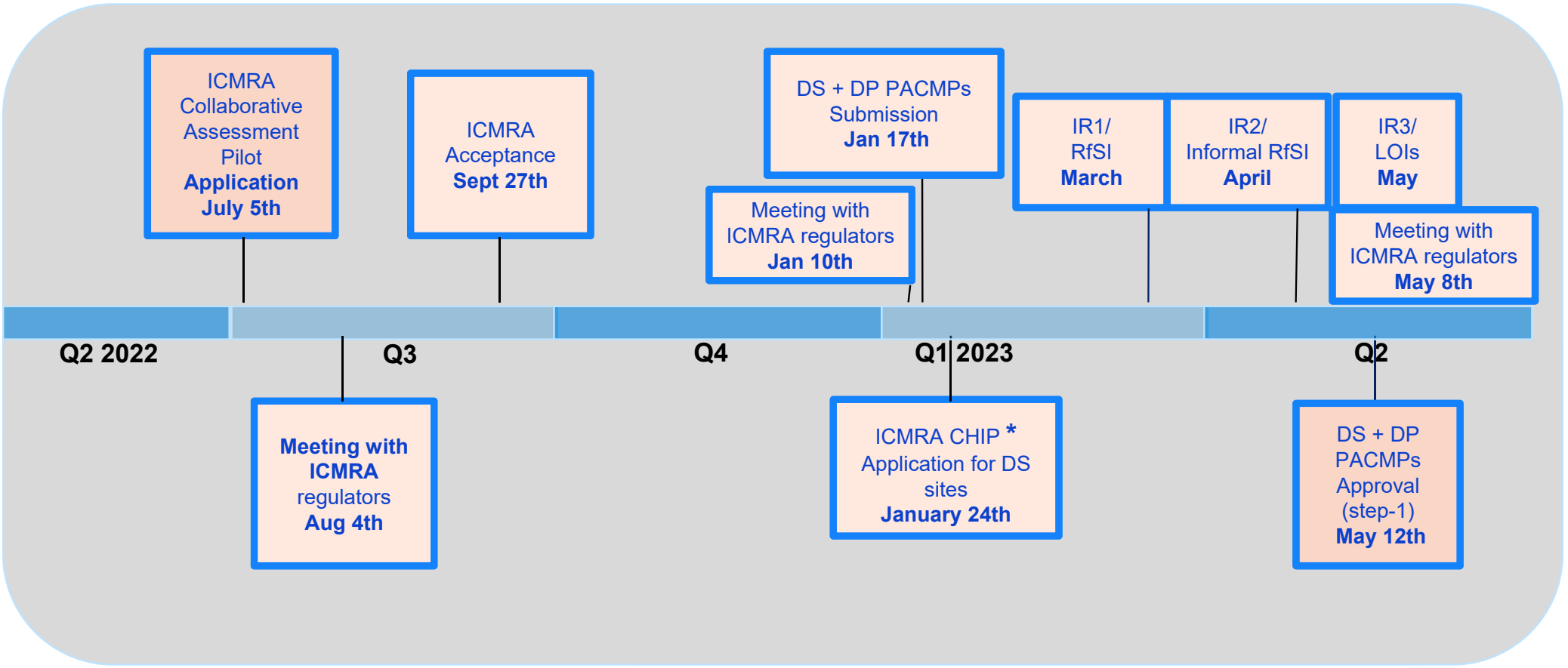
2. Collaborative Hybrid Inspection Pilot (CHIP)

Aim of the ICMRA collaborative Hybrid Inspection pilot

- ✓ Use a combination of on-site inspectors in the facility and distant inspectors (through a virtual platform) to conduct a hybrid inspection/assessment.
- ✓ Overcome Travel Restrictions
- ✓ Facility inclusion in the pilot will be based on the mutual interest of regulators, voluntary participation by the manufacturer and its facility, and the facility having the technology capable to support distant assessment.
- ✓ Potential for collaborative assessment of facility when applications submitted to multiple regulators.
- ✓ Evaluation of the inspection outcome and any enforcement action, if needed, should remain a matter for each participating authority.
- ✓ The pilot is voluntary for regulators and industry.

3. Roche’s ICMRA PACMP Pilot Application

Timeline – Roche ICMRA PACMP pilot



*) ICMRA agreed to Roche's proposal for a CHIP inspection in Q1/2024 during MAb batch production

Scope of Roche Drug Substance and Drug Product PACMPs

Relatively broad scope of a PACMP for the EU and US for a monoclonal antibody (with US-breakthrough designation) which received initial approval in an oncology indication, comprising of:

- **Additional Drug Substance manufacturing site** and process changes
- **Additional DS QC testing sites** for IPC, release and stability
  - Changes to DS IPC, release and stability specifications
- **Additional Drug Product manufacturing site** and process changes
- **Additional DP QC testing site** for IPC and release for US only
  - Changes to DP IPC, release and stability specifications
- **Additional DP secondary packaging site** for US only

Timeline for Collaborative Assessment Pilot

ACTIVITY	TIMELINE
Submission Receipt Date	Day 0
Project Start	Day 3
Initial Filing/Completeness Assessment	Day 10
Sponsor Meeting	TBD
Information requests to Sponsor	Day 20-60
Complete Filing Review	Day 60 or earlier
Information requests to Sponsor	After Day 60
Draft Quality Assessment by Lead Regulatory Authority	Day 106
Complete Quality Review	Day 113
Final/Action Letter Issued	Day 120

Slide from "ICMRA Collaborative Pilots: Vision and Achievements Leading to Regulatory Alignment and Efficiencies in Global CMC Assessment and Inspection Activities"--Presented by Susan E. Polifko, FDA @ ISPE Annual Conference Oct. 2023

Overview of Roche ICMRA Collaborative Assessment pilot

- **Roche was the first company to submit (and receive approval) for a PACMP (step-1) in the ICMRA pilot**
- **EMA was the lead assessor, FDA participated and PMDA was observing**
- Submission was done in parallel to both HA's through respective submission portals, same dossier was provided
- We received a **harmonized list of questions** with region-specific questions noted (3 IRs) and these were issued in parallel by both HAs. Responses were submitted to both HAs in parallel.
- Per our request, EMA/FDA noted when a question was Agency-specific.

- **Approval was granted by EMA & FDA on the same day (!) and the same content and conditions were approved**
- **As a result the change category (for step-2) was downgraded from Type II to Type IB for EU and from PAS to CBE-30 for US**
  - Step-2 Type IB/CBE-30 will also be collaboratively reviewed as part of the ICMRA pilot.

Roche's experience with ICMRA PACMP Assessment Pilot

- The **overall experience** we had with our PACMP collaborative review procedure was indeed **very collaborative**.
  - Flexibility from EMA to submit one DS PACMP with two sites, in alignment with US supplement.
  - Flexibility granted for response timeline.
  - Clarification meeting was proactively offered and granted on very short timeline to discuss the IR3/LOIs.
- **Very open and transparent engagement from all ICMRA regulators involved**; they **truly streamlined and coordinated their processes** so that the actual pilot did not add any significant additional work on us as the sponsor
- The end result – **approval of essentially the same content and conditions for both protocols on the same day by FDA and EMA** – is unprecedented in our experience and shows already the significant value of the ICMRA pilots.

ICMRA PACMP Assessment Pilot – initial agency posts

CDER collaborates with global regulators on pharmaceutical quality assessments and inspections

Share | Tweet | Linkedin | Email | Print

By: Theresa Mullin, Ph.D., CDER's Associate Center Director for Strategic Initiatives, and Michael Kopcha, Ph.D., R.Ph., director of CDER's Office of Pharmaceutical Quality

FDA and the European Medicines Agency (EMA) recently completed the first collaborative assessment of a proposed post-approval change for a critical oncology biologic with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) serving as an observer. The work, in which FDA and EMA reviewed and approved a proposal to add new manufacturing and quality control sites, can help assure the supply of the medicine.

For the first application reviewed under the pilot program, the FDA/EMA collaborative assessment teams had a positive and productive experience, which produced a common set of highly aligned information requests and comments to the applicant. Not only did this assessment result in an FDA approval, but there was no delay in the standard assessment timeline. In fact, it was completed under the four-month goal window for a standard manufacturing supplement assessment. The EU also approved the submission on the same day as FDA, marking a significant accomplishment in aligning FDA and EMA on the assessment process and timeline. This assessment experience also received positive feedback from industry on the coordination of efforts between the FDA and EMA.

European Medicines Agency
264,032 followers
1h • Edited •

Collaborative assessments of manufacturing sites can improve supply of medicines 🏥💊

This was an international premiere: on 12 May 2023, EMA and the US FDA concluded for the first time a collaborative assessment 🤝 to add new manufacturing and quality control sites. These sites are linked to the production of the orphan medicine Lunsumio, a #cancer treatment. The collaboration could significantly contribute to the continuous supply of this medicine. The Japanese Pharmaceuticals and Medical Devices Agency, the PMDA, participated as an observer.

This work marks the beginning of an international pilot programme that aims to bring regulators together and build up regulatory reliance to allow faster supply of critical medicines. Future assessments under this pilot will involve more regulatory authorities worldwide 🌍🤝.

📌 Some key highlights of this procedure were that:

🔷 All regulators involved were open and highly collaborative;
🔷 The issues raised during the procedure were mutually agreed upon, confirming good alignment between the EU, the US and Japan;
🔷 The pilot did not cause any delays in approval timelines;
🔷 It received positive feedback from the industry.

4. July 2023 ICMRA Stakeholder workshop

ICMRA held another stakeholder workshop on July 20, 2023

Great opportunity to discuss PACMP pilot case study experience

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

On 20 July 2023, ICMRA and The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) will be hosting a joint virtual workshop on the development of a global Pharmaceutical Quality Knowledge Management System (PQ KMS).

The ICMRA PQ KMS project aims to leverage collective resources and information sharing between regulatory agencies. This will be achieved through the alignment of applications data submissions, expectations, and assessments, as well as inspections. In turn, this will help to significantly reduce the need for multiple separate submissions from sponsors, avoid duplicative assessments, and facilitate inspection reliance.

As part of this project, ICMRA is overseeing two pilot programmes on collaborative assessments of post-approval changes and hybrid inspections (CHIP) by multiple regulatory authorities. The upcoming workshop will comprise a mix of presentations and panel discussions, including an update from the PQ KMS Working Group on the work undertaken in the project to date, and the status of ongoing activities.

Both industry and regulators will provide feedback on their experiences with the ongoing pilots, and discuss future direction while looking at the benefits and the challenges.

ICMRA stakeholder workshop on July 20, 2023

PACMP pilot panel discussion

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

Panelists: Regulators

- Sau (Larry) Lee, FDA
  Deputy Director of Science, Office of Pharmaceutical Quality/CDER/FDA
- Yasuhiro Kishioka, PMDA
  PhD, Review Director, Office of Cellular and Tissue-based Products
- Evdokia Korakianiti, EMA
  Head of Quality and Safety, Human Medicines Div, EMA
- Susan Polifko, FDA
  PharmD, RAC-US, Commander, U.S. Public Health Service
- Ranjit Thomas, FDA
  Associate Director, Business Informatics Governance Staff (BIG), Office of Strategic Programs/CDER/FDA

Panelists: Industry

- Christine Wu, Roche
  PhD, Regulatory Program Director
- Diane Wilkinson, AstraZeneca
  PhD, Executive Director, CMC Reg. Affairs, AstraZeneca
- Nina Cauchon, Amgen
  PhD, Director Regulatory Affairs, Amgen Inc.
- Sylvie Meillerais, MSD
  Global CMC Policy Director, MSD-Europe, Brussels
- Wan-Li Liao, Merck/ EMD Serono
  PhD, CMC Regulatory Intelligence Associate Director, Healthcare R&D, Global Regulatory Affairs

ICMRA - Hopes for the pilot and future state

At the ICMRA-industry virtual workshop on Development of a Pharmaceutical Quality Knowledge Management System on July 20th, 2023 (follow-up to July 2021 WS), a panel of regulators and industry representatives discussed experiences and lessons learned from the pilots as well as hopes for the future. The following key points were discussed:

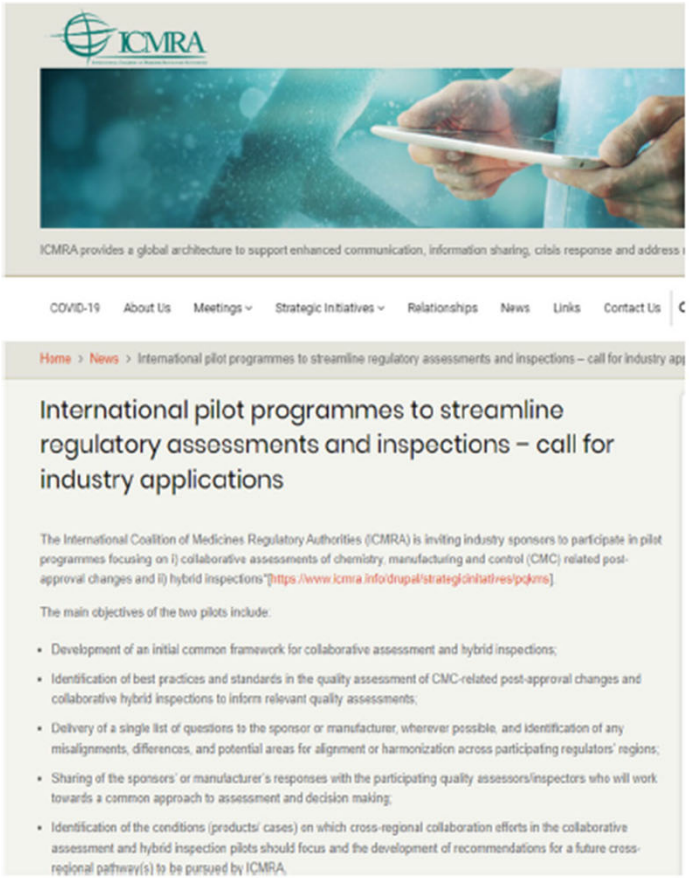
- **Positive experience from both regulators and industry leading to an extension of the pilot and encouragement for more industry participants**
- **Desire for expanded engagement from regulators for the pilot**
- **Long term goal of global convergence and reliance for both PACs and inspections.**

➔ Recording, agenda and slides from the 2023 ICMRA-Industry Workshop: can be found here

5. Summary

Collaborative Assessment Pilot (PACMP)

- Open call to Industry since June 2022
- **14** proposals submitted for collaborative assessment of Post Approval Change Management Protocols (PACMP)
  - ✓ Planned to accept three proposals
  - ✓ **Five proposals have been accepted**
- **One** Assessment completed successfully by EMA (Lead), FDA (Participating) and PMDA (Observing) on 13-May-2023
- Currently focused to complete collaborative assessments on **four** additional PACMP submissions.
- Efforts are ongoing to develop recommendations on next steps



Slide from "ICMRA Collaborative Pilots: Vision and Achievements Leading to Regulatory Alignment and Efficiencies in Global CMC Assessment and Inspection Activities"--Presented by Susan E. Polifko, FDA @ ISPE Annual Conference Oct. 2023

Summary

- The Covid-19 pandemic provided a rich set of experiences and CMC / GMP learnings, on which to base future collaborative efforts by all stakeholders and enabling us to be more agile and better prepared
- It is vitally important for industry and regulators to work together to explore how these approaches (e.g. site-transfer PACMPs) can be implemented efficiently
- It is critical for regulatory authorities to establish principles for agency collaboration and alignment prospectively and ICMRA is leading the way in this regard, e.g., with its PQ-KMS pilots
- The collaborative ICMRA pilots gained significant attention and interim results, especially for the PACMP pilot, are very positive
- The ICMRA PACMP pilot is also a welcome opportunity to further promote this important tool, which has been introduced on a global level in ICH Q12 (more detailed information on PACMP utilization can be found in the official ICH Q12 training material)
- Ultimately, close collaboration leading to regulatory reliance amongst agencies will be a key pillar in securing future supply of critical medicines to patients.

Acknowledgements (Roche-Genentech colleagues)

- Christine Wu
- Wassim Nashabeh
- Andrea Kurz
- Bob Iser
- Julia Edwards

Thank you!

Back-up slides

Background information – July 2021 Stakeholder workshop

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

Wednesday, July 7, 2021

Background – July 2021 ICMRA Stakeholder workshop

ICMRA-Industry Virtual Workshop on
Enabling Manufacturing Capacity in the COVID-19 Pandemic
Wednesday, July 7, 2021
6:00-9:00 EST | 12:00-15:00 CEST
AGENDA

6:00 - 6:05 **ICMRA Chair Welcome**
Emer Cooke, EMA and Chair ICMRA

6:05 - 6:10 **Industry perspective**
Greg Perry, IFPMA

6:10 - 6:25 **Regulatory Presentation: "Regulatory flexibilities to support the rapid increase in manufacturing capacity for COVID-19 therapeutics & vaccines"**
Sean Barry, HPRA, and Evdokia Korakianiti, EMA
Description – In this session, regulators will provide perspectives on the current science- and risk-based approaches employed by ICMRA regulatory authorities to enable rapid increases in manufacturing capacity for COVID-19 therapeutics and vaccines.

6:25 - 6:40 **Industry Presentation: "Science and Risk-based Approaches to Enable the Rapid Increase of Manufacturing Capacity for COVID-19 Therapeutics and Vaccines"**
Connie Langer, Pfizer (presenting on behalf of Industry)
Description – In this session, Industry will **(1)** provide an overview of the challenges that hinder manufacturers' abilities to rapidly increase capacity for COVID-19 therapeutics and vaccines, **(2)** identify the priority regulatory mechanisms and flexible CMC approaches that Industry views as being critical to success to rapidly increase manufacturing capacity for COVID-19 products, and **(3)** present recommendations to national regulatory authorities (NRAs) on science- and risk-based approaches that should be utilized to enable rapid increases in manufacturing capacity for COVID-19 products, mitigate drug shortages for non-COVID-19-related products, and facilitate timely patient access to quality medicines and vaccines.

6:40 - 6:55 **Discussion**
Moderated by Emer Cooke, EMA, and Theresa Mullin, FDA
Panelists:
- *Sean Barry, HPRA, and Evdokia Korakianiti, EMA*
- *Connie Langer, Pfizer*

6:55 – 7:10 **Regulatory Case Studies**
Stelios Tsinontides, FDA, and Karl Cogan, HPRA
Description – In this session, regulators will present case studies with specific examples to detail **(1)** regulatory approaches used to facilitate the approval of CMC changes that address manufacturing capacity issues during COVID-19 and **(2)** regulatory challenges as appropriate.

7:10 – 7:25 **Industry Case Studies**
Matt Popkin, GSK, Boris Zimmermann, Genentech/Roche, and Graham Cook, Pfizer
Description – In this session, Industry will present three 5-minute case studies with specific examples that will highlight **(1)** positive experiences with NRAs and various regulatory mechanisms and flexible approaches during the COVID-19 pandemic and **(2)** regulatory areas for improvement in addressing manufacturing capacity issues during COVID-19.

7:25 – 7:35 **Break**

7:35 – 8:50 **Panel discussion --** featuring three 25-minute panel discussions

Panel 1 – Priority Regulatory Mechanisms and Flexible CMC Approaches Lessons Learned
Moderated by Sau "Larry" Lee, FDA

Panelists: Regulators	Panelists: Industry
Stelios Tsinontides, FDA	*Matt Popkin, GSK*
Karl Cogan, HPRA	*Boris Zimmermann, Genentech/Roche*
Raphael Sanches Pereira, ANVISA	*Graham Cook, Pfizer*
Maria Baca-Estrada, HC	*Connie Langer, Pfizer*

Description – Panelists will further explore the concepts, challenges, and approaches highlighted by the Regulatory and Industry case studies of this Workshop. Panelists will discuss COVID-19 successes and lessons learned to date, as well as challenges and opportunities with the utilization of certain key regulatory mechanisms and flexible CMC approaches to enable rapid increases in manufacturing capacity for COVID-19 therapeutics and vaccines.

Background information – July 2021 Stakeholder workshop

Panel 2 – Lifecycle Management – Tools, Challenges, and Key Learnings During the COVID-19 Pandemic

Moderated by Markus Goese, Roche (EFPIA)

Panelists: Regulators	Panelists: Industry
Evdokia Korakianiti, EMA	*Thierry Gastineau, Sanofi Pasteur (Vaccines Europe)*
*Patricia Aprea, ANMAT**	*Diane Wilkinson, Astra Zeneca (Vaccines Europe)*
Raphael Sanches Pereira, ANVISA	*Suresh Jadhav, Serum Institute of India Pvt. Ltd. (DCVMN)*
Maria Baca-Estrada, HC	
Mohammed A. AlMuteri, SFDA	

*invited

Description – Panelists will discuss challenges related to the lifecycle management of COVID-19 therapeutics and vaccines, the unique application of specific lifecycle management tools during the pandemic, and opportunities to optimize the use of such tools to expedite patient access to COVID-19 products as well as minimize the regulatory complexity and resource burden of post-approval change management for both regulators and manufacturers during the remainder of the pandemic.

Panel 3 – Inspections, Alternative Tools, and Reliance Practices During the COVID-19 Pandemic

Moderated by Lorraine Nolan, HPRA

Panelists: Regulators	Panelists: Industry
Derek Smith, FDA	*Rajiv Desai, Lupin Ltd. (IGBA)*
Brendan Cuddy, EMA	*Steve Mendivil, Amgen (PhRMA)*
Mohammed Alaqeel, SFDA	*Caroline Bell, Kindeva Drug Delivery (PBOA)*
Paula Walker, MHRA	

Description – Panelists will discuss current challenges and near-term solutions or recommendations related to regulatory oversight of manufacturing facilities during the COVID-19 pandemic, including utilization of alternative tools (e.g., virtual inspections) and reliance practices for inspection reports and other GMP documents.

8:50 – 8:55 **Industry Concluding Remarks**
David Jefferys, IFPMA

8:55 – 9:00 **ICMRA Chair Concluding Remarks**
Emer Cooke, EMA and Chair, ICMRA

Key Workshop Materials / Reference:

- **SLIDES** – All Workshop presentations have been combined into a single slide deck which can be found on the ICMRA website here.
- **Day One VIDEO Recording** – The Zoom Recording (MP4 version) of the joint regulator-industry session has been transferred to the ICMRA website and can be found here.
- **Workshop Summary Report** – A report summarizing key learnings and discussions from the Workshop has been published on the ICMRA website.