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## Data Integrity and Automated Systems

*presented by:*

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## OUTLINE

- Discuss current regulatory requirements for automated systems from the perspective of electronic records and data integrity
- Describe FDA's Inspection Programs relevant to data integrity and electronic data
- Present the upcoming CDER Part 11 Inspection Initiative

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## Regulatory Requirements

- 21CFR Part 11 is an FDA regulation that imposes certain requirements when a regulated entity chooses to maintain FDA-required records in electronic form

- Part 11 requirements are intended to help assure the integrity, validity and trustworthiness of electronic records

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### Characteristics of Trustworthy Records

- National Archives & Records Administration
  - Reliability: trusted to be complete & accurate
  - Authenticity: proven to be what it purports to be
  - Integrity: Complete & unaltered
  - Usability: can be located, retrieved, presented & interpreted

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### Part 11

For electronic records and submissions to have the same integrity as paper records, they must be developed, maintained, and used under circumstances that make it difficult for them to be inappropriately modified.

[Preamble, p. 13464]

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### Typical controls for automated systems intended to provide assurance of data integrity

- Written Procedures
- Validation
- Change Control
- Security (Physical & Logical)
- Electronic Signatures
- Audit Trails
- Back up & Retrieval

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### What will an FDA Investigator be looking for?

- That you have adequate controls in place for your automated systems to ensure your regulated data is trustworthy
  
- Verification of your data
  - Hard copy records
  - Electronic records

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### Current Policy

- Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application- August 2003
  - FDA will exercise enforcement discretion in regard to certain Part 11 requirements

- FDA will continue to enforce all predicate rule requirements, including requirements for records and recordkeeping

8

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### Predicate Rules

- For Finished Drugs
  - a written record of the program shall be maintained along with appropriate **validation** data  
[21CFR211.68]

– [Revised as of April 1, 2009]

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### Predicate Rules

- GLP NONCLINICAL LABORATORY
  - Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control **shall be of appropriate design and adequate capacity** to function according to the protocol [21CFR58.61]

– [Revised as of April 1, 2009]

10

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### Predicate Rules

- Investigational New Drug- Investigator records;
  - An investigator is required to prepare and maintain **adequate and accurate** case histories ... [21CFR312.62(b)]

– [Revised as of April 1, 2009]

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### Predicate Rules

- Investigational Device Exemption- Investigator records,
  - A participating investigator shall maintain **accurate, complete**, and current records relating to the investigator's participation in an investigation [21CFR812.140(a)]

– [Revised as of April 1, 2009]

12

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### Predicate Rules

- Institutional Review Boards
  - an IRB shall prepare and maintain **adequate** documentation of IRB activities  
*[21CFR56.115(a)]*
  
- Investigational New Drug- sponsor records,
  - A sponsor shall maintain **adequate** records  
*[21CFR312.57(a)]*

13

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### Predicate Rules

- Investigational New Drug- Contract Research Organizations
  - A contract research organization that assumes any obligation of a sponsor **shall comply with the specific regulations** in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. *[21 CFR312.52(b)]*

14

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### What records will be subject to Part 11 requirements?

- Part 11 will apply when electronic records are used in place of paper records
- Part 11 will NOT apply when:
  - Computers are used to generate paper printouts of electronic records;
  - These paper records meet all predicate rule requirements; and
  - Persons rely on paper records to perform regulated activities

15

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**PRE-APPROVAL  
INSPECTIONS/INVESTIGATIONS**

- Compliance Program 7346.832
  - This program is designed to provide close inspectional and analytical attention to **the authenticity and accuracy of data in applications** and to provide information regarding facilities.

16

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**PRE-APPROVAL  
INSPECTIONS/INVESTIGATIONS**

- **REGULATORY/ADMINISTRATIVE STRATEGY**
  - Some significant problems include, but are not limited to:
    - Application misrepresents data or conditions relating to pre-approval batches
    - There are other inconsistencies and/or discrepancies raising significant questions about the validity of records

17

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**POST APPROVAL AUDIT  
INSPECTIONS**

- Compliance Program 7346.843
  - describes that based on allegations of misconduct in the generic drug industry, FDA conducted a thorough investigation of generic drug manufacturers and uncovered major findings to include: < on next slide>

18

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**POST APPROVAL AUDIT  
INSPECTIONS**

- submitted fraudulent samples for bioequivalence testing.
- submitted false records or data in their ANDAs to FDA so as to gain approval for marketing.
- falsified batch records for commercial production so as to conceal from FDA that they were not following the conditions of approval.
- falsified inventory control records, purchasing records, etc. to cover other fraudulent records.

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**POST APPROVAL AUDIT  
INSPECTIONS**

- Compliance Program 7346.843
  - findings which bring into question the reliability of the provided records should be corroborated by examination of alternate records and interviews of personnel

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**Chapter 48 – Bioresearch Monitoring  
GOOD LABORATORY PRACTICE  
(Nonclinical Laboratories)**

- Compliance Program 7348.808
  - To verify the quality and integrity of data submitted in a research or marketing application.

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**GOOD LABORATORY PRACTICE**  
(Nonclinical Laboratories) CPG 7348.808

- Directed inspections are assigned to achieve a specific purpose, such as:
  - Verifying the reliability, integrity, and compliance of critical safety studies being reviewed in support of pending applications.
  - Investigating issues involving potentially unreliable safety data and/or violative conditions brought to FDA's attention.

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**GOOD LABORATORY PRACTICE**  
(Nonclinical Laboratories) CPG 7348.808

- **INSPECTIONAL- Data Audit**
  - the inspection should include the audit of at least one completed study. ... The audit will include a comparison of the protocol (including amendments to the protocol), raw data, records, and specimens against the final report **to substantiate that protocol requirements were met and that findings were fully and accurately reported.**

23

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**Chapter 48 - Bioresearch Monitoring**  
**SPONSORS, CONTRACT RESEARCH**  
**ORGANIZATIONS AND MONITORS**

- **Compliance Program 7348.810**
  - Inspections under this program will be conducted to determine:
    - How sponsors assure the validity of data submitted to them by clinical investigators.

24

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**SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS**

- **Compliance Program 7348.810**
  - Automated Entry of Clinical Data
    - Directs a series of questions to be asked relative to software validation, data collection, audit trails, system security, backup plans, and procedures

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**CHAPTER 48- BIORESEARCH MONITORING CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS**

- Compliance Program 7348.811
- The objectives of this BIMO Program include:
  - To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications

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**CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS CPG 7348.811**

- Regardless of the type of system used by the clinical site, an important principle to understand when evaluating clinical research data is that the regulatory requirements for the clinical data do not change whether clinical data are captured on paper, electronically, or using a hybrid approach. **Data must be reliable and usable** for evaluating the safety and/or effectiveness of FDA-regulated products.

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**CLINICAL INVESTIGATORS AND SPONSOR-  
INVESTIGATORS CPG 7348.811**

- **Determine** whether electronic records and data meet the requirements applicable to paper records. For example, are electronic records used to meet case history requirements attributable, legible, contemporaneous, original, and accurate (ALCOA)?

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**CLINICAL INVESTIGATORS AND SPONSOR-  
INVESTIGATORS CPG 7348.811**

- The following criteria are relevant to FDA's classification of inspections of clinical investigator sites:
  - For OAI classification, The regulatory violation(s) uncovered is/are significant/serious and/or numerous, and the scope, severity, or pattern of violation(s) support a finding that:
    - **c) Data integrity or reliability is or has been compromised.**

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**CLINICAL INVESTIGATORS AND SPONSOR-  
INVESTIGATORS CPG 7348.811**

- **Data Integrity: Submission of False Information to FDA or the sponsor**
- False or misleading reports were prepared and/or submitted
  - 21 CFR 312.70; 312.64;
  - 21 CFR 511.1(c);
  - 21 CFR 812.119, 812.150(a)

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## Summary

- Controls for automated systems are intended to provide assurance that data they generate, store, or present is reliable, trustworthy, has integrity
- FDA inspects both the controls and the data/records that may reside within, or may have passed through automated systems

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## CDER Part 11 Inspection Initiative

- FDA will inspect Part 11 controls relating to drugs as they are described in the 'Part 11, Electronic Records; Electronic Signatures — Scope and Application' guidance (August 2003)
- This initiative will help us evaluate industry's current compliance and understanding of Part 11 in light of the guidance (now over 6.5 years since finalized)
- FDA may use the inspectional findings as part of its reevaluation of Part 11 regulation, guidance, etc.
- FDA may take appropriate enforcement action for issues raised during these inspections

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# THANK YOU!

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