Reflections on the regulatory experience of remote approaches to GCP and GMP regulatory oversight during the COVID-19 Pandemic

1. Background and purpose of the paper

During the COVID-19 pandemic, international regulatory authorities adapted their inspection approaches to ensure regulatory oversight of GxP activities. Due to restrictions to protect public health, regulatory authorities utilised digital technologies, such as video conferencing software and devices to enable continuity of compliance oversight. The International Coalition of Medicines Regulatory Authorities (ICMRA) COVID-19 group set up this working group to review the adaptation of both GCP and GMP inspections during the COVID-19 pandemic to remote approaches. The working group was chaired by MHRA and had had representatives from US-FDA, EMA, Health Canada, Swiss-medic, HPRA Ireland, AEMPS Spain, ANSM France, PEI Germany, MHLW/PMDA Japan, TGA Australia, ANVISA Brazil, HSA Singapore, WHO and Saudi-FDA.

The purpose of this paper is to reflect on the combined experience during remote conduct of evaluations, inspections, and assessments during 2020-21, providing transparency to stakeholders on approaches taken to date during the pandemic. These reflections are based on the combined experience of GCP and GMP regulatory activities conducted globally, shared through working group discussions, and incorporate experience from both national and international inspections (current at the time of writing). It should be noted that there is variable experience across inspection types and areas, sites, and jurisdiction. Based on the relatively limited experience, and variability, this paper reflects emerging considerations. It should be noted that local legislation and guidance in the scope and conduct of inspections and protection of personal data are also critical considerations in the use of digital technologies in inspections and are not superseded by this reflection paper. Thus, a fully harmonised approach to the use of remote assessment of regulatory compliance in all scenarios should not be assumed. A specific case in point is the fundamental terminology used for the concept in question with some authorities/groups accepting the term “remote inspection” for the assessment of regulatory compliance in suitable cases during the pandemic, whereas others consider that this concept can be best described by “distant” or “remote assessment” owing to the limitations of the remote approach and/or related in some cases to the difference in legal framework governing inspections and remote evaluations.

While the ICMRA group have found remote inspections an enabling tool to maintain at least a minimal regulatory oversight during the pandemic, it is not the view of the group that remote inspections would fully replace an on-site inspection programme. Notable limitations, with current available technological means, have been identified during the experience with the use of remote assessment of regulatory compliance and are described in the relevant subsections.

2. Definitions/Terminology

A variety of terms have been used for remote inspection activities across international regulatory authorities based upon national regulations, such as “remote evaluation,” “remote assessment”, “remote inspections”, “desktop inspection”, and “distant assessment”.

An inspection means, for the purpose of this document, an act by regulatory authority(ies) of conducting an official review of activities, documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the work performed and that may be located at an investigator site of a clinical trial, a manufacturing site, at the sponsor's and/or contract research

organisation's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Use of the term "inspection" in this document does not mean that all regulatory authorities view activities covered by the definitions herein to be inspections for purposes of their programs. This document uses the following terminology:

Term	Definition
On-site Inspection	An inspection conducted physically on-site.
Remote inspection/ Distant assessment/ Evaluation	The process of conducting inspections, evaluations or assessments at a distance/virtually, supported by technology for communicating, sharing, reviewing, accessing systems, without the inspectors being physically present at the sites where the activities subject to an inspection have taken place/where the inspection would routinely be hosted.
Hybrid Inspection/assessment	An inspection/assessment performed using a combination of on-site and remote means.
Collaborative inspections	Inspections involving two or more regulatory authorities.

3. Application of remote approaches to inspections

Risk assessment & risk management

Throughout the pandemic, inspectorates have assessed the need for inspection on a case-by-case basis and applied established quality risk management principles and tools in their decisions when deciding on their regulatory oversight approach. This decision-making process has typically been performed by the lead inspector in consultation with operational management following discussions with the inspectee. Factors considered by regulatory authorities during the pandemic have included:

- Local or international restrictions that have been in place to deal with the public health emergency
- The need to protect the health and safety of the inspector, the inspectorate staff, and staff at the inspected facility, including reducing burden while dealing with the pandemic itself
- The regulatory compliance history of the inspectee; for example, considering if there have been repeat deficiencies identified or issues associated with information provided that could have potentially been misleading to an inspector
- The scope and objectives (pre-approval, routine or for cause) of the inspection
- The type of site (e.g. investigator, bio-analytical, sterile manufacturing) and intrinsic risks/suitability for remote assessment in order to fulfil the inspection objective
- The complexity of the activities of the site in terms of how challenging it may be to observe and adequately assess these remotely and by considering factors that may indicate regulatory compliance-related risks associated with the site
- How recently the site was inspected on-site as well as the findings from the inspection
- Changes at the site since the previous inspection
- Activities delegated to CROs and service providers
- Accessibility of electronic systems owned and managed by service providers, CROs and sponsors and whether these are accessible remotely owing to confidentiality rules
- Access to source documents (e.g. participant medical records, signed informed consent forms, validation methods, Process Performance Qualification data etc.) while complying with applicable regulations and/or institutional policies
- Where redaction of documents has to be performed to safeguard privacy and confidentiality

- The inherent risk associated with the activities conducted by the site, the types of products and the need for the product (e.g. whether high unmet medical need)
- Ability of inspectees and inspectors to conduct inspection remotely considering resources and technical proficiency and suitability of the site
- Whether the location of the inspectee made it more efficient or practical to use the remote approach to enable regulatory compliance verification

Note: GCP and GMP subsections provide further specific considerations and factors relevant to each area.

Risk management outcome

In the event that the risk assessment determined that the use of the remote oversight approaches was not suitable for regulatory compliance activities, two approaches were typically taken. Either the inspection/regulatory compliance activity was postponed until the risk assessment changed or the pandemic conditions ensured that an on-site approach was suitable; or a hybrid approach was adopted. The primary factor that altered the initial risk assessment was the change in national or local rules to manage the public health emergency, which typically resulted in the postponement of the inspection until the rules were changed.

Hybrid inspections

Hybrid inspections were used during the pandemic as a mechanism to balance regulatory oversight against risks of individual exposure to COVID-19. These were performed when the assessment process identified that a combination of remote and on-site verification of activities was appropriate. Examples of the formats are as follows; note this is not an exhaustive list:

- Assessment of some aspects of the pharmaceutical system remotely, followed by on-site follow up of manufacturing facilities.
- Follow up with on-site verification of activities that could not be performed remotely or with appropriate clarity.
- Assessment of quality management systems and procedures remotely followed by on-site follow up of data in use.

Experience gained by the ICMRA working group during the pandemic has highlighted specific technical areas and sites where there has been suitable use of remote approaches (dependent on inspection scope), as well as sites where the application of remote approaches have been harder to suitably implement.

During the pandemic regulatory authorities have applied remote oversight to the following areas:

- Sharing of documents;
- Facility tours;
- Review of data and access to the relevant electronic systems; and
- Interviewing subject matter experts.

Applications and considerations are described in more detail below for these four areas:

3.1 Remote facility tours

Experience during the pandemic from the ICMRA working group has found the application and availability of technology to enable virtual facility tours to be a key area for consideration to determine the suitability of the remote approach. The ICMRA working group has found that an ability to conduct virtual facility tours has been aided by the hardware and software that can provide an appropriate

field of vision, clarity and stabilisation of the picture, while simultaneously facilitating conversation between the inspector and tour host.

The ICMRA working group members have considered the use of pre-recorded video tours only in exceptional circumstances, and not during inspection of high-risk activities in which the inspector is not able to verify the suitability of the facility. The ICMRA working group has found that discussing expectations on this early in the planning process is beneficial to both parties.

3.2 Direct Access to documents/raw/source data

Access to documentation, electronic and paper based, by inspectors is a requirement for a successful inspection to take place. During the pandemic, a number of approaches have been taken, including providing inspectors with direct read-only access to computerised systems, or providing a member of staff to access the system under the direction of the inspector.

During the pandemic, the regulatory authorities on the ICMRA working group have found that inspectees have sometimes been apprehensive around providing direct access for inspectors to electronic systems and have offered to provide a member of staff to access the system under the direction of the inspector. Direct access to documentation by inspectors is an expectation, electronically or otherwise, whether the inspection is on-site or remote; the ICMRA group have found the facilitated approach supported by site staff may be acceptable, provided that the inspection is not negatively impacted. Experience has shown that this approach may be time-consuming for the inspectee, and occasionally the inspector, and therefore not suitable for all sites.

For GCP inspections, some electronic systems owned and managed by service providers, (CROs) and sponsors, have not been accessible remotely due to their internal business confidentiality rules as these systems contain other organisations' (sponsors, vendors, third parties) information not related to the trial(s) subject or data to be inspected. The ICMRA working group has found that alternative methods or procedures are needed by sites to enable access in this case. It should also be noted, in case direct access is given to the inspectors, appropriate measures have been put in place not to jeopardise the validation status of the firm's computerised system(s) and the security of data.

3.3 Duration of access to documentation

The ICMRA working group reflected on the need for access to documentation after the closing meeting. Although the time inspecting is usually completed by the closing meeting, documentation requests have, in rare circumstances, been made after this point. The purpose of these requests has been to assist in writing the inspection report, or to clarify a deficiency already raised to ensure the facility can appropriately address the deficiency identified. Consequently, it has been expected that requested documentation is available to the inspectors until the inspection is formally closed and the inspectee has been informed of the inspection outcome.

3.4 General IT considerations

Regulatory authorities on the ICMRA working group have found that basic factors associated with the general IT infrastructure of both the regulator and the inspectee impact on the success of the inspection. Experience has shown that involvement of IT representatives from both parties in the early stages of logistical discussions is advantageous. There have been certain restrictions imposed by some regulatory authorities' IT departments on the use of additional software, devices, applications as well as access to cloud computing services and file transfer protocols for downloading documents, all of which could affect the planned inspection. Regulatory authorities have also found that the use of dry runs has been helpful to test the systems used and ensure any potential glitches could be identified and fixed beforehand.

Experience of the ICMRA working group has shown that to achieve a successful remote inspection the bandwidth and signal strength of both parties is important to enable sharing of large data files, and therefore this is helpful to discuss early on in the inspection planning. In addition, due to the volume and nature of information being shared during a remote inspection, security is an important consideration, to safeguard privacy and confidentiality of all parties.

Whichever technology platform has been mutually agreed to, experience has shown that enabling the right user permissions to facilitate exchange of information during the inspection is key.

4. General inspection considerations

4.1 Logistical considerations

The ICMRA working group has found there to be several logistical challenges associated with performing remote inspections, which are detailed below.

4.1.1 Time & Scheduling considerations

During the pandemic, while remote inspections have been found by the ICMRA working group to take place over a longer period of days as compared to an on-site inspection, it should be noted the group experience was that the duration of inspection activities has been consistent following the adoption of the remote approach.

Several factors have contributed to a remote inspection having a longer duration:

- Differences in time-zones impacting upon the available time to inspect
- More time associated with document reviews due to the turnaround time of requests (which the ICMRA working group has found to be longer as requests are not always ‘real-time’ as compared to being in the room with inspectees)
- Subject matter expert availability during inspections (e.g. due to (local) working times)
- Translation requests that have not been performed spontaneously or in a timely manner
- The relatively new approach to inspection, and the learning process for the inspectee and the inspectorate

The IT capabilities of the inspectee to support communication can be a challenge, for example the ability to share documents and when required, to share live camera footage or sharing of screens, with factors including network bandwidth, multifactor authentication, cellular signal coverage, Wi-Fi coverage, device battery life when performing virtual tours, camera image stabilisation, and camera image quality. The ICMRA working group found that these factors could be mitigated through inspection planning, prospective document requests, performing “dry runs” and discussion with the inspectee. The experience of the group so far is that the duration of inspections that take place in different time zones took longer. This is also true for on-site inspections that are conducted internationally, however this impact when on-site would be known prior to the commencement of the inspection.

4.1.2 Language considerations

While there was limited experience of the ICMRA working group on international inspections during the pandemic, where they did occur, as with routine international inspections, there was the need to access translation services. When working remotely, translation services were not always readily available; this impacted the inspectors’ ability to ask spontaneous questions as compared to when translation services are used in ‘real time’ on-site. However, it should be noted that the ICMRA members did have experience where live translation services were possible remotely and were

accessed to facilitate translation of documents or media, and this was factored into inspection planning discussions with the inspectee.

4.1.3 Video and audio-conferencing software

The ICMRA working group has found video conferencing a valuable tool in developing an experience as close as possible to an on-site inspection, including for building rapport with the inspectees. The ICMRA working group has found that early discussions between inspectors and inspectees exploring feasible audio and video conferencing software to be used for the conduct of inspections for opening and closing meetings and interviews helpful, wherein adequate safeguards are implemented to protect privacy and confidentiality. The ICMRA working group has also found that when conversations are being held through video conferencing technology, it was helpful to have the video enabled to aid conversations and discussions around potential deficiencies or findings, i.e. replicating the on-site experience as much as possible. It was acknowledged by the group that there are several limitations to this, including some limitation on visibility, which could lead to additional attendees to the ones being interviewed and whether censoring of replies might be performed.

Video conferencing software can also be used to obtain live footage from manufacturing areas using Wi-Fi or mobile networks. Special attention has to be given to hazardous areas that require intrinsically safe devices, such as head mounted devices, cell phones, tablets or any other webcam that is connected to the video conferencing software.

Video conferencing tools can also be utilised to review data integrity approaches of the inspectee via, for instance, screen sharing of computerised systems (preferred option), retrieval of data using a stand-alone computer, or review of exported audit trails. It has to be noted that in case of screen sharing, the inspectee ensures that the installation of video conferencing tools on computers used in GxP environments takes place under QA oversight and that the computerised system(s) remain in a validated state.

The ICMRA working group reflected that in general it was helpful to discuss any recording (audio/ vide/screenshots) taking place during the inspection process to enable all parties to agree upfront.

4.2 Other Regulator considerations

The following aspects have been found by one or more members of the ICMRA working group to be important additional considerations when inspecting remotely:

4.2.1 Training of new inspectors

The use of remote inspections has impacted the ability to train new inspectors as they could not encounter the same situations and perform the same assessments as on-site. The ICMRA working group regulatory authorities therefore reflected on the need to consider how to incorporate technologies into their inspector training programmes, and how competency can be assessed both for remote and on-site elements, to ensure that full scope inspector training was achieved as per respective agency procedures. The working group noted however that the use of remote technologies facilitated additional inspectors taking part in inspections for training purposes (in an observational capacity).

Depending on their familiarity with the electronic systems used in the inspection, some inspectors have undertaken training where necessary. Any training requirements have formed part of the inspection planning process to facilitate the inspection, to ensure it did not delay the inspection process.

4.2.2 Collaborative Inspections

Members of the group have found that collaborative inspections have increased the complexity of the logistical issues discussed in this paper, however the regulatory burden to inspectees overall was decreased through the collaborative inspection. It is acknowledged that joint and/or observed inspections experience has been limited.

4.2.3 Inspectorate activities

Based on the remote inspection experience of the ICMRA working group during 2020/21 it was noted that inspectors benefitted from being "out of office" and not being contactable during time allocated to inspections. When conducting inspections remotely, inspectors and authorities have been vigilant to ensure that time allocated to inspections is not interrupted unless necessary.

4.2.4 International Regulatory collaboration

Core to any collaborative agreement is the establishment of equivalence between the respective inspection practices. In establishing a collaborative agreement, there is a confidence building period where parties involved build assurance in the systems of each party by evaluating and determining the equivalence of the respective inspection programs. Careful consideration has been made to ensure the ongoing maintenance of such agreements when one or both parties' plan has integrated remote approaches within their inspection framework during the pandemic.

The considerations have been important for mutual reliance among international partners. It has been essential to ensure harmonised approaches have been applied amongst global partners within their inspection framework. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) have developed a number of tools which have assisted in this area.

During the pandemic, ICMRA has recommended effective cooperation among global partners to ensure any changes implemented within inspection programs have enabled continued confidence in the ability to rely upon the exchange of regulatory compliance information under both collaborative agreements and mutual reliance initiatives.

4.3 Remote inspection limitations: On-site activities

The ICMRA working group has found that there are several key inspection techniques that cannot be replicated through the use of technology due to the restricted visual, auditory, and interactive abilities.

The ICMRA working group has reflected that conducting effective interviews under remote inspection approaches is not as effective as on-site, as inspectors are not able to assess body language fully and identify evasive and nervous behaviours. Due to the potential lack of spontaneous response when working remotely, this also creates some challenges in knowing how well inspectees know their own procedures and follow them, due to availability of additional response preparation time. Other limitations identified, but not necessarily only related to a remote approach, have included:

- The dynamics of meetings held virtually have been found to be intrinsically less conducive to the free flow of information between involved parties, and within inspection teams.
- Delays in availability of personnel or documents has raised uncertainties in terms of interference or provenance.
- Extensive paper-based source records systems have not been found amenable to remote inspections. Inspectors have found requesting records in advance of a live remote interaction to be helpful.
- Experience from on-site inspection raises questions as to whether important site design features would have been missed if sites had only been inspected virtually.

- Additional senses that cannot be replicated remotely is smell and sound, which could be indicative of risk in manufacturing plants including via hearing alarms, machinery & equipment etc.

For specific GCP/GMP sites, activities or scenarios that were not considered suitable for only remote inspection/distant assessments – see sections 5 and 6.

4.4 Inspection of third-party vendors

Third party service providers can play an important role in the operations of facilities and data management, through provision of software, subject matter experts and support staff. Discussions have been held between the inspector and inspectee to determine whether any vendor(s) needed to be available during the inspection, in the same way as for on-site inspections.

4.5 Novel approaches utilised by some authorities

Some authorities in the ICMRA working group have purchased software packages that are widely used by stakeholders to facilitate remote data review. For example, chromatography data systems have been set up remotely for the purposes of analytical data review. This has assisted the review of data generated within bioequivalence studies or chromatography data generated as part of the release testing of manufactured products. This could be a time intensive process on-site, and the time saved by conducting this element remotely could be used to focus on other activities while on-site. However, such an approach is not widely trialled or evaluated across the group.

The use of visual technologies & video streaming glasses is being evaluated by several authorities to facilitate inspections of facilities. As with other applications, this would require the infrastructure to support their use.

To facilitate international inspections, some use has been made of other locally based government officials. These officials have conducted facility tours using video technology whilst being guided by the inspectors remotely. This approach has been utilised at the discretion of the inspectee and purely to verify the physical premises, however legal constraints and/other risk assessments precluded such an approach in some authorities.

4.6 Regulatory action considerations

Of importance to the respective authorities has been ensuring that appropriate legal consequences and operational processes for hybrid and remote inspections enable similar legislative and/or regulatory powers for regulatory compliance and enforcement as would apply to on-site inspection (e.g. license suspension where required).

Considerations for legal instruments by the ICMRA working group has included ensuring inspectors are provided with authorities equivalent to on-site inspection to:

- Evaluate a site through a telecommunication or other remote means to enable conduct of an inspection.
- Require records (i.e. electronic or paper records) to be made available.
- Examine or make copies of records.
- Require co-operation and prevent interference.

When inspections are conducted abroad, there has also been consideration over the applicable laws within the respective countries. The ICMRA working group reflected on the fact that data protection laws vary between countries and that the use of cameras to film facilities may not be permitted as a

result. These factors have been considered as part of the risk assessment process, including obtaining permissions from those inspectees who were recorded.

5 GCP

5.1 Areas where remote oversight has been proficiently applied in GCP during the pandemic

Digital technology has been applied for remote inspections of electronic systems used for clinical trial conduct, including electronic trial master files, electronic case report forms, electronic patient reported outcomes, interactive response technologies, electronic document management systems etc. noting the caveats identified above under limitations and considerations, such as confidentiality rules, format and structure.

5.2 Areas where remote oversight was most challenging when applied in GCP during the pandemic

In the area of GCP, remote inspections at investigator sites were often considered unfeasible by some authorities, because it was crucial to avoid any undue additional burden on investigator site staff during the time of the pandemic (e.g. to provide access to appropriate paper-based documentation), and the inspection of source documents may not be possible due to local legal requirements concerning accessibility and data protection. Furthermore, some authorities experienced instances where there was limited access to relevant electronic systems by investigational site staff and/or by inspectors.

It should be noted that within the EU remote inspections at investigator sites are not considered to be feasible (reference 2).

Digital technology has not replaced the need for on-site inspections. It has provided a tool to enable regulatory oversight under circumstances where it would not otherwise have been feasible. Some of the following facility types and activities have not always been considered possible to review by remote means however, including full data verification and data integrity checks. Other areas not always considered suitable for remote activities include:

5.2.1 Facilities

- Hospital wards, clinics, pharmacies, aseptic facilities, intensive care facilities or clinical laboratory facilities.
- Remote access to identifiable source documents (including paper-based/electronic medical records, signed informed consent documents etc.) due to institutional/regulatory policies on privacy and confidentiality (noting that some authorities have had experience of this but many have country-specific limitations).

5.2.2. Phase I Clinics

- Reviewing protocol and handling of emergency scenarios.
- Checks of crash trolleys and associated equipment.
- Suitability of facilities, including on-site testing of alarms/ call buttons.
- Witnessed procedures such as dosing or blood draws.

5.2.3. Bioequivalence Facilities

- Checks of crash trolleys and associated equipment.

- Suitability of facilities.
- Witnessed procedures such as dosing or blood draws.
- Chain of custody verification.
- Laboratory practices (e.g. labelling).
- Laboratories containing analytical instruments (noise).

5.2.4 Analytical Laboratories

- Suitability of facilities.
- Chain of custody verification.
- Laboratory practices (e.g. labelling).
- Laboratories containing analytical instruments (noise).

5.3 Risk management process

The following aspects were highlighted by the group as areas that the ICMRA working group regulatory authorities have considered as part of their risk-based approach to remote inspections during the pandemic.

The lead inspector has typically been responsible for implementing a risk-based approach for the feasibility and scope of the remote inspection.

Inspectors have conducted a pre-inspection discussion (via tele-/videoconference or email) with the inspectee to assess feasibility and the possible risks that impacted the scope of remote inspections. Some of these risks have included:

- Remote access to information

Inspectors have required remote access to standard operating procedures, trial master files, including designated investigator site files, source documents and case report forms for the remote inspection.

However, remote access to source documents (e.g. participant medical records, signed informed consent forms etc.) has been contingent on applicable regulations and/or institutional policies being adhered to. Identifiable source documents have been redacted where necessary to safeguard privacy and confidentiality. Inspectors have been aware of the possible administrative burden imposed on inspectees to redact source documents and have altered the scope of the remote inspection to avoid remote source document review or source document verification where this still enables the aim of the inspection to be fulfilled.

- Duration of remote access for GCP Inspections

Remote access to information has been provided from inspection preparation to inspection closure to allow the inspectors to prepare, conduct and follow up appropriately. This has been beneficial to the inspection process.

5.4 Specific regulatory considerations

Facility Tours

The ICMRA working group has found there has been a potential risk that non-trial patients, trial participants and/or their associated records could be observed during remote tours of facilities if sufficient security protocols were not implemented. Inspectors have been conscious of the level of

intrusion and impact of remote inspection activities on the delivery of routine clinical care, and therefore minimised this to the lowest level possible.

Considering the above, the ICMRA working group members have carefully considered the potential conduct of a remote inspection on a case by case basis following a risk based approach, using the same quality risk management approach as used for on-site inspections to determine the areas of interest and whether suitable scrutiny could be applied remotely, whilst ensuring that the administrative burden does not unduly impact on the day to day activities of the organisation being inspected. The inspection team require the ability to discharge their duties effectively, regardless of whether this is remotely or in person.

The main body of this document describes the aspects required for a successful remote inspection, but additional consideration for GCP has been given to:

- The original format of trial-based records (e.g. paper, electronic, hard copy imaging etc.) and the amount of work required to provide these in a suitable format.
- The availability of electronic systems to facilitate remote access to information. Remote access to source documents (e.g. participant medical records, signed informed consent forms etc.) is contingent on applicable regulations.
- The ability of inspection teams being given access to all areas and systems containing trial related documentation (supported by clear instructions/training on their use and guidance on where documentation could be located). Where this is done in person, it is usually simple to be guided or to ask for assistance, but this has been harder remotely.
- Access and management of unblinded data. Some possible considerations and approaches have included restricting access to an unblinded inspector and supporting company staff, limiting access to unblinded information to a specific area/trial site, use of a different account to access the data or accessing the unblinded data on-site.

Access to unblinded data

For remote inspections of ongoing, randomised, double-blind clinical trials, inspectors have adopted a risk-based approach to assess whether the scope of the remote inspection required access to unblinded data. As remote access to unblinded data posed additional challenges to maintenance of the study blind, inspectors adopted a pragmatic approach in requesting access to unblinded data. It is expected that the sponsor would have a procedure in place to enable this access for regulatory authorities. Some possible considerations have included restricting access to an unblinded inspector, limiting access to unblinded information to a specific area/trial site, sharing the unblinded data via screen sharing during the remote inspection. It was noted that if the trial is closed and reported, then access to unblinded data did not require an additional risk assessment.

There had been no expectation of differences in the inspection powers between on-site and “remote” activities as the standards remain the same.

6 GMP

6.1 Areas where remote oversight has been successfully applied during the pandemic

The ICMRA working group reflected that while remote inspections would not regularly replace a routine on-site GMP inspection, some regulatory authorities have included remote inspection reports in the assessments for GMP and it has permitted many regulatory authorities to continue with their quality oversight programme remotely. For those regulatory authorities where remote inspections cannot replace the on-site inspection due to legislation, information including

technology obtained from questions asked has allowed informed decisions on GMP clearance extension or further intelligence gathering on the manufacturing site.

The remote inspection assessments have been able to provide some useful information about the manufacturing site. For this reason, there may be use for these type of remote inspections using digital technology in the future, especially, but not only, where travel and safety constraints prevent inspectors from being on-site for the inspection.

It was considered that there were situations where remote inspections were a useful tool in enabling a regulator to gain sufficient assurance of regulatory compliance of a site when it was not feasible to perform an immediate on-site inspection, due to travel and safety restrictions. It was felt that a remote inspection provided an alternative approach that reduced the potential public health risk, compared to an alternative scenario where all inspections are deferred until travel and safety situations improved.

6.2 Areas where remote oversight is most challenging when applied in GMP during the pandemic

In the area of GMP, remote inspections of sites that required detailed observation were often found to be unfeasible and required a hybrid approach with a supplementary on-site inspection. Examples of processes that required detailed observation included aseptic manufacturing sites and sites that handled potent actives (i.e. with low Permitted Daily Exposure (PDE)) with multi-use equipment and facilities.

Some facilities were found to be unsuitable to support complete virtual tours due to interference with Wi-Fi/mobile phone signals limiting the technology, this varied between sites, but could include:

- Instrument rooms (e.g. housing large numbers of HPLCs).
- Walk-in metal chambers (e.g. refrigerators or stability sample rooms).
- Utility/technical areas (e.g. housing air handling units and plant rooms for water/steam systems).

Some aspects of inspection could not be performed to the same rigour as if an inspector was on-site, examples include:

- The limited field of view, position, resolution and focus of cameras were found to make simple observational checks that an inspector would do on-site very inefficient when performed remotely, with the inspector having to provide detailed instructions and explanation to the person responsible for the remote camera. Examples include inspecting microbiology samples in incubators and observing general facility condition, such as for evidence of damage to ceilings.
- The inability for an inspector to walk up to and point at equipment during virtual tours made communication more challenging and the inspection process significantly slower, for example if reviewing complex pipe layouts for processes or water systems when discussing potential dead-legs in equipment design. It was considered that these systems are better observed on-site.

6.3 Risk management process

It was reflected that for GMP inspections a risk assessment could consider the complexity of the activities of the site in terms of how challenging it may be to observe and adequately assess these

remotely and by considering factors that may indicate regulatory compliance-related risks associated with the site.

It was reflected that where specific risks are identified, actions may be identified that could reduce the risk to enable a remote inspection/distant assessment to be performed, or other aspects might be considered, such as reducing the time before re-inspection of a site or supplementing data with information from a trusted source. It was reflected that some aspects that may be useful to consider if developing a risk assessment tool might include:

Consideration of Observational Complexity

This could reflect the complexity of the site operations, its processes, and its products in terms of the ability to assess the activities remotely and considering the intended scope of the inspection. It was discussed that experience of general indicators of complexity in terms of an observational inspection i.e. an inspection entailing an inspector observing an operation or activity, included but not limited to:

- Aseptic manufacturing processes – were considered highly complex processes for observation.
- Sites handling potent actives (i.e. with low PDEs) with a low level of dedication of equipment and facilities (e.g. Air Handling Units) were considered highly complex processes for observation.
- Low bioburden biotechnology, active substance manufacturing and blood derivative product manufacturing process were considered complex.
- Depending on the type of activity, sites performing relatively simple Investigational Medicinal Product (IMP) packaging operations were considered moderately complex for observation.
- Sites handling non-potent products or sites handling only a single product were moderately complex for observation.
- Sites dedicated to terminal sterilisation were moderately complex for observation.
- Sites that performed only secondary packaging operations generally had a lower level of observational complexity.
- 'Virtual' sites, e.g. the offices of virtual importers that had contracted out all activities, were considered as having a very low level of observational complexity and were found to be generally suitable for remote inspection.

The observational complexity of a limited scope inspection, for example when verifying Corrective Actions & Preventative Actions (CAPAs) from a previous inspection could vary depending on the scope of inspection. For example, where the scope was only to verify records in the quality system, then this was a very low level of observational complexity. However, where the scope was to verify improvements in aseptic manufacturing practices, then this was considered a highly complex process for observation.

7 Information Management

7.1 General considerations

Inspectors are bound by privacy and confidentiality laws in their respective countries and are thus required to maintain privacy and confidentiality throughout inspections. Regulatory authorities in the ICMRA working group agree that separate Confidentiality Disclosure Agreements are not required to be signed by inspectors for remote inspections, and this is no different to an on-site situation. This

includes for accessing standard operating procedures, documents, data, electronic systems, medical/health records etc.) for the inspection.

As remote inspections have required remote access to information, inspectees have ensured that access provided to inspectors was read-only, secure, and limited, and inspectors were trained to navigate the electronic systems before the remote inspections. Additional safeguards have been required to be implemented to ensure privacy and confidentiality are protected.

7.2 Document requests

The ICMRA working group has found that remote inspections have generally not limited inspectors' access to information (e.g. documents viewed during a remote inspection generally did not differ content wise) in accordance with legislative requirements.

Inspectors and inspectees have explored feasible file sharing platforms that allow inspectors to access and download documents/data for inspections.

7.3 Document retention

The provision of documents/ electronic data to regulatory authorities during a remote inspection is potentially greater than on-site inspections, and the experience of the ICMRA group in general is that so far this has not resulted in additional retention of data by the regulatory authority, as compared to on-site inspection. Some remote inspections have also required less documentation provision due to more focussed scope.

It was noted by some in the ICMRA working group that the retention of data and documents would be in line with on-site inspection processes.

7.4 Inspection Reporting

Inspections conducted during the pandemic by the ICMRA working group members have been reported in accordance with regulatory agency procedures. Some regulatory authorities have modified or adjusted the reporting process/certificate issued to reflect the type of inspection performed i.e. remote, hybrid or on-site. Reports have also covered the areas reviewed (and not reviewed) to inform the next inspector of areas that would require focus on-site. Some regulatory authorities have also provided a preamble on the tools used, as well as limitations with the technology.

8 Conclusion

In conclusion, the ICMRA working group has found the use of digital technologies in the remote conduct of inspections, evaluations, and assessments a key business continuity tool for regulatory oversight of certain activities and sites during the COVID-19 pandemic, which has proved valuable in the protection of public health in this emergency situation.

It should be noted that some regulatory agencies are currently evaluating whether to utilise remote approaches going forward. While some ICMRA working group members do not currently think it will fit within their regulatory framework, a number of regulators have expressed an interest in supplementing an inspection, or in some cases, replacing the need for an on-site inspection with remote and/or hybrid approaches, such as for addressing a narrow concern, contributing to an application assessment and approvability decision, or verifying certain corrective/preventive actions.

While the full extent of its use in normal operation outside of a public health emergency remains to be defined, and acknowledging there are limitations and challenges associated with the use of

remote inspections, assessments and evaluations, the ICMRA working group has concluded that remote approaches could continue to be a tool in the inspection 'toolkit' of regulatory authorities, post pandemic.

9 References

1. ICH Guideline for good clinical practice E6 (R2): ICH E6 (R2) Good clinical practice | European Medicines Agency (europa.eu)

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3. US FDA guidance for industry (and FDA staff) on Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency, April 2021: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remote-interactive-evaluations-drug-manufacturing-and-bioresearch-monitoring-facilities-during-covid