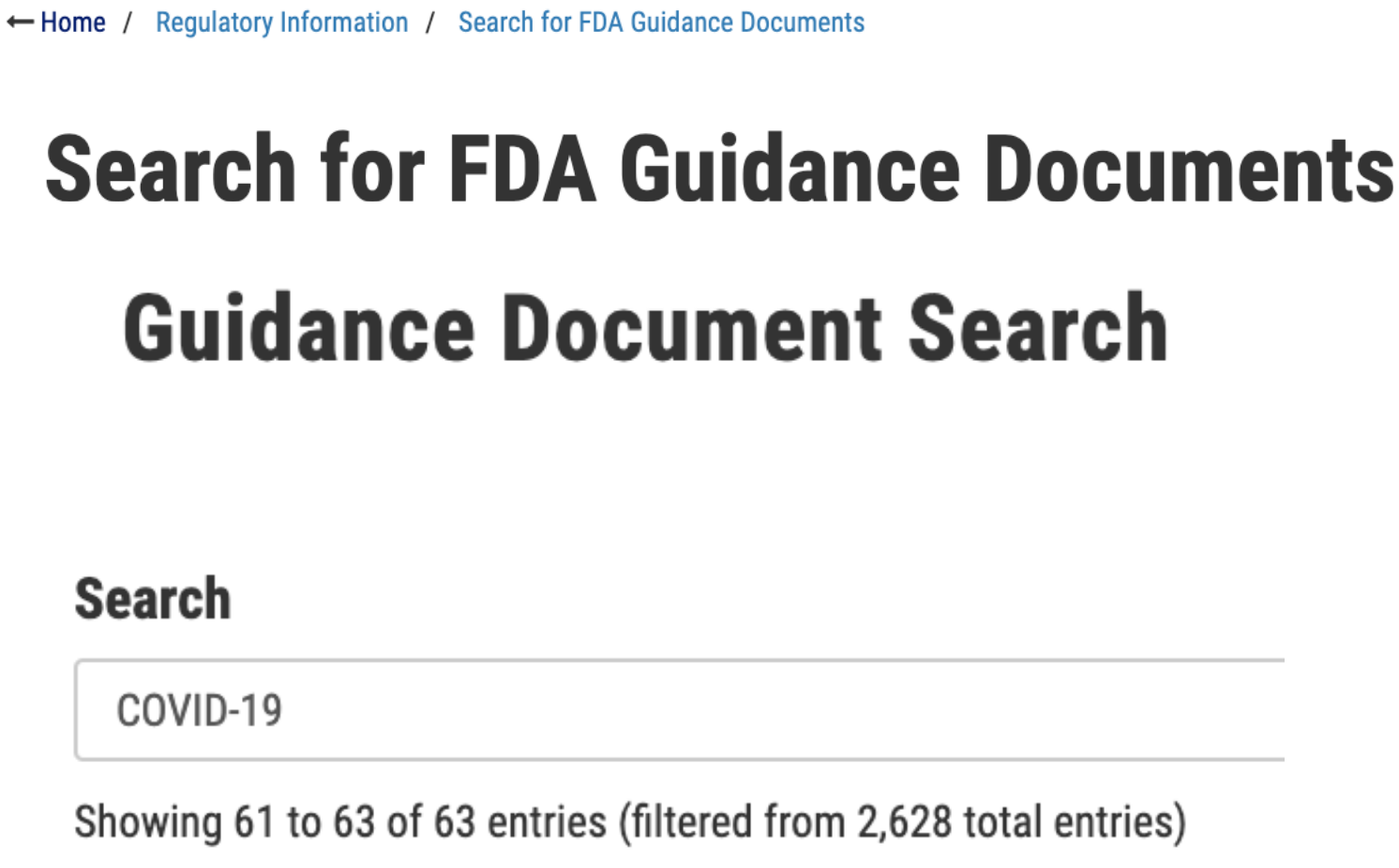
FDA Inspections
During COVID-19 Emergency

- Background/Timeline of Inspection Delays
- FDA Guidance(s) for Industry
- "Mission Critical" Designation (for On-site)
- FDA's "Alternative Tools" (≠ Inspection)
  - FD&C Act FDSIA Sec. 704 Records Request
  - "Virtual" Assessments (Remotely)
- Dependent on "Trajectory of the Pandemic"

Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency



https://www.fda.gov/regulatory-information/search-fda-guidance-documents

** FDA "GFI" = Guidance for Industry;*

Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency

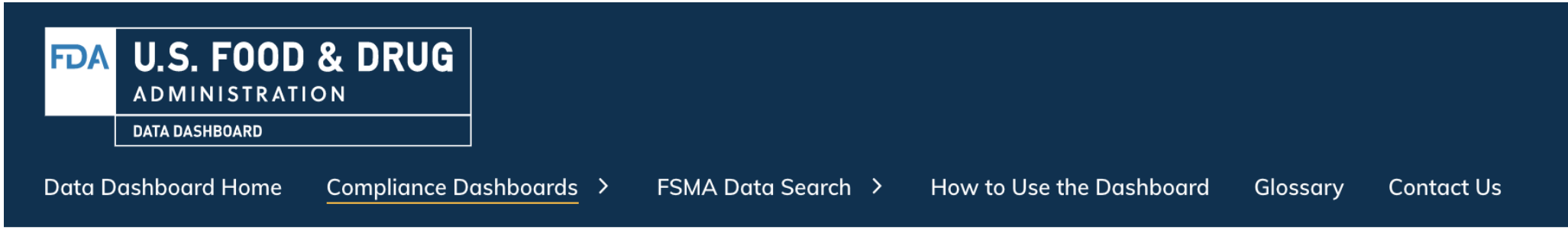
- March 10: FDA suspends foreign inspections
- March 18: FDA suspends domestic surveillance inspections, except for “mission critical” & certain "for-cause” inspections
- May 11: FDA states continued postponement of domestic and foreign inspections “except certain mission critical inspections.”
- June 2: Congressional testimony,

  Oversight of Foreign Drug Manufacturing Inspection Process

- *June 30: FDA issues GFI, COVID-19 Vaccines*

Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency



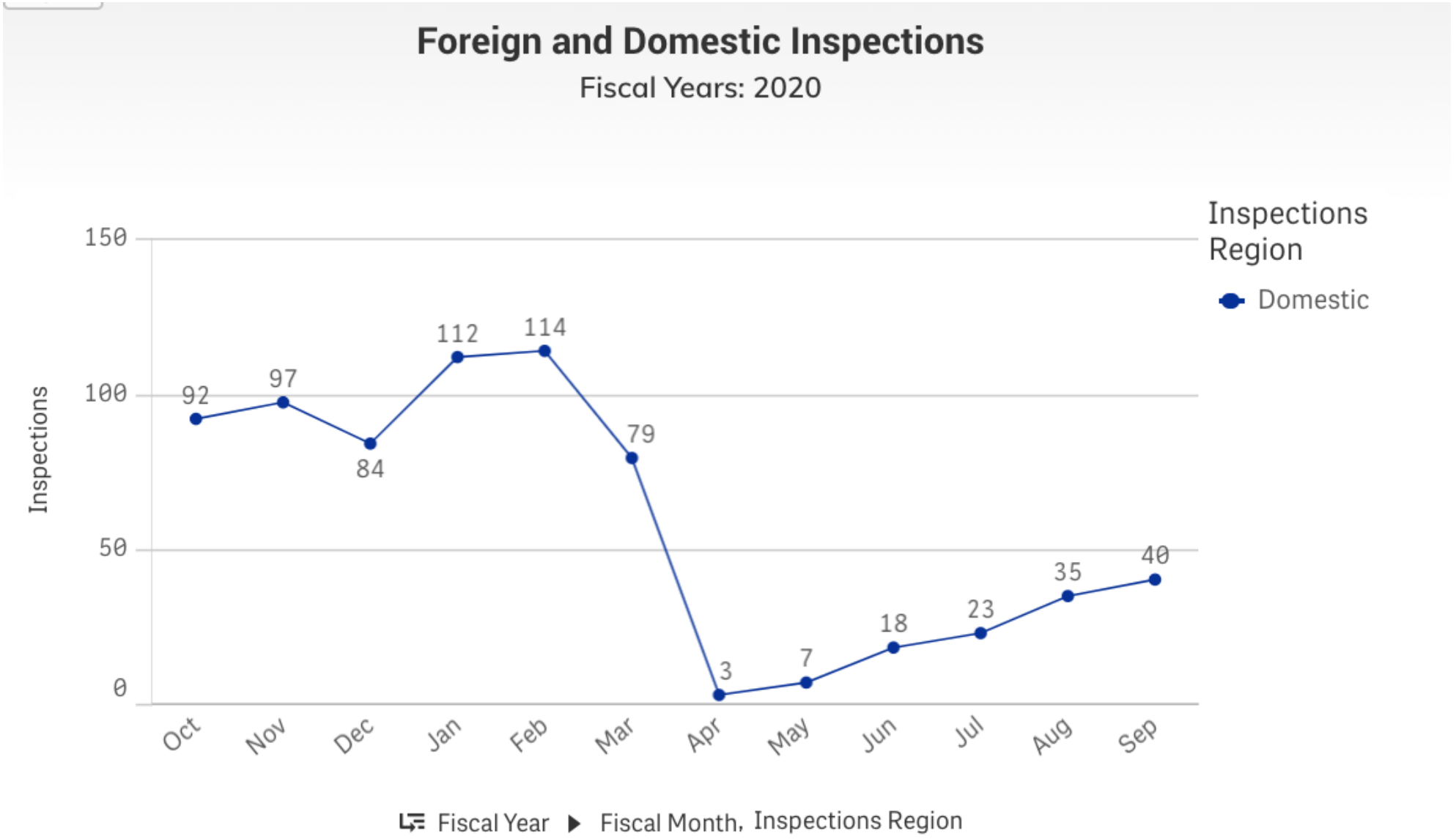
https://datadashboard.fda.gov/ora/cd/inspections.htm

July 20: FDA resumes limited, prioritized domestic inspections

- Pre-Announce; Adhere to National (CDC), state & local guidance on COVID-19
- Example: Eli Lilly August inspection

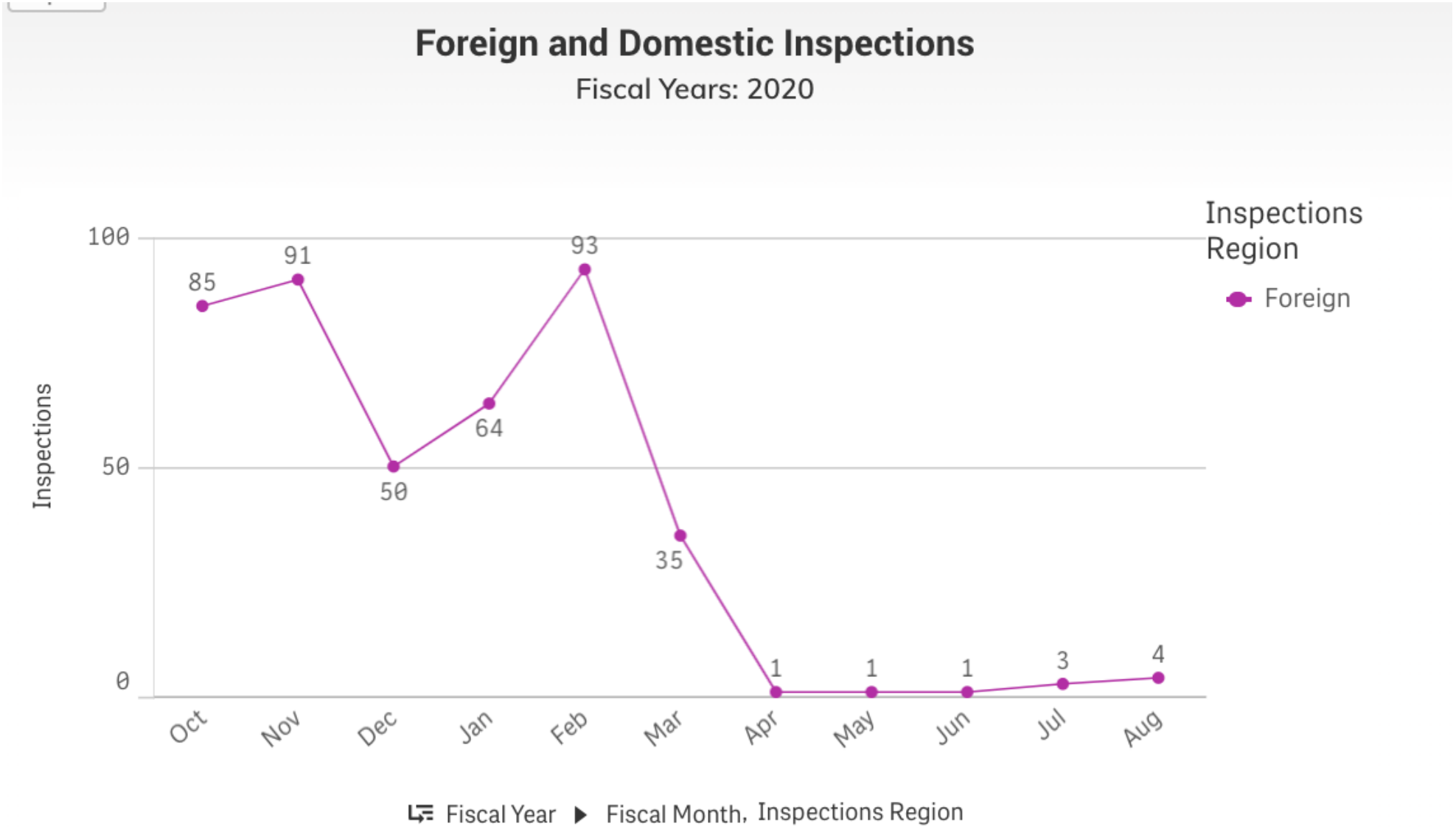
Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency



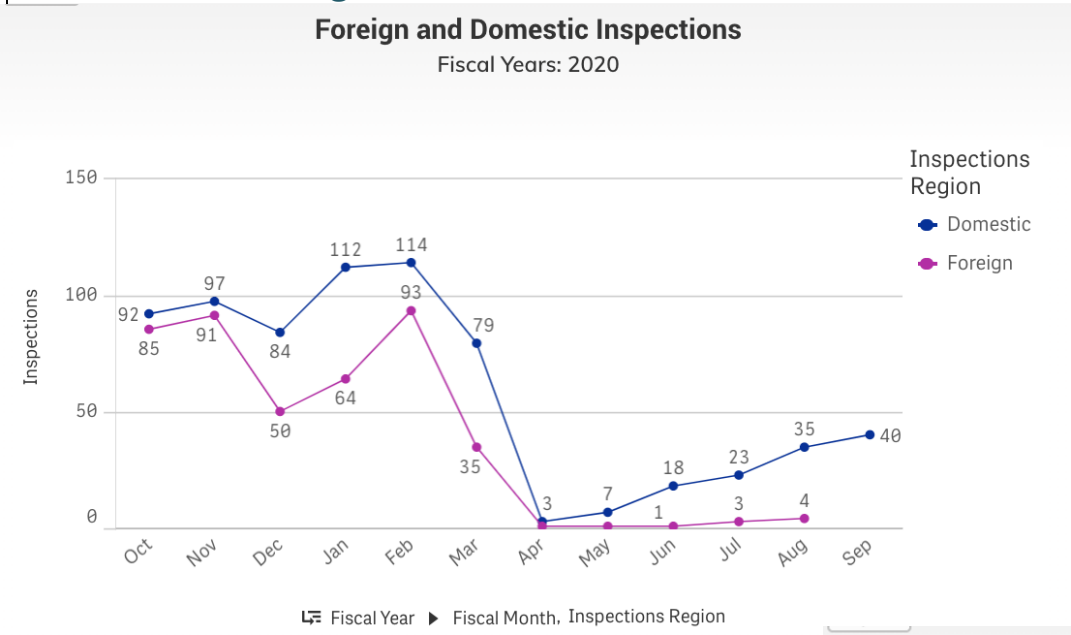
Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency

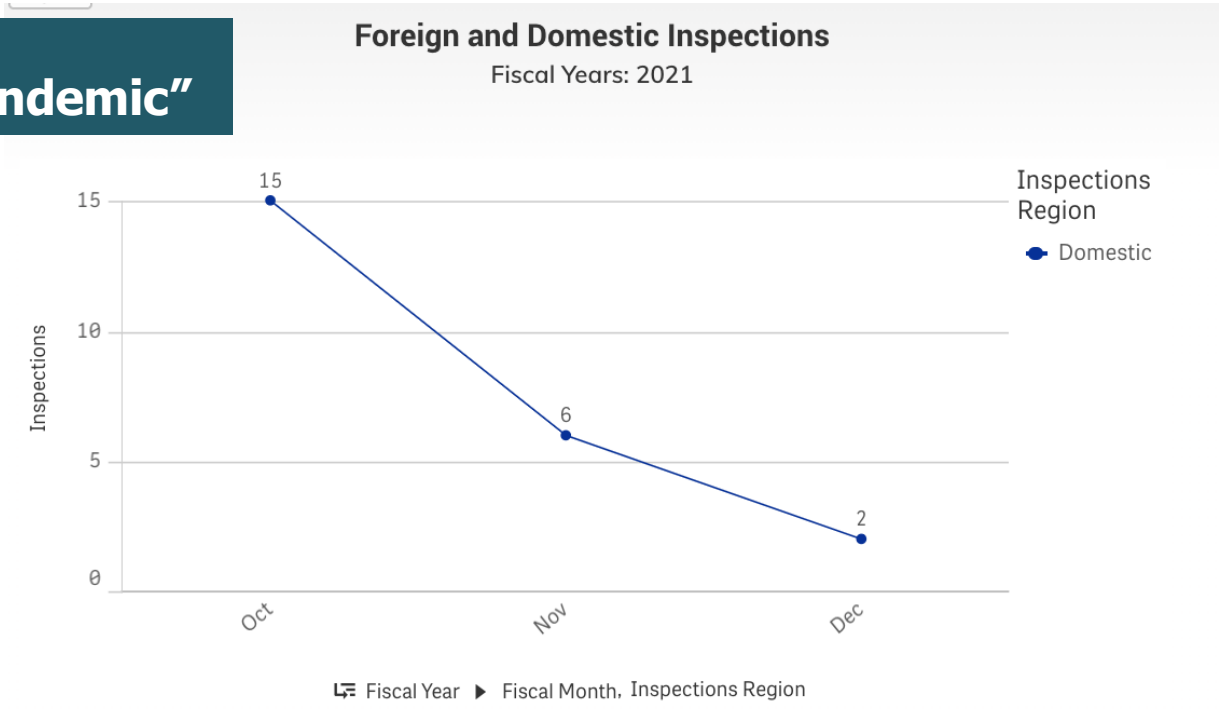


Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency



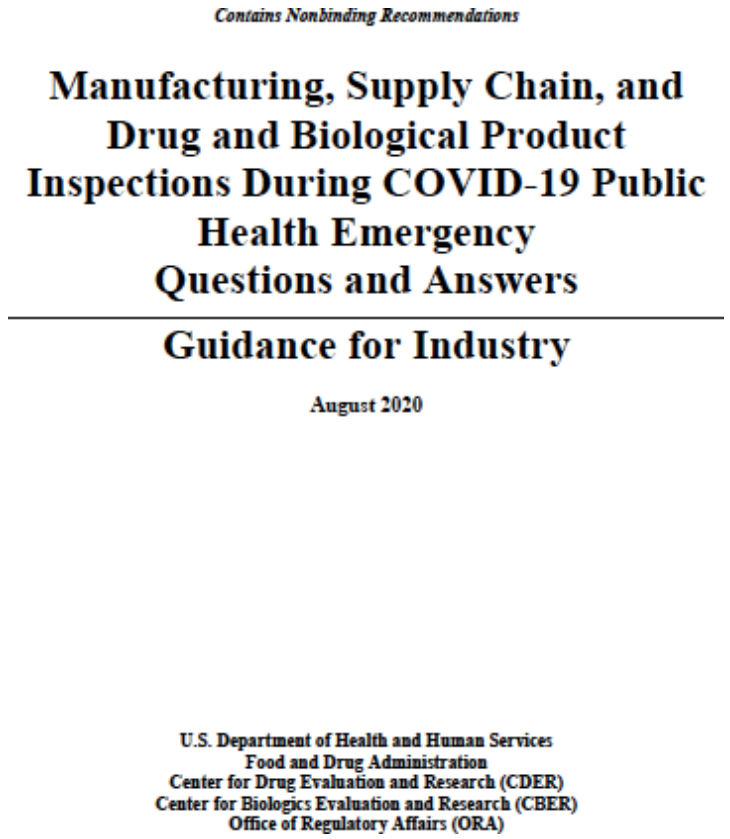
Dependent on "Trajectory of the Pandemic"



Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency

- August 19: FDA *GFI, Questions and Answers*



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)

Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency

Inspections Q&A Guidance: Key Points

- Q1: Reiterates domestic inspections resumption, within COVID-19 Advisory Levels to safely resume priority domestic inspections, e.g. PAI & surveillance inspections.

- Q2: Explains "mission critical," including new factors such as "breakthrough" designation or products used to diagnose, treat, or prevent a serious disease… with no appropriate substitute."
    - Rare Disease client: Denied breakthrough designation, got CRL delay due to PAI req't/delay

- Q5: Use **"additional tools"** to determine need for inspection and assess NDA/BLA 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 use of additional tools.
    - Myovant Sciences approval, including Japanese CMO (Bushu Pharmaceuticals)
    - Alonza Cruse (ORA): FDA is using additional innovative ways to do inspectional work (i.e. requesting records in advance of or in lieu of an inspection)

Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency

Inspections Q&A Guidance: Key Points

- Q6: Explains when FDA will issue a **Complete Response Letter (CRL)**
  - If, based on available information, FDA determines an inspection is necessary for approval but PAI cannot be conducted, FDA will issue CRL
    - Rare Disease client: CRL delay, up to 12 months, due to PAI req't/delay
    - Resubmissions are now Class 2, which is a 6-month PDUFA review (December GFI)
  - If not enough information to make a determination, FDA will defer the action date
  - Base NDA/BLA Decisions on the **"totality of information provided to the Agency."**

- Q7-Q10: Addresses **Post-Approval manufacturing changes:**
  - Adding or changing a facility: Follow established guidance
  - "FDA uses multiple tools to facilitate manufacturing changes implementation: **Risk-based reduction in supplement reporting categories & flexible assessment practices**."

Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency

- September: FDA *GFI*, *Resuming Normal Drug & Biologic Manufacturing Operations During COVID-19*

Contains Nonbinding Recommendations

Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency

Guidance for Industry

September 2020

Summary of FDA Inspectional Responses to Delays

During the COVID-19 Public Health Emergency

FDA Activity: March to September

- Due to suspension of routine surveillance inspections:
  FDA focused on overall drug safety/quality maintenance, import controls and "mission critical" operations

- **“Breakthrough # 1”: FDA expanded “alternative tools” use**, in lieu of on-site inspections, e.g. Sec. 704 Records Requests
  - However, still ≠ inspection

- Still, FDA left many open questions:
  - "Informal” Processes for “alternative tool” usage (e.g. Sec. 704)
    - What are “alternative tools” and how & when will FDA use them?
    - During COVID-19 (now) and After the Emergency (future considerations)
  - What is “mission critical”?
    - For cause? Pre approval? COVID-19 related?
    - Case-by-case evaluation

Summary of FDA Inspectional Responses to Delays

During the COVID-19 Public Health Emergency

Key FDA Limitation:
Using "Alternative Tools" is NOT an Inspection

- FDA: Inspections are **on-site only** (*PDA Webinar, June 20)*
  - FD&C Act (FDASIA) Section 704(a)(4) Info requests ≠ **"virtual inspection"**
  - Video conferences or follow-up phone calls related to Sec. 704(a)(4) records requests are **not the same as on-site inspections**

- FDA still requires inspection to close out WL/OAI site status
  - Although RPM allows FDA to close out Warning Letters without inspection

- When inspection cannot be conducted due to COVID-19, and "alternative tools" are inadequate or not appropriate, then:
  - 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

Summary of FDA Inspectional Responses to Delays

During the COVID-19 Public Health Emergency

"Alternative Tools": Sec. 704(a)(4) is still "primary tool" in lieu of inspections

- When inspection cannot be conducted due to COVID-19**:**

  FDASIA Sec. 704 (a)(4) Request and Review Records, "in advance of or in lieu of" an inspection

  - Provision explicitly applies to drugs and biologics, not medical devices
    - *Relying on voluntary records requests for Devices and BIMO*

- SMG 9004.1 outlines process for 704(a)(4) records request

STAFF MANUAL GUIDE (SMG) 9004.1

FDA STAFF MANUAL GUIDES, VOLUME IV – AGENCY PROGRAM DIRECTIVES

GENERAL OR MULTIDISCIPLINE

POLICY AND PROCEDURES FOR REQUESTING RECORDS IN ADVANCE OF OR IN LIEU OF A DRUG INSPECTION

Effective Date: August 25, 2017
Changed: August 31, 2017

1. Purpose
2. Policy
3. Responsibilities and Procedures
4. Effective Date
5. Document History

Attachment A- Records Request Template
Attachment B- Receipt Confirmation Template[1]

Summary of FDA Inspectional Responses to Delays

During the COVID-19 Public Health Emergency

- Taking into account: **Facility Inspection & Compliance History**

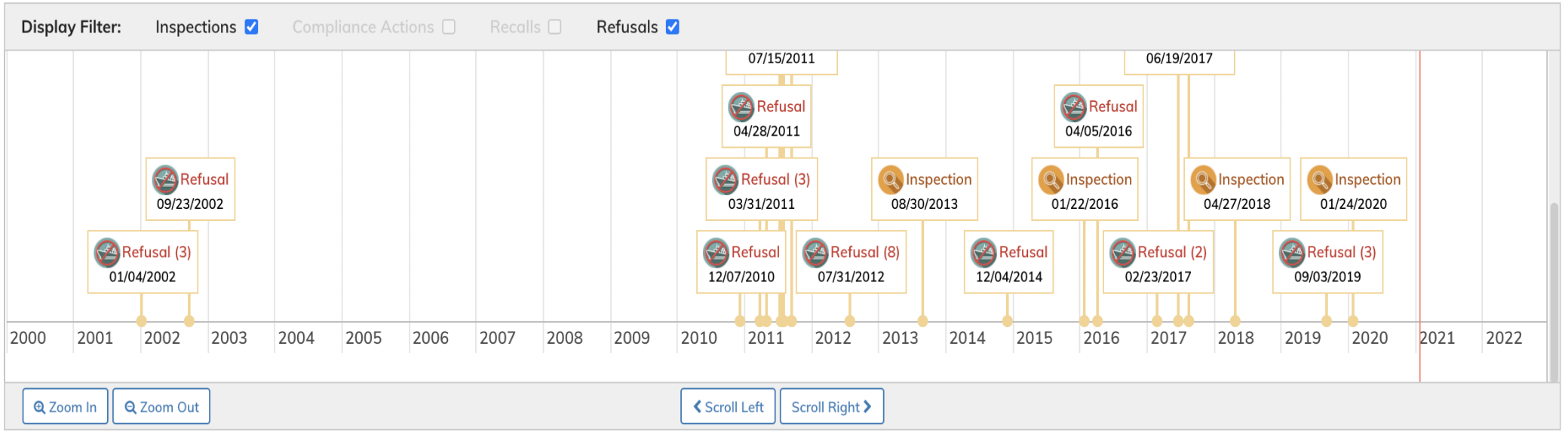
FEI Number [redacted]

Firm Name [redacted]

Firm Address [redacted]

Back to Top | FDA Actions Timeline | Inspections | Compliance Actions | Recalls | Import Refusals | Import Alerts | Warning Letters

FDA Actions Timeline



https://datadashboard.fda.gov/ora/firmprofile.htm?FEIi=0123456789

Summary of FDA Inspectional Responses to Delays

During the COVID-19 Public Health Emergency

- Taking into account: **Facility Inspection & Compliance History**

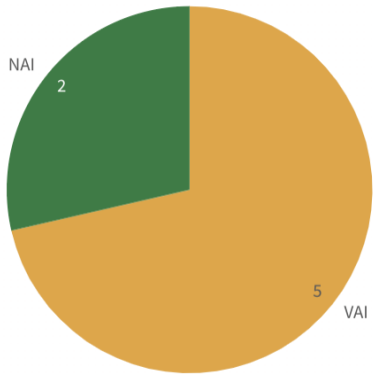
Inspections	Classifications
5	7

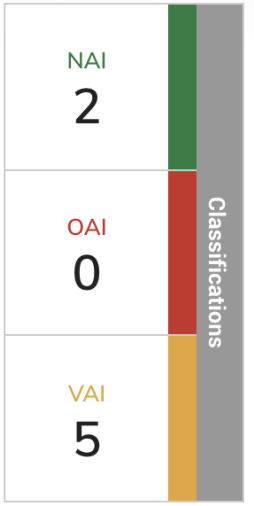
Inspection Classifications by Fiscal Year

Fiscal Years: 2011 - 2020

Inspection Classifications by Type

Fiscal Years: 2011 - 2020





Inspections Details Help

Inspection ID	Inspection End Date	Project Area	Product Type	Classification
1118319	01/24/2020	Drug Quality Assurance	Drugs	VAI
1118319	01/24/2020	Monitoring of Marketed Animal Drugs, Feed, and Devices	Veterinary	VAI
1049889	04/27/2018	Drug Quality Assurance	Drugs	VAI
1049889	04/27/2018	Monitoring of Marketed Animal Drugs, Feed, and Devices	Veterinary	VAI
964127	01/22/2016	Drug Quality Assurance	Drugs	NAI
848381	08/30/2013	Drug Quality Assurance	Drugs	NAI
746755	09/13/2011	Drug Quality Assurance	Drugs	VAI

Summary of FDA Inspectional Responses to Delays

During the COVID-19 Public Health Emergency

"Alternative Tools"

- Taking into account: **Facility Inspection & Compliance History**
- **MRA** process (e.g. EU): flexibility/rely on trusted foreign authorities
- **PIC/S:** leverage reports by "capable authority" inspections (ex-EU)
- **Import controls**, Physical exams & product sampling at the US borders
  - Appearance standard to refuse entry of imported product
  - New FDA Import Alert category; including denying entry of unsafe products
- Includes cases of drug shortage, or PAIs needed for approval of novel drugs or drugs related to the treatment of COVID-19

Summary of FDA Inspectional Responses to Delays

During the COVID-19 Public Health Emergency

If inspection can't be conducted due to COVID-19:

- If "alternative tools" are still inadequate or not appropriate, then:
  - PAIs and therefore approvals may be delayed (missed goal dates, CRLs)
    - Japanese Company: With "previously un-inspected CMO; 12-mo. delay
    - Australian Company with overseas CMO with delay
    - Alkermes (Ohio): delayed due to 704 Records Request "Misunderstanding"…
    - BMS/Celgene (Texas): High-profile Facility Inspection missed PDUFA date
    - Eli Lilly August inspection
  - OAI status may linger (which may continue to delay approvals)
    - CRL - Nabriva Therapeutics (Italian API supplier) – since MAY
  - Shortages and other avoidable consequences

Developing FDA Inspectional Process

During the COVID-19 Public Health Emergency and Beyond

- Sept.-December*:* PDA, PBOA, RAPS & FDLI conferences
  FDA gave info, data & expectations Re: alternative tools & inspections:
  - For Israel: No foreign inspections (except a few ”mission critical”)
  - Elizabeth Miller (ORA): FDA reassured industry that many expected approvals won’t encounter inspection-related delays
    - Conducted > 200 “mission critical inspections” during COVID-19
    - Predominantly domestic; Very Limited foreign (3 in July in EU)
  - Priority inspections within PDUFA dates “will use benefit versus risk calculation factors for public health & access to critical therapies.”
  - Elizabeth Miller (ORA): Able to make judgments on quality of hundreds of drug manufacturing facilities without visiting them
  - Alonza Cruse (ORA): “In some cases, FDA has resumed prioritized domestic inspections”; Sept. 2020 PDA/FDA Joint Regulatory Conf.
  - Pre-Announced, Domestic inspections have resumed on a prioritized, “case-by-case” basis, using inspector & company risk assessments posed by infection rates in given regions and federal, state and local governments guidelines

Timeline of FDA Inspectional Delays

During the COVID-19 Public Health Emergency

Contains Nonbinding Recommendations

Review Timelines for Applicant Responses to Complete Response Letters When a Facility Assessment Is Needed During the COVID-19 Public Health Emergency

Guidance for Industry

December 2020

Additional Resources

For further information, drug manufacturers are encouraged to visit the following FDA web page: Manufacturing, Supply Chain, and Drug Inspections: COVID-19, *available at* https://www.fda.gov/drugs/coronavirus-covid-19-drugs/manufacturing-supply-chain-and-drug-inspections-covid-19

Developing FDA Inspectional Process

During the COVID-19 Public Health Emergency and Beyond

- December: FDA issues *GFI, Review Timelines - NDA/BLA Responses to CRLs When Facility Assessment Is Needed.*
- *So…It's still dependent on the "Trajectory of the Pandemic"*
  - Alonza Cruse (ORA): On-site Inspections are uniquely constrained, by HHS rules, Health & Safety concerns, CDC domestic rules/data & lack of overseas data + limited travel options & Quarantines of FDA inspectors
  - Safety 1st : Inspections only possible if COVID-19 Advisory Level permits Resurgence of cases or state/local guidance could shut down inspections
- ORA: "Use additional innovative ways to do inspectional work."
  - ORA/CDER weekly meetings
  - FDA is well aware of goal dates, doing best not to miss them
  - Virtual inspections become a more realistic possibility
  - It will take time for FDA to identify
- 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)*

Developing FDA Inspectional Process

During the COVID-19 Public Health Emergency and Beyond

- 4th Quarter: ORA/CDER weekly meetings
- November: Brian Hasselback (CDER): FDA is preparing COVID-19 GFI Guidance "specifically on remote evaluations using interactive video or other types of interactive tools and techniques"
  - FDA is well aware of goal dates, doing its best not to miss them

- *January:* "Breakthrough # 2": *"Virtual Assessment" GFI (Pending)*
  - Guidance to "describe basic expectations for industry"; "indicate what to expect from FDA" & "use of interactive engagement in FDA decision making about pending applications"
  - Exploring whether video will be voluntary, or could be made mandatory
  - Scope may also include GMP surveillance, for-cause and BIMO
  - Requested feedback on remote inspections/video for drug industry *FDLI Annual Conference (Judy McMeekin, ORA, October 2020)*
  - FDA Tested use of live video during inspections of two produce farms
  - FDA may pilot a virtual inspection program for devices
- *January:* "Breakthrough # 3": *"Virtual Inspection" GFI (Possibility?)*
  - Virtual inspections become a more realistic possibility
  - EMA Analog + Other Countries Initiatives (e.g. Russia)

Developing FDA Inspectional Process

During the COVID-19 Public Health Emergency and Beyond

"VIRTUAL" OPPORTUNITIES

- DO Provide requested records fully, accurately & within the requested timeframe (SMG 9004.1). Consider follow up with requests for video or teleconference to provide context for all records
- DO Ensure necessary infrastructure & SOPs are in place to efficiently handle remote assessment (e.g., appropriate personnel and technology are available, trained and in working order)
- DO Recognize differences between inspection and remote assessment.
- DO Recognize potential for different outcomes
- DO 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

RISKS IN INFORMAL PROCESSES

- DON'T Delay, deny, limit or refuse any aspect of the document production request or otherwise: *"Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection"*
- DON'T Disregard the importance of a remote assessment
- DON'T Create any perception that the information you are providing to FDA (either verbally or in writing) may be anything less than complete and accurate.
- DON'T Miss opportunities to communicate directly with FDA or to clear up possible misperceptions
- DON'T Record anything without notification and agreement

Developing FDA Inspectional Process

During the COVID-19 Public Health Emergency and Beyond

"Virtual" Opportunities Moving Forward

- FDA is facing external pressure to think carefully about inspection processes
- FDA appears to be listening to and carefully considering industry suggestions –
- Will use of these "alternative tools" continue beyond COVID-19?
- Inspection Q&A Guidance & recent speeches are an excellent start, but industry need further clarity/transparency on how FDA will utilize the tools it has and how it will expand its toolbox…
- Awaiting FDA guidance be published:
  - New and more formalized ways to rely on the 704(a)(4) records requests and other tools
  - What will be these more standardized processes?
  - 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?
- 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
- FDA may even be considering "virtual inspections", but what will that look like?
  - When might there be regulations and guidance on that?

aam Association for Accessible Medicines

Bio Biotechnology Innovation Organization

PBOA PHARMA & BIOPHARMA OUTSOURCING ASSOCIATION

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Developing FDA Inspectional Process

During the COVID-19 Public Health Emergency and Beyond

"Virtual" Opportunities Moving Forward

August 20, 2020

To:

Judith A. McMeekin, PharmD., Associate Commissioner for Regulatory Affairs, FDA
Peter Marks, M.D., PhD, Director, Center for Biologics Evaluation and Research, FDA
Patrizia Cavazzoni, M.D., Acting Director, Center for Drug Evaluation and Research, FDA

Subject: ***An Industry Proposal: Risk-based Approaches to Inspections and Records Requests During and After the COVID-19 Public Health Emergency***

FDA Inspections
During COVID-19 Emergency

Q&A before Panel Discussion

(due to change in plans for today)

Backup Slides

Records Requests Under FDASIA Sec. 704(a)(4)

Summary of FDA Inspectional Responses to Delays

During the COVID-19 Public Health Emergency

Records Requests Under FDASIA Sec. 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.
- ORA relies on information from "remote assessments" to set priorities for site inspections and help focus them
- FDA received requests for a more **formalized process** for communicating outcomes from a records request and closing it out. It is under consideration at FDA.
- FDA launched an initiative to use remote regulatory assessments for programs to which the 704(a)(4) authority does not explicitly apply. (Devices, BIMO)
- Industry encouraged FDA to follow process spelled out: **Staff Manual Guide SMG 9004.1**, *Policy & Procedures for Requesting Records in Advance of or In Lieu of a Drug Inspection.*

424 records requests to drug mfg. facilities

229	*Foreign facilities*
195	*Domestic facilities*

111 (of 424) supported application reviews

77	*Approval recommendation*
15	*Withhold recommendation*

123 records requests to biologic 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)