CDER SBIA Webinar Series

U.S. FOOD & DRUG ADMINISTRATION

Postmarketing Drug Safety and Inspection Readiness

June 19, 2018
Center for Drug Evaluation and Research (CDER)
Small Business and Industry Assistance (SBIA) Webinar

United States Food and Drug Administration (FDA)
CDER / Office of Compliance
Office of Scientific Investigations (OSI)
Division of Enforcement and Postmarketing Safety (DEPS)
Postmarket Safety Branch (PSB)

This one file contains all the slides used in the AFTERNOON sessions of the webinar.

Lunch Break

U.S. FOOD & DRUG ADMINISTRATION

Session 3:
Inspection Readiness

Outline

- ORA
- Inspection Readiness: PADE Inspections
- REMS

What does an inspection look like?

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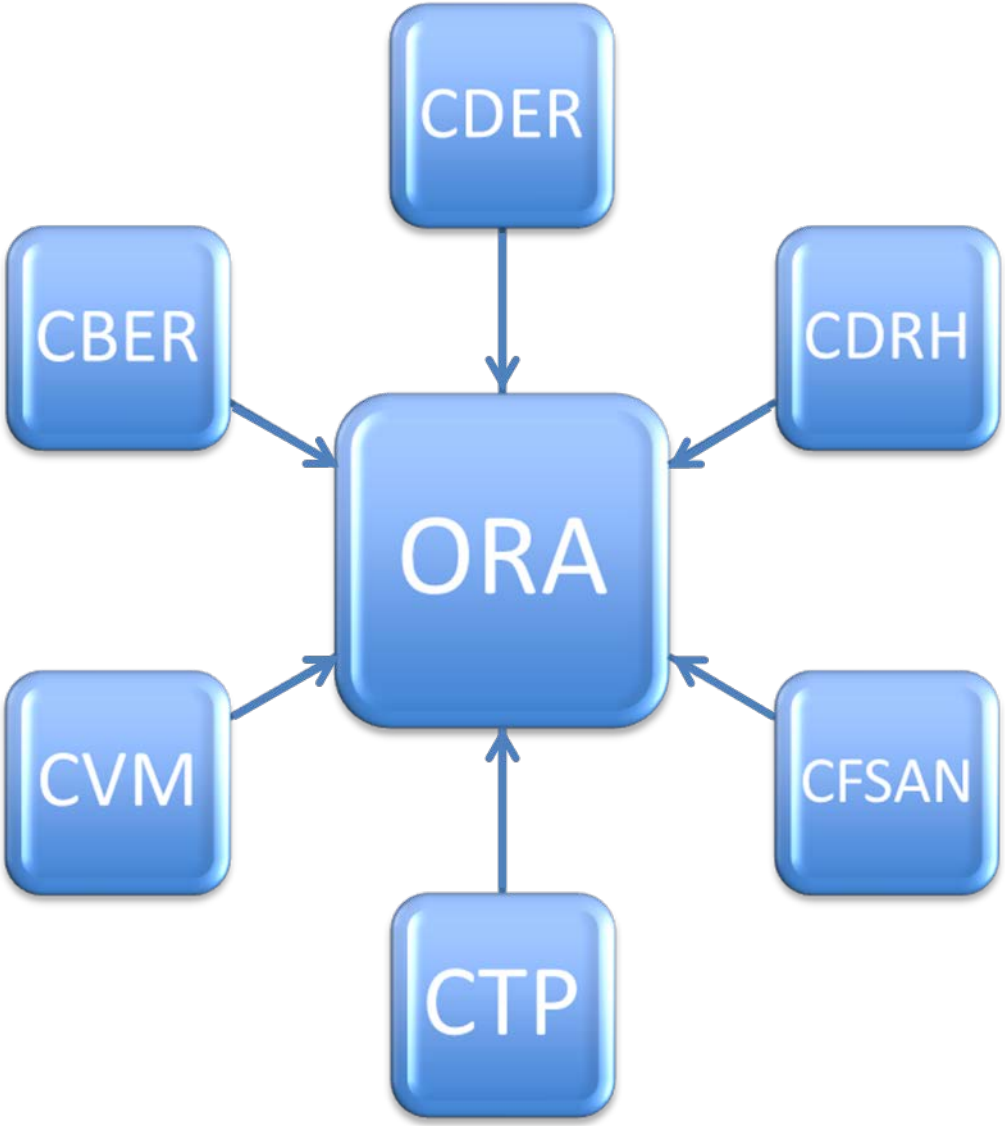
BIORESEARCH MONITORING PROGRAM EXPERT
OFFICE OF BIORESEARCH MONITORING OPERATIONS
OFFICE OF REGULATORY AFFAIRS | FDA

Objectives

- Provide an overview of the FDA BIMO program and the role of the Office of Bioresearch Monitoring Operations.
- Provide an overview of the general elements of an FDA inspection and the basics of a BIMO inspection.

FDA Structure (field operations)



FDA Structure (field operations)

Office of Bioresearch Monitoring Operations (OBIMO)

- OBIMO oversees all domestic and foreign field **inspectional operations** related to the BIMO Program, including all clinical and nonclinical research conducted in support of preapproval, licensing, premarket and marketing clearance applications submitted to the agency for products regulated by all FDA product centers.

BIMO Program Inspection Goals

- **Protect** the rights, safety and welfare of subjects involved in FDA-regulated clinical and nonclinical trials;
- **Verify** the accuracy and reliability of clinical and nonclinical trial data submitted to FDA in support of research or marketing applications; and
- **Assess** compliance with statutory requirements and FDA regulations governing the conduct of clinical and nonclinical trials.

BIMO Program Inspections

Establishment Types

- Establishments inspected include Sponsors, Monitors, Contract Research Organizations (CRO), Clinical Investigators, Institutional Review Boards (IRB), Radioactive Drug Research Committees (RDRC), In Vivo and In Vitro Bioequivalence/Bioanalytical Clinical and Analytical Sites (BEQ), and Nonclinical Laboratories (GLP).
- It also includes Postmarket Adverse Drug Experience (PADE) reporting and Risk Evaluation and Mitigation Strategies (REMS) inspections, both of which are post approval activities.

BIMO Program Inspections

Inspection Basis

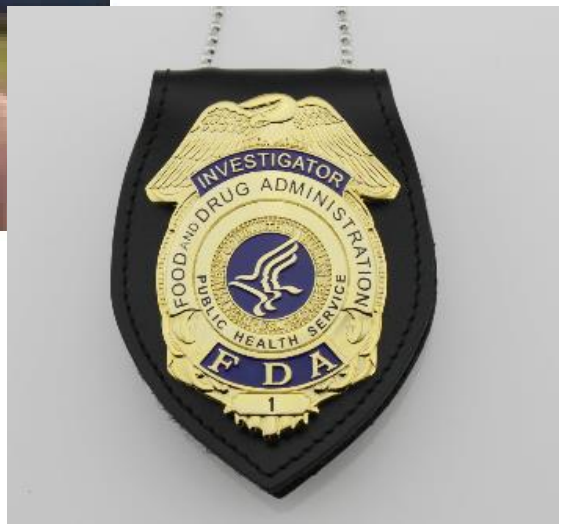
- **Surveillance** - Inspection is conducted as a routine assignment with no other indicators of non-compliance.
- **Compliance** - Inspection is conducted to investigate potential violations that have not already resulted in an official agency action.
- **Consumer Complaint** - Inspection is conducted in direct follow-up to a consumer complaint.

Pre-announced vs Unannounced

- The following inspections will be pre-announced unless otherwise instructed in the inspection assignment: Clinical Investigators, Sponsors/CROs, IRBs, RDRCs
- The following inspections will be unannounced unless otherwise instructed in the inspection assignment: BEQ clinical, BEQ analytical, GLP, REMS, PADE
- All international inspections are pre-announced

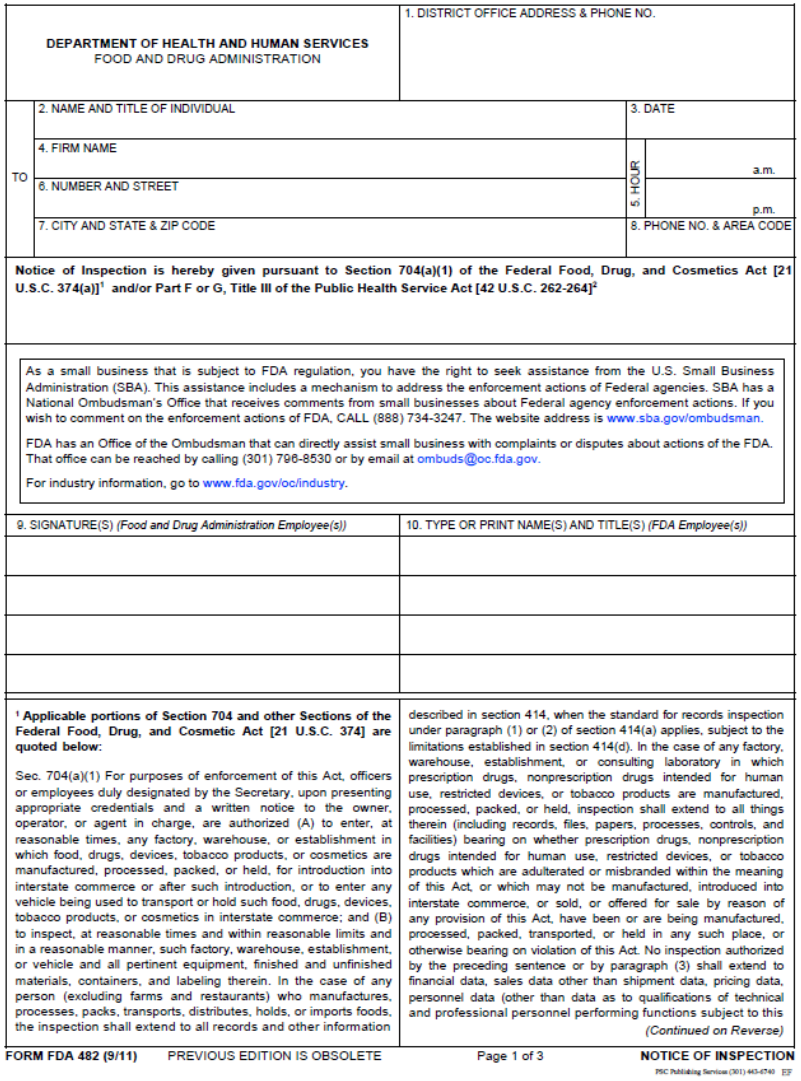
Opening Interview

Present Credentials



Opening Interview

Issue FORM FDA 482-Notice of Inspection



DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	1. DISTRICT OFFICE ADDRESS & PHONE NO.

TO	2. NAME AND TITLE OF INDIVIDUAL	3. DATE
	4. FIRM NAME	5. HOUR a.m.
	6. NUMBER AND STREET	p.m.
	7. CITY AND STATE & ZIP CODE	8. PHONE NO. & AREA CODE

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has a National Ombudsman's Office that receives comments from small businesses about Federal agency enforcement actions. If you wish to comment on the enforcement actions of FDA, CALL (888) 734-3247. The website address is www.sba.gov/ombudsman.

FDA has an Office of the Ombudsman that can directly assist small business with complaints or disputes about actions of the FDA. That office can be reached by calling (301) 796-8530 or by email at ombuds@oc.fda.gov.

For industry information, go to www.fda.gov/oc/industry.

9. SIGNATURE(S) *(Food and Drug Administration Employee(s))*	10. TYPE OR PRINT NAME(S) AND TITLE(S) *(FDA Employee(s))*

[1] Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

Sec. 704(a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414, when the standard for records inspection under paragraph (1) or (2) of section 414(a) applies, subject to the limitations established in section 414(d). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this

(Continued on Reverse)

Opening Interview

- Describe the scope and basis of the inspection (i.e. routine surveillance, for-cause, compliance follow-up inspection, etc.).

- Inspections should be sufficient in scope to cover special instructions in the assignment and to determine if the site's practices and procedures comply with the appropriate regulations.

Opening Interview

The FDA investigator will offer to have daily discussions regarding the inspection progress.

Refusal

- A **refusal** is refusal to permit an inspection or prohibiting the FDA investigator from obtaining information to which FDA is entitled under the law.
- In the case of drug inspections, inspection refusals, as well as delaying, denying, or limiting the ability to conduct the inspection, may cause a drug to be deemed adulterated under Section 501(j) of the FD&C Act [21 U.S.C. 351(j)].

Inspectional Scope

- Compliance Program (CP)
- Assignment memo from center
- Investigations Operations Manual (IOM)

Inspectional Scope

- The CPs are based upon the establishment type to be inspected and provide instruction on what to cover during the inspection.
- The assignment memo includes specific instructions regarding studies/protocols and/or products to be covered during the inspection.
- The IOM provides general instruction on inspections and specific information on BIMO.

Inspectional Scope

Bioresearch Monitoring Program (BIMO) Compliance Programs

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Program #	Compliance Program Title	On-line Availability	
7348.001	In Vivo Bioequivalence	HTML	PDF(78 kb)
7348.003	In Vivo Bioavailability-Bioequivalence Studies - Clinical		PDF
7348.004	In Vivo Bioavailability-Bioequivalence Studies - Analytical		PDF
7348.808	Good Laboratory Practice (Nonclinical Laboratories)		PDF(117 kb)
7348.808A	Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit Inspections	HTML	PDF(38 kb)
7348.809	Institutional Review Board	HTML	PDF(293 kb)
7348.809A	Radioactive Drug Research Committee		PDF (155 kb)
7348.810	Sponsors, Contract Research Organizations, and Monitors	HTML	PDF(80 kb)
7348.811	Clinical Investigators	HTML	PDF(2437 kb)
7353.001	Postmarketing Adverse Drug Experience (PADE) Reporting Inspections		PDF (335 kb)
7353.001C	Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections		PDF

https://www.fda.gov/ICECI/ComplianceManuals/CompliancePrograms Manual/ucm255614.htm

Good Documentation Practices

ALCOA

- **A**ccurate
- **L**egible
- **C**ontemporaneous
- **O**riginal
- **A**ttributable

Form FDA-483 Inspectional Observations

- Upon completion of the inspection and before leaving the premises, the FDA investigator will provide to the highest management official available the inspectional findings on a form FDA 483 - Inspectional Observations.
- The issuance of written inspectional observations is mandated by law and ORA policy.

Form FDA-483 Inspectional Observations

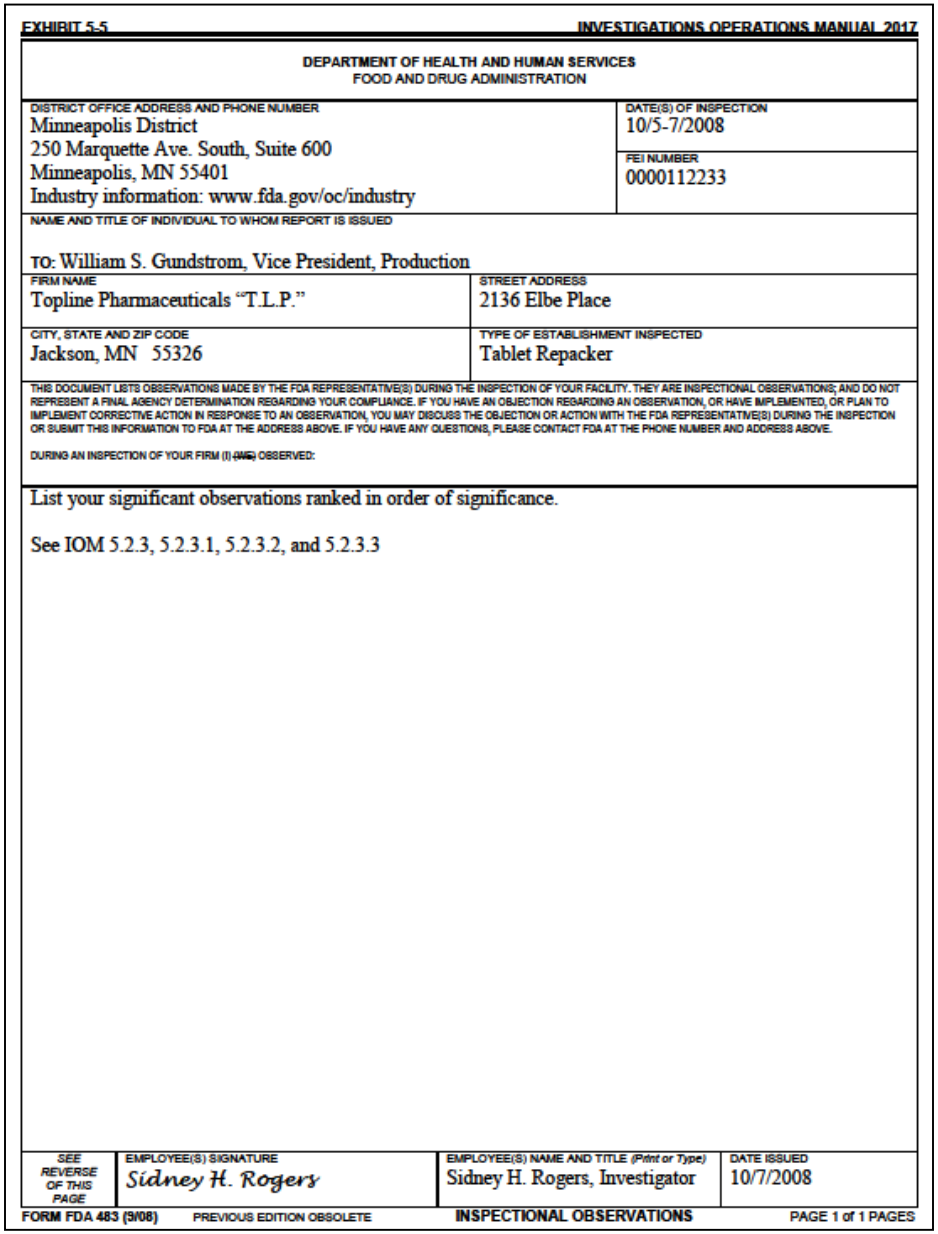


EXHIBIT 5-5 INVESTIGATIONS OPERATIONS MANUAL 2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Minneapolis District 250 Marquette Ave. South, Suite 600 Minneapolis, MN 55401 Industry information: www.fda.gov/oc/industry	10/5-7/2008
	FEI NUMBER 0000112233

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: William S. Gundstrom, Vice President, Production

FIRM NAME	STREET ADDRESS
Topline Pharmaceuticals "T.L.P."	2136 Elbe Place
CITY, STATE AND ZIP CODE Jackson, MN 55326	TYPE OF ESTABLISHMENT INSPECTED Tablet Repacker

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) ~~(WE)~~ OBSERVED:

List your significant observations ranked in order of significance.

See IOM 5.2.3, 5.2.3.1, 5.2.3.2, and 5.2.3.3

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Sidney H. Rogers	Sidney H. Rogers, Investigator	10/7/2008

FORM FDA 483 (5/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 1 of 1 PAGES

Form FDA-483 Inspectional Observations

- The FDA 483, Inspectional Observations is intended for use in notifying the inspected establishment's top management in writing of significant objectionable conditions, relating to products and/or processes, or other violations of the FD&C Act and related Acts which were observed during the inspection.

Inspection Classification

- Upon completion of the inspection, ORA recommends an initial inspection classification.

  - **No Action Indicated (NAI)** - No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further FDA action).

Inspection Classification

- **Voluntary Action Indicated (VAI)** - Objectionable conditions were found and documented but the District and/or Center is not prepared to take or recommend any of the regulatory (advisory, administrative, or judicial) actions since the objectionable conditions do not meet the threshold for regulatory action

- **Official Action Indicated (OAI)** - Objectionable conditions were found and regulatory action should be recommended

Inspection Classification

- The assignment issuing Center has final classification authority.

- The centers will determine and assign the final classification for the inspection, and initiate regulatory actions, if warranted.

Resources

- **BIMO Program**
  https://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/ucm160670.htm

- **CPGMs**
  https://www.fda.gov/ICECI/ComplianceManuals/CompliancePrograMManual/ucm255614.htm

Inspection Readiness: PADE Inspections

Marcia Gelber, RPh

Consumer Safety Officer

PADE Compliance Team

Objectives

1. Describe the PADE inspection process
2. Explain how FDA uses inspection information
3. Recognize best practices for PADE inspections

PADE Inspection Coverage

Written procedures

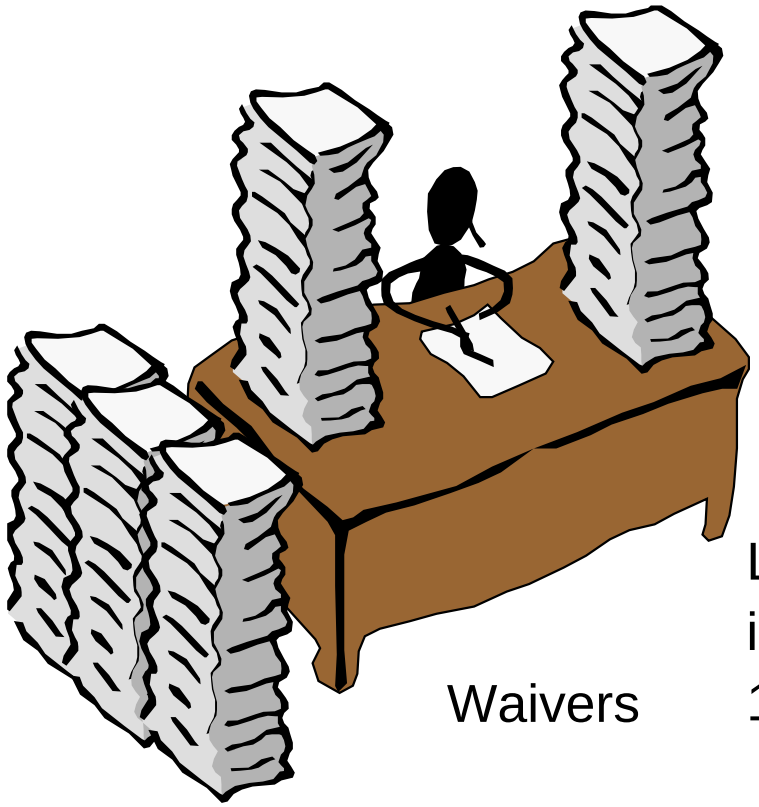
Organization, roles and responsibilities

Safety Contracts / Agreements

Business partners

Training documents

Confirmations for electronic submissions



Product list (approval date, status, etc.)

Late or missing periodic reports

Late or missing annual reports

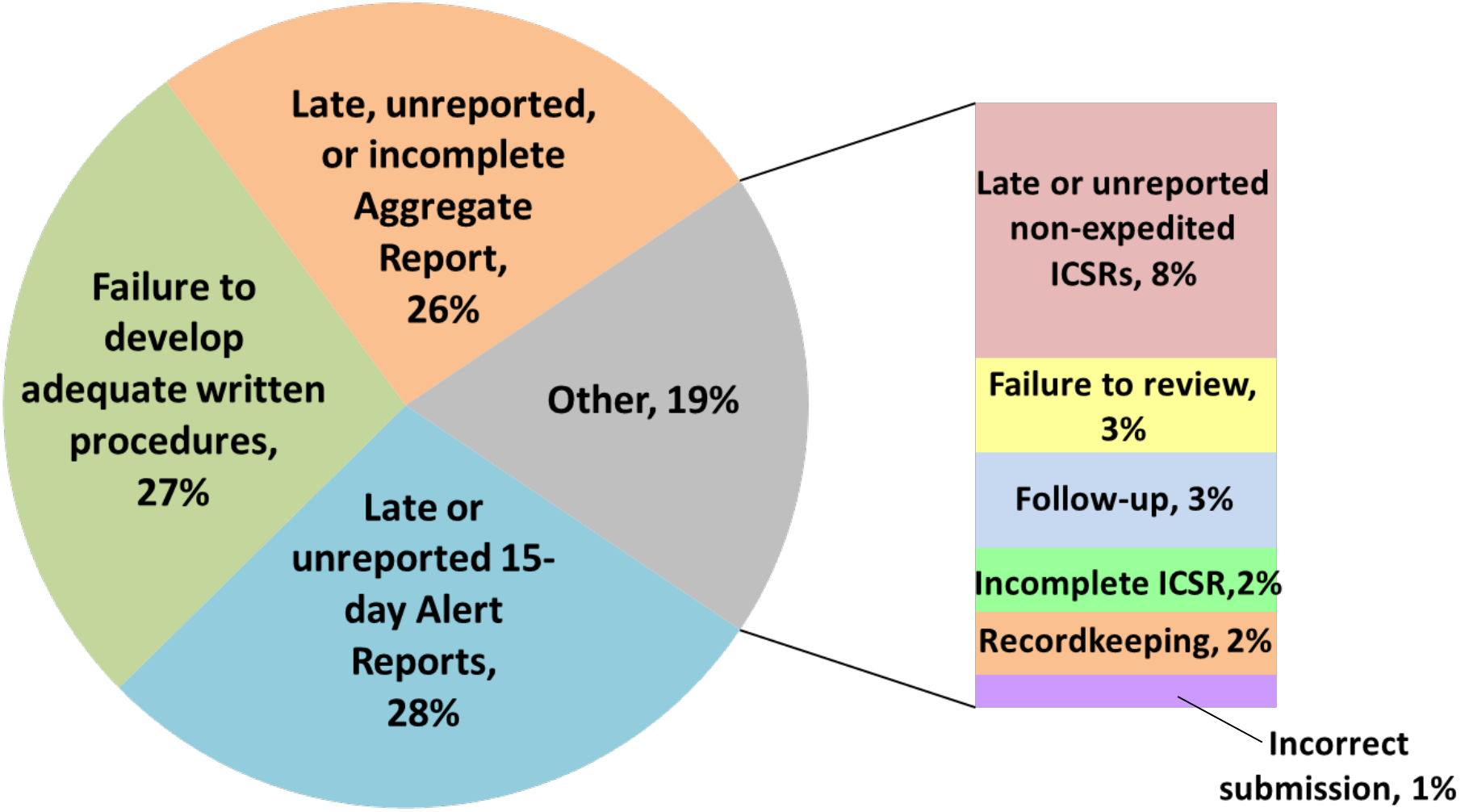
Late, missing, incomplete, or inaccurate 15-day reports

Waivers

Root cause analyses and corrective actions for deviations

ADEs from all sources

PADE Inspection Trends: PADE Citations on Form FDA 483 (FY2015-FY2017)



Common Inspection Observations

1. Failure to develop adequate written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences

   21 CFR 314.80(b)

   21 CFR 600.80(b)

   21 CFR 310.305(a)

Written Procedures Must Address…

Surveillance	Receipt	Evaluation	Reporting

• Account for all sources
• Spontaneous
• Solicited
• Internet sources (firm-sponsored)
• Literature
 	
…and more!
	• ADE info
	  • Initial
	  • Follow-up
	
	• Receipt from ***any*** source
		• Seriousness
		• Expectedness
		• Relatedness
		
		• ADEs from ***any*** source
		
		• Follow-up procedures
			• 15-day Alert Reports
			• Non-expedited individual case safety reports (ICSRs)
			• Aggregate Reports
			• All info must be submitted electronically

Common Inspection Observations

2. Failure to submit all adverse drug experiences that are both serious and unexpected to FDA within 15 calendar days of initial receipt of the information

21 CFR 314.80(c)(1)(i)

21 CFR 600.80(c)(1)(i)

21 CFR 310.305(c)(1)(i)

Common Inspection Observations

3. Failure to report each adverse drug experience not reported under 21 CFR 314.80(c)(1)(i) or 21 CFR 600.80(c)(1)(i) at quarterly intervals for three years from the date of approval of the application, and then at annual intervals

   21 CFR 314.80(c)(2)(i)

   21 CFR 600.80(c)(2)(i)

What makes a good Corrective Action Plan?

Investigate and identify actual and potential causes of non-compliance

Correction-

Correct instances of non-compliance

Corrective Action-

Eliminate causes of non-compliance

Document!

Preventative Action-

Implement measures to prevent future occurrences

Assessment-

Verify timeliness of actions and effectiveness of plan

Four Reasons to Submit a Complete and Timely Written Response

1. May be considered in an FDA compliance decision
2. Demonstrates your acknowledgment and understanding of the observations to the FDA
3. Demonstrates your commitment to correct the observations to the FDA
4. Establishes credibility with the FDA

Regulatory Procedures Manual at: www.fda.gov/ora/compliance_ref/rpm/pdf/ch4.pdf

Points to Consider for Written Responses

1. Include a commitment from senior leadership
2. Address each observation separately
3. Note whether you agree or disagree
4. Provide both corrective and preventive actions
5. Provide both completed and planned actions
6. Provide timelines for completion
7. Provide a method of verification or monitoring the effectiveness of the actions
8. Submit documentation (training, SOPs, CAP, records)
9. SUBMIT THE RESPONSE WITHIN 15 WORKING DAYS

What if I miss the 15-day deadline?

We acknowledge receipt of your written response dated [Month dd, yyyy,] to the Form FDA 483 but note that this response was received past the fifteen (15) business days from close of the inspection. Thus, while we have reviewed the response, we have not included a discussion of the response in this letter as per the Commissioner's Enforcement Initiative announced August 11, 2009.

Take Away Messages

- Adequate preparation for an FDA inspection may result in a more positive outcome
- Remember to refer back to PADE regulations whenever possible to ensure that your pharmacovigilance activities meet the regulatory requirements
- Remember to submit a ***well-reasoned, complete, and timely*** written response

PADE Statutory Provisions / Regulations: Prescription Drug Products for Human Use

FDCA, Subchapter V, Part A, Section 505 (21 USC §355)	New drugs
21 CFR 310.305	New drugs: Records and reports concerning ADEs on marketed prescription drugs for human use without approved new drug applications
21 CFR 314.80	New drug applications: Postmarketing reporting of ADEs
21 CFR 314.81(b)(2)	New drug applications: Annual reports
21 CFR 314.90	New drug applications: Waivers
21 CFR 314.98	Abbreviated applications: Postmarketing reports
21 CFR 314.540	Accelerated approval of new drugs for serious of life-threatening illnesses: Postmarketing safety reporting
21 CFR 314.630	Approval of new drugs when human efficacy studies are not ethical or feasible: Postmarketing safety reporting
21 CFR Part 4, Subpart B	Postmarketing safety reporting for combination products

PADE Statutory Provisions / Regulations: Licensed Biological Products for Human Use

PHS Act, Subchapter II, Part F, Subpart 1 (21 USC §262)	Regulation of biological products
21 CFR 600.80	Biological products: Postmarketing reporting of adverse experiences
21 CFR 601.28	Biologics licensing: Annual reports of postmarketing pediatric studies
21 CFR 601.44	Accelerated approval of biological products for serious of life-threatening illnesses: Postmarketing safety reporting
21 CFR 601.70	Postmarketing studies: Annual progress reports of postmarketing studies
21 CFR 601.93	Approval of biological products when human efficacy studies are not ethical or feasible: Postmarketing safety reporting
21 CFR Part 4, Subpart B	Postmarketing safety reporting for combination products

PADE Statutory Provisions / Regulations: Unapproved, Non-prescription Products (e.g. OTC monograph)

FDCA, Subchapter VII, Part H, Section 760 (21 USC §379aa)	Serious adverse event reporting for nonprescription drugs
21 CFR 329.100	Postmarketing reporting of ADEs under section 760 of the FDCA
21 CFR Part 4, Subpart B	Postmarketing safety reporting for combination products

REMS Inspection Readiness

Haley Seymour, MS

Reviewer, REMS Compliance Team

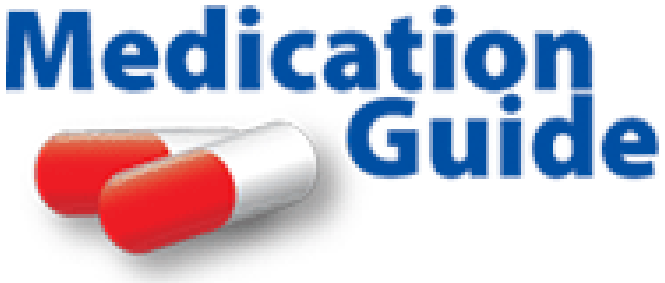
Preparing for REMS Inspection

"The best way to survive an FDA inspection is to be prepared for it!"

- Be familiar with FDA Compliance Programs applicable to your industry sector
- Train staff so that they understand the process and can follow the SOPs
- Communicate clearly during and after the inspection

Medication Guide REMS – What the applicant should do

- The applicant should provide a copy of the Medication Guide and patient package inserts in the version or format (hardcopy) that is provided to each patient.



Communication Plan REMS – What the applicant should do

1. The applicant should provide copies of all communication materials distributed
2. The applicant should provide documentation of communication information from professional journals, along with the dates, volume, and issue
3. The applicant should provide dates the REMS information was presented at scientific meetings

ETASU A REMS – What the applicant should do

- Provide documentation of the firm's activities related to the implementation of ETASU A
- Provide documentation that healthcare providers receive a notification that they have been certified in the REMS program
- Provide documentation of maintenance of a validated, secure database of healthcare providers who are certified
- Provide documentation of any non-compliance

ETASU B REMS – What the applicant should do

- Provide documentation of notification of certified pharmacies, practitioners or healthcare settings that dispense the drug
- Provide documentation of maintenance of a validated, secure database of certified pharmacies, practitioners or health care settings
- Provide documentation of assessment of pharmacist, practitioners, or clinical setting designee's understanding of risk messages and/or REMS program requirements; site audits
- Provide documentation of any non-compliance

ETASU C REMS – What the applicant should do

- Provide documentation of mechanism to address non-compliant healthcare settings or wholesaler/distributor
- Provide documentation that drug is shipped only to certified facilities
- Provide documentation of applicant's activities related to assessment of targeted stakeholder's compliance of REMS program requirements
- Provide documentation of applicants activities related to surveillance of the risks addressed by the REMS program

ETASU D REMS – What the applicant should do

- Provide documentation that drug is dispensed to patients with safe use conditions
- Provide documentation that certified prescribers are able to submit completed forms documenting safe use conditions
- Provide documentation of maintenance of a validated, secure database
- Provide documentation of maintenance of a REMS Program Call Center

ETASU E REMS – What the applicant should do

- Provide documentation that patients received monitoring specified in the approved REMS
- Provide documentation that the required monitoring takes place according to schedule
- Provide documentation the applicant identifies and addresses pharmacy, practitioner, patient, or health care setting non-compliance

ETASU F REMS – What the applicant should do

- Applicant should provide documentation of activities related to the implementation of ETASU F
- Applicant should provide evidence that the registry is in place
- Applicant should provide documentation of patient registry enrollment non-compliance if applicable

Implementation System
What the applicant should do

- Applicant should provide documentation of maintenance of a REMS Program Call Center
- Applicant should provide documentation of maintenance of a REMS program website
- Applicant should provide summary of audits and documentation of an ongoing audit plan if applicable

How to respond to FDA

- You should ensure that the communication **provides an adequate response to FDA's observations** (483, Untitled/Warning letter), is easy to follow, and there are corrective actions in place to fix the issues.

- Each response should address the central issue(s) raised in the observations and **provide factual objective evidence** that permits evaluation and aids in understanding of the response.

How to respond to FDA

- Include a commitment from senior leadership
  - -Address each observation separately
  - -Note whether you agree or disagree
  - -Provide both corrective and preventive actions
  - -Provide both completed and planned actions
  - -Provide timelines for completion
- Provide a method of verification or monitoring the effectiveness of the actions
- Submit documentation (training, SOPs, CAP, records)

Questions for the Panel

Click for resources:

- 2018 Investigations Operations Manual (IOM)
- Bioresearch Monitoring Program (BIMO) Compliance Programs
- PADE Compliance Program
- REMS Compliance Program

Open Q&A begins shortly – type in your questions now.

Please send any questions we do not have time for to:
CDERSBIA@fda.hhs.gov

Learn about other resources from CDER Small Business & Industry Assistance:
Visit Our Website!

Click Here for Evaluation and Certificate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