June 29, 2020 PDA Webinar

Remote Assessments and Inspections during the COVID-19 Pandemic: Regulator Perspectives

Summary Notes:

The following summary notes from the webinar were developed by the PDA COVID-19 Task Force

Globally the COVID-19 pandemic has required changes in the way regulators globally have been approaching the inspection of manufacturing facilities. This webinar focused on this evolving area and provided participants insight into how regulators are approaching this challenge.

Moderator:

- Tom Cosgrove, Partner, Covington & Burling

Heath Authority Participants:

- David M. Churchward, Deputy Unit Manager, Inspectorate Strategy and Innovation, MHRA
- Alonza E. Cruse, Director, FDA/ ORA/ Office of Pharmaceutical Quality Operations
- Stelios Tsinontides, Director, FDA/ CDER/ Office of Pharmaceutical Quality/ Office of Pharmaceutical Manufacturing Assessment
- Derek Smith, Associate Director Regulatory Affairs (Acting), FDA/ CDER/ Office of Pharmaceutical Quality/ Office of Pharmaceutical Manufacturing Assessment
- Ewan Norton, Senior GMDP Inspector, MHRA

On June 29, 2020, FDA and MHRA officials addressed the topic of inspections during the COVID-19 pandemic during the Parenteral Drug Association webinar “Remote and Virtual Inspection during the COVID-19 Pandemic: Regulator Perspectives”.

Stelios Tsinontides gave an FDA presentation (see slides) that explained the CDER Office of Pharmaceutical Quality team-based Integrated Quality Assessment (IQA) and pre-approval inspections. He explained that the Office of Pharmaceutical Manufacturing Assessment gathers information to support a facility assessment. He indicated that during COVID-19, when onsite inspections may not be possible, FDA can gather facility information through: 1) a records request under FDA's statutory authority under 704(a)(4); 2) using information shared by other regulatory agencies, for example, under a mutual recognition agreement (MRA) and confidentiality agreements; and, 3) by requesting additional information from the applicant.

Tsinontides explained the 704(a)(4) records request process. He also discussed the facility risk assessment process and how that assessment is used for determining the need for a preapproval inspection (PAI). He indicated that if it is determined that a PAI is needed, a records request may be used to assess the capability of the facility and its quality systems to perform the manufacturing operations. Generally, if FDA has not conducted a previous inspection at the facility, an inspection is required. A 704(a)(4) records-only request will not satisfy the inspection requirement.

Tsinontides indicated that during COVID-19, onsite inspections include mission critical PAIs. Mission critical may include situations involving Breakthrough Therapy Designated (BTD) products, drug shortages, and products used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute. Factors in determining mission criticality include safety of all those involved in inspections and the public health benefits of the drug product under review; for example, the clinical benefit, medical necessity and safety concerns of the drug product. FDA indicated that if a site is under a consent decree / warning letter, an onsite inspection will be required.

Tom Cosgrove mentioned that there may be confusion in the regulated community about the relationship between the 704(a)(4) records request and inspections. Cosgrove noted that someone recently told him they believed they were undergoing a virtual FDA inspection and thought they had received a Form FDA 482 from the agency. Cosgrove said he was "pretty sure that that company wasn't getting a virtual or remote FDA inspection," he added that "it also is pretty clear that there were some robust discussions going on … that might look like those that were happening in a real inspection." Cosgrove concluded that the firm in question wasn't under inspection and that there is confusion because companies may feel like they are in an inspection.

Alonza Cruse talked about how FDA is getting their work done. He indicated that an onsite inspection determines compliance, and that the FDA is supplementing that by obtaining additional inspection information through other means such as: 1) reviewing the firm's previous inspection history; 2) using information sharing from other foreign governments as part of the MRA; and, 3) through PIC/S GMP inspection reliance using confidentiality agreements with other health authorities. The FDA are still evaluating if this can be expanded to include MRA/PIC/S audits for facilities in third country locations (i.e., not the country of either regulator). Cruse indicated that Facetime or other types of technologies are not yet being used by FDA and reiterated that a 704(a)(4) records request is not considered an inspection.

The FDA officials indicated that FDA will entertain alternatives and indicated a willingness to consider the arguments. "I'm going to be open to receiving feedback and certainly listening to the questions," Cruse said. Tsinontides echoed that statement in the context of preapproval inspections. "Already there

are some sponsors that have proposed to the agency some novel approaches on how we could possibly mitigate the risk for not being able to do an onsite inspection," he said. "We haven't turned anyone down in terms of listening and engaging with them in regard to those proposals. I would encourage the industry that if they have any proposals, they engage with us. We are willing to hear. And obviously, we will certainly learn from this experience and there may be some way that we need to modify as we move forward, even beyond the COVID-19 experience."

David Churchward and Ewan Norton talked about how the MHRA is handling inspections during COVID-19. Norton indicated that the desktop inspection approach was developed at the end of March 2020 following suspension of onsite inspections and the first remote inspection conducted in April of 2020. The MHRA to date have conducted approximately 120 desktop inspections. The process involves a pre-inspection records request followed by a remote inspection covering Quality Management System compliance. A GMP certificate is then issued with a statement included that it was based on a remote inspection. A shorter on-site inspection covering the areas not previously assessed (facilities), would then be planned once travel restrictions were eased and the GMP certificate from that inspection would have no clarifying remarks included. Churchward explained that when they return to onsite inspections, it is likely this will take the form of a hybrid approach, taking into consideration procedures around social distancing and that they would be using some technology. The hybrid approach would therefore involve a pre-inspection records request, an onsite inspection with some remote elements used whilst on site to mimimise the volume of social interactions.

Churchward indicated that some things you really have to do on site. That when they are looking at remote inspections, they evaluate exactly what they need to for the compliance decision they want to make. He indicated that they have tried to be clear and honest about what they ask for and how much information they can obtain this way. MHRA has used closed circuit TV to perform some aspects of an aseptic processing inspection and they are also using hybrid approaches like with the Oxford University and the COVID-19 vaccine inspection where some aspects were conducted remotely with an abbreviated onsite presence. Development of this process followed experience gained through the Flu pandemic (2011) and Ebola outbreak (2013). MHRA are also using MRA/PIC/S audit information in absence of performing international inspections at this time. They mentioned that early engagement was key to agree on a path forward for key submissions and to be clear on any restrictions in place.

Cruse indicated that follow-up to an FDA records request (Form FDA 4003) could involve follow-up phone calls, or an additional records request. He indicated that no program is perfect. That FDA is not set up to use video conferencing at this time. He indicated that the FDA records requests under 704(a)(4) authority is also using a hybrid approach (like MHRA). He indicated that the investigator who emails the FDA records request will review the records remotely and will generally be the investigator that follows-up with the onsite inspection especially for domestic facilities. That the follow-up onsite inspection will be announced to help allow for adequate preparations (i.e., having personnel on site, PPE available, training prepared, etc.).

Thirty (30) minutes was devoted to Q&A at the end of the session and are summarized below.

<u>Q&A Session</u>

1. Cosgrove talked about inspection risks considering visiting individual sites vs. patient risk of not receiving the medication under review. He asked how many medically necessary drugs are being subjected to PAI assessment and if that amount was steady.

   Derek Smith responded that FDA has not seen a slowdown in the number of applications filed or pre-approval inspections assigned. FDA has approved 15 submissions using alternate tools. Factors FDA considers when deciding if a PAI is needed include if this is a new/innovative drug product or manufacturing process to FDA. Also, if the company can give the agency information regarding similar products already manufactured for the US from the facility, this would aid in the assessment. Also, sponsors may consider domestic supply chain alternatives given foreign travel restrictions.
2. Cosgrove asked about medically necessary products and how FDA's evaluation evolved in light of recent events.
   a. Smith indicated that we are using the tools available to perform facility assessments. He indicated that FDA is evaluating alternative tools when necessary and he added that early engagement to discuss compliance information is important.

3. Cosgrove asked where (using alternative tools) can go in the future.
   a. Cruse indicated to stay tuned as FDA is evaluating the situation. That FDA will work to keep industry informed via these types of webinars, through issuance of guidance documents, etc. Cruse acknowledged that we are all going to be challenged in this environment and that we all must work towards global solutions.
   b. Tsinontides indicated that FDA is engaging with industry and will entertain proposals to meet regulatory needs. That we will work together to find solutions, especially for medically necessary products.

4. Cosgrove asked what people should be considering doing differently in the coming months and asked for advice regarding getting applications over the line.
   a. Smith indicated that FDA is giving almost the same advice they have given prior with medically necessary products; make sure you have redundancies in your supply chains. When you have choices regarding who can manufacture your drugs this allows agility in conversations and solutions. With respect to records requests he indicated that companies provide information just like you would for inspections.
   b. Tsinontides indicated that single source supply chains may not be adequate in our current situation.

5. Cosgrove asked what information can sponsors provide to the agency about the strength of their quality systems
   a. Tsinontides indicated that COVID-19 has demonstrated that companies with strong Quality Management Systems, including but not limited to KPI metrics and continued process improvement programs can demonstrate an effective quality system.

6. Cosgrove asked what regulatory pathway or channel could be used to communicate needed facility information.
   a. Smith indicated that information comparing the current application under review to previous applications for similarities is helpful.

b. Churchward indicated that they use application meetings to discuss what kinds of information could be helpful and what records are needed to be reviewed. He noted that some paper-based records cannot be scanned in short periods of time.

7. Cosgrove asked now that several inspections have been executed what learnings can be shared and asked if there have been any technological barriers.
    a. Norton indicated that he has conducted 10 remote inspections and bandwidth can impact the ability to hear others clearly. That they must accept that there will be limitations to the technology and that inspections need to be planned and may take potentially 50-100% longer. He indicated that the inspections can be very tiring and that they try to send a list of document requests a couple of weeks early. That they define a transfer system (not email) so information can be transmitted and organized. He indicated that having an opening meeting and using video is helpful and at the end of the opening meeting he provides a further list of requests based on the review of the documents already supplied, so that the process runs as smoothly as possible. He indicated that he asks questions via email (and ask for acknowledgements of receipt of questions) and establishes timelines for response to the questions. That preparation is paramount here and scheduling touchpoints during the day is helpful. He indicated that he finds a daily review of what was reviewed at the end of each day is helpful.

8. Cosgrove indicated that the Japanese HA have used Google Glass and other technologies and asked if the MHRA is considering that technology.
    a. Norton indicated that the MHRA has not used that technology specifically but is considering for the future. He was only aware of one virtual walkthrough that has taken place at a Singapore facility.

9. Cosgrove asked if a 704(a)(4) records request be used to close out an OAI inspection and reclassify sites from official action indicated to voluntary or no action indicated without sending an investigator back to the site.
    a. Cruse indicated that at this time, those types of activities are going to require an onsite inspection. He indicated that FDA is thinking about new ways to solve problems
    b. Cruse and Smith confirmed that there are no remote or virtual inspections for the FDA yet.

10. Final thoughts
    a. Churchward indicated that harmonization of efforts may be difficult due to the evolving situation in so many different geographic regions. Groups like PIC/S continue to work towards harmonization, but this may not be possible in all cases. It was noted that the 2020 PIC/S conference's scope has been amended to focus on remote inspections.
    b. Tsinontides indicated that health authorities are leveraging each other's resources so that together they have a better set of tools to address compliance risk during COVID-19; and they will continue to work towards international harmonization.