ICMRA efforts to achieve Regulatory Convergence and Reliance –

A Progress Report on the Collaborative Assessment and Hybrid Inspection Pilots

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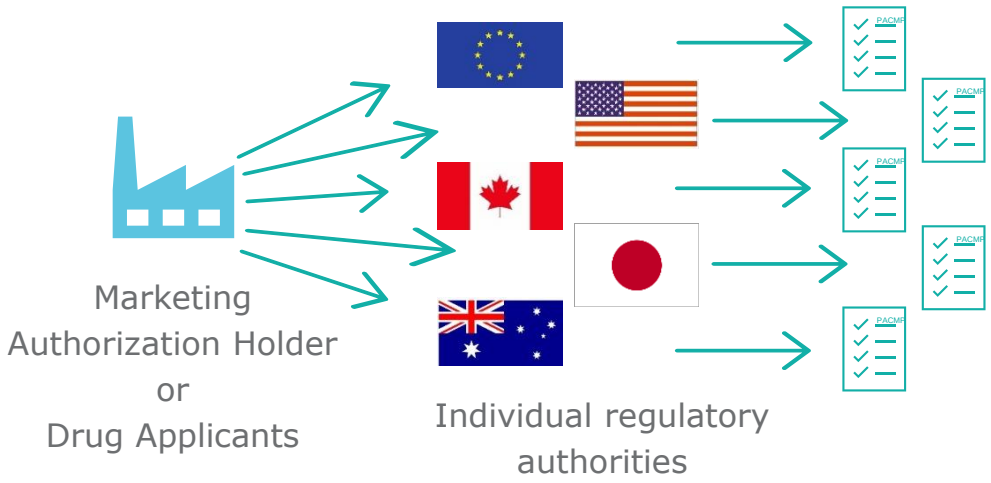
Overview

- Problem Statement
- Background of ICMRA Pilots
- Outcomes ICMRA Collaborative Assessment Pilot
- Outcomes ICMRA Collaborative Hybrid Inspection Pilot
- Acknowledgement

Current Landscape



Multiple submissions

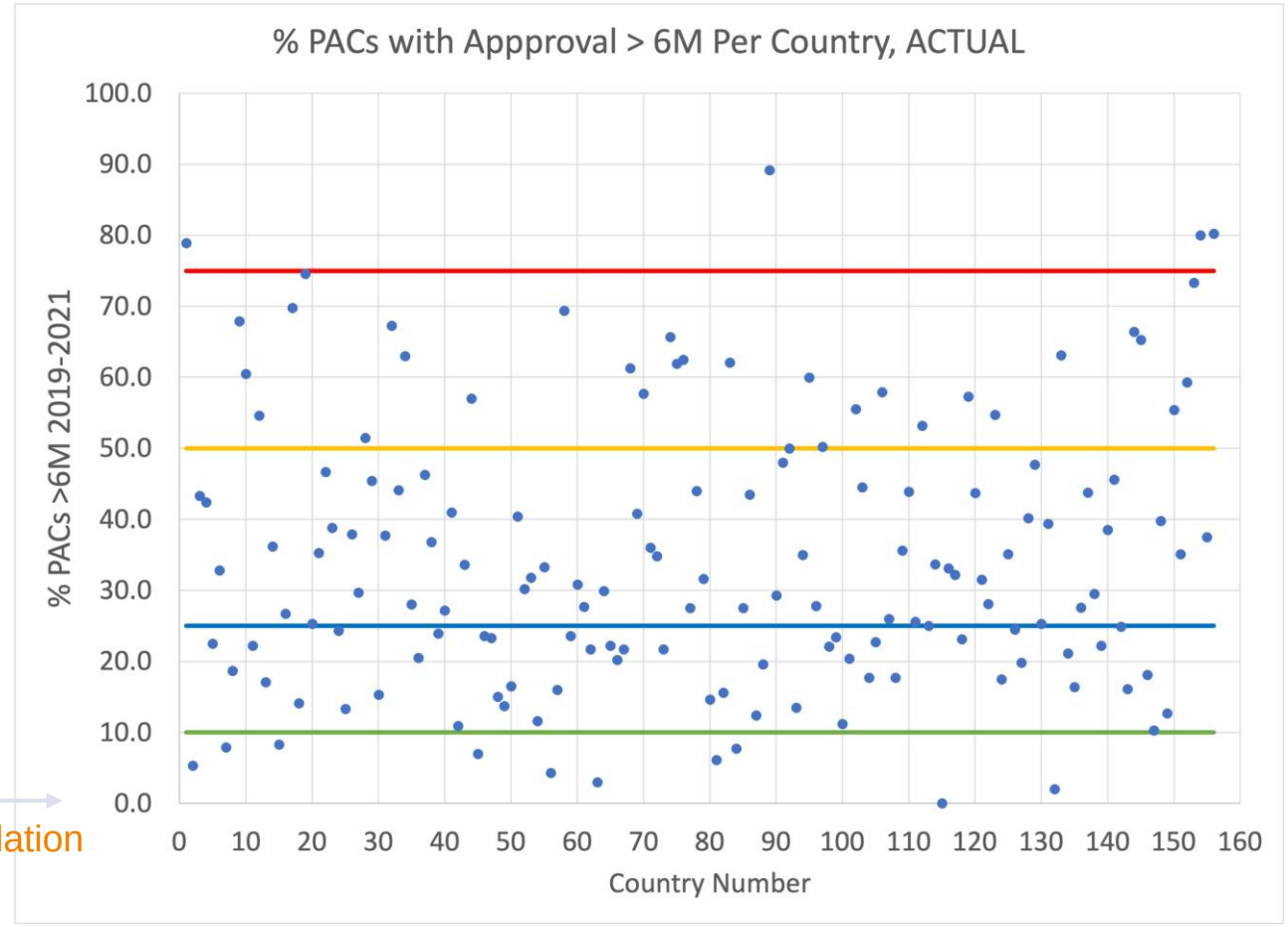
Multiple assessments

Multiple outcomes

Complexity, cost, and delay in implementing changes and managing quality

>125,000 PAC Data Points Demonstrate PAC Global Regulatory Complexity is a Huge Problem

Y-Axis: Percentage of all PACs that took more than 6 months for approval per country



WHO recommendation

X-Axis: Individual countries 1-156

>125,000 PAC data points collected from 16 of the top 25 pharma companies over a period of 3 years (2019-2021)

It usually takes 3-5 years for full global approval of each PAC

The long approval timelines increases supply chain complexity and risk of drug shortage

Less than 10 % of all (156) countries had at least 90% of all PACs taking no more than 6 months (WHO guideline) for approval

Vinther, Ramnarine, Gastineau, O'Brien, Brehm, Fryrear. Therapeutic Innovation & Regulatory Science https://doi.org/10.1007/s43441-024-00614-9

ICMRA Pilots

- In July 2021, the International Coalition of Medicines Regulatory Authorities (ICMRA) held a workshop on the learnings from the pandemic, where regulators and manufacturers faced an unprecedented challenge to rapidly increase manufacturing capacity for production of COVID-19 therapeutics and vaccines to meet global demand.
- Following the workshop, ICMRA launched **two regulatory pilots** aimed at enhancing global regulatory collaboration with a goal to remove duplication in assessments and inspections and facilitate **faster access of important medicines to patients** around the world.

ICMRA Collaborative Assessment Pilot (CAP)

Collaborative Assessment Pilot Objectives

- Pilot a multi-agency **collaborative assessment** of Post Approval Change Management Protocols (PACMP) aiming to **facilitate the introduction of changes important to supply of critical or high priority medicines**
  - Deliver a collaborative and harmonised assessment outcome based on science- and risk-based approach respecting the regional requirements, without increasing the regulatory burden for industry or any delays in approval as a result of the pilot.
  - Facilitate timely approval and implementation of important to supply CMC changes for global markets.
  - Develop a process that enables collaborative assessment within the regional regulatory procedures for post approval CMC changes.
  - Identify best practices in the quality assessment of CMC post-approval changes.
  - Enhance international regulatory cooperation and foster interactions among participating regulatory authorities.
  - Identify misalignments, differences, and potential areas for future harmonization across regions.
  - Identify the areas where cross-regional collaborative assessment efforts could focus on to provide the highest positive impact to public health.

Roles and Responsibilities for Collaborative Assessment

Lead Authority

- Assess application
- Propose IRs
- Coordinate collaborative assessment interactions
- Lead on project calls
- Consolidates LoQs or IRs
- Applicants' main contact

Participating Authorities

- Conduct independent assessment
- Participate in discussion meetings
- Propose LoQs or IRs

Observer Authorities

- Participate in discussion meetings
- Cannot raise LoQs or 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

ICRMA Collaborative Assessment Pilot Outcomes

Collaborative Assessment Pilot

- Multi-agency collaborative assessment of Post Approval Change Management Protocols (PACMP) within the established regional procedures and framework
- 14 applications received - prioritized based on impact to supply of **critical medicines**, potential for **agreed regulatory approach**; Applications not in line with regional frameworks not eligible to the pilots
- 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 regulatory authorities
- Permission given by applicants to share confidential commercial information (CCI) between the participating regulatory authorities
- All 5 collaborative assessments completed successfully

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

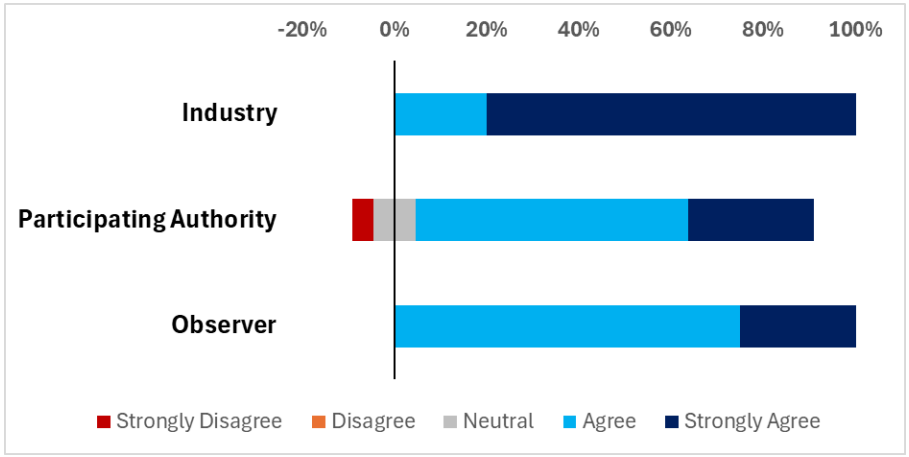
- 88% of all assessment IRs were harmonized
- Required discussion among regulators to reach a consensus
- Some regional specific IRs, e.g. method transfer data, requirement for certain validation reports
- A small number of region-specific administrative questions, e.g. applicant forms, GMP documentation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

Success Metrics/KPIs

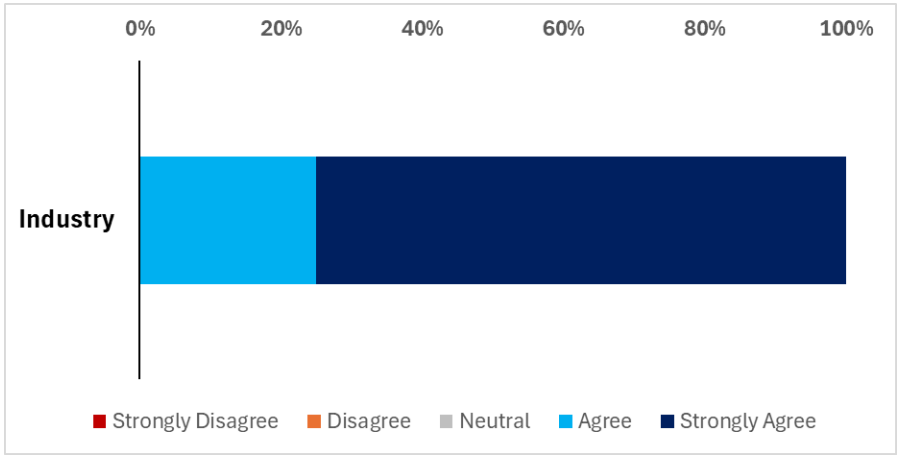
Area	Achieved
Harmonised timetable & milestones achieved	✓
Efficient Document Collaboration	?
Timely & efficient communication	✓
Consistency in decision making	✓
Required confidentiality agreements in place	✓
Observers joined discussions & benefited from participation.	?
Identified areas of divergence 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	✓

Positive Outcome based on Survey Results

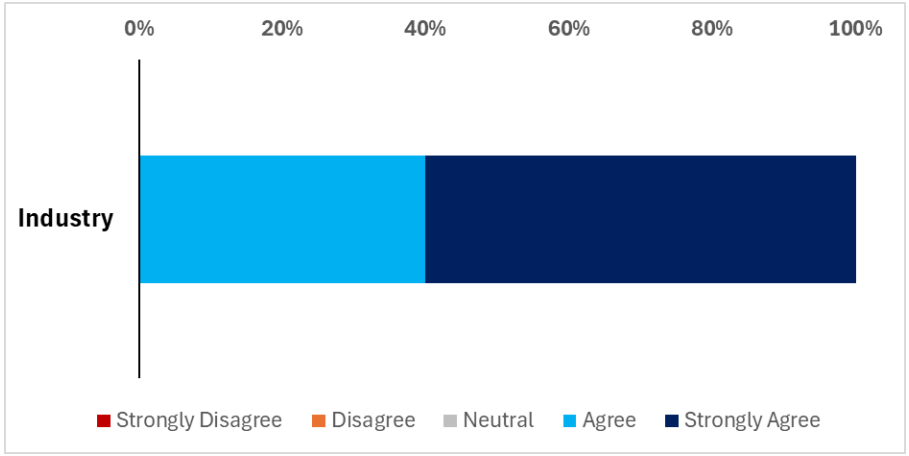
The overall experience was positive and support the continuation of collaborative assessment programme



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



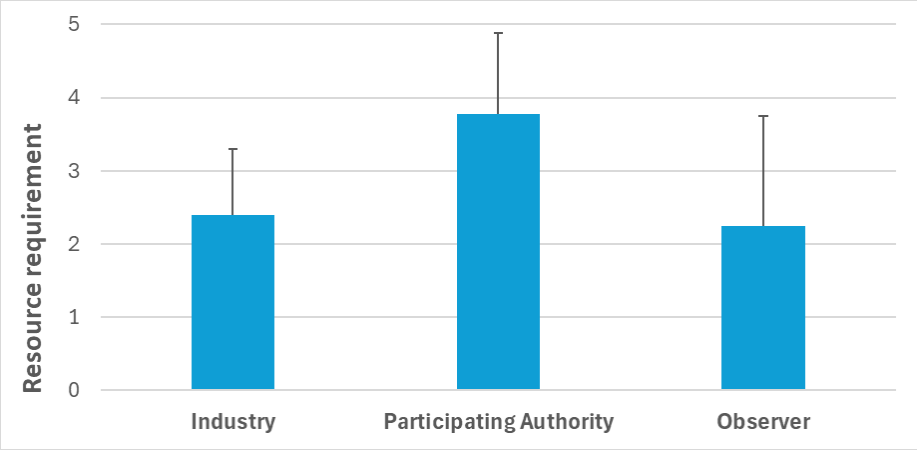
Participation in the pilot did not impact standard approval times



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

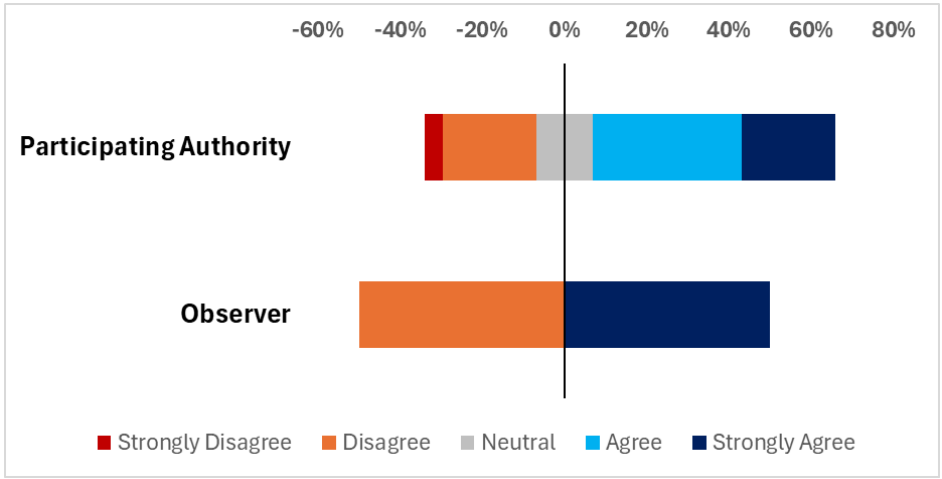


Did the benefits outweigh any additional resource requirements?

	% 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 should be a priority →



Key Achievements

- Positive and productive collaborations
- Agreed collaborative assessment with standard 120-day timetable, embedded within the regional regulatory procedures
- Same assessment outcome, which helped to facilitate approval of under their regional frameworks on the same day or within days of each other
- Overall positive feedback from regulators and industry participants
- Survey feedback highlighted the benefit to continue the program and areas of further development and improvement

Key Learnings

- Given the increased regulatory resource requirements - target optimal use of resources to maximize patient benefit. Current thinking to focus on:
  - Innovative manufacturing technologies
  - Post approval changes which impact supply
- Need for IT enablers
- Consider better the role of observers
- Need leadership to ensure science- and risk-based assessment (not additive questions and comments) and provide adequate oversight of the programme to ensure the delivery of agreed scope
- The collaborative assessment program could be used in conjunction with other global programmes such as OPEN, Orbis, PIC/S, Access Consortium, parallel scientific advice, etc.

ICMRA Collaborative Hybrid Inspection Pilot (CHIP)

Collaborative Hybrid Inspection Pilot Objectives

- Develop a Pilot Program that describes how stakeholders in site inspections (Regulators and Industry) can engage to allow evaluation of a facility via a hybrid inspection approach. The scope of the pilot will initially be targeted to inspections where multiple regulatory agencies have an interest in the facility and products to be covered by the on-site inspectorate.
- Conduct collaborative facility assessment by a combination of using of on-site inspectorates at a facility and utilizing virtual technology to allow participation of other inspectorates in the GMP inspection.
- Identify best virtual platforms and information technology (i.e., video) to facilitate concurrent onsite inspection and distant assessment.
- Identify best practices to prepare and conduct the hybrid inspection to ensure that both on-site and distant inspectorates obtain the desired information to complete respective assessments and meet their objectives.
- Develop a framework to accommodate time zone differences between the facility location and the distant inspectorates.
- Identify misalignments, differences, and potential areas for alignment or harmonization in GMP expectations – one area of focus here might be in how the inspection is reported and how deficiencies are classified.
- Provide collaboration and dialog opportunities for industry participants to understand the impact of the hybrid approach on industry.

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**

ICRMA CHIP Outcomes

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 was collected via a survey and is being analyzed in a report.
- Efforts are ongoing to finalize our report with recommendations on next steps

CHIP 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.

CHIP Anticipated Timeline

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

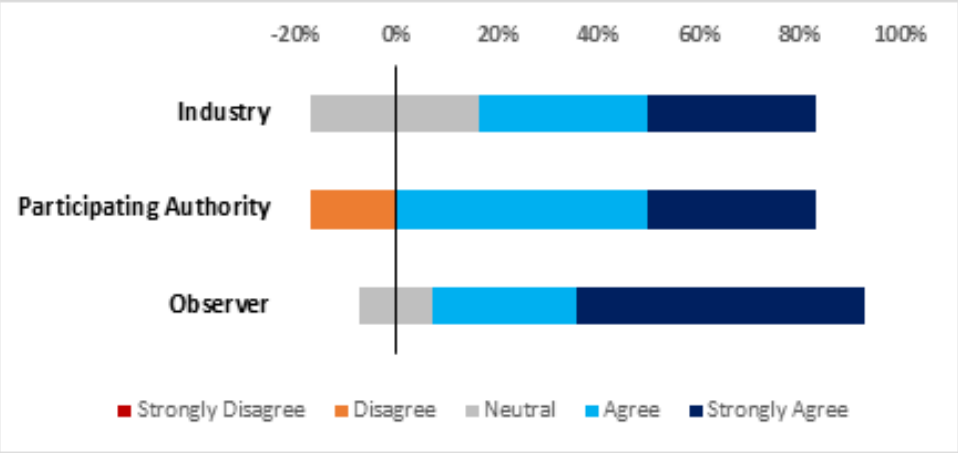
CHIP Preliminary Specific Findings

Majority authorities and companies indicated CHIP required significant extra resources.

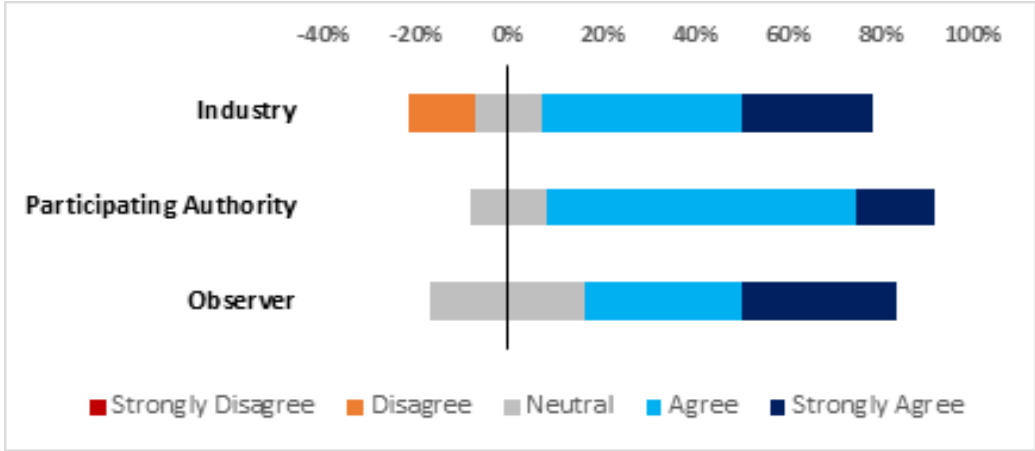
Participating authorities and companies agreed there was observable impact on public health.

Preliminary Survey Results

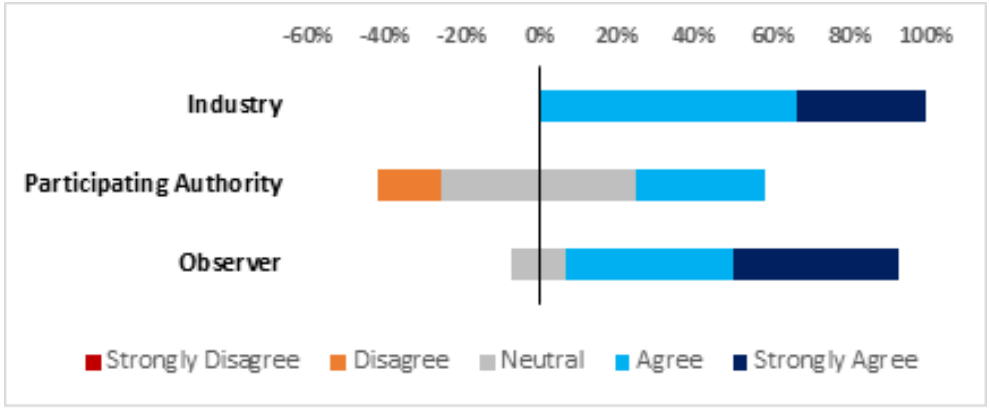
The overall experience of the participation to the pilot is considered positive



Would you consider participation in the future?

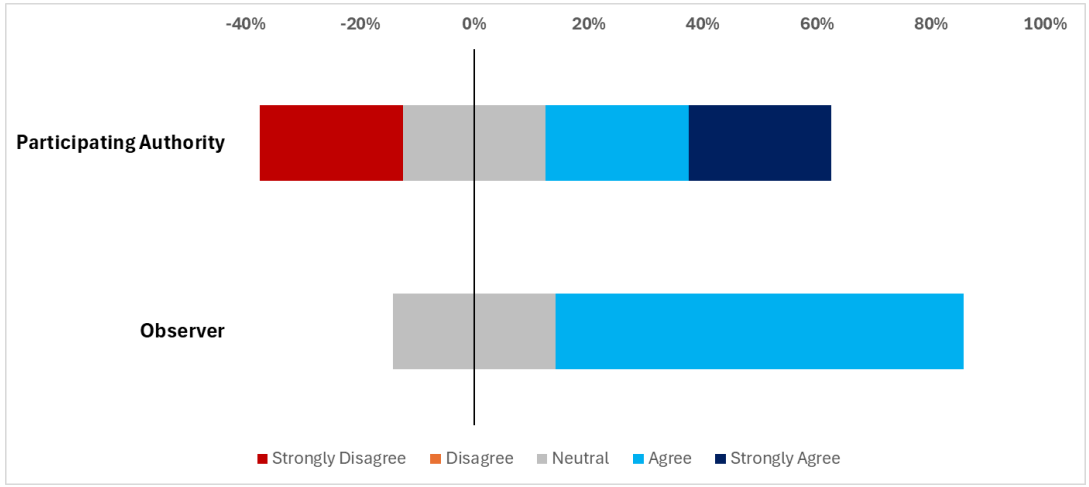


Do you feel the collaborative hybrid inspection process could develop into an operationalized tool that can be deployed in the future?

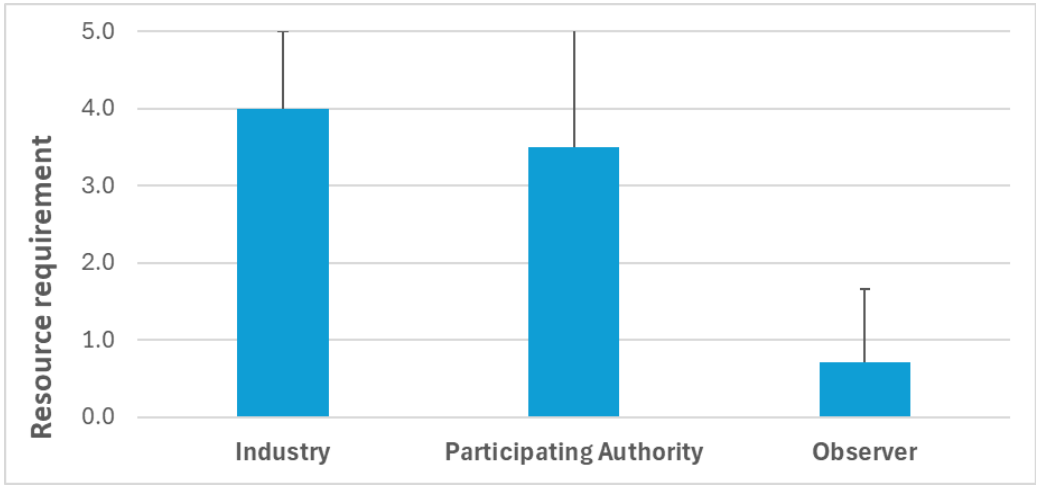


Preliminary Survey Results

All participating authorities were able to agree on a single list of deficiencies, including region specific, and on a final decision



What was the resource requirement needed to participate on the collaborative hybrid inspection? Rate on a scale from 0 to 5, with 0 = no additional resources and 5 = Significantly more additional resources



CHIP Lessons Learned

- Expectations document posted on the ICMRA website on 31-Aug-2023 very helpful to Industry
- 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 was collected
  - Target to issue a summary report by end of 1Q2025
- 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 CAP 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

Scan the 2D barcode using your phone for all information needed concerning the collaborative pilots

ACKNOWLEDGMENTS – ICMRA PAC Sub-Working Group

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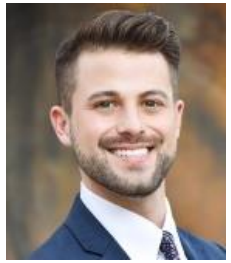

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Thank You!