U.S. FOOD & DRUG ADMINISTRATION

704(a)(4) Record Reviews

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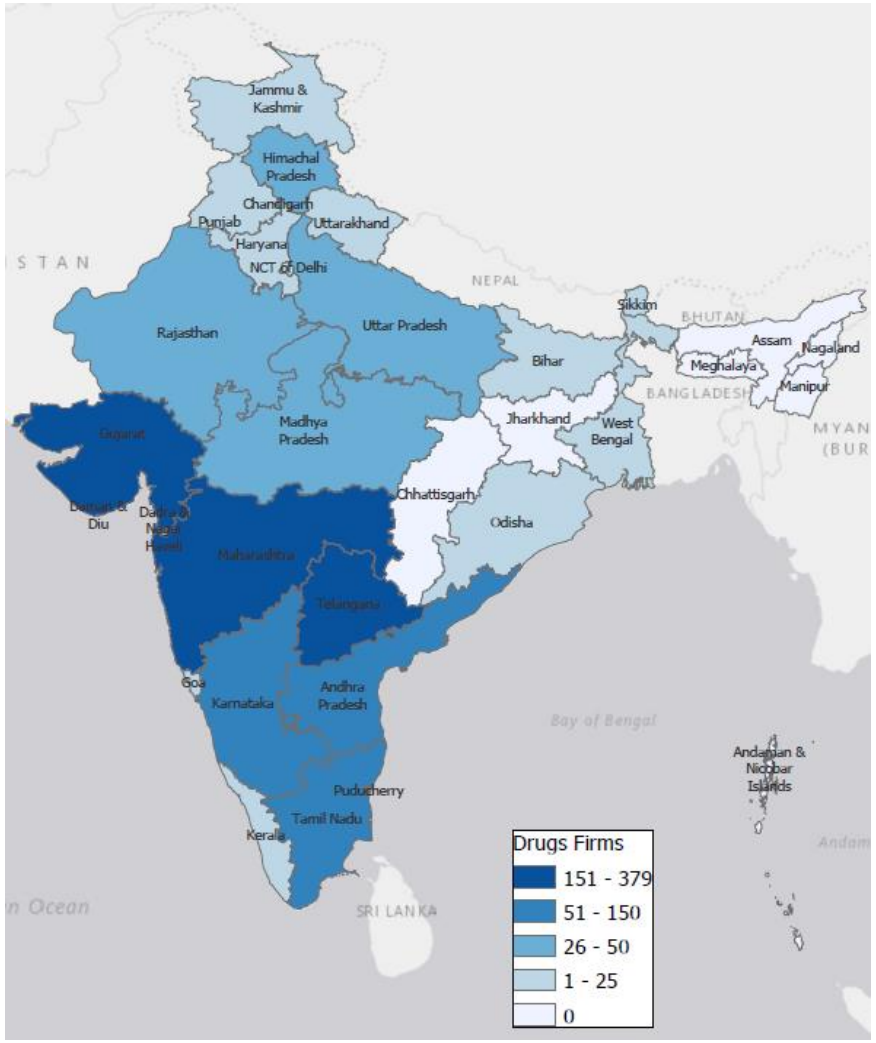
India



- Largest number of FDA-registered drug manufacturing facilities outside of the U.S.
- India is one of the largest exporters of drug products to the U.S.

2020 Inspections during a Pandemic

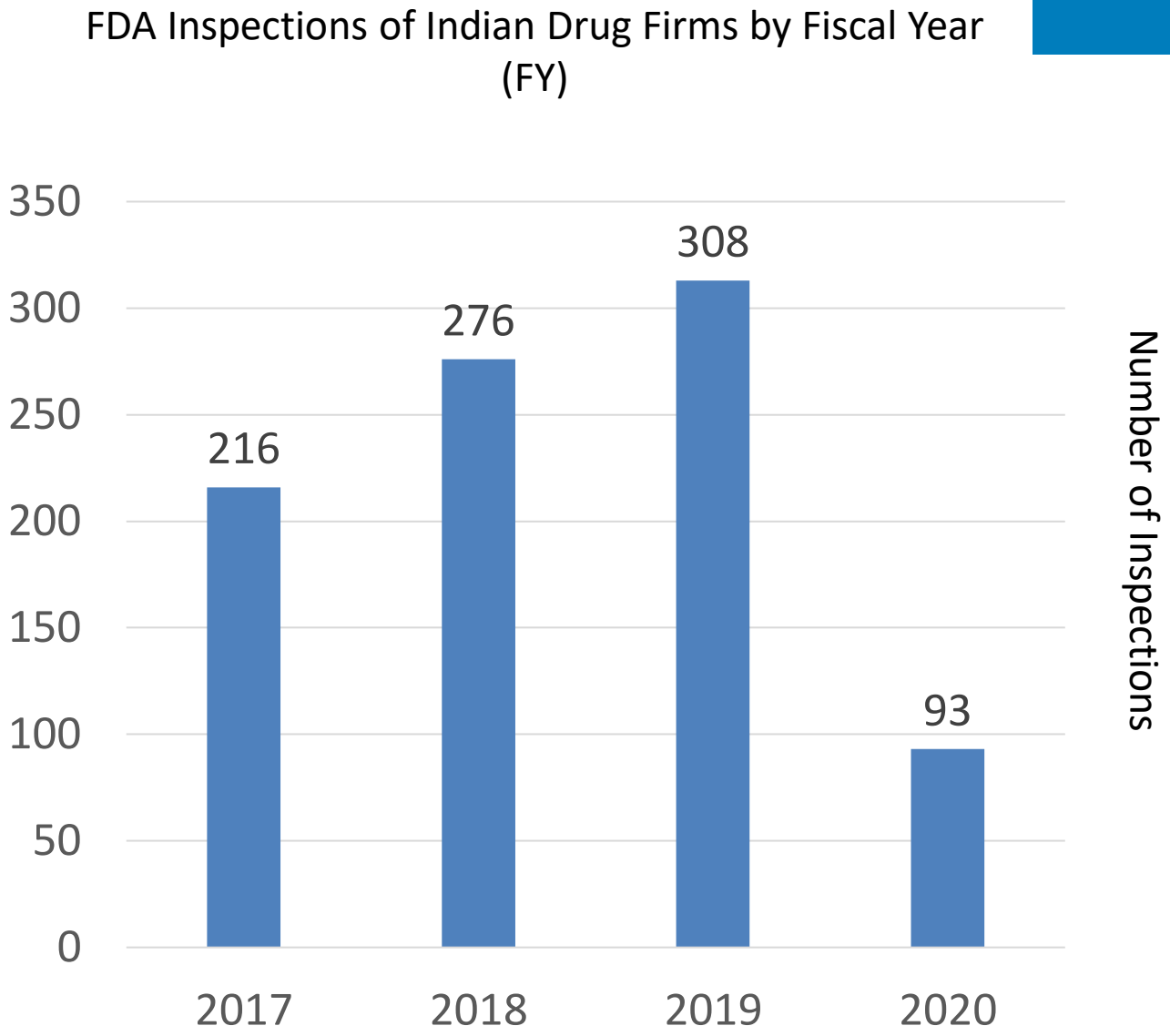
- On March 3, 2020 - FDA suspended on-site inspections (possible exception if there is a great risk of harm to public health)

- FDA is using section 704(a)(4) of the Food, Drug and Cosmetic Act to request for records in advance of, or in lieu of inspections

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

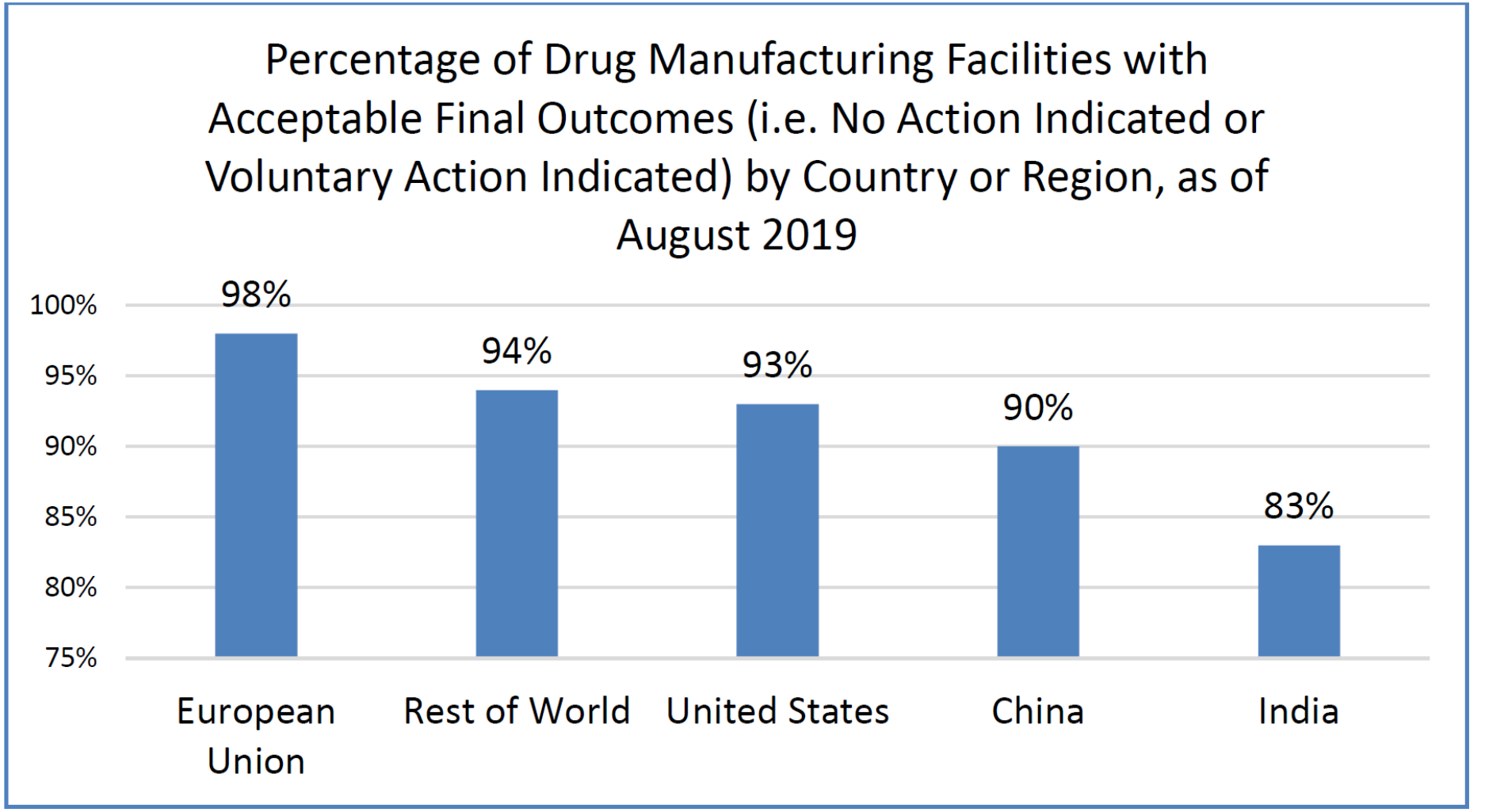
Guidance for Industry

August 2020



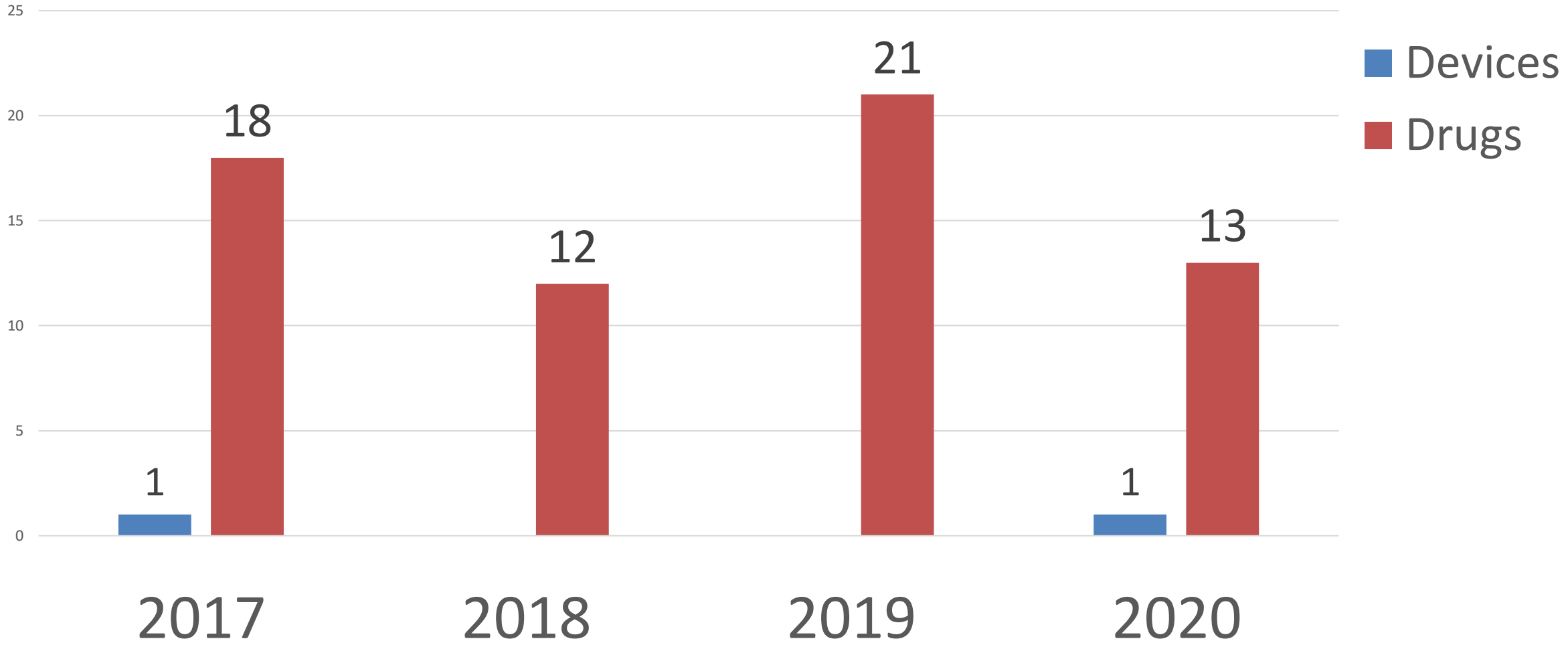
FY begins October 1st ends September 30th of the following year, for example FY19 = 10/1/2019 to 9/30/2019, FY2020 data does not include 704(a)(4) reviews

Compliance Rate by Country/Region



https://docs.house.gov/meetings/IF/IF02/20191210/110317/HHRG-116-IF02-Wstate-WoodcockMDM-20191210.pdf

Warning Letters Issued to India Drug and Device Manufacturers



Lesson: Flexibility and Adaptability – FDA Inspections

- Due to travel restrictions, quarantine requirements and personnel safety concerns, in-person inspections were suspended.
- Agency had to “pivot” to identify strategies to conduct assessments of applications and facilities remotely.

FDA Remote Regulatory Assessments

- Preparedness prior to a crisis – FD&C Act 704(a)(4) was in place before COVID-19 (Under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 371(a)(4)])
- Gives FDA the authority to request records in advance of an inspection, or in lieu of inspection
- Pre-COVID-19, CSOs routinely used this authority to request records from foreign establishments in advance of trip, especially if translation was needed
- FDA already had a procedure in place, staff manual guide (SMG 9004.1)

Are Remote Regulatory Assessments an Inspection?

- In-person inspections are not being conducted unless they are ‘mission critical’ and not under domestic Indian travel restrictions.
- Remote assessments:
    - Are NOT inspections and do not replace an inspection
    - No written observations (FDA 483s) are issued on remote assessments
    - Do not result in a final agency classification (NAI, VAI, or OAI)
- FDA is working to resume routine surveillance onsite inspections for certain U.S. establishments.

Practical Tips for FDA Remote Regulatory Assessments

- Remote assessments are via email
- Give all information/documents requested the first time, be thorough when sending all the requested documents
- No special characters in file names. Please do NOT use: - _“, # ( ) ! ~ % ^ & in file names
- For document submissions, there should be a unique numbering system. For example: Do not have five files numbered, 1.1, but rather 1.1a, 1.1b, 1.1c, etc. *If there is a second request, continue the numerical order from the first request, do not start back at number 1*. *Do NOT repeat any document file numbers throughout the document review process*

Practical Tips for FDA Remote Regulatory Assessments (cont.)

- Documents are submitted by firms through email or box.com
- Compress larger documents prior to sending
- Do not send zip files, submit as individual documents
- Submit files as pdf, excel, word, or PowerPoint
- *If a file is made in Excel, do not convert to a pdf when submitting*
- Pictures, diagrams, site maps need to be clear and legible. Sufficient detail when enlarged or magnified

704(a)(4) Review Challenges

- Firm delays in sending records (or not complete)
- IT/power outages/internet speed
- Uploading of all received documents, >770 files in one case
- Files not always readable on FDA computers
- Current submission system cannot accept symbols in file names
- Review may lead to further record requests
- Final Reviews before submission delayed due to competing priorities

What Tools Does FDA Have to Enforce Regulations and Laws?

- Warning Letters
- Untitled Letters
- Import Alerts
- Administrative Detention
- Regulatory Meetings
- Injunctions
- Seizures
- Consent Decrees

Conclusions from 704(a)(4) reviews

Pre-Approval 704(a)(4) Review

- 96 PAI 704(a)(4) have been completed
- 104 application approvals and 24 application withholds

Surveillance 704(a)(4) review

- >400 GMP 704(a)(4) completed

Conclusions from 704(a)(4) reviews (cont)

- 2 sites have been placed on IA #99-32, "DETENTION WITHOUT PHYSICAL EXAMINATION OF PRODUCTS FROM FIRMS REFUSING FDA FOREIGN ESTABLISHMENT INSPECTION"
- 3 sites have been placed on IA #66-40, "Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs"

Thank you. Any Questions?

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