Inspection Expectations for ICMRA Collaborative Hybrid Inspection Pilot (CHIP) Participants

Hybrid inspection, as defined in this context as a combination of on-site and remote, allows for multiple regulatory agencies to participate in an inspection at the same time with the goal to make one regulatory decision. A 'hybrid' inspection is in general similar to joint inspections where all inspectors are present on site. To allow a smooth process only one authority will be on-site while inspectors from one or more authorities will be remote. The remote team(s) will follow the on-site inspection team procedures to conduct the inspection in order to align to the on-site team's practice.[1] Typically, and when feasible, the on-site lead inspectorate is the local one (country where the site is located).

Benefits to Participation

- An opportunity to reach agreement from multiple authorities on the compliance of a site with a single inspection activity without adding additional effort, cost and time to facilitate on-time regulatory approval of a dossier/variation.
- A possibility to receive a single list of information requests, comments, questions from multiple regulatory authorities, which will allow for increased efficiency in regulatory submissions from a marketing authorization holder's perspective.
- An opportunity to contribute views and approaches for post-authorization inspections (routine inspection) after the pilot, which will facilitate identifying common principles for performing inspections and serve as a foundation for future international and global convergence efforts (e.g., by PIC/S).

Pre-inspection activities

The **on-site lead inspectorate** will be the **one single voice** of the participating Regulatory Authorities (RAs) that the facility will need to engage with. The on-site lead inspectorate will coordinate all the organizational and logistical aspects of the hybrid inspection with the site and it will liaise with the remote inspectorates as necessary. Pre-inspection activities between the RAs may occur 30-60 days prior to the inspection.

Workforce and technical capabilities of the facility will be discussed and assessed during the planning phase to ensure that the facility has the resources necessary to host, support and accommodate the needs of a hybrid inspection.

The planned scope of the inspection will be agreed in advance and should be the same for each participating RA.

The on-site inspection lead will coordinate scope of coverage with facility and remote team by

[1] ICMRA participating authorities may use different terminology with respect to remote assessments or participation during inspections depending on their individual laws, regulations, and cooperative agreements. Terminology used by the ICMRA CHIP is not intended to supersede any laws or regulations or guidance documents issued by a participating authority.

- obtaining site information prior to inspection. The information requested from the facility should be based on globally recognized information (i.e., Site Master File based on PIC/S);
- planning activities to be observed, liaising with on-site facility personnel for up-to-date information (e.g., production schedule) and providing feedback to the remote team for decision on which activities to observe;
- coordinating remote set-up with the facility;
- overseeing on-site and virtual engagement with the facility.

The participating RAs will discuss and determine the anticipated agenda and length of the hybrid inspection depending on the scope, and the Lead RA will communicate the results to the facility in advance of the inspection. The participating RAs will **strive to limit the inspection time based on risk to potentially the shortest possible timeframe**. The Lead RA will aspire to plan the hybrid inspection to be no longer than a normal on-site inspection. Also, every effort will be made to ensure the inspection takes place within the submission timeframe and will allow simultaneous decisions across inspectors of different RAs.

The details of the closing meeting will be discussed between the RAs prior the conduct of the inspection, and this information can be shared with the inspected facility during the pre-inspection activities.

Staffing the inspection

In order to collect data during the pilot that is reflective of future implementation, the number and roles of inspection participants should replicate, as much as possible, realistic staffing levels for long-term implementation. This includes the investigator and coordinator roles.

IT tools and Wi-Fi connectivity

Remote connection via a supported platform (depending on the firm's and RA's restrictions and firewalls and the respective security policies). The Lead RA will work with the Participating RAs to ensure the site has the capability to support the channel of communication.

- All parties (RAs and facility) will need to agree and establish a communication channel to communicate with the facility.
- Participating RAs will agree and establish a separate communication channel for RAs to communicate between the on-site and remote teams.

Communication among the inspectors should be facilitated using a coordinating officer (assigned by the lead inspectorate team) who can handle the logistics for the remote team. Since questions can be coming from the on-site and the remote team there should be a dedicated facilitator from the firm who would manage the remote team's requests and upload all the documentation and find the subject matter expert (SME), or to set up specific interviews.

With regard to the document exchange, several IT platforms can be used for the exchange of documentation with the remote team. Some RAs request using their systems (e.g., EU IRIS-platform). As it is critical to maintain adequate tracking of requests, the firm should make sure to build a coherent structure to keep the documents adequately sorted and directed to the requesting individual dealing with the topic or sending out the requests. System and structure to be discussed between the RAs and the facility and agreed upon during the planning phase. RAs should ensure coordination amongst participating health authorities to ensure availability and sharing of documents, as appropriate.

Potential problems with website connection (stability), audio, background noise, or other issues should be assessed and discussed with the facility in advance of the inspection. Connection should be tested upfront before the inspection occurs, to identify 'dead zones'.

Conducting the inspection

Opening Meeting:

During the opening meeting the on-site inspectorate and the remote RAs introduce themselves to management and the key personnel of the facility:

- The role of the **lead inspector** is defined: The lead inspector **coordinates the overall inspection conduct and scope coverage**, including but not limited to the timing of activities to be observed, liaison between the facility personnel, the on-site and remote inspection personnel, as well as the inspection closing.

- The role of the **coordinating officer** is defined: The coordinator is the inspection facilitator and **ensures good communication and information sharing** between the regulators on a continuous basis. This will avoid redundancy and duplication of work, discussions, documentation review, etc. This support is crucial to facilitate the conduct of a multi-agency inspection. The coordinating officer has to be able to accommodate the local site time zone and the remote team's and be able to debrief with the on-site and brief with the remote team.

The hosting site can present the facility overview and introduce its Quality management system and the production schedule.

The inspection team schedule is presented to the key personnel of the facility with outlining the purpose and scope of the inspection.

In case of any logistics and organizational issues the facility should highlight them in advance of the plant tour.

Inspection of the plant facility(ies):

The scope of the inspection will be based on the production schedule critical manufacturing activities performed by the operators, document review, etc.

The **participation of the remote team on the plant tour virtually has to be explored with the facility during the 'pre-inspection activities' phase**; However**,** in case the virtual tour is not considered feasible due to multiple time zones / major time difference or connectivity problems within the facility the remote team may rely on the on-site team.

In the case that the remote inspectorates can participate together with the on-site team in a plant tour it is important to plan a virtual meeting for technical testing (as highlighted above) on how this will be accomplished accounting for the facility physical and operational constraints.

Considerations should be made in relation to the check of the internet connection and its stability within the facility and in relation to the limitation of camera positions and the optimal angle to observe operations, and the person that should take the camera. It is normally expected that the cameraperson is a person of the facility to assure a safe and non-intrusive walk-through of ongoing facility operations.

The on-site inspection team can make requests on where to focus the camera and relay requests from the remote team to the personnel operating the camera as agreed before starting the plant tour and allowed by the communication tools in place.

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 GMP.

Review of documentation and interviews:

During the phase of review of documentation and interviews of personnel, different breakout rooms can be created in order to facilitate the conduct of the interviews and documentation review.

In general, the **remote team should be able to access and review documentation** as this phase can be conducted off-line especially when there are different time zones. Documents should be requested in advance by the remote team, via the coordinating officer, for efficient review.

Interviews:

In general, the **on-site inspector team will manage necessary interviews**. Remote teams should provide their requests to the on-site lead inspector, or via the coordinating officer. If an interview is deemed necessary by the lead inspector or coordinating officer, the facility lead representative, or designee, should identify the appropriate SME(s) to participate in the interview to prevent interference or disruption of the inspection.

All questions from the remote team should be channeled through the coordinating officer pathway in order to avoid confusion.

Each day the RAs will discuss and share impressions/take aways and what they would like to focus on the next day. The lead inspector will inform the facility at the end of the day of the next day's planned focus so that the facility can prepare.

During the course of the inspection, sufficient time should be made available for the on-site and remote team to discuss issues identified.

The on-site lead inspector will coordinate with the remote team(s) for daily close-out meetings with the facility.

Concluding the collaborative hybrid inspection

Closing meeting[2]

During the closing meeting, the **lead inspector should summarize the GMP deficiencies** and comments with representatives of the facility.

There might be times when multiple authorities see an observation differently, but in this case **the authorities will discuss to see if there is common ground**. However, it is still up to each RA to determine the significance of the observation to their regulations.

[2] The closing meeting will be based on legal requirements of the on-site inspectorate.

In case of differences in GMP deficiencies or outcomes, the lead inspector, with support from remote RAs, will clarify the reasons for the differences to facility participants at the meeting based on the rationale determined during the pre-closing meeting.

Post-inspection activities

The post-inspection activities and timelines will be discussed with the inspected site during the close-out meeting. The **RAs** will follow their internal processes and regulatory frameworks and **will work together to align the timelines for the outcome of the inspection**. Once the submission of corrective and preventive actions (CAPAs) is received from the manufacturer, it is envisioned that participating RAs will collaboratively assess the submission information in a coordinated manner within an agreed timeframe. Participation in this pilot should not cause any additional delays in assessment timelines.

The participating RAs, whenever possible, will **deliver a single inspection outcome** unless different regional legislations will not permit.

Anticipated timelines[3]

Activity	Timeline (calendar days)
Pre-inspection planning between RAs	30 - 60 days before the start of the inspection
Communication with the facility to test IT and communication capabilities	7 - 14 days prior to the inspection
Start of the inspection	0
Close-out meeting to provide the firm with a consolidated list of observations	5 - 8 days after initiating the inspection
RAs receive CAPAs	30 days after close-out meeting
Engagement with facility to clarify CAPA plan(s), if necessary	10 days post receipt of CAPAs from the facility
Preliminary inspection report reviewed by the RAs	60 days post inspection
Final inspection report(s) sent by RAs (GMP certificate or equivalent issued/ or statement of GMP Non-Compliance, if applicable) to facility	90 days post inspection

References

- **PQKMS Website**
- **Overall Plan for Hybrid Inspection**

[3] The ICMRA participating authorities will strive to align the inspection process timelines. The timeline may vary and will be based on the internal process and legal requirements of the on-site inspectorate. This will be discussed with the inspected site during the Pre-inspection activities phase and the close-out meeting.