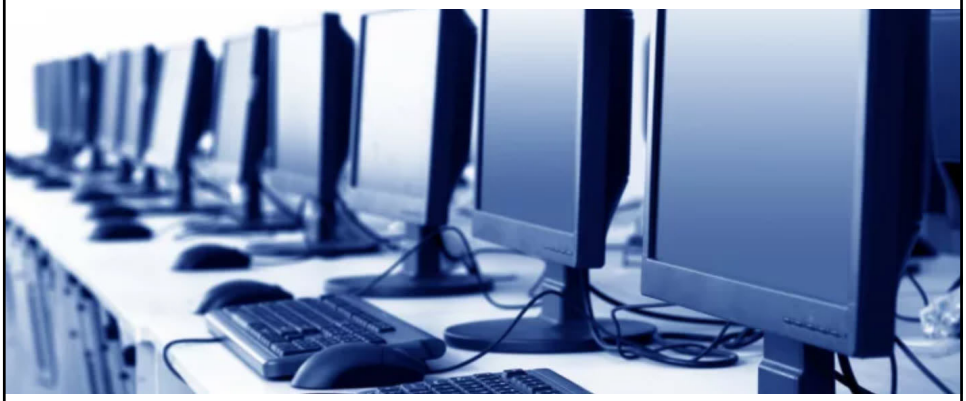
propharma

VALIDATION CENTER



Preparing for a Software Quality Audit

v.26.05

1

Today's Presenter

- Debra Bartel, MBA, CQA, PMP
- VP, Quality Assurance
- 30+ years experience specializing in software quality assurance, validation and regulatory compliance, Information Systems project management, and process design.
- Previously 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

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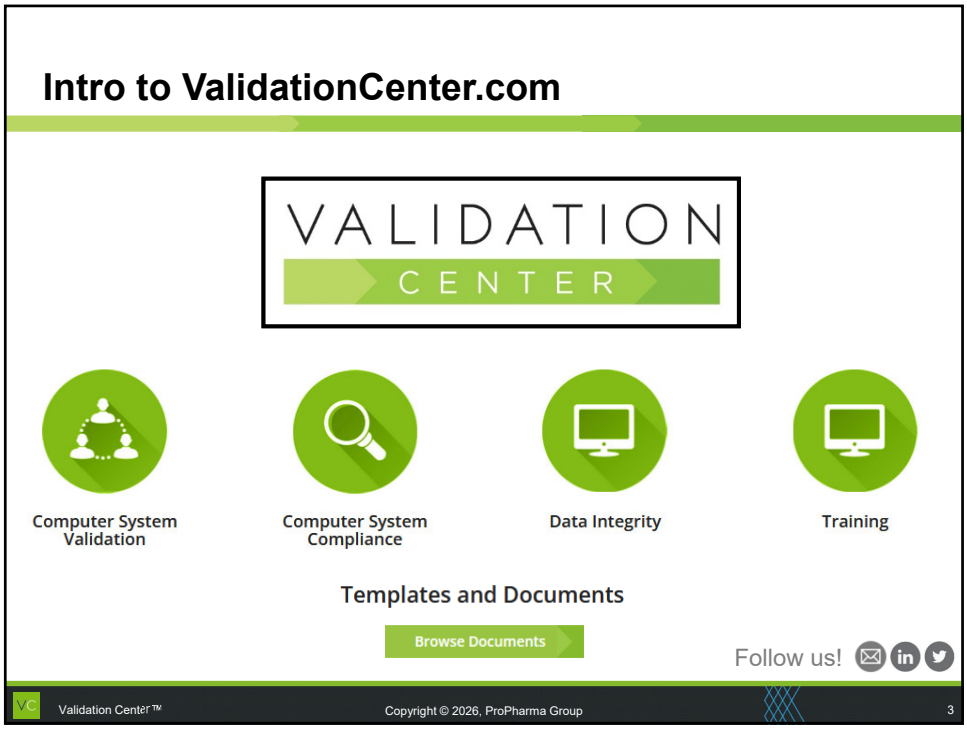

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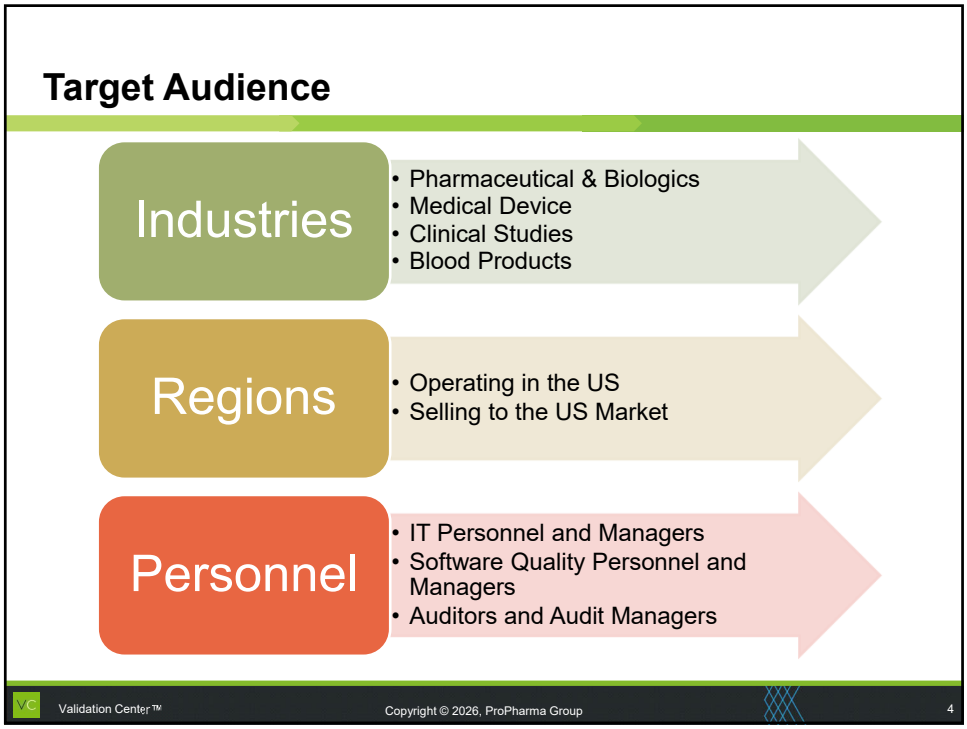

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Webinar Outline

1. Audit Framework
2. Audit Preparation
3. Audit Execution
4. Post Audit

5

Audit Framework

Part 1

6

Audit Framework

- Section Overview
  - Basic Audit Terminology
  - Audit Types
  - Audit Roles
  - Audit Process

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Basic Terminology

Audit	Assessment	Inspection
1. Planned 2. Documented	1. Planned 2. Documented	1. Planned 2. Documented

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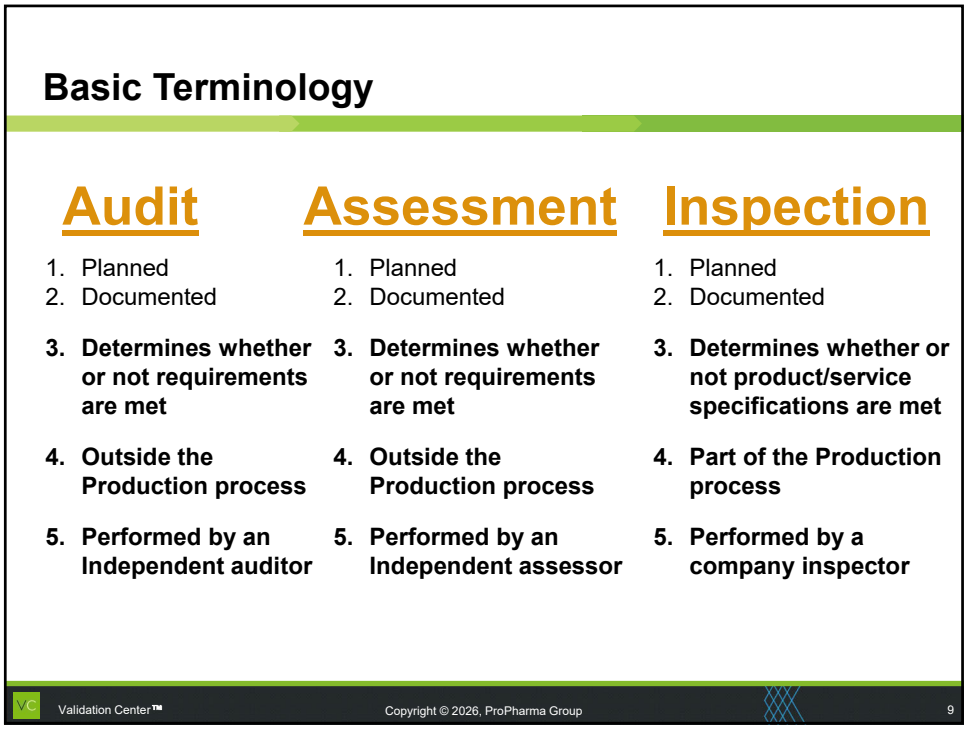

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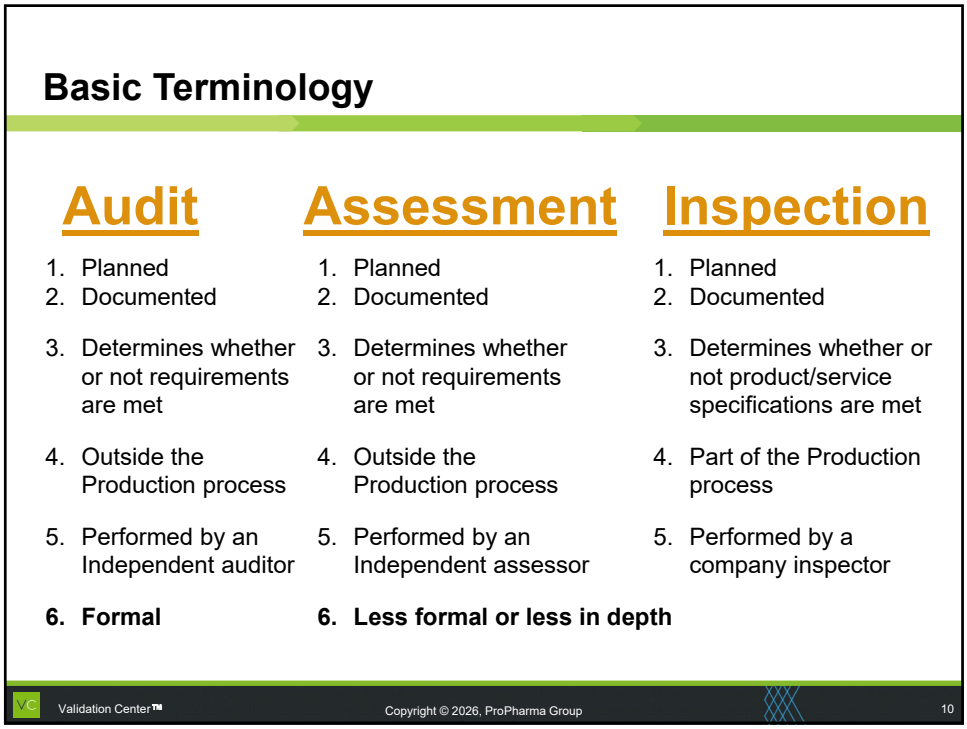

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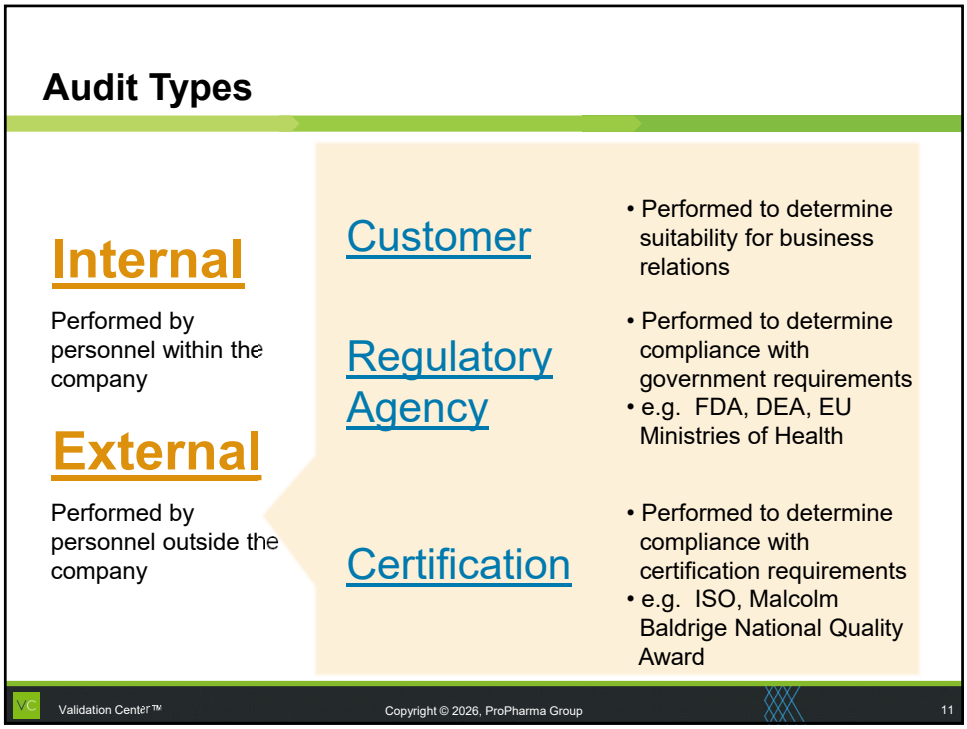

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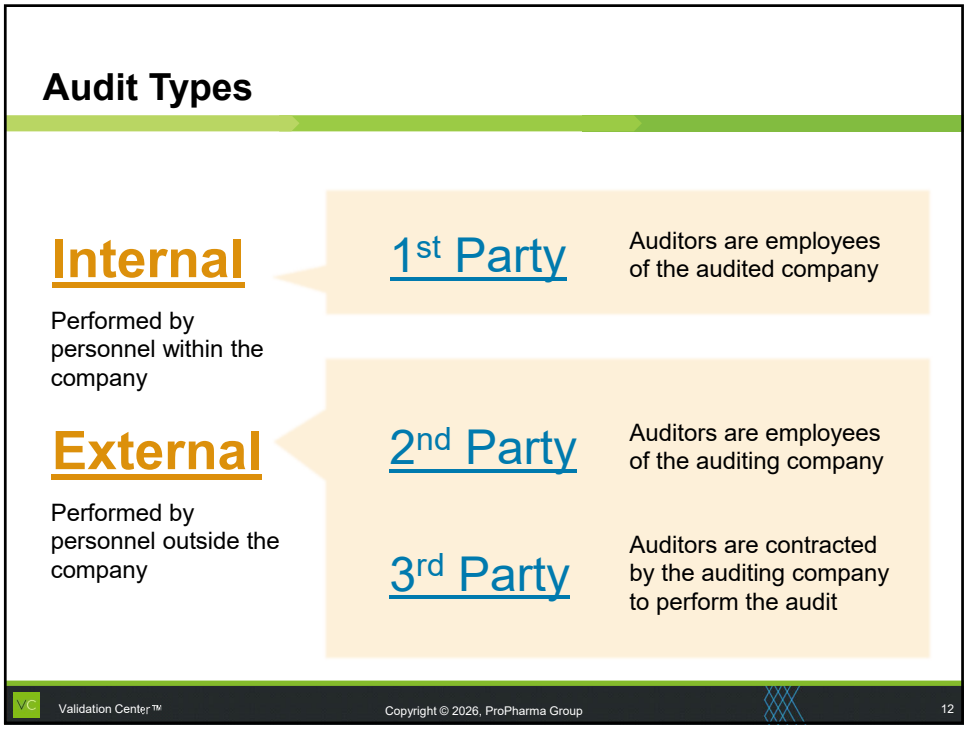

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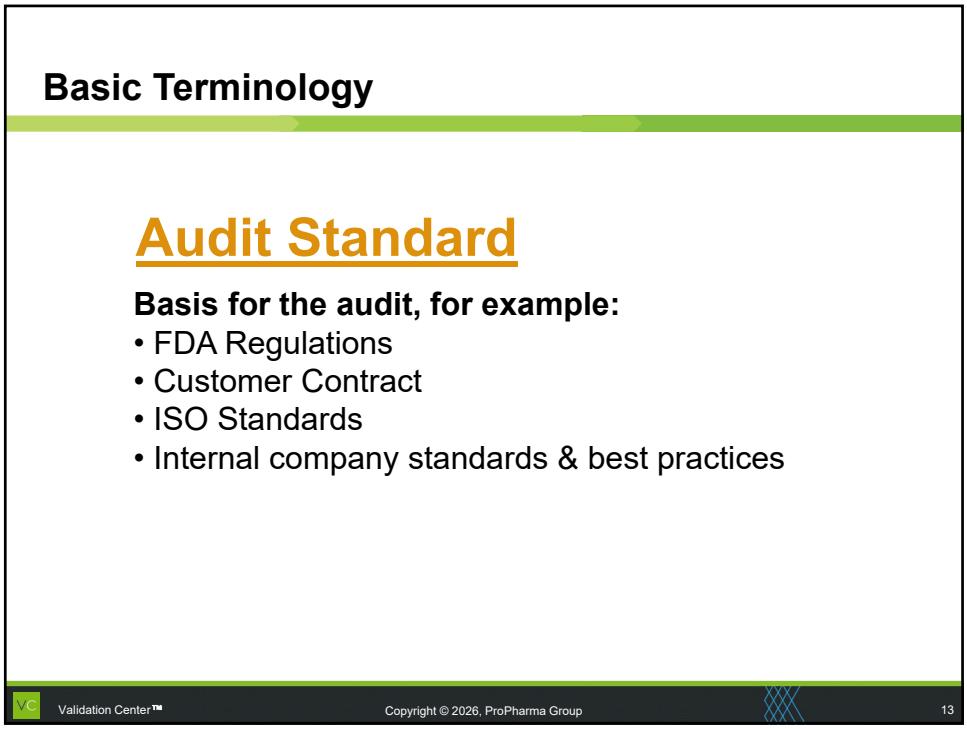

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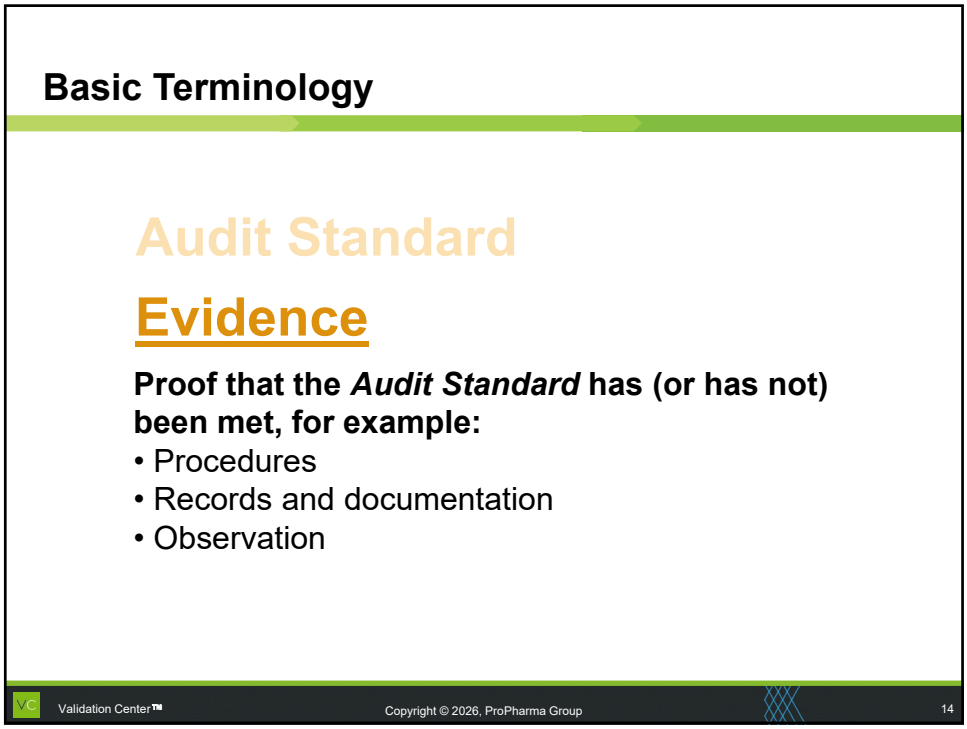

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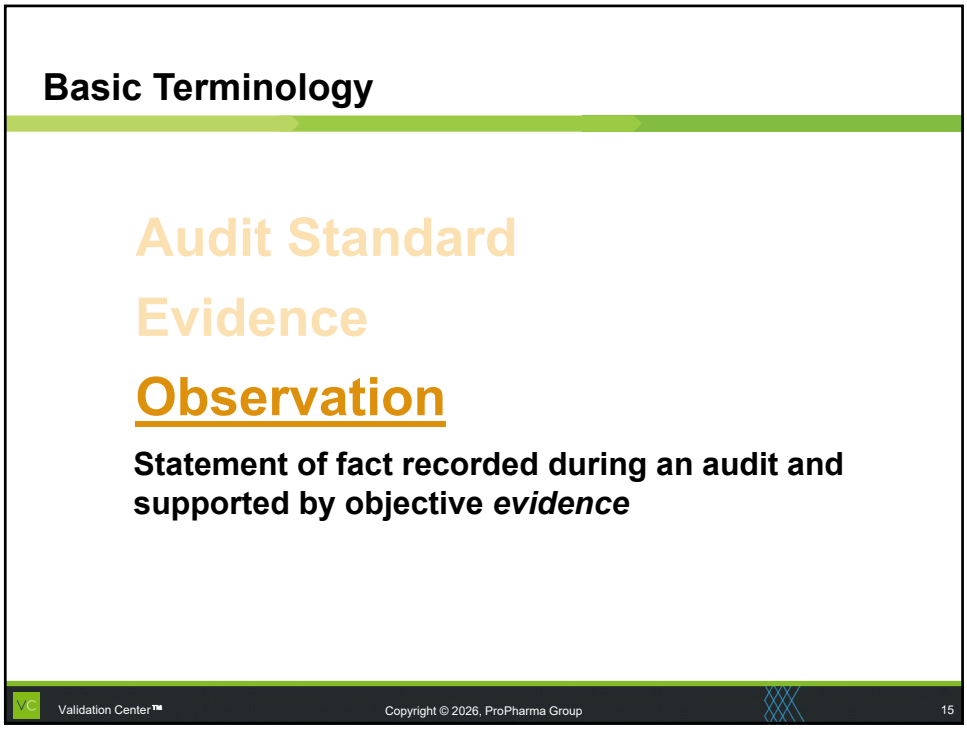

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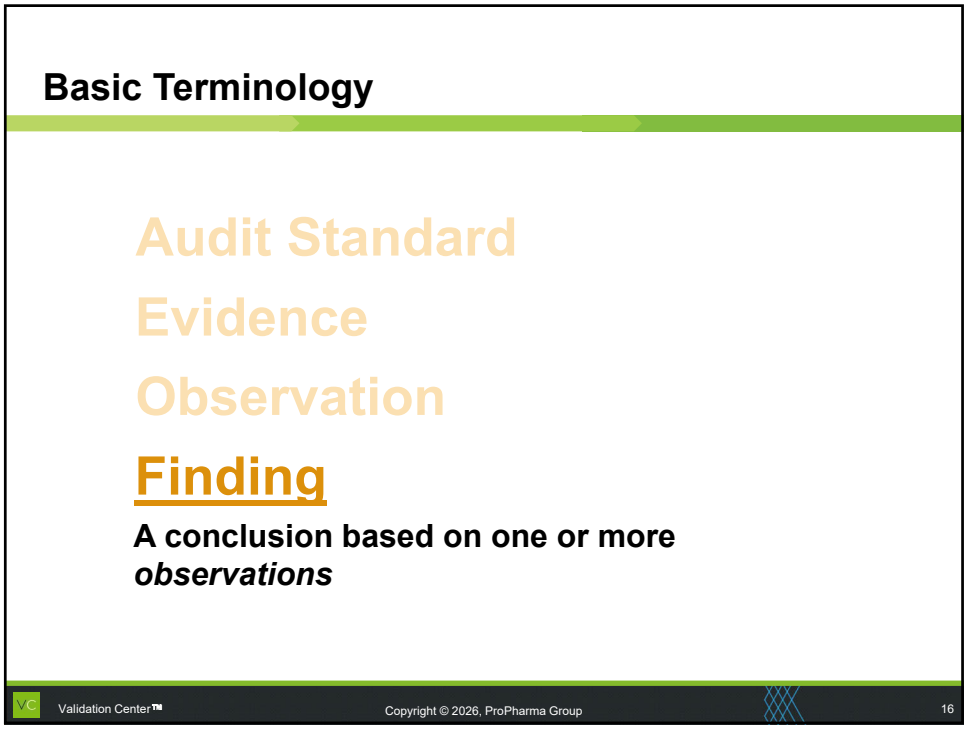

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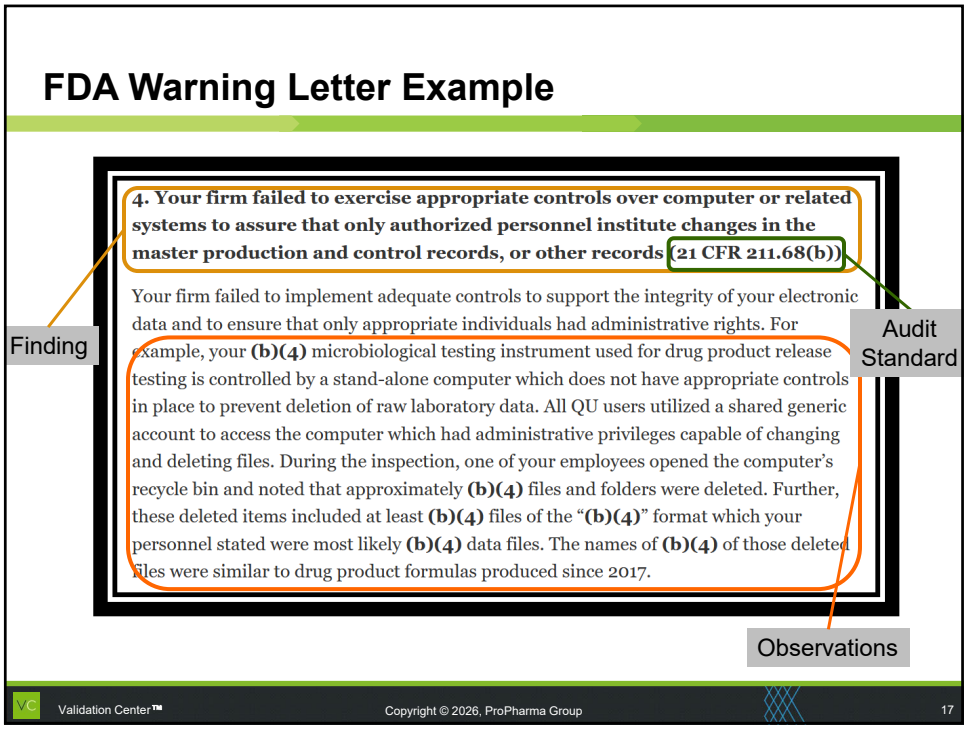

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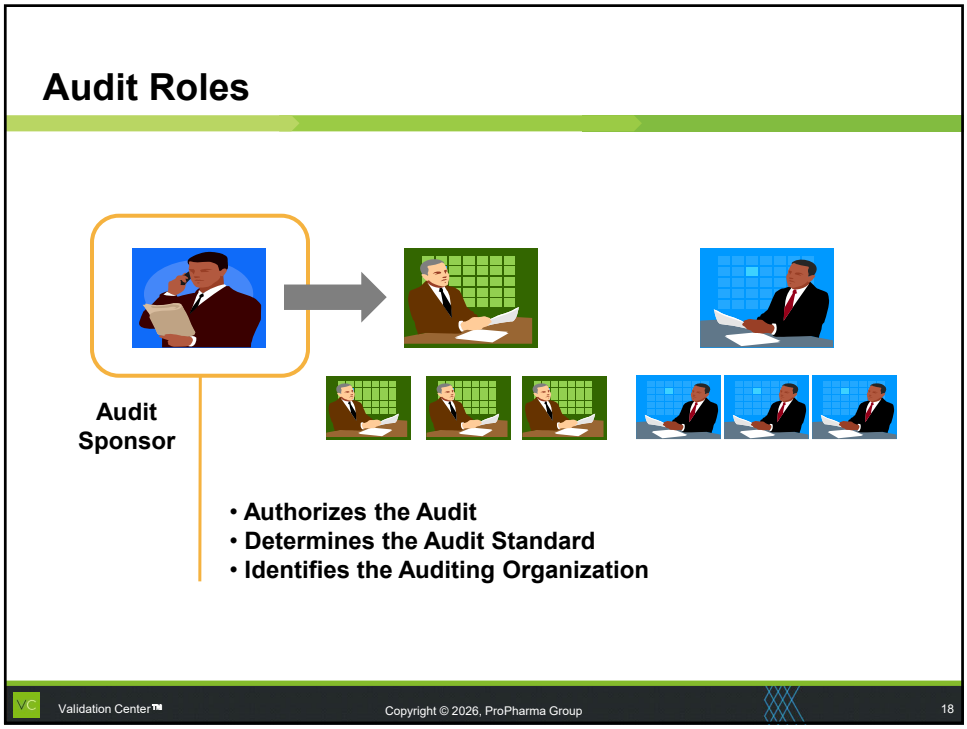

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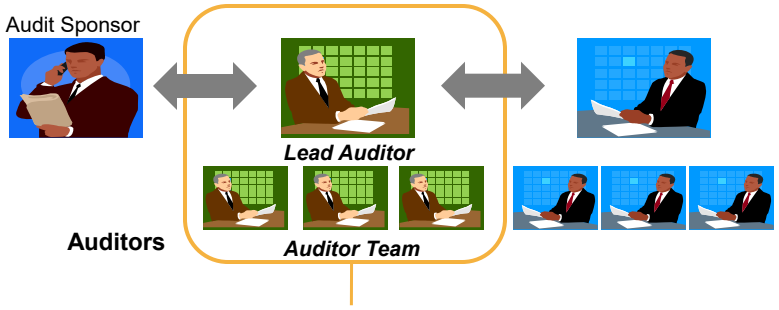
Audit Roles



- **Communicates with the Audit Sponsor and Auditee**
- **Makes audit arrangements with Auditee**
- **Conducts Audits and Documents Results**
- **Reports results to Audit Sponsor**

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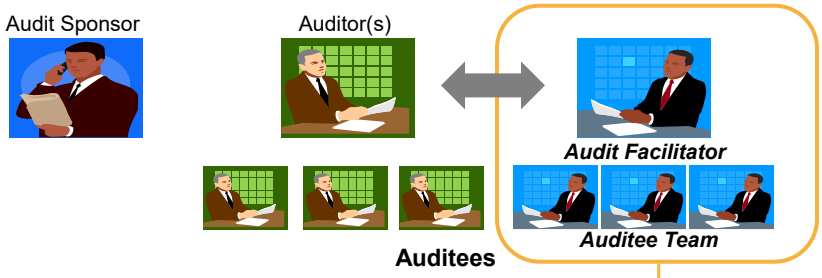
Audit Roles



- **Makes logistical arrangements**
- **Escorts auditors**
- **Provides information needed by auditors**

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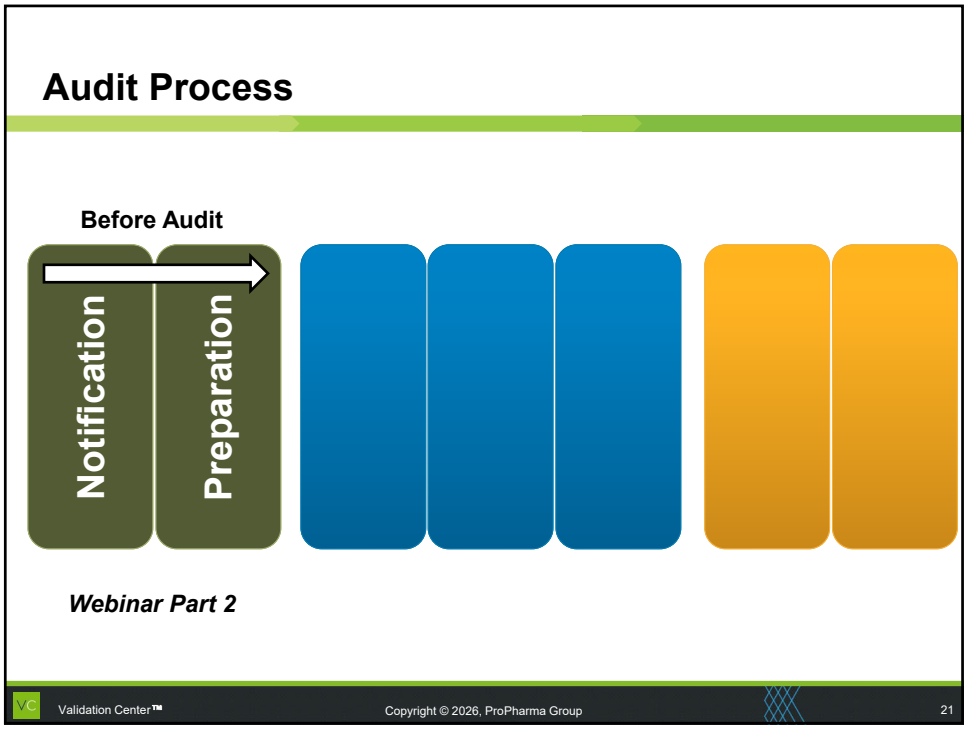

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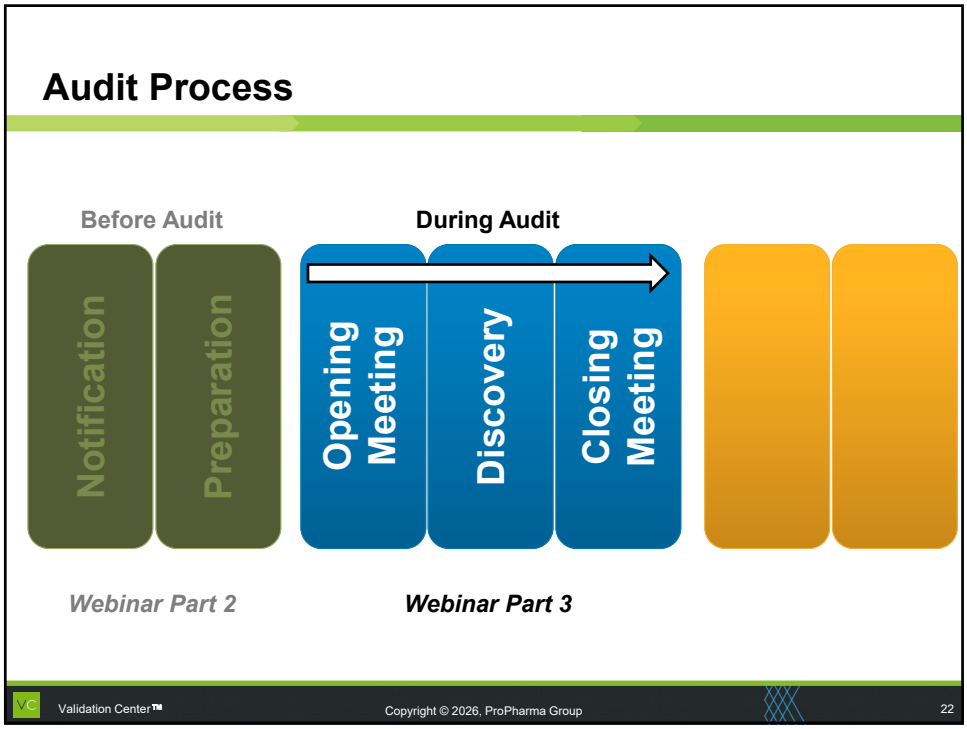

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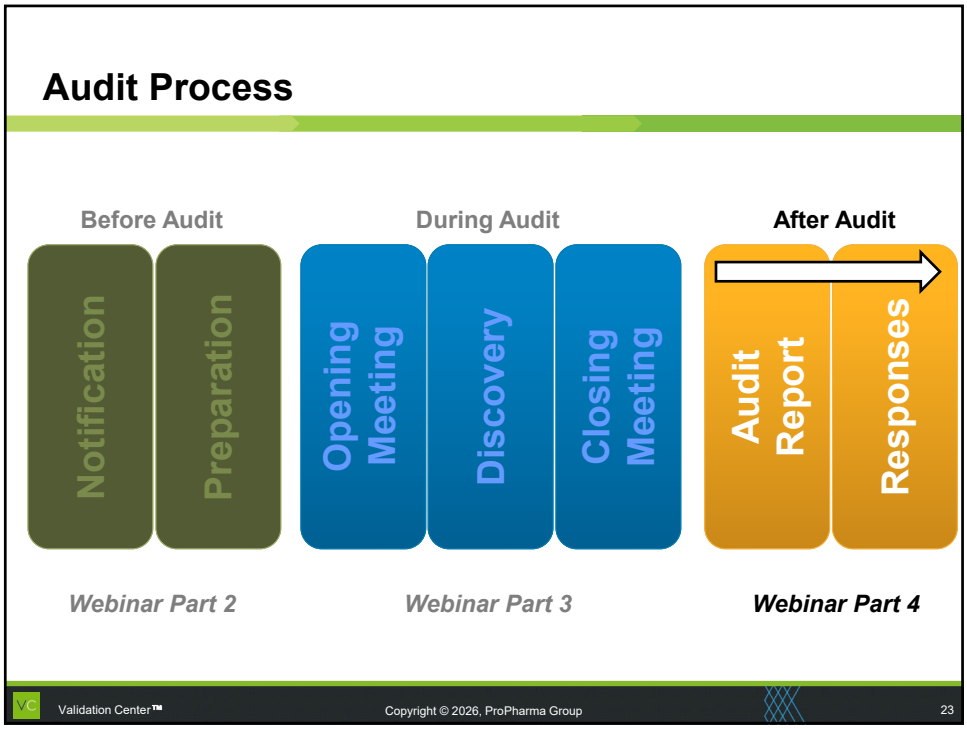

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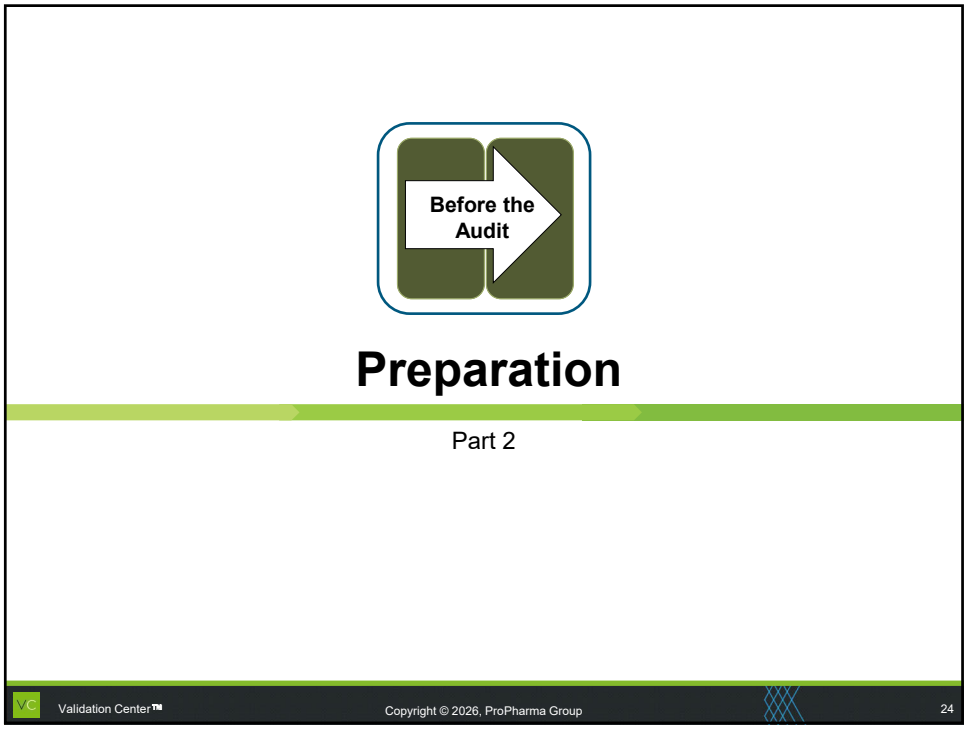

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Preparation

- Section Overview
  - Audit Notification
  - General Preparation Steps
  - FDA & International Regulations (Audit Standards)
  - Systems in Scope
  - Internal Checklists
  - Auditee team
  - Documentation Preparation
  - Prioritization

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Audit Notifications

- Agree to Dates
- Obtain details or clarification regarding:
  - Audit Scope
  - Audit Schedule
  - Audit Standards
  - Number of Auditors
- Confidentiality Agreement or Non-Disclosure Agreement
- Send Requested Documents

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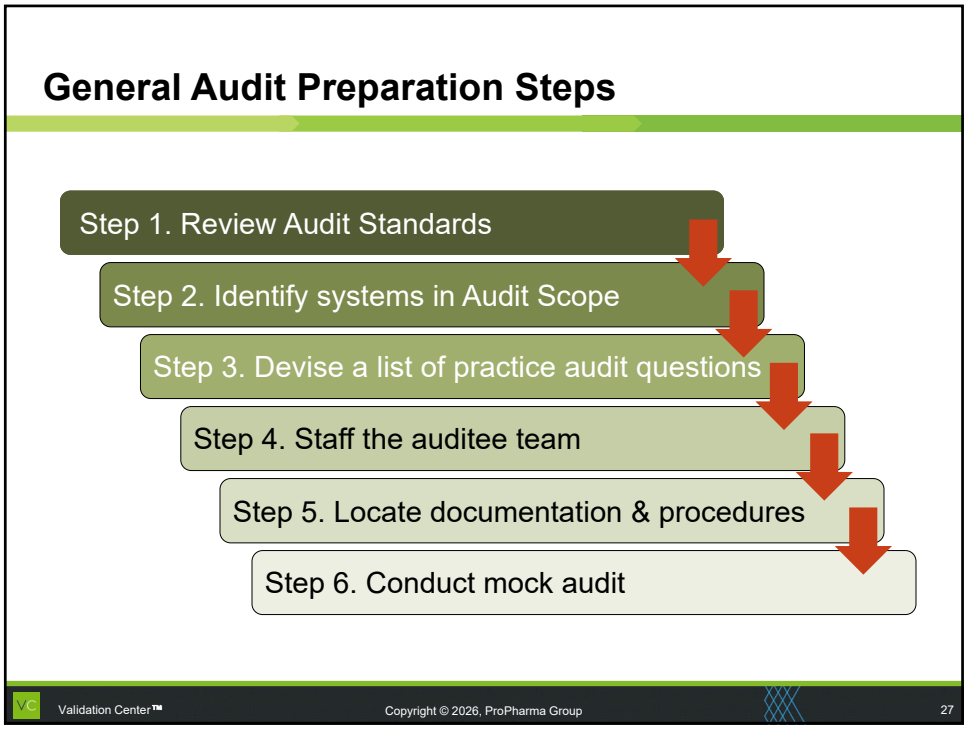

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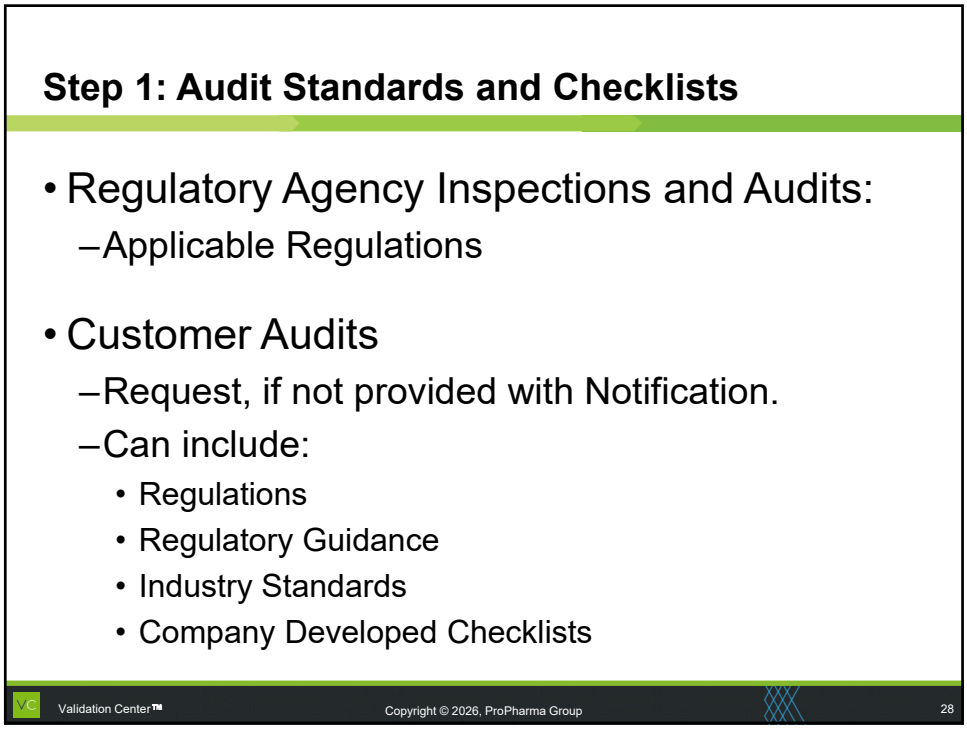

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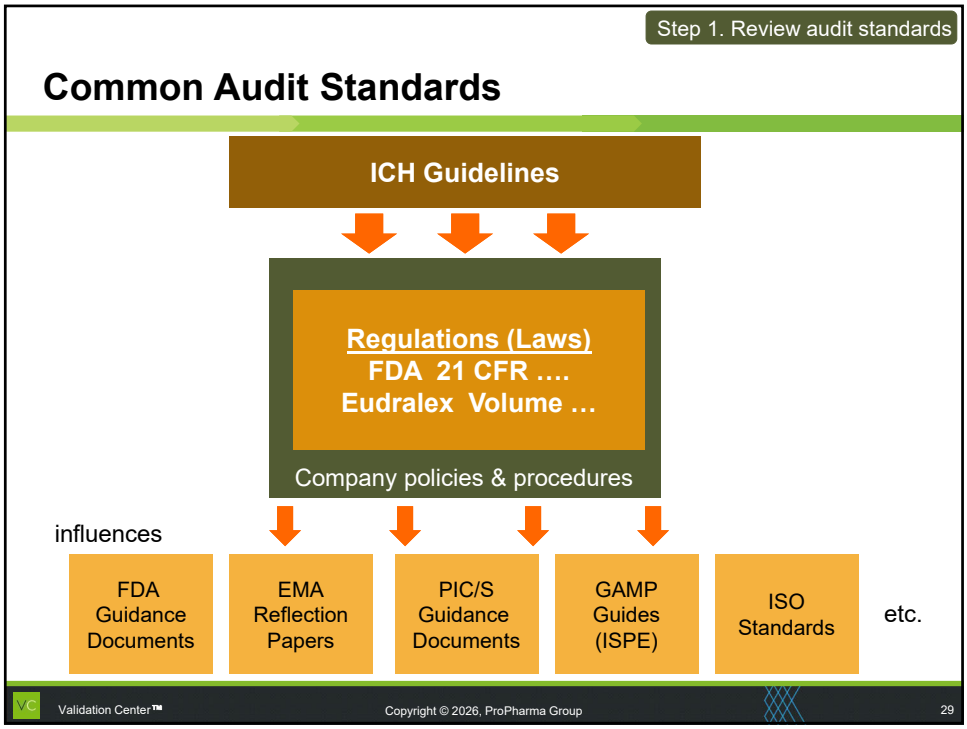

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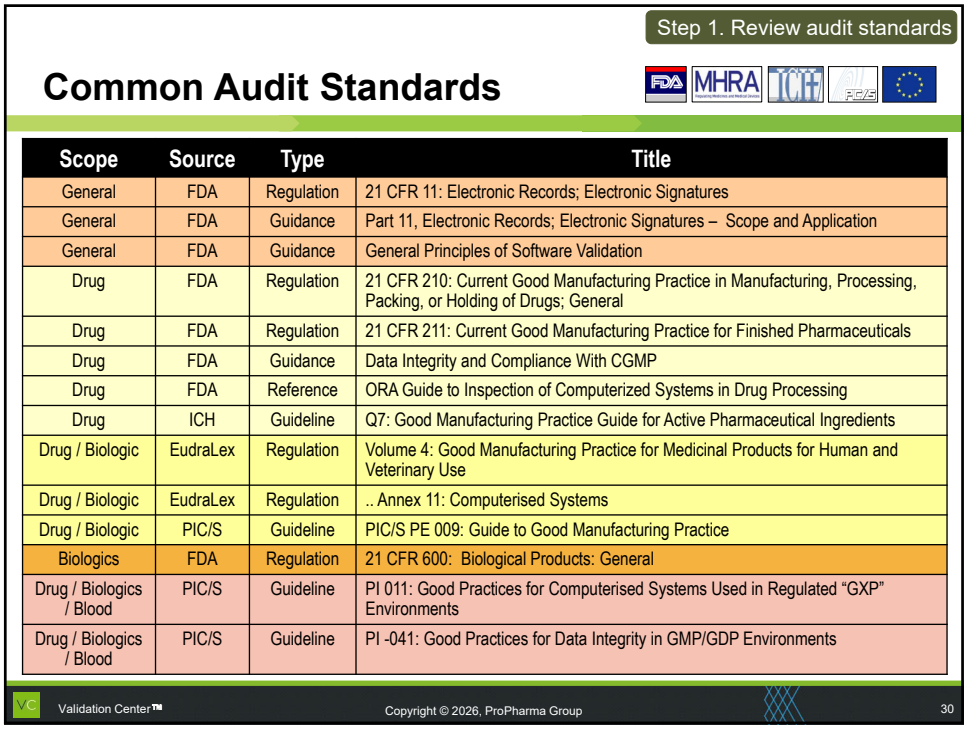

Scope	Source	Type	Title
General	FDA	Regulation	21 CFR 11: Electronic Records; Electronic Signatures
General	FDA	Guidance	Part 11, Electronic Records; Electronic Signatures – Scope and Application
General	FDA	Guidance	General Principles of Software Validation
Drug	FDA	Regulation	21 CFR 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
Drug	FDA	Regulation	21 CFR 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
Drug	FDA	Guidance	Data Integrity and Compliance With CGMP
Drug	FDA	Reference	ORA Guide to Inspection of Computerized Systems in Drug Processing
Drug	ICH	Guideline	Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
Drug / Biologic	EudraLex	Regulation	Volume 4: Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use
Drug / Biologic	EudraLex	Regulation	.. Annex 11: Computerised Systems
Drug / Biologic	PIC/S	Guideline	PIC/S PE 009: Guide to Good Manufacturing Practice
Biologics	FDA	Regulation	21 CFR 600: Biological Products: General
Drug / Biologics / Blood	PIC/S	Guideline	PI 011: Good Practices for Computerised Systems Used in Regulated "GXP" Environments
Drug / Biologics / Blood	PIC/S	Guideline	PI -041: Good Practices for Data Integrity in GMP/GDP Environments

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Step 1. Review audit standards

Common Audit Standards

	Source	Type	Title
Medicine / Device / Blood	MHRA	Guideline	'GXP' Data Integrity Guidance and Definitions
Device	FDA	Regulation	21 CFR 820: Quality System Regulation
Device	FDA	Guidance	Computer Software Assurance for Production and Quality Management System Software
Blood	FDA	Regulation	21 CFR 606: Current Good Manufacturing Practice for Blood and Blood Components
Blood	PIC/S	Guideline	PE 005: Good Manufacturing Practice Guide for Blood Establishments
Clinical	FDA	Regulation	21 CFR 50: Protection of Human Subjects
Clinical	FDA	Regulation	21 CFR 56: Institutional Review Boards
Clinical	FDA	Guidance	Computerized Systems Used in Clinical Investigations
Clinical	FDA	Guidance	Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations
Clinical	ICH	Guideline	E6: Guideline for Good Clinical Practice
Clinical	EudraLex	Regulation	Volume 10: Clinical Trials
Clinical	EudraLex	Regulation	.. Annex III: Guidance for the Conduct of GCP Inspections – Computer Systems
Clinical	EMA	Guideline	Guideline on Computerised Systems and Electronic Data in Clinical Trials
Lab	FDA	Regulation	21 CFR 58: Good Laboratory Practice for Nonclinical Laboratory Studies

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Step 2. Identify Systems in Scope

Step 2: Identify Systems In Audit Scope

- Refer back to Audit Standards
- Identify systems where:
  - Processes are supported by computer systems
  - Records are created or retained by computer systems
- Look for:
  - Specific computer system requirements
  - Record and data requirements

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Step 3: Develop Practice Questions

- Review questions asked during past audits
- Pull questions from the PIC/S Checklist in
  - PI 011 Good Practices for Computerised Systems Used in Regulated "GXP" Environments
- Develop questions from the Audit Standards

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Practice Questions, Example 1

Audit Standard: 21 CFR 211: lab records must contain "complete data derived from all tests necessary to assure compliance with established specifications" and must include "the initials or signature of the person who performed each test and the date(s) the tests were performed"

Practice Questions:

1. Does the lab system include the initials or signature of the person who performed each test?
2. Has the lab system been validated?
3. Is the validation documentation available?
4. Does the validation documentation include testing of the initial or signature feature?
5. Does the electronic signature meeting Part 11 requirements (e.g., audit trail, human readable, secure, two-components, etc.?

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Practice Questions, Example 2

Audit Standard: 21 CFR 820: requires that complaint records include device name, complaint date, device ID numbers, complainant info (name, address, phone), problem description, date & results of investigation, etc. Also requires records to be retained for the life of the device, but no less than 2 years after distribution.

Practice Questions:

1. Does the complaint system include fields for all the required data?
2. Has the complaint system been validated?
3. Does the validation documentation demonstrate the required features?
4. Per procedure, are the complaint records retained for the required duration?
5. Are there approved procedures for using and maintaining the system?
6. Are there records that users were trained prior to obtaining access?

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Common Audit Questions

General Quality Topics

	Question	Evidence
1	Is there an overall program to ensure software quality? Does the program include a software life cycle, testing practices, documentation requirements, and responsibilities?	• Quality Manual • Quality Policy
2	Is there a list or inventory of all computerized Systems by name and application? Does the list indicate validation status and risk assessment rating?	• Validation Master Plan (VMP) • GxP Inventory List
3	Is the Quality Assurance (QA) organization independent from the IT organization? Does QA have a role in the system life cycle – especially in validation and system release?	• Organization Chart • QA Job Description • SDLC SOP
4	Does QA perform periodic audits of system quality, documentation, and procedural compliance?	• Internal Audit SOP • Internal Audit records

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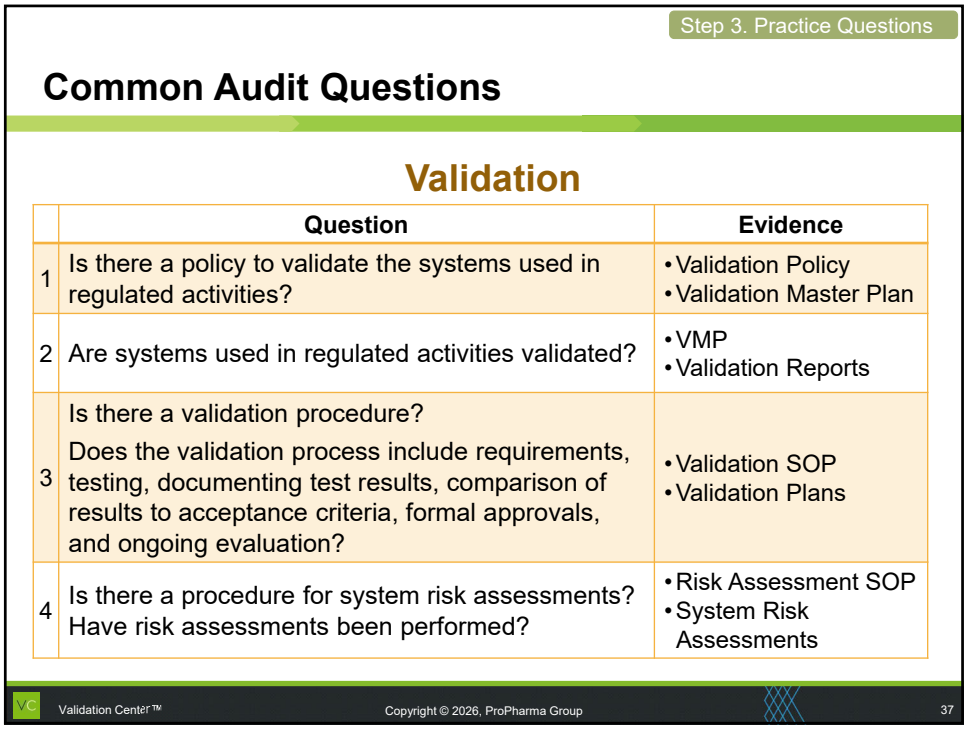

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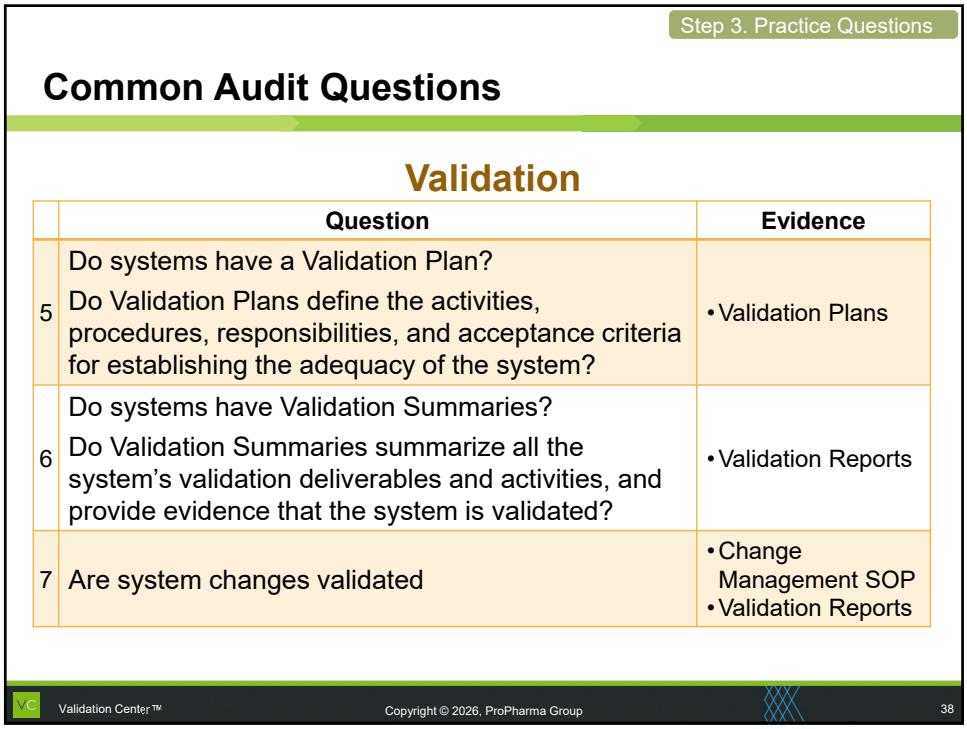

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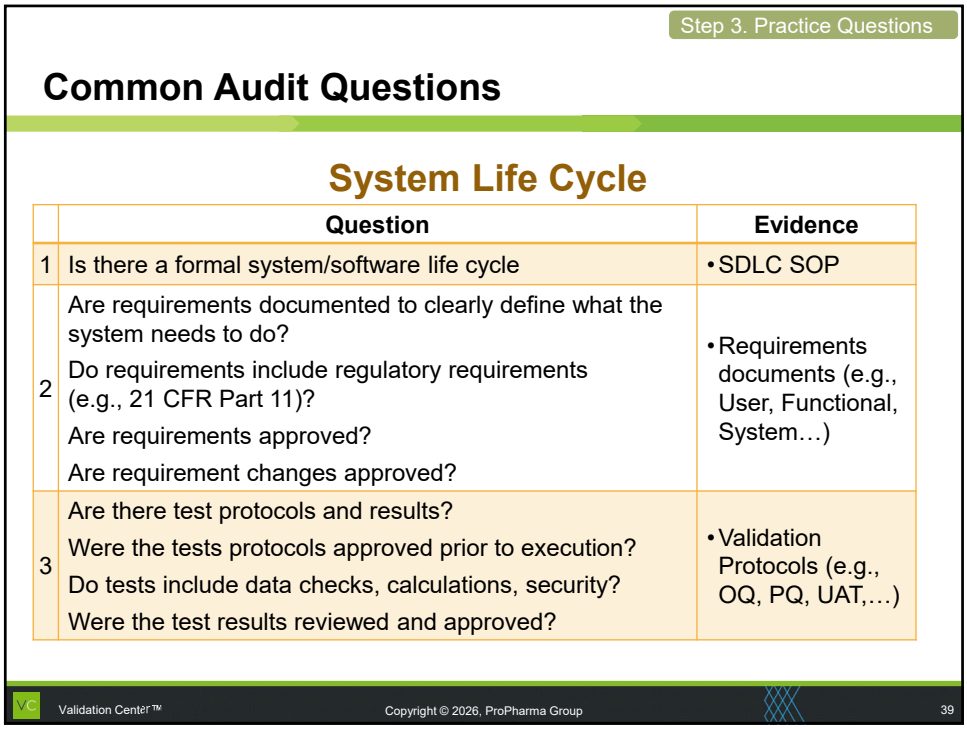

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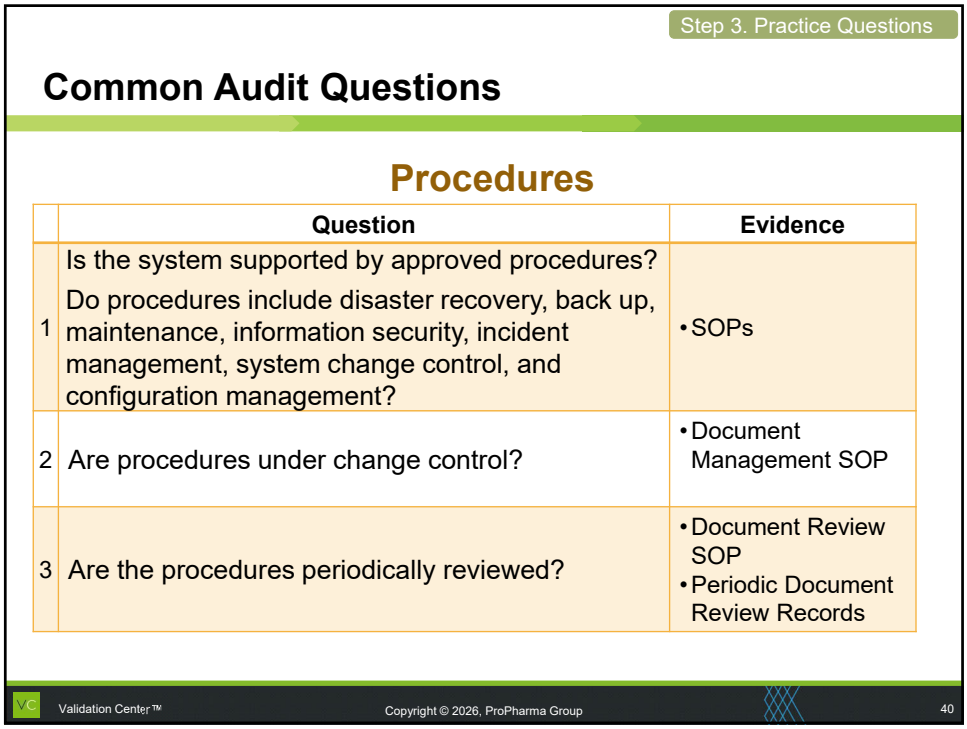

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Common Audit Questions

System Documentation

	Question	Evidence
1	Does the system have up-to-date documentation, including configuration settings, data structures and flows, interactions with other systems, design & architecture?	• Software Design • Architecture Diagram • Configuration Specification
2	Is the documentation updated each time a change is made?	• Examples of the documents, above
3	Is documentation managed using change control?	• Document Management SOP • Document change records

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Common Audit Questions

Change Management

	Question	Evidence
1	Are system changes documented? Are system changes approved?	• System Change records
2	Are changes evaluated for the need to validate?	• Records of evaluations
3	Are configuration changes documented?	• Configuration Change records
4	Is system documentation updated when changes are made	• Updated documentation
5	Are users and support personnel retrained when changes are made?	• Training records

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Common Audit Questions

Incident Management

	Question	Evidence
1	Are system incidents documented?	• Incident records
2	Are system incidents evaluated to determine correction and prevention activities?	• Incident records • CAPA records
3	Are system users made aware of critical system defects?	• Notification examples
4	Can each incident be tracked to a resolution (or decision w/rationale to not resolve)?	• Incident records • CAPA records

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Common Audit Questions

Data Integrity & Protection

	Question	Evidence
1	Is the system secured by unique user-ids and passwords	• Security SOP • Validation Protocols
2	Are there controls to ensure that data can only be entered and changed by authorized personnel?	• Security SOP • Validation Protocols
3	Is access to high levels of access (e.g., Super User) restricted to a few individuals	• Security SOP • Access records
4	Is critical data verified by a 2nd person, or by a validated electronic method?	• User SOPs • Validation Protocols
5	Are back-ups retained in a separated, secure location? Are back-ups retained for the duration required?	• Back-up SOP • Back-up records
6	Is there a disaster recovery plan (DRP)? Has the plan been executed and validated?	• DRP • DRP execution records

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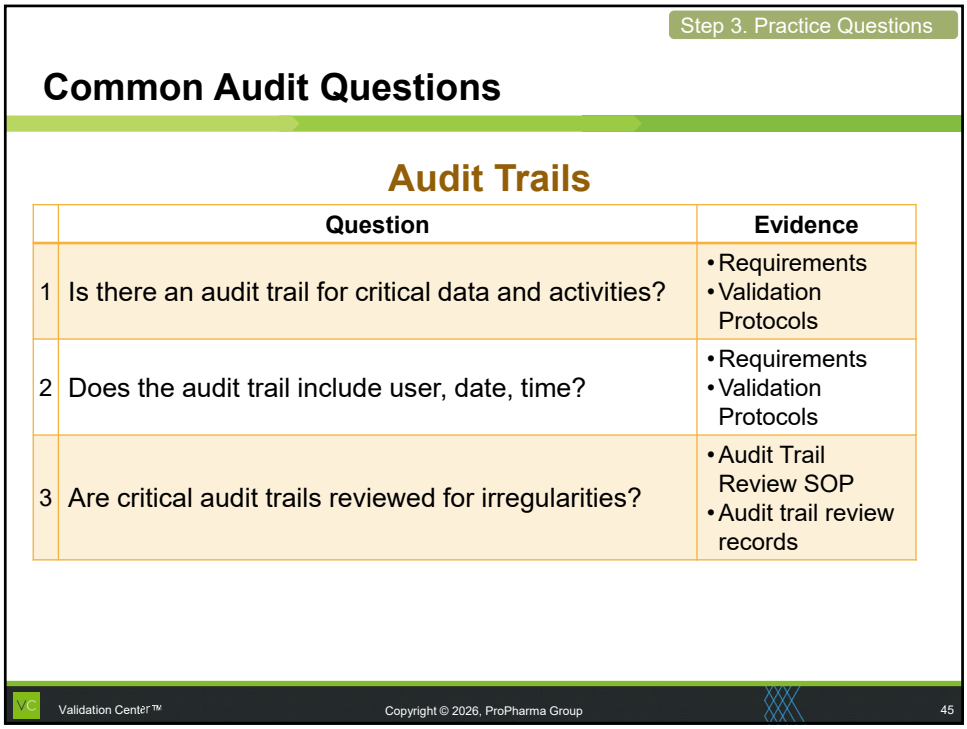

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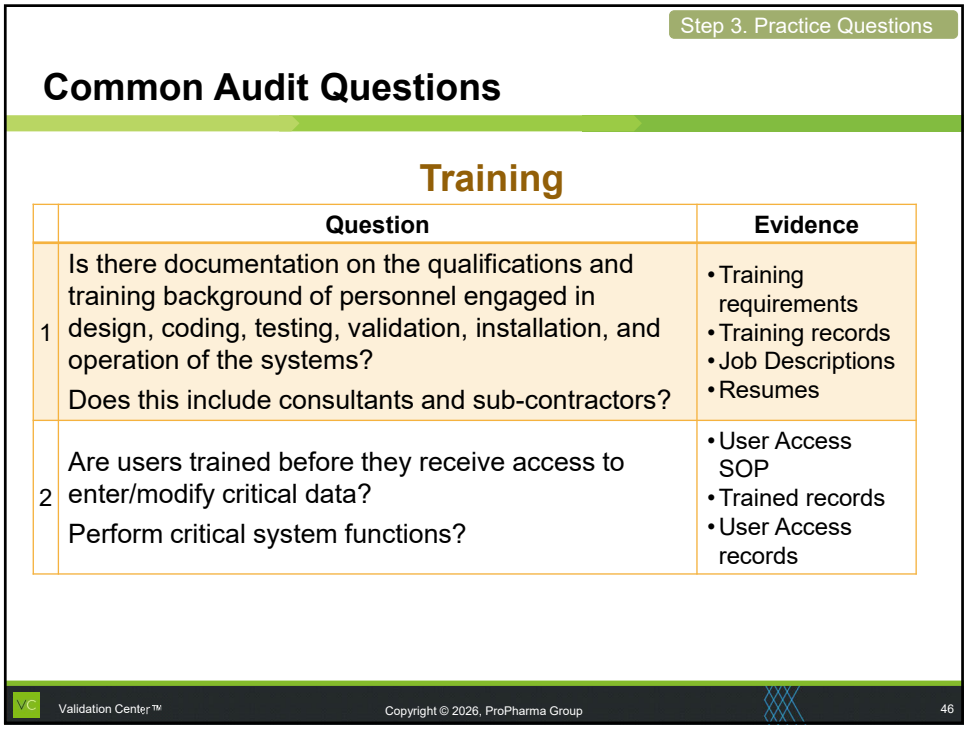

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Common Audit Questions

Vendors & Service Providers

	Question	Evidence
1	Are there policies and procedures for assessing potential suppliers of hardware, software, and related services?	• Vendor Qualification SOP • Vendor Qualification records
2	Is validation documentation provided by the vendor reviewed and approved internally?	• Document Review and Approval records

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Step 4: Staff the Auditee Team

- Identify auditee team members
- Determine who will
  - Speak to each topic during the audit
  - Lead the facility tour *
  - Present the overview during the opening meeting *
  - Escort the auditors during the audit *
  - Take minutes of audit *
- Provide audit interface training

* These activities are typically, but not always, done by the Audit Facilitator

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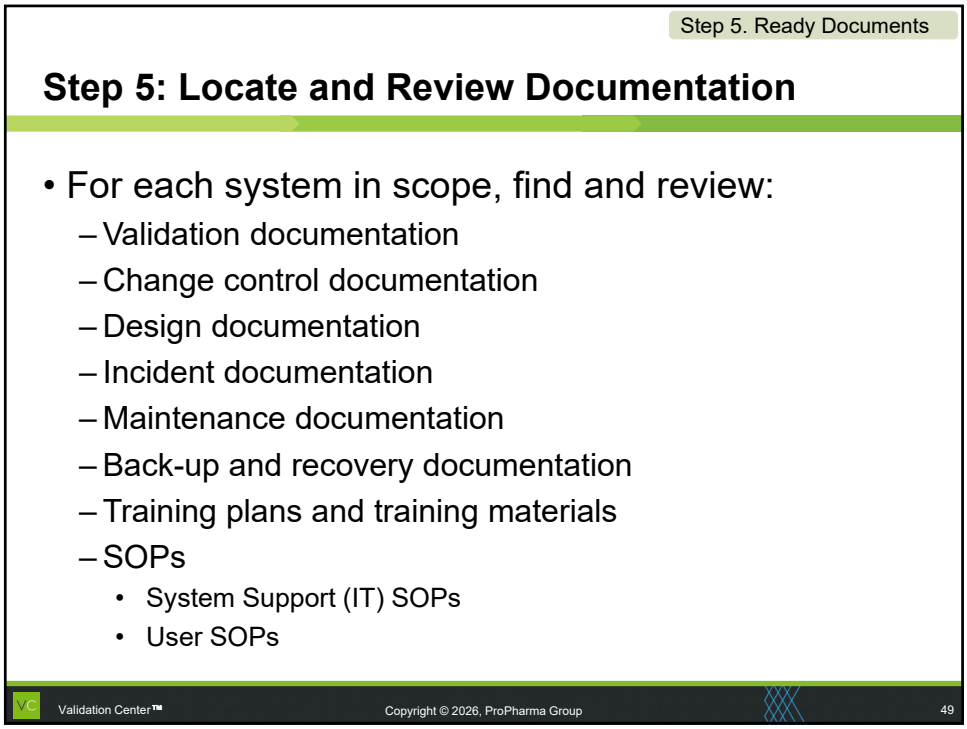

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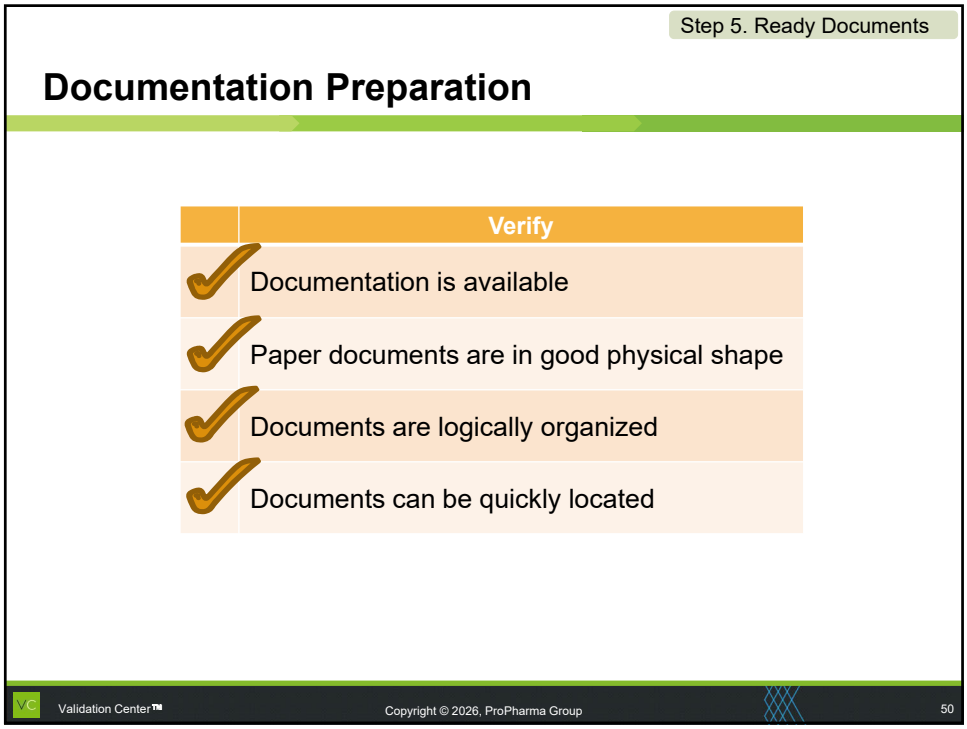

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Documentation Preparation

	Verify
✓	Previous documentation conventions are understood
✓	Testing results support validation conclusion
✓	Signatures are not missing

Plan Actions to address known issues

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Step 6: Practice

- Hold a practice audit
  - Audit Facilitator – Play Auditor Role
  - Auditee team – Reply to questions for designate area

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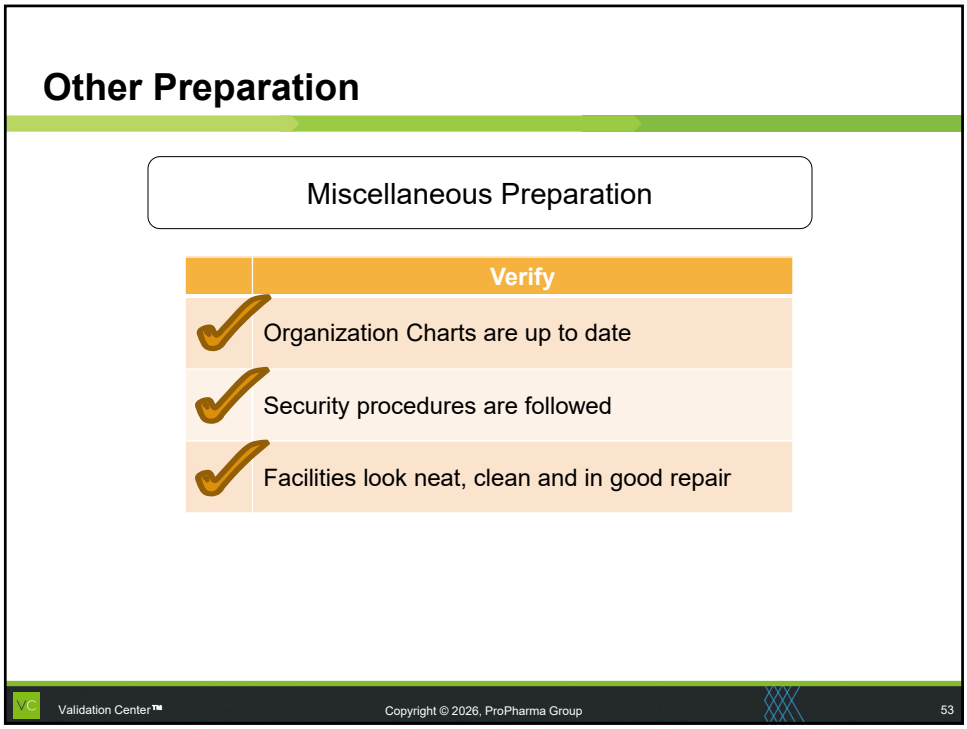

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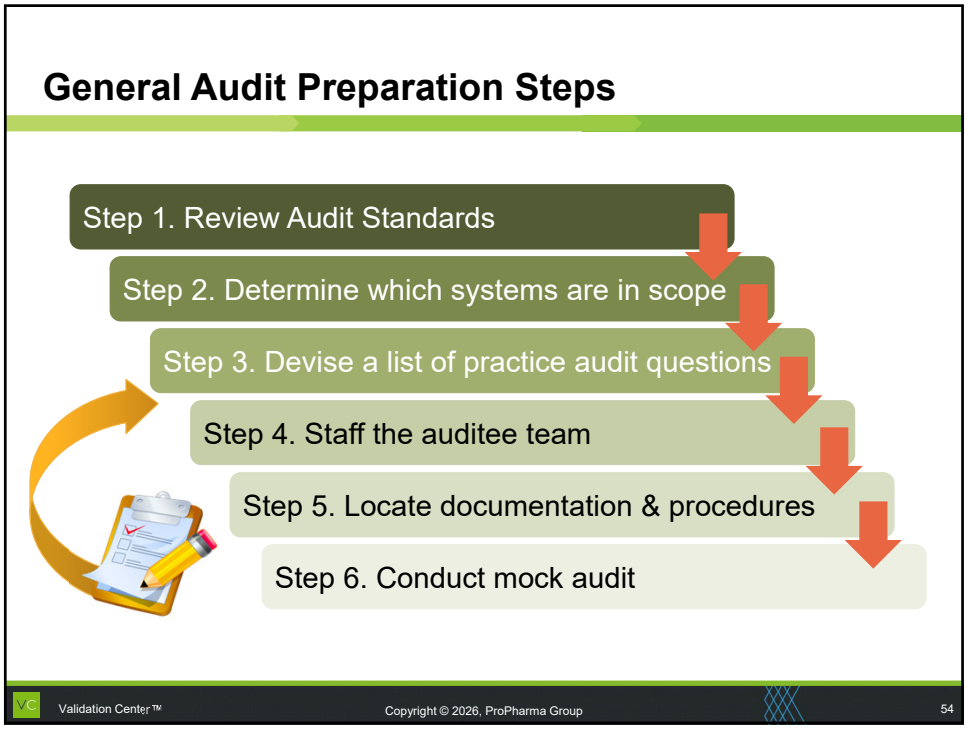

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Prioritization

How can it all be done in time for the audit?

Perhaps it can't!

So, Prioritize

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Prioritization Guidance

- Data Source
  - FDA Warning Letters related to Software and Computers
  - 3 Year Date Range: 2023 through 2025
- Summaries
  - By system type
  - By topic
    - By validation topic

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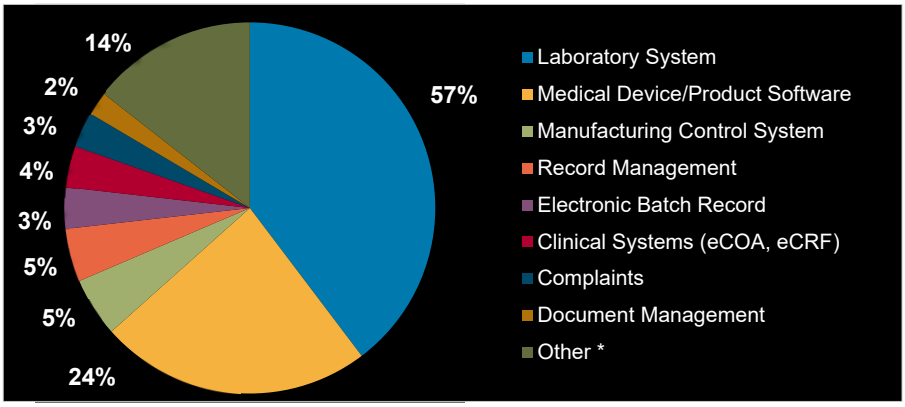
Software & Computer Warning Letter Citations

3 Year Summary by System Type



* "Other" system types include systems for Certificates of Analysis, Label Management, Product Inspection and Testing, Printer Software, Environmental Monitoring, Product Design, and IRB Software

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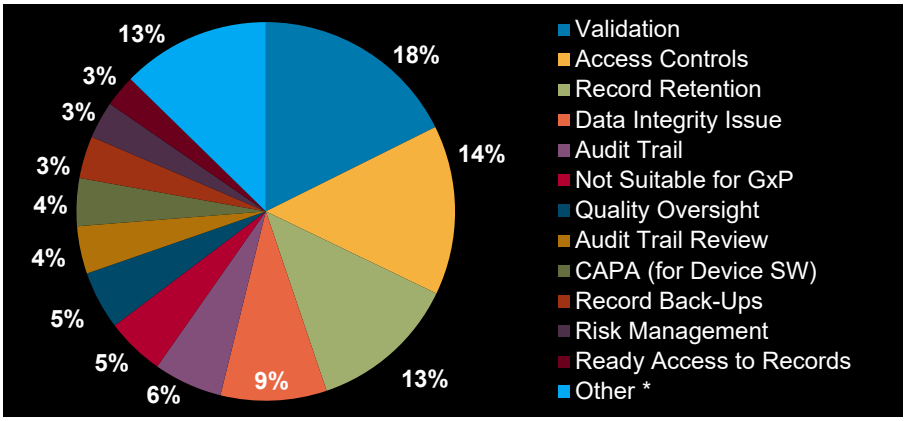
Software & Computer Warning Letter Citations

3 Year Summary by Observation Topic



* "Other" observation topics include Critical Software Defects, System Change Control, Device Software Issue Reporting, IT Vendor Management, Data Accuracy, Software Recalls, Device Software Branding, Cyber Security, and eRecord Archival

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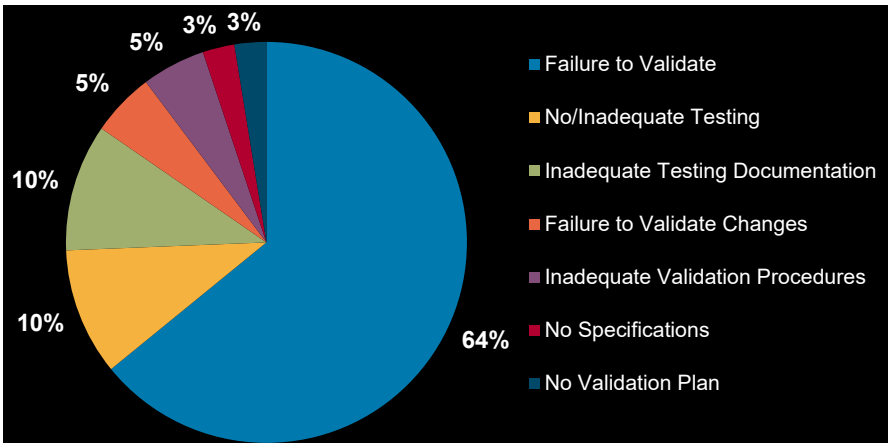
Software & Computer Warning Letter Citations

3 Year Summary by Observation Topic – Validation Only



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During the Audit

Audit Execution

Part 3

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Audit Execution

- Section Overview
  - Logistics
  - Auditee behavior
  - Tricky situations
  - FDA requests for data or system access

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Logistics

On Site

- Security Procedures
- Meeting Space
- Back Room
- Escorts
- Safety Procedures

They're Here!

Remote

- Online Meeting
- Online Document Access

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Opening Meeting

- Facilitator
- Attendees
- Agenda
  - Introductions
  - Audit details
  - Logistics
  - Overview

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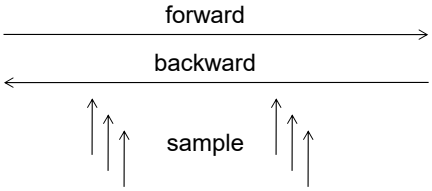
Auditor Approaches

- Sampling
- Trace Forward
- Trace Backwards
- Checklists



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Auditor Techniques

Interview and Observe
Open ended questions
Paraphrasing

Silence / Long Pause
Empathy
Aggression
Good Cop – Bad Cop

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Auditee Conduct

- Who should answer the auditor's question?

The auditee team member designated for the topic

- What if the team member doesn't know the answer?

Reply, "will get back with an answer"

Find someone who knows the answer

Respond to question

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Auditee Conduct

DO

- Professional
- Courteous
- Friendly
- Accurate
- Honest
- Concise
- Ask for clarification
- Defend company position
- Record questions asked and answers provided*

* Recorded by Audit Facilitator or designated scribe

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Auditee Conduct

DON'T

- Evasive or misleading
- Guess
- Volunteer unrequested information
- Argue with auditor
- Argue within auditee team
- Implicate other parts of the company
- Negative body language
- Waste time
- Bribe

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Auditee Conduct

- When the auditor requests documentation…

DO

- Locate quickly
- Explain delays
- Note the documents requested and provided *

DON'T

- Bring unrequested documents into the room
- Leave auditor alone with binders, open system access, etc.
- Bring unofficial documents

* Recorded by Audit Facilitator or designated scribe

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Validation Documents

- Frequent FDA validation document reviews

1. Validation Report (Validation Summary, System Certification…)
2. Validation Plan (Quality Assurance Plan, Quality Plan…)
3. Test Protocols and Results
4. Change Authorization

70

Non-Conformances

- What if the auditor finds a non-conformance?
  - Don't panic
  - Don't deny it
  - Don't make excuses

If simple → make correction → show auditor

If Action Plan exists → show auditor

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Demos

- What if an auditor asks for a system demo?
  - Contact an experienced user
  - Arrange demo
    - at desk
    - in conference room (better)

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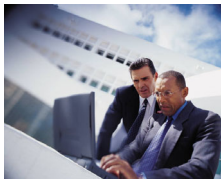
System Access

- What if an auditor asks to access a system?
  - Follow your procedures!
  - Explain that you have training requirements and access procedures
  - Offer to have an experienced user access the system while the auditor watches
  - Never leave the auditor in the room alone with the computer



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Downloads

- What if an auditor asks for a data download?
  - Contact technical support for assistance in running a custom query to download only the data requested
  - Have a 2nd person verify the query logic
  - Place output on a new CD, DVD, flash drive…
  - Use common, simple format, such as a spreadsheet or database, if possible
  - Provide auditor with a copy of the query and record count – upon request
  - Keep a copy of request and the data provided *

* Recorded by Audit Facilitator or designated scribe

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Closing Meeting

- Facilitator
- Attendees
- Agenda
  - Observations
  - Findings
  - Preliminary Audit Report

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Post Audit

Part 4

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Post Audit

- Section Overview
  - Audit outcomes
  - Audit responses

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Customer Audit Report

- Summary of the audit purpose, scope, dates, location, participants, audit standard
- Findings
  - Supporting Observations
- Corrective Action Requests
- Approvals

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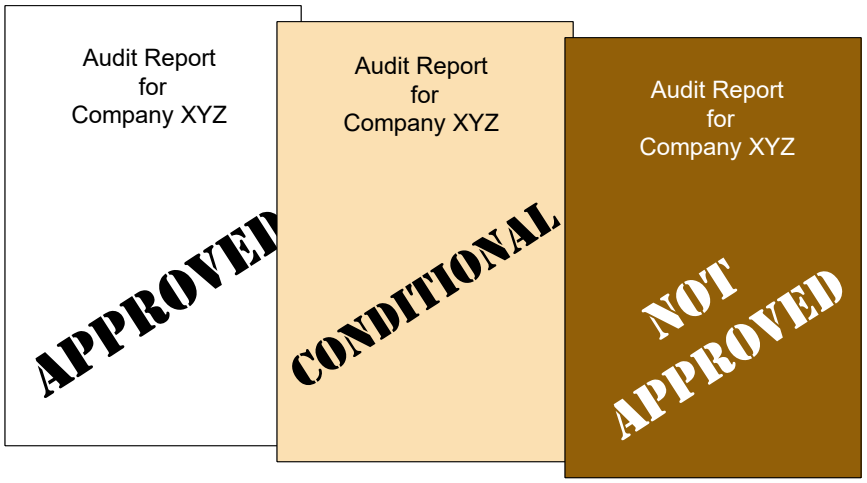
Customer Audit Outcomes



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Customer Audit – Corrective Action Requests

- Determine
  - Root cause
  - Correction needed
  - Timeline
  - Responsibility
- Respond to customer
- Track to closure
- Monitor effectivity

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FDA Audit Outcomes

EIR

Establishment Inspection Report

- No findings
- Approval for new facility, process, product

- Failed approval
- Form 483
- Warning Letter
- Product Seizure
- Injunctions
- Civil Penalties
- Criminal Prosecution
- Consent Decree

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FDA Audit – Reponses

- Determine
  - Root cause
  - Correction needed
  - Timeline
  - Responsibility
- Respond to FDA
- Track to closure
- Monitor effectivity

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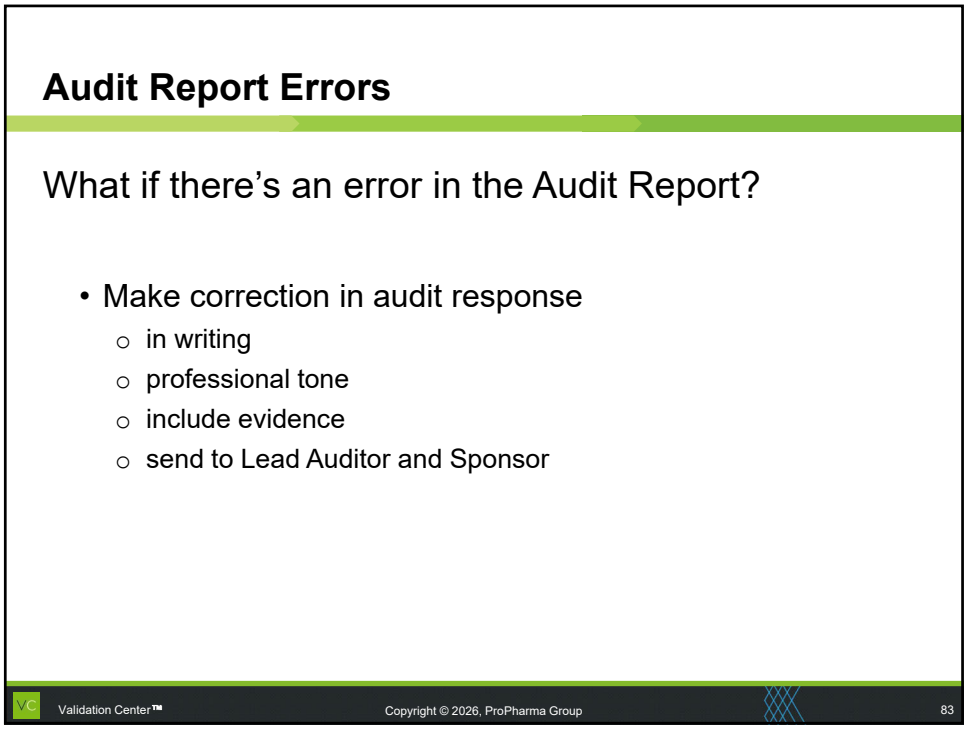

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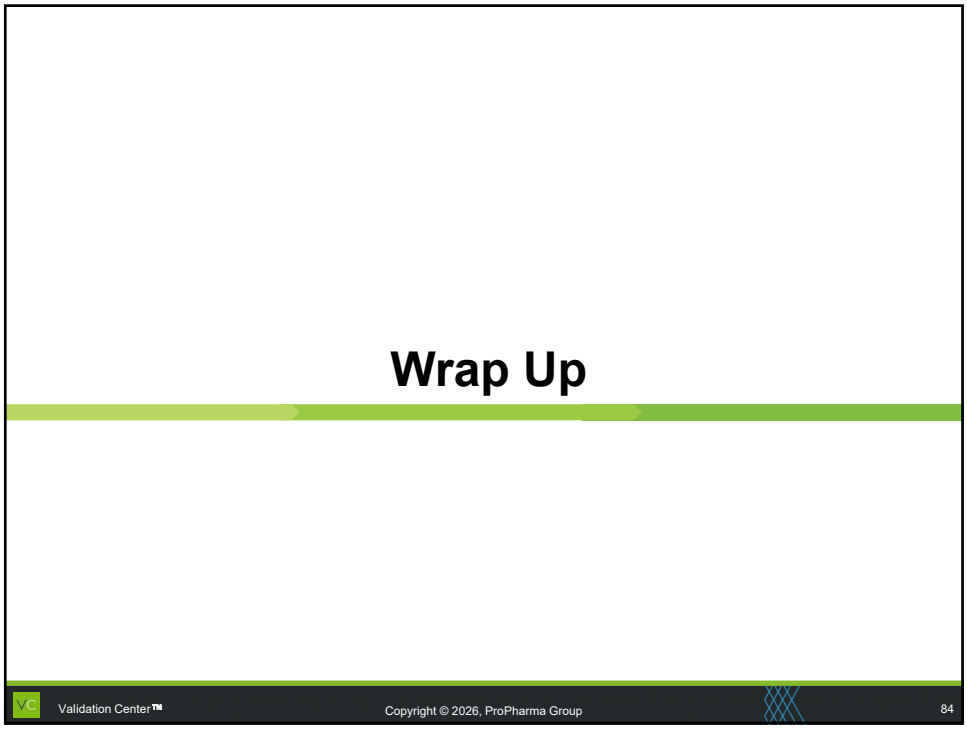

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Warning Letter Example

Regulatory Reference	21 CFR 820 (Medical Devices)
System Type	ERP

There are **no procedures** describing the qualification and maintenance of the Majesty Enterprise Resource Planning (ERP) software for production planning and maintenance of quality records.

- There are **no records** documenting that the Majesty system is validated or meets user needs and intended uses.
- There are no documents that define the **system's features and functions, operating environment, or hardware requirements**.
- The Majesty ERP software was updated to version 28.6 by the vendor. There are no procedures or documents that **describe changes and version updates** to the Majesty ERP system.

The procedure which addresses vendor selection qualification and requalification of suppliers has not been not implemented. There is no documentation that the supplier of Majesty ERP software, was **qualified or re-qualified as a supplier**.

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Warning Letter Example

Regulatory Reference	21 CFR 211 (Pharmaceuticals)
System Type	Laboratory

Firm fails to maintain a backup file of data entered into the computer system. Electronic raw data does not exist for most HPLC assays over two years old because **data is deleted** to make space for the most recent test results.

- Firm has **not implemented security** control of laboratory electronic data.
- All laboratory analysts share the **same password** for the HPLCs in the QC analytical chemistry lab and Omnilog in the microbiology lab.
- In addition, analysts have access to the HPLCs which allow them to **create and/or modify validated methods**.

Firm's SOP does not have provisions for any **audit trail reviews** to ensure that deletions and/or modifications do not occur.

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Warning Letter Example

Regulatory Reference	21 CFR 312 (Investigational Drugs)
System Type	Clinical Study

Failure to retain Electronic case report forms (eCRFs). Firm's study coordinator used a sponsor-provided laptop to enter data each subject. During the closeout visit, the sponsor's monitor took the sponsor-provided laptop computer containing the eCRFs.

However, it was the investigator's responsibility to **retain copies of the eCRFs for two years** after the investigation was discontinued and FDA was notified.

The study coordinator stated that she transcribed vital-sign data from the dialysis center's Patient Treatment Records onto the study flowsheets, and used the flowsheets to enter the data into the eCRFs. However, a review of the data suggests that for some visits, the study coordinator recorded the **post-dialysis vital-sign** data on the study flowsheets rather than the **pre-dialysis vital-sign data**.

This discrepancy raises questions about the **reliability of the data**.

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Need Help?

ValidationCenter.com Library of SOPs

Online and Classroom CSV Training

Software QA and Validation Program Implementation
Validation Services

Audit Readiness Assessments

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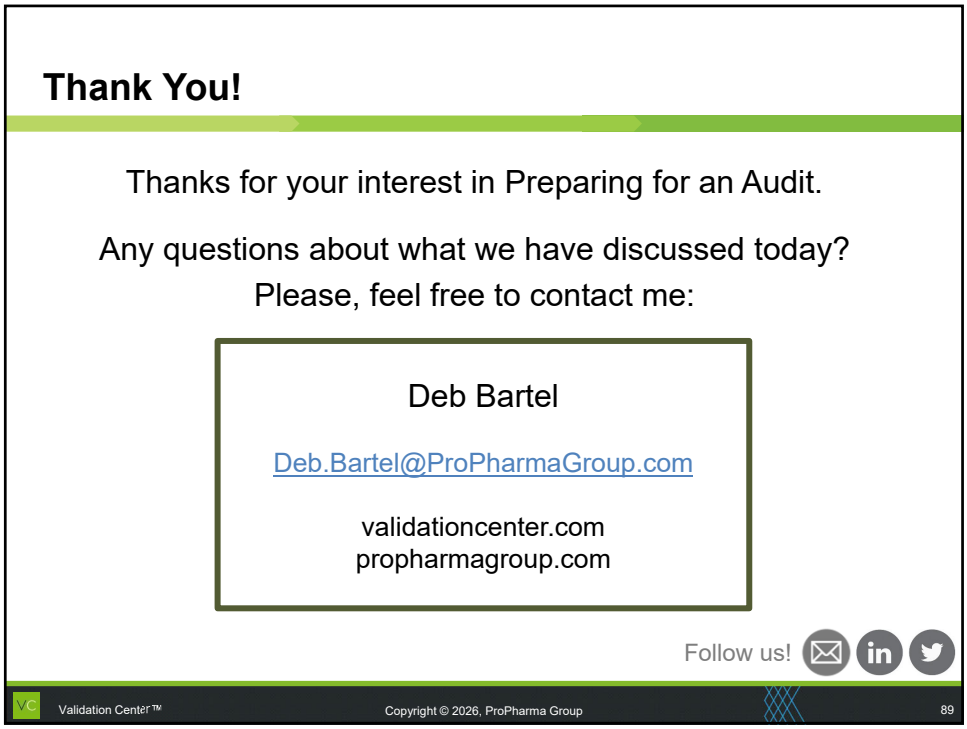

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