IMPLEMENTATION PLAN
ICMRA Pilot Program for Collaborative Assessment of COVID-19 Related CMC Post-approval Changes

1. INTRODUCTION

Following the July 2021 ICMRA-Industry virtual workshop on enabling manufacturing capacity in the COVID-19 pandemic,[1] ICMRA is commencing a pilot program for collaborative assessment with initial focus on chemistry, manufacturing, and control (CMC) post-approval changes that help to improve manufacturing capacity for production of critical medicines during COVID-19. The pilot program will allow for collaborative assessment of the same post-approval changes by multiple regulatory authorities simultaneously. It is envisioned that the pilot will:

- Allow industry participants (or sponsors) to submit a single submission with proposed CMC changes for assessment by multiple regulatory authorities.
- Strive to deliver a shared set of communications (e.g., a common set of information requests, comments, or questions for a participating manufacturer) and a single regulatory decision regarding the joint assessment.
- Identify both commonalities and differences among regulatory authorities in working towards a common assessment approach.
- Serve as a starting point for future international convergence of regulatory actions.

2. OBJECTIVES

- Develop and share an initial framework for collaborative assessment, which provides a platform for multiple regulatory authorities to participate in a collaborative assessment of post-approval CMC changes, with an initial focus on *post-approval change management protocols (PACMPs)* as described in chapter 4 of ICH Q12.
- Identify best practices and standards in the quality assessment of CMC post-approval changes
- Identify misalignments, differences, and potential areas for alignment or harmonization across regions
- Provide collaboration and engagement opportunities for industry participants who are interested in global engagement and multi-region filing
- Build upon and improve the communication, collaboration, and convergence framework between different regulatory authorities

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

3. PILOT PROGRAM OVERVIEW

The objective of the pilot is for multiple regulatory authorities to assess the same post-approval changes simultaneously. Once the submission is received from a sponsor, it is envisioned that participating regulatory authorities will collaboratively assess the submission information in a coordinated manner within an agreed timeframe *(see Section 5 for details)*. Participation in this pilot should not cause any additional delays in assessment timelines. The following describes general expectations of this pilot for the participating regulatory authorities.

- To ensure feasibility of the pilot, it is foreseen that **a small number of regulatory authorities, consisting of 3-5 with some regulatory authorities participating as an observer**, will participate in such collaborative quality assessments, which can then be extended as more experience is gained. For the first three applications of the pilot, the regulatory authorities or organizations of ICMRA Organizing Working Group (OWG) members (i.e., FDA, EMA, HPRA, and PMDA/MHLW) will participate and form an *assessment working group* for collaborative assessment. Depending on the nature of proposed applications by industry, additional regulatory authorities may be invited as either an active participant or observer, as appropriate.
- Based on the framework developed by and agreed among the participating regulatory authorities and with established **mutual confidentiality agreements**, the quality assessors from these regulatory authorities will meet to discuss their assessments and make the best of effort to align their risk- and science-based assessment approaches. This effort aids to minimize or eliminate the need for regulatory authorities to generate multiple, independent lists of comments and questions. The sponsor's responses will be shared between the participating quality assessors who will work towards a common approach to the application assessment and decision making.
- Nonetheless, under the collaborative mechanism, it is foreseen that some participating regulatory authorities may need to issue information requests specific to their region. In this situation, their information requests would be shared and discussed with the other regulatory authorities to minimize these additional requests whenever possible, as well as to ensure that they are fully justified (e.g., due to regional requirements imposed by regulations, laws, or user fee commitments), prior to communication with the applicant through the lead participating regulatory authority (see below). This mechanism is expected to provide the necessary flexibility while remaining **committed to apply the same risk- and science-based approach and work toward generating a single outcome across regions, if possible**.
- The duration of the pilot will be approximately one year, which may be extended based on ICMRA members' interest. During this period, the goal is to run collaborative quality assessment for no more than three applications**. Ideally, the first application should focus on CMC post-approval changes utilizing a PACMP, in which the participating regulatory authorities have prior experience in assessing these changes**. All applications will be selected based on interest and potential for convergence *(see Section 4 for details)*.

- The scope of the pilot will focus initially on **COVID-19 related CMC post-approval changes**.[2] Other **post-approval changes for non-COVID-19 related products (e.g., PRIME or Breakthrough) that are deemed critical by the participating regulatory authorities** may also be considered for inclusion in the pilot.

4. CRITERIA FOR POTENTIAL APPLICATIONS

The pilot program will initially focus on COVID-19 related post-approval changes that are considered a high priority for multiple regulatory authorities or post-approval changes of other types of products that are deemed critical by the participating regulatory authorities. CMC post-approval changes subject to this pilot should include, among others, the priorities identified at the ICMRA-Industry virtual workshop. PACMP submissions are highly recommended because an agreement on a global protocol has the potential to be widely applicable.

As the pilot will focus on a small number of applications, it is essential that the most appropriate cases are chosen to deliver meaningful results. For the pilot to be successful, some conclusions of this pilot need to be shared in the public domain. The extent of the information which is made public can be agreed on a case-by-case basis between the participating regulatory authorities and sponsor. It is expected that at least a high-level summary should be published, which is similar to the level of information made available by regulatory authorities in public assessment reports.

The criteria for applications to be considered under this pilot are summarized below:

- The proposal should be based on planned CMC post-approval change(s). Products that are distributed under an emergency use mechanism and not a marketing application should not be considered. *Emergency use authorizations may allow for different flexibilities than approved marketing applications and thus, not be as useful in convergence for post marketing changes. This might be especially problematic when the product is approved under different mechanisms in different regions*.
- The proposal should focus on therapeutics (including both small molecule and biological products), which can include products intended for the treatment of patients with COVID-19, Breakthrough/PRIME products, or products deemed medically necessary/critical medicine. *Initially, vaccines will not be considered for this pilot.* However, they may be considered in the future if the pilot is extended.
- The submission should be intended to be submitted to multiple regulatory authorities at the same time.

[2] COVID-19 related post-approval changes can be referred to post-approval changes that help to improve manufacturing capacity for production of critical medicines during COVID-19 (e.g., manufacturing site changes).

- The submission should ideally involve an area where there is an opportunity for regulatory convergence.
- The same submission should be provided to all participating regulatory authorities.
- There should be no restrictions on sharing data among the regulatory authorities participating in the pilot.
- There should be agreement by the application holder to publicly share some high-level data and results of the collaborative assessment.
- Applicant representatives should be willing to participate in a virtual discussion meeting(s) to have open dialogues with regulators from multiple regions on technical and regulatory issues related to their applications.

5. COLLABORATIVE ASSESSMENT APPROACHES

In this pilot, the following approaches will be followed to guide the collaboration among the participating regulatory authorities and their interactions with industry in delivering *one quality voice* to the sponsor of each of three regulatory applications related to CMC post-approval changes:

- For the first three applications of the pilot, the regulatory authorities or organizations of ICMRA Organizing Working Group (OWG) members (i.e., FDA, EMA, HPRA, and PMDA/MHLW) will participate and form an *assessment working group* for collaborative assessment. Depending on the nature of proposed applications by industry, additional regulatory authorities may be invited as either an active participant or observer as appropriate. For EU the assessment will be performed by the Rapporteurs team. The participating regulatory authorities will work with each other and the regulated industry under OWG's guidance to develop and implement a process to solicit the first three applications from industry for this pilot, based on the criteria developed above.
- Once the application is selected, one of the regulatory authorities in the assessment working group will be selected to lead the collaborative assessment process and perform the following:
    - Ensuring a confidentiality agreement is in place between all relevant participants.
    - Providing a lead project manager to:
        - Lead coordination and collaborations among quality assessors from the participating regulatory authorities,
        - Manage meetings (virtual using IT tools such as Teams and Zoom) and communications among these quality assessors and between the participating regulatory authorities and the sponsor,

        - Develop (in collaboration with OWG and other regulatory authorities) timeline and milestones (e.g., the timing of information requests) amenable to regional requirements of the participating regulatory authorities,
        - Manage progress according to the timelines and milestones agreed upon regulatory authorities.
    - Preparing a written assessment document (using the lead authority's standard template) that represents the working group's consensus view and includes an executive summary and a list of questions or comments to the sponsor, based on input from and consensus built upon quality assessors from other participating regulatory authorities.[3] This document will represent the primary output or deliverable of application assessment done collaboratively by quality assessors within the assessment working group.
    - Facilitating discussions to resolve any disagreement and build consensus on quality assessment and regulatory decisions, with the aim of delivering one single outcome.
    - Developing in collaboration with all participating regulatory authorities a report that summarizes the learnings from the collaborative assessment of each application after the assessment is completed. The individual report for each application will be used to develop the final report that summarizes the findings (including lessons learned, best practices and standards, etc.) of this pilot *(see Section 7 for Pilot Program Deliverables)*.
- The participating regulatory authorities will rotate to serve as a lead for each application submitted for this pilot. In this case, there will be three different leading regulatory authorities, one for each of three applications.

6. BENEFITS TO PARTICIPATION

The potential benefits for industry or regulatory authorities to participate in this pilot include:

- An opportunity to reach agreement from multiple authorities on proposed CMC post-approval changes including PACMP;
- A possibility to obtain a single list of information requests, comments, questions from multiple regulatory authorities, and corresponding responses from a sponsor, which will allow for increased efficiency in regulatory submissions and assessments from a sponsor's perspective;
- An opportunity to have an agreed approach to a post-approval change strategy (particularly PACMP), which may increase the likelihood that the same strategy could be used on a global basis for other products that share similar risk profiles;

[3] The participating regulatory authorities can use the assessment document drafted by the lead regulatory authority to develop their own assessment document using their template to meet the requirements within their authority.

- An opportunity to exchange views and assessment approaches for post-approval changes after the pilot, which will facilitate identifying common principles and serve as a foundation for future international convergence and global convergence efforts; and
- Contribution to the effort of cross regional convergence in assessment practices of CMC changes, aiming ultimately to a single submissions and collaborative assessments.

7. PILOT PROGRAM DELIVERABLES

It is anticipated that the pilot program will deliver the following:

- Following the successful completion of collaborative quality assessments, the findings that are summarized in the reports for 3 submissions (including lessons learned, best practices and standards, etc.) will be published in the ICMRA website.
- Areas of commonality and differences between regulatory authorities in quality assessments of post-approval changes will be identified, while the participating authorities strive to deliver a single outcome whenever possible.
- The pilot will create a forum for discussions aimed at promoting future convergence.
- Based on the results, the pilot may be extended and/or proposals will be generated for next steps in improving international convergence and global convergence.

8. APPLYING TO BE PART OF THE PILOT

The submission requirements of the regulatory authorities participating in the pilot should be followed. During the duration of this pilot, if a collaborative platform that allows quality assessors to conduct their assessment using a single document becomes available, then the OWG and the assessment working group will consider their use.

Details of how to apply for the Pilot will be published on the ICMRA website.

9. CONCLUSION

This pilot is anticipated to be an important driver for future global convergence and convergence practices among international regulatory authorities. While the pilot, by its nature, may not directly result in international convergence and global convergence, it is an important first step towards that goal.