US FDA INSPECTION OVERVIEW

OCTOBER 25, 2017

CORPORATE COMPLIANCE
Medical Quality Assurance

TOPICS

- FDA Notification: Immediate Next Steps
- Inspection Overview
- Inspection Preparation

FDA NOTIFICATION:
The FDA makes contact – immediate next steps

IMMEDIATELY NOTIFY

E-mail MedicalQAInspectionMgmt@pfizer.com with the following:

- ✓ *Protocol Number*
- ✓ *Site Information (Principal Investigator Name, Site No., Contact Details such as phone number and e-mail, and Address)*
- ✓ *Name of Inspector [if known]*
- ✓ *Dates of Inspection*

ENSURE AVAILABILITY

- All subjects' medical records
- Source documents
- Investigator Site Files

COORDINATE LOGISTICS

- Identify all relevant personnel
- Reserve an inspection room for at least a week's duration
- Coordinate preparation activities

INSPECTION OVERVIEW:
FDA's Bioresearch Monitoring (BIMO) Program

BIMO PROGRAM OBJECTIVES	TYPES OF INSPECTIONS	POTENTIAL OUTCOMES
1. Protect the rights, safety, and welfare of subjects in FDA-regulated trials. 2. Determine the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and 3. Assess compliance with FDA's regulations governing the conduct of clinical trials, including those for informed consent and ethical review.	1. Routine - New Drug Applications 2. Directed - Investigate problems that have been identified at the Investigational new Drug (IND) stage (e.g., data audits) 3. For Cause - Investigate complaints (e.g., allegations of falsification, lack of oversight, inadequate monitoring) - Compliance follow-up for previous deficiencies	1. No observations with or without discussion points. 2. Warning Letter 3. Disqualification of clinical investigators [21 CFR 312.70] - *Repeated and deliberate failure to comply with the requirements.* - *Repeated or deliberate submission of false information to the FDA or to the sponsor in any required report,* - *FDA provides notice of matter to investigator and provides opportunity to explain (Notice of Initiation of Disqualification Proceedings and Opportunity to Explain – NIDPOE).* - *May result in ineligibility to receive investigational drugs.*

INSPECTION OVERVIEW: General Inspection Steps

1 Pre-Inspection

- Inspectional assignments from the FDA Center
- FDA Center selects sites

SITE SELECTION CRITERIA

- ✓ *Is there a specific safety concern at a particular site or sites (based on review of AEs, SAEs, deaths, or discontinuations)?*
- ✓ *Is there a specific efficacy concern based on review or data?*
  - → *Final outcome driven by a particular site or sites.*
  - → *Efficacy outcome other than expected based on mechanism of action.*
- ✓ *Clinical investigator history*
- ✓ *Imbalance or outlier in an important attribute- can be too many or too few*
- ✓ *Regional or country diversity*

2 Opening Meeting

- Form FDA 482 "Notice of Inspection" is issued to the most responsible person.
- Explains why the FDA is there and what records and documents will be reviewed.

3 Inspection Conduct

- Review of Records

Source Documents & Medical Records
↓
Case Report Forms
↓
Data Listing Submitted
→*Primary Efficacy*
→*AEs/SAEs*
→*Safety: Labs, etc.*

- Copying and collection of exhibits
- Facility Tour
- Interviews

4 Closing Meeting

If applicable, Inspector issues Form FDA 483, which are:

- Significant deviations from Regulations.
- Observations are based only on the FDA Investigator's review of available records and information.
- Observations do not represent final Agency determination regarding compliance.

If a Form FDA 483 is issued, assistance is available:

- Findings should be responded to within 15 business days.
- Corrective actions should be taken for deficiencies, AND preventative actions to prevent recurrence.
- Documentation of completion of actions should be provided with the response (e.g., updated SOP).

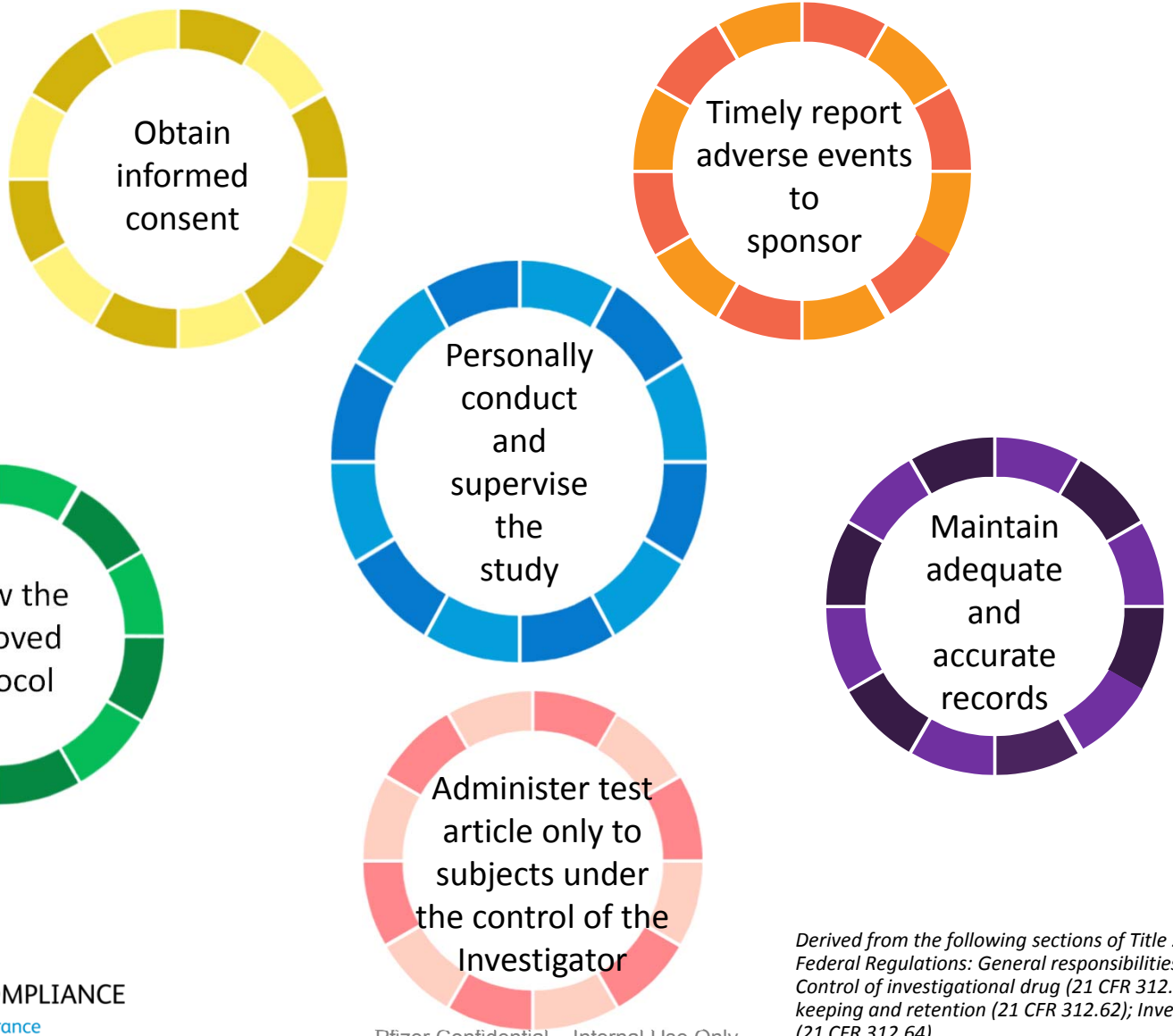
5 Post-Inspection

- Inspector prepares Establishment Inspection Report (EIR) and recommends classification.
- FDA Center reviews and classifies findings:

  - ✓ ***NAI: No Action Indicated*** *[no objectionable conditions or practices found (or the objectionable conditions do not justify further regulatory action)]*
  - ✓ ***VAI: Voluntary Action Indicated*** *[objectionable conditions or practices found, but agency is not prepared to take or recommend any administrative or regulatory action]*
  - ✓ ***OAI: Official Action Indicated*** *[regulatory and/or administrative actions recommended]*

- Inspected entity will receive a copy of the EIR. Please forward to MedicalQAInspectionMgmt@pfizer.com.

INSPECTION PREPARATION:
Primary Commitments in Form FDA 1572



Derived from the following sections of Title 21, Code of Federal Regulations: General responsibilities (21 CFR 312.60); Control of investigational drug (21 CFR 312.61); Record keeping and retention (21 CFR 312.62); Investigator reports (21 CFR 312.64)

Common BIMO Observations for Clinical Investigators

- Failure to follow the investigational plan and/or regulations
- Protocol Deviations
- Inadequate record-keeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – failure to report AEs and informed consent issues

INSPECTION PREPARATION: Common Preparation Areas

Discussion Points

- Site Organizational Structure
- Subject Recruitment
- Protocol & Protocol Amendments
- Processes: Informed Consent, IRB Reporting, SAE Reporting, Delegation, Training, Oversight, IP
- Data Handling & Responsibilities
- Monitoring

Facilities & Equipment

- Suitability to meet protocol requirements
- Maintenance and proper use

Documentation

- Available, organized, and complete
- Evidence that all data are aligned
- Evidence of proper informed consent process
- Evidence that IP handling and dispensing are appropriate
- Evidence of adequate communications with the IRB
- Evidence of monitoring and follow-up to and by the sponsor

Interview

- Understand the question and seek clarification – do not interpret
- Answer only the question as asked
- Answer honestly – do not be evasive or give false/misleading info
- Answer succinctly
- Refer to SMEs, when appropriate
- Be comfortable with silence

If you remember nothing else, when the FDA calls…

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Thank You