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ADVANCING BIOPHARMACEUTICAL DEVELOPMENT
LATIN AMERICA 2024

Session I
6 August

Session II
13 August

# "ICMRA efforts to achieve Regulatory Convergence and Reliance Through a Pharmaceutical Quality Knowledge Management (PQKM) Capability."

13 August 2024

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ICMRA
INTERNATIONAL COALITION OF MEDICINES REGULATORY AUTHORITIES

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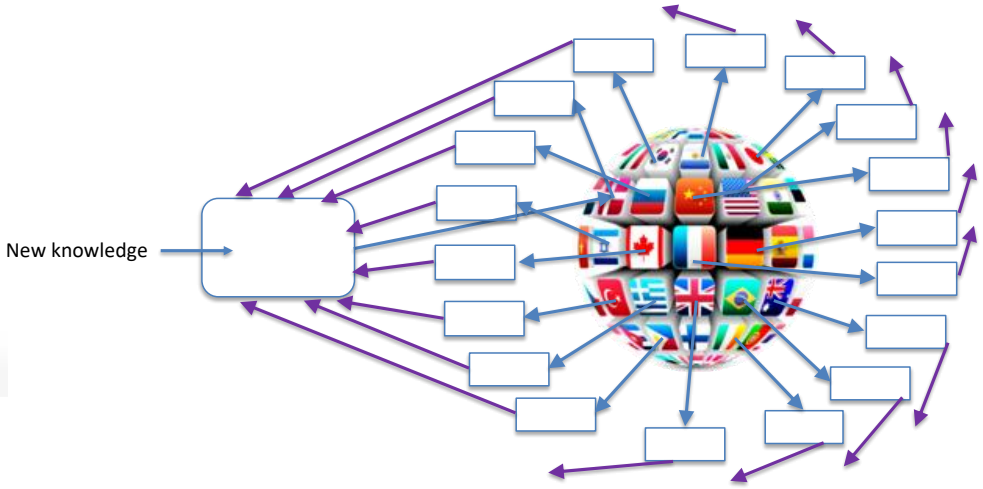
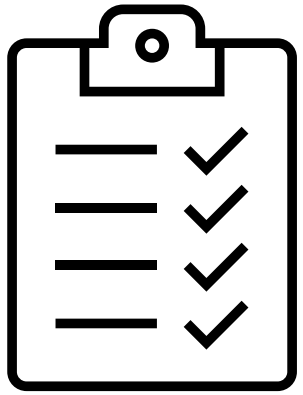
# Effective Pharmaceutical Quality Management requires Post Approval Changes (PACs) to regulatory filings

- Today -- Many PACs require separate prior approval by the regulatory authority where the product is marketed
- Creates regulatory complexity, cost, and delay in implementing changes and managing quality
- Enabling greater reliance among regulators could reduce need for multiple, separate and different review processes and timelines





# Some Key Enablers of Regulatory Reliance:



- ✓ Alignment of regional **laws and regulations**
- ✓ Harmonized **regulatory requirements** across regions
- ✓ **Comparable**/convergent basis for making **regulatory assessments**
- ✓ Readily **accessible and usable "reports"** for reference by other regulators
- ✓ Assure **non-disclosure** of confidential trade secret information
- ✓ Regulators reviewing **same product, quality dossier, PAC-related submissions, etc.**
- ✓ **IT tool(s)** to facilitate review and collaboration

# ICMRA working with ICH, PIC/S and IPRP to coordinate work to address these key enablers

| Enabler | Efforts under way |
|---|---|
| **Harmonized regulatory requirements** across regions | **ICH** Q GLs; Q12, M4Q(R2), SPQS (*expected start 11/24*) |
| **Comparable/convergent basis for** making regulatory **assessments**; reports | **ICMRA** PQKM--PACMP and CHIP collaboration pilots<br>**IPRP** QWG & surveys |
| **Readily accessible** and usable **"reports"** for reference by other regulators | **ICH** PQKM Task Force<br>**PIC/S** – more structured data in inspection reports |
| Assure **non-disclosure** of confidential trade secret information | **ICMRA** PQKM pilot design<br>**ICH** PQKM Task Force |
| Regulators reviewing **same product, quality dossier, PAC-related submissions, etc.** | **ICMRA** PQKM WG on Identifiers to enable greater reliance |

# ICMRA
# Collaborative Assessment Pilot

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# Collaborative Assessment Pilot

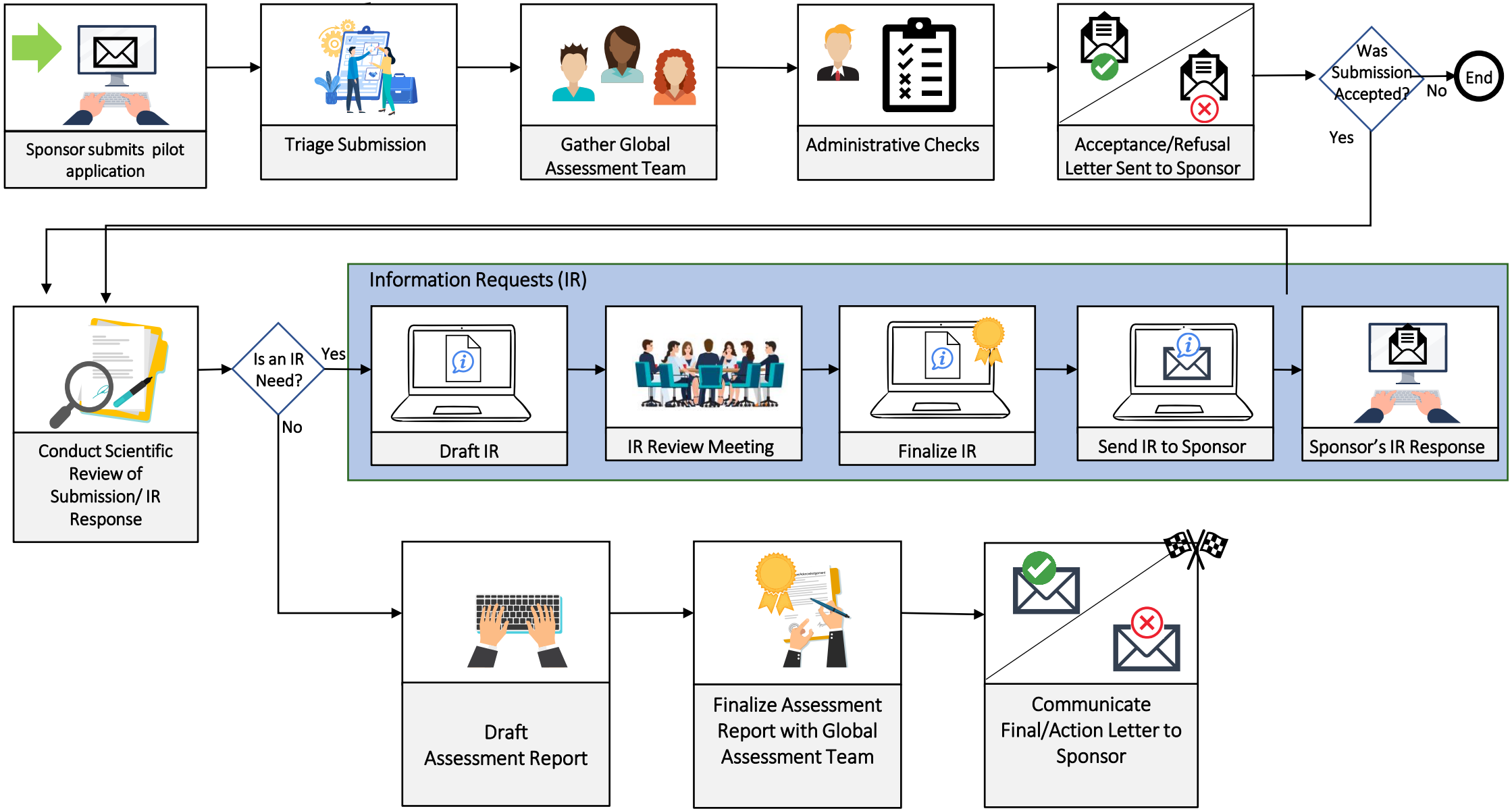
- Multi-agency collaborative assessment of Post Approval Change Management Protocols (PACMP)
- 14 applications received - prioritized based on impact to supply of **critical medicines**, potential for **agreed regulatory approach**
- Five proposals accepted:
  - New DS & DP manufacturing sites, new QC testing sites, changes to the DS manufacturing process
  - 2 x small molecules, 2 x mAbs, 1 x ADC
- Identical submission sent to all participating agencies
- All 5 collaborative assessments completed successfully

# Global Assessment Teams

| Lead Authority | Participating Authorities | Observer Authorities |
|---|---|---|
| • Assess application<br>• Propose IRs<br>• Coordinate all activities<br>• Lead on project calls<br>• Consolidates IRs<br>• Applicants' main contact | • Conduct independent assessment<br>• Participate in discussion meetings<br>• Propose IRs | • Participate in discussion meetings<br>• Cannot raise IRs |

| Applicant | Lead Authority | Participating Authorities | Observers |
|---|---|---|---|
| **Roche** | EMA | FDA | PMDA |
| **AstraZeneca** | FDA | EMA | PMDA, Health Canada, HSA, ANVISA |
| **Merck Healthcare KGaA** | PMDA | FDA, EMA, MHRA, Swiss Medic | HSA, Health Canada, TGA |
| **Gilead** | FDA | EMA, MHRA, Swiss Medic | Health Canada |
| **MSD** | EMA | FDA, PMDA, Health Canada | HSA, Swiss Medic |

# New 120-day process developed to support collaborative assessment



# Anticipated Timeline for Collaborative Assessment Pilot

| Activity | timeline |
|---|---|
| **Submission – receipt date** | **Day 0** |
| **Project start** | Day 1 |
| **Regulatory Authorities specific steps [1]** | Day 1-105 |
| **Assessment teams internal meetings** | Day 20 - 105 |
| **Information Requests (IR) to Sponsor [2]** | Day 20 - 105 |
| **Sponsor meeting [3]** | TBD |
| **Regulatory Authorities specific steps [1]** | D105 - 113 |
| **Draft Quality assessment by Lead regulatory Authority** | Day 106 |
| **Decision making [1]** | Day 113 – 120 |
| **Project end** | **Day 120** |

[1] Due to different legal frameworks each Authority needs to meet internal regulatory milestones, e.g. FDA: initial filling/ completeness assessment, complete filing review; EMA: validation, developing AR for CHMP comments/ adoption, etc.

[2] There may be multiple IR throughout this period

[3] Flexibility based on the needs of the participating authorities

# Global assessment teams actively collaborated on harmonized IRs

Harmonization of IRs was achieved across the entire Module 3

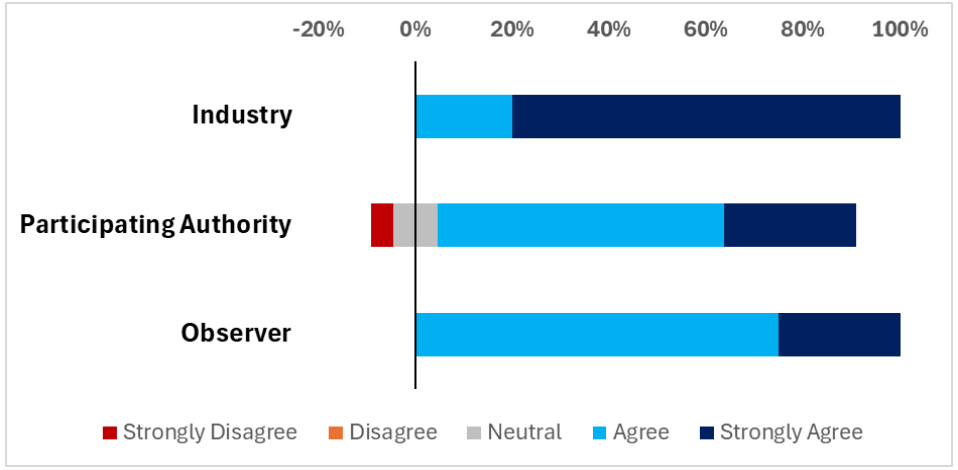
| Question area | No. harmonised IRs |
|---|---|
| Comparability | 26 |
| Reporting category | 7 |
| Stability | 5 |
| Control strategy | 4 |
| Analytical methods & validation | 3 |
| Process validation | 3 |
| Viral safety | 3 |
| Impurities | 2 |
| Manufacturing site details | 2 |
| Method transfer | 2 |
| Batch traceability | 1 |
| Container closure | 1 |
| Equipment details | 1 |
| Extractables & leachables | 1 |
| Sterility assurance | 1 |
| Transport validation | 1 |

Discussion meetings resulted in **~25% reduction** in #IRs

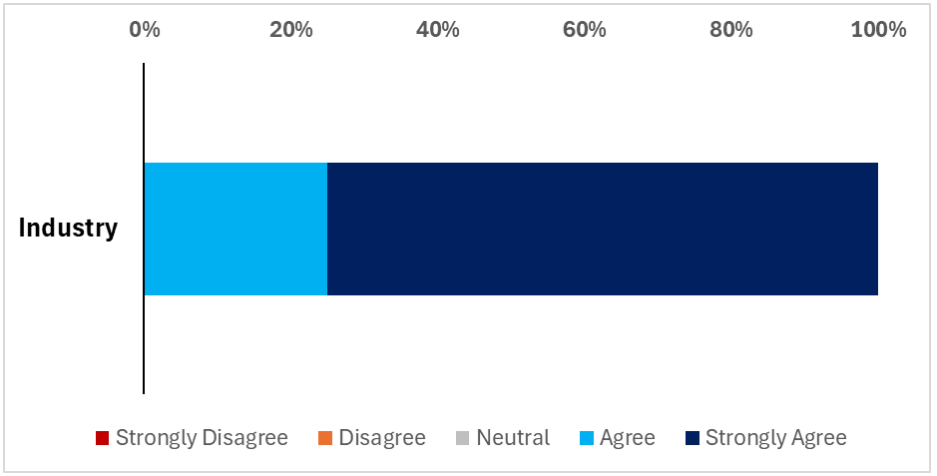
- 88% of all assessment IRs were harmonized
- Required discussion among regulators to reach a consensus
- Some regional specific IRs, e.g. method transfer data, requirement for certain validation reports
- A small number of region-specific administrative questions, e.g. applicant forms, GMP documentation

# Positive outcome based on survey results

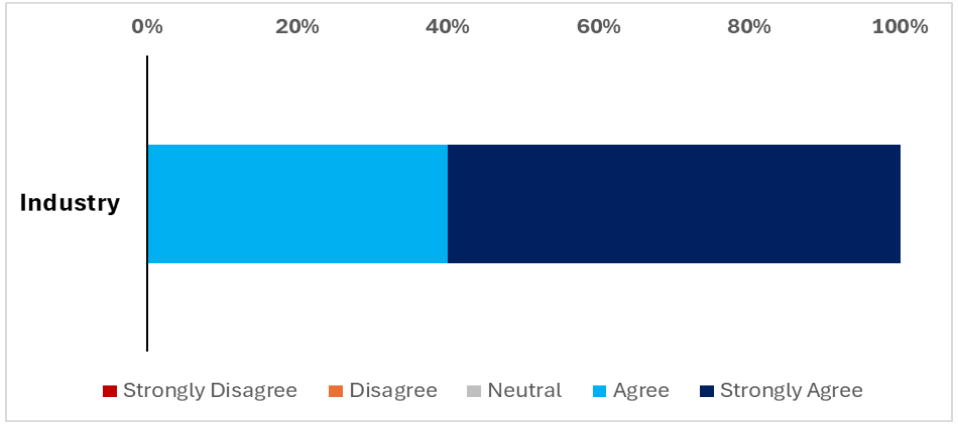
## The overall experience was positive and support its operationalisation into a global regulatory program




## Participation in the pilot had a measurable impact on public health and/or availability of medicines




## Participation in the pilot did not impact standard approval times

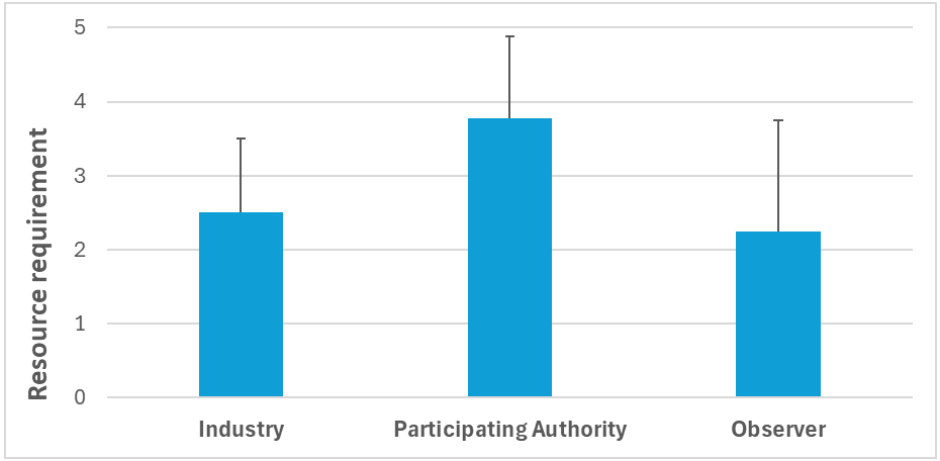



| Overall duration (days) | Max difference in approval dates between participating authorities |
|---|---|
| 115 | 0 |
| 118 | 0 |
| 105 | 0 |
| 122 | 2 |
| 119 | 12 |

# Impact on resources & areas of further development

Resource impact 0 = no additional resources and

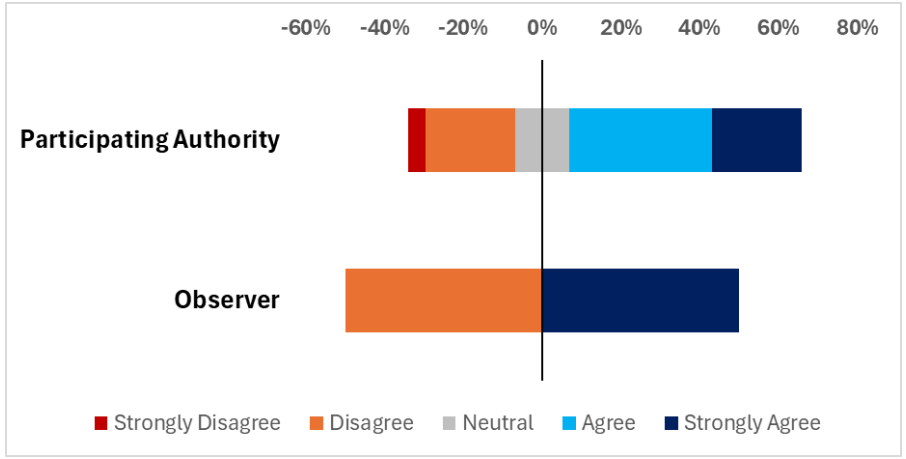
5 = Significantly more additional resources




Did the benefits outweigh any additional resource requirements?

| | % Respondents who answered yes |
|---|---|
| **Industry** | 100% |
| **Participating Authority** | 95% |
| **Observer** | 100% |

It was possible to use a single IT platform




→ Developing a dedicated shared IT platform is a priority

# Success metrics/KPIs

| Area | Achieved |
|---|---|
| Harmonised timetable & milestones achieved | ✓ |
| Efficient Document Collaboration | ? |
| Timely & efficient communication | ✓ |
| Consistency in decision making | ✓ |
| Required confidentiality agreements in place | ✓ |
| Observers joined discussions & benefited from participation. | ? |
| Identified areas of divergence for future harmonisation | ✓ |
| Benefit of participation outweighed increased resource requirements | ✓ |
| Effective knowledge sharing | ✓ |
| No impact  on approval times or increase regulatory expectations | ✓ |
| Final decision issued within a similar timeframe. | ✓ |
| Decisions were transparent | ✓ |
| Pilot provided data for development of a global regulatory pathway. | ✓ |
| Stakeholder satisfaction | ✓ |
| Impact on Public Health | ✓ |

# Achievements & Lessons Learned

- Positive and productive collaborations
- Agreed process with standard 120-day timetable
- Agreement on data requirements across numerous areas of CMC - majority of information requests were harmonized
- Lead & Participating Authorities approved applications within days of each other
- Positive feedback from industry participants
- Resource-intensive exercise to achieve aligned decisions
- Survey feedback highlighted areas of further development and improvement

# Future directions

- Pilot results support further **development** of a **global** collaborative assessment **pathway**
- Ongoing activities:
  - Develop governance structure and dedicated project management capability
  - Refine collaborative assessment process with harmonized milestone dates, standard templates etc.
  - Target increased participation by additional ICMRA member agencies.
- Develop a dedicated globally shared secure **IT platform**
- Given the increased regulatory resource requirements - target optimal use of **resources** to maximize patient benefit:
  - Innovative manufacturing technologies
  - Post approval changes which impact supply
- The collaborative assessment process can be a key enabler of global regulatory convergence and reliance in conjunction with other global programmes such as OPEN, Orbis, PIC/S, Access Consortium, parallel scientific advice etc.
- First steps toward the ultimate goal of **one submission = one global approval**

# ICMRA
# Collaborative Hybrid Inspection Pilot

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# Collaborative Hybrid Inspection Pilot (CHIP)

- Three proposals submitted for collaborative hybrid inspection pilot (CHIP)
  - Planned to accept three proposals
  - Two proposal accepted; third CHIP was a reinspection
  - One proposal withdrawn
- Three collaborative hybrid inspections completed without technical difficulties
- Post inspection feedback is being collected via survey
- Efforts are ongoing to develop recommendations on next steps

# CHIP

- **1st and 3rd collaborative hybrid inspections**
  - Addition of a new DP manufacturing site located in USA
  - Initial inspection completed successfully in Sept. 2023
  - Reinspection completed successfully in May 2024

- **2nd collaborative hybrid inspection**
  - Addition of a DS manufacturing/analytical testing site located in Switzerland
  - Completed successfully in February 2024

# CHIP - Proposals Accepted and Regulatory Authorities

| Applicant | Lead 'Onsite' Authority | Remote Authority | Observers |
|---|---|---|---|
| **Roche** | Swissmedic | FDA | EMA and Health Canada |
| **Gilead*** | FDA | Health Canada | PMDA, Swissmedic, MHRA, MoH Israel, EMA, HPRA |

*** using a CMO**

# Achievements

- Positive and productive collaborations with supporting tools developed
  - Regulators - Joint Inspection Protocol w/ agreed timetable for inspections
  - Sponsors & Facilities – Industry Expectations Guidance and timely communication and response to deficiencies.
  - Sponsors achieved approvals w/ sites securing CGMP Compliance Status.

- Lead and Remote Regulatory Authorities aligned on inspection procedure and findings
  - Agreement on deficiencies, significance and post-inspection activities.
  - Harmonized approach towards unfavourable compliance status in participating regions with no supply from facility pending resolution. Achieved in different ways.

- Continuous communication among the RAs
  - Use of IT platform to securely share information between participating inspectorates before, during and post inspection.

# Anticipated Timeline for Collaborative Hybrid Inspection Pilot

| Activity | Timeline (calender days) |
|---|---|
| **Pre-inspection planning between RAs** | 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 |

# Lessons Learned

- Needed to clarify expectations for industry in hosting a collaborative hybrid inspection
  - Expectations document posted on the ICMRA website on 31-Aug-2023
- A lot of effort taken to align regulatory processes, clarify roles and requirements to enable collaboration of different RAs and to facilitate communication with company (joint report, one voice for all, one CAPA)
  - Balance of different Regulatory Commitments
- Need to consider in which cases this regulatory tool would be of value in the future (output of the pilot)
  - How to Initiate (Sponsor, Regulator)
  - How to combine with dossier review decision-making and timelines
  - Inspection Types
- Need for a common secure IT Framework

# Next Steps – Future Directions

- Feedback from participating sponsors, Sites and Regulators is being collected
  - Target to issue a summary report by end of December 2024

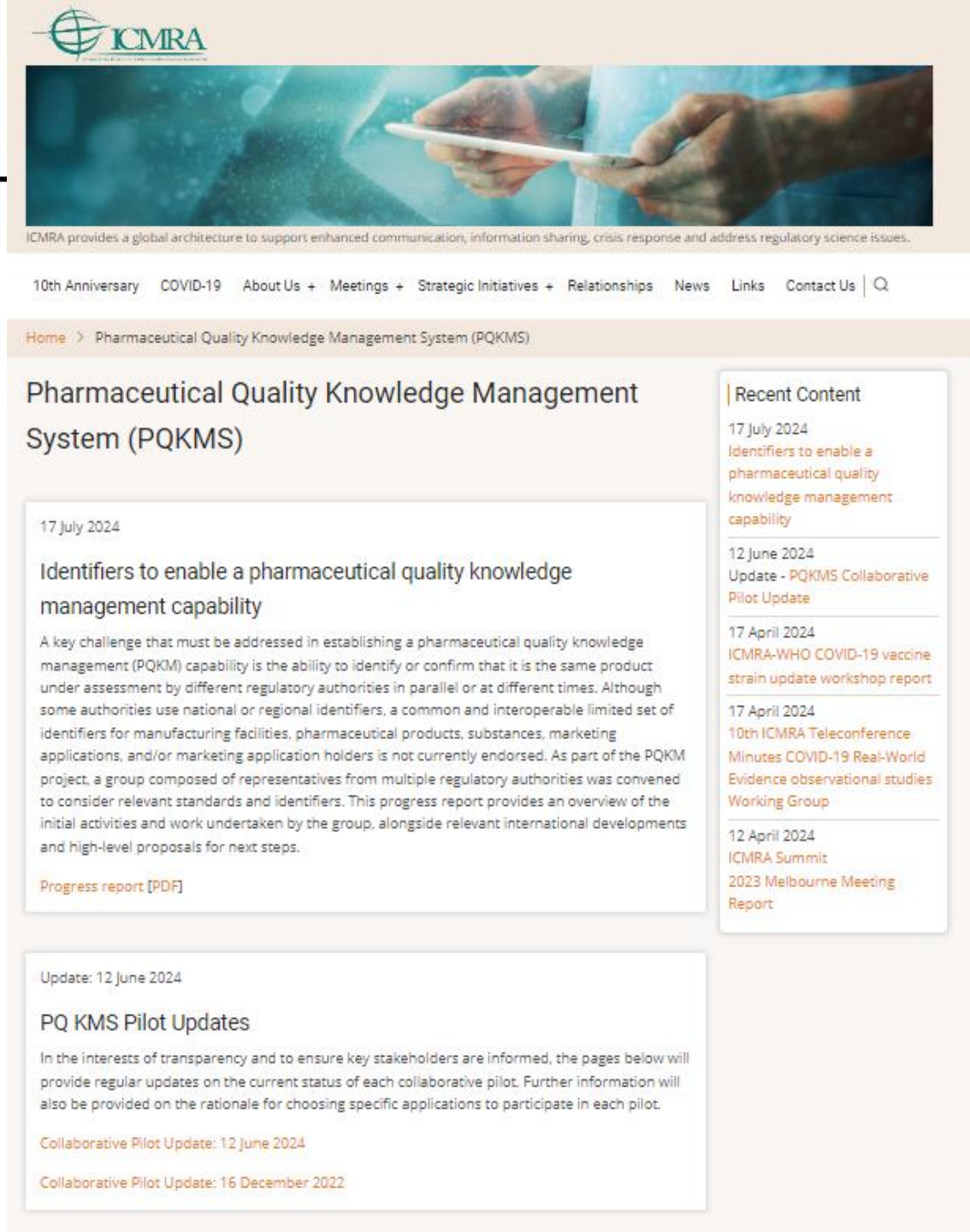
- The CHIP continues to accept applications.  For information on how to apply refer to ICMRA's webpage (next Slide).

- Incorporate the CHIP into the Operational Plan being prepared for PAC noted earlier.
  - One dedicated globally shared secure **IT platform**
  - Set of directions & supportive documents for planning, executing and reporting CHIP inspections
  - Requirements for Global Authorities to be part of CHIP

- First steps toward the ultimate goal of **one submission = one inspection (when necessary) = one global approval**

# Collaborative Pilots: Pharmaceutical Quality Knowledge Management System (PQ KMS) Website

See links for all information needed concerning the collaborative pilots



# ACKNOWLEDGMENTS

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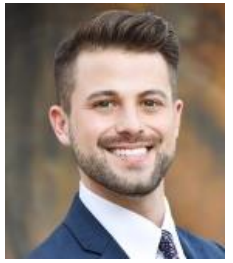

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