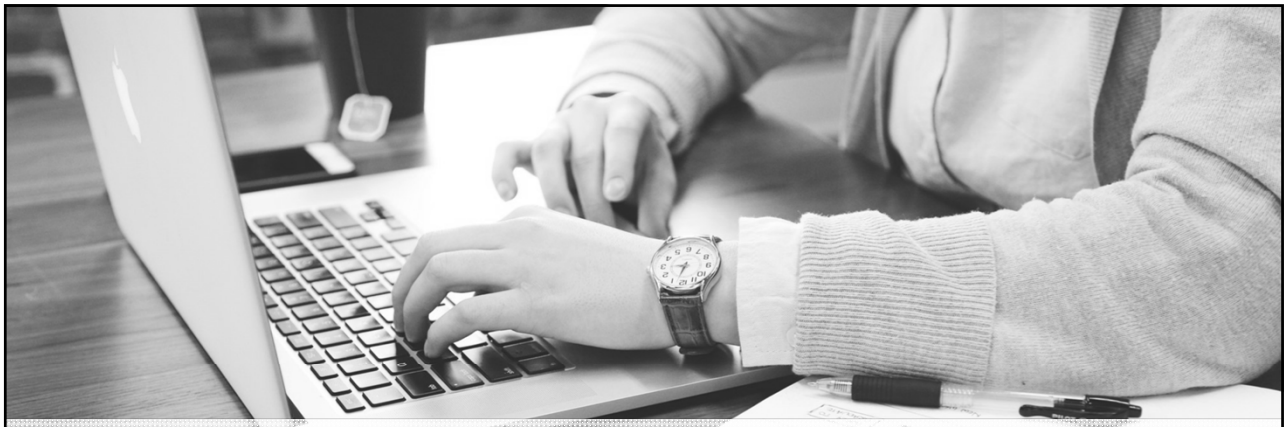

Facilitating Compliance with 21 CFR Part 11

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Disclosure

MICHAEL HURLEY
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Complion, Inc.

I have no relevant financial relationship(s) in connection with this educational activity.

Learning Objectives

To better understand…

- ✓ The purpose and scope of 21 CFR Part 11
- ✓ The intent and process to perform a 21 CFR Part 11 compliance validation audit
- ✓ Organizational best practices to expand awareness

Audience Poll

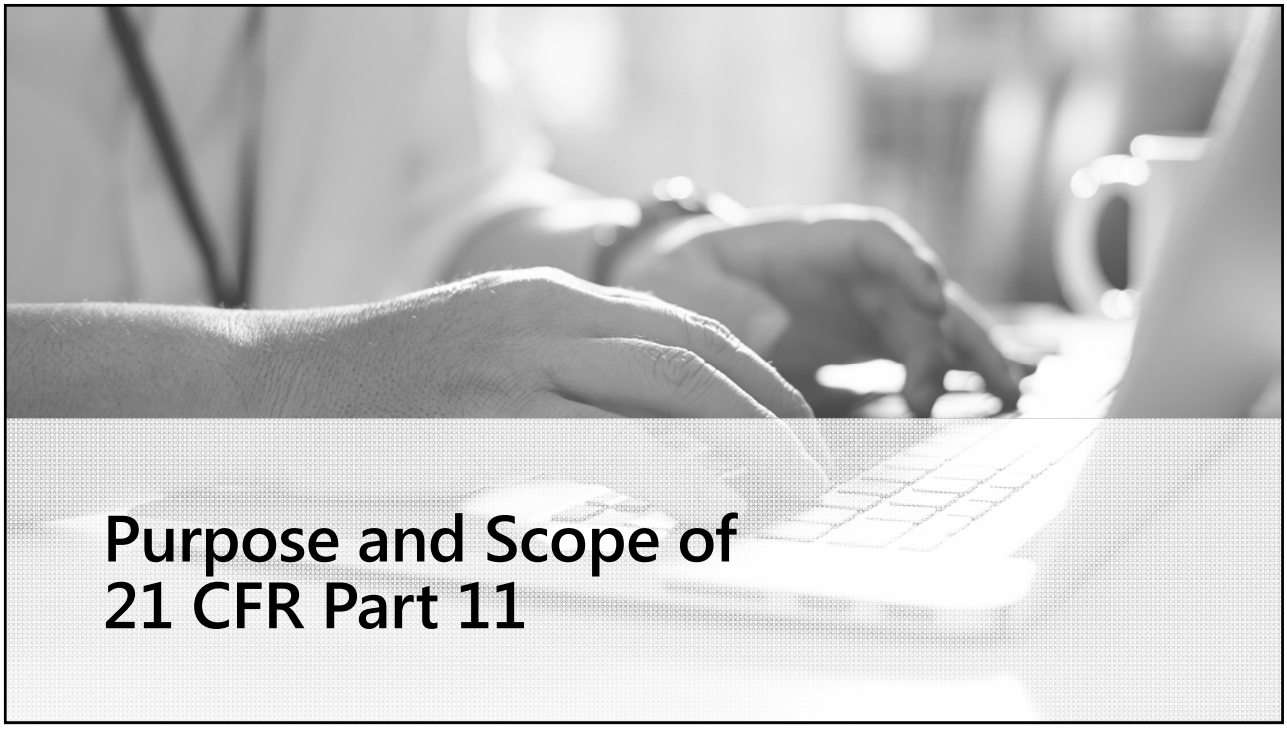
Please stand if your answer is "yes" to any of the following scenarios at your site:

- Do you utilize a fully electronic system (e.g. shared network drive, CTMS, EMR or eReg) as the source of the truth or auditable copy?
- Do you use an electronic system as the source of the truth or auditable copy of documents that do not require signature? For example, documents are stored only electronically and during an audit, you provide a USB to monitors and print-outs for the FDA.
- Do you post to or reference study documents (e.g ICF, protocol, case histories) in a shared drive, CTMS or other electronic system?

Audience Poll

For everyone standing, please sit if your answer is "yes" to ALL of the following:

- Per the new requirement in GCP R2, do you define or maintain a record of the location(s) of your essential documents (e.g. do you define that the auditable copy resides in a specific electronic system or paper binder)?
- Do you have a written plan for Part 11 compliance (identifying the risks, system features to support requirements, and system roles)?
- Do you identify and document how the system is to be used?
- Do you provide training to your staff on how to use the system?
- Do you have a plan to document validation of the system?



Purpose and Scope of 21 CFR Part 11

What is 21 CFR Part 11?

- Title 21 - Food and Drugs
- Code of Federal Regulations
- Part 11 establishes the FDA's requirements for electronic records and electronic signatures

What Does Part 11 Govern?

Electronic records:
- Controls for closed/open systems
- Signature manifestations
- Signature/record linking

Electronic signatures:
- General requirements
- Components and controls
- Controls for codes/passwords

What Documents are in Scope?

- Documents associated with Predicate Rules
- Example: 21 CFR 312.62 is the FDA's IND regulation that spells out an investigator's recordkeeping and record retention requirements:

> *Investigators must maintain records of drug disposition and case histories for each individual administered the investigational drug*

- If a research site keeps and relies on an electronic case history then that document is within scope of Part 11

Part 11 ICH GCP Guidance

ICH GCP Guidance

- International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP)

GCP Addendum – ICH GCP E6 (R2)

- Accounts for modernization within clinical trial practice, including advances in technology
- Now includes specific requirements for demonstrating validation of electronic trial data systems

Considered guidance by the FDA

- Often a requirement by sponsors

Myth Busters

- Part 11 doesn't apply to our site because we don't use electronic signatures. Instead, we use wet signatures and then scan our study records
- Our site avoids Part 11 because we print out and store a hard copy version of our study files
- We are compliant with Part 11 because we use an outsourced electronic case management system
- Part 11 compliance is more critical for Sponsors and IRBs than research sites

Does Part 11 Apply to My Site?

Part 11 applies to your site if you rely on electronic records or electronic signatures to meet an FDA requirement.

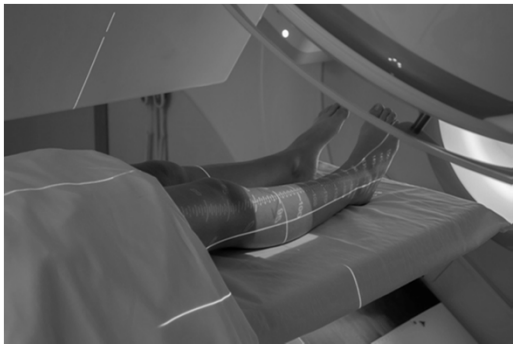
Does Part 11 Apply to My Site?

- There is another FDA requirement to maintain records ("predicate rule")
- You choose to meet this requirement by keeping electronic records
- You use electronic signatures to document that certain events or actions occurred
- You are submitting electronic records to the FDA

Risks of Non-Compliance

Non-Compliance Consequences

- Patient safety risks and privacy violations
- "Killer" software bugs
  - Eligibility
  - Dosage
  - Drug administration history
- Faulty software can cause injury or death



Site Ramifications

- FDA Form 483
- FDA Warning Letters
- Damaged reputation
- Lost business
- Breach of contract
- Product recall
- Debarment

Computer System Validation

Validation

FDA

Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled. (21 CFR 820.3)

ICH-GCP

Validation of computerized systems is a process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. (ICH-GCP E6 (R2) 1.65).

Who is responsible for validation?

- If you keep electronic records, the research site is responsible for Part 11 compliance
- Regardless of whether or not you use an in-house or vendor system

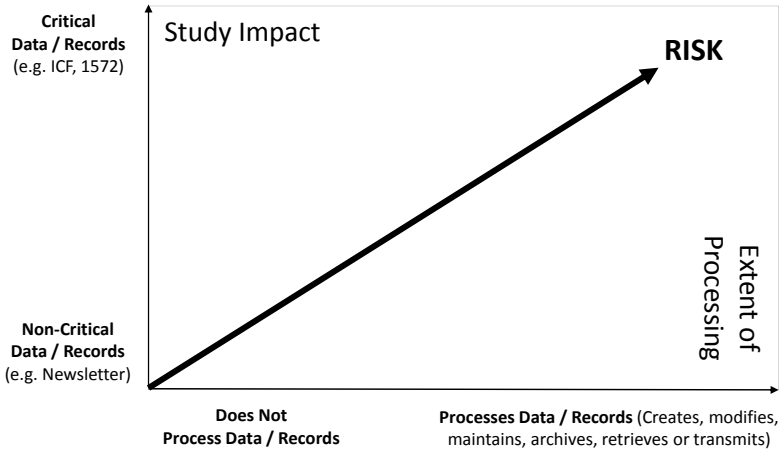
Myth Busters

- Our site does not need to worry about validation because we only use an internal network server, not an electronic cloud-based platform
- Our vendor told us they are Part 11 compliant and provided a letter of compliance, so we do not need to conduct a vendor audit
- My sponsor provided me with a system, so it's already Part 11 compliant.
- We have electronic records but since the official/inspectable version is paper, Part 11 does not apply
- Our IT team takes care of Part 11 compliance (like HIPAA)

Leverage a Risk-Based Approach

- The extent of validation depends on a risk assessment – the impact a system may have on
  - Product quality
  - Patient safety
  - Record integrity
- An electronic system should be validated if those systems process critical records that are submitted to the FDA

A Risk-Based Approach



The extent of validation should be tailored to the nature of the system, its intended use, and the potential of the system to affect product quality, safety, and record integrity.

A Risk-Based Approach

The extent of validation depends on a risk assessment – the impact a system may have on product quality, patient safety, and record integrity.*

An electronic system should be validated if those systems process critical records that are submitted to the FDA.**

*FDA Guidance, Part 11, Electronic Records; Electronic Signatures – Scope and Application (April 2003)

**FDA Draft Guidance, *Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers* (June 2017)

Core Components

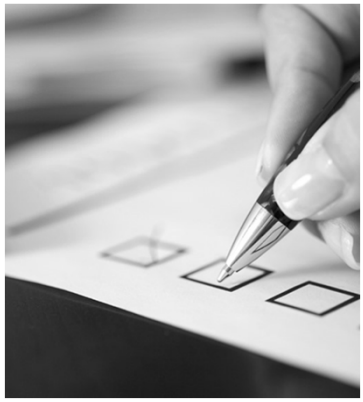
- Policies & Procedures
- System Functionality Review
- Training
- Validation

Policies & Procedures

Policy	Description
Vendor Selection/Audit	Outlines the procedures of performing vendor audit to ensure software providers are selected based on their capability to provide quality software and documentation for system validation.
Records Management	Outlines required records and the corresponding system of truth as well as how and who will be managing documents Including Certified Copies, Retention, and Accessibility.
Software Implementation and Maintenance	Outlines initial Validation, User Acceptance Testing (UAT), ongoing Maintenance and Change Control procedures.
Electronic Signature Policy	Attests that users understand that their electronic signature holds them accountable. Note, a letter of Non-Repudiation Agreement for digital signatures must be submitted to the FDA prior to change. (Citation: FDA - Letters of Non-Repudiation Agreement)
Training	Ensure users have adequate training and agree to terms of using the system.

System Functionality Review

- ❑ Intended use
- ❑ Export throughout the retention period
- ❑ Audit trails
- ❑ Prevention of unauthorized access
- ❑ Statement of Testament associated with Signature
- ❑ Electronic manifestation of Signature
- ❑ Linking of signature to the record



Training

- Training on how to use system
  - Best practice: Training integrated within system
- System updates
  - Part 11 or non Part 11 updates
  - Frequency
- Documentation of training

Demonstrating Part 11 Validation

1. Develop and document a validation plan
2. Follow the validation plan
3. Document the validation results

*Validation is a **process**, not a feature*

Performing Validation

Requirements
- What the system needs to do
- Inclusive of Part 11 and Predicate requirements

Functional Specifications
- How the system will meet the requirements

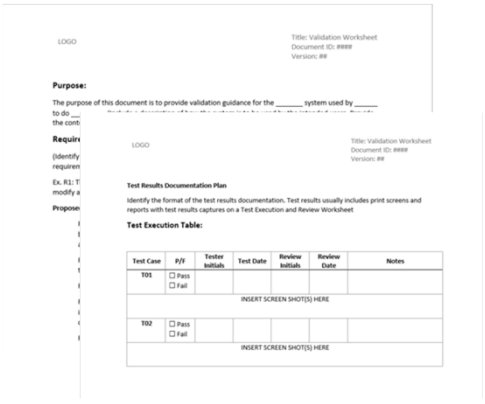
Test Cases
- Specific tests to ensure it can do what it's supposed to do

Required Documents

Documentation for FDA:
- Validation Records for every release (including Installation Qualification for onsite software)
- eSignature Certification Letter (i.e. FDA Letter of Non-Repudiation)

Internal SOPs and Policies:
- User Training Records
- eSignature Policy Attestations

Vendor Documentation (if using a third-party vendor):
- Vendor Qualification / Audit Records
- Vendor Service Agreement and Other Procedures / Agreements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Purpose:

The purpose of this document is to provide validation guidance for the _____ system used by _____ to do _____ the cont

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Test Results Documentation Plan

Identify the format of the test results documentation. Test results usually includes print screens and reports with test results captures on a Test Execution and Review Worksheet

Test Execution Table:

Test Case	P/F	Tester Initials	Test Date	Review Initials	Review Date	Notes
T01	☐ Pass ☐ Fail					
INSERT SCREEN SHOT(S) HERE						
T02	☐ Pass ☐ Fail					
INSERT SCREEN SHOT(S) HERE						

Validation Process Considerations

- Identify the extent of validation based on a risk assessment (e.g. not every combination needs to be tested)
- Send requirements to IT or vendors to confirm if they can meet Part 11 compliance and required features
- IT and vendors can produce several options of spec's based on your req's
- Factor in time for configuration / setup, pre-testing to ensure no bugs and dry run prior to validation
- Have a second verifier to review test case acceptance

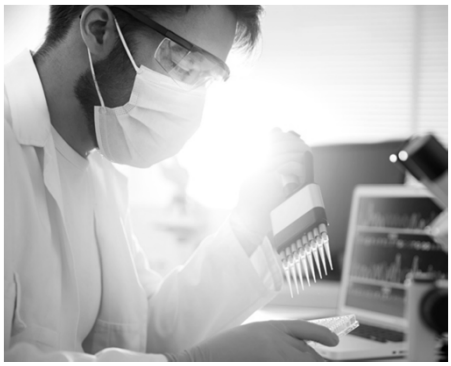
Best Practices

Expanding Organizational Awareness

- Educate organizational stakeholders on Part 11
- Clarify what Part 11 is and is not
  - Is a combination of SOP, training, technology
  - Not just an IT or IT system responsibility
  - Not an IT vendor responsibility
- Define roles and responsibilities for your site

Facilitating Compliance

- Identify which systems fall under Part 11
- Develop a risk based approach for validation
- Build a plan to perform validation
- Perform validations as needed



Questions to Ask Internal IT or Vendor

- Who should be involved and what are the responsibilities of research, internal IT and/or vendor?
- How do they identify what requires validation?
- How often will re-validation occur?
- What does the communication & planning process look like?
- How will training materials and support be modified/updated?

Preparing for an Audit / Qualification

- Preparation and organization is key
- What documentation will you initially provide?
- Ensure a line of communication from central compliance team and site coordinator
- Answer questions directly, don't provide more than asked

In Conclusion

- Discussed the purpose and scope of 21 CFR Part 11
- Defined how to perform a Part 11 compliance audit
- Reviewed organizational best practices to expand awareness

Additional Resources

- FDA Guidance, Part 11, Electronic Records; Electronic Signatures – Scope and Application (April 2003) https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm125125.pdf
- FDA Draft Guidance, Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers (June 2017) https://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/proposedregulationsanddraftguidances/default.htm
- Researcher, Ensuring Compliance with Part 11: A Site's Perspective (April, 2017) http://resources.complion.com/clinical-researcher-ensuring-compliance-with-part-11
- Webinar, Document Management Success: A Guide to Part 11 System Validation (June, 2017) http://resources.complion.com/document-management-part-11-system-validation
- Webinar, Demystifying the Cloud with 21 CFR Part 11 Compliance (March, 2017) http://resources.complion.com/demystifying-the-cloud-with-21-cfr-part-11-compliance