COVID Original Research

The Utility of Remote Inspections During the COVID-19 Health Emergency and in the Postpandemic Setting

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ABSTRACT

Purpose: The COVID-19 pandemic has affected the management and operation of regulatory agencies and the pharmaceutical industry around the world. It has prompted regulatory authorities to consider new ways of working and introduced, among others, remote inspections to validate the integrity of the regulatory data submitted by companies, to evaluate the quality of production and manufacturing sites, and to ensure the conformity with Good Regulatory Practices with the overall goal of guaranteeing patient safety during the crisis.

Method: This article summarizes and discusses remote inspection guidelines and other related information made available by the Therapeutic Goods Administration (Australia), the European Medicines Agency (EMA), the Pharmaceutical and Medical Devices Agency (Japan), the Medicines and Healthcare Products Regulatory Agency (United Kingdom), and the US Food and Drug Administration (FDA). We also analyze the effect of the pandemic on inspections conducted by the inspectorates of the EMA and the FDA.

Findings: The regulatory authorities that we studied all recognized the importance of implementing regulatory policies on remote inspections in response to the COVID-19 pandemic. The remote inspection guidelines from the 5 selected regulatory authorities aimed at mitigating the impact of the pandemic but, while providing valuable advice to the pharmaceutical companies and being similar in intent, were not always aligned in terms of approach and solutions.

Implications: On-site inspections are likely to continue to be the norm and the preferred standard for the foreseeable future. However, health authorities will need to further adopt a risk-based inspection approach and stimulate the increased uptake of inspection reliance as proposed by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme not to overwhelm the pharmaceutical companies with repeat and redundant inspections. Remote inspections have proven to be a new inspection tool, but health authorities should align on their approach to remote inspections in terms of methods applied and documentation requested. (*Clin Ther.* 2021;43:2046–2063.) © 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Key words: COVID-19, pandemic, regulatory agilities, remote inspections.

INTRODUCTION

The COVID-19 pandemic (SARS-CoV-2) has had a profound effect on the management and operation of regulatory agencies and the pharmaceutical industry around the world. It has prompted regulatory authorities to consider new ways of working and has driven them to implement and adopt more agile or flexible approaches to maintain an efficient and functioning regulatory environment suited to meet the challenges of the pandemic.[1] Among those approaches adopted is the use of remote inspections. They are not new, and the first remote inspection was conducted by the European Inspectorate already in 2009[2] at a time where no official guideline had yet been developed.

Inspections are conducted by regulatory authorities, normally through face-to-face on-site inspections, to validate the integrity of the regulatory data submitted by companies, evaluate the quality of production and manufacturing sites, and ensure the conformity with Good Regulatory Practices with the overall goal of guaranteeing patient safety. Since the onset of the pandemic, regulators and industry alike have explored ways to continue with inspections, considering lockdown measures and travel restrictions put in place by various national governments.

Indeed, health agencies have had a high level of reactivity in the face of the crisis. A review published in 2020 noted that approximately 22% of the documents published by health authorities were guidelines that aimed at providing recommendations and direction to manufacturers of medical products to minimize the disruption caused by the pandemic in conducting clinical trials or ensuring the supply of medicines for patients in need.[1]

The present study summarizes the guidelines issued and processes adopted by 5 select regulatory authorities comprising the Therapeutic Goods Administration (TGA, Australia), the European Medicines Agency (EMA), the Pharmaceutical and Medical Devices Agency (PMDA, Japan), the Medicines and Healthcare Products Regulatory Agency (MHRA, United Kingdom), and the US Food and Drug Administration (FDA) regarding remote inspections during the COVID-19 pandemic. We also analyze the effect of the pandemic on inspections from 2 of these inspectorate bodies, namely, the EMA and the FDA. We provide an analysis of our findings and propose future considerations on the adoption of remote inspections beyond the current pandemic.

METHODS

Data and information for this study, specifically on guidelines, were collected through the public databases of the TGA, EMA, PMDA, MHRA, and FDA. In our study, we did not discriminate against any product type, such as drug, vaccine, or device, or regulatory discipline but included any information and all Good Practice (GXP) guidelines that comprised Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), and Good Pharmacovigilance Practice that we could find that were related to remote inspections in our analysis. These agencies were selected because of their active involvement in inspection activities around the world and for their pioneering adoption of remote inspections during the COVID-19 pandemic.

Additional and more granular information was also collected from the FDA inspection database and the European Union Drug Regulatory Authorities Good Manufacturing Practice Database (EudraGMDP) to understand and visualize how the COVID-19 pandemic affected regulatory inspections conducted by these, 2 of the worlds' largest, inspectorates. The information collected included but was not limited to the type of products concerned by the inspection (medicinal products for human use, investigational medicinal products, or products for veterinary use), the type of manufacturing operations concerned by the inspections, the clarifying remarks, the use of video conference, and the conduct of a virtual site tour. The analysis was performed by investigating the number of inspections before and during the COVID-19 pandemic (from January 2020 to March 2021) and identifying when alternative measures were used in the inspection process, including mutual recognition agreements, confidentiality agreements, remote inspections, or remote reviews.

A literature review was also conducted to complement the findings and discussions in the study. The preferred database to support our literature search was PubMed (https://pubmed.ncbi.nlm.nih.gov/), which we interrogated with search phrases such as *mutual recognition agreement, GMP inspections*, and *Good Manufacturing Practice*.

RESULTS

Agency Perspectives

Table I presents guidelines on remote inspections released by the 5 regulatory authorities in the scope of this study (EMA, FDA, MHRA, PMDA, and TGA) during the COVID-19 pandemic. The MHRA was the first regulator to release a guideline on good inspection practices (covering GXP) during the COVID-19 crisis,[3] followed by the EMA,[4–7] FDA,[8,9] TGA,[10,11] and PMDA.[12,13] Although each guideline has its own specificities, including the wording related to remote inspections, they all offer information to pharmaceutical companies the help them adapt their ways of working on how the inspection processes should be modified by the fact that they will be conducted remotely.

The TGA published 2 major guidelines that detailed expectations on overseas inspections that could be conducted as fully remote inspections or as hybrid inspections. The EMA published specific guidelines on the topic of remote inspections, taking into consideration the specificities of pharmacovigilance, GCPs, and good pharmaceutical practices. The FDA guidelines had been expected for quite some time, and after allowing a certain number of regulatory flexibilities, the FDA finally authorized the conduct of remote inspections and provided guidelines on the conduct of them. The MHRA positioned itself as an innovative agency and shaped the regulatory landscape by publishing the first COVID-19 remote inspection guidelines. The PMDA issued procedures not only for remote GCP inspections but also Good Postmarketing Study Practice (GPSP) guidelines to meet the COVID-19 pandemic. Although not detailed in Table I, the work of the Russian State GMP Inspectorate should be noted. Since the onset of the pandemic, the Russian GMP Inspectorate appears to have focused on remote inspections as evidenced by the fact that it has conducted a total of 111 remote inspections with an established legal basis to conduct them.[14]

The EMA Approach

The first remote inspection, conducted by a European agency, was performed by the French National Authority for Health (L'Agence nationale de sécurité des medicaments et des produits de santé, ANSM) in 2009. The remote inspection was conducted on a manufacturing site in Pennsylvania.[15] At that time, no specific guideline had yet been developed on remote inspections.

Before the COVID-19 pandemic, the only guideline on remote inspections available within the European Union was the pharmacovigilance remote inspection guideline from 2012 (Figure 1).[7] This guideline provides information on instances when regulatory authorities may need to opt for alternative methods to conduct risk-based inspections when there is a need to prioritize, reduce, or postpone certain inspections related to pharmacovigilance activities. The guideline has since been updated in 2020. The updated version provides more detailed information on how to prepare for inspections and is aligned with other available guidelines on remote inspections that since then have been released.

The COVID-19 pandemic has served as a catalyst for additional remote inspection guidelines being released in the European Union (Figure 1). In April 2020, the EMA published a guideline in the form of a question and answer (Q&A) document that addressed the effect of the COVID-19 pandemic on its regulatory activities, including those relating to inspections, and provides advice to stakeholders on the implementation of specific flexibilities to ensure the continuity of regulated activities.[4] This guideline has been updated by the EMA on a regular basis as a means for the regulator to rapidly issue advice to companies on specific topics.[16]

In the Q&A document, the EMA extended the validity of most GMP certificates until the end of 2021, which significantly reduced the number of required inspections for the agency. Extending the validity of GMP certificates aims to reduce the effect that international travel limitations have on product batch releases for which inspections are required. The guideline reminds manufacturers and the industry as a whole of their responsibility and legal obligations to respect and comply with GMP provisions to furnish quality medicines to patients, even when surveillance and routine on-site inspections have been suspended.

Remote GMP inspections are explicitly addressed in this early guideline through what is referred to as *distant assessment*. More specifically, the guideline states that a distant assessment may be conducted for new sites inside or outside the European Economic Area that have never been inspected or authorized to evaluate if it could be authorized without an on-site preapproval inspection.[4]

Table I. Summary of remote inspection guidelines published by the TGA, EMA, FDA, MHRA, and PMDA during the COVID-19 pandemic from March 2021 to March 2021.[3–12]

TGA Guidelines	EMA Guidelines	FDA Guidelines	MHRA Guidelines	PMDA Guidelines
TGA expectations for overseas manufacturing sites hosting remote inspections during the COVID-19 pandemic (July 2020)	Notice to stakeholders; questions and answers on regulatory expectations for medicinal products for human use during the COVID-19 pandemic (April 2020)	Coronavirus (COVID-19) update: FDA updates on surveillance inspections during COVID-19 (May 2020)	New arrangements for MHRA Good Practice inspections due to coronavirus (COVID-19) (March 2020)	Amended guidance for GCP and GPSP inspections in medicines (August 2020)
GMP approach to overseas manufacturers of medicines and biologicals during the COVID-19 pandemic (July 2020)	Guidance on remote GCP inspections during the COVID-19 pandemic (May 2020)	Coronavirus (COVID-19) update: FDA prepares for resumption of domestic inspections with new risk assessment system	MHRA regulatory flexibilities resulting from coronavirus (COVID-19) (April 2020)	Amended guidance for GCP and GPSP inspections in regenerative medicine products (September 2020)
	Remote pharmacovigilance inspections of MAHs during a crisis situation- points to consider (October 2020)	Manufacturing, supply chain, and drug and biological product inspections during COVID-19 public health emergency questions and answers (August 2020)	Guidance for industry on MHRA's expectations for return to United Kingdom on-site inspections (August 2020; updated in March 2021)	New guidance on implementation procedures for remote GCP and GPSP inspections in medicines and regenerative medicine products (November 2020)
	Guidance related to GMP/GDP and PMF distant assessments (November 2020)	Manufacturing, supply chain, and drug inspections | COVID-19 (January 2021) Remote interactive evaluations of drug manufacturing and bioresearch monitoring facilities during the COVID-19 public health emergency (April 2021)	Innovative licensing and access pathway for medicines (December 2020)	

EMA = European Medicines Agency; FDA = US Food and Drug Administration; GCP = Good Clinical Practice; GMP = Good Manufacturing Practice; GPSP = Good Postmarketing Study Practice; MAHs = marketing authorization holders; MHRA = Medicines and Healthcare Products Regulatory Agency; PMDA = Pharmaceutical and Medical Devices Agency; TGA = Therapeutic Goods Administration.
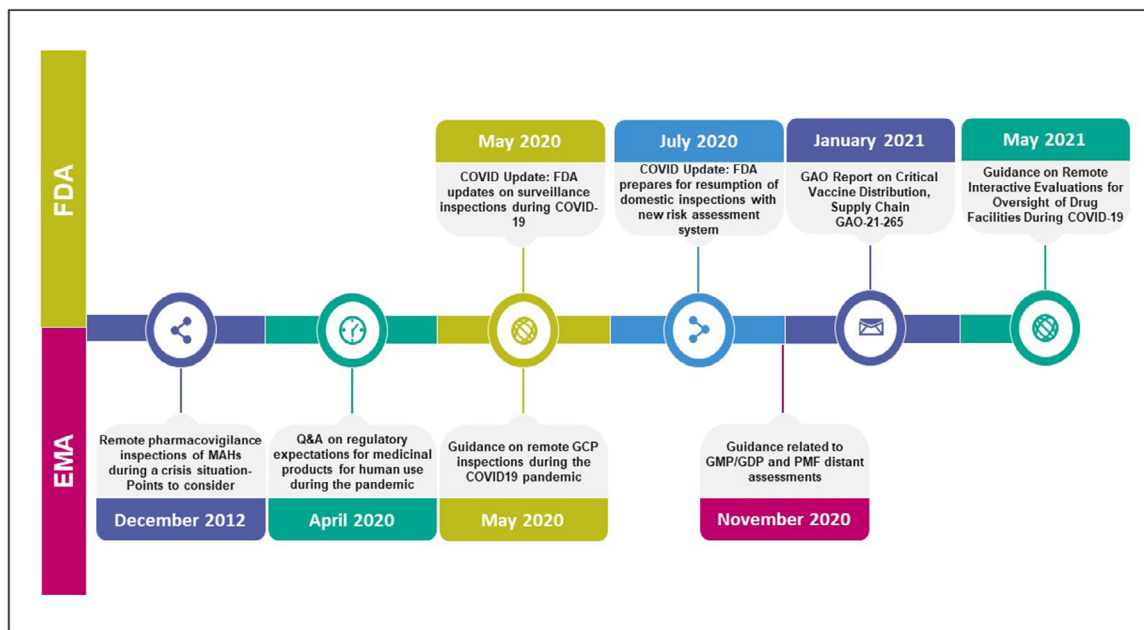
Figure 1. Timeline summarizing key positions and communications on remote inspections issued by the European Medicine Agency (EMA) and the US Food and Drug Administration (FDA). GAO = US Government Accountability Office; GCP = Good Clinical Practice; GDP = Good Distribution Practice; GMP = Good Manufacturing Practice; PMF = plasma master file; Q&A = question and answer.

Since the release of the Q&A document, several other guidelines have been drafted to incorporate information on remote inspections. These guidelines include the guideline on remote GCP inspections during the COVID-19 pandemic[5] and the guideline related to GMP and Good Distribution Practices (GDP) and plasma master files (PMFs).[6] The guideline on remote GCPs outlines the process that should be established to allow for the review of documents, facilities, records, and any other resources that are deemed by the authorities to be related to the conduct of a clinical trial and should be provided by the sponsor of the clinical trial. On the other hand, the guideline related to GMP/GDP and PMF distant assessments[6] specifies the scope of the remote inspections and outlines the general steps that will take place during a remote inspection, including feasibility assessments, preparation steps, the actual remote inspection activities, and other postinspection requirements or activities.

In the different guidelines that the EMA has issued and in the EudraGMDP, the agency refers to remote inspections as *distant assessments*, defined as "the assessment of the compliance of a site with the Union GMP/GDP principles performed by officials of Union Competent Authorities on the basis of documents and interviews and supported by technology for communicating, accessing systems, sharing and reviewing documents and other information, without the inspectors being physically present at the sites where the activities subject to the assessment have taken place and where the inspection would ordinarily be hosted."[6]

In general, the feasibility of a remote inspection is evaluated before any decision to conduct one is made. The feasibility assessment considers the following technical aspects: appropriate platforms, use of teleconference and videoconference, live sharing of screens displaying read-only access systems, live camera footage or video recording of the sites, time zones, and specific languages used.[6]

The FDA Approach

Figure 1 details different milestones in the FDA approach on inspections during the pandemic from May 2020 to April 2021. It is evident that the FDA

approach was dynamic and evolved over time and that the agency carefully introduced measures over time to adapt as the pandemic developed, especially after the different waves of SARS-CoV-2, each of which precipitated additional restrictive measures.

In August 2020, similar to the EMA, the FDA published a Q&A document[9] that addresses inspections during COVID-19 in which it reaffirmed its commitment to provide timely guidelines and support on specific issues faced during the pandemic, including on how inspections would be affected by COVID-19 and what types of inspections would be considered mission critical. On-site inspections considered as mission critical inspections or those that may influence the health security of US patients are prioritized. Several factors are considered when determining whether an inspection qualifies as mission critical, namely, if the product is a breakthrough designated therapy; an RMAT (regenerative medicine advanced therapy) designated one [17]; or is used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute.[9]

For-cause and preapproval inspections also qualify as mission-critical inspections. For-cause inspections are triggered by a specific problem that has come to the FDA's attention,[18] for instance, issues related to data integrity and validity,[19] whereas preapproval inspections are conducted after a company submits an application to the FDA to market a new product or to approve a new plant installation.[18]

In terms of inspecting non–mission-critical manufacturing sites, the FDA has adopted a variety of tools and processes, including assessments based on existing inspection reports provided by other inspectorates or information and records obtained directly from the applicants.[20]

In a recent update to the August 2020 Q&A guideline,[9] the FDA specified that it is working directly with the facilities to communicate issues identified through a review of requested records and that they will consider responses from the facilities before taking any action on a pending application, such as documentation of corrective actions that should be implemented by the site. In a recent communication, the FDA discusses the use of technologies and tools for remote inspection at overseas sites,[21] including but not limited to a review of historical adherence documents of facilities (eg, recalls and product complaints), information shared by trusted states, or local and foreign regulatory partners (Mutual Recognition and Confidentiality Agreements).[21]

In addition to the above, the FDA decided to also include alternative tools and resources to assess manufacturing site GMP adherence.[21] These alternative tools were introduced after the FDA initially announced a return to domestic on-site inspections in July 2020[22] and after the US Government Accountability Office (GAO) published a report on January 2021[23] that included recommendations specifically to the FDA on addressing backlogs of inspections and ensuring regular inspection activities to help meet drug oversight objectives. Measures included the use of remote interactive evaluations through remote livestreaming video, teleconferencing, or screen sharing. In fact, the FDA adopted a risk-based approach on the use of live footage and live touring of facilities. This approach was first implemented at human and animal food production facilities and then progressively extended to medical device inspections.[24]

For medical devices, the FDA released a guideline in April 2020 (updated in December 2020) on the extension and expansion of temporary extraordinary measures related to Medical Device Single Audit Program (MDSAP) audits during COVID-19 quarantine orders and travel restrictions (remote audits).[25] This guideline communicates the agency's position on the conduct of remote audits of medical device facilities. The MDSAP, created by the International Medical Device Regulators Forum,[26] allows firms to undergo one audit by an accredited third party to satisfy quality regulations for the United States, Canada, Brazil, Japan, and Australia.

The updated guideline released in December 2020[25] provides information on 4 types of remote or hybrid audits performed by the FDA under the MDSAP. These audits are (1) a desktop audit, which is an audit performed remotely through a review of documentation; (2) a remote audit, which is an audit performed off site using information and communication technology; (3) a hybrid audit, which is partially performed off site using information and communication technology and partially performed on site by at least 1 qualified MDSAP auditor; or (4) a surrogate audit, which is partially performed off site using information and communication technology and partially performed on site by at least 1 qualified non-MDSAP auditor.

In the guideline entitled: Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Mon-

itoring Facilities During the COVID-19 Public Health Emergency,"[27] the FDA redefined remote inspections as remote interactive evaluations, which refer to the use of any combination of interactive tools, such as remote livestreaming video of operations, teleconferences and screen sharing for preapproval inspections, prelicense inspections, postapproval inspections, surveillance inspections, follow-up and adherence inspections, and bioresearch monitoring inspections.[28] Technological requirements are extensively discussed in this FDA guideline to ensure that the overall quality is sufficient and adequate to remotely review, observe, examine, and evaluate the documentation requested.[27]

In May 2021, the FDA published a report that described its inspection performance during the pandemic and laying out the agency's roadmap on inspections going forward.[29] The report notes that the FDA will continue to conduct most mission-critical inspections and prioritize surveillance inspections but that other types of inspections that do not match these criteria may be postponed because of the pandemic. The roadmap discusses 3 scenarios for future inspections (base case, best case, and worst case scenario), which will depend on the emergence of virus variants and the upholding of travel restrictions. In all 3 scenarios, the FDA would remain agile and nimble through, for instance, the use of remote interactive evaluations and livestreaming video of drug manufacturing facilities[27]) or prioritizing inspections that have an effect on the product's availability or public health.[29]

The MHRA Approach

The MHRA published its first guideline on remote inspections in March 2020,[30] which since then has been withdrawn and replaced with an updated guideline.[31] In connection with the release of the updated guideline, the MHRA recently announced that they would resume on-site domestic inspection.

In the first guideline, the MHRA established their definition of remote inspections as "organisations being asked to provide electronic copies of documents and other information for review off-site, with teleconferences and email to follow up."[32] The guideline also describes the use of alternative approaches for routine regulatory oversight, such as office-based inspections,[3] which are audits conducted through collaboration between the applicant and the inspectorate during which electronic copies of documents are requested and reviewed remotely[33] and teleconferencing is sometimes

involved. However, the guideline does not mention whether a virtual live tour of the facility would be in scope or not.

The MHRA recognized the importance of the Pharmaceutical Inspection Convention (PIC) and Pharmaceutical Inspection Co-operation Scheme (PIC/S) reliance procedures[33] during the COVID-19 pandemic. Through these collaborations, 56 inspectorates across the globe coordinate efforts through mutual recognition agreements and confidentiality arrangements. The MHRA also established an incident group, comprising members of the Inspectorate Strategy and Innovation Unit, to provide expert advice to the agency's COVID-19 task force addressing technical and regulatory issues raised by stakeholders on remote inspections.[33]

The PMDA Approach

In the third quarter of 2020, the PMDA amended 2 guidelines related to GCP and GPSP inspections.[12] These amendments were introduced to describe the detailed procedure of remote inspections, clarify how to proceed with the necessary documentation, and reflect expectations on video conferencing systems. In November 2020, the PMDA released an English translation of their new guideline on conducting remote inspections for drugs and regenerative medical products and is the first PMDA guideline to advise on the conduct of remote inspection.[12]

Digitalization is at the core of the guideline, and the guideline mentions the use of a cloud-based system and video conferencing tools to facilitate the remote review of documents.

Remote inspections conducted by the PMDA are divided into 2 phases: the preinspection and the main inspection phases. During the preinspection phase, several quality documents are shared with the regulatory authority. Sharing quality documentation with the inspectors can be done with external data storage media, such as CDs or DVDs, or through a cloud-based platform at least 10 days before the main inspection.

During the preinspection phase, inspectors review the documentation provided by the applicant and identify the target areas that they would like to focus on during the main inspection phase. As for the main inspection, the PMDA contacts the applicant by telephone or e-mail to inform them of an on-site inspection or, in sanitary circumstances, a remote inspection. As discussed in the Procedure

for Remote Inspection section, which is part of the adherence inspection on drugs and regenerative medicine products guideline, the PMDA inspectors are not open to live footage tours of facilities.

The TGA Approach

In 2 guidelines on remote inspections,[10,11] the TGA underscores the importance of adherence with GMP standards, even when inspections are postponed. They emphasize the importance of a close collaboration and communication with manufacturers of medical products to guarantee the tolerability, quality, and efficacy of health products. To this end, the TGA requires that a remote inspection host is nominated at the manufacturing facility. This person would be the single point of contact for the TGA for any questions or problems that need to be sorted.

The to-be-inspected site must establish a strategy as soon as the notice of the inspection and the preinspection checklist have been communicated. Documentation following a predefined checklist has to be provided by the manufacturer and helps the TGA to determine whether a remote inspection is considered feasible or not. Table II provides the documentation that must be made available to the TGA according to the inspection checklist. The documentation requested depends on the level of risk that the manufactured products represent. The checklist and the associated documentation have to be shared with the TGA within 2 weeks of the receipt of the notification of an inspection.

In preparation for an inspection, the TGA requires manufacturers to prepare a virtual tour of relevant areas by prerecorded videos of the site and its operations to allow the inspectors to visualize the site ahead of the actual remote inspection. How to handle time zones, language differences, and other technical and practical barriers during the inspection are outlined in the guideline and need to be properly addressed and prepared for by the manufacturer. Regarding the quality management system, the inspectorate requires a read-only access to the quality management system to review any complaints, deviations, and out-of-specifications as they deem fit. During the pandemic, remote inspections conducted by the TGA were first performed on domestic facilities and then extended to overseas facilities after the successful experience gained at domestic level. The TGA noted that "2,700 overseas manufacturers rely on desk-top clearance and

the experience has been very positive."[36] A reinspection is only decided in borderline cases as well as when the dosage form is different.

EMA AND FDA INSPECTIONS DURING THE COVID-19 PANDEMIC
The EMA

Figure 2 shows the number of on-site inspection and remote inspections that were conducted by the European inspectorates in the 2020-2021 timeframe and is based on an analysis of the EudraGMDP database. In March and April 2020, a decrease occurred in overall inspections conducted, following travel restrictions and confinement measures put in place across European countries in response to the first wave of the pandemic. However, the European inspectorate restarted on-site inspections in May, with a gradual increase up to September, after which there again was a decrease in the number of inspections parallel to reconfinement measures being put in place by various national governments in response to the second pandemic wave. Figure 2 also illustrates how remote (GMP) inspections are added to the armamentarium beginning in April and continuing onward. Between April and August, one can observe a gradual increase of remote inspections, accounting for approximately 20% of the total number. From September onward, there was a gradual decrease in remote inspection to <5% in December. Confinement measures and travel restrictions are likely the main factors that limit the number of inspections conducted in March, April, November, and December 2020 and April 2021.

The EudraGMDP allows for a more specific breakdown of the type of remote inspection conducted. Figure 3 shows the distribution of remote inspections versus remote inspections conducted with live footage between January 2020 and April 2021. These inspections resulted in 121 GMP certificates being issued, and an analysis of these certificates revealed that 5 were related to vaccines manufacturing sites, whereas the remaining ones were related to pharmaceutical products.

Figure 4 shows the distribution of remote inspections conducted by some member states in the European Union regulatory network during the COVID-19 crisis. Poland (29%), Belgium (28%), and Ireland (21%) were the most active inspectorates and
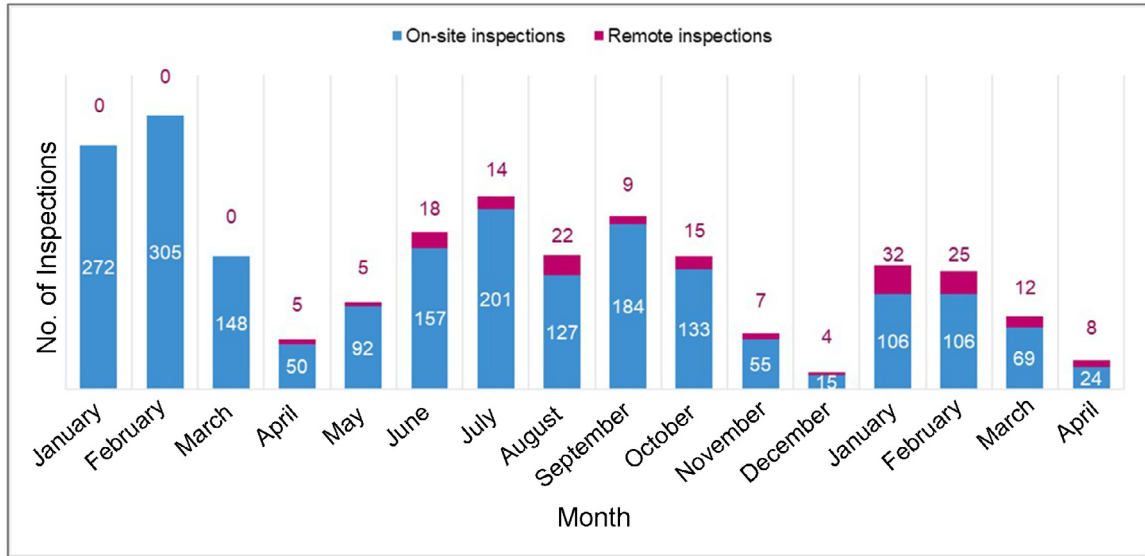
Figure 2. Evolution of the number of on-site and remote inspections conducted by the European inspectorate during the COVID-19 pandemic from January 2020 through April 2021.[37]
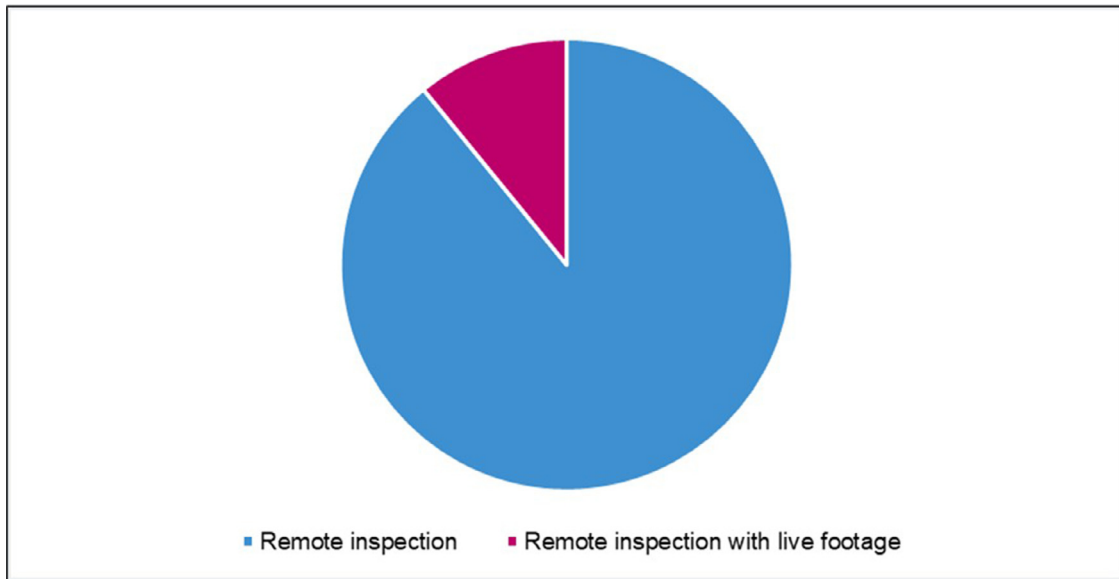

Figure 3. The number of remote inspections with and without live footage conducted by the European inspectorate during the COVID-19 pandemic based on an analysis of the European Union Drug Regulatory Authorities Good Manufacturing Practice Database.[37] Although some inspectorates provide details on the type of remote inspection conducted, it is not always clear from the data source whether the inspection was the result of a remote review of quality documents only or conducted with or without the use of live footage. Our analysis is based on the clarifying remarks found in the GMP certificates that were issued after the remote inspections and covers the period from April 2020 through April 2021.

Table II. Three examples of documents (for nonsterile and sterile products and for contractors) required by the Therapeutic Good Administration for Compliance Verification Assessments (remote inspections).[34,35]

All Nonsterile Dosage Forms and APIs	Sterile and Biotech APIs and Sterile Dosage Forms	Contract Testing Laboratories and Contract Sterilizers
Current GMP certificate	Current GMP certificate	Current GMP certificate
A list of all regulatory inspections conducted within the past 3 years and a copy of the most recent inspection report	A list of all regulatory inspections conducted within the past 3 years and a copy of the most recent inspection report	A list of all regulatory inspections conducted within the past 3 years and a copy of the most recent inspection report
Details of any regulatory actions in the past 3 years	Details of any regulatory actions in the past 3 years	Details of any regulatory actions in the past 3 years
Site master file, quality manual, or equivalent	Site master file, quality manual, or equivalent	Quality manual or laboratory manual or equivalent
GMP agreement between the sponsor and the manufacturer	GMP agreement between the sponsor and the manufacturer	GMP agreement between the sponsor and the contract test laboratory or sterilizer
List of products intended for supply in Australia	List of products intended for supply in Australia	A list of test a laboratory is authorized to perform
Copy of the procedures for release for supply of products included in the clearance application	Copy of the procedures for release for supply of products included in the clearance application	For botanical ingredients, evidence that authenticated standard reference materials are used
	Validation master file	
	Latest product quality review	

APIs = active pharmaceutical ingredients; GMP = Good Manufacturing Practice.

accounted jointly for 78% of the total number of remote inspections performed during the pandemic.

The FDA

Figure 5 shows the number of inspections conducted by the FDA before and during the COVID-19 pandemic and clearly indicates the effect of travel restrictions and confinement measures that were put in place in the United States and globally in the beginning of 2020. Between February and December 2019, a total of 4407 inspections were conducted compared with only 536 during the same period the following year, which constitutes an 87% decrease. Of the 536 inspections, most were domestic ones, which is in concordance with the declaration by the FDA in July 2020 to prioritize domestic (on-site) inspections.

According to the FDA, approximately 200 mission critical inspections were conducted from March to June 2020 (Figure 5 shows mission-critical and other inspections).[40] These inspections were conducted because the facilities were either associated with drug shortages or inspections were required for the approval of new drugs or drugs related to the potential treatment of COVID-19.[40]

Figure 6 shows the number of 483 forms issued (a 483 form is issued at the conclusion of an inspection and notifies the company's management of objectionable conditions) by the FDA between 2015 and 2020 for drugs and biologics. There is an approximately 40% reduction in the total number of forms issued in 2020, and this decrease is consistent with the finding that fewer inspections were conducted and the number of remote inspections conducted were limited.[41]

DISCUSSION

Regulatory authorities worldwide have recognized the importance of alignment on implementing regulatory policies during the COVID-19 pandemic as evidenced
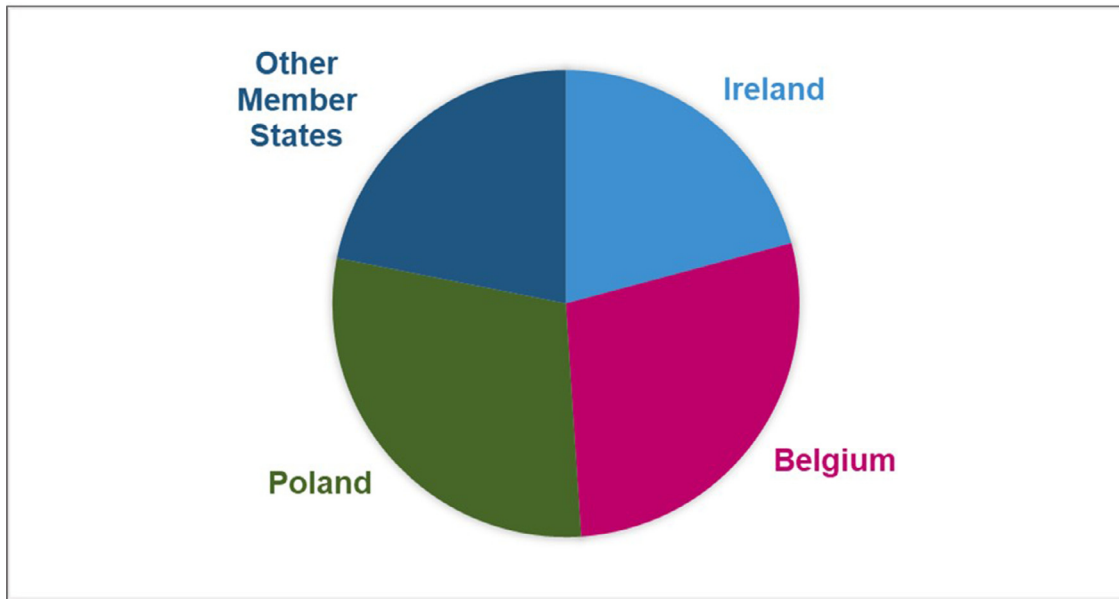
Figure 4. Proportion of remote inspections conducted by the most active member state inspectorates in the European Union regulatory network.[37]
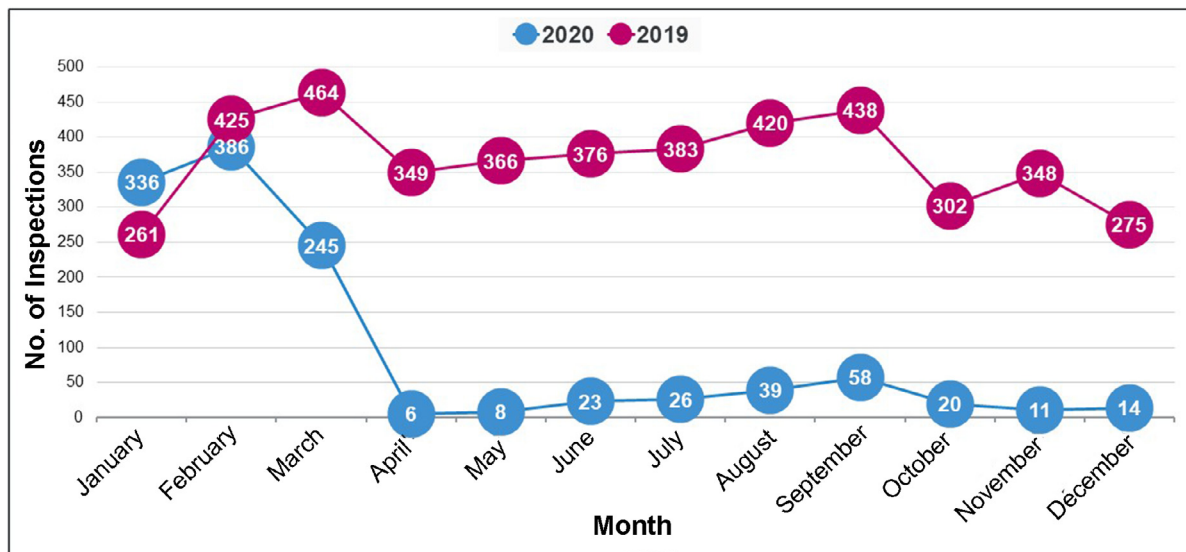

Figure 5. Evolution of the number of inspections conducted by the US Food and Drug Administration Center for Drug Evaluaton and Research and Center for Biologics Evaluation and Research before and during the COVID-19 pandemic.[38,39]
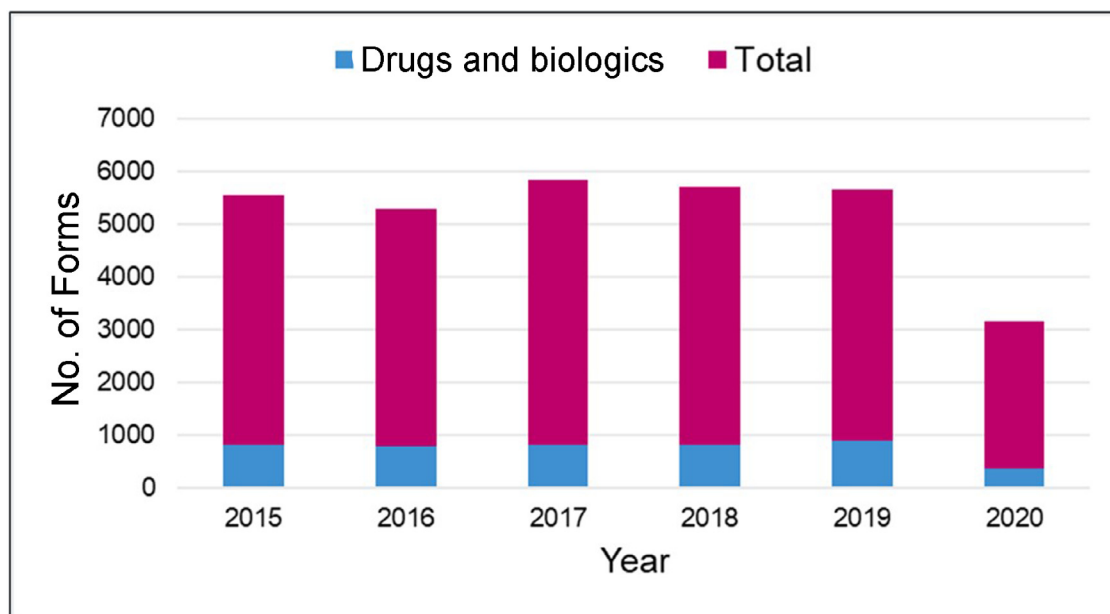
Figure 6. Evolution of the number of 483 forms issued by the US Food and Drug Administration from 2015 through 2020.[42]

by a statement in April 2020 by the International Coalition of Medicines Regulatory Authorities (ICMRA).[43] The ICMRA established a COVID-19 Working Group to provide in-depth recommendations on priority topics in the context of COVID-19 and to the widest extent possible stimulate different regulatory jurisdictions to converge on common approaches to tackle the crisis.

In 2018, the PIC/S guideline on GMP inspection reliance, which was based on an ICMRA draft, was put into action.[44] This guideline has served as a basis for practical solutions to GMP inspections during the COVID-19 pandemic. It has laid out a general process for remote inspections, such as how to conduct remote inspections of overseas facilities, and has identified instances where an acceptable level of GMP adherence could be confirmed and ensured by activities of another regulatory authority or other authorities without the need for an additional on-site inspection. Indeed, this guideline aimed to establish appropriate GMP inspection processes from the convenience of a desktop.

The Results section of this study provides evidence on the guidelines from the 5 selected regulatory authorities on remote inspections all aimed at mitigating the impact of COVID-19; however, although similar in intent, these guidelines were not always aligned in terms of approach and solutions. Indeed, although the guidelines issued covered the full range of GXP inspections (Table I), there was no uniform division, approach, or timing by which the different authorities chose to publish their remote inspection guidelines, making it hard to draw any meaningful conclusions at such a granular level. Notwithstanding this, these authorities provided valuable guidelines on how inspections should be conducted and what strategies should be applied to uphold systematic and meaningful inspection processes during the pandemic, for example, providing information and technical considerations on the use of the cloud, wi-fi, and video live touring of facilities. These agencies demonstrated the possible adoption and implementation of remote inspections, complementing the PIC/S guideline on GMP inspection reliance.[45] The PIC/S guideline has served as a guide for regulators during the COVID-19 pandemic to establish new ways of working in relation to inspections. Many of these guidelines have focused on the use of digital solutions and the practicalities

of conducting remote inspection, which indicate how different stakeholders have quickly adopted alternative approaches to specific regulatory processes.

Indeed, the adoption of remote inspections was driven by a common objective: to ensure health security for all citizens by limiting the disruption of supply chains, notably for essential medicines. This is an important evolution because a rather large proportion of active pharmaceutical ingredients (APIs) and drug products currently are being produced in, and procured from, developing countries.[46]

According to an earlier analysis by Bolislis et al,[1] the medicine and medical devices supply chain was severely disrupted during the pandemic. The main reason for this was the closing of borders between countries, which prevented APIs from arriving in drug product manufacturing sites. Low- and middle-income countries have been particularly affected by shortages.[47]

In response to constraints on API supplies, the European Commission put forward a proposal for a regulation[48] to reinforce the role of the EMA, especially in relation to mitigating shortages. In a statement on safeguarding pharmaceutical supply chains in a global economy,[46] the FDA noted that the production of APIs has progressively been offshored to China (13% of worldwide API production occurs in China) and India (18% of the worldwide API production), which has increased the dependence of the United States and the European Union on these countries. For this reason, remote inspections have become an attractive option for regulatory authorities to partially address manufacturing and supply chain constraints, especially in a pandemic travel restricted setting.

The MHRA has pushed the regulatory science envelope rather significantly on remote inspections in as much that they have conducted >750 remote GXP inspections during the pandemic.[49] The MHRA also chose to uphold their international inspections program and performed inspections in Canada, United States, Central and South America, Africa, Eastern Europe, Commonwealth of Independent states, Middle East, Pacific, Asia, Australia, and New Zealand. The inspectorate modified its ways of working and tested and implemented a wide variety of methods.[33] According to the MHRA, these new ways of working are to be maintained because they have decided to continue performing desktop assessments according to a risk-based program.[33]

According to a GAO report, the FDA may face an inspection backlog if the agency continues to postpone inspections and continues to prefer on-site inspections over deploying alternative tools such as conducting inspections remotely.[23] The GAO report noted that at the end of the pandemic establishments that have never been inspected or that have an outdated inspection (>5 years) should be prioritized. The risk, however, is that the establishments identified by this model may not be inspected in a timely manner.[23] The FDA is actively tracking the sites that need to be inspected and noted that the size of the backlog will depend on the extent to which alternative inspection tools are used. To cope with the backlog, the FDA recently published a guideline stating that they will use alternative (remote) inspection tools.[21]

Remote inspections undoubtedly come with some technical challenges. For instance, to facilitate the live remote monitoring of a manufacturing site, it is important to have a stable internet connection with sufficient bandwidth. Internet connection can be an issue for manufacturing sites located in areas that lack the required infrastructure to support a high-speed internet connection. This issue should in principle be an addressable obstacle of a transient nature that eventually would be overcome as the internet grid is continuously expanded and upgraded. Another consideration is that abundant metal pipes and production steel vessels at production sites can cause signal perturbation or blind spots. Other considerations in this regard include availability of secure digital drop boxes, limits to the size of e-mail attachments, access to contemporary video conferencing tools, or firewall security settings. This list is a minimum of items that should be addresses before any remote inspection can be planned and executed.

Few imagined that remote inspections would become a reality, but many companies were compelled to go virtual with audits and move operations to the cloud. As an illustration, the head of regulatory chemistry, manufacturing, and controls operations at a company claimed that it has hosted >60 on-site, virtual, and hybrid inspections from 15 agencies during the pandemic.[50]

The pursuit and implementation of a robust quality management system, which is an integral part of the corporate culture, are at the heart of patient safety and therefore a top priority to pharmaceutical companies.

This is conducive, and possibly a prerequisite, to stimulating the further uptake and wider implementations of remote inspections. The importance of ingraining a quality mindset in pharmaceutical operations has been spearheaded by the FDA through several communications in the recent past.[51,52]

Opportunities and Considerations

Regulatory agencies are under mounting pressure to improve performance and facilitate timely access to tolerable, effective, and quality medicines. This goal has become increasingly challenging during the COVID-19 pandemic, with increasing public expectations and political pressure. The introduction and adoption of remote inspections during the COVID-19 pandemic is an example of regulators demonstrating resilience and agility in the face of a crisis. Notwithstanding this, some regulators are eager to resume onsite inspections once the pandemic is over and argue that these are much better suited to uncovering violations of GXP practices.[53]

Managing Resources Through Reliance

The PIC/S guideline on GMP inspection reliance was introduced in response to the limitations of on-site inspections imposed by the pandemic. Through this, regulatory authorities could avoid duplication of work, reduce the regulatory burden experienced at manufacturing sites, and allow for prudent stewardship and more efficient deployment of global inspection resources. Through reliance, the requesting agency can trust an assessment (of the GMP adherence of the manufacturing site) conducted by a national or a local competent authority to evaluate whether the level of adherence can be confirmed without the need for an additional on-site inspection.

Reliance can be progressively embedded and implemented through additional guidelines or regulations focused on GXP, as evidence by the European Union GMP inspections guideline as well as the Chinese National Medical Products Agency remote inspection guideline. As noted by both the PIC/S and the Irish Health Products Regulatory Authority, most aspects of the EMA remote inspections guideline are aligned with the PIC/S guideline on GMP reliance.[45,54] The importance of regulatory reliance is nicely summarized by the Australian government: "…if a system, service or product has been adopted under a trusted inter-national standard or risk assessment, no additional requirements should be imposed for approval…"[55]

Indeed, PIC/S member inspectorates could prioritize domestic inspections, which could then be relied on by the other members and would make repeated inspections unnecessary. The total number of inspections could be reduced and resources redirected to inspect facilities with high-risk operations or facilities that never have been inspected before. Moreover, we believe it would be beneficial to the sector and the patients it serves to encourage the extension of the current inspection Mutual Recognition Agreement to cover additional product types, including vaccines, plasma-derived medicines, and investigational medicinal products, as is anticipated to occur by July 15, 2022.[56]

Features of On-site Inspections

First impressions count, and industry facilities are the proud shop front of their production and manufacturing operations. On-site inspections provide the full visual context and are instrumental in building confidence because the inspectors can meet and have discussions with the operators on the shop floor in addition to the people leading the inspection. This is the concept of the Lean and Six Sigma principles of the Gemba Walk.[57] On-site inspections are not limited by technology but allow the inspectors to experience in person the ambience, visualize the site, and interact with the staff. The person-to-person interaction during an on-site inspection is also important for the inspected site to experience the general feeling of how the inspection is going and anticipate the outcome.

When conducted during normal times, on-site inspections allow for the sites to prepare and properly and efficiently furnish records and documentation to the inspectors on request, which allows for a rapid evaluation of documentation and exploration of topics of interest. Conversely, a remote inspection requires manufacturers to set aside significant resources in terms of staff and time to list, scan, sometimes translate, and upload a high number of diverse documents that are requested before and after the actual inspection.

Notwithstanding the above, new models and paradigms emerge. One model is the hybrid inspection scheme in which the authority sends a (local) inspector to the site while the rest of the inspection team would conduct the inspection remotely. The front-line inspector on site can effectively gauge the totality of information and identify issues by virtue of

physically being on site. The front-line inspector can quickly browse information, zoom in on specifics, and hand that information over to the remote inspector colleagues for a deeper analysis.

Remote inspections have proven their value and often fill a purpose. For instance, the global population could experience further manifestations of the pandemic that could lead to an increase in caseloads and hence a need to increase the availability of a particular drug(s), and regulatory authorities may need to inspect facilities to quickly mitigate shortage situations. Alternatively, there may be situations in which on-site visits are not possible and remote access is preferred, for instance, when travel restrictions have been put in place, when the security situation is questionable, or when entry VISAs are hard to obtain.

Notwithstanding this, the sector has developed a well-functioning and proven inspection management system that before the COVID-19 pandemic was routinely used to host many on-site inspections each year. Although remote inspections have proven their value in certain circumstances and now must be considered to be part of the regulatory armamentarium, we do not think they should become the default modus operandi yet and believe on-site inspections should still play a key role.

Remote Inspections Still Need Some Refinements

To many inspectorates, remote inspections are rather new, and the standards by which they are conducted are still diverse in terms of process method applied and range of supporting documents demanded. To limit the resource burden associated with preparing for remote inspections, it is important for the health authorities to align on their approaches and methods, in particular regarding the documentation requested before the remote inspection.

We suggest using available standard documents, such as the documentation master file format, or alternatively another preestablished and agreed set of documents, such as the site master file or the annual product quality review (which includes many of the most frequently requested documents, such as variations, complaints, recalls, and deviations). We are rather agnostic as to the chosen documents as long as a practical consensus is achieved. This consensus is important because the number and types of documents that need to be submitted in front of a remote inspection are often greater than those typically requested during an on-site inspection. The situation is further complicated because documents sometimes need to be translated and furnished with very short timelines.

So far, no uniform or agreed-on remote inspection model has emerged, but different agencies have implemented their own approaches, each one with its own pros and cons. For remote inspections to be performed as efficiently as possible, it is important that health authorities work on aligning and synchronizing their respective approaches. This synchronization should include the preread documentation packages as well as inspection methods, tools, and technologies that are used during the remote inspection process. Similarly important is that intellectual property, proprietary art, and confidential data can be properly safeguarded and cyber secured as more information is being exchanged across cloud-based systems between the inspected entity and the inspectorate and duplicated at health authority levels. Finally, it is central to recognize that remote inspections be regarded as having the same standard as on-site inspections—not requiring a second follow-up on-site inspection because of perceived lower standards. The outcome of a remote and an on-site inspection should be the same and carry an equivalent quality stamp.

CONCLUSIONS

Before the COVID-19 pandemic, remote inspections were considered, but their utility and implementation had not been reported, and they were still far from commonplace. Precipitated by the pandemic, regulatory authorities and industry alike have quickly adopted the use of alternative methods to ensure business continuity and to guarantee the availability of medical products for patients around the world. One such value adding regulatory agility that was introduced during the pandemic that has served its purpose, and hence society and patients, during this health crisis was the introduction of remote inspections that allowed regulators to verify adherence of site operations in accordance with applicable laws and regulations. Although remote inspections may not fully substitute on-site inspections, they have proven their value and should accordingly remain a tool in the regulatory toolbox as we move into a postpandemic setting. We believe the best way forward for the sector and the patients it serves is (1) to increase the uptake of GMP inspection reliance, (2) for on-site

inspections to continue to play a key role, and (3) for health authorities to align on their approach to remote inspections in terms of methods applied and documentation requested.

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