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21 CFR Part 11 Fundamentals

By Praxis Life Sciences

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21 CFR Part 11 Fundamentals

v.17.04

Your Praxis Facilitator

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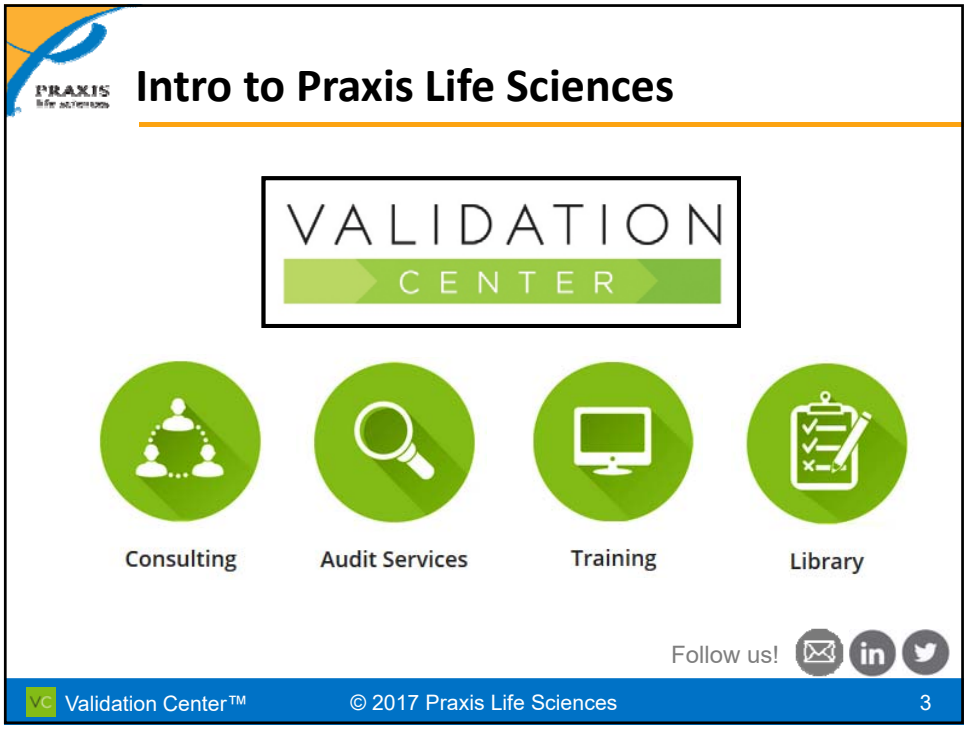
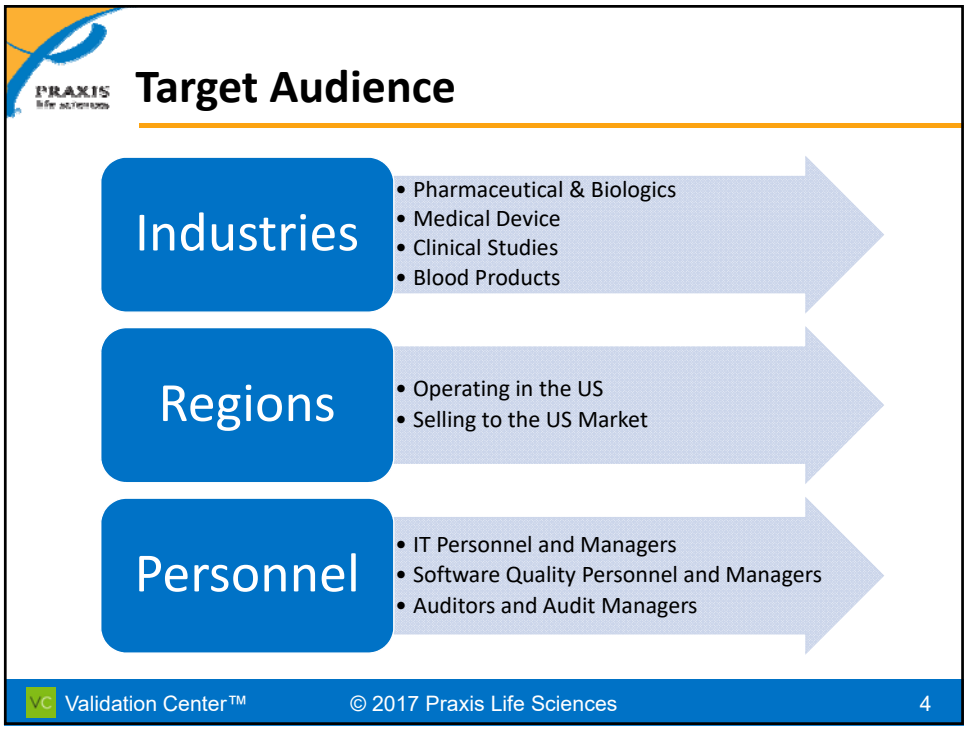
- Principal, Praxis Life Sciences
- 25+ years experience specializing in software quality assurance, validation and regulatory compliance, Information Systems project management, and process design.
- Prior to joining Praxis, held management positions in the pharmaceutical industry in both Quality Assurance and Information Systems organizations
- Active member of American Society for Quality (ASQ), Northeastern Illinois Section, Software Division





Why Attend This Webinar?

- 21 CFR Part 11, *Electronic Records; Electronic Signatures*, is one of the many FDA regulations.
- Compliance with FDA regulations is critical for success in FDA-regulated industries such as pharmaceuticals, biologicals, medical devices, and clinical trials.
- Knowledge of the Part 11 will aid the professionals who build, validate, support, and audit computerized systems in understanding the role that computer systems play in support of FDA cGMP (current good manufacturing practices), cGLP (current good laboratory practices), and GCP (current good clinical practices).

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21 CFR Part 11 Webinar Outline

1. History & Importance
2. Scope & Applicability
3. The Regulation
4. The Guidance
5. Related Regulations & Guidelines
6. Spreadsheet Challenges
7. FDA Enforcement
8. Ensuring Compliance
9. Future of Part 11

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History & Importance

Part 1

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Part 1: History & Importance

Section Overview

- Events leading to Part 11
- Reaction to Part 11
- Events after Part 11
- Significance of Part 11

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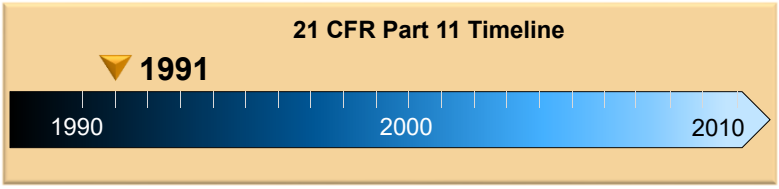
Why Was Part 11 Developed?

- Requested by the Pharmaceutical Industry in the early 1990s
  - Computerized systems were widely used
  - Desire to reduce or eliminate paper-based records and signatures
  - Asked the FDA to provide guidelines

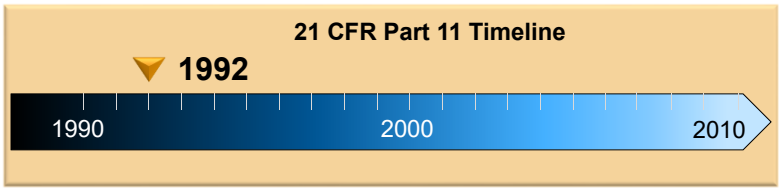


First Steps



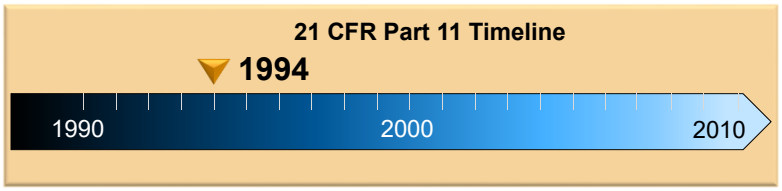
- Pharma industry members met with the FDA
  - **Objective:** paperless record systems under the cGMP regulations in 21 CFR Part 210 and 211
- The FDA created a Task Force

Introduction to the Public



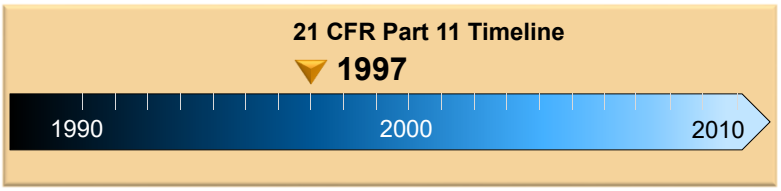
- Working Group recommended publication of an advance notice (ANPRM) to obtain public comment
- The FDA Published an ANPRM in the Federal Register
  - 53 Comments Received

Proposed Rule



- The FDA published the proposed rule in the Federal Register
  - 49 Comments received

Final Rule



- The FDA published the final rule, 21 CFR Part 11 Electronic Records, Electronic Signatures, in the Federal Register
  - Part 11 applied to all FDA program areas
  - Stated that the use of electronic records is voluntary
- Part 11 went into effect

Early Years

- Wide variation in interpretation and implementation approaches
- Unsure which systems and records were within the scope
- Unclear on how to implement the requirements

Examples:

- How long did a company have to make an existing system compliant?
- Once an electronic record is created, what does in need to remain in electronic format until its retention has expired?
- Are word processing tools and fax machines in scope?
- Are draft documents considered “audit trails”?
- What is an acceptable approach to Software Validation?

Guidance

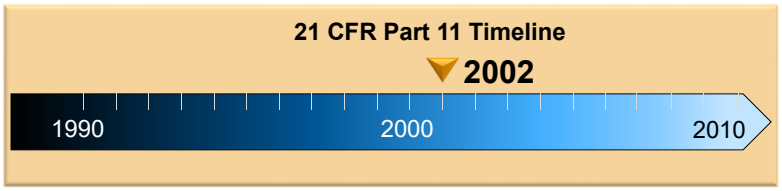
- The FDA published a Compliance Policy Guide (CPG) and drafted Guidance Documents:
  - CPG 7153.17: Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures
  - Guidance: 21 CFR Part 11; Validation
  - Guidance: 21 CFR Part 11; Glossary of Terms
  - Guidance: 21 CFR Part 11; Time Stamps
  - Guidance: 21 CFR Part 11; Maintenance of Electronic Records
  - Guidance: 21 CFR Part 11; Electronic Copies of Electronic Records

Consistent Uncertainty

- In spite of the FDA's efforts, Industry felt that 21 CFR Part 11:
  - Restricted the use of technology
  - Significantly increased the cost of using technology
  - Discouraged innovation and technological advances
  - Failed to provide significant benefit to public health
- Part 11 compliance was also impeding companies from embracing PAT's* beneficial, data centric technologies

* Pat = Process Analytical Technologies (PAT)

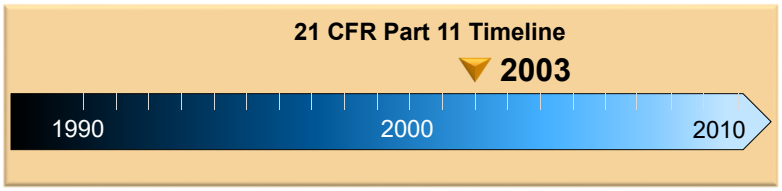
21st Century cGMPs



- The FDA announced a modernization initiative, Pharmaceutical cGMPs for the 21st Century

  … A Risk-Based Approach, to encourage adoption of need technological advances and implement risk based approaches

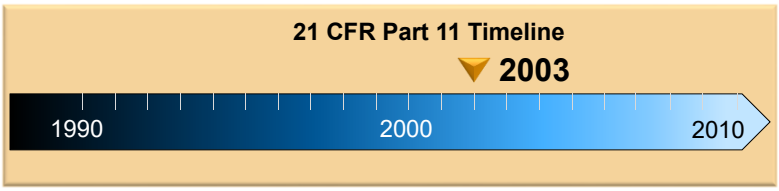
Revocation and Withdrawal



- The FDA revoked CPG 7153.17: Enforcement Policy
- The FDA withdrew the five Part 11 guidance documents

Note: The 21 CFR Part 11 regulation is still in effect!

Re-Examination and Narrow Scope



- FDA Published a new Guidance for Industry titled Part 11, Electronic Records; Electronic Signatures – Scope and Application
  - *Messages:*
    - » Part 11 remains in effect
    - » Part 11 will be re-examined
    - » The FDA will narrowly interpret the scope of Part 11 and apply enforcement discretion during re-examination period

Importance of Part 11

- 21 CFR Part 11 regulations set forth the criteria under which the FDA considers:
  1. electronic records,
  2. electronic signatures
  3. handwritten signatures executed to electronic records

  to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper

- Part 11 was enacted to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine

Benefits of Part 11

- Protection and retrieval of electronic records
- Operational consistency
- Improve productivity and efficiency through automation
- Minimize or eliminate management of paper documentation
- Enable faster data-related searches
- Enable trending
- Electronic submissions to the FDA

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Scope & Applicability

Part 2

Part 2: Scope & Applicability

Section Overview

- Companies that must comply with Part 11
- Predicate rules
- Systems that must comply with Part 11

Companies that Must Comply with Part 11

- Applicable Scope:
  - US-based and international life science companies that are marketing its product(s) in the United States, or supports any domestic or international life science company(ies) that markets or is planning to market its product(s) in the United States

Predicate Rules

Predicate, Foundational, Base, Root

Predicate Rules are the requirements that were already within the FDA's scope of regulations when 21 CFR Part 11 went into effect

Predicate Rule Examples
- 21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceuticals
- 21 CFR 820 Quality System Regulation (Medical Device GMP)
- 21 CFR 600 Biological Products: General
- 21 CFR 606 Current Good Manufacturing Practice for Blood and Blood Components
- 21 CFR 50 Protection of Human Subjects
- 21 CFR 58 Good Laboratory Practice for Nonclinical Laboratory Studies
- 21 CFR 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products

Predicate Rules

The predicate rules regulate processes and records

The predicate rules are the same whether manual or automated, paper or electronic

For example…
If the predicate rule requires 5 year record retention, and you keep the records electronically, the retention rule applies to your computer system's records

OR

If the predicate rule requires 2nd person verification, and you perform the function electronically, then your system must accommodate 2nd person verification

Predicate Rules

21 CFR 211.150 Distribution procedures. Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

(a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

(b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Predicate Rules

Subpart J--Records and Reports
21 CFR Part 211.196 Distribution Records

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.

Subpart J--Records and Reports
21 CFR Part 211.180 General requirements.

(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch.

Scope: Records/Systems

Records/Systems that Must Comply with Part 11

21 CFR 11: Records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency [FDA] regulations.

FDA Clarification – Electronic Records

Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format *in place of paper format.*	Records that are required to be maintained under predicate rules, that are maintained in electronic format *in addition to paper format, and that are relied on to perform regulated activities*	NOTE: Records that are not required to be retained under predicate rules, but that are nonetheless maintained in electronic format, are not Part 11 records

Scope: Signatures

Records/Systems that Must Comply with Part 11

21 CFR 11: Records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency [FDA] regulations.

FDA Clarification – Electronic Signatures

Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. approved, reviewed, and verified).	NOTE: Signatures that are not required to be retained under predicate rules, but that are nonetheless maintained in electronic format, are not Part 11 signatures

Scope: Electronic Submissions

Records/Systems that Must Comply with Part 11

21 CFR 11: Electronic records submitted to the agency under requirements of the *Federal Food, Drug, and Cosmetic Act and the Public Health Service Act*, even if such records are not specifically identified in agency regulations.

FDA Clarification – Electronic Submissions

Part 11 applies to records submitted to the FDA under predicate rules in electronic format.	NOTE: A record that is not itself submitted, but is used in generating a submission, is not a Part 11 record unless it is otherwise required to be maintained under predicate rule and is maintained in electronic format.	NOTE: Part 11 does not apply to paper records that are, or have been, transmitted by electronic means

Scope: Records

Which of these records are in the scope of FDA 21 CFR Part 11?

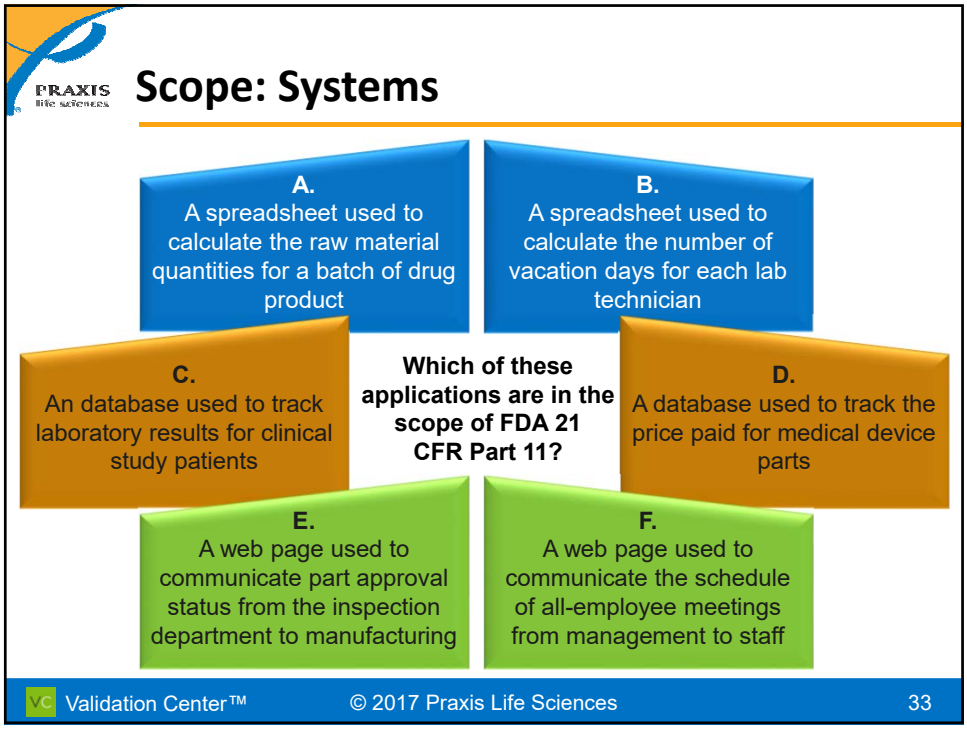
A. Electronic records of training on QA SOPs

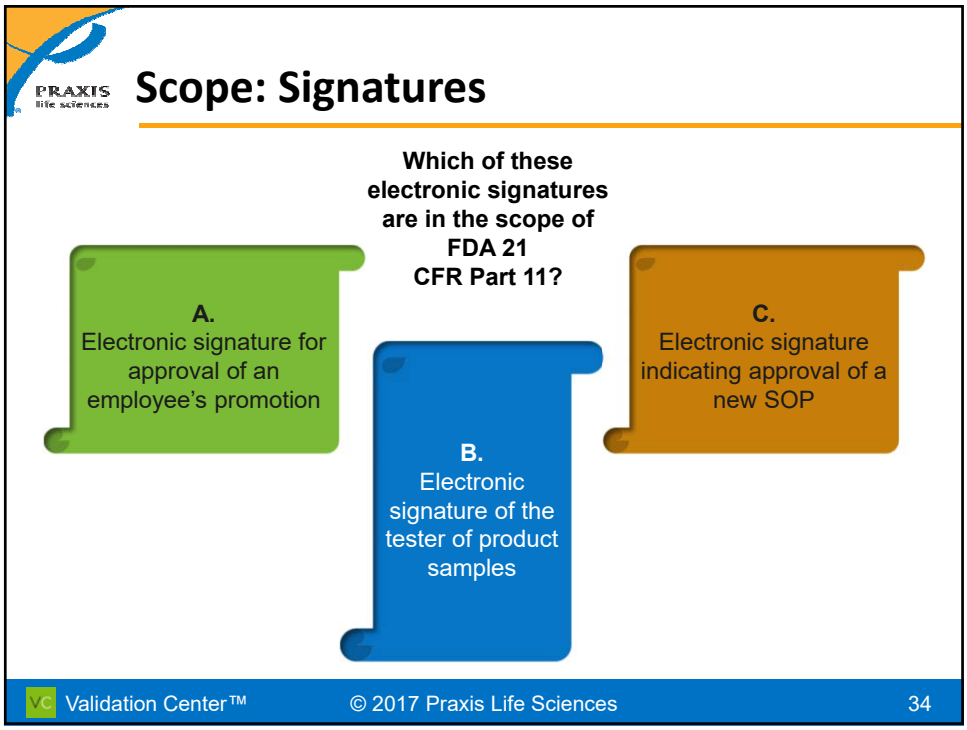
B. Electronic lab notebook records

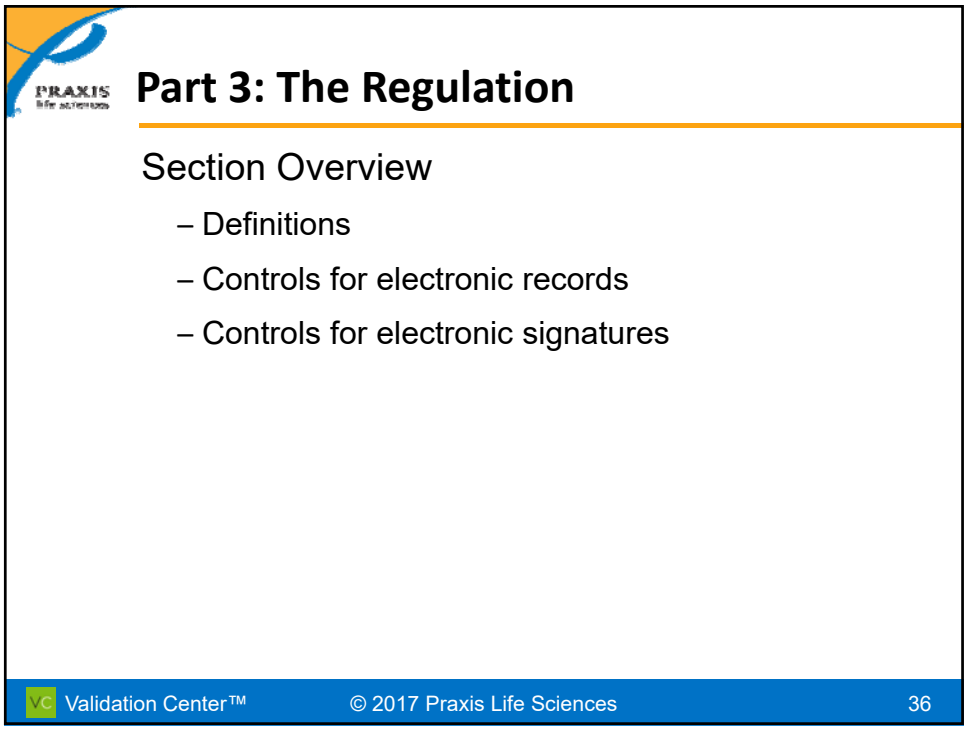
C. Electronic records submitted to the FDA for a New Drug Application (NDA)

D. Paper lab notebook records that are scanned, then sent to the FDA for an NDA

E. Electronic records of product labels







Definitions

Definition 11.3 (b) (4) **Closed System**

An environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.

Definition 11.3 (b) (9) **Open System**

An environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Definition 11.3 (b) (7) **Electronic Record**

Any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

Definitions

Definition 11.3 (b) (7) **Electronic Signature**

A computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

Definition 11.3 (b) (8) **Handwritten Signature**

The scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.

Definition 11.3 (b) (3) **Biometrics**

A method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable

Closed Systems

Controls for Electronic Records in Closed Systems

Electronic Records Controls

Requirement 11.10 (a) **Validation**

Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

Requirement 11.10 (b) **Copies for Review**

The ability to generate accurate and complete copies of record in both human readable and electronic form suitable for inspection, review, and copying by the agency.

Requirement 11.10 (c) **Record Protection**

Protection of records to enable their accurate and ready retrieval throughout the records retention period.

Electronic Records Controls

Requirement 11.10 (d) **Access**

Limiting System access to authorized individuals.

Requirement 11.10 (g) **Authority Checks**

Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

Electronic Records Controls

Requirement 11.10 (e) **Audit Trails**

Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.

Record changes shall not obscure previously recorded information.

Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

NOTE: *Reason for change is not required by Part 11, but in many cases is required by the predicate rule*

Electronic Records Controls

Requirement 11.10 (f) **System Checks**

Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

Enter data → Verify data entry → Route for approval → Report

Receive raw materials → Test materials → Release for use

Requirement 11.10 (h) **Device Checks**

Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

- Access only from appropriate domains
- Input from equipment or instruments

Electronic Records Controls

Requirement 11.10 (j) **Personal Accountability**

The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

Requirement 11.10 (i) **Personnel Qualifications**

Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks

- Review developer, tester, … Curriculum Vitae (resume)
- Require developer training before working on system
- Require user training before using system
- Implement record keeping for these activities

Electronic Records Controls

Requirement 11.10 (k) **Documentation Controls**

Use of appropriate controls over systems documentation including:

(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.

(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems.

Electronic Signatures

Controls for Electronic Signatures

John Hancock

Electronic Signature Controls

Requirement 11.50 (a) **Signature Components**

Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

(1) The printed name of the signer;
(2) The date and time when the signature was executed
(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

Requirement 11.50 (b) **Signature Components**

The items, above, shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

Electronic Signature Controls

Requirement 11.200 (a) **Non-biometric Signatures**

Non-biometric based signatures shall:

(1) Employ at least two distinct identification components such as an identification code and password.

(2) Be used only by their genuine owners.

(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.

Requirement 11.200 (b) **Biometric Signatures**

Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

Electronic Signature Controls

Requirement 11.100 (a) **Uniqueness**

Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

Requirement 11.300 (a) **Uniqueness**

Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

Requirement 11.100 (b) **Personnel Identification**

Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.

Electronic Signature Controls

Requirement 11.300 (b) **Periodic Checks**

Ensuring that identification code and password issuances are periodically checked, recalled, or revised.

Requirement 11.300 (d) **Reporting of Attempted Unauthorized Used**

Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

Electronic Signature Controls

Requirement 11.300 (c) **Compromised Tokens**

Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

Requirement 11.300 (e) **Testing of Tokens**

Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

Electronic Signature Controls

Requirement 11.70 **Signature/Record Linking**

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Electronic Signature Controls

Requirement 11.100 (c) **Certification**

Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.

- One time requirement
- Certifications must be in paper form and signed with handwritten signatures
- Send to ORA/ORO, at 12420 Parklawn Drive, Element Building, Rockville, MD 20857
- ORA/ORO maintains the certification documents in an electronic database

http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm103301.htm

Open Systems

Controls for Electronic Records in Open Systems

Open System Controls

Open System - Definition

An environment where system access is not controlled by persons who are responsible for the content of the electronic records that are on the system

Requirement 11.30 **Open System Controls**

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt.

Open System Controls

Requirement 11.30 **Open System Controls**

Such procedures and controls shall include those identified in 11.10 [closed systems], as appropriate, and additional measures such as

document encryption and
use of appropriate digital signature standards

to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

Open System Controls

Is an Electronic Signature the same as a Digital Signature?

Traditional Electronic Signature

Combines a user's approval with a record or document **within** an electronic system

Digital Signature

- Allows a record or document to be signed by people **without** access to a specific computer system.
- Can also include a graphical image of the physical signature (but does not need to include a graphical image)
- Can use PKI (public key infrastructure) technologies

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The Guidance

Part 4

Part 4: The Guidance

Section Overview

- Guidance History
- Reasons for Guidance
- Enforcement Approach

Part 11 Guidance History

- **1997:** Final 21 CFR Part 11 regulation was published in 1997
- Several detailed FDA guidelines followed
  - E.g., Time Stamps (time zone issues, etc.), COTS software, Audit Trails
- **February 2003:** FDA stunned the industry by announcing that all existing Part 11 guidelines were withdrawn and the agency was re-evaluating the Part 11 regulation.
- **February 2003:** FDA published a new 21 CFR Part 11 Guidance Document

Reasons for New Guidance on Part 11

- **Part 11 was dampening technical progress**
  - Rigorous enforcement and compliance with the requirements was preventing many new applications from seeing the light of day.
  - Industry interpretation was restricting use of electronic technology
- **Part 11 was discouraging adoption of other innovation and technological advances recommended by the FDA**
  - Especially FDA's PAT (Process Analytical Technology) initiative
- **Part 11 was significantly increasing costs**
- **The FDA has said that a new version of Part 11 was coming**
  - (We're still waiting….)

Change of Enforcement

- **FDA intends to enforce predicate rule requirements for records within the scope of 21 CFR Part 11**
- **FDA intends to interpret Part 11 narrowly**
  - Fewer records than originally thought are within the scope of Part 11
  - Records and associated signatures that are not required to be retained by predicate rules are not considered to be within the scope of Part 11
  - If an electronic record is created that is not required by predicate rules to be retained, then Part 11 does not apply (intermediate drafts)
  - If a system is merely incidental to creating another form of the record, then Part 11 does not apply (the typewriter rule – once the letter is typed, no one cares about the typewriter)

Enforcement Discretion

- **FDA will not normally take regulatory action to enforce compliance with the Part 11 requirements for**
  - Validation
  - Audit trail
  - Record retention
  - Record copying requirements

…as long as the electronic records are maintained in accordance with the underlying regulatory requirements (a.k.a. the Predicate rules)

Enforcement Discretion

- **FDA will not normally take regulatory action to enforce compliance with the Part 11 requirements for**
  - Validation
  - Audit trail
  - Record retention
  - Record copying requirements

…as long as the electronic recor th the underlying regulatory requiremer (a.k.a. the Predicate rules)

The FDA recommends that that your decision to validate computerized systems, and the extent of the validation, take into account the impact the systems have on your ability to meet predicate rule requirements.

You should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures.

Enforcement Discretion

- **FDA will not normally take regulatory action to enforce compliance with the Part 11 requirements for**
  - Validation
  - Audit trail
  - Record retention
  - Record copying requirements

…as long as the electronic recor he underlying regulatory requiremer (a.k.a. the Predicate rules)

The FDA recommends that you base your decision on whether to apply audit trails on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity.

Enforcement Discretion

- **FDA will not normally take regulat with the Part 11 requirements for**
  - Validation
  - Audit trail
  - Record retention
  - Record copying requirements

…as long as the electronic records a underlying regulatory requirements (a.k.a. the Predicate rules)

The FDA recommends that your decision on how to maintain records be based on predicate rule requirements and that you base your decision on a justified and documented risk assessment and a determination of the value of the records over time.

The FDA does not intend to object if you decide to archive required records in electronic format to non-electronic media such as microfilm, microfiche, and paper, or to a standard electronic file format (examples of such formats include, but are not limited to, PDF, XML, or SGML).

Enforcement Discretion

- **FDA will not normally take regulatory action to enforce compliance with the Part 11 requirements for**
  - Validation
  - Audit trail
  - Record retention
  - Record copying requirements

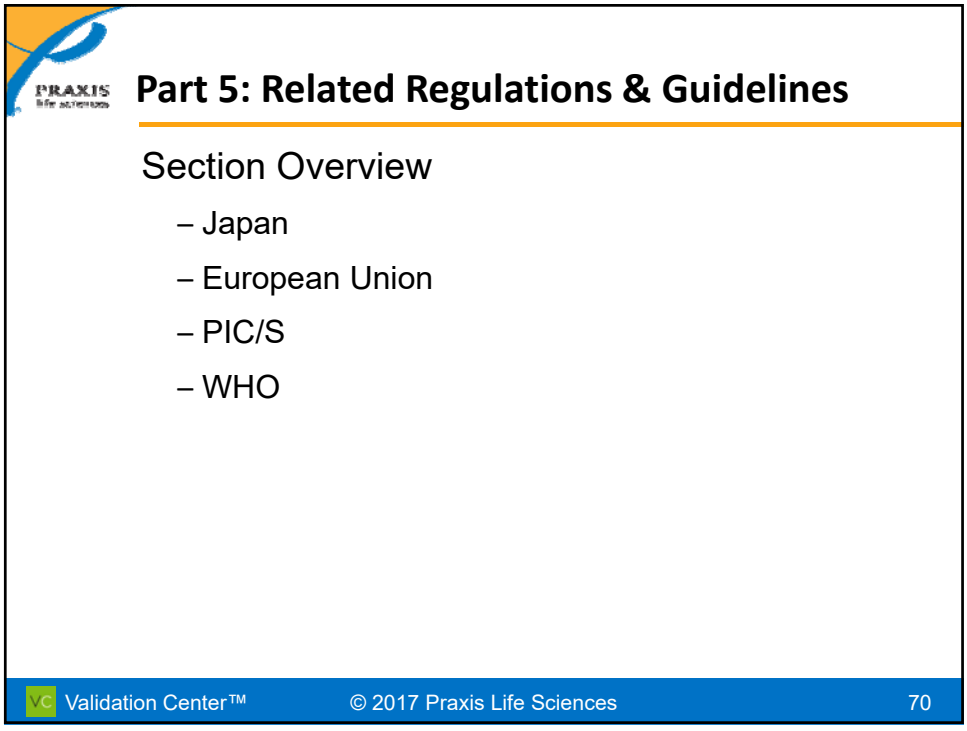
…as long as the electronic record… underlying regulatory requirement… (a.k.a. the Predicate rules)

The FDA recommends that you supply copies of electronic records by:

- Producing copies of records held in common portable formats when records are maintained in these formats
- Using established automated conversion or export methods, where available, to make copies in a more common format (examples of such formats include, but are not limited to, PDF, XML, or SGML).

Intent to Enforce

- **FDA intends to enforce provisions related to the following controls**
  - Limiting system access to authorized individuals
  - Use of operational system checks
  - Use of authority checks
  - Use of device checks
  - Determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
  - Establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
  - Appropriate controls over systems documentation
  - Controls for open systems
  - Controls for Electronic Signatures



Japan

Ministry of Health, Labour and Welfare of **Japan**

Guideline on Management of Computerized Systems for Marketing Authorization Holders and Manufacturers of Drugs and Quasi-drugs

Examples

- The Marketing Authorization Holder should establish fundamental policies on development, validation, and operations management of the computerized systems, and…
- Provide education and training plan for persons engaged in the activities using the computerized system
- Configure access privileges of persons in charge of input, modification, deletion, etc. of data and to take preventive actions against unauthorized accesses
- Backup the software and the data

European Union

Eudralex: The Rules Governing Medicinal Products in the European Union

European Union members include

Austria	Germany	Netherlands
Belgium	Greece	Poland
Bulgaria	Hungary	Portugal
Croatia	Ireland	Romania
Cyprus	Italy	Slovakia
Czech Republic	Latvia	Slovenia
Denmark	Lithuania	Spain
Estonia	Luxembourg	Sweden
Finland	Malta	United Kingdom
France		

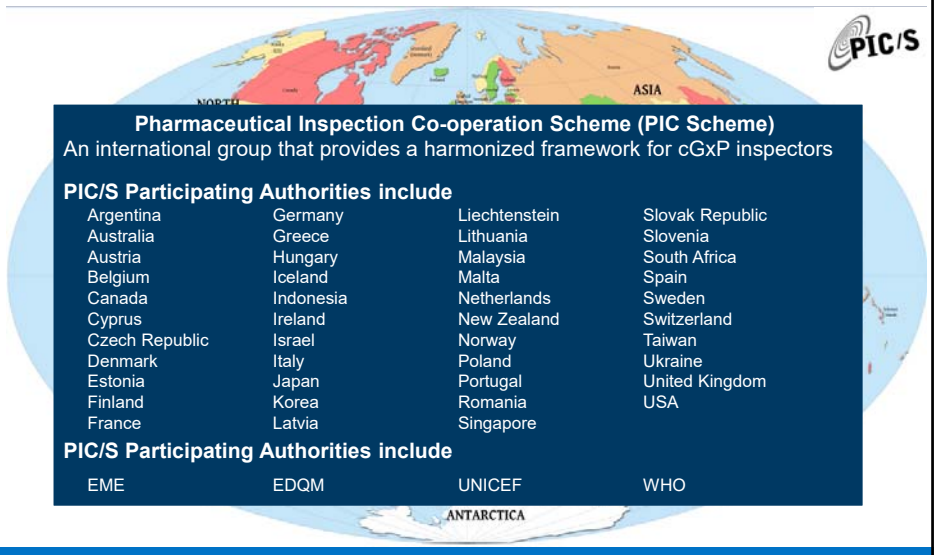
European Union

Volume 4: *Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use* **Annex 11:** *Computerised Systems*

Examples

- Electronic signatures are expected to (a) have the same impact as hand-written signatures (b) be permanently linked to their respective record (c) include the time and date that they were applied.
- Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.
- The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.

PIC/S



Pharmaceutical Inspection Co-operation Scheme (PIC Scheme)
An international group that provides a harmonized framework for cGxP inspectors

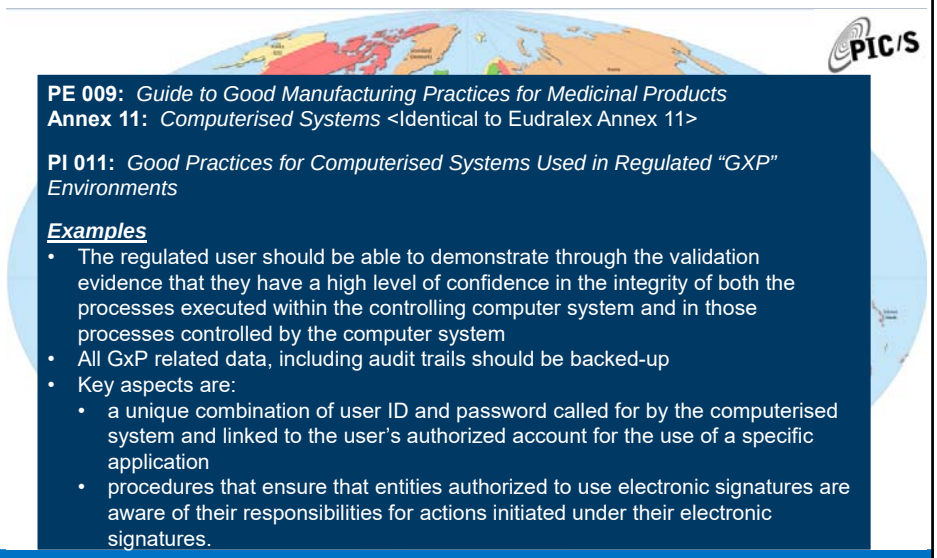
PIC/S Participating Authorities include

Argentina	Germany	Liechtenstein	Slovak Republic
Australia	Greece	Lithuania	Slovenia
Austria	Hungary	Malaysia	South Africa
Belgium	Iceland	Malta	Spain
Canada	Indonesia	Netherlands	Sweden
Cyprus	Ireland	New Zealand	Switzerland
Czech Republic	Israel	Norway	Taiwan
Denmark	Italy	Poland	Ukraine
Estonia	Japan	Portugal	United Kingdom
Finland	Korea	Romania	USA
France	Latvia	Singapore	

PIC/S Participating Authorities include

EME	EDQM	UNICEF	WHO

PIC/S



PE 009: *Guide to Good Manufacturing Practices for Medicinal Products*
Annex 11: *Computerised Systems* <Identical to Eudralex Annex 11>

PI 011: *Good Practices for Computerised Systems Used in Regulated "GXP" Environments*

Examples

- The regulated user should be able to demonstrate through the validation evidence that they have a high level of confidence in the integrity of both the processes executed within the controlling computer system and in those processes controlled by the computer system
- All GxP related data, including audit trails should be backed-up
- Key aspects are:
  - a unique combination of user ID and password called for by the computerised system and linked to the user's authorized account for the use of a specific application
  - procedures that ensure that entities authorized to use electronic signatures are aware of their responsibilities for actions initiated under their electronic signatures.

WHO

World Health Organization

WHO membership includes: international regulatory agencies, EU, IFPMA, IGPA, IPEC, PIC/S, UNICEF, BSP and USP

WHO Expert Committee Report on Specifications for Pharmaceutical Preparations

Examples

- If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer,
- There should be a record of changes and deletions
- Access should be restricted by passwords or other means
- Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means.
- It is important that, during the period of retention, the data are readily available.

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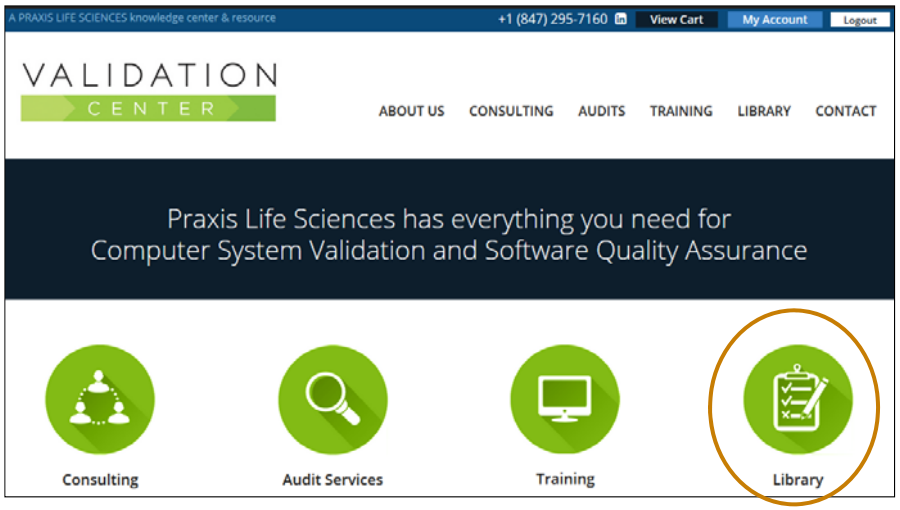

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Spreadsheet Challenges

Part 6

78

Part 6: Spreadsheet Challenges

Section Overview

- Easily Met Part 11 Requirements
- More Challenging Part 11 Requirements
- Difficult Part 11 Requirements

Easy to Meet Part 11 Requirements

Part 11 E-Record Requirement:

" Controls shall include…

- Validation

  11.10(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

- Documentation

  11.10(k) Use of appropriate controls over systems documentation including:

  (1) Distribution of, access to, and use of documentation for system operation and maintenance.
  (2) Change control procedures to maintain an audit trail that documents time-sequenced development and modification

- Record Protection

  11.10(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

Easy to Meet Part 11 Requirements

Part 11 E-Record Requirement:

" Controls shall include…

• Sequencing Functionality	11.10(f) Use of operational system checks to enforce permitted sequencing of steps and events.
• Training	11.10(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.
• Copies	11.10(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the [FDA] agency.
• Accountability	11.10(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

More Challenging Part 11 Requirements

Part 11 E-Record Requirement:

" Controls shall include…

11.10(d) Limiting system access to authorized individuals.

11.10(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

Spreadsheet Compliance Tactics

- Limit access by keeping spreadsheet in secured folder, doc management system, etc.
- Use the capabilities of the network, document management system, etc. to check authorization to input or alter a record
- Can also password protect spreadsheets and cells

Difficult Part 11 Requirements

Difficult due to lack of security features

Part 11 E-Record Requirement:

" Controls shall include…

11.200(a) Electronic signatures not based upon biometrics shall:

(1) Employ at least two distinct identification components such as an identification code and password.
(2) Be used only by their genuine owners;
(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration.

11.100(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

11.300(a) Maintain the uniqueness of each combined identification code and password, such that no two individuals have the same combination.

11.70 Electronic signatures shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or transferred to falsify an electronic record by ordinary means

Difficult Part 11 Requirements

Difficult due to lack of security features

Part 11 E-Record Requirement:

" Controls shall include…

11.300(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised.

11.300(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

11.50(1) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
(1) The printed name of the signer;
(2) The signature date and time
(3) The meaning of the signature

11.50(b) The items, above, shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

Difficult Part 11 Requirements

Difficult due to lack of audit trail features

Part 11 E-Record Requirement:

" Controls shall include…

11.10(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.

Record changes shall not obscure previously recorded information.

Audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copy

Spreadsheet Compliance Tactics

- Very difficult requirement for spreadsheets – no audit trails
- For very simple (single record) spreadsheets, could use a document management system with versioning

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FDA Enforcement

Part 7

86

Part 7: FDA Enforcement

Section Overview

- Enforcement of Part 11 Topics
- Warning Letter Examples

FDA Warning Letter Example

Audit Finding

4. Your firm has failed to exercise appropriate controls over computer or related systems to assure that changes in master production and control records, or other records, are instituted only by authorized personnel [21 CFR 211.68(b)].

For example:

a. Your firm did not put in place requirements for appropriate usernames and passwords to allow appropriate control over data collected by your firm's computerized systems including UV, IR, HPLC, and GC instruments. All employees in your firm used the same username and password. In addition, you did not document the changes made to the software or data stored by the instrument systems. Without proper documentation, you have no assurance of the integrity of the data or the functionality the software used to determine test results.

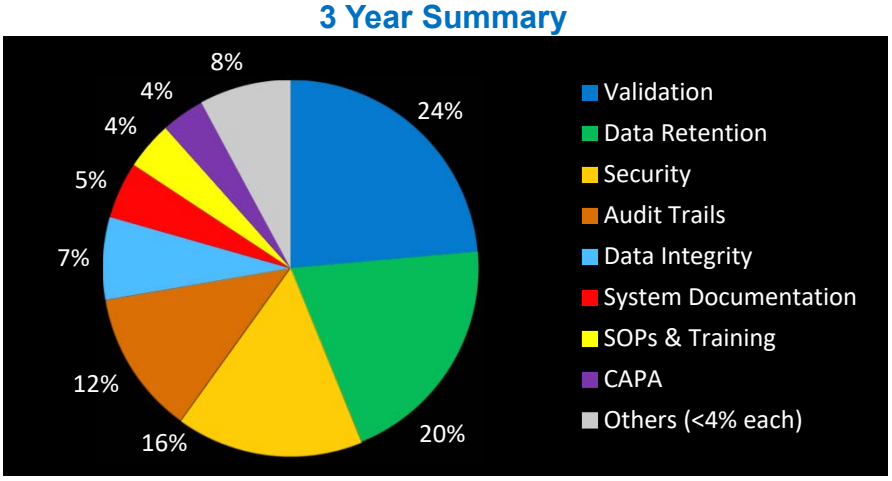
b. Your firm had no system in place to ensure appropriate backup of electronic raw data and no standard procedure for naming and saving data for retrieval at a later date.

Observations

Enforcement Data Review

- The FDA Letters related to Software and Computers
- 3 Year Date Range: 2014 through 2016
- Summarized by topic

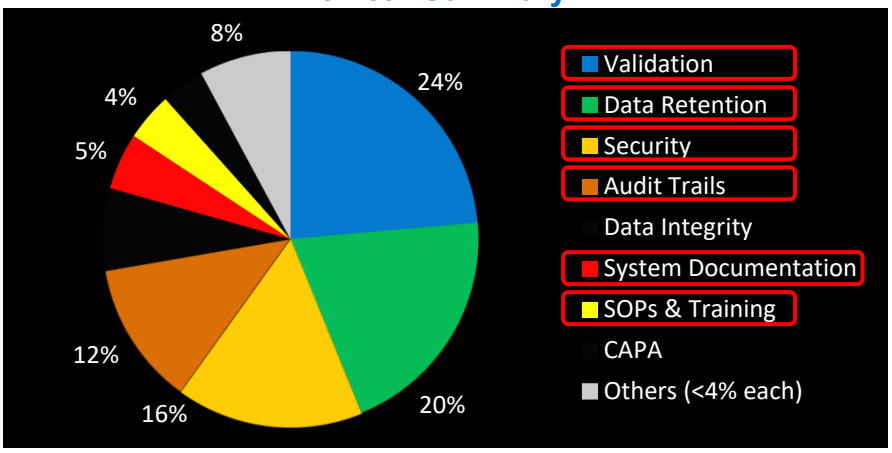
Software & Computer Warning Letters



"Other" observation topics include Change Control, Suitability for Use, Quality Oversight, Risk Analysis, Electronic Signatures, Vendor Management, and Data Accuracy

Software & Computer Warning Letters

3 Year Summary



"Other" observation topics include Change Control, Suitability for Use, Quality Oversight, Risk Analysis, Electronic Signatures, Vendor Management, and Data Accuracy

Warning Letter Excepts

24%

VALIDATION

- Software used to set specifications was not validated
- The assay results generated by the spreadsheet were not verified for accuracy. Company continued to release products based on results generated by the spreadsheet that have not been verified.
- Validation testing did not include verification of file backup and restoration
- Firm did not maintain documentation of the validation of the computer software used to (a) receive encrypted patient treatment data and decrypt/encrypt it; (b) convert decrypted patient data into codes that are sent to your contract manufacturer's milling machines to produce compensators
- Company did not ensure that its design verification and validation process detected design discrepancies causing memory error codes and data corruption

Warning Letter Excepts

DATA RETENTION — **20%**

Firm lost its entire electronic complaint database due to a hardware failure. Firm failed to maintain back-up procedures for saving or restoring electronic complaint records.

During the inspection, you stated that the source documents were not available because the computer "crashed."

Quality unit personnel informed the investigators that the computer software was upgraded and the raw data was lost during the software upgrade. We [FDA] have serious concerns about your firm's implementation of changes to your computerized systems (e.g., software upgrade).

Your firm fails to maintain a backup file of data entered into the computer system. During the inspection, you informed our investigators that electronic raw data would not exist for most HPLC assays over two years old because data is not backed up and storage space is limited. Data is deleted to make space for the most recent test results.

Warning Letter Excepts

SECURITY — **16%**

…. failed to implement an adequate system for authorizing, granting, and rescinding computer access to functions in the XXXXXXXX and adequate computer security provisions to assure data integrity. Current users do not use appropriate access such as passwords and user-id and personnel who have changed jobs still have access to the system .

Laboratory Managers (QC and R&D) gained access to the XXXXXXXX computer system through a common password. Analysts …. operated the system following the login by laboratory managers.

System administrator privileges … include the ability to modify and delete raw data files and to lock/unlock projects for reprocessing in the chromatographic data acquisitions system. Our [FDA] investigators documented numerous instances where these privileges were reassigned without documentation or justification some of which resulted in extensive manipulation of data.

Warning Letter Excepts

AUDIT TRAILS — **12%**

Your system does not have an audit trail to document changes.

Changes in study data could not be detected as there was no audit trail.

This system does not include an audit trail or any history of revisions that would record any modification or deletion of raw data or files. Your laboratory computer system lacks necessary controls to ensure that data is protected from tampering, and it also lacks audit trail capabilities to detect data that could potentially be compromised.

Review of audit trails is not required.

There is no specific requirement regarding any review of the audit trails. Such an audit may well have detected the date manipulation which was occurring at your facility.

Warning Letter Excepts

SYSTEM DOCUMENT-ATION — **5%**

There are no written procedures describing computer software functional requirements or description of functions, and there is no computer manual.

There is no written procedure describing the deviation types currently existing in the deviation report database. Furthermore, you have not documented the changes made to the drop down list tables.

Design changes have not been documented. For example, the change from using a serial port to using a USB port on the printed circuit board for connecting the measurement device to a computer has not been documented.

Firm updated the Sorting software to address a “glitch” when sorting brachytherapy seeds and their respective activity into properly labeled containers. There are no procedures or documents that describe changes and version updates to the Sorting software. There are no documents that define the software's features and functions, operating environment, or hardware requirements.

Warning Letter Excepts

4%

SOPs & TRAINING

Procedures for entering critical comments were inadequate.

CAPA procedures did not describe use of an electronic system.

The adverse drug experience reporting system has not been fully validated because the application was released into production using an Interim Validation Report (IVR) that is still not final. Critical issues (deviations) identified in your interim validation report include the following: lack of training for your system support team, incomplete SOPs and Work Instructions.

Computer System is incomplete because it fails to provide detailed instructions to ensure correct specimen identification. A technician identified the specimen by scanning the barcode on the collection record instead of the barcode on the specimen. Consequently an incorrect blood group was entered into the database and the patient received incompatible red cells.

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Ensuring Compliance

Part 8

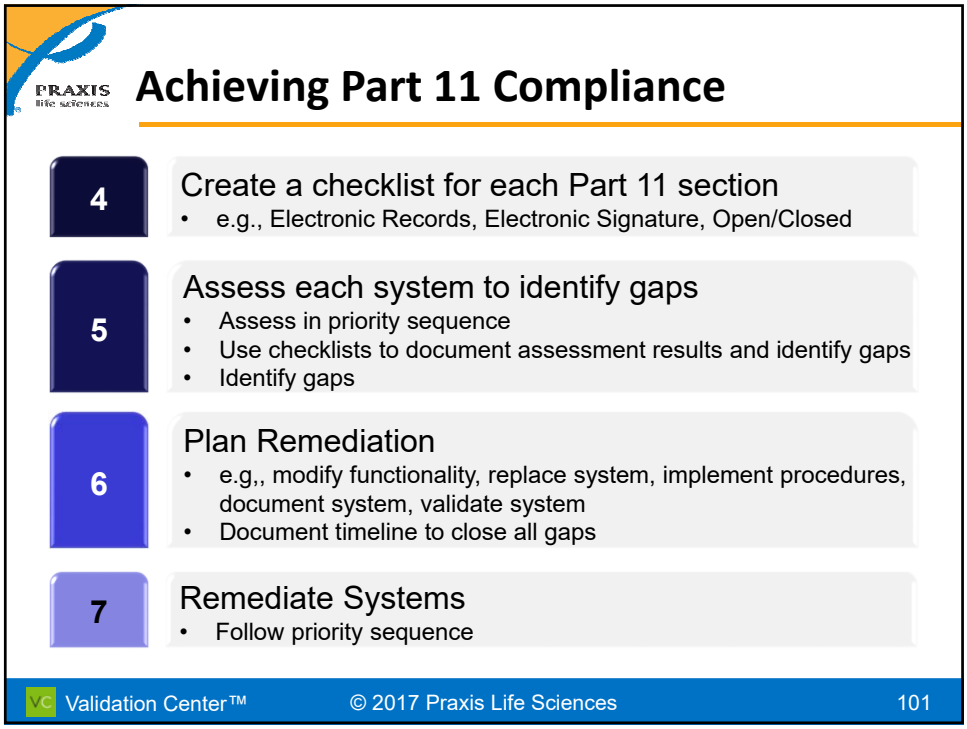
Part 8: Ensuring Compliance

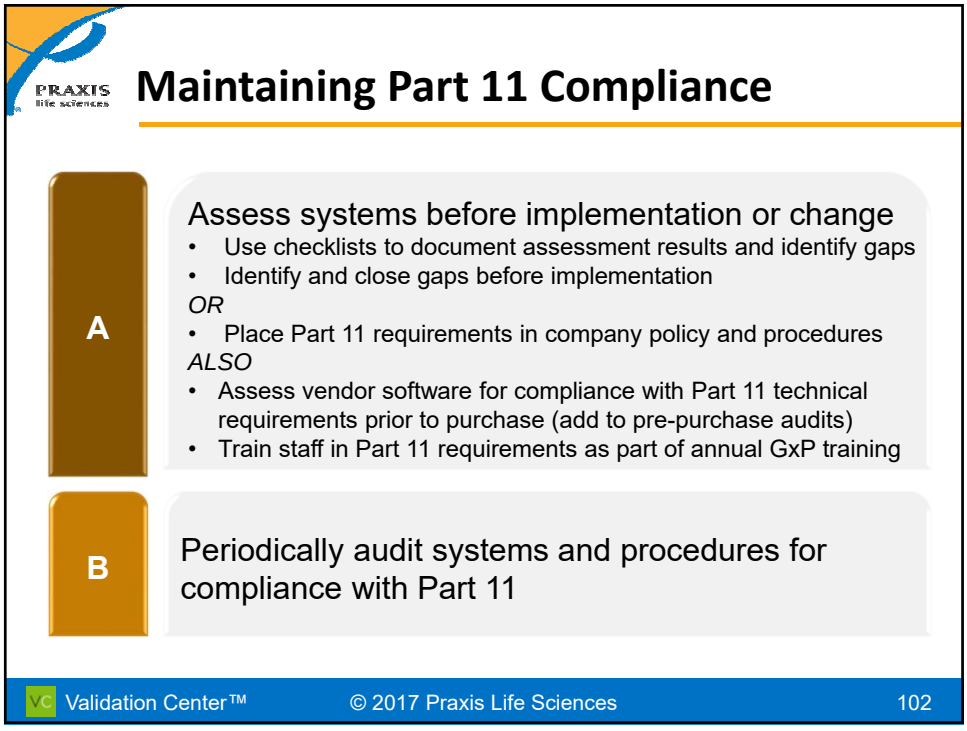
Section Overview

- Achieving Compliance
- Maintaining Compliance

Achieving Part 11 Compliance

1. Inventory All Systems
2. Review each system to identify which Part 11 sections apply
   - e.g., Electronic Records, Electronic Signature, Open/Closed, Does not Apply
   - Refer to FDA Guidance on Part 11 scope; Refer to predicate rules
   - Document decision for each system
3. Prioritize systems
   - Top Priority: systems with direct impact on patient health/safety, systems with direct impact on product quality
   - Lower Priority: systems with indirect impact on patients, products





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Future of Part 11

Part 9

103

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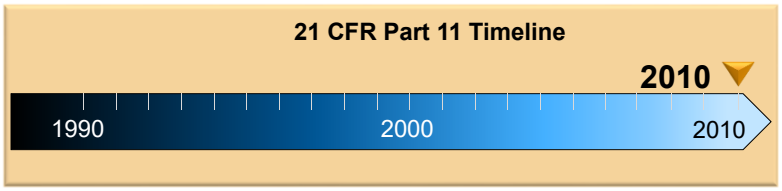
FDA Announcement



FDA To Conduct Inspections Focusing on 21 CFR 11 (Part 11) requirements relating to human drugs

Announcement

The Agency (FDA) will be conducting a series of inspections in an effort to evaluate industry's compliance and understanding of Part 11 in light of the enforcement discretion described in the August 2003 'Part 11, Electronic Records; Electronic Signatures — Scope and Application' guidance (Guidance). The Agency intends to take appropriate action to enforce Part 11 requirements for issues raised during the inspections that do not fall under the enforcement discretion discussed in the Guidance.

FDA Announcement Update

The 21 CFR part 11-focused inspections are currently being performed and, where necessary, compliance issues brought to the attention of company management in the form of FDA-483 observations and, when applicable, warning letters.

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm204012.htm

Possible Outcomes

- Amendment of 21 CFR Part 11
- Amendment or revocation of the current 21 CFR Part 11 guidance
- Additional 21 CFR Part 11 guidance
- Amendment of the FDA inspection policies and guides that contain outdated interpretations of Part 11 requirements

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Validation Services

Audit Readiness Assessments

Thank You!

Thanks for your interest in 21 CFR Part 11

Any questions about what we have discussed today?
Please, feel free to contact me:

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