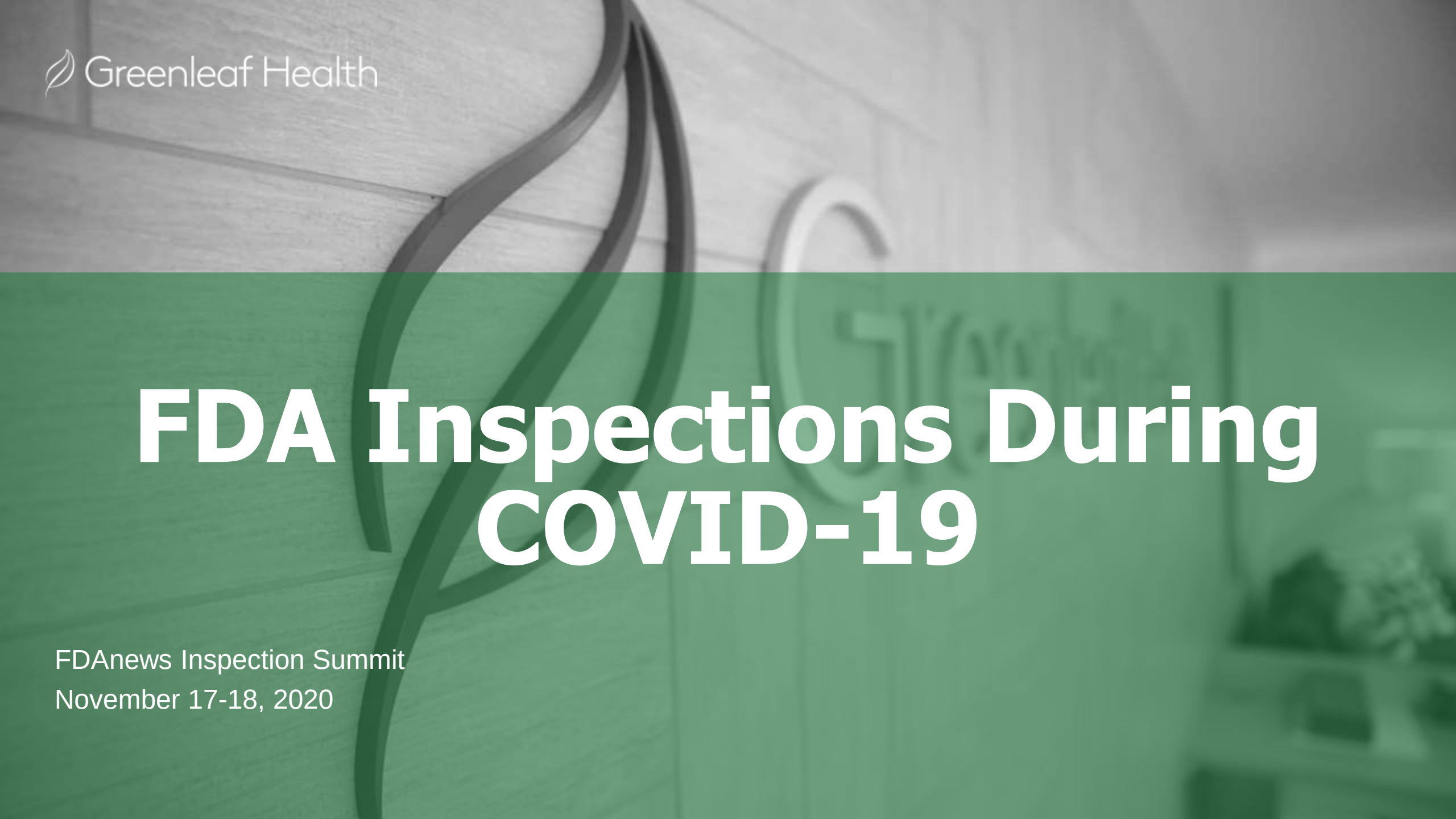

FDA Inspections During COVID-19

FDAnews Inspection Summit

November 17-18, 2020

Timeline

- March 10: FDA announces suspension of most foreign inspections
- March 18: FDA announces suspension of routine domestic surveillance inspections, except "mission critical" (to include for-cause)
- May 11, 2020: FDA states that it will continue to postpone domestic and foreign routine surveillance inspections "with the exception of certain mission critical inspections."
- June 2, 2020: Testimony before Congress, *Oversight of the FDA's Foreign Drug Manufacturing Inspection Process*
- June 2020: *Guidance, Development and Licensure of Vaccines to Prevent COVID-19*
- July 10: FDA announces it will resume domestic inspections on July 20
- August 19: FDA issues *Guidance for Industry, Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers*
- September: FDA issues *Guidance for Industry, Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency*
- September, October, November*:* At various conferences FDA hints that virtual inspections are possible, and mentions possible forthcoming guidance (PDA, RAPS, FDLI), FDA also presents more data about alternative tools and on-site inspections

What Happened from March to August?

FDA Activity: March to July

- Most foreign and domestic inspections suspended
- FDA focused on maintaining safety/quality of drugs, mission critical operations, and “alternative tools” in lieu of inspections
- But open questions
  - What is “mission critical”?
    - For cause? Pre approval? COVID-19 related?
    - Case-by-case evaluation
  - What are the “alternative tools” and how and when does FDA use them?

What are "Alternative Tools"

- **704(a)(4) authority:** requesting and reviewing records "in advance of or in lieu of" an inspection
  - FDA has authority to request, in advance or in lieu of an inspection, records or information FDA may inspect under section 704(a). *Section 704(a)(4) of the FDCA*
  - This provision explicitly applies to drugs and biologics, not medical devices
    - *Note: FDA also believes 704(a)(4) does not apply to BIMO inspections*
    - *Relying on voluntary records requests for BIMO and devices*
  - SMG 9004.1 outlines process for 704(a)(4) records request
- **Inspection and compliance history** of a facility
- **MRA** process with the EU: flexibility to rely on recognized foreign authorities
- **PIC/S:** leveraging reports from "capable authority" inspections outside EU
- **Import controls**, including denying entry of unsafe products into the U.S. and physical examinations and/or product sampling at US borders
  - Appearance standard to refuse entry of imported product
  - New FDA Import Alert category

"Alternative Tools" Are Not Inspections

- FDA believes inspections are on-site only (*PDA Webinar, June 20)*
  - Information requests under 704(a)(4) are **not a "virtual inspection"**
  - Video conferences or follow-up phone calls related to 704(a)(4) requests are **not the same as on-site inspections**
- FDA still requires an inspection to close out WL/OAI status of a site
  - Even though RPM does allow FDA to close out Warning Letters without an inspection
- If an inspection cannot be conducted and "alternative tools" are inadequate or not appropriate
  - PAIs and therefore approvals may be delayed (missed goal dates, CRLs)
  - OAI status may linger (which may continue to delay approvals)
  - Shortages and other avoidable consequences

Contains Nonbinding Recommendations

Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers

Guidance for Industry

August 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

Inspections Q&A Guidance: Key Points

- Reiterates FDA's approach for resuming domestic inspections – COVID19 Advisory Level to safely resume "**prioritized domestic inspections**, which generally include pre-approval and surveillance inspections." (Q1)
- Further explanation of **"mission critical,**" including new factors such as breakthrough or RMAT designation or products used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute." (Q2)
- Continue to use **"additional tools"** in determining the need for an inspection and assessing an application; "CDER and CBER are continuing to evaluate applications, strategically applying a holistic approach in the decision-making process to determine if an inspection is warranted or if an inspection is no longer needed due to information gained through the use of the additional tools mentioned above" (Q5)

Inspections Q&A Guidance: Key Points Cont'd

- Further explanation of when FDA will issue a **Complete Response Letter (CRL) (Q6)**
  - If, based on available information, FDA determines an inspection is necessary for approval but PAI cannot be conducted, FDA will issue CRL
  - If not enough information to make a determination, FDA will defer the action date
  - Decisions about applications will be made based on the **"totality of information provided to the Agency."**
- Addresses **manufacturing changes (Qs7-10)**
  - Adding or changing a facility: follow established guidance
  - Post-approval changes: "FDA is using multiple tools to facilitate implementation of manufacturing changes such as **risk-based reduction in supplement reporting categories** and **flexible assessment practices**."

What’s Happened Since August?

FDA Activity: August & September

- Domestic inspections have resumed on a prioritized, “case-by-case” basis, based on an assessment of risk posed by infection rates in a given region and on guidelines put in place by state and local governments.
  - All preannounced
  - No foreign inspections (except ”mission critical”)
- FDA has conducted inspections since July announcement
  - Limited data on location, number, type, and nature of resumed inspections
  - But, appear to be similar in nature and scope to pre-COVID inspections
  - Look for data on approvals, 483s, WL closeouts, etc. in the coming months
  - Good examples: Eli Lilly August inspection; missed BMS PDUFA date (inspection not scheduled)
- Even with domestic inspections, continuing to rely on “alternative tools”

“[I]n some cases [FDA] has resumed, prioritized domestic inspections”

Alonza Cruse, *September 2020 PDA/FDA Joint Regulatory Conference*

Recent FDA Statements
Goal dates important; alternative tools frequently used

- PDA/FDA Conference (Sept 2020)
  - Using additional innovative ways to do inspectional work (i.e. requesting records in advance or in lieu of an inspection) (Alonza Cruse, ORA)
  - Reassurance that many expected approvals will not encounter inspection-related delays (Elizabeth Miller, ORA)
    - Priority to conduct inspections with pending user goal dates "using a benefit versus risk calculation that will factor public health and access to critical therapies."
  - ORA has been able to make judgments on the quality of hundreds of drug manufacturing facilities without visiting them (Miller)
- RAPS Conference (Sept 2020, Bill Maisel, CDRH)
  - "Very creative in trying to make sure that their inspections are efficient, focused, and minimize any risks to either their inspectors or to the company being inspected," being inspected,"
  - Maisel is counting on a "transition back to normalcy" for facility inspections – "but what that timeline looks like, I think really hasn't yet been established."

Recent FDA Statements Cont'd
In person inspections possible; alternative tools still important

- FDA has conducted over 200 "mission critical inspections" during COVID
  - Foreign and domestic
  - Includes "inspections of facilities for which there may be a drug shortage, or inspections needed for approval of a novel drug or drugs related to the treatment of COVID-19"
  - Well aware of goal dates, doing best not to miss them (ORA/CDER weekly meetings)
- 704(a)(4) is still "primary tool" in lieu of inspections
  - Considering remote records requests/assessments for programs where 704(a)(4) does not apply (e.g., BIMO, devices)
- Tested use of live video during inspections of two produce farms
  - Requested feedback on remote inspections/video for drug industry

FDLI Annual Conference (Judy McMeekin, ORA, October 2020)

Recent FDA Statements Cont'd
Virtual inspections coming?

- IPAC-RS Conference (Brian Hasselback, CDER, November 2020)
  - FDA is preparing COVID-19 guidance "specifically on remote evaluations using interactive video or other types of interactive tools and techniques"
  - Guidance will "describe basic expectations for industry and indicate what to expect from the FDA" and will describe "how we'll use that interactive engagement in our decision making about pending applications"
  - Scope may also include GMP surveillance, for-cause and BIMO
  - Exploring whether video will be voluntary, or could be made mandatory
- K&S Annual Medical Device Summit (November 2020)
  - FDA may pilot a virtual inspection program for devices

"Alternative Tools" Continue To Be Critical

- Foreign inspections still only mission critical
- Domestic inspections only possible if COVID-19 Advisory Level permits (safety first)
  - Resurgence of cases or state/local guidance could shut down inspections
- Even if inspections conducted, still priority inspections only
- Alternative tools FDA has mentioned will continue to be essential – FDA continues to allude to those alternative tools in recent speeches, even as virtual inspections become more realistic possibility
- But, remember FDA
  - Still does not consider those tools to be an inspection
  - Has not conducted virtual inspections (although it may)

Records Requests Under 704(a)(4)

- **FDA is clearly relying heavily on 704(a)(4) records requests** (multiple FDA officials have referred to 704(a)(4) as a "primary" tool in recent months)
- Relying on information from "remote assessments" to set priorities for site inspections and help focus them
- Received requests for more formalized process for communicating outcomes from a records request and closing it out (under consideration)
- Launched an initiative to use remote regulatory assessments for programs to which the 704(a)(4) authority "does not explicitly apply."
- Industry encouraged to follow the process spelled out in Staff Manual Guide 9004.1, *Policy and Procedures for Requesting Records in Advance of or In Lieu of a Drug Inspection.*

424 records requests to drug manufacturing facilities	
229	*Foreign facilities*
195	*Domestic facilities*
111 (of the 424) supported application reviews	
77	*Approval recommendation*
15	*Withhold recommendation*
123 records requests to biologic manufacturing facilities	
15	*Foreign facilities*
108	*Domestic facilities*
95% response rate from industry	

Data from E. Miller as of Aug 31, 2020 (PDA/FDA Joint Regulatory Conference 2020)

DO

- Provide requested records fully, accurately and within the requested timeframe (SMG 9004.1) and consider following up with a request for video or teleconference to provide context for the records
- Ensure the necessary infrastructure is in place to efficiently handle the remote assessment (e.g., appropriate personnel and technology are available, trained and in working order)
- Recognize the difference between an inspection and a remote assessment and potential different outcomes
- Ensure full factual information is provided to and understood by FDA and respond promptly to any identified issues
- Consider creating policies or SOPs in advance of receiving a records request

DON'T

- Delay, deny, limit or refuse any aspect of the document production request or otherwise (*Guidance, Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*)
- Disregard the importance of a remote assessment
- Create any perception that the information you are providing (verbally or in writing) may be anything less than complete and accurate.
- Miss opportunities to communicate directly with FDA or to clear up possible misperceptions
- Record anything without notification and agreement

In Other Words…Opportunity

- FDA is facing external pressure to think carefully about inspection processes
- FDA appears to be listening to and carefully considering industry suggestions
- But what does that mean?
  - FDA is considering “virtual inspections”, but what will that look like? When will guidance be published?
  - Agency also considering new and/or more formalized ways to rely on the 704(a)(4) records requests and other tools? What are these more standardized processes? Will there be guidance on that?
  - How will agency prioritize on-site inspections, including PAIs and sites looking to remove OAI status?
    - How much time is enough for advance notice of an inspection?
    - What are best practices for on-site safety protocols during an inspection?
  - Will use of these “alternative tools” continue beyond COVID-19?
- FDA continues to stress that it wants to encourage new approaches and partner with industry – industry has and should continue to take advantage of this
- Inspections Q&A Guidance and recent speeches are an excellent start, but need further clarity/transparency on how the agency will utilize the tools it has, and how/whether it will expand upon the toolbox…learn from experience!

Panel Discussion and Q&A