IMPLEMENTATION PLAN

ICMRA Pilot Program for Collaborative Hybrid Inspection

Protocol for carrying out a Collaborative Hybrid Inspection between Regulatory Authorities and Industry during the ICMRA Collaborative Hybrid Inspection pilot.

The protocol will include information on how to prepare, execute and report findings during the ICMRA Collaborative Hybrid Inspection pilot.

1. Background

In March 2020 the COVID-19 pandemic forced most regulatory authorities to pause inspections, with exception of mission critical work, to mitigate the spread of the COVID-19 virus. Business operations for inspections were adapted to provide the necessary oversight to regulated industry while protecting the health of all those involved. Many regulatory authorities leveraged a host of available tools and implemented innovative approaches to conduct their work, including the use of remote/distant facility assessments. As regulatory authorities have gained more experience with these new remote tools the value and opportunity for enhanced collaboration between regulatory authorities has become more apparent.

Following the July 2021 ICMRA-Industry virtual workshop on enabling manufacturing capacity in the COVID-19 pandemic,[1] ICMRA recognizes the need to assess the feasibility of a collaborative hybrid inspection to better understand the challenges and benefits of this new approach to Regulators and Industry.

2. Scope

The scope of the pilot will be limited to Pre-approval and Pre-license drug inspections (PAI/PLIs, respectively) and will not include surveillance drug inspections. The pilot may be extended to other applications, which may include post-approval changes of other types of products (e.g., PRIME or Breakthrough) that are deemed critical by the participating NRAs.

The Collaborative Hybrid Inspection Pilot may coordinate activities with the Collaborative Assessment Pilot when a Post-Approval Change Management Plan (PACMP) is submitted, and PAI/PLI is needed to support the post-approval change proposed in the submission.

The scope of the collaborative hybrid inspection should be well defined and align with the legal requirements and standards of the participating NRAs. This will allow the participating NRAs to make an informed decision on compliance and assurance of quality to support the approval/ licencing of the drug product.

Data from this pilot will be used to evaluate feasibility of collaborative hybrid inspections and identify opportunities for operational changes. The pilot also aims to evaluate operational efficiency and cost efficacy; however, due to the limited sample size it is anticipated that further evaluation will be needed to determine the full impact of this new approach on regulatory authorities' operations and costs.

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

English will be the designated language of the programme unless a special case is identified where another language is agreed upon by the participating NRAs and facility. If English is not used, or if the manufacturer normally works in a language other than English, appropriate arrangements by the lead inspectorate should be made to ensure adequate (simultaneous, if possible) translation to ensure clear communication during the inspection.

3. Objective

The objective of the pilot is for multiple regulatory authorities to engage in an interactive, collaborative assessment while inspecting a manufacturing facility using a combination of on-site inspection and remote assessment of a manufacturing facility, preferably included in COVID-19 applications and related CMC post-approval changes.

The Collaborative Hybrid Inspection Pilot aspires to conduct 3-5 inspections to support the scope and objectives. The inspections should build in complexity in terms of the participating NRAs as the pilot progresses.

In the absence of a suitable submission as described above, or in the event of continued travel disruption preventing inspectors from travelling internationally, NRAs and Industry may propose other facilities of common interest to be included in the pilot to gain experience with collaborative hybrid inspections.

The ICMRA pilot for collaborative hybrid inspection will guide regulatory authorities to gain information on **how to prepare, execute and report** a collaborative hybrid inspection and describes how participating stakeholders (Regulatory Authorities and Industry) can engage to allow evaluation of a facility via a collaborative hybrid inspection approach.

With the planned sample size of 3-5 inspections, the goal of the pilot is to understand how the collaborative hybrid process may work, gain an initial understanding of costs and benefits this additional alternative approach presents to all involved and determine next steps to assess feasibility for implementation on a larger scale. The lessons and information collected from this effort will need to be evaluated by each regulatory authority to determine how it aligns with their inspection program. This is not meant to change each regulatory authority's inspection process.

4. Definitions

Collaborative Hybrid Inspection: refers to a facility assessment performed by more than one National Regulatory Authority (NRA) using a combination of on-site inspectorate (by one NRA) and remote inspectorate (by at least one NRA) connecting at the same time to the ongoing activities at the facility using virtual technology.

ICMRA Organizing Working Group (OWG): is comprised of regulatory authorities, such as FDA, EMA, HPRA, and PMDA/MHLW. They are responsible for the overall coordination, oversight, and evaluation of the conducted pilots.

Participating Regulatory Authority: is any regulatory authority taking part in the collaborative hybrid inspection.

Lead Inspectorate: will be selected based on criteria listed in the collaborative hybrid inspection protocol. They will be the onsite inspectorate. The lead inspectorate has the overall responsibility for coordinating the inspection planning, contacting the facility to be inspected, leading the inspection, and taking overall responsibility for the inspection report as described in the following sections of the protocol. The lead inspectorate will be expected to complete the pilot questionnaire.

Lead Inspector: will be identified by the lead inspectorate. The onsite inspectorate, which should be comprised of at least two inspectors, should have capacity to support the remote NRAs through control of the videography, if possible.

Coordinating Officer: will be from the lead inspectorate and facilitate communication between the on-site, remote, and observing inspectorates. The individual should understand the inspection and manufacturing processes. Will provide logistical support to the NRAs and to the facility, as necessary. The officer will be identified by the lead inspectorate.

Remote Inspectorate(s): will be selected based on criteria listed in the collaborative hybrid inspection protocol. Remote inspectorate(s) are responsible for participating in the hybrid collaborative inspection and keeping the lead inspectorate informed about identified CGMP deficiencies and comments. They are also responsible for providing input to the closing meeting and inspection report as directed by the lead inspectorate. The remote inspectorate(s) will be expected to complete the pilot questionnaire.

Observing Inspectorate(s): will not interact with the lead inspectorate onsite or remote inspectorate(s) during the inspection. Their participation will be determined by the lead inspectorate, participating regulatory authorities and facility to maintain an efficient and effective process for all parties involved. They will be expected to complete the pilot questionnaire.

CGMP Deficiencies: when referenced in the protocol, this term refers to items identified during the collaborative hybrid inspection that raise concerns to the inspectors about facility compliance to CGMPs and assurance to product quality. For a complete description of the different types of deficiencies refer to PIC/S Guidance issued 2019[2].

Pre-approval and Pre-license Inspections (PAI/PLI): inspections that are performed to contribute to the assurance that a facility named in a drug application, can manufacture the drug to be marketed, and that submitted data are accurate and complete. PAI is specific to small molecule applications. PLI is specific to large molecule applications. These two types of inspections may have different terminology across NRAs.

5. Benefits to participation

The benefit for a participating facility in this pilot is that the facility will be assessed from an inspectional requirement (PAI or PLI need) by multiple NRAs at the same time in one single engagement. This should save the facility time, effort, and resources. The collaborative hybrid inspection will also allow multiple NRAs to take action and thus potentially accelerate the availability of critical medicines in multiple markets.

6. Limitations

This pilot is limited by the following:

- Harmonisation and the desired convergence cannot be achieved only through the few pilot cases
- Each region is still bound to its existing regulatory and legal framework; any differences cannot not be bridged through this pilot
- Confidentiality agreements
- CGMP deficiencies based on the regulations of each regulatory authority

The NRAs are not bound in any way by inspections conducted as part of this pilot. The information gathered during the collaborative hybrid inspection pilot will be shared between NRAs through

[2] PIC/S GUIDANCE ON CLASSIFICATION OF GMP DEFICIENCIES

confidentiality agreements as with tools used to assess information to support submission actions. However, there is no upfront binding that all NRAs participating in the collaborative hybrid inspection will take the same action; or use the information the same way within their regulatory systems.

7. Criteria for participation

To ensure feasibility of the pilot, it is foreseen that a small number of regulatory authorities (3-5 with some regulatory authorities participating as an observing inspectorate) will participate in such collaborative hybrid inspections. Participation is limited during the pilot to those regulatory authorities listed in **Appendix 1**. As more experience is gained the pilot may be extended to additional NRAs. Even though initial participation is limited, requests for participation from other regulatory authorities during the pilot may be received and discussed by participants.

The minimum active participation will be two NRAs (one on-site and one remote). The participation of more than one on-site NRA will be considered and agreed upon by the NRAs and facility. The number of NRAs actively taking part in a particular collaborative hybrid inspection will be determined by the participating NRAs to allow an efficient and effective process for all parties involved.

The identified facility should be located on the territory of one of the participating regulatory authorities preferably to ensure the availability of an inspection team to perform the on-site inspection.

The pilot will limit inspection type to preapproval and pre-license drug inspections, ideally focusing on COVID-19 therapeutics. In addition, the pilot will consider facility history, facility size, and type of facility (e.g., manufacturer, testing laboratory) in identifying inspections for pilot inclusion.

Each participating regulatory authority agrees to be an active and timely contributor to the pilot programme as established. Failure in this respect, such as non-participation in maintaining or exchanging updated inspection information, as outlined in this protocol, may result in a participant being requested to withdraw from the pilot programme.

Each participating **regulatory authority** has, and agrees, to maintain a functioning inspectorate and agrees to the following:

- The lead inspectorate is responsible to guide the participating NRAs on the use of appropriate CGMP guidance with accompanying regulations and supervision for products under their legal framework;
- If a specific request is made by a participating NRA, it will be considered and agreed upon by the lead and remote inspectorates, as appropriate;
- Has and maintains current confidentiality arrangements with all other participating regulatory authorities;
- Participates in teleconferences, joint inspections, and other communications throughout the collaborative hybrid inspection process;
- Provides information to other participating regulatory authorities about inspections such as results of feasibility assessments (for distant/remote inspection), findings of non-compliance and inspection reports/summary outcomes from previous inspections for the facility being inspected;
- Maintains a high standard for CGMP inspection capability, utilizing a variety of mechanisms to do so, such as working with other participating regulatory authorities through PIC/S membership or other appropriate means;
- Has technical capabilities as defined in the IT tools section the protocol;

- Participating regulatory authority has a procedure/policy regarding inspectors' conflict of interest;
- Participating regulatory authority ensure a translator (from facility, NRA, or independent) is available, if needed, based on the language in the documentation/location of the facility.

Participating **facilities** are responsible for the following (in addition to the responsibilities associated with receiving any regulatory inspection):

- The facility agrees the participating NRAs will share information to support the collaborative hybrid inspection;
- Providing the application and availability of technology to enable remote facility tours;
- Providing the platform for document sharing. This should include direct access to documentation, electronically or otherwise, by inspectors, and in formats which can be downloaded/printed as required and, if feasible, in 'searchable' form;
- Safeguarding the privacy and confidentiality of all parties;
- Confirm they are in compliance with CGMP;
- Confirm they are ready for inspection.

8. General principles

8.1. Time and duration of the pilot

The pilot is anticipated to last a year after endorsement of this pilot protocol by the ICMRA Executive Committee or another appropriate committee of ICMRA (e.g., PQ KMS).

The duration of each collaborative hybrid inspection will try to reflect the typical duration of an on-site inspection. Preparation for inspection and post-inspection activities may require a little more time than typical timelines given the need for collaboration and alignment between the NRAs participating in the collaborative hybrid inspection. These times will be captured in the performance metrics listed in **Appendix 2**.

After the conclusion of the pilot programme the participating regulatory authorities will perform an assessment of the programme considering the assessment data listed in **Appendix 2**. This assessment is intended to inform ICMRA members of the operational/logistical requirements, as well as the benefits and challenges associated with conducting collaborative hybrid inspections. A report with conclusions and recommendations will be published accordingly.

To avoid duplication of inspections, and to accelerate the duration of this pilot programme, regulatory authorities and industry are strongly encouraged to participate and collaborate throughout this pilot programme to demonstrate the value on NRA's reliance upon each other's inspections and to foster confidence building and collaboration between regulatory authorities and industry.

8.2. Facility selection

The regulatory authorities of the ICMRA Organizing Working Group (OWG) members will select the facilities that meet the criteria for collaborative hybrid inspection. NRAs or Industry, with an applicable facility, can submit their request(s) via a pilot proposal summary form requesting participation in the pilot. The request form should be sent to ICMRA Collaborative Pilots shared mailbox. The mailbox will be posted with the announcement of the Pilot from ICMRA. The request will be assessed by the OWG using the criteria identified in section 7 to determine if the facility meets the scope of the collaborative hybrid

inspection pilot. When the OWG determines the facility meets the scope of the pilot, they will notify the participating regulatory authorities and the facility.

8.3. Roles of participants

Any regulatory authority taking part in the inspection is considered a 'Participating regulatory authority'. The regulatory authority who will carry out the on-site portion of the inspection will be the 'Lead Inspectorate'. The Regulatory Authority/Authorities who will be taking part remotely will be the 'Remote Inspectorate'.

It may be possible for an authority to join the inspection as an observing inspectorate (either on-site or remotely), subject to the agreement of the participating NRAs and the facility. An observing inspectorate will not issue findings or contribute to the inspection report but will be expected to complete the pilot questionnaire.

Between the Lead and Remote Inspectorates, there should be an agreement as to which application/platform will be used to share information during the inspection. This is in recognition of the fact that it may not be appropriate for confidential exchanges between Inspectors to be shared via applications provided by the inspected facility.

The collaborative hybrid inspection team will be composed of an appropriate number of inspectors from the participating regulatory authorities in order to rationalise the use of the inspectorates' resources, as well as to ensure effective conduct of the inspection at the site.

The lead inspectorate has the responsibility to:

- Inform the site about the upcoming inspection and the participating regulatory authorities
- Determine the working language of the inspection and the arrangements for (simultaneous) translation,
- Define the length of time the inspector expects to be at the premises,
- Clarify the objectives of the inspection.

In addition, the lead inspector has the following duties:

- Preparation for the inspection of the site in collaboration with the other inspectors on the team (e.g., via web conference).
    - Planning of the inspection considering the inspection scope and the facilities to be covered and expected timeframe on-site and take into account the time zones of the participating regulatory authorities.
    - Establishing a draft inspection schedule of the inspection in cooperation with the involved participating inspectors and taking into account the remote elements of the inspection.
    - Determining if daily wrap-up meeting will be held with the inspected facility
    - Setting a reporting deadline in agreement with all team members taking into account any specific national or procedural deadlines such as transparency initiatives for posting inspection results online etc.
    - Ensuring all confidentiality arrangements are in place to fully conduct the hybrid inspection.
    - Providing notification to the local regulatory authority of the planned inspection, if required (if different from the Lead authority).

8.4. Preparing for the Collaborative Hybrid Inspection

Participating regulatory authorities identified for the pilot (or feasibility assessment) should meet to discuss and familiarize themselves with the protocol prior to initiating a collaborative hybrid inspection. The meeting should cover the following areas:

- Objective of the pilot, including the how success will be measured
- General role of the on-site and remote NRAs
- Overview of the protocol
- Overview of the survey questions
- Inspectors' role in data collection and reporting

Following the meeting and announcement of the inspection, the lead inspectorate will ask the facility to provide the agreed documents requested by the participating NRAs. The documents may include the following depending on the scope of the inspection and type of submission (but not limited to):

- Site Master File and Validation Master Plan
- List of significant changes to equipment, processes and key personnel
- List of complaints
- List of products manufactured/imported by the company
- Detailed production and testing schedules for the inspection timeframe

The lead and participating regulatory authorities will coordinate roles and responsibilities, agree on the scope and plan inspection coverage by:

- Reviewing the management structure of the company (organization chart)
- Identifying some of the documentation which may be required during the inspection (e.g., layouts of the plant)
- Reviewing the production schedule prior to the inspection
- Identify critical activities to observe. This would help coordinating and adjusting the inspection schedule, as required.
- Agree on whether there will be one or more separate reports at the end of the inspection. In case of separate reports, each inspection authority will issue an inspection report or document according to their own regulatory and legal framework.

The lead inspector, in coordination with the participating regulatory authorities, will prepare an inspection plan which may include:

- The objectives and the scope of the inspection, in light of previous inspections
- Identification of the inspection team members and their respective roles, (include the on-site and remote inspectors)
- The date and place, where the inspection is to be conducted
- Identification of the organisational units to be inspected
- The expected time and duration for each major inspection activity (premises, processes, etc.)
- Samples (if any) to be taken

- The schedule for the final meeting
- The approximate schedule for the transmission of the inspection reports

The participating regulatory authorities should exchange available information on the site to inspect, including but not restricted to:

- Sterile medicinal product name(s),
- Active pharmaceutical ingredient name and destination markets (if available);
- Site Master File and Validation Master Plan;
- Product Quality Review;
- Inspection reports from previous inspections;
- Follow-up actions (if any) arising from previous inspections;
- Manufacturing process description (at least flowchart);
- Building/lines to be inspected;
- Previous risk assessment or site compliance dossier/file;
- Any other relevant information on the sites to be inspected;
- Notifications of Deviations/OOS
- Recalls or quality defect where the site was involved;
- Changes performed at manufacturing site with a review of any variations to the manufacturing authorisation

The inspectors will review all the information available before conducting the inspection. All preparation for the inspection and collaboration between the participating regulatory authorities should take place sufficiently ahead of the inspection.

8.5. IT tools

IT tools used for meetings, virtual plant tours and documentation sharing have to be agreed among all parties (Inspectorates and Facility) upfront and they have to ensure that **privacy, security and confidentiality** are preserved.

- IT tools used for the exchange of communication among the inspectorates should also be agreed between the lead inspectorate and the remote inspectorates.
- Before the inspection the IT platforms and connection should be tested in advance.
- Security access to the platform should be checked by all participants.
- Signal strength and bandwidth capacity should be high enough to allow a stable and fast connection.
- Broadband should be available in all areas especially when the inspectorates will carry out the virtual plant tour that may need video streaming. The live streamed video quality of the tour can be affected by the limitations of the reach of the WIFI signal within the manufacturing facility.
- Considerations should be made by the company for the video frame stability and the audio feed especially during the plant tour.

- It may be necessary to have training sessions of the agreed IT tool to get familiar with the functionalities of the platforms.
- The inspected company should provide IT professional in the preparation and during the inspection to support the technology aspects.
- IT back-up plans should be in place in case of unforeseen issues e.g., connection, use of mobile phones.
- Including break out rooms/multiple virtual meetings for discussion or review of documentation (both on-site and remote). This should be tested during the premeeting.

8.6. Conducting the Inspection

8.6.1. Opening Meeting:

The lead inspectorate and the remote inspectorate(s) should meet and introduce themselves to management and the key personnel of the facility to discuss the inspection schedule.

During the opening meeting the Lead authority should:

- Outline the purpose and scope of the inspection
- Outline the inspection process, including the close-out process and follow up actions.
- Obtain an updated production schedule

During the opening meeting, the facility should:

- Describe the Quality Management System, when requested
- Explain significant changes in facilities, equipment, products and personnel since the last inspection
- Explain how CGMP deficiencies have been resolved if this information has not already been forwarded to the competent authorities
- Designate the people to accompany the inspector during the inspection
- Allocate a room for the inspector when requested.
- Explain the flow of material and personnel following the layouts
- Describe the data management system(s)
- Understand that different actions might be taken by the participating NRAs due to the slightly different processes and jurisdictions.

8.6.2. Inspection of the plant facilities:

The lead and remote inspectorates will participate together in a plant tour for familiarisation with the site and any major changes. The plant tour may follow the logical flow of the starting materials, goods inwards warehouse, through the production areas, quality control areas to the warehouse for released finished goods, taking into account the detailed guidelines of CGMP.

The participating regulatory authorities will use a risk-based approach when conducting the inspection. The scope of the inspection will be based on the production schedule critical manufacturing activities performed by the operators, document review, etc.

During the inspection the lead and remote inspectorates should interview and question various levels of personnel and subject matter experts and observe practices versus the approved procedures to assess the knowledge and competence of these personnel, as deemed necessary.

The coordinating officer will organize daily meetings after each inspection day with all participating inspectors. Information gathered will be conveyed to the remote NRA(s) to inform remote NRA(s) of on-site findings, concerns being evaluated along with the plans for the day. Similarly, requests can be received from the remote inspectorates for transfer to the onsite inspectorate. The CGMP deficiencies raised should be agreed on between the inspectorate(s).

The coordinating officer can be in constant dialogue with both onsite and remote inspectorates for the entire duration of the inspection.

8.6.3. Review of documentation:

The whole system of documentation, based on specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the different production, quality control and distribution operations should be checked by examining particular examples both during use and after compilation into complete batch records. The lead inspectorate will take the responsibility to request all documents to be reviewed. The documentation can be checked 'live' review and off-line review by the remote inspectorate who receives the documents. For electronic data management systems, the documentation review should include the source data, as well as systems configuration settings.

While a general CGMP inspection will normally include review of the following (not all inclusive), in order to assess compliance with the terms and conditions of the manufacturing authorisation the PAI may focus on specific aspects relevant for the respective submission:

- Conformity with current good manufacturing practice
- Compliance with marketing authorisation
- Quality Management
- Personnel
- Premises and equipment
- Documentation
- Production
- Quality control
- Contract manufacture and analysis
- Complaints and product recall
- Self-inspection

A product-related inspection (PAI/PLI) will normally include review of the following specific documentation relating to one or several completed batches of a specified product (not all inclusive), in order to assess compliance with the specifications of the marketing authorisation:

- Specific standard operating procedures (SOPs)
- Product quality review, if available for a new product
- Manufacturing formulae, records and instructions
- Process Validation

- Stability data

8.7. Concluding the Collaborative Hybrid Inspection

Once the lead and remote inspectorates have concluded their responsibilities with respect to the inspection, the lead inspector will relay to the facility that the inspection has been concluded and will arrange a time with facility for the closing meeting.

The lead inspector will also arrange a pre-closing meeting with the NRAs to discuss the findings/outcomes of the inspection and agree how they will be reported to the facility. The lead inspector and remote inspectors should make every effort possible to agree on the final list of CGMP deficiencies that will be provided to the facility. In the event a consensus cannot be reached each authority will issue their own list of CGMP deficiencies. The CGMP deficiencies for which consensus was not reached, and the rationale, should be explained thoroughly in the post inspection inspector survey.

Note that even though a consolidated list of CGMP deficiencies will be agreed upon, each regulatory authority should follow their own regulatory and legal framework to issue deficiencies on their regulatory form at the closing meeting.

In addition, the NRAs should also discuss and agree if a single inspectional report will be issued by the collaborating NRAs, or if each NRA will issue their own inspectional document. If a single report will be issued, it is expected that the NRAs discuss and agree on the format of the report and the timeline for it to be issued.

The lead and remote inspectorates will agree on response timeframes for both the regulatory authority and facility to follow. Again, this will be dependent on the regulatory authorities participating on the pilot.

8.8. The Collaborative Hybrid Inspection Closing Meeting

At an agreed timing, the inspecting NRAs will hold a closing meeting with the facility. During the closing meeting, the lead inspector should summarise the CGMP deficiencies and comments with representatives of the facility.

The lead inspector will be responsible for conveying if there are CGMP deficiencies and/or comments that come from only a certain participating NRA(s). In case of differences in CGMP deficiencies or outcomes, the lead inspector with support from remote inspectors will clarify the reasons for the differences to facility participants at the meeting based on the rationale determined during the pre-closing meeting.

Each regulatory authority should follow their regulations and issue their own form with the CGMP deficiencies at the close of the inspection.

Lead inspector will provide directions to the facility on how to respond to CGMP deficiencies. The preferred approach would be for the lead inspectorate take the responsibility to manage communication post inspection and collect responses from the facility.

The lead inspector will also communicate timing for the facility to provide a response to the CGMP deficiencies. The lead inspectorate should share communication received from the facility with the remote inspectorate(s).

The facility may need to communicate with the remote inspectorate during the response period, other than the lead inspectorate. In these instances, established communication channels should be used. As necessary the remote inspectorate should share this communication with the lead inspectorate.

The lead inspectorate will inform the facility if a single follow up report will be issued by the collaborating NRAs, or if each authority will be issuing their own reports.

8.9. Post-Inspection Actions and Reporting

After the conclusion of the collaborative hybrid inspection, the lead inspectorate and remote inspectorate(s) will hold a meeting to discuss and agree on how the final report should be drafted and issued (e.g., should there be one report or should each NRA report separately) and any other actions necessary from each participating NRA.

The lead inspector will remain in communication with the remote regulatory authorities after the closing meeting.

The facility is expected to reply with a Corrective and Preventative Action Plan (CAPA) to address the CGMP deficiencies raised during the inspection per the direction given at the closing meeting. The CAPA will be sent to the lead inspectorate. The lead inspectorate will distribute to the remote and observing NRAs for review.

The CAPAs will be reviewed by the participating NRAs and they will agree on how to handle the closure of the collaborative hybrid inspection. The NRAs will agree on how to handle the response to the CAPA assessment (one or individual NRA reports). The Lead Inspectorate will be responsible to communicate to the facility on what to expect post-submission of the CAPAs.

In general, each participating regulatory authority is responsible for any follow-up actions within their jurisdiction. All outcomes should be captured in the post-inspection survey to the participating NRAs. Participating regulatory authorities shall complete the post-inspection survey within 30 calendar days of receipt of the survey. All participating NRAs shall issue the final GMP-documentation e.g., GMP-certificate/non-compliance letter (EU), EIR (US)) according to the regulatory requirements in their jurisdictions, as applicable.

Continued collaboration throughout the compliance life cycle of the facility is encouraged and organization of the teams involved in the collaborative hybrid inspection.

8.10. Reporting of the pilot by the ICMRA OWG

The OWG will have the responsibility to distribute the questionnaire, see **Appendix 3**, to participating regulatory authorities and responsibility to assemble and evaluate performance data, such as those listed in **Appendix 2**, at the conclusion of each pilot inspection. The outcomes collected will be summarized in terms of positive and negative aspects into a single report that will be presented to ICMRA Executive/PQ KMS Committees.

Appendices:

Appendix 1: Participating regulatory authorities

EMA, HC, FDA, MHRA, ANVISA, PMDA/MHLW. This is not meant to be an inclusive list. NRA participants will be considered on a case-by-case basis dependent on the facility selected to support the pilot.

Separate main participants (taking part in the pilot) and potential observers from other NRAs will be considered.

Appendix 2: Pilot Assessment Data

Supporting information / data gathering will be collected to support the feasibility and continuation of this pilot. Performance metrics will be defined based on the initial findings of the pilot.

- Total sites identified as a candidate for Collaborative Hybrid Inspection during the pilot.
- Total number of hybrid inspections performed during the pilot
- Number of participating regulatory authorities during the pilot.
- Number of common opinions on inspection outcomes
- Number of divergent opinions on outcome of inspection
- Number of marketing authorizations approved (and number of countries) or refused as a result of hybrid inspections carried out in the pilot
- Duration of Preparatory Period
- Duration of the Hybrid Collaborative Inspection
- Duration of Post-Inspection Activities (time to issuance of Final Report with CGMP deficiencies to the Facility)
- Full Time Employee (FTE) Cost of inspection / cost saving due to travel
- Translation / technology cost
- Number of inspectors on-site (Did you need another person, where you able to collect the information that you requested?)

Appendix 3: Collaborative Hybrid Inspection Pilot Questionnaire