Tony Cruz

Philippe Forgues

Mayda Mercado

THE NEW NORM: A GLOBAL VIRTUAL GCP PRE-APPROVAL EMA INSPECTION

The coronavirus disease 2019 (COVID-19) pandemic has caused major disruptions in daily life. Faced with this new reality within the biopharmaceutical industry, the European Medicines Agency (EMA) implemented a series of measures to address the effect of disruptions on the drug review and approval process. Specifically, in terms of reviewing and reconstructing all components of a successful study and eventually approving potential new life-saving therapies.

Briefly, the biopharmaceutical company (sponsor) submitted a Marketing Authorisation Application (MAA) and was notified of a pre-approval EMA GCP inspection (hereafter EMA inspection) months before the COVID-19 pandemic arrived. By the time the inspection date arrived in mid-April, the EMA and sponsor had to revise plans to conduct their respective pre-approval GCP inspections according to the 'new global norm'. The EMA developed procedures to conduct inspections without delay, regardless of the pandemic. This inspection was among the first to be conducted via a virtual and remote process. Data and essential documents from the sponsor's novel drug therapy were reviewed and the study was reconstructed by the sponsor according to GCP.

This article describes how the EMA and sponsor collaborated to successfully complete a global, fully virtual and remote EMA inspection. Ultimately, a robust plan, flexibility and innovative use of appropriate resources, logistics and electronic tools were key components of the successful EMA inspection that led to a positive recommendation. The EMA issued guidance documents pre-inspection and post-inspection to specifically address virtual and remote inspections. Notably, the conduct of global EMA inspections has been beneficially transformed within the biopharmaceutical industry.

SETTING

The global COVID-19 pandemic triggered events and decisions that affected the healthcare industry and health authorities worldwide. Shelter-in-place orders, travel restrictions and directives issued by local and global governments to contain the spread of the infection, prevented travel except for essential workers. Thus, an onsite EMA inspection was not possible.

Never in the prior 100 years had a pandemic prevented people from going to their offices. In the current unprecedented situation, technological advances granted the work force the option of working from home with electronic meeting platforms and shared file space.

BACKGROUND

The sponsor submitted an MAA and received a preliminary EMA inspection notification months before the COVID-19 pandemic arrived. By mid-April 2020 when the sponsor received the inspection date, the onsite EMA inspection was no longer possible due to the COVID-19 pandemic. Yet, applicable EMA guidance documents or procedures did not exist to allow for the conduct of virtual and remote inspections. Thus, the plan was modified to ensure that the EMA inspection could proceed, meet timeline requirements and ensure timely review of the MAA (EMA guidance documents were issued to address challenges posed by the COVID-19 pandemic[1,2]).

ENVIRONMENT

The EMA approached the sponsor with a proposal to conduct one of the first-ever global, virtual and remote EMA inspections. Before the inspection occurred, the EMA and sponsor met to discuss regulatory requirements and the use of electronic meeting platforms in cooperation with other health authorities. By mid April, an Inspection Readiness Plan was finalised with the EMA health authorities in the EU and the sponsor in the United States (US).

The purpose of the virtual and remote EMA inspection was two fold:

1. The investigational product submission could be reviewed, reconstructed and approved to ensure patients received much needed therapies.

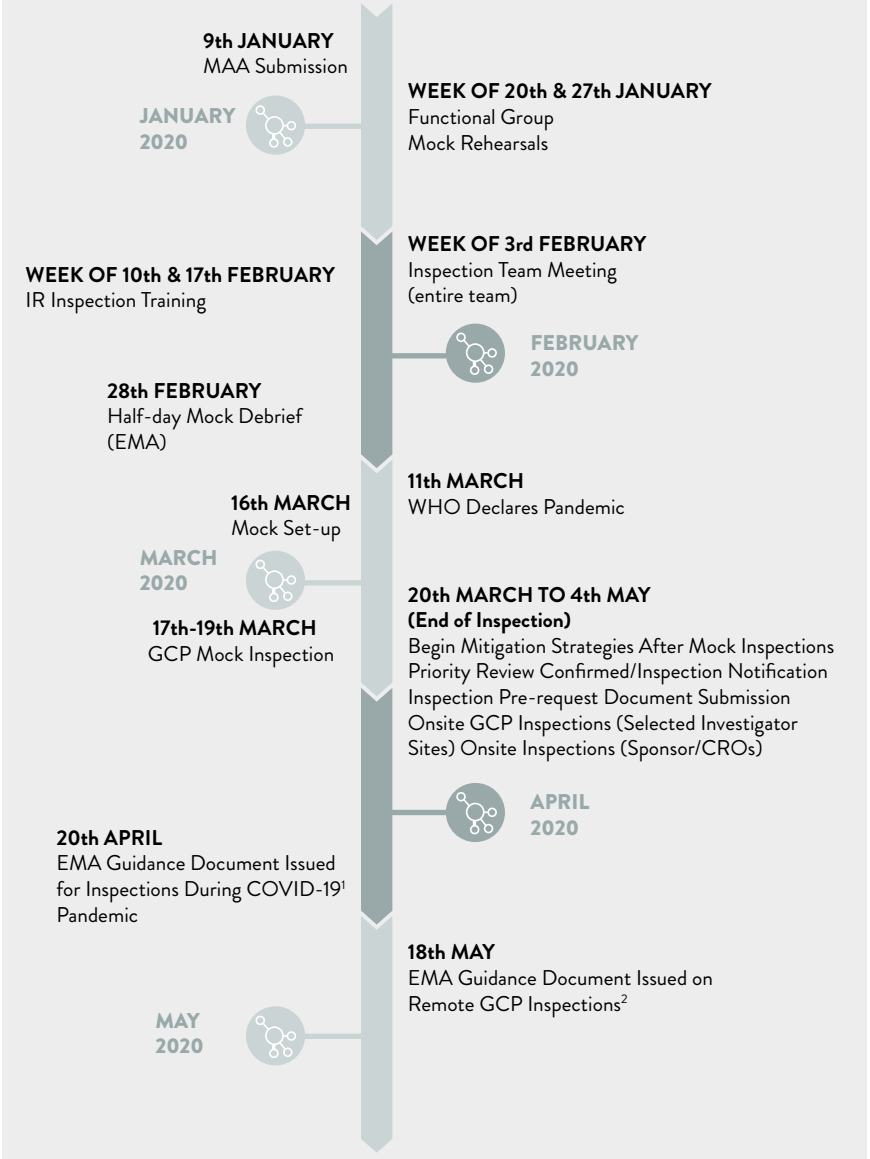
2. To orchestrate a virtual and remote EMA inspection without compromising the regulatory requirements of the inspection processes. A guidance document was issued pre-inspection[1] and post-inspection[2] to address the unprecedented nature of this EMA inspection[1]

During the conduct of the inspection, new measures and processes were taken to ensure adherence to GCP during the review of the respective study. These measures also provided guidance to stakeholders. Notably, the EMA inspectors were able to conduct regulatory review.

SUBMISSION TIMELINE

A timeline of the submission through the EMA inspection is presented in Figure 1.

FIGURE 1. TIMELINE FROM SUBMISSION TO EMA INSPECTION



STAKEHOLDERS

Numerous stakeholders were involved in the EMA inspection. The key stakeholders included the EMA inspection team and the sponsor. The EMA inspection team was composed of inspectors and observers from the EMA and observers from other health authorities who were present at the virtual and remote inspection. The sponsor inspection team comprised all the clinical development functional areas, service providers and vendors (all termed sponsor). The EMA sponsor inspection was 100% virtual and remote.

To facilitate planning, scheduling and execution of the EMA inspection, new sponsor roles were created. The individual roles and functions of key stakeholders for the sponsor inspection are presented in Table 1. More than triple the number of sponsor inspection team members were needed to support and manage the virtual and remote EMA inspection versus an onsite inspection. Notably, the technology and inspection software support staff members comprised approximately one-quarter of the sponsor's team and twice the staff were needed versus an onsite inspection.

INSPECTION PROCESS

Several key processes and tools were developed by the sponsor to conduct a virtual and remote inspection. An overview of the virtual and remote GCP inspection process is presented in Figure 2. The difference between onsite and virtual inspection processes is the establishment of electronic platforms and user logistics needed to ensure continuous virtual communication throughout the inspection.

Five key areas were identified as essential to the conduct of a virtual inspection. Key processes and tools were developed as described in Table 2.

TABLE 1. KEY STAKEHOLDERS FOR SPONSOR INSPECTION

ROLE	VIRTUAL ROOMS	DESCRIPTION OF ROLE AND RESPONSIBILITY	PEOPLE NEEDED TO CONDUCT PRE-APPROVAL INSPECTIONS	
			FACE-TO-FACE	VIRTUAL
HEALTH AUTHORITY MEMBERS				
Lead Inspector	Inspection	Single point of contact for EMA and inspection team. Negotiates, communicates inspection expectations to the sponsor and leads all inspection activities.	1	1
EMA Inspectors	Inspection	Before the inspection, EMA inspectors provided all requested documentation of the virtual/remote inspection via electronic file sharing software During the inspection, EMA inspectors followed up on questions and verifications on review of the provided sponsor study documentation At inspection conclusion, EMA inspectors worked with the lead inspector to generate the inspection findings, issue an initial inspection report providing the sponsor a window of time to respond, review sponsor inspection responses and issue the final report.	~2	3+
EMA Observers Health Authority Observers	Inspection	EMA and other health authority observers requested attendance during the first virtual inspection.	Not Applicable	2 3
TOTAL			~3	9+
SPONSOR MEMBERS[a]				
Executive Sponsor	Inspection	Head of development at sponsor company updated on inspection progress daily. Strategic role to ensure that tasks are completed. Single point of contact to escalate and mitigate challenges and issues. Further communicates inspection preparation status, communicate and follow-up on direct report action items to stakeholders as needed.	1	1
Senior Quality Representative	Inspection	Day-to-day management of the Inspection Readiness Team; with primary contact with the Executive Sponsor and health authorities (EMA).	1	3
Inspection Readiness Lead/ Coach	Back	Point of contact to manage the Inspection Readiness Team, track all components of the Inspection Readiness Plan and the respective deliverables.	1	1
Primary Host	Inspection	Document/interpret EMA inspection questions, provide communication to inspector requests and directly confirm documentation requests to respond to inspectors.	1	2
Study Expert Host*	Inspection	Supports the primary host and SMEs by providing expertise on the study sponsor GCP processes. Helps interpret requests.	0	2+

ROLE	VIRTUAL ROOMS	DESCRIPTION OF ROLE AND RESPONSIBILITY	PEOPLE NEEDED TO CONDUCT PRE-APPROVAL INSPECTIONS	
			FACE-TO-FACE	VIRTUAL
Request Strategist Floater*	Inspection and Back	Floats between rooms to strategise, interpret and communicate inspector requests to the back room. Works directly with the inspection host to ensure that document requests address the questions and enable the EMA inspectors to reconstruct the clinical study.	0	1
Host Support	Back	Navigates back room team and ensures the requested and supporting documents are provided to the inspectors; supports host throughout the inspection.	1	2
Presentation Support*	Inspection and Back	Mainly in the virtual inspection room, but floats between virtual rooms to ensure that all queued slides are ready upon request; prepares the next slides to be presented per EMA inspection agenda.	0	3
Scribe	Back	Documents all notes, dialog, questions, comments, verbatim for future use.	2	4
Videoconferencing Support*	Inspection and Back	Manages videoconferencing logistics, troubleshooting, manages access to 'breakout rooms' for inspection SMEs (allow SMEs to enter and exit the inspection room).	0	4
Communication Lead	Back	Draft and send notification emails/texts. Drafts meeting minutes.	1	2
IT Lead and Team	Back	Trains both health authorities and sponsor inspection readiness team. Check connectivity and access for both inspection and preparation room.	1	3
IT Support Team Coordinator	Back	Provides access to virtual breakout rooms, communicates current status to team members and informs and allows SMEs to enter breakout inspection and back rooms as needed.	1	8
IT Request Managers	Back	Manages and assigns requests made by the inspector to processors. Oversees call functions.	1	5
Request Processor	Back	Familiarity with sponsor systems and processes. Responsible for filling requests with SMEs and vendors.	1	3
Quality Check	Back	Responsible for confirming inspector request is fulfilled and ensures documentation is in order before entering the inspector's file sharing folder.	2	6
Strategist Room Lead	Back	Manages strategy chats and videoconferencing logistics for breakout rooms and moves requested folders into file sharing folder.	1	4
Strategist	Back	This role is essential to clarify requests and provide each SME entering the virtual inspection room with background and context to ongoing discussions and questions. After exiting, the SME debriefs with the strategist to provide the background and context to ongoing discussions and questions.	1	3
Inspection Oversight	Back	Oversees logistics and troubleshoots all challenges and issues. Backup videoconferencing logistics support.	1	4
Strategy Oversight *	Back	Oversees strategy and SME movement between the preparation meeting and inspection meeting.	0	3
TOTAL			17	64+

eTMF=electronic trial master file; FDA=Food and Drug Administration; GCP=good clinical practice; IT=information technology; SME= subject matter expert

Note: virtual rooms were used. The inspection team was located in the inspection room (also known as the front room) and the back room is also known as the preparation room.

a Sponsor includes the clinical development team from the sponsor, clinical research organisations and the service providers/vendors.

*Unique to this virtual inspection.

FIGURE 2. OVERVIEW OF THE VIRTUAL GCP SPONSOR INSPECTION PROCESS

*See Stakeholder Section and Table 2 for details. Note: EMA Guidance Documents were issued before the inspection[1] and after the inspection concluded[2].

TABLE 2. KEY AREAS AND TOOLS DEVELOPED TO CONDUCT A VIRTUAL INSPECTION

KEY AREAS	TOOLS AND/OR METHODS	CHALLENGES	BENEFITS/RISKS
INFORMATION TECHNOLOGY	Cloud-based applications and video/audio/message conference solutions were selected and tested for the virtual inspection.	All participants required the following tools: 1. Consistent internet connectivity with strong bandwidth 2. High quality audio and video computer hardware microphone and camera 3. Before inspection, testing the cloud-based applications and video/audio conference solutions were required.	**Benefits** New modality allowed for instant breakout rooms to address limited physical meeting space (both in physical size and in total number of stakeholders). Breakout rooms are not possible with onsite inspections. **Risks** Non-functional technology.
	Training all participants with various technological literacy across digital platforms.	Ensure training on the following items: • Inspection platform • Systems • Processes • Tools (i.e. mute audio and turn off video to mitigate distraction).	**Benefits** Allow successful participant interactions and focus on subject matter. **Risks** Non-functional technology.
	Sponsor IT staff available throughout the inspection.	Technology issues occurred that had to be identified and resolved quickly.	**Benefits** Able to mitigate technological issues quickly in timely manner. **Risks** IT staff availability.
LOGISTICS	Comprehensive planning, creating, testing, training and executing all phases of the virtual inspection to identify and mitigate disruptive events that could impede activities.	Time zone differences on two continents meant that participants worked outside of normal business hours.	**Benefits** Willingness to have a flexible schedule was key to completion of inspection. Participant roles are described in Table 1. **Risks** Team member availability, one vendor refused to attend.
	Project Manager to oversee key activities.	Coordinate movement between participants, understand roles and be able to contact any participants quickly.	**Benefits** Able to contact participants quickly. **Risks** Ensure needed participant is in the correct virtual room at the appropriate time and topic.
	Participants and division of labour.	Virtual environment increased the number of tasks and movement between rooms and was not conducive to multitasking.	**Benefits** Multiple breakout rooms available. **Risks** Key SME can only participate in one discussion simultaneously.
	To fulfil inspection requests, a role and process was developed to facilitate rapid retrieval of essential study documents electronically, while quality checking, tracking and archiving for post-inspection reference.	Participants responsible for request always need to be informed.	**Benefits** Allowed real-time visibility of request to all participants. **Risks** Participants may have multiple tasks.

KEY AREAS	TOOLS AND/OR METHODS	CHALLENGES	BENEFITS/RISKS
RESOURCE MANAGEMENT AND TRAINING	Available core inspection team with backup support staff.	Intense eight days (approximately four hours/day) in which individuals participated (≥ 3X members vs onsite inspection) and were on standby to provide documentation and evidence	**Benefits** Participants continuously available. **Risks** Personnel relieved of daily job to attend inspection.
	Facilitated multiple training sessions.	15 training sessions were conducted as follows: • Inspection readiness • Mini-mock interviews • Platform, systems, processes and tools.	**Benefits** Able to provide virtual training in multiple time zones **Risks** More sessions needed to ensure availability.
AGENDA MANAGEMENT	Dashboards, file sharing systems, and resources. Pre- and post-inspection daily debrief. Agenda topics planned 1-day before then discussed, clarified and negotiated between inspectors and sponsor members.	Large volume of information and fast flow overwhelming to participants. Requires flexibility, organisation and communication to ensure orderly and expeditious flow.	**Benefits** Communication tools must be updated continuously. Participants ask questions, seek clarification and give and receive feedback. **Risks** Communication closely monitored, with continuous updates.
GENERAL INSPECTION CONSIDERATIONS	Communication plan that informs the inspection process and maintains inspector expectations.	Subject matter experts represent the sponsor. They must be prepared, have good presentation skills and be engaged without distractions. Non-verbal cues are not observed virtually and may lead to miscommunication.	**Benefits** An effective plan is vital to a success with the potential to create greater efficacy, reduce costly errors and provide a feedback mechanism. **Risks** Ineffective communication could lead to an unsuccessful outcome.
	Participants with intimate knowledge about study conduct.	Retrieval of study-related (electronic Trial Master File, large volume) documentation and data retrieved real time.	**Benefits** Provides data quickly. **Risks** Able to understand request, find and retrieve data.
	Role playing.	Anticipate problems before they arise.	**Benefits** Comfortable with reconstructing the study. **Risks** No personal involvement.

Abbreviations:

IT: Information Technology
SME = Subject Matter Expert

CHALLENGES TO A VIRTUAL INSPECTION

The EMA approached the sponsor with the request to conduct a virtual and remote inspection. Pre-approval GCP inspections are always complex, but the virtual and remote inspection process resulted in additional challenges versus an onsite process as follows:

1. When a discussion began regarding the possibility of a remote inspection, no guidance existed regarding its conduct. Thus, the EMA issued pre-inspection[1] guidance to assist with the inspection. Moreover, a post-inspection guidance[2] document was written after completion of the remote inspection to further assist in the conduct of virtual and remote inspections. The guidance suggests that the EMA believes virtual inspections are here to stay.

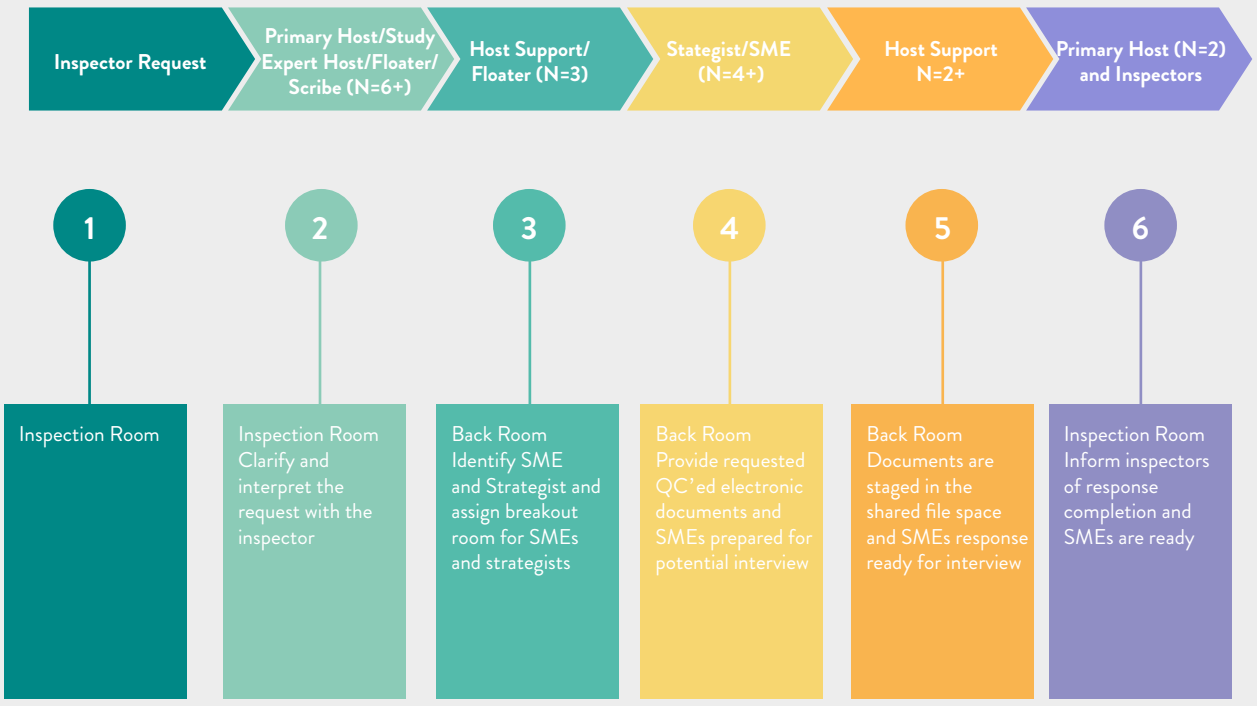
2. Extensive training by IT support teams was required to ensure that all stakeholders (EMA and sponsor) had sufficient equipment, experience and a level competency with electronic inspection tools.

3. Before the inspection, a more robust plan and extensive preparation was crucial. The number of personnel needed to conduct a virtual and remote inspection more than tripled versus a face-to-face inspection. Notably, the technology and inspection software support staff members comprised approximately one quarter of the sponsor's team and twice the staff were needed versus an onsite inspection.

4. There were time zone challenges, so the sponsor and EMA adjusted their inspection schedules and extended their workday. Specifically, the sponsor in the US met with the EMA predawn to midday, then prepared for the next day, and ended the day after all inspection requests were prepared and sent to the health authorities to review before the start of the inspection on the next day.

5. An overview of the process used to manage the inspection requests is presented in Figure 3. In an onsite inspection, an inspection and back room are used, with runners moving between rooms and requests provided in paper form. In a virtual inspection, the requests are provided electronically with a virtual inspection room, a virtual back room and multiple breakout rooms. Briefly, the EMA inspectors provided requests to the sponsor's hosts in a virtual environment. Then subject matter experts prepared responses and supporting documentation in response to each request. Moreover, the subject matter experts prepared to meet with the inspectors virtually upon request. This process was repeated for each request.

FIGURE 3. INSPECTOR REQUEST PROCESS IN A VIRTUAL ENVIRONMENT



QC'ed= quality control checked; SME=subject matter expert; Note: The sponsor roles presented are defined in Table 1.

LESSONS LEARNED

Inspections are a large component of the drug approval process, regardless of the global environment. In the end, electronic technology advances allowed for a 100% virtual and remote inspection. However, at the time the EMA proposed a virtual and remote inspection, it was not clear that a successful EMA inspection that adhered to all tenants of GCP and reconstruction of the clinical study was possible.

Compared with an onsite inspection, key components to the successful inspection included a robust inspection management plan, flexibility, the appropriate resources, logistics and electronic tools. A nimble, strategic and knowledgeable team was crucial to manage large volumes of data, resources, time zone differences and multiple inspector requests during the inspection. Team members rapidly responded to inspection requests and were able to find, collate and synthesise electronic data quickly. Moreover, data must be reviewed by the EMA to corroborate GCP compliance and enable the inspectors to virtually ensure patient safety and the integrity of the study. Flexibility on the part of vendors and service providers was equally crucial to the success of virtual and remote EMA inspections. The availability of vendors and service providers to respond electronically to requests throughout the inspection demonstrated a level of commitment by the sponsor to ensure accountability for their respective roles and responsibilities. Lastly, experienced technology and software teams ensured that continuous communication was achieved during the inspection.

Both the sponsor and health authorities had to revise existing inspection procedures on managing EMA inspections to ensure they were conducted virtually with electronic inspection tools and systems. On the health authority side, collaboration between the health authorities was necessary to ensure that study site inspections could be conducted in the US. Moreover, new guidance documents were issued both pre-and post-inspection to address the unprecedented circumstances of the EMA inspection[1,2]. On the sponsor side, extensive preparation and planning was necessary to address the challenges of performing the EMA inspection from remote locations. Ultimately, the number of personnel that participated in the virtual EMA inspection tripled versus an onsite inspection.

As one of the first 100% virtual and remote EMA inspections, the data and essential documentation of the sponsor's novel drug therapy were reviewed and reconstructed according to GCP and local requirements, as applicable. The inspection resulted in a conditional marketing authorisation from the Committee for Medical Products for Human Use. Post-pandemic, virtual inspections may become common practice.

Notably, the health authorities and the sponsor demonstrated that a 100% virtual and remote inspection could be performed successfully and has beneficially transformed the conduct and management of inspections within the biopharmaceutical industry. The sponsor appreciates and acknowledges the support of the EMA.

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PROFILES

Tony is DVM, Senior Vice President for Quality at InClin Inc with over 20 years of industry experience in building R&D Quality Management Systems, Managing Health Authority Inspections globally in the areas of GLP, GCP and GVP.

Philippe is MS Vice President of Clinical Operations and Data Management at Kite Pharma, a Gilead Company. He has over 25 years of clinical trial experience focused on quality deliverables and regulatory compliance for the biotech and pharma industry.

Mayda is MBA, Executive Director of Global Quality and Compliance at Kite Pharma, a Gilead Company. She has over 25 years of experience with a successful record of leading global change, managing GCP, GMP inspections/audits, improving processes and engaging talent to deliver sustainable results in the regulated industry.

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