Session Presenters

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FDA Alternative Inspection Approaches – The New Normal

Remote Regulatory Assessments

Specific Topics & Format

- Background of the Remote Regulatory Assessment (RRA) Process
- Authority
- General Process Overview
- Lessons Learned
- Benefits Seen and Future Plans
- Going Forward
- References

Introduction and Background

COVID-19 Pandemic's Impact on FDA's Operations

- Balancing safety of FDA staff
- Balancing safety of individuals at inspection locations
- Balancing the need to meet our mission to public health

Alternative Assessment Methods

- Usage of Mutual Recognition Agreements (MRA) with partner nations
  - ➢ allows facility assessments to be based on drug inspections conducted by capable authorities
- Usage of FDA's authority under section 704(a)(4) to request records in advance of or in lieu of an establishment inspection

Authority

The Food and Drug Administration Safety and Innovation Act (FDASIA) - Passed on July, 9 2012

- Section 706: grants the FDA authority to request records from drug manufacturers *"in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, and in either electronic or physical form"*

- Section 704(a) of the FD&C Act was amended with the addition of subsection (4) to provide statutory authority to request records listed in section (a) in advance of or in lieu of an inspection.

- The authority is primarily applicable to drugs
  - Other program areas (food and medical device) are piloting voluntary engagement programs

Authority

- After FDASIA was passed in 2012 the agency planned and developed policies and procedures for the 704(a)(4) remote regulatory assessment process.
  - Piloted successfully for foreign surveillance and pre-approval assessments.
  - Allowed for fast mobilization at the start of the pandemic.
  - Assessments have now been utilized more broadly for both foreign and domestic drug surveillance and pre-approval assessments.

Remote Regulatory Assessment (RRA)

- What is an RRA?
  - Remote regulatory assessments (RRAs) include voluntary interactive evaluations (such as remote livestreaming video of operations, teleconferences and screen sharing) in addition to requests to review records and other information under existing statutory or regulatory authority.
  - RRA's are not considered inspections.

Decision to initiate or request an RRA is made by FDA. An RRA may be initiated or requested when:

- Travel limitations brought on by pandemics, natural disasters, or other unstable situations
- An RRA will assist FDA in conducting elements of establishment oversight or support regulatory decisions. (i.e. Preparing for a planned inspection, following up on a consumer complaint, and supporting the review of a marketing submission)

General Process Overview

Factors considered when determining whether to initiate or request an RRA:

- Firm Location
- Inspection history
- Complexity of the product and process
- Travel restrictions

General Process Overview

Two Types of Drug 704(a)(4) RRA's

- Routine Surveillance Assessments (Human & Animal Drugs)
- Pre-Approval Assessments (Human & Animal Drugs)

Similarities

- Forms and Document Request Templates
- Format for submitting and receiving of information
- General communication platforms

Differences

- May include CDER/CVM Reviewers – Pre-Approval
- Can be a streamlined review of the area of interest – Pre-Approval
- Records requested will be used to determine if appropriate GMP systems are in place - Surveillance

General Process Overview

Drug Surveillance and Pre-Approval 704(a)(4) Remote Regulatory Assessment Process

Step 1: Issuance of the FDA form 4003 *FDA Inspection Records Request* and Form 4003 attachment

- Email should be acknowledged within 72 hours of receipt

Step 2: Records provided (typically 15 days or 30 days for foreign if translation is required) via e-mail, ESG, or possible through cloud storage account

Step 3: Records will be Reviewed

- Additional Cycles (with shorter timeframes for document submission) if necessary, until all questions are addressed

Step 4: Review is complete, FDA will draft an Observations or No Observations Letter

- Details any issues or concerns identified during the review process
- Provides an opportunity for the firm to respond to identified issues

Step 5: Issuance of the FDA form 4003a *FDA Inspection Records Receipt Confirmation,* Form 4003a attachment, Observations Letter (or No Observations Letter)

- Response within 15 business days

General Process Overview

Observation Letters

Background and Concerns:

- Surveillance and Pre-Approval Assessments are completed the same way
- Firms were unaware of deficiencies which may impact approval

Process Moving Forward:

- Observations Letter or No Observations letter will be sent to the firm in email along with the FDA form 4003a and 4003a attachment
- Letters will be issued if concerns were identified or not
- Instructions for responding and where to direct the response will be included in the letter
- Responses should be provided within 15 business days
- Responses will be reviewed by ORA and CDER (final determination made by CDER for PAIs)

General Process Overview

Remote Interactive Evaluations (RIEs)

- Any interaction with a facility other than inspection or a record request (e.g., 704(a)(4))
- Conference calls, live streaming video of facility and operations, screen sharing of records, etc.
- FDA will host the interaction
- Voluntary
  - Facility is not obligated to participate
  - If done jointly with a 704(a)(4) request, the RIE is voluntary, but the record request is not voluntary

RIE (continued)

- No Form 482, Notice of Inspection, is issued.
- Investigator(s) will not display credentials upon initiation of the RIE.
- Upon completion of the RIE, the investigator(s) will have a closeout meeting with the facility's management.
- In general, if the RIE was conducted jointly with a 704(a)(4) assessment, this assessment should also be closed during the closeout meeting.
- During the closeout meeting, the investigator(s) will typically share with the firm a written list of observations noted during the RIE and 704(a)(4)(if any).
- Facility is encouraged to respond in writing to the observations within 15 U.S. business days.

Current Outcomes

704a4 assessment activities (domestic and foreign)

	Completed
Surveillance	~600
Pre-Approval	~300
Total	~900

Actions:

- Application recommendations
  - ~300 approval and ~70 withhold
- ~30+ Import Alerts issued

Lessons Learned & What to Expect for the Future of Remote Assessments

Lessons Learned

- Focus the Document Request
  - Misunderstanding of the request

- Missing the human interaction
  - Clarification needed
  - Details not explained in documents
  - Referenced documents not included

Lessons Learned

- Firms do not receive the initial request
  - Firm's need to make sure registrations and US Agents are updated with current contacts
- Timeliness of review

- Sending/Receiving Documents
  - Technical Challenges

- Identifying the docs
  - Firms use the attachments and will populate response into the 4003 attachment

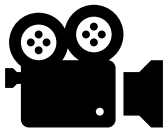
Benefits

- 704s have assisted FDA in verifying corrections in response to inspections
- We have uncovered significantly deficient practices, which as lead to regulatory actions, triggered inspections, and affected future inspection planning
- Helped support and reduce delays of approvals of marketing applications

Going Forward

What to expect…

- Majority of travel has resumed. 704s will still be used for areas we cannot travel to
- Continued collaboration with other regulators
  - Expansion of use of the MRA program
- Continue exploring of use of enhanced remote assessments
  - Including interactive video options or hybrid (video and 704a4 document request) options



Main Resources

- Conducting Remote Regulatory Assessments, Draft Guidance for Industry

- Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency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