ICMRA Collaborative Assessment Summary Report

January 17, 2025

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1. Executive Summary

1.1. Overview of the collaborative assessment pilot

Global supply chain management is a complex process, requiring regulatory approvals from many regulatory authorities with different requirements and approval timelines. This complexity can have a negative impact on the timely availability of medicines for patients across the world.

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 pilots aimed at enhancing global regulatory collaboration with a goal to make best use of regulators' resources, remove duplication in assessments/inspections, and facilitate faster access of important medicines to patients around the world.

The first pilot, called the collaborative assessment pilot, focused on increasing the collaboration among regulators across different regions in the assessments of quality/CMC (Chemistry, Manufacturing, and Controls) Post-Approval Change (PAC) submissions. The second, known as the collaborative hybrid inspection pilot (CHIP), was aimed at improving global cooperation in inspections of manufacturing facilities. The overall goal of both pilots was to improve collaboration and convergence among global regulators through assessment of post-approval CMC changes and inspection of manufacturing facilities. This report outlines the findings of the collaborative assessment pilot, while a separate report will summarize the findings of the CHIP.

The collaborative assessment pilot involved multiple regulatory agencies, assessing the same post-approval changes submissions within an agreed timeframe, and aiming to deliver the harmonized assessment outcome with no additional regulatory burden for industry. While the changes were submitted and finalised in accordance with the established regional regulatory procedures, appropriate adjustments in the normal assessment timelines and enhanced interactions and coordination among participating regulatory authorities were introduced to enable the effective and efficient collaboration in quality assessment. The pilot focused on assessment of Post Approval Change Management Protocols (PACMPs) to facilitate an agreement between regulatory authorities and applicants (or marketing application holders) on the planning and implementation of future CMC changes. The assessors or assessment teams from participating regulatory authorities first conducted their own assessment, and then had a series of interactions to share their assessment and align their science- and risk-based evaluation of the submission.

As a result of these interactions, the participating regulatory authorities were able to agree on a list of questions (LoQs) or information requests (IRs).[1] At the end of the assessment period, all participating regulatory authorities reached a harmonized assessment outcome for all the applications examined. Initially, the pilot aimed to accept three applications over an 18-month period. Owing to the overall positive feedback and growing interests from both regulators and industry, the pilot was extended to allow more regulatory authorities to be involved (either as participants or observers), and a total of five applications were completed over 22 months. The pilot ran from July 2022 to May 2024.

[1] For the purpose of this document, the terms of LoQs, IRs, and Request for Supplementary Information (RSI) can be used interchangeably, since both terms means questions and comments that are sent to applicants seeking their responses in support of regulatory assessment of their applications.

1.2. Summary of key findings and outcomes

The applications submitted to the pilot addressed various key aspects of post-approval changes relating to increase of manufacturing capacity, including the addition of new manufacturing sites, addition of new quality control (QC) testing sites, changes to the manufacturing process, changes in QC testing, and container closure modifications. The products varied from monoclonal antibodies to chemical small molecules as well as antibody-drug conjugates. Each application was assigned a lead regulatory authority responsible for overall project management during the collaborative assessment, including coordinating and facilitating meetings between assessors from different regulatory authorities, consolidating and streamlining comments sent to applicants, and documenting the commonly agreed assessment recommendations. For each pilot, the lead regulatory authority was either the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), or the Pharmaceuticals and Medical Devices Agency (PMDA). In addition, the following regulatory authorities took part either as full participants or observers; the Medicines and Healthcare products Regulatory Agency (MHRA), Swissmedic, Health Canada, the Agência Nacional de Vigilância Sanitária (ANVISA), the Therapeutic Goods Administration (TGA), and the Singapore Health Sciences Authority (HSA).

To facilitate collaboration and coordination among participating regulatory authorities during the assessment phase, a standardized process was developed. Although standard timetables for PACs may vary among regions, a harmonized 120-day timetable was successfully established. During the 120-day period, IRs could be sent to applicants, and the assessors or assessment teams from the participating regulatory authorities agreed on a common science- and risk-based approach to assessment of applications and industry's responses to IRs. All applications were completed within the agreed timetable, successfully demonstrating that a collaborative assessment is possible under existing regional legal frameworks without adding delays to standard approval timelines. Furthermore, the ability to receive a harmonised assessment outcome from multiple regulatory authorities with an agreed 120-day timeline represents a significant efficiency improvement compared to submitting independently to each regulatory authority. As a result of this collaborative effort, each application was approved or given a positive opinion[2] by the participating regulatory authorities under their regional framework on the same day or within days of each other. This outcome represents a significant accomplishment of the pilot, facilitating the fast implementation of changes necessary to support supply chain resilience for critical medicines.

During the collaborative assessment, the discussions among the regulatory authorities allowed a consensus on IRs to be sent to the applicants in the majority of cases. For the technical related IRs (i.e., all questions apart from purely administrative questions), harmonised agreement was achieved for 88% of questions sent to applicants. These harmonised IRs covered a wide range of Module 3 data, including comparability, process validation, stability, and others. This high level of consensus among participating regulators is particularly noteworthy, as currently industry often receives different types of questions that can lead to different outcomes for the same submission.

This pilot programme highlights not only the benefit of collaboration among different regulatory authorities, but also that it is feasible for such a meaningful collaboration to happen under existing legal and regulatory frameworks. Importantly, the process of finding consensus on the regulatory

[2] In some regions, the application is approved by the relevant regulatory body based on the assessment outcome of the associated participating regulatory authority. For example, in the EU system the EMA's Committee for Medicinal Products for Human Use (CHMP) conducts the scientific assessment of marketing authorisation applications and the modifications or extensions ('variations') to an existing marketing authorisation and issues an Opinion, recommending the granting (or refusal) of the application to the European Commission (EC). The EC, based on the Opinion of the CHMP, issues the Decision to grant a Marketing Authorisation, or a modification or an extension thereof, which is legally binding to all EU Member States.

data expectations or requirements was not achieved simply through inclusion of all questions or IRs from all regulatory authorities, rather through the process in which assessors from different regulatory authorities applied and agreed on a science- and risk-based approach. This collaborative effort resulted in an overall 25% reduction in the number of IRs, compared to what would have been the case had the applications been submitted separately to each regulatory authority. Therefore, participation in the pilot did not result in any increase in regulatory burden for the industry applicants, and it was a valuable experience for regulators to help building further convergence in assessment practices and/or approaches.

In some instances, a small number of regional-specific technical IRs were raised and were indicated to the applicants. There were also a small number of administrative, regional-specific IRs related to issues such as regional application forms and GMP documentation. Of all region-specific IRs, 60% were related to administrative issues. Importantly, these region-specific questions would be addressed in the PACMP implementing Step 2 submission and did not impact the PACMP assessment timelines.

On completion of each application, comprehensive feedback was gathered from all participants via a survey. The survey results indicated an overall positive experience, particularly among industry participants. However, the collaborative assessment process led to an increased workload for regulators, primarily due to the additional time required for discussions, knowledge exchanges, and reaching consensus among the assessors, as well as project management to coordinate application assessment among multiple regulatory authorities.

Based on the positive feedback from regulators and industry, it is proposed to extend the pilot to take additional submissions and broaden its scope to cover more types of products for a period of 12 months (starting in the beginning of 2025). Given the resource requirements for such collaborative assessments, future collaborative assessments should prioritise high-impact changes for medically important treatments and applications which will have a positive impact on medicine supply and support manufacturing innovations that could also strengthen medicine supply.

2. Introduction

2.1. Overview of global post-approval CMC changes

Post-approval CMC changes are critical to promoting manufacturing innovation and continual improvement, as well as ensuring the continued global availability of medicines to patients. Post-approval changes can encompass a wide array of areas, including the introduction of new manufacturing sites, changes in the manufacturing process, adoption of new testing methods, changes to specifications, among others. Depending on the nature of the change, supporting data may need to be evaluated by the relevant regulatory authorities before the change can be implemented on the market. However, each regional authority may have different data expectations or requirements, assessment approaches, and approval timelines. Consequently, it may take several years before a single modification to a medicinal product can be implemented globally, leading to logistical challenges and the necessity for manufacturers to maintain multiple product versions. This regulatory complexity poses a significant burden on the pharmaceutical industry. Furthermore, the protracted global regulatory approval times represent a risk to global availability and timely supply of critical medicines to patients.

2.2. The role of ICMRA

During the July 2021 ICMRA-industry virtual workshop on enabling manufacturing capacity in the COVID-19 pandemic, collaboration in the assessment of post-approval changes was identified as a key enabler in supporting the increase manufacturing capacity of critical COVID-19 related vaccines and therapeutics. Following this workshop, ICMRA established a working group to explore ways to enhance cooperation among global regulators. This group proposed to the ICMRA Executive Committee to run a pilot programme for collaborative assessment of post-approval CMC changes. The focus of the pilot was on PACMPs since they outline agreed-upon plans for future changes. This allowed the collaborative assessment to focus on a science- and risk-based approach for implementation of post-approval manufacturing changes, based on the already approved quality standards specific to each region. The ICMRA Post-approval Change (PAC) Sub-Working Group oversaw the establishment, implementation, and operation of the collaborative assessment pilot.

3. Project Scope and Objectives

The primary aim of the pilot was to enable industry participants or sponsors to submit the same CMC submission for simultaneous assessment by multiple regulatory authorities under their existing regulatory procedures in a collaborative and coordinated manner. At the outset, the regulatory authorities involved committed to deliver a commonly agreed set of communications for the applicant and to reach a single and harmonised assessment outcome, supporting the regulatory decision across regulatory authorities on or around the same time. It was agreed to share and discuss IRs between participating authorities prior to external communication with applicants. Although the pilot initially targeted COVID-19 therapeutics, it later broadened its scope to encompass other critical medicines.

The objectives of the pilot were as follows:

- Deliver collaborative and harmonised assessment outcomes based on science- and risk-based approach 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 to global markets.
- Develop a process that enables collaborative assessment within the regional regulatory procedures for post approval CMC changes.
- Identify best practices and standards 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 impact to public health.

The fundamental principle guiding all these objectives was to ultimately facilitate increased patient access to critical medicines.

4. Applications received and criteria for acceptance into the pilot programme

The call for applications was opened in July 2022, and fourteen proposals were received in total. The applications covered a range of post-approval changes, and an overview is provided in Table 1. The most frequently proposed changes included the addition of new manufacturing sites for both drug substance and drug product. Other proposed changes included addition of new QC testing sites, change to primary packaging, alternative source of container closure, increase in drug product manufacturing scale, and change to QC testing methods.

Table 1. Overview of the applications received

Application number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Addition of DS manufacturing site							x				x	x		
Addition of DP manufacturing site	x		x		x	x	x			x				
Addition of QC testing site							x			x				
Change to manufacturing process				x										
Change to primary packaging														x
Alternative source of container		x												
Increase in DP manufacturing scale													x	
Change to QC testing								x	x					

Applications were prioritized based on perceived impact, considering, factors such as the impact on supply of critical medicines, the potential for an agreed assessment outcome, the proposed number of regions involved, and existence of confidentiality agreements between Regulatory Authorities. In total, six applications were accepted; however, one application was subsequently withdrawn by the applicant prior to formal submission.

5. Overview of the accepted applications

Details of the participating companies, and regulatory authorities for the five accepted applications are shown in Table 2.

Table 2. Participating sponsor companies and regulatory authorities

Applicant	Lead Authority	Participating Authorities	Observers
AstraZeneca	FDA	EMA	PMDA, Health Canada, HSA, ANVISA
Gilead	FDA	EMA, MHRA, Swissmedic	Health Canada
Merck Healthcare KGaA	PMDA	FDA, EMA, MHRA, Swissmedic	HSA, Health Canada, TGA
MSD	EMA	FDA, PMDA, Health Canada	HSA, Swissmedic

Roche	EMA	FDA	PMDA

The products included two small molecules, two monoclonal antibodies and an antibody drug conjugate (ADC). The indications for these products included several cancer and orphan indications. The post-approval changes covered the following areas: new manufacturing sites, new quality control testing sites, and changes to the drug substance manufacturing process. The number of regulatory authorities involved ranged from three to eight, and included EMA, FDA, PMDA, Health Canada, Swissmedic, MHRA, ANVISA, TGA, and HSA.

6. Development of the collaborative assessment process

A new international regulatory process, which could be embed within the existing regional processes, was developed to facilitate the collaborative assessment involving multiple regulatory authorities. At the start of the process, the sponsor submitted a proposal to the ICMRA PAC Sub-Working Group using a dedicated ICMRA email address. Each submission was triaged, discussed with the sponsor and considered for inclusion in the pilot programme based on the factors described above. The regulatory authorities involved in each pilot were selected based on several factors, including proposals from the sponsor, expected impact of the change, the overall number of participants and observers, and the availability of confidentiality agreements between the regulatory authorities.

To facilitate the collaboration in the assessment and maximize its efficiency and effectiveness, the assessment activities of each application was coordinated by a lead regulatory authority (see below for details on its responsibility), with scientific evaluation conducted by all participating regulatory authorities. Observing regulatory authorities could join in regulator meetings as observers and have access to the documents being reviewed but did not participate in the assessment. Assessors or an assessment team from each participating regulatory authority was assigned or formed, respectively, as per regional procedures and supported by a project manager from the respective participating regulatory authority. Once the relevant administrative checks were performed by each participating regulatory authority, the application was formally accepted into the pilot programme and the applicant was notified of the PAC Sub-Working Group decision. Each applicant then signed a Sponsor Authorization Letter with each participating and observing regulatory authority, which facilitated the sharing of information between the regulatory authorities. In all cases, the same CMC information was submitted to each regulatory authority through the established regional channels, and no issues with confidentiality were encountered as the applicant provided permission in writing allowing the regulatory authorities to exchange trade secret and confidential information for that product and manufacturing process.

A first key requirement for the success of the pilot was to reach agreement on a harmonised assessment timetable which could be adopted by all participating regulatory authorities. Given the differing legal and regulatory processes in the various regions, development of an agreed synchronised timeline that contained key milestones was a considerable challenge. Nonetheless, it was possible, for the first time, to agree on a standardised timetable among all regulatory authorities. This standardized timetable offered clarity and predictability to industry stakeholders while providing a structured framework for more coordinated regulatory evaluations. A 120-day schedule with interim milestones was developed, outlined in Table 3.

Table 3. Timetable for collaborative assessment

ACTIVITY	TIMELINE
Submission Receipt Date	Day 0
Project Start	Day 0
Collaborating assessment teams meet to develop IRs	Day 20 - 100
IRs sent to Applicant	Day 20 - 100
Receipt of applicant responses	Response timeline agreed between regulatory authorities and applicants
Collaborating assessment team review applicant's responses	Assessment timeline defined by the Lead Authority
Draft Quality Assessment report by Lead Authority	Day 106
Final/Action Letter / Opinion Issued and shared with applicants via established regional processes	Day 120

The lead authority coordinated all activities, including leading project calls and consolidating and streamlining IRs. Following the regulatory submission, each regulatory authority carried out the initial filing validation check or completeness assessment as per their own standard regional procedure. Each participating regulatory authority conducted its own independent assessment and shared and discussed its assessment findings (e.g., IRs) with the other authorities to reach consensus. Observing regulatory authorities could join all discussions in a listening mode, but not actively participate.

To facilitate communication with the applicant, the agreed IRs were sent to the applicant from the Lead Authority between Day 20 and Day 100 using a "rolling review" style assessment approach. While multiple rounds of queries were permitted, the assessment was required to conclude within 120 days. Before IRs were sent to applicants, the assessors or assessment teams from participating regulatory authorities held a dedicated teleconference to discuss all IRs and work toward a harmonised list of IRs where possible. Collaboration was facilitated through a dedicated Microsoft Teams Channel.

A date for submission of responses was agreed with each applicant, and the assessment of the responses was discussed among the assessors or assessment teams from participating regulatory authorities, with further IRs issued as necessary again in an iterative and coordinated manner. Once all IRs were satisfactorily addressed, all the participating authorities reached a final consensus on the assessment outcome and communicated to the applicant. This assessment outcome was then used for the regional decision making as per existing procedures.

This new international regulatory process allowed effective cross-regional collaboration and coordination in the assessment while the relevant regulatory procedures were running as per the regional frameworks except for the agreed duration of the assessment period to be 120 days (e.g., under current EU regulations, EMA must issue a formal list of questions by Day 60). Each participating regulatory authority adjusted its internal assessment timeline, when necessary and permissible, to align with the ICMRA collaborative assessment timeline (e.g., PMDA adjusted their assessment timeline to accommodate 120 days, see below for details), while also adhering to their region-specific requirements or procedures, such as internal clearance processes, adoption by Scientific Committees, etc.

7. Key findings and pilot evaluation

7.1 Adherence to timelines

The potential for a harmonised assessment timeline was a key goal of the pilot. All pilot applications were successfully completed within 4 months, and the duration of each pilot case ranged from 105 - 122 days (Table 4). This is within standard timelines for several international regulatory authorities such as EMA and FDA and highlights that participation in the collaborative assessment pilot did not result in approval times over and above what would be expected in a single region submission. It is noteworthy that PMDA significantly reduced the typical 12-month approval timeline for Standard Review Supplements for biologics to accommodate participation in the pilot.

For three of the applications, same day Approval/Opinion was also achieved among the participating authorities. Notably, in one case, all five regulatory authorities approved/ issued an Opinion for the application on the same day (see Table 4). In one of the pilots, four participating authorities approved/ issued a positive Opinion for the application within two days of each other. In another pilot, three of the participating authorities granted same-day approval/ issued a positive Opinion, while the fourth authority approved/ issued a positive Opinion within 12 days due to workload demands and internal clearance procedures.

Table 4. Duration of the pilot applications

Pilot	Submission date	Completion date	Overall duration (days)	Max difference in Approval/Positive Opinion dates between participating authorities
Pilot 1	Jan 2023	May 2023	115	Same day
Pilot 2	Jun 2023	Oct 2023	118	Same day
Pilot 3	Nov 2023	Feb 2024	105	Same day
Pilot 4	Sep 2023	Jan 2024	122	2 days
Pilot 5	Jan 2024	May 2024	119	12 days

7.2. Harmonisation of information requests

For each pilot application, between two to five meetings took place where the assessors or assessment teams from participating regulatory authorities strived to agree on a harmonised list of IRs. A harmonized template was developed to facilitate sharing and agreement of IRs. Active discussions between the regulators enabled consolidation of related questions and agreement to delete some questions based on a science and risk-based approach. It also facilitated a harmonised approach to assessing the applicants' responses. Based on the initial number of IRs proposed by each regulatory authority, discussion meetings between the participating authorities resulted in an average 25% reduction in the number of IRs. This reduction was due in part to related IRs from different regulatory authorities being harmonized, but importantly some of this reduction was also due to IRs being removed following discussions. Therefore, the number of IRs was not merely a reflection of the cumulative questions from all regulatory authorities but a true harmonised and streamlined list of questions agreed among all participating authorities. This data clearly highlights that rather than collaborative assessment leading to an increase in the number of

IRs, discussions between regulatory authorities can facilitate a reduction in the number of IRs, highlighting the benefit of the discussions and information sharing between regulatory authorities and setting a foundation for more potential convergence in assessment practices and/or approaches.

The harmonised IRs raised across the five pilot applications spanned various aspects of Module 3 information. The IRs were categorised based on the nature of the question and the section of the Module 3 dossier as indicated in Table 5. Harmonized IRs were achieved in areas such as comparability, stability, control strategy, process validation, and others. The successful alignment of IRs between multiple regulatory authorities across a broad spectrum of CMC areas clearly highlights the effectiveness of the collaborative assessment.

Table 5. Areas of successful regional harmonisation and associated number of IRs

Question area	No. harmonised IRs
Comparability	26
Stability	8
Reporting category	7
Control strategy	4
Process validation	4
Analytical methods & validation	3
Method transfer	3
Viral safety	3
Administrative	2
Container closure	2
Impurities	2
Manufacturing site details	2
Specifications	2
Batch traceability	1
Equipment details	1
Extractables & leachables	1
Sterility assurance	1
Transport validation	1

An analysis of the number of IRs from the five applications showed that 88% of all assessment related IRs were harmonised among all participating regulatory authorities. Of the remaining 12% of the assessment related IRs which were region-specific (10 questions across 5 applications), 5 questions were related to requirements for method transfer. This highlights regulatory data requirements for method transfer as an area which may benefit from further global alignment efforts. The remaining 5 region-specific IRs included requirements for nitrosamines risk assessment, additional batch data requirements, transport validation, and process validation. In addition, there were some regional-specific administrative questions regarding issues such as regional application forms and GMP documentation requirements. These regional-specific administrative questions were not considered to represent a lack of harmonization in assessment, but rather are reflective of certain regional legal requirements for application documentation.

Table 6. Numbers of harmonised and region-specific information requests

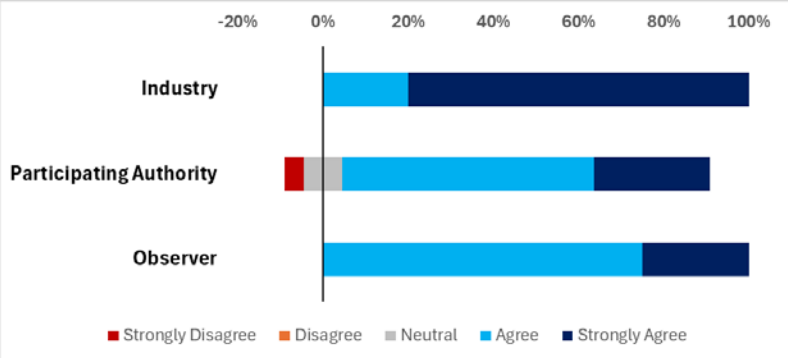
Pilot	#harmonised assessment related IRs	#region-specific assessment related IRs	#region specific administrative IRs
Pilot 1	46	4	3
Pilot 2	7	2	1
Pilot 3	3	0	3
Pilot 4	5	3	2
Pilot 5	12	1	6

7.3. Survey results

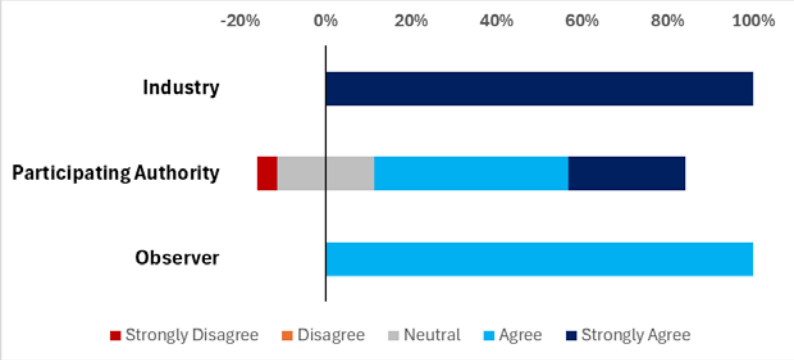
Following the completion of each of the five pilots, a survey was sent to each participating company and regulatory authority. The survey used a five-point Likert scale, ranging from strongly agree to strongly disagree. The results are presented visually with the following colour codes: strongly agree (dark blue), agree (blue), neutral (grey), disagree (orange), and strongly disagree (red). The percentage of responses in each category is shown below with graphs centred on the x-axis around neutral responses. Positive responses (strongly agree, agree) are displayed to the right of the centre, while negative responses (disagree, strongly disagree) are displayed to the left of the centre. There were 5 industry responses, 22 responses from participating authorities (including responses from assessors/reviewers and project managers), and 4 responses from observer authorities. The survey questions addressed five general categories (1) overall pilot satisfaction, (2) operational outcomes, (3) resource requirements, (4) clarity and communication, and (5) regulatory interaction, and are discussed in turn below.

Overall pilot satisfaction

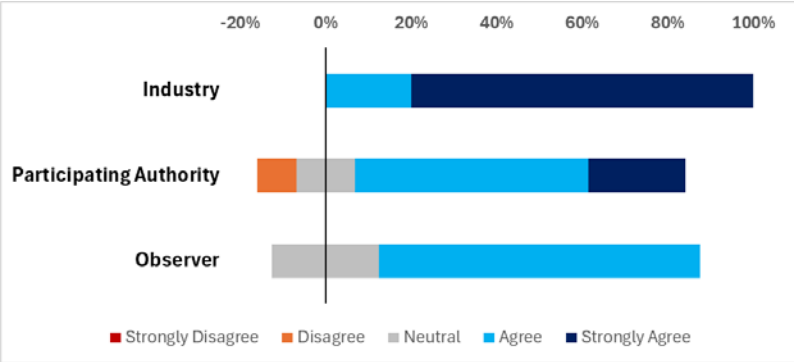
Question 1. The overall experience of the participation to the pilot is considered positive and support its operationalisation into a global regulatory program.



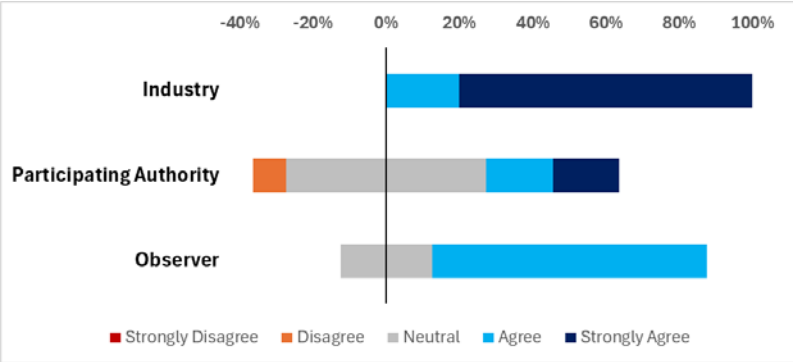
Question 2. Would you consider participation in the future?



Question 3. Do you feel the collaborative pilot process could develop into a global regulatory programme?



Question 4. Overall, do you feel participation in the pilot had a measurable impact on public health and/or availability of medicines on the market?



Industry respondents reported a high level of overall satisfaction with the pilot. All industry respondents agreed that their experience was positive and expressed willingness to participate in future pilots. Similarly, all industry respondents agreed that the pilot has the potential to evolve into a global regulatory programme enabling future collaborative CMC assessments under regional procedures. This strong positive feedback highlights the industry participants' endorsement of the collaborative assessment process and their recognition of the positive outcomes from the pilot. While it is acknowledged that this data represents the viewpoint of only five pharmaceutical companies, considering the industry's strong emphasis on pursuing global regulatory reliance, particularly regarding lifecycle management, it is reasonable to anticipate that this positive

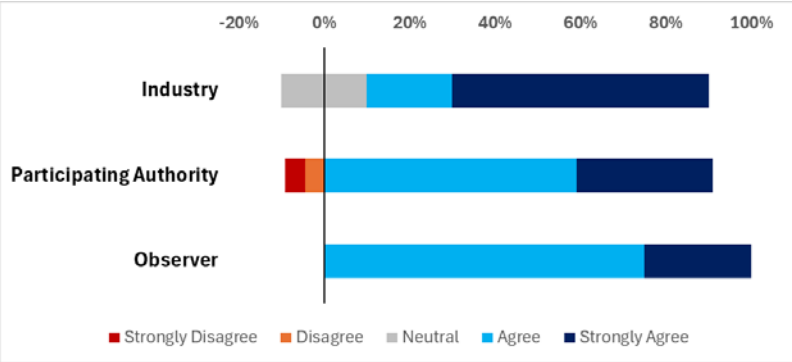
sentiment would extend to other pharmaceutical companies if they were to participate in future collaborative assessments.

The feedback from regulators, while generally positive, did not reach the same level of enthusiasm as that from industry respondents. Specifically, 86% of participating regulatory authority respondents either agreed or strongly agreed that the overall experience was positive. Additionally, 73% expressed agreement or strong agreement regarding their potential participation in future pilots. Interestingly, 100% of observer regulatory authorities provided a positive response to this question. The difference in the overall positive experience between participating and observing authorities may be attributable to differing implications for resource allocation, as indicated in question 9. Surprisingly, 23% of the participating authorities were neutral or disagreed that the collaborative pilot process could develop into a collaborative regulatory assessment programme. The reason for this hesitancy is unclear. However, it may reflect the assessors' unfamiliarity with the program's aims and its potential benefits for patients. Additionally, concerns may include unclear expectations, new processes (such as IT support tools), increased resource demands, and the added effort required to achieve consensus among a larger group of assessors in this pilot program. This suggests that any future considerations for pilot extension or expansion need to balance the effort from regulatory authorities versus the expected benefit for patients.

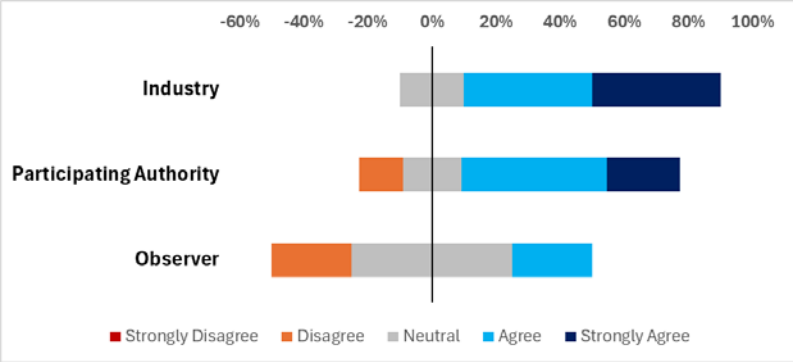
All industry respondents agreed that participation in the pilot had a measurable impact on public health and/or availability of medicines. However, over half of participating regulatory authority respondents gave a neutral response to this question. Industry respondents are likely to have a more comprehensive understanding of how their participation in the pilot influenced the availability of the medicines which they manufacture. Such insights into individual supply chains might not be immediately evident, which may be a factor in the differing responses between industry and regulators. In addition, industry can readily see the benefit of simultaneous approval of their CMC post-approval change submission by multiple regulatory authorities, which can dramatically reduce the uncertainty regarding the implementation timeline for these CMC changes across different regions. Future collaborative assessment initiatives could explore gathering additional data on the impact of collaborative assessment or reliance strategies on medicine availability. These data could prove valuable when advocating for investment of resources in future global collaborative assessment activities and could help define the scope of such initiatives to maximise the positive impact for patients.

Operational outcomes

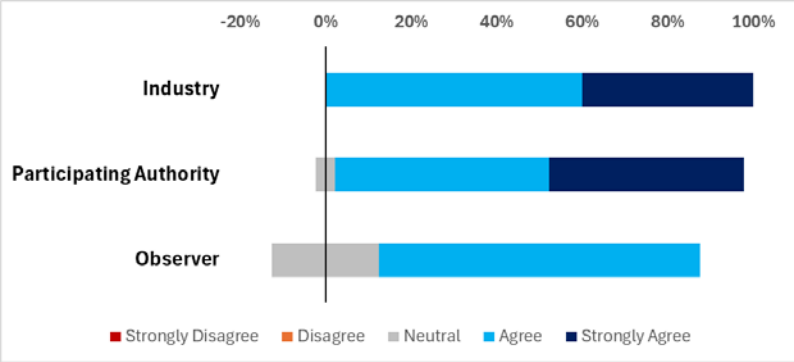
Question 5. It was possible to utilize a harmonised assessment timetable agreed between all participating authorities, including agreed interim dates for sending lists of questions/IRs.



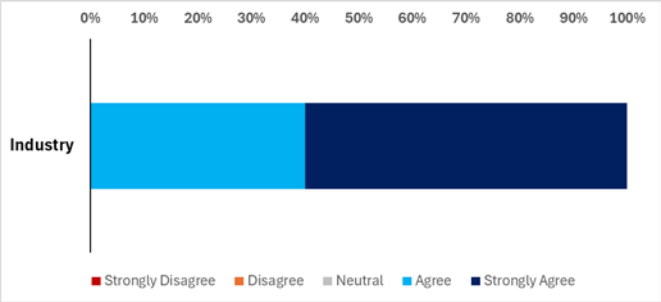
Question 6. Participation in the pilot did not lead to an overall increase in regulatory expectations for Sponsors, compared to standard requirements.



Question 7. The final decisions were transparent and there was a clear and documented rationale behind the regulatory decision made.



Question 8. Participation in the pilot did not have a negative impact on standard or expected approval times.



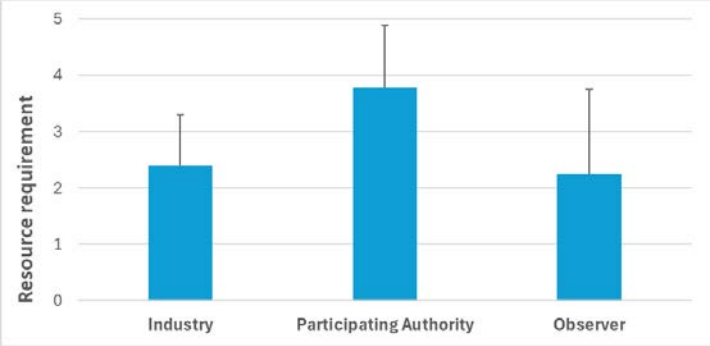
Eighty percent of industry respondents, 91% of participating regulatory authority respondents, and 100% of observers agreed that a harmonised assessment timetable could be established between all participating authorities. Nonetheless, several comments were raised from industry respondents highlighting challenges in this regard. All regions must still adhere to their legally mandated assessment milestones, making it difficult in some cases to seamlessly integrate these dates into the collaborative assessment timetable. Industry stakeholders emphasized the importance of having a single agency communicate the timetable instead of each participating agency doing so independently, specifically highlighting this as an area requiring improvement. These challenges

underscore the need for future efforts to further streamline the collaboration process including timelines.

Collaborative assessment inherently involves multiple global regulators raising IRs which are then discussed between the assessors or assessment teams from participating regulatory authorities. There was an initial concern that this process might inadvertently elevate the standard requirements in each region, with the strictest requirements from one participant becoming the norm. However, according to industry feedback, this has not been the case. Eighty percent of industry respondents agreed or strongly agreed that participation in the pilot did not result in an overall increase in regulatory expectations for sponsors compared to standard requirements. Moreover, all industry respondents confirmed that participating in the pilot did not adversely affect standard or expected approval times. In contrast, 68% of participating authorities and 25% of observers either agreed or strongly agreed that there was no increase in regulatory expectations. The majority of respondents concurred that the final decisions were transparent, with a clear and documented rationale behind the regulatory decisions made. Such transparency and open decision-making are crucial for the success of any future collaborative assessment initiatives.

Resource requirements

Question 9. What was the resource requirement needed to participate on the collaborative assessment? Rate on a scale from 0 to 5, with 0 = no additional resources and 5 = Significantly more additional resources.



Question 10. Did the benefits (if any) in terms of addressing the stated objectives of the pilot outweigh any additional resource requirements?

	% Respondents who answered yes
Industry	100%
Participating Authority	95%
Observer	100%

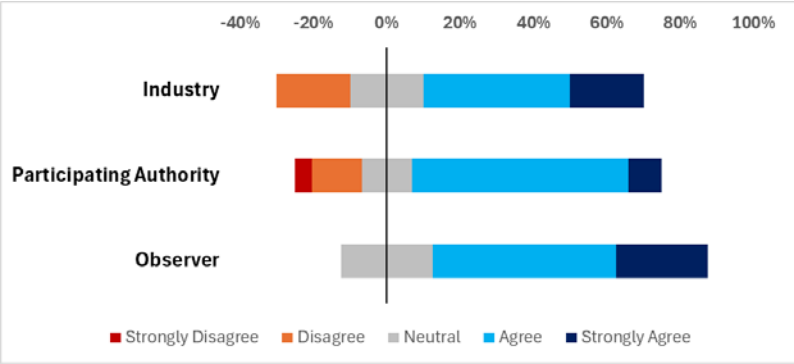
Participation in the pilot required increased resource commitment for all participants. However, there was a notable contrast in the additional resource needs between industry and participating authorities. On a scale from 0 to 5 (0 being no additional resources and 5 being significantly more additional resources), the average resource increase required for industry was 2.5, compared to

3.8 for participating authorities, with observers averaging 2.3. This aligns with feedback from the assessors or assessment teams from participating regulatory authorities, who estimated that completing a collaborative assessment took approximately twice as long as a standard submission. This increase in resource requirements can be attributed to (1) the time to learn and understand the logistics due to the novelty of the pilot, (2) lack of effective IT tools for information sharing and conducting collaborative assessment, (3) the need for a dedicated project management to coordinate assessment related activities and communications between the participating regulatory authorities and between the participating regulatory authorities and company, (4) the need for several discussion meetings to consider input from all participating regulatory authorities, which included an initial meeting with applicants, as well as (5) multiple teleconferences between the assessors or assessment teams from participating regulatory authorities throughout the assessment process. However, as the pilot program progressed, improvements were observed. Communication channels between the regulatory assessors or assessment teams from participating regulatory authorities were further streamlined, leading to greater efficiency during the initial assessment period.

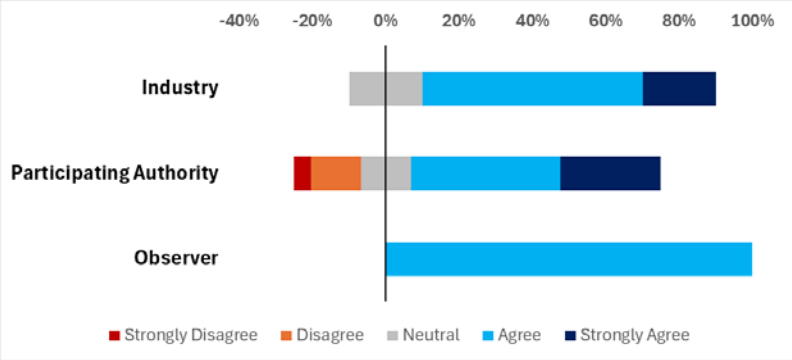
It is important to highlight that regardless of the increase in resources, greater than 95% of all respondents agreed that the benefits of the pilot outweighed any additional resource requirements. Nonetheless, the additional resource burden for regulators should be considered when determining the scope and any next steps for the collaborative assessment initiative.

Clarity and communication

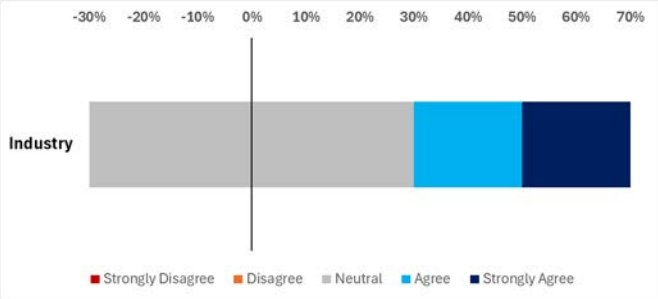
Question 11: Sufficient guidance was provided in the preparation phase of the submission (e.g., regarding procedural and practical aspects of the submission.



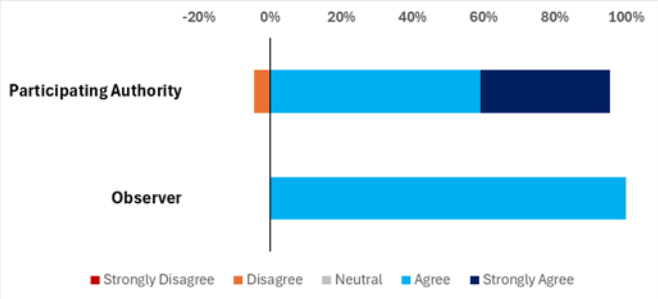
Question 12: Communication from participating authorities was timely and efficient. There were no significant delays in communication which impacted on assessment activities or agreed timelines.



Question 13. There was sufficient clarity from beginning to the end, regarding next steps and expectations regarding submission format, content and submission requirements.



Question 14. All participating authorities actively engaged in communication to find consensus when misalignments were identified.



Sixty percent of industry respondents, 68% of participating authority respondents, and 75% of observers agreed or strongly agreed that sufficient guidance was provided during the preparation phase of the submission. The preparation meetings held between applicants and the assessors or assessment teams from participating regulatory authorities were highlighted as being particularly beneficial in setting clear expectations for the process. Industry respondents emphasized the desirability of a common IT platform, citing potential time savings for both applicants and

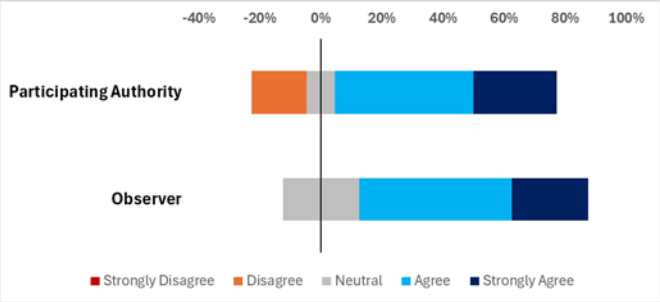
regulatory authorities. Additionally, one industry respondent suggested that a written procedure for applicants or FAQs on the process would be helpful. Another industry respondent stated that confirmation on the lead, participating, and observer authorities one month prior to the start of the procedure did not give sufficient time to coordinate the submissions. Some regulators expressed the need for a clearer understanding of the procedure, timelines, and relevant documentation before commencing the assessment. Based on these survey responses it is recommended that future collaborative assessments prioritise the development of a clear procedure description, dedicated project management support, concise timelines, and an FAQ document.

Eighty percent of industry respondents, 68% of participating authorities, and 100% of observers agreed or strongly agreed that communication from participating authorities was timely and efficient, with no significant delays. However, when asked about the clarity regarding next steps and expectations regarding submission format, content, and submission requirements, 60% of industry respondents remained neutral. Several industry respondents highlight some initial uncertainty around timelines at the beginning of the procedure, and some respondents highlighted the benefit of having more detailed submission instructions. Procedures to improve the understanding around submission requirements and timelines should therefore be considered for future pilots.

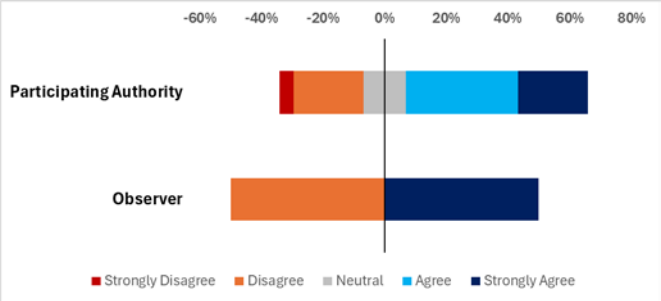
A significant majority of participating and observer authorities (>95%) confirmed that all participating authorities actively engaged in communication to reach consensus. This collaborative effort to discuss issues and find consensus among global regulators emerged as a key outcome from the pilots. It echoes the findings discussed above, where 88% of all assessment related IRs were harmonized. Such harmonization could only have been attained through active discussions and consensus-building among the global regulatory assessment team, which is a unique feature of the collaborative assessment pilot.

Regulatory interaction

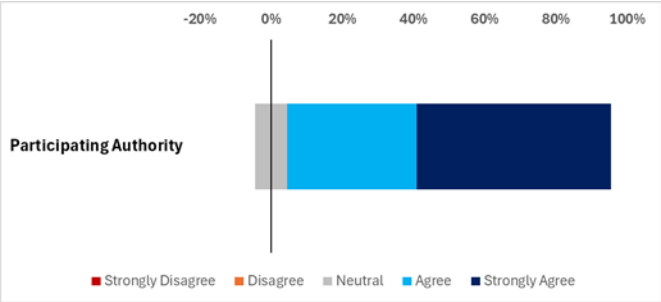
Question 15. The required confidentiality agreements were in place prior to the start of the collaborative assessment.



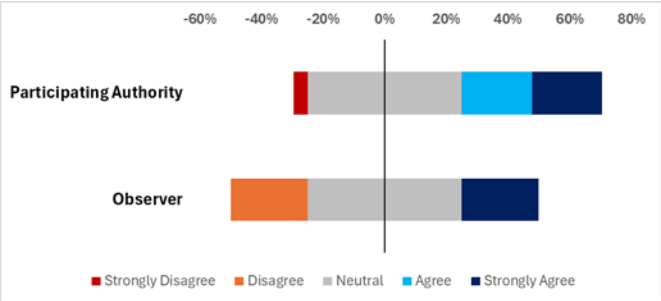
Question 16. It was possible to use a single IT platform for seamless information sharing among all participating and observing authorities.



Question 17. It was possible for all participating authorities to issue their final decision within a similar timeframe.



Question 18. Observing authorities were able to join in relevant discussions and derived benefit from participation.



Confidentiality agreements were required before the start of each assessment. This included the requirement for existing confidentiality agreements between regulatory agencies, as well as dedicated Sponsor authorisation letters granting permission for each participating and observing regulatory authority to discuss the submission amongst each other. The majority of participating and observer authorities agreed that the confidentiality agreements were in place prior to the start of the collaborative assessment.

Sixty percent of participating authorities and 50% of observers agreed or strongly agreed that utilizing a single IT platform for information sharing was feasible. The identified issues were primarily in relation to accessing the shared spaces used during the pilot (Microsoft Teams and SharePoint). Given that multiple regulatory authorities were involved in each pilot, with different CMC reviewers in each team, this necessitated arranging access for dozens of individuals. The

situation was further complicated by the varied IT systems used in each agency and the resulting security arrangements. It is evident from these observations that the future success of collaborative programs will require appropriate IT solutions.

The majority of participating authorities agreed that it was possible to issue their final decision within a similar timeframe. This was borne out by the official approval dates, where all participating authorities issued approvals within days of each other.

From the outset of the pilot programme, the role of observers was considered crucial to the overall impact of the pilot. By joining as an observer, even if a post approval change was not formally filed in their jurisdiction, observers still had the opportunity to be part of the collaborative assessment process and get a greater insight into how other regulatory authorities assessed these important post approval changes. Such interactions may be helpful in fostering a common global approach to CMC assessment. There was a mixed response from observers when asked when they were able to join in relevant discussions and derive benefit from participation. One observer authority stated that the open discussion was particularly informative in relation to downgrading of reporting categories and harmonization of decisions amongst regulatory authorities. However, other observers responded that the application documents and response to IRs were not shared among the observers. As the Sponsors were not formally submitting a post-approval change to those regions, the application documents were not formally sent to the observers from the Sponsors. In some instances, there were difficulties with observers accessing the required documentation in the shared platform. Based on the earlier pilot experience, it was possible for observers to access the documents in a pilot started at later stage. However, documentation sharing with observer participants in all applications remains a priority for future collaborative assessment.

7.4. Evaluation of the pilot success

To objectively evaluate the success of the collaborative assessment pilots, a number of key performance indicators (KPIs) were developed prior to the start of the pilot, considering the objectives of the pilot stated in Section 3. These KPIs reflect the key outcomes that signify the effectiveness and efficiency of the collaborative assessment processes. The evaluation of the KPIs outlined in Table 7 show that 14 out of 16 of were fully achieved, whereas two KPIs were only partially achieved. The successful completion of 88% of all KPIs points to the overall success of the pilot.

Table 7. Evaluation of pilot success based on agreed KPIs

KPI No.	Area	Agreed KPI	KPI achieved Yes/No/ Unclear?	Basis for answer
1.	Harmonised timetable for assessment	A harmonised assessment timetable could be agreed between all participating authorities, including agreed interim dates for sending lists of questions/IRs.	Yes	A 120-day timetable was established. Interim dates for sending IRs were agreed among all participating authorities.
2.	Efficient document collaboration	It was possible to use a single IT platform and common template for seamless information sharing among all participating and observing authorities.	Unclear	An MS SharePoint platform was used. However, some issues were noted with timely access for participants and observers.
3.	Pilot conducted according to agreed timeline	There were no delays in communication between all stakeholders (internal/external meetings, sending IRs) which impacted on assessment activities or agreed timelines.	Yes	All agreed timelines were met. Improvements in communication aspects has been highlighted as an area of further improvement.
4.	Quality of communication	Communication between all stakeholders was timely and efficient. The assessors or assessment teams from participating regulatory authorities could engage in active discussions to find alignments/misalignments. Any identified misalignments could be addressed to find a consensus.	Yes	While communication has been highlighted as an area of improvement, discussions were successful in agreeing harmonized lists of IRs through consensus.
5.	Consistency in decision making	Consensus was reached on a single list of questions/IRs (which may have included region specific questions but kept to at a minimum when feasible), and on a final decision.	Yes	All IRs sent to applicants were agreed by the assessors or assessment teams from participating regulatory authorities and a final harmonized decision was issued.
6.	Confidentiality arrangements	The required confidentiality agreements were in place prior to the start of the collaborative assessment. Confidentiality-	Yes	The confidentiality agreements were in place. While confidentiality issues in principle did not impact the assessment process, the

		related issues did not hinder any aspect of the assessment process.		requirement for inter-agency confidentiality agreements could limit future participation for some regions.
7.	Observer participation	Observer authorities were able to join all relevant discussions and derived benefit from participation.	Unclear	The experience of observers was mixed, and the benefit is currently not universally agreed. Progress was made as improvements were implemented based on early pilot experience. However, this is an area highlighted for future improvement.
8.	Identification of focus areas	It was possible to identify areas of divergence for future harmonisation activities.	Yes	Areas of divergence included the requirements for analytical method transfer. Future harmonization of the requirements for method transfer could be considered.
9.	Impact on workload	The benefit derived from participation in the collaborative assessment outweighed any increases in resource requirements.	Yes	The workload was significantly higher for regulators compared to applicants under this pilot. However, there was broad agreement that the benefit to public health outweighed the increased resource requirements.
10.	Knowledge sharing	There was effective sharing of knowledge and best practices among the assessment teams.	Yes	The assessment teams engaged in active collaboration and information sharing.
11.	Impact on approval times and regulatory burden	Participation in the pilot did not have a negative impact on standard approval times or lead to an overall increase in regulatory expectations for Sponsors compared to standard requirements for individual regulatory authority submissions.	Yes	All applications were approved with a standard 4-month timetable. No notable increases in regulatory expectations were seen.
12.	Simultaneous final decisions	It was possible for all participating authorities to issue their final decision within a similar timeframe.	Yes	Approvals were issued within days of each other.

13.	Quality, and transparency	The final decisions were transparent and there was a clear and documented rationale behind the regulatory decisions made.	Yes	There was full transparency among the assessors or assessment teams from participating regulatory authorities.
14.	Pilot extension feasibility	The pilot cases provided sufficient data to inform the decision whether or not to develop the process into a collaborating regulatory pathway within the regional procedures.	Yes	Despite the limited number of pilot cases, which is acknowledged, the pilot has yielded useful insights which can be invaluable in developing a global collaborative assessment programme.
15.	Stakeholder satisfaction	Industry and regulatory authority participants were satisfied with how the process was managed.	Yes	Overall, there was broad satisfaction, albeit several areas were highlighted for future improvement.
16.	Impact on public health	Participation in the pilot had a measurable impact on public health and/or availability of medicines on the market.	Yes	100% of industry participants indicated that the pilot had a positive impact on public health.

8.0 Conclusions

The ICMRA collaborative assessment pilot successfully completed five applications across a range of products and post-approval changes. Multiple participating and observing regulatory authorities were involved throughout the course of the pilot. For the first time, a standardised assessment timetable was developed, which facilitated collaboration, and coordination among the assessors or assessment teams from participating authorities and provided clear milestones for applicants under existing regional legal frameworks. Consensus on data expectations to support quality assessment and regulatory decision making was achieved across numerous areas of CMC, and participating regulatory authorities successfully agreed on harmonized IRs, with a small number of region-specific requests. All approved changes related to manufacturing capacity increase.

In each case, achieving the above outcome required several discussions between the assessment teams from the participating regulatory authorities and leadership from the ICMRA project team. These discussions occasionally challenged regional assessment practices or approaches from a science and risk perspective. This process ensured that the final list of IRs was not simply a compilation of questions from all participating authorities, but a carefully refined list of harmonized IRs. There was a broad agreement that participation in the pilot did not add regulatory burden to industry participants. However, there was a notable increase (almost double) in the resource needed for regulators, partly due to the need for increased interactions to consider feedback from all participating regulators and partly for technical reasons due to the absence of IT tools that would enable an efficient collaboration. Each application was completed within an agreed 4-month timetable. In each case, the applications received same day approval/Opinion from the participating authorities or were approved/given a positive Opinion by the participating authorities within a few days of each other.

The evaluation of KPI success metrics and survey analysis confirmed that the pilot program achieved its stated objectives, clearly demonstrating the benefits of collaboration among global regulators. The pilot has successfully demonstrated that it is possible for global regulators to reach harmonised scientific outcomes within 120 only days within the existing regulatory framework of each participating regulatory authority. Such timely outcomes can have a positive impact on medicines supply and availability, as it allows manufacturers to implement faster manufacturing changes to increase capacity and thus respond with more agility to increased market demands or disruptions of global supply chains.

Given the resource requirements for such collaborative assessments, future collaborative assessments should prioritise high-impact changes for medically important treatments and applications which will have a positive impact on medicine supply, and support manufacturing innovations that could also strengthen medicine supply.