



U.S. Food and Drug Administration

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The background of the slide is a grayscale medical scan, likely an MRI or CT scan, showing a cross-section of a human head. A prominent feature is a bright, multi-colored (yellow, orange, red) area in the center, which appears to be a tumor or a region of abnormal tissue. The surrounding areas are in shades of blue and gray, representing normal brain tissue.

Electronic Source Documentation in Clinical Investigations

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CDER Small Business Assistance –
Clinical Trial Workshop

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Overview

1. FDA's Part 11 Regulation

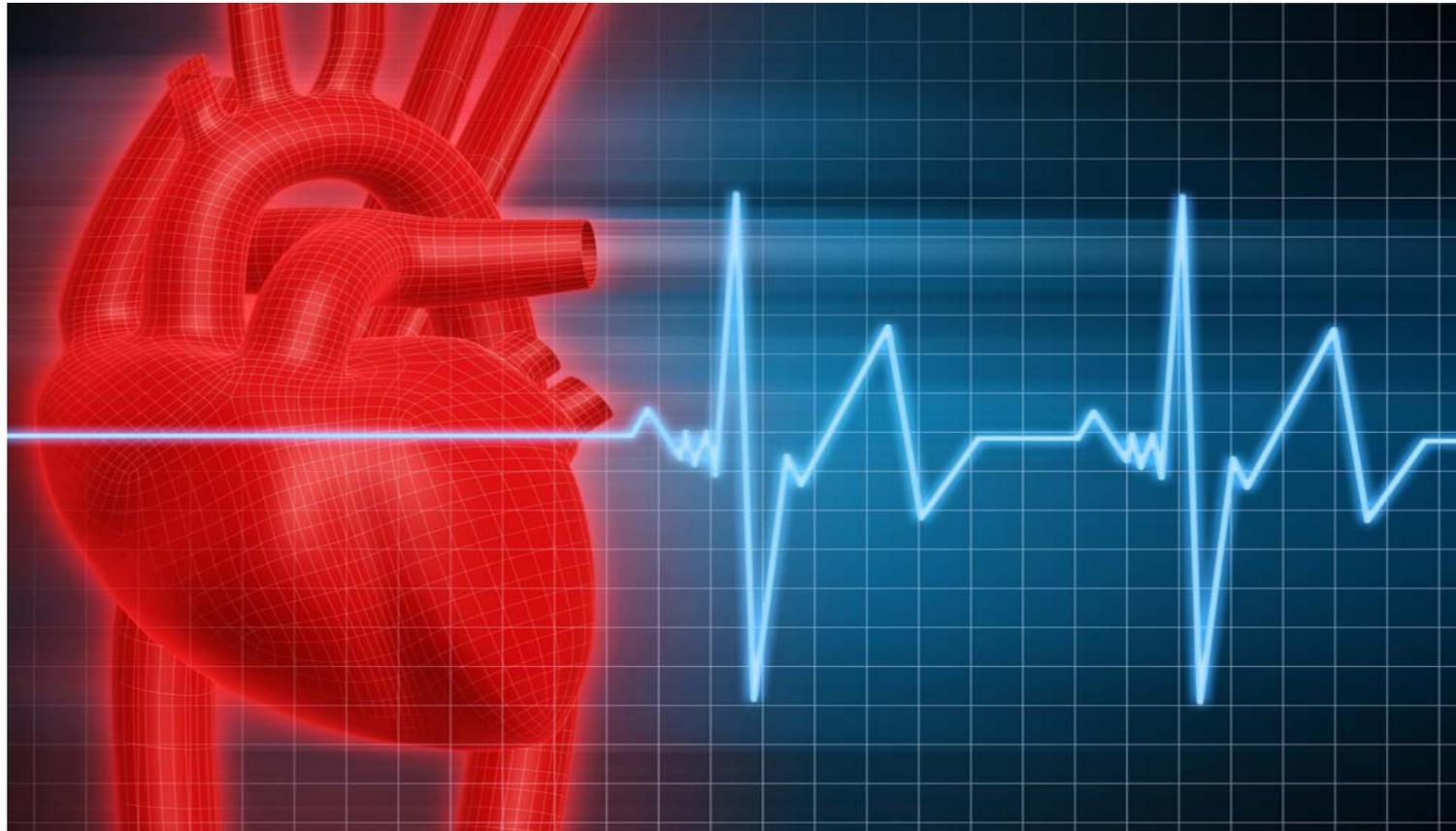
2. Part 11 Guidance

3. Regulatory Challenges

4. Inspection Expectations

5. Draft eSource Guidance

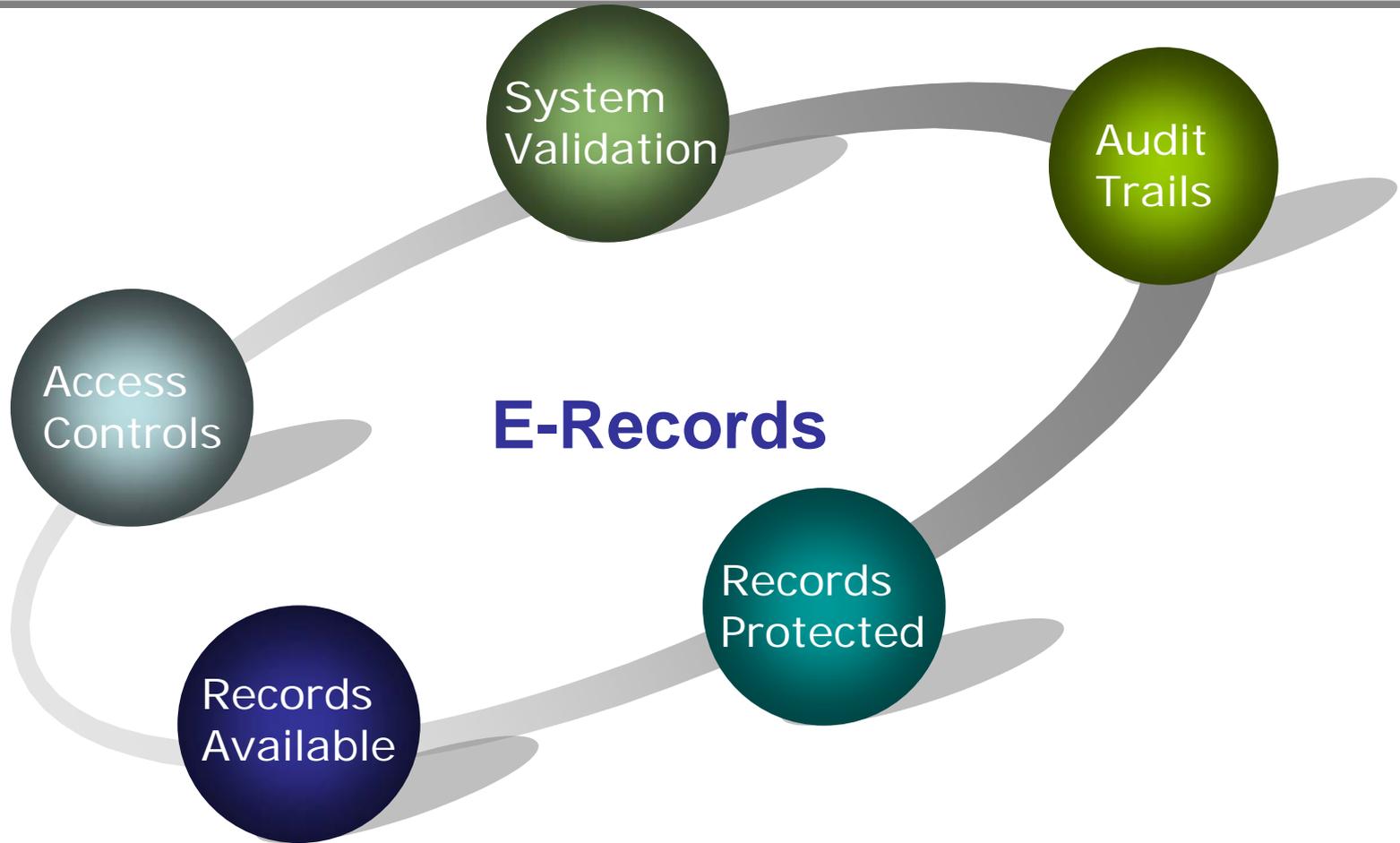
FDA's Part 11 Regulation E-Record and E-Signatures



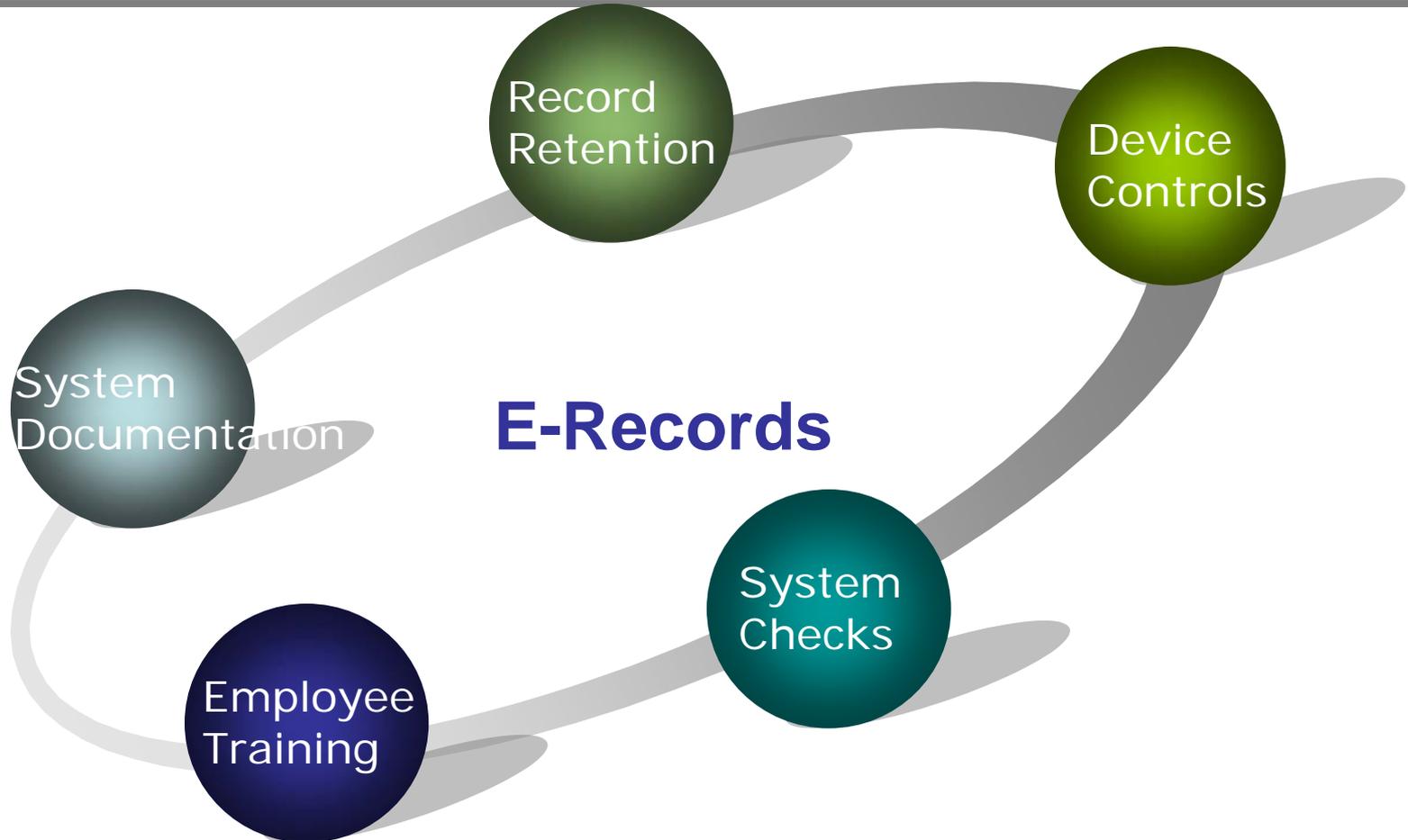
What is Part 11?

- FDA regulation describing requirements for maintaining FDA-required records and signatures in electronic form
- Requirements are intended to ensure the integrity, validity and trustworthiness of e-records and e-signatures
- Regulation went into effect August, 1997

Key Elements - 21 CFR 11.10



Key Elements - 21 CFR 11.10 (cont)



Key Elements - 21 CFR 11.70, 11.100-200

E-signature controls

- Signature/record linking
- Signature manifestations/purpose (*review/approve/verify*)
- Access Controls
 - Distinct password (or biometric) protected user account
 - Used only by genuine owners
 - Password and token protections utilized (checked, revised, etc.)
- FDA Certification
- Written Policies – SOP describing how signatures are assigned and used
- Employee Training

Part 11 Guidance and FDA's Current Enforcement Policy

- Part 11 Scope and Application Guidance (Aug 2003)
- Computerized Systems used in Clinical Investigations (May 2007)
- Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (Dec 2009)

Key Components



Fewer Records Subject To Part 11 controls

FDA does not intent to take Action Under Certain Conditions

FDA will enforce predicate Rules (21 CFR 312, 812, 50, 56, etc)

Firms can Use a risk-Based Approach For Part 11 controls

Fewer Part 11 Records

- “Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations.”
- “Part 11 also applied to electronic records submitted to the Agency under the FD&C Act and the Public Health Service Act even if such records are not specifically identified in Agency regulations”
- “Records that are not required to be retained under predicate rules but that are nonetheless maintained in electronic format, are *not part 11 records*.”

Electronic Records that Remain in Scope

- “Records that are required to be maintained under predicate rules are maintained in electronic format *in place of paper format.*”
- “Records that are required to be maintained under predicate rules, that are maintained *in addition to paper format*, and that *are relied on to perform regulated activities.*”
- “Electronic signatures that are intended to be the equivalent of handwritten signatures, initials and other signings required by predicate rules.”

Enforcement Discretion

- “We (FDA) do not intend to take enforcement action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of part 11”
- “However, records must still be maintained or submitted in accordance with the underlying predicate rules, and the Agency can take regulatory action for noncompliance with such predicate rules.”

Risk-Based Approach to Part 11

- Firms (e.g., sponsor, CI, IRB, CRO) decide *when* and *to what extent* the following controls need to be utilized based on a *documented risk assessment*
 - Validation of computerized system (software, firmware, hardware)
 - Audit trails that document who/what/when/why records were created/modified (computer generated, other procedures)
 - Access Controls (e.g., use passwords, biometrics)
 - Electronic record preservation (paper, electronic, etc.) ¹³

Risk-Based Approach to Part 11 (cont)

- “Certified copy” - copies of records **must** be generated using a verified process that produces copies with same content and meaning as original record (see CPG # 7150.13)
- If a firm has the ability to search, sort or trend records, copies made available to FDA must preserve this same capability
- Other parts of part 11 remain intact!

More Guidance

- **Computerized Systems used in Clinical Investigations (2007)**
 - Audit trails, record retention
- **Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (2009)**
 - ePRO

Regulatory Challenges

- Requirements for clinical data *do not change* for paper, computer, or hybrid approaches
- Computerized systems should meet all regulatory requirements with the same degree of confidence as that provided with paper systems.

General Suggestions

- Utilize appropriate controls to ensure that e-records/data and electronic signatures are *trustworthy, accurate, and complete*
- Use appropriate controls to ensure that clinical data are *protected* so that study related activities *can be reconstructed*
- Use a *risk-based approach* for designing/utilizing computerized systems for clinical data
 - flexible regulations support a risk based approach (e.g., case history, monitoring)

Risk Management Principles

Risks in Clinical Trials



Harm to
Subjects

Incorrect information
can harm subjects

Subject
Rights

Unlimited access
compromises
confidentiality

Data Quality
and Integrity

Compromise via
unapproved
changes

Electronic Health Records and Clinical Research

- Must maintain requirements of predicate rules
- Controls such that data is accurate, legible, contemporaneous, original, attributable
- If eHR is used to directly populate eCRF, it must be made available for inspection – and adequately controlled for study reconstruction



Inspection Expectations

- Records must to preserved to meet regulatory requirements
 - Available for FDA inspection and copying
 - Retained for appropriate length of time
 - **Independently preserved at clinical site** and/or some other designated site (e.g., technology provider)
- Audit trails are not explicitly required in GCP/HSP regulations; however to reconstruct study, we need these details

Expected Controls

- Access must be limited to authorized individual [21 CFR 11.10(d)]
- A firm should utilize password protected, individual accounts; tokens; biometrics for trained employees
- System features should limit access attempts and idle periods

Validation

- A firm needs to assess and document its decision as to *what and when* to validate
- Remember predicate rules (accurate/adequate case histories)!
- Changes that exceed previously established operational limits or design specs should be validated
- Effects of changes should be evaluated and validated, based on a risk-based assessment

Draft eSource Guidance

Electronic Source Documentation in Clinical Investigations

FDA Draft Guidance Overview

<http://www.fda.gov/downloads/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/UCM239052.pdf>



Guidance Overview

- Defining Electronic Source (eSource) Data & Documentation with common examples
 - Data Elements & Data Element Identifiers
- Electronic creation, modification, transmission, and storage of eSource (3 Tiers of Data)
- Investigator Responsibilities for review, archiving, and transmission of eSource clinical data
 - Data Integrity & Communication with Sponsor
- Information Sponsors should provide as part of protocol, investigational plan, and site inspections



Definition of eSource

- *eSource documents* and *eSource data* are used to describe source documents and source data for which the original record and certified copies are initially captured electronically
 - eCRFs
 - ePRO
 - Data initially documented in an EHR
 - Electronically generated lab reports
 - Medical Images



Data Elements

- A *data element* in an eCRF represents a single observation associated with a subject in a clinical study
 - Blood Pressure
 - BMI
 - WBC Count
 - Pain Measurement



Data Element Identifiers

- *Data element identifiers* are those attributes that identify:
 - The originators of data elements, including those entered manually (e.g., by the investigator), and automatically (e.g., from a device or instrument)
 - The date and time the data elements are entered into the eCRF
 - The study subject to which the data elements belong.



Examples of Data Elements and Data Element Identifiers

Field in CFR	Data Element	Data Element Identifier
Patient ID#	AD0012	Randomization algorithm in central computer/June 1 st , 2008/3.00 pm AD0012
Sex	male	*Investigator Dr R Smith/June 1 st , 2008/10.53 am AD0012
Age	25 years	*Investigator Dr R Smith/June 1 st , 2008/10.53 am AD0012
Hemoglobin	15.3 g/l	Co-op labs/June 2 nd , 2008/12:06 pm AD0012
Date blood was drawn for Hemoglobin determination	June 1 st , 2008	*Investigator Dr R Smith/June 1 st , 2008/10.53 am AD0012
Radiological report	"Right upper lobe consolidation"	Dr P Brown, radiological associates/ June 1 st , 2008/4.12 pm AD0012
Blood pressure	124/88	*AB instrument systems/ June 1 st , 2008/10.53 am AD0012
Concomitant medications	**Lasik 40mg QD	Investigator Dr R Smith/June 1 st , 2008/10.53 am AD0012



Three Tiers of Data

- Tier 1: Data Entry
- Tier 2: Data Review
- Tier 3: Data Processing and Transmission



Investigator Responsibilities

- The eCRF should permanently carry the electronic signature of the investigator who reviewed it
- The clinical investigator should generate a write-protected copy of the eCRF for the study archives following review & sign off
 - Make available for purposes of an FDA inspection
- When an investigator has transcribed data elements from paper documents into an eCRF, the investigator must also retain the paper documents for review by FDA



Sponsor Responsibilities

- Protocol should include information about the intended use of computerized systems during the conduct of a clinical study
 - Description of the security measures employed to protect the data
 - Detailed diagram and description of the transmission of electronic data
- Describe electronic tools intended to be used to detect events in the eCRF such as, but not limited to, data inconsistencies, missing data, and entries out of range

References

- Preamble to 21 CFR 11
 - http://frwebgate.access.gpo.gov/cgi-bin/getpage.cgi?position=all&page=13430&dbname=1997_register
- Part 11 regulation
 - <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11>
- Part 11 Scope and Application Guidance
 - <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126953.pdf>
- Computer Systems Used in Clinical Investigations
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf>

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Thank
you for
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time