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The FDA Inspection Landscape in Mid-2020 and a Look at Virtual Inspections

RESOURCE TYPE

IN THIS SUMMARY WE IDENTIFY

- Trend analysis of FDA inspections through mid-2020.
- Strategies for preparing and hosting virtual inspections.
- New technologies to support virtual inspections

WRITTEN BY

JERRY CHAPMAN
SENIOR GMP EXPERT, REDICA SYSTEMS

PUBLISHED BY

REDICA SYSTEMS
6800 KOLL CENTER PARKWAY
SUITE 120
PLEASANTON, CA 94566

SUPPORT@REDICA.COM
844-332-3320

What is your risk of being inspected? What is the state-of-the-art of virtual inspections? What can you do to prepare for a virtual inspection? And how is hosting a virtual inspection different?

FDA has halted most in-person manufacturing facility inspections during the COVID-19 pandemic, but some physical inspections are still being performed—for example, for-cause inspections where the public health could be at risk or pre-approval inspections for important new therapies. FDA can also perform virtual inspections or those based on records review.

How is the agency deciding which firms to inspect? What is the chance that your firm will be inspected?

In mid-June, the law firm Arnold & Porter sponsored a webinar, "FDA Inspection Alternatives During the COVID-19 Pandemic: Requesting, Preparing for and Responding to FDA Virtual Inspections," featuring two speakers formerly with FDA, Howard Sklamberg and Ricki A. Chase.

Sklamberg is a partner at Arnold & Porter who spent seven years at FDA, most recently as Deputy Commissioner for Global Regulatory Operations and Policy when he left the agency for private practice three years ago. Ricki A. Chase is Executive Director, Compliance at Lachman Consultant Services, and spent 16 years with FDA, most recently as Director, Investigations Branch in Chicago before joining Lachman four years ago.

Sklamberg spoke about the current FDA inspection landscape and Chase addressed how firms can prepare for virtual inspections.

This report contains four parts:

Part 1: Yes, FDA Is Still Performing Pharma Inspections, Using Risk-Based Criteria: What Is Your Risk for Inspection?

Part 2: A State-Of-The-Art Virtual Inspection Methodology Using Mixed Reality Technology Gets High Marks from European Medicines Agency Inspector

Part 3: Preparing for A Virtual FDA Inspection: Advice from Former FDA Investigator and Investigations Director Ricki Chase

Part 4: Hosting A Virtual FDA Inspection: Advice from Former FDA Investigator and Investigations Director Ricki Chase

Part 1: Yes, FDA Is Still Performing Pharma Inspections, Using Risk-Based Criteria: What Is Your Risk for Inspection?

In his portion of the webinar, Sklamberg specifically addressed:

- FDA inspection status
- Preapproval inspections
- For cause, surveillance, and warning letter close out inspections
- Inspection alternatives
- Putting yourself in FDA's shoes
- When physical inspections might resume

During the Q&A at the end, he answered questions regarding virtual inspections and warning letter issuance from a virtual inspection.

FDA Inspection Status

Sklamberg explained that most of FDA's physical inspections have been suspended, but that "mission-critical" inspections will proceed. According to FDA, for cause inspections and preapproval inspections for important therapies or to address shortages will take place. "Anecdotally, some of

those are occurring," he said. "I know that a client of ours has gotten a surprise for cause inspection in the pharmaceutical area."

There are also some preapproval inspections taking place. "Now that we know the pandemic will be around for a while, FDA is ramping up virtual inspections," Sklamberg said. "FDA has said that it is working with the Center for Disease Control and Prevention (CDC) to develop a phased approach to resuming inspections, and that would be largely domestic."

States and localities are at different stages in the process of reopening, and some have reopened and then partially closed again. FDA will send investigators in when the states' and localities' rules and laws permit it. That is going to vary geographically. If your company has a site in a state when it completely opens up, FDA will be able to perform an inspection there.

During the COVID-19 crisis FDA has talked about some inspection alternatives, "but they are really of limited benefit to the agency," Sklamberg maintained. "They have talked about sampling, use of mutual recognition agreements, records review, virtual inspections, and import alerts."

The limited benefit is that, for example, sampling as FDA has said, is not a substitute for an inspection. Mutual recognition agreements work. FDA has used its mutual recognition agreement with Europe, but Europe has limits on its inspections as well. "Records review and virtual inspections are areas that we all think FDA will ramp up in the coming months," Sklamberg said.

Preapproval Inspections

In terms of preapproval inspections, FDA has broad discretion on when to inspect and how to inspect. It must find a manufacturing facility suitable. Compliance Program Guidance Manual (CPGM) 7346.832 lists the criteria for priority pre-approval inspections (**Figure 1**).

Priority pre-approval inspections are based on risk, Sklamberg maintained. Risk increases when applicants have less experience, drugs are more difficult to manufacture, or have an Official Action Indicated (OAI) status, for example.

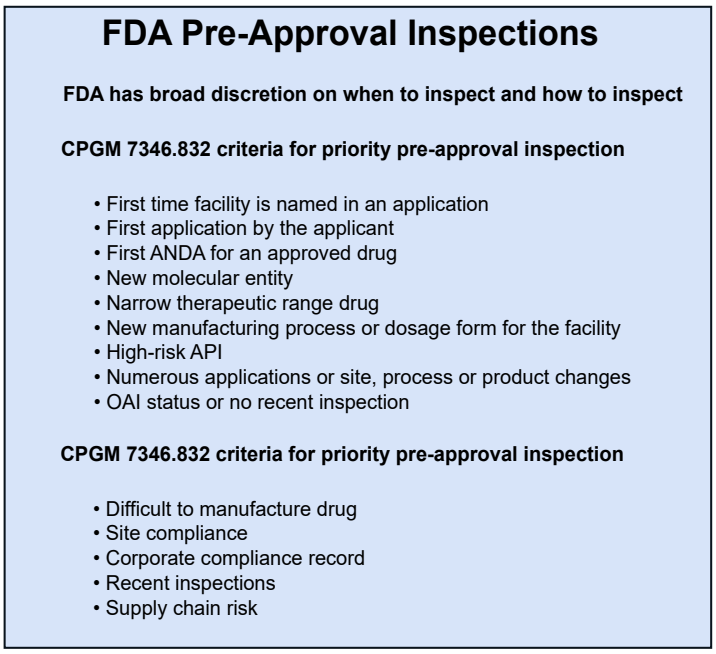

Figure 1: FDA Pre-Approval Inspections Criteria

FDA has some more general criteria aside from priority preapproval inspections, "but they kind of mirror the criteria we just talked about. Again, risk for the product, risk for the facility, risk related to the compliance record of the company itself."

Sklamberg pointed to the supply chain risk at the bottom of the list and noted that FDA has increasingly emphasized this at top levels in the agency, especially in the last year or so. And with the Covid-19 crisis, it is concerned about risks created by extended supply chains and supply chains that have problematic compliance records, particularly global supply chains, he pointed out.

For Cause, Surveillance, and Warning Letter Close Out Inspections

Surveillance inspections are the ones that are "the least mission-critical from FDA's perspective, as they are not tied to cause," Sklamberg maintained. "But they are nevertheless relevant because the CDER Manual of Policies and Procedures (MAPP) 5014.1 on this topic gives you a particularly good idea as to what FDA thinks is going to cause it to really want to inspect" (**Figure 2**).

"When looking at those criteria, you can apply them to FDA thoughts about the need for a pre-approval inspection and when it can waive inspection. If you look at these criteria, they are just like the CPGM ones that we talked about. They focus on risk from the facility, risk from the compliance history, risk related to the product, risk related to the company, and then specific instances of risk like patient exposure and hazard signals."

"These would cause FDA to want to inspect or at least do a virtual inspection for an application rather than just waive the inspection. And there are also for cause inspections, which, as I indicated, FDA is doing domestically."

According to Sklamberg, FDA has the extremely broad authority in the international realm to issue an import alert without an inspection. Oftentimes, when FDA gets a signal, it will quickly

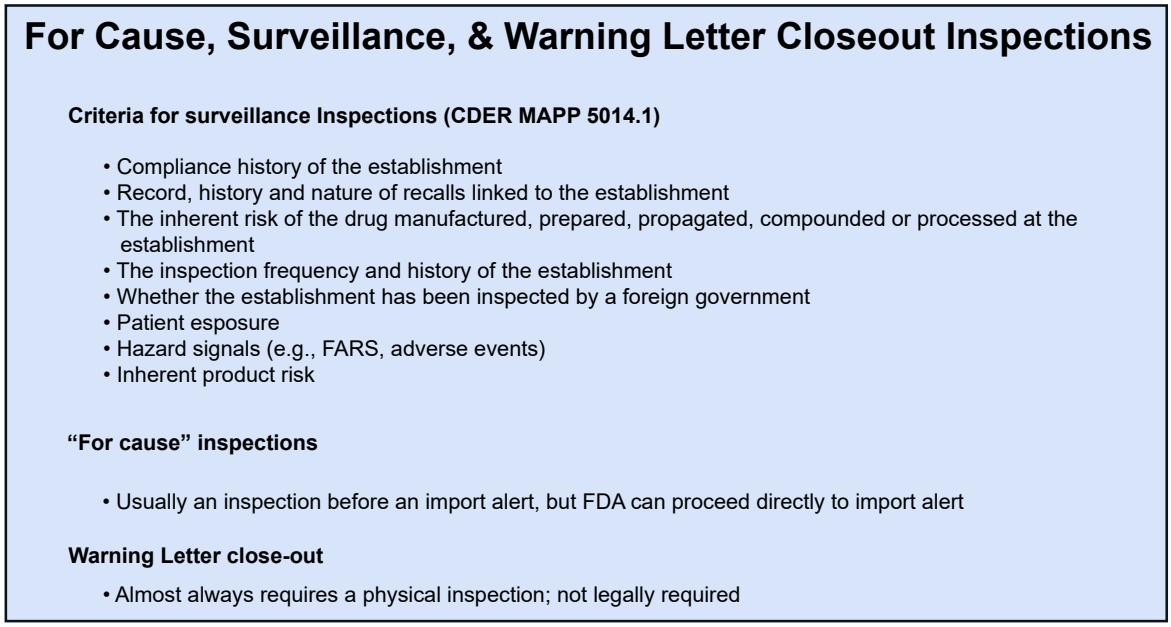

Figure 2: For Cause, Surveillance, & Warning Letter Close Out Inspection Criteria

do an inspection and then issue an import alert afterwards. However, if there is a troublesome enough issue FDA might reach out to a company and ask for a recall. They also could just issue an import alert. The statutory standard is the appearance of a violation, which does not require an inspection to meet.

Regarding warning letter closeouts, "if you are thinking of instances where a firm wants an inspection, it would be to get their application approved or to close out a warning letter after remediation. The overwhelming majority of times the agency requires a physical inspection to close out a warning letter. But that is not required by statute. The whole warning letter process is something that is within FDA's control. If FDA wanted to, it could rely on virtual inspections to close out warning letters."

Inspection Alternatives

One alternative to performing an inspection is to waive the inspection. And for some particularly simple or less risky products, waiving inspection might be something FDA would do more frequently now than it would in the past, the Arnold & Porter partner said (**Figure 3**).

It is also important to understand that FDA is very aware of its user fee goals and user fee negotiations heading toward reauthorization of user fees a couple of years from now. "And they do not want to be missing a lot of goals. They are also probably aware that it would be hard for them to do physical inspections for all the products that are out there."

As indicated, Europe has not been doing much inspecting outside of small areas. That is changing a bit as Europe is opening up. So, we may have increasing situations where European regulatory bodies can access European sites and that inspection report can be used by FDA for approvals.

The mutual recognition agreement with Europe only covers facilities in Europe and the US. There is an open question about whether FDA could rely on European inspections outside of Europe—for example, if a European agency inspected a facility in India. "I think if this crisis goes on for a longer period, there will be more of an incentive for FDA to use that" he said.

FDASIA section 706 applies to pharmaceuticals and gives FDA the authority to get records in

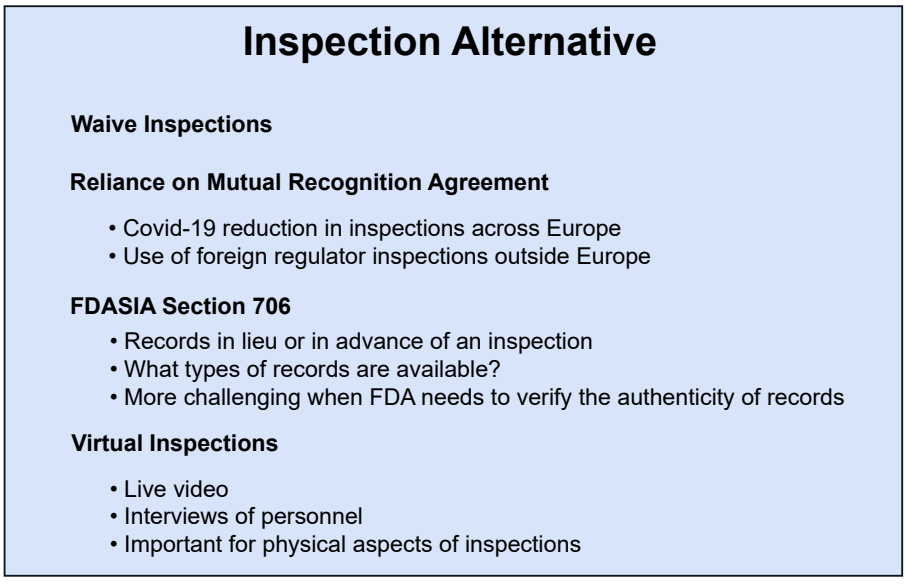

Figure 3: Inspection Alternatives

lieu of or advance of an inspection. The utility for a records inspection depends on what FDA is inspecting, Sklamberg pointed out.

"If they are looking at, for example, a follow up regarding investigation reports or out-of-specification (OOS) investigations, a lot of that work can be on paper. If it is something more physical where FDA is looking at an issue regarding equipment, obviously paper would not cut it nearly as much. And that is where a virtual inspection would be much more appropriate, where you can use live video interviews of personnel and look at some of the physical aspects of inspections."

There is an open question about whether FDA could rely on European inspections outside of Europe.

Sklamberg shared that FDA has reached out and informally told associations and some of his firm's clients and others that "if you think your situation is one where it is appropriate to have a virtual inspection, make a proposal and make it specific. For example, if you have a warning letter close out and you think FDA can verify that without physically being there, tell them specifically how they could do it and how that would meet their needs. It would be the same thing for an application. How can FDA be satisfied that the company can make this product from this facility?"

Put Yourself in FDA's Shoes

"As a former regulator," Sklamberg said, "I would say to put yourself in FDA's shoes.

- What does FDA want from that inspection?
- Why is FDA physically there normally?
- What are they looking at?
- And what can you provide them?

If there is an issue with equipment, then you would propose something visual. And I would be proactive with the agency in how specifically they can accomplish their goals. There are some concerns FDA would have, for example, if there is a big data integrity concern. FDA has said that would be extremely difficult to address remotely."

"Spontaneous interviews, as you know, are an important part of an FDA inspection. From their perspective it is harder to do when it is not visual. When you have a video inspection, there can be other people in the room that FDA might not see, just like there will be other people in the room at FDA that you might not see. And that affects the spontaneity."

He noted that some of his company's clients have thought that a virtual inspection would be easier because the investigator is not there. "And I think it is just the opposite," the former regulator said. "FDA is going to want to be sure that it is getting the information to satisfy itself. It knows it is being scrutinized. And you have the ability at FDA, instead of just having one or two investigators at a site, have a couple of them appearing on the computer screen but a whole bunch of people in the room."

When Will Physical Inspections Begin Again?

"You hear lots of rumors from folks at FDA, at various levels of the agency about when they are going to restart their domestic or foreign inspection program," Sklamberg noted. "But I can pretty much guarantee you that no one in the agency knows because it is an incredibly complex question."

It relates to not just what FDA wants to do, but the whole federal government and its policy. It relates to what foreign countries will permit as far as travel by folks from the US. "And even at FDA, it relates to labor issues, as most of FDA's inspection force is in a union. And if there are going to be dangers to any of the investigators, that becomes

a labor issue. FDA is a public health agency that is not looking to endanger its employees."

"So, there are a lot of intangibles here. But I think one thing is for sure: There are going to be sharp limits on physical inspections for quite a while. And FDA is going to want to be able to approve important therapies and not miss a lot of its goals. So, they are going to be relying on virtual inspections, paper inspections, and other inspection alternatives."

Editor's Note: On July 10, 2020 – more than a month after the webinar – FDA announced a plan to resume domestic inspections. Of particular interest is a statement that for the foreseeable future all FDA inspections (except undercover operations for tobacco) will be preannounced.

Q&A Focuses on Virtual Inspections and Warning Letter Issuance

In the Q&A at the end of the webinar, questions addressed to Sklamberg focused on the circumstances under which FDA might perform virtual inspections and on the agency's ability to issue a warning letter based on a virtual inspection.

Several of the attendees wanted to know if a virtual inspection is possible for a site that has never been inspected by FDA before, and whether a virtual inspection could be used for an OAI site that wants to close out a warning letter.

Sklamberg replied, "the answer to both is yes. There is no legal limitation on FDA that requires it to do an in-person inspection, either for a warning letter close out or for new f acility."

"I think the way to look at it is the fact that a facility is OAI or that it is new makes it a higher inspection priority for FDA. What that means is it is much less likely the FDA is going to want to waive inspection for an application."

"Whether it can do a virtual inspection or not I think it might depend on some other factors. For example, if it was an OAI site and the OAI issue was related to a big data integrity issue, I think it would be harder for FDA to do a non-physical inspection, as I mentioned earlier."

"Some other types of warning letters are much more amenable to FDA following up without being there physically. As I mentioned before, if FDA is reviewing data, if they are reviewing a third party consultant evaluation of your OOS investigations, that can be done well with records remotely. There are certain types of issues in inspections that FDA can verify visually through video."

"For a new facility, which is a high risk for FDA, it is unlikely they are going to want to waive inspection, but they could do it virtually. In both those instances, if you are the entity that wants

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the inspection—maybe for preapproval or to close out a warning letter—be proactive with FDA and try to anticipate what FDA concerns would be and then try to address them."

"For a new facility, which is a high risk for FDA, it is unlikely they are going to want to waive inspection, but they could do it virtually. In both those instances, if you are the entity that wants the inspection—maybe for preapproval or to close out a warning letter—be proactive with FDA and try to anticipate what FDA concerns would be and then try to address them," Sklamberg advised.

Another question directed to Sklamberg asked whether it will be possible for FDA to issue a warning letter or take other enforcement action because of a virtual inspection.

Sklamberg replied in the affirmative. "One way we know this is FDA issues warning letters based on illegal claims that are on the Internet without ever going to do an actual inspection. It can issue a warning letter based on FAQs on a firm's website that make disease cure claims without going down to the firm, issuing a 482, and then looking at the computer system."

"The thing about warning letters is they are quite formal in the way FDA has developed procedures, but the structure and details of a warning letter are not part of FDA's statute," he explained. "They are something that FDA came up with to get voluntary compliance. So, FDA has a lot of flexibility. It can issue a warning letter. It can withhold approval of applications. It can do an import alert. The thing that might get tricky is if it were to take judicial action. But judicial action is uncommon."

Part 2: A State-Of-The-Art Virtual Inspection Methodology Using Mixed Reality Technology Gets High Marks from European Medicines Agency Inspector

At the ISPE Biopharmaceutical Manufacturing conference held virtually in early June 2020, Thermo Fisher Scientific Regulatory Affairs Manager Monica Commerford discussed how her firm built and uses a virtual inspection system in a presentation titled, Virtual Inspections: Navigating the New Paradigm.

"We have already been using this technology for our clients," she explained. "And we recently concluded an EMA inspection at our Alachua, Florida site. Our experience has shown us that this is a viable platform that will really revolutionize how we perform inspections."

Commerford noted that the technology itself "has not gone unnoticed by the regulatory authorities. In fact, the EMA inspector said, 'This has been a new thing for us and has been a positive experience…you may not realize it, but I have this on a bigger screen, and the audit is almost life-size!' We could not find a better endorsement."

In her presentation, Commerford provided an overview of the current regulatory landscape and why virtual inspections are a useful resource, the advantages that virtual inspections provide over traditional onsite inspections, the technology used, and what she thinks regarding the use of virtual facility inspections in the coming years.

Regulators, Industry Go Virtual for GMP

The Thermo Fisher manager maintained that one major challenge during the COVID-19 pandemic has been how to allow regulatory authorities to keep their commitments to the public by performing necessary inspections.

"Both the FDA and the EMA have scaled back regulatory inspections. In its statement to the public, FDA indicated that it may evaluate records in lieu of an onsite inspection. Also, the EMA has been considering allowing remote assessments of compliance."

Pharmaceutical companies, Commerford said, have reached out to FDA and suggested that virtual inspections may be key and the way to go to allow for CGMP verification. "Virtual inspections during a pandemic can really help to ensure continuous supply of much-needed drugs, not just for the United States, but worldwide."

She explained that the virtual inspection system her company developed "has allowed us to maintain business continuity without sacrificing client and regulatory responsibilities."

What Technology is Used?

The heart of the virtual inspection system, Com-

merford explained, includes a 360 degree camera mounted on an IV pole with wheels, the Microsoft HoloLens virtual reality device (**Figure 4**), Avatour software, and the use of Microsoft Teams software to review documents during inspection.

"For our setup, we would simply attach the camera to a cell phone or iPad and mount it on an IV pole. This pole can be wheeled around a facility on smooth surfaces allowing real time online video streaming tours of the GMP facilities. And a camera itself has a high enough pixel resolution to read documents and labels and logbooks during the tour. The other advantage to using this type of setup is its cleanability. If needed, you can go in and out of rooms with this if you have the appropriate cleaning studies performed."

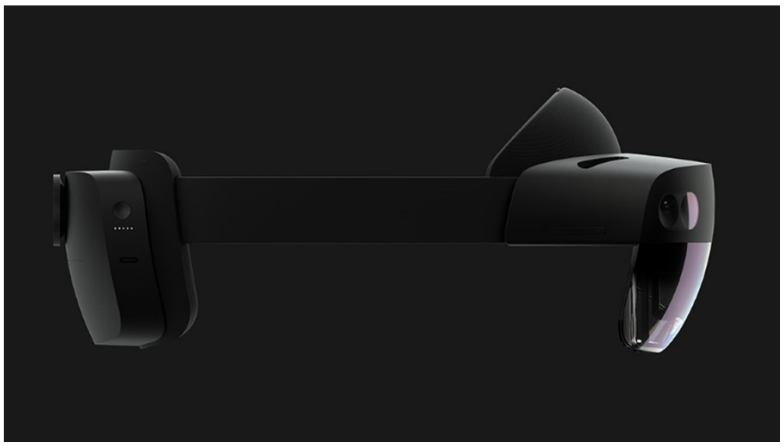
With this technology virtual inspections can occur in all GMP spaces. However, depending on the floor surface, "you may need to transition to another piece of technology. So, for example, you do not really want to roll an IV stand around on a bumpy surface. Or there may be some surfaces or activities that are not accessible by this 360 degree camera."

"In these cases, we can use the Microsoft HoloLens," Commerford explained. "This is a piece of virtual reality technology that allows us to show and perform activities that we may not be able to show otherwise using the 360 degree camera. For example, showing an activity in the biosafety cabinet or opening filters to show how clean they are is something that the HoloLens can be used for."

In addition, as part of the virtual inspection experience, one other piece of technology that is used is the Matterport 3D technology mapping (**Figure 5**). This is commonly used by realtors to virtually map homes for online viewing. Thermo Fisher Scientific has virtually mapped its facilities to orient auditors and inspectors to the facility prior to giving them the virtual livestream tour using the 360 degree camera.

The Matterport 3D technology is only used to orient visitors to the facility and should not replace the livestream tour for the inspection, Commerford maintained. "The live use and streaming using the HoloLens or the 360 degree camera with the Avatour software is really where the action is."

Microsoft HoloLens



Microsoft HoloLen is a pair of mixed reality smartglasses developed and manufactured by Microsoft. HoloLens was the first head-mounted display running the Windows Mixed Reality platform under the Windows 10 computer operating system. The front of the unit houses many of the sensors and related hardware, including the processors, cameras and projection lenses. HoloLens features IEEE 802.11ac Wi-Fi and Bluetooth 4.1 Low Energy (LE) wireless connectivity. – Wikipedia

Figure 4: Microsoft HoloLens

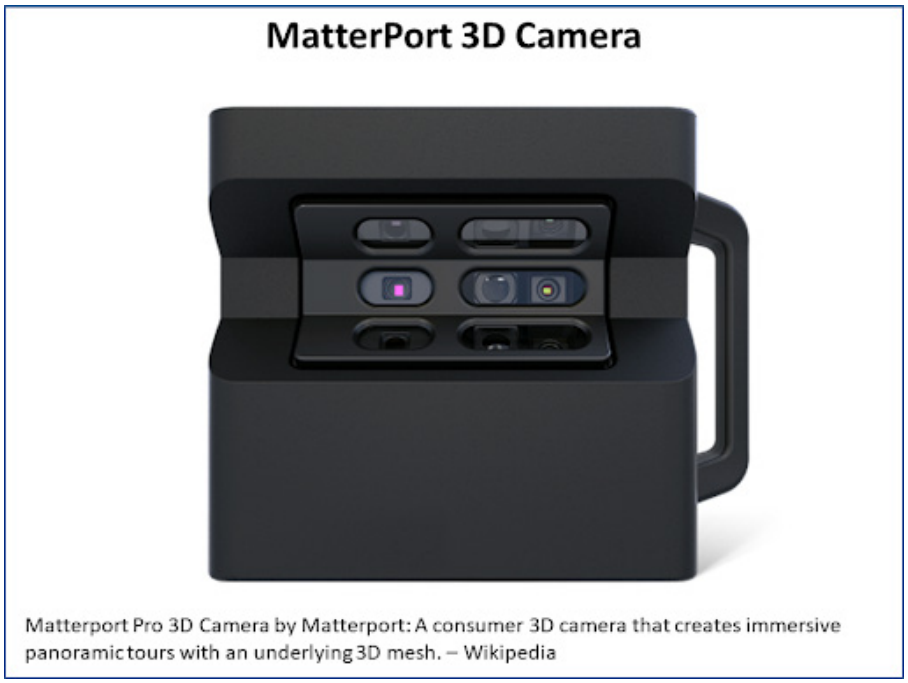


Figure 5: Matterport 3D Camera

She displayed a video of what the Matterport 3D mapping looks like and commented that the resolution is excellent. (For an example of how this technology works, see 3D Mapping the Exploratorium with Matterport.)

According to Avatour's website, "The Avatour platform allows remote guests to visit a real place, in real time, using inexpensive mobile 360° capture technology. You will need a low-cost 360° camera, along with a selfie stick and audio headset. These tools enable you to give live virtual tours while speaking directly with your remote guests."

"Using the Avatour Host app on your smartphone or tablet, schedule a time for clients and participants to meet. They receive calendar invites. Guests can attend using any modern web browser, or with a VR headset for a fully immersive experience. At the meeting time, up to 5 guests from anywhere in the world can join you virtually, using either a VR headset or any mobile device or desktop." For an example of what an Avatour experience looks like, click here.

Commerford pointed out that the combination of the 360 degree camera using the Avatour software that can be live streamed using the HoloLens and 3-D mapping along with the document review using Microsoft teams allows for virtual inspections that rival in-person inspections.

She pointed to the importance of the document review piece, in which documents are organized in a way that facilitates review by inspectors and allows document storage in a controlled manner. "While Microsoft Teams can be viewed on a native application, as in software on your computer, it can also be viewed solely for the web. We found this to be an advantage during our recent regulatory inspection," she explained.

Using this process, the company had control over the documents, and their recent experience was that EMA "was accepting of viewing files that were temporarily on the Web," Commerford said.

She explained that the "web-based browser has the same functionality as native software on the computer, but that the risk of downloading viruses is low and having other issues is lower be-

cause both regulators and organizations have their own tools in place to ensure that their own internal IT infrastructure is not compromised."

Implementing Virtual Inspection Strategies and Lessons Learned

During the implementation and conduct of virtual inspections, Thermo Fisher discovered similarities and differences in roles and responsibilities, security concerns, and digital support needs as compared to traditional inspections. Instructive lessons were also learned and shared.

Commerford said the same roles typically apply between onsite inspections versus virtual inspections. For example, there will still be escorts, scribes, a ready room, and a strategy room. In addition, a new player becomes important – digital support. "This group becomes key now to help ensure a smooth experience for ourselves and for either client auditors or inspectors."

As in a traditional in-person inspection, who has access to what areas and data is important.

As in a traditional in-person inspection, who has access to what areas and data is important.

In a traditional audit, a person can be physically posted at a door to control access to the strategy room or ready room. Here, controlled access must be performed digitally.

To ensure a smooth inspection experience, Commerford recommends performing wireless access datapoint mapping to gauge the wireless signal strength in all the manufacturing areas. "Our site already had a long history of using cell phone communication between rooms. So, the concern for signal strength was low for us," she explained.

Also recommended is having multiple 360 degree cameras that can run Avatour software staged throughout the site at places you know you will be touring and that inspectors will want to view. This will reduce cleaning and transition time and minimize dead airtime during the tour.

The use of 5G LTE, Commerford said, "lends credibility to your inspection. For example, when the power goes out, the inspectors are going to able to see what you do when the power goes out and what activities go on. Also, logistically, you do have to think about evaluating the ability of your equipment if you are using the types of equipment that we are we are using."

Lastly, she recommended to emphasize to all participants, whether they are inspectors or client auditors, that a live inspection and a live tour are being conducted and the same rules apply regarding recordings or screenshots as during an in-person inspection.

Pre-meetings and Training Also Facilitate a Good Inspection Experience

Other lessons learned when conducting virtual inspections include the importance of training participants in the virtual reality and mixed reality platforms, ensuring participants have the appropriate computer skills to participate in virtual document reviews, and of pre-meetings to convey expectations and areas of concern or interest.

Commerford emphasized the importance of training on the use of the technology being employed, and how mock inspections help with learning the tools and knowing what to inspect (**Figure 6**). For example, if staff will be using t he HoloLens to perform an activity or to show a space that is not accessible by the camera, it is important to mock that ahead of time to help the team get comfortable in the virtual reality environment.

She pointed out that inspectors and auditors may also need to be trained to a certain degree.

It is important that they have the computer skills needed, for example, to perform a virtual document review. This is one item that can be discussed in a pre-meeting.

Pre-meetings with clients or auditors also help the company gauge their level of understanding of the software – for example, how much help they may need to navigate the platform. Pre-meetings help build credibility for the platform, "so they can see that it is just like an onsite inspection and they are able to get access to the information they need," Commerford said.

"Pre-meetings also provide you with opportunities to learn ahead of time without the pressure of being in an inspectional environment, to start building that rapport that you sometimes lack when you have virtual meetings, whether it is through Zoom or other types of software," she said.

In the pre-meeting it is important to talk about pre-inspection document requests and to schedule what the inspectors want to see and when during their tours or during the inspection. This level of planning up front helps ensure that the inspection runs on time.

Advantages and Disadvantages

While there are some advantages and disadvantages to both in-person onsite and virtual inspections, Commerford maintained that virtual inspections are superior in many ways (**Figure 7**).

Both take up a similar amount of time, the pre-meeting notwithstanding, she said. "And in our recent EMA inspection, we had four half-days rather than two full days of inspection. This allowed us to maintain work during business hours and to use the other four hours to answer questions or to prepare."

In either type of inspection, the final day is typically a wrap up to share findings and help ensure closure of any open items.

"In terms of time, we have also found that the inspectors like to stick together and cover similar material, which did lead to a slightly slower inspection dynamic, whereas in a traditional onsite inspection they may use a divide and conquer type approach," Commerford said.

Performing inspections virtually also allows holding the inspection over nonconsecutive

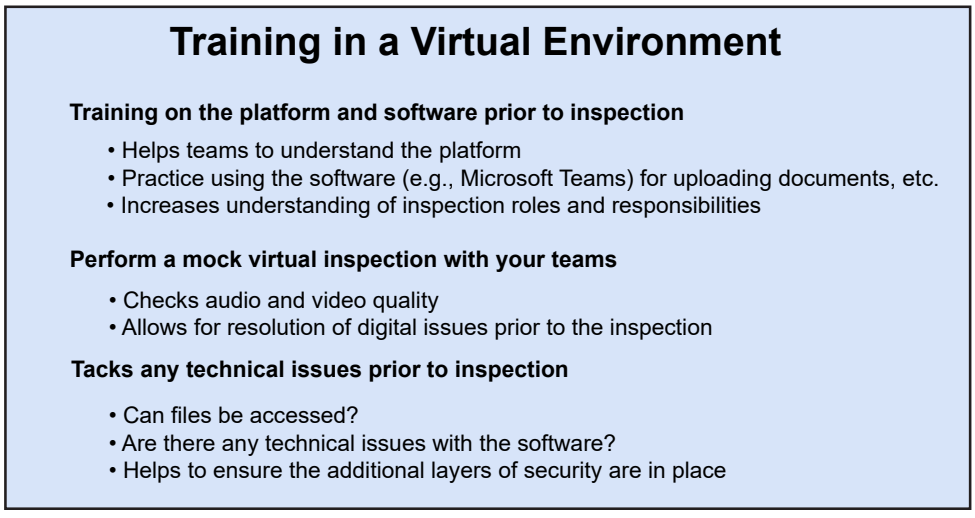


Figure 6: Training in a Virtual Environment

days, which helps to ease the burden of the hosting responsibilities.

Commerford noted one different inspection dynamic: Questions typically posed during normal tour discourse or during sit downs or in the audit rooms or the inspection rooms were frequently replaced by quick questions that become part of a daily list that inspectors provide to the sites at the end of the inspection day.

"You may see this as a disadvantage because that may slow the inspection down a little bit," she said. "But we found this to be the advantage for us because we had time to prepare responses and present those responses in our next interaction or the next inspection day. And if it was a nonconsecutive inspection day, that gave us more time to prepare."

"Virtual inspections during a pandemic can really help to ensure continuous supply of much-needed drugs, not just for the United States, but worldwide."

Another advantage is that subject matter experts (SMEs) from multiple sites can participate in a virtual inspection and be able to answer questions live without traveling.

One disadvantage is the inability to read body language. "Sometimes it is hard to get a great read on the status of the inspection. So, we asked questions regarding whether we could move on."

As previously mentioned, there is some prep work associated with the training to use the software and the technology. "But this initial work is needed for the experience," Commerford pointed out. "And once you put the work in and it becomes standard, it simply just needs to be maintained rather than repeated."

It is also important to have the use of the equipment reviewed by company health and safety

Traditional Onsite Inspections vs. Virtual Inspections

	Traditional Onsite Inspections	Virtual Inspections
Advantages	• Faster paced than a virtual inspection • Typical inspection duration is over a period of consecutive days • Instant communication and discussion	• Decreased travel time and costs • Enables business continuity during challenging times • Similar "total" time as a traditonal inspecton • Provides a chance to meet prior to the inspection • Option for non-consecutive inspection days • Inspectors can "work on their own time" to review documents outside the inspection • Typically stays on task and schedule • Increased verbal communication between site and inspectors • SMEs from multiple sites and participate, available online and in real-time during tours • Virtual inspection can occur in all GMP spaces
Disadvantages	• Increased travel time and costs • Can get behind of off schedule • Site personnel often work beyond business hours • SMEs may potentially need to travel onsite	• Daily list of questions provided to the site • Lack of body language and context • Tours may take longer than expected • Additional preparation associated with training

Figure 7: Advantages and Disadvantages

personnel to ensure that the operators are trained appropriately in the safe use of the equipment. "When you are in a virtual reality environment, you may experience some instability while walking, for example," she said. "So, your safety team really needs to be involved and you may want to follow their guidance on using augmented reality in difficult or dangerous situations."

Commerford maintained that a lot of the disadvantages are because the use this platform is in its infancy, and that as it is used more the disadvantages will be overcome.

"What success looks like to us is that the auditors can adequately assess the environment and have access to effective procedures and SMEs," she said.

"During the close out for our recent EMA inspection, the EMA inspector even used the phrase, 'during the tour.' It was not qualified with 'virtual' or 'live stream,' simply 'tour.' And we thought this showed that he had the same experiences that he would have on site."

To learn more about the technology, Commerford provided the following contact: Doug Rufino, PSG Thermo Fisher Technical Operations Senior Director; email: douglas.rufino@thermofisher.com; phone (919) 452-3136.

Part 3: Preparing for A Virtual FDA Inspection: Advice from Former FDA Investigator and Investigations Director Ricki Chase

Chase began her remarks at the mid-June webinar sponsored by the law firm Arnold & Porter by acknowledging that many firms are concerned about the impact of delayed FDA inspections, particularly on approvals or when it has to do with a firm's compliance status—for example, if the company is under a warning letter and is looking to get that cleared. "There has been a lot of discussion about how FDA is going to manage remote inspections and how to request one if you think that you should be eligible for one, to move your product or your process along," she said.

Chase discussed the elements that should be in place to increase a company's chances of having a successful remote inspection, how to prepare for one, and requesting one. "Regardless of whether you make the request or FDA imposes this upon you, it is important that you make sure that you are prepared and that these elements are in place," she emphasized.

Keep in mind that FDA can inspect your facility at any time, she pointed out. "We all know that FDA's motto is, 'if you are open for business, then we can come and inspect you.' A virtual inspection can be the same way. It could be preannounced or it may not be. In at least one instance that we know of FDA called the very day of the start of the inspection."

"Imagine you are sitting at your desk and you are thinking everything is fine. Suddenly your phone rings and someone says, 'Hi. I am investigator Chase with the U.S. Food Drug Administration. I am here to conduct an inspection.' You may not know exactly how to react. It is important that you practice and that you get prepared for any scenario that FDA could throw at you," Chase emphasized.

An exception to unannounced inspections is for medical devices if it is purely a medical device and not a combination product. It is FDA policy that device inspections are preannounced three to five days in advance.

There are some exceptions—for example, if the company is currently under a warning letter or has an official action indicated (OAI) status, or if

it is for cause, then FDA does not need to pre-announce. "I have not heard anything and I am not aware of whether they are holding to their three to five-day preannouncement policy in the case of a virtual inspection," Chase said.

It is important that you practice and that you get prepared for any scenario that FDA could throw at you.

It is also possible that FDA may send your company an email. And in that email, they may request documents and they may request those to be provided to them by a certain deadline. There are a lot of ways that FDA can engage with companies for a virtual inspection.

Remember that for FDA to have the legal authority to conduct a true inspection and collect records for that purpose they need to issue the 482 notice of inspection to the company.

Types of FDA Inspections Reviewed

There are several types of inspections that FDA can conduct.

There is the routine surveillance inspection. "One of the things I would like to point out particularly given this weird time where we have MDUFA (Medical Device User Fee Amendment) and PDUFA (Prescription Drug User Fee Amendment) deadlines, is that FDA also has a two-year statutory requirement for medical devices. They are technically supposed to conduct an inspection of their entire medical device inventory at least every two years. We know that sometimes they have been hit or miss on that, but this would be particularly challenging at a time where they cannot necessarily get out there to do the inspections."

There is also a directed inspection, in which the agency is looking for specific information, and for-cause inspections. There are triggers for those, such as a company filing MDRs (Medical Device Reports) or recalls or field alerts.

In the pharma industry REMS (Risk Evaluation and Mitigation Strategies) inspections and pharmacovigilance inspections are smaller in scope. So rather than being a general surveillance inspection, it might be easier to conduct these types of inspections virtually or with a records review, particularly with pharmacovigilance, because they are focused on a very particular subject matter.

Questions to Ask FDA

Chase explained that FDA may or may not engage in dialogue with you. They may or may not be open to discussion at the onset of the inspection. It is important, though, if they are that you ask certain questions so that you can make sure that you understand exactly how they plan to conduct the inspection.

Here are some examples she provided of questions a company might want to ask FDA:

- How we are supposed to provide our responses?
- If we are sending documentation, can we expect to have it returned?
- Will we have live interaction meetings before, during, or after document review?
- Will this be a live inspection using real-time document submission and interaction over video conference? If not, what is the format?
- How should we communicate—for example, e-mail, document rooms, or through the U.S. Postal Service?
- It is particularly important that you under-

stand the expectations so that you know how to respond appropriately.

"Two of the most important concepts for virtual inspection include ensuring you having the opportunity to provide context to the documents they request and understanding how you will have a chance for dialogue if a 483 is issued," Chase said.

She pointed to the situation in a live in-person inspection when the investigator requests a document and a review of that document in the back room prior to giving it to the investigator indicates that there will likely be questions. "Think about doing this virtually, particularly if you are communicating through sending documents and you are not having, say, a WebEx live inspection, how do you get to explain or give context to the things that they may see and want to know more about?"

She emphasized the importance of thinking through this type of situation and how the context can be provided when a response is submitted in writing. She recommended asking the agency how you will have that opportunity.

Review Your Documents

With a virtual inspection, just as with any other inspection, you want to make sure that you are reviewing your documents in advance. You want to think about how FDA is going to be able to determine your state of compliance and control. Unless you are able to use a system like the one developed by Thermo Fisher Scientific and detailed in Part 2 above, FDA will not be able to really see and evaluate your manufacturing site.

As Howard Sklamberg said in Part 1 of this article, spontaneous interviews are important to FDA. Without the ability to do that, without those tools in their tool kit, how are you going to be able to demonstrate that you are compliant?

You need to make sure that you maintain your state of readiness, including reviewing your SOPs to see if they are current. Do not keep old ones around. If you are doing an inspection virtually, review them ahead of time.

Make sure your quality metrics are current and not only current but have been evaluated and you know what they are indicating. Trends in your quality metrics will be reviewed. Know what those are and how you can show that you are addressing quality signals and that you have taken appropriate actions where necessary.

Always make sure that your complaints, deviations, nonconformances, and CAPAs are reviewed. "We know that those are top 483 observations. You want to make sure that not only are those reviewed and they are complete, but you have all the documentation to support any actions that you may have taken," Chase advised.

Review out-of-specification (OOS) investigations, ensuring that you have complete investigations and supporting data. Also review evidence of supplier quality agreements, your company's current approved supplier list, and evidence of internal audits including the audit schedule and documentation of completion.

If you manufacture combination products with, for example, the pharma product being the lead, make sure you meet the requirements of the other regulatory provisions, such as 21 CFR 820, the quality system regulation.

"You cannot assume that because they are doing a pharma-lead, a CDER-led inspection, that they are not going to ask questions about how you are filling the gaps on the device side if you have a drug/device combination product. You need to make sure that you have things such as evidence of management review and established quality objectives, because it is highly likely that they would ask for those things."

For medical devices or combination products,

the design history files (DHF) are often extremely large, and it would be unlikely to have an entire DHF requested for a remote review. Ensure the DHFs for your most high-risk and/or new products are complete. Common requests would be for the design development plan (DDP), risk analysis, input/output matrix, and Design and Use Failure Mode Effects Analysis (DFMEA/UFMEA) documents.

Changes are always a point of interest. If you have put in a new piece of major equipment, started any new processes, or made any major changes to your facility or your products, those are usually areas that become a point of focus.

For example, if new, major production equipment has been installed, be prepared with a diagram or schematics to help the investigator visualize the change. Ensure that IQ/OQ/PQ (Installation Qualification, Operational Qualification, and Performance Qualification) documents are complete. Many times, these are large files. Ensure that the sections are clearly identified. Usually, the Protocol and Report sections are the primary ones to be reviewed.

Where new or changed processes have been implemented, or where there is a high-risk process, ensure the current process validation documentation is complete and approved, and that any deviations of non-conformances are clearly explained and justified.

For facilities, particularly aseptic facilities, environmental and microbiological controls are key. Ensure you have trending data on your environmental monitoring and that any necessary actions were discovered, completed, documented, and corrected or prevented. Corrections to excursions should be a point of focus.

Submit High-Quality Documents and Keep in Mind Inspections Focus on Risk

It is particularly important when you are providing documents to FDA that you ensure your documents are clear and legible and free from extraneous comments and sticky notes, etc. with no pages missing.

"We have all been in a situation where we have opened a batch record and we see that somebody has written a note on it on a sticky and they stuck it in the file. You want to make sure that you do not have any of those extraneous documents stuck in a file that should not be there."

You need to have all the pages accounted for. You will not be sending original documentation. You are either going to send scans or photographs. You want to make sure that the material copies well and the investigators can read it. You do not want them to continually ask for different copies because they cannot read what you sent them.

It is also important when you are sending something like a log or a notebook that you are only sending the data which has been requested. "We know that sometimes in our notebooks maybe a page is shared with the beginning of another test. You want to make sure that you are only providing the information relevant the question and you are not allowing that extra information to be shared unless it is specifically requested from the investigator," Chase said.

She pointed out that investigators specifically target higher-risk products and processes.

"Inspections generally are supposed to focus on risk," Chase pointed out. "FDA has a limited amount of time. An audit is just an audit. They are asked to look at those areas which are higher risk and to focus on those areas as a measuring stick for the rest of your quality system."

"If there are gaps in your high-risk areas, it really becomes easy for them now to say, 'you have some gaps in a critical area, so we want to look at what might be underlying those gaps.' That is when they start asking questions about whether you have enough resources available, or have

done the proper training, and if your documents support your current process."

"They are probably going to start with high-risk areas. But as they find deficiencies in those, they will start looking at areas that you might think are of less importance to substantiate their claims on the higher risk areas. The message is that in those areas which you think would by necessity be lower risk, doing the training and having the proper document control becomes important."

Part 4: Hosting A Virtual FDA Inspection: Advice from Former FDA Investigator and Investigations Director Ricki Chase

Chase began her remarks in the webinar on hosting a virtual inspection by pointing out that we all know there are certain behaviors we should exercise when we have a live, in-person inspection. Those apply to virtual inspections as well.

"A great quality system ensures constant readiness," she maintained. "This includes practicing your inspection management. You should follow your normal processes, the ones that you are familiar with. You need to practice and follow them. Where you need to adjust for the mode of communication, make your adjustments. But do not throw everything to the wind and start from scratch just because it is a virtual inspection. Stick with what you have practiced and what you know."

Virtual Inspection Best Practices

Designate a single point of contact (POC) for the receipt of the questions and the document requests. If you are not doing a live inspection—for example, by video conferencing, WebEx, Zoom, or something like that—they are probably going to be sending questions and document requests to you via email. Make sure you have a single point of contact for that because you do not want anything to get lost.

And just like any other type of inspection, you need to make sure that you understand the requests. If you do not, ask for clarification.

You should have a standard team that participates in an inspection.

Know who your subject matter experts (SMEs) are. Make sure that the SMEs are a part of the process. One thing to consider, if they are doing a video inspection with you, is whether you want the SMEs in the room on camera. "Do they present the best to FDA? Or do you want them in the back room supporting the person who is in the room and visibly in front of the FDA on the video conference? These are things that you should normally consider in your course of preparedness for any type of inspection," Chase maintained.

However, you cannot be assured if it is a virtual inspection that FDA will only work with a single spokesperson. It is very possible that they will ask to speak to the person whose name is on the document—the person who authored it or the person who reviewed it. Just because it is a virtual inspection does not mean that you should not have the relevant personnel available.

"When you send a document in the room when FDA is on site, you would expect that the individuals responsible for that would be available in case they have a question. It is no different here. You need to make sure that they are available."

As in your normal process, make sure you independently review your documents prior to submitting them. If they are doing a video conference with you, you should be running that backroom the same way that you always do. They make a request. You review it. Remember, this is not the time to make changes to your documents.

If they have made a request to you in writing and

asked you to submit certain documentation via email or standard mail, it is important that you do not go back and make changes in those documents. What you do want to do is review them and anticipate what the follow up questions may be so that you can immediately begin preparing answers for those anticipated follow up questions.

Communication is Key

It is also important when you are communicating via teleconference to remember that the investigator is listening to you, but not seeing you. Your tone and your delivery are extremely critical. You want to make sure you communicate clearly.

"I tend to be a fast speaker," Chase said. "If you are as well, you may want to make sure that you are taking a breath and slowing yourself down, giving the investigator time to interject with questions. You want to make sure you watch your tone so that it does not seem that you are being defensive or that you are being irritated by the fact that they are trying to conduct a remote inspection."

Finally, it is important if you are doing a video conference that you dress professionally. "We all know that it shows respect. It creates confidence in your abilities and in your organization. If you are going to be on video, make sure that you look the part of your role and responsibility."

Make sure that the SMEs are a part of the process.

Make sure that if you communicate in writing—not just on phone or video—that your words are chosen to be clear and concise and that you are not using any type of inflammatory language and you are not appearing to be argumentative.

"I would also like to point out that context is important," Chase stressed. "Where you need to provide context, you should provide the context. Just ensure that you are not allowing the provision of context to now move into lengthy storytelling or unnecessary verbiage or the entire history of a situation which turns out to not be relevant or may be an overshare. Particularly if you are providing that context in writing, you need to have an extra layer of review to make sure that what you are communicating is clearly what you intend to communicate."

Adjust Your Logistics

We have discussed having a virtual inspection, mailing/emailing documents, teleconferences, and video conferencing. These are not the normal ways we usually work with FDA on inspections. "You need to think about what your logistics are. You need to make sure right now, today, before FDA calls you on the phone and says they are going to do an inspection, that you are ready."

You need to make sure that you can provide the documents in a format and file type that FDA can receive and read them in. If you are using some type of proprietary internal software and you send them a digital data file and they cannot read it, that is very frustrating for them. You do not want to frustrate them. Make sure you are communicating and understanding what they have the capability to receive and what you have the capability to send.

Be mindful of file sizes as well. Submit your records and your data the way that they specifically ask for them, e.g., if they give you identifiers, ask you specifically to write a question number on your reply or request you to restate the question that you are answering so that they can marry the documentation up with their information, follow the request. Help them be successful in conducting the inspection.

Make sure your telephone and conferencing and videoconferencing equipment works. If you do not have I.T. on your team, engage with I.T. and start getting them in the practice of doing this

and being immediately available, looking at your systems and ensuring these systems would be adequate for this type of inspection.

You want to make sure that your printing, scanning, and copying functions function. We take these for granted. But occasionally these things break down and you cannot get a serviceperson in there. You need to know what you have available at your fingertips to get this job done.

"Make sure that your email is considered part of the official record," Chase advised. "And be incredibly careful about your e-mail communication. Anything that you send to the agency can become part of the official record. This includes text messages. I would strongly recommend that you do not get into a text messaging habit with your investigators. Keep it in a format which can be maintained and be official."

Remember that when you do send an email that your email can be altered and the context could be changed. "We would never presume that anybody would do that. But we also want to protect ourselves and make sure that we are not providing opportunities. So perhaps the email says, 'please see the enclosed.'

The context that you need to provide or the description of your documents might exist in a word document that has been approved by your team. Put that conversation or context along with the documents in a PDF format so that it is secure and becomes part of the official record," she advised.

Finally, just like in any other inspection, do not record your investigator or the inspection. "If you feel so strongly that you need to do that, you certainly need to have that conversation with the investigator before things happen, because if you do they are required by policy to record as well. My recommendation is do not record. It makes things awkward and uncomfortable."

You need to maintain an inspection binder just like in any inspection. Include all the submissions to FDA at their request. Ensure that every document is cross-referenced to any electronic file or correspondence that you have provided context for so that your record is complete. The investigators should be able to easily understand what you submitted to them. And they should understand which inquiry your response marries up to. You want to make it easy for them to follow what you sent them in response to their request.

Anything that you send to the agency can become part of the official record.

If you are the point of contact, "now is not the time to get a little behind on your email. Make sure that you are monitoring your email and that you are very attentive to any communication you get from FDA so that you can respond in a timely way," Chase recommended. "Minimize your email traffic internally. Make sure that you answer your telephone." If they must call you because they are not clear about something and it is easier to discuss on the phone, you need to call and have that conversation with them.

"You should handle this like you would any other inspection," Chase advised. "If you have a request and the team is working in the backroom—which is where they should be—then be in the backroom or be in your conference room managing the inspection the way you normally would rather than and each of you sitting at your desk and sending a lot of email traffic around. That creates a record. It also can be challenging to communicate via email. So have your backroom and run it like you normally would."

Closeout Meeting

Say you get through your virtual inspection and it has been great. You have given all the requested documents. You have answered all questions. Now, it is time for the closeout.

To prepare for the closeout, make sure you know who is going to be in the room and ensure you take accurate notes. "We would hope that if you are having a virtual inspection and there is going to be a 483 issued that you are going to get a closeout meeting. I certainly would not expect them to put a 483 in the mail or the e-mail with no discussion."

Assume that you are going to get a closeout meeting. You want to make sure that you have only those who are necessary in the room. They are going to want to issue the 483 to the most responsible individual at the site. You want to make sure that person is around to be able to receive the 483 if one is issued.

And as always, you want to make sure you listen closely, particularly if they are giving you verbal warnings or discussing items that are not written on the 483 for you to go back and refer to. You want to make sure you have a really good record of that so that you can address those as well.

"Again, do not argue an observation," Chase recommended. "Now is not the time to be argumentative. If the 483 contains incorrect information, politely tell them you think that there is a mistake. For example, 'I think it is supposed to be lot number one, two, three, not X, Y, Z.' That way they can change it. There is nothing wrong with doing that. You do not want the 483 to be incorrect. They do not want it to be either."

If you do you disagree with an observation, you can state why you disagree. But do not be argumentative. Just clearly state why you do not think the investigator got that right. Do not expect the investigator to change the 483. "They might listen to you. They might take notes on it. They might report it in their Establishment Inspection Report (EIR). But it does not mean that they are going to go back and change the 483. Be aware of that."

Follow your policy for responding to a 483 if one is issued. You must ensure that your team and your leadership receive the 483 as soon as the inspection is over. You have a deadline. You want to hit that 15 business day deadline with a solid response. Make sure that you communicate quickly with your team and your leadership so that you can get started if you do get a 483.

Now is not the time to get a little behind on your email.

If you made some corrections during the inspection it is perfectly fine to ask if you can present those during the closeout. And hopefully the investigator will be open to that. They will take some notes and put that in the report.

"Finally, do not ask the investigator what they are recommending – for example, voluntary action indicated (VAI) or official action indicated (OAI). By policy, they do not have the authority to answer that question. So do not ask them."

There are many options for FDA when they conduct a virtual inspection and there are a lot of ways that they can communicate with you. The key to being successful is probably the same thing that it has always been:

- You need a solid program of continuous quality improvement.
- You need to make sure that you have ongoing inspection preparedness.
- You need to train and practice with your team.
- You need to anticipate where the pinch points are. We all know where our weaknesses are.

- Make sure that your communication is clear, concise, and professional.
- Practice your inspection process and you follow your routine process so that it seems more natural to you.

"Communications and logistics are probably going to be your biggest challenges because this is just a whole new way of doing business," Chase commented.

"It is important that you check those things out now and that you are prepared and are not dealing with those problems when you get a virtual inspection."

ABOUT THE AUTHOR

Jerry Chapman is Govzilla's Senior GMP Quality Expert. He brings 40 years' experience in the pharma industry, including 31 years at Eli Lilly where he worked in product development, biosynthetic human insulin manufacturing, and site and corporate quality roles. In corporate quality, he designed and implemented a comprehensive GMP Intelligence process to identify, analyze, and archive pertinent drug GMP regulations, inspection findings, trends, and best practices in the US and internationally. Jerry was founder and chairman of the GMP Intelligence subgroup of the Midwest Discussion Group from 2005 to 2010. He served as Senior Editor at International Pharmaceutical Quality for six years, has been an invited speaker at PDA, AAPS, ISPE, and RAPS, and was a consultant for the animal health and compounding pharmacy industries prior to joining Govzilla.