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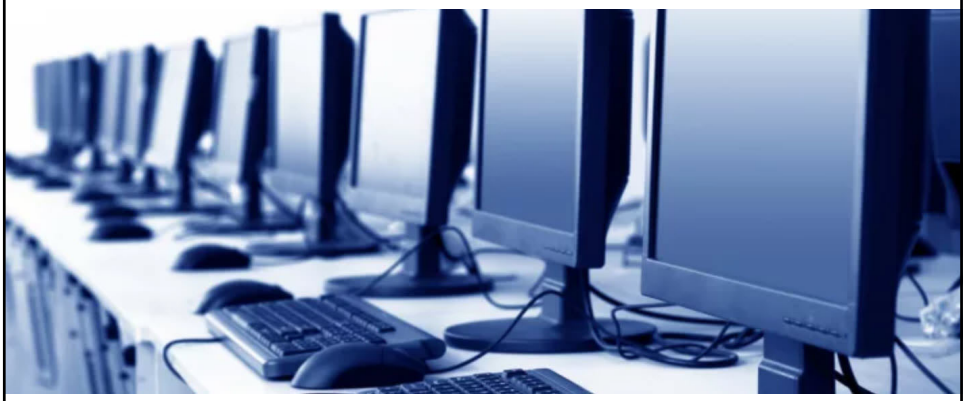
VALIDATION CENTER



Risk Based Approach to Software Quality and Validation

v 25.10

1

Your Presenter

- Debra Bartel, MBA, CQA, PMP
- SVP, 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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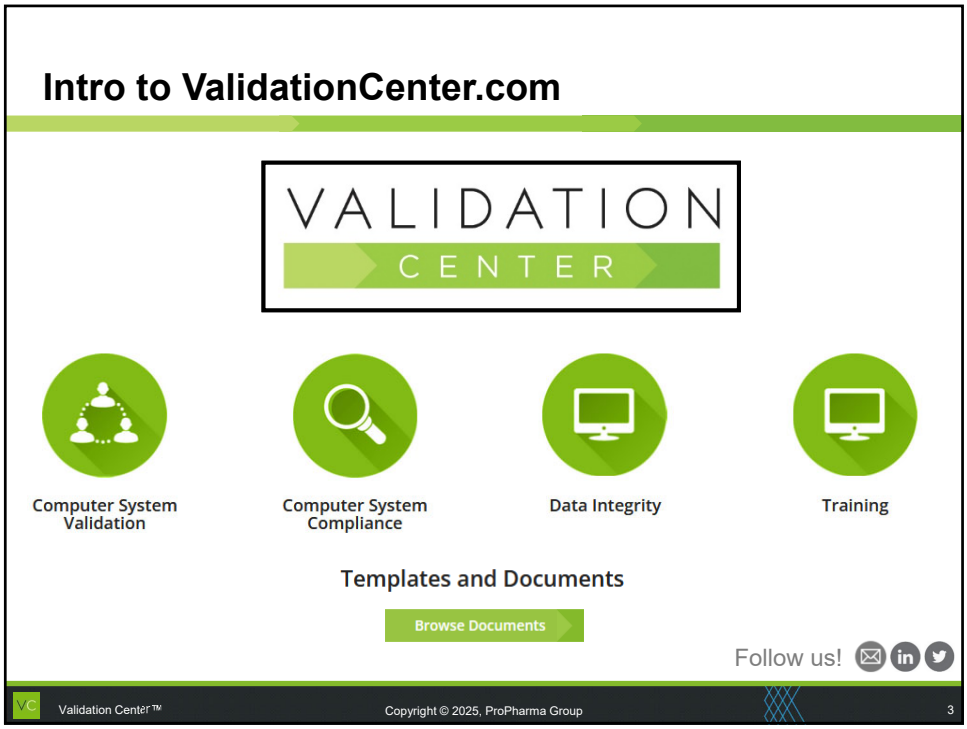

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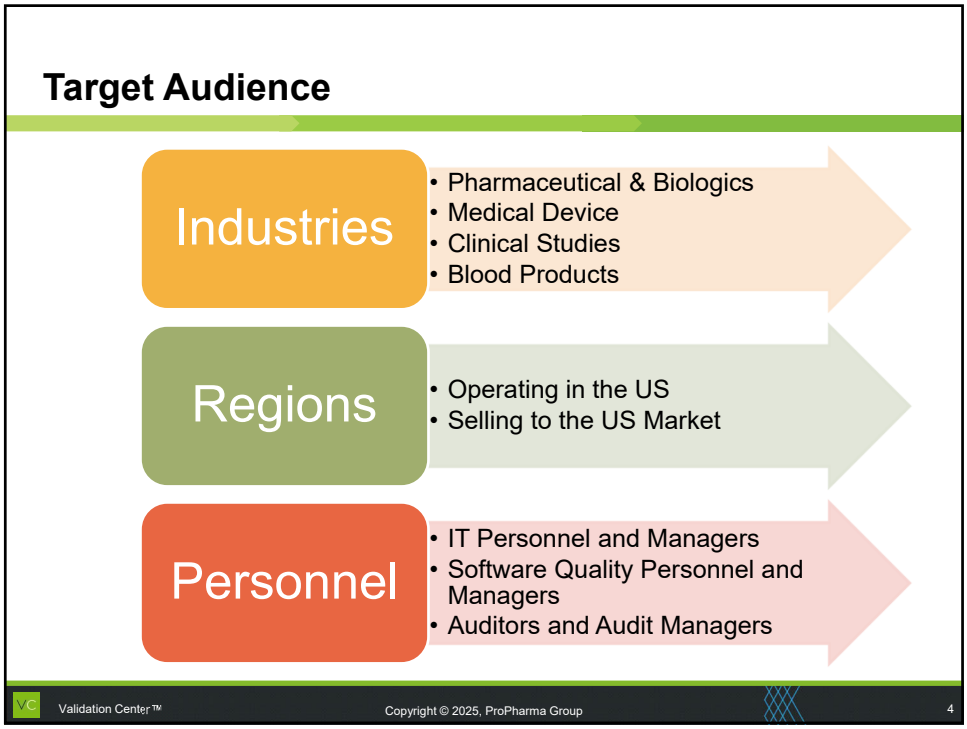

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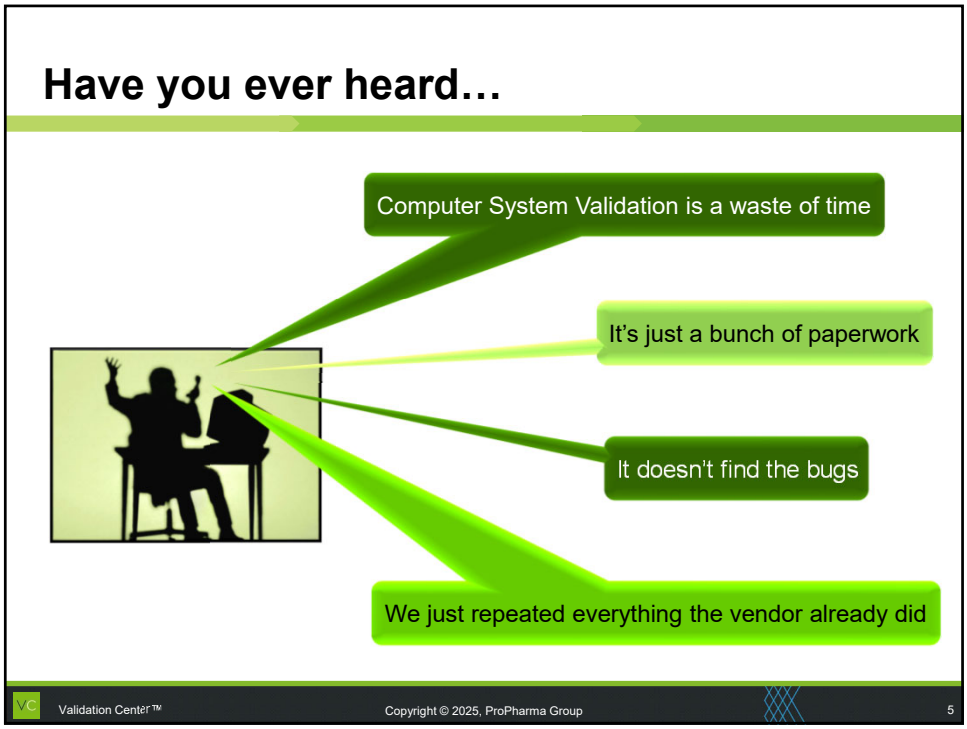

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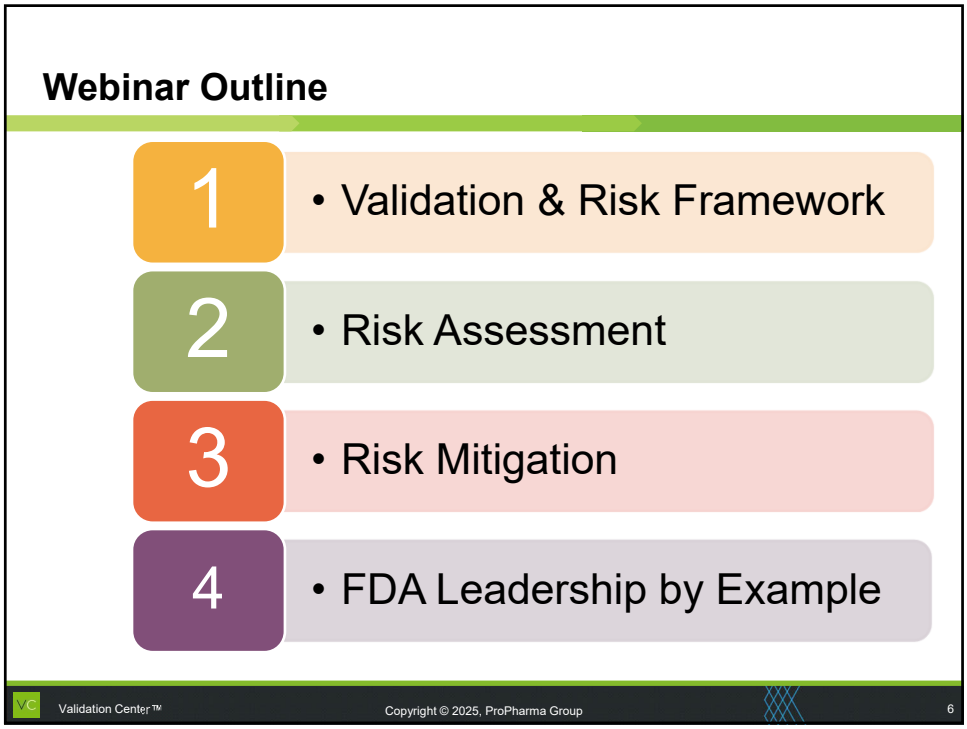

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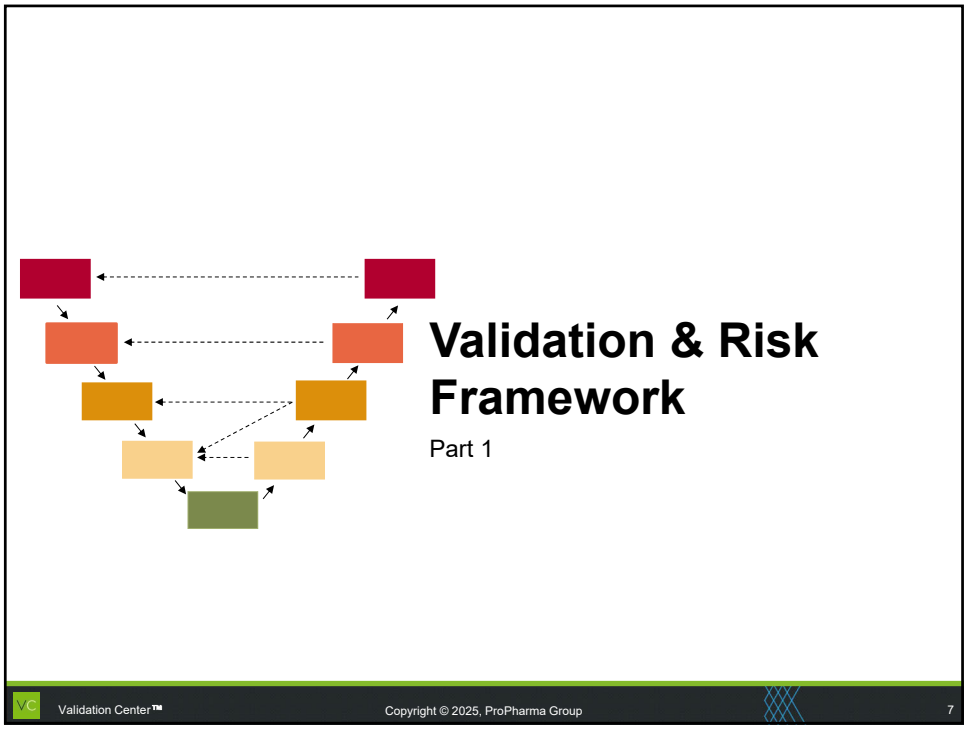

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Part 1: Validation & Risk Framework

- Section Overview
  - Validation Terminology
  - Validation Process
  - Validation Roles & Responsibilities
  - Risk Terminology
  - Risk Process

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Terminology

VALIDATION

Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.

VERIFICATION
…consistency, completeness, and correctness of the software and its supporting documentation, ….

- URS Approval
- FS Approval
- Design Review
- Code Walkthrough
- Unit Testing
- Trace Matrix
- Validation Report
- Performance Qualification
- Operational Qualification
- Installation Qualification
- SOP Review
- Training Review

QUALIFICATION
Formal testing to demonstrate that the software meets its specified requirements.

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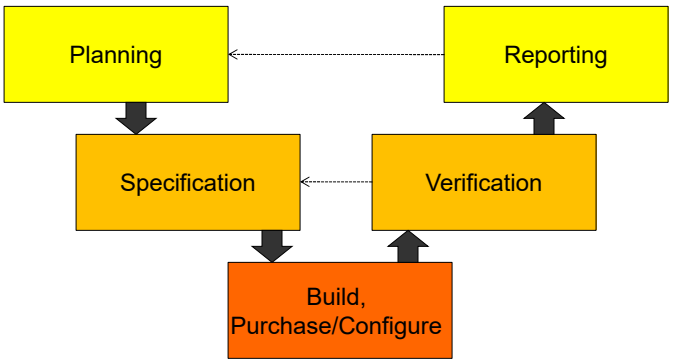
Validation Life Cycle



GENERAL APPROACH

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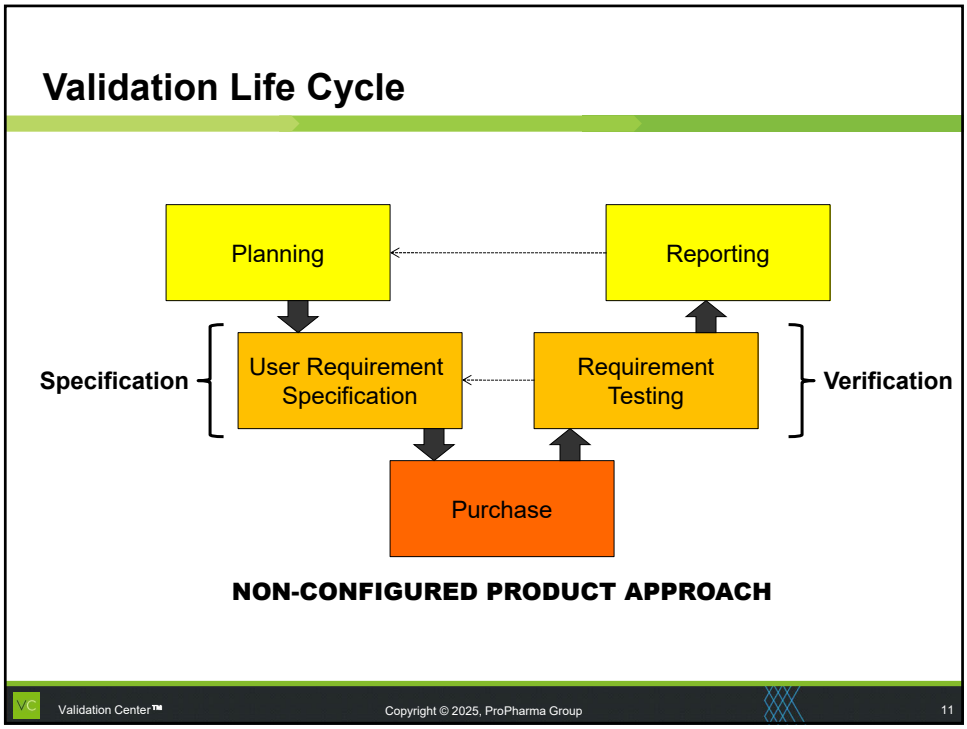

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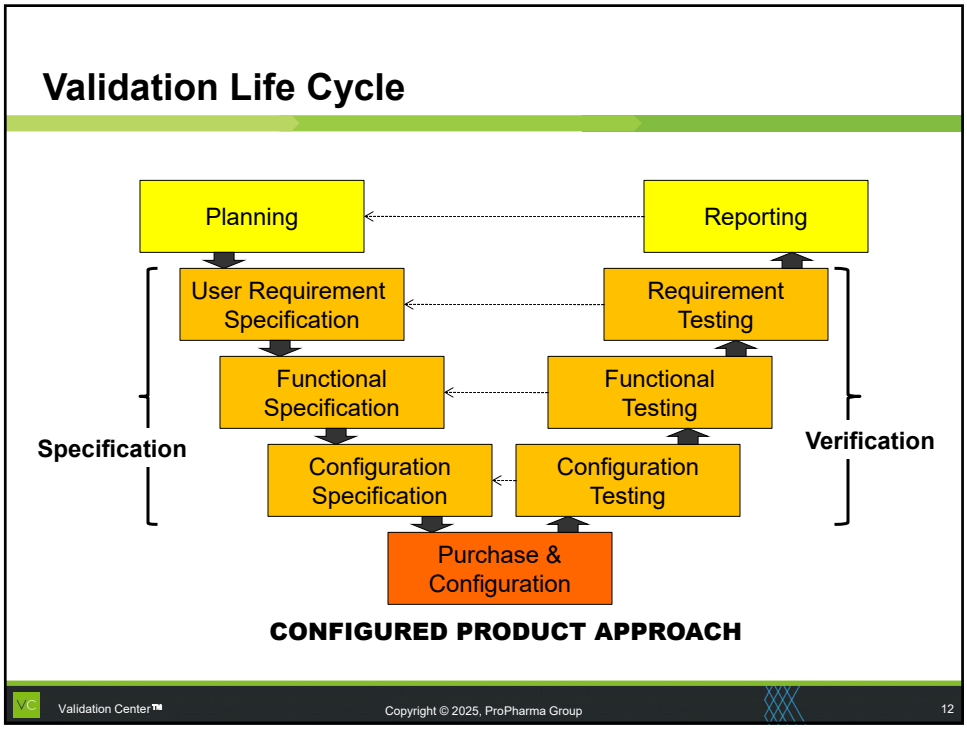

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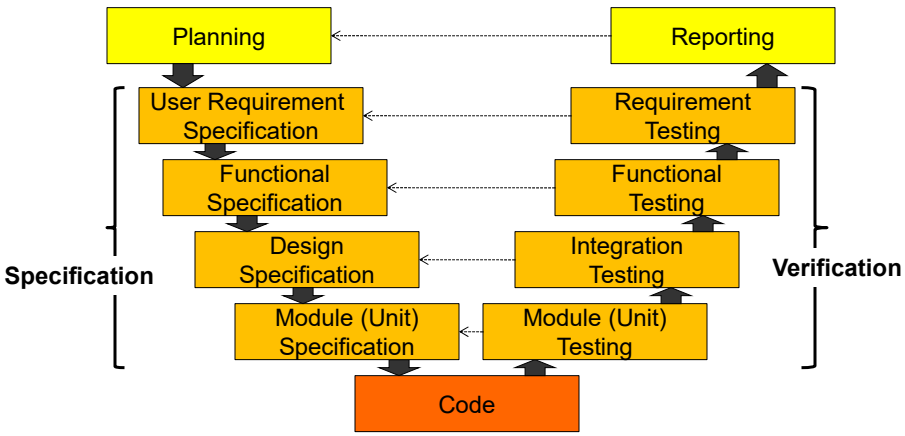
Validation Life Cycle



CUSTOM CODED PRODUCT APPROACH

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Validation Roles

Business Process Owner

- **Manages the business process that uses the computer system**
- **Ensures that the system is appropriate for the business process**
- **Assigns Subject Matter Experts (SMEs) to participate in requirements definition and verification**

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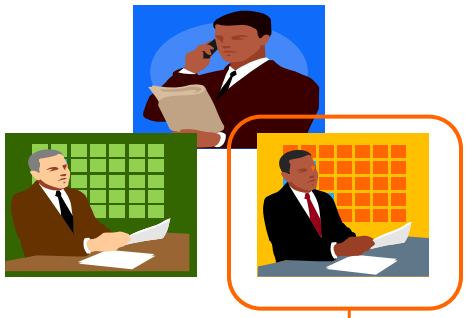
Validation Roles



- **Manages the implementation and support of the computer system**
- **Ensures that the system is available to support the business process**
- **Assigns technical experts to participate in all phases of the validation life cycle**

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Validation Roles

- **Ensures that the computer system meets all internal standards**
- **Ensures that the computer system meets all applicable regulations**
- **Ensures that the computer system is ready for inspection**

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Basic Risk Terminology

Hazard

A potential source of harm

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Basic Risk Terminology

Hazard — A potential source of harm

Risk

The combination of the probability of occurrence of a harm and the severity of the harm

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Basic Risk Terminology

Hazard — A potential source of harm

Risk — Harm severity and probability

Risk Assessment

A comprehensive evaluation of risks and associated impacts

Severity:

A.

B.

C.

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Basic Risk Terminology

Hazard — A potential source of harm

Risk — Harm severity and probability

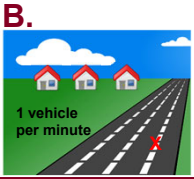
Risk Assessment

A comprehensive evaluation of risks and associated impacts

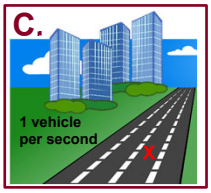
Probability:

A.

B.



C.



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Basic Risk Terminology

Hazard	A potential source of harm
Risk	Harm severity and probability
Risk Assessment	Evaluation of risk and impact

Risk Mitigation

Actions taken to reduce the risk


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Basic Risk Terminology

Hazard	A potential source of harm
Risk	Harm severity and probability
Risk Assessment	Evaluation of risk and impact
Risk Mitigation	Action to reduce impact

Risk Management

A systematic approach to assessment and mitigation of risks throughout the system life cycle

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Risk Management Framework

Risk Management Process

Risk Assessment	SOP System Risk Assessment				
Risk Mitigation	SOP Risk Based Validation	SOP Audit Trails	SOP Audit Trail Review	SOP Software Vendor Assessment	
	SOP User Training	SOP Incident Management	SOP System Backup	SOP Business Continuity	Etc.

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Risk Assessment

Part 2

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Part 2: Risk Assessment

- Section Overview
  - Regulatory Guidance
  - Risk Assessment Process
  - Documentation

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USA

FDA *Glossary of Computerized System and Software Development Terminology*

Risk = A measure of the **probability** and **severity** of undesired effects. Often taken as the simple product of probability and consequence. (Source: IEEE)

Risk Assessment = A comprehensive evaluation of the **risk** and its associated impact (Source: DOD).

FDA 21 CFR 820 *Quality System Regulation* (Medical Device GMP)

- Design validation shall include software validation and **risk analysis**, where appropriate.

FDA Guidance*: Off-The-Shelf Software Use in Medical Devices*

- Existing international standards indicate that the estimation of **risk** should be considered as the product of the **severity of harm** and the **probability of occurrence of harm**.
- It is more appropriate to manage **software safety risk** based on the **severity of harm** rather than the **software failure rates**.

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ICH

ICH Q9, *Quality Risk Management*

Risk assessment consists of the identification of hazards and the analysis and evaluation of **risk**s associated with exposure to those hazards.

Three fundamental questions:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

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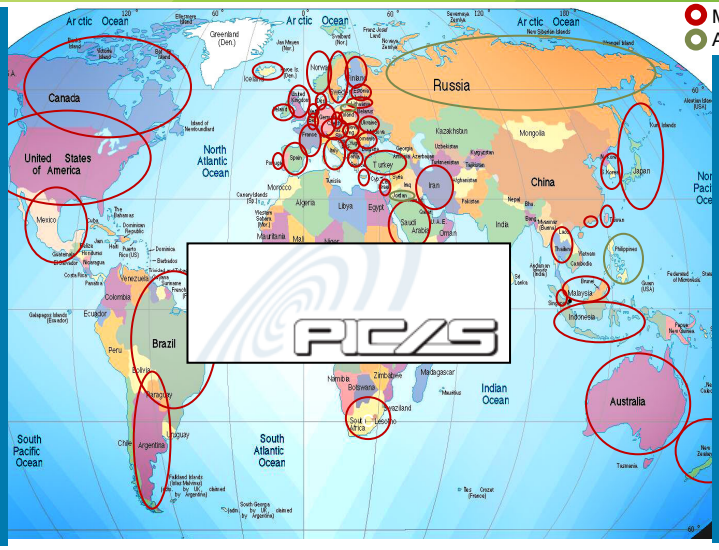
PIC/S

Argentina
Australia
Austria
Belgium
Brazil
Bulgaria
Canada
Chinese Taipei
Croatia
Cyprus
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hong Kong
Hungary
Iceland
Indonesia
Iran
Ireland
Israel
Italy
Japan
Korea, Rep. of
Latvia



Members
Applicants

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Liechtenstein
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New Zealand
Norway
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Romania
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Slovenia
South Africa
Spain
Sweden
Switzerland
Thailand
Turkey
Ukraine
United Kingdom
USA

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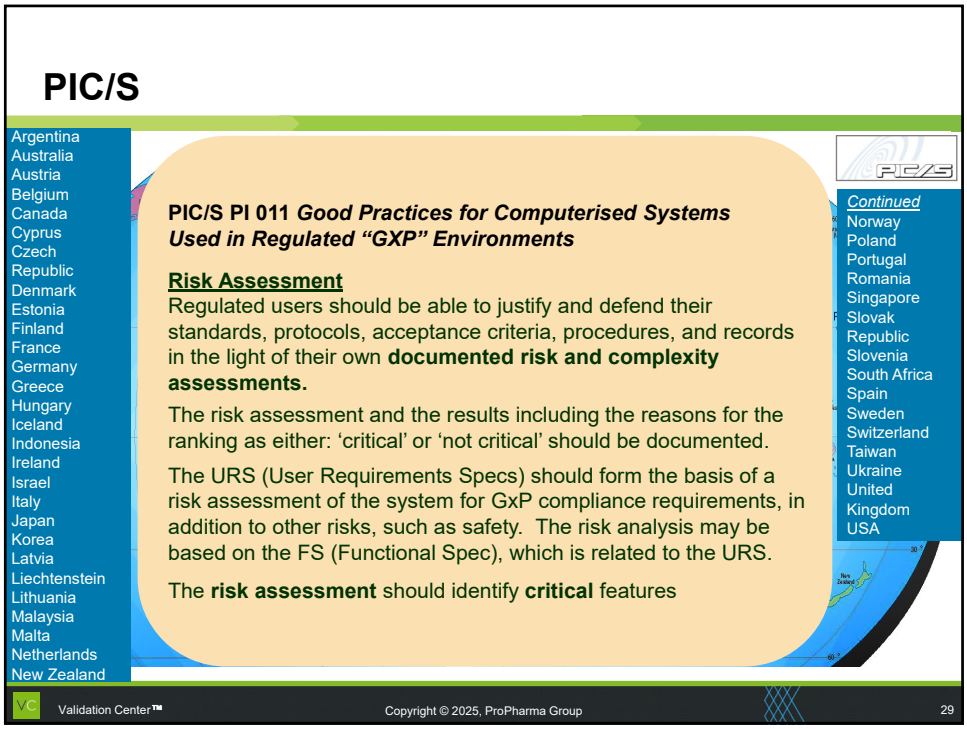

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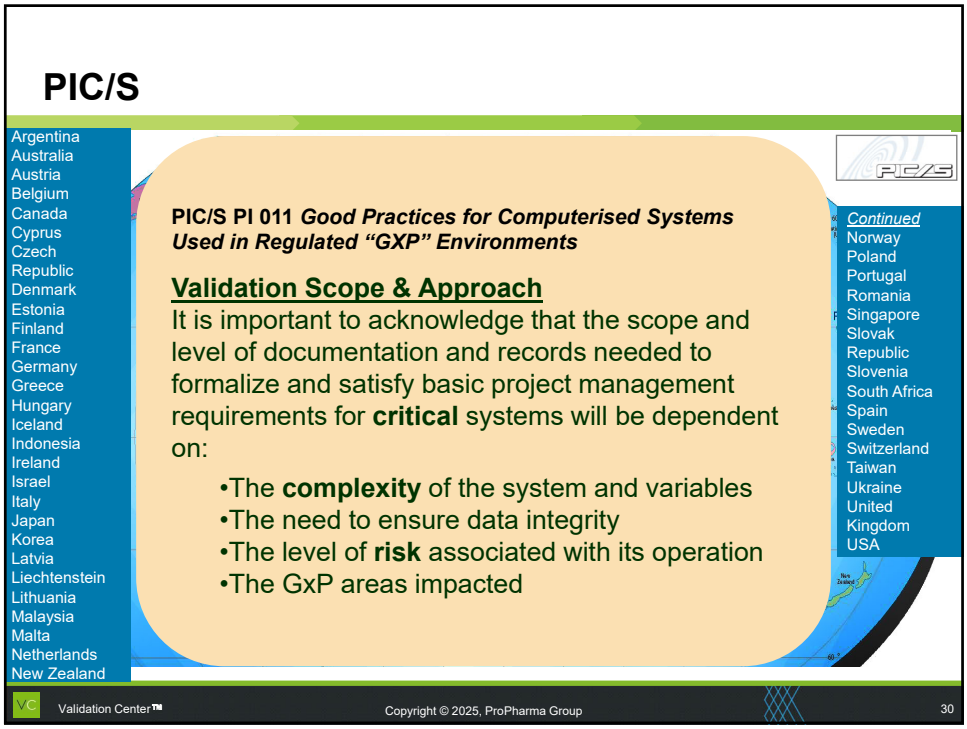

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Risk Management Framework

Risk Management Process

Risk Assessment	SOP System Risk Assessment				
Risk Mitigation	SOP Risk Based Validation	SOP Audit Trails	SOP Audit Trail Review	SOP Software Vendor Assessment	
	SOP User Training	SOP Incident Management	SOP System Backup	SOP Business Continuity	Etc.

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Risk Assessment Roles

Business Process Owner
Identify, Evaluate, and Classify Risks

Quality Assurance
Evaluate any risks associated with regulatory compliance and company policies

Technology Owner
Provide information on how the software works and where it could fail

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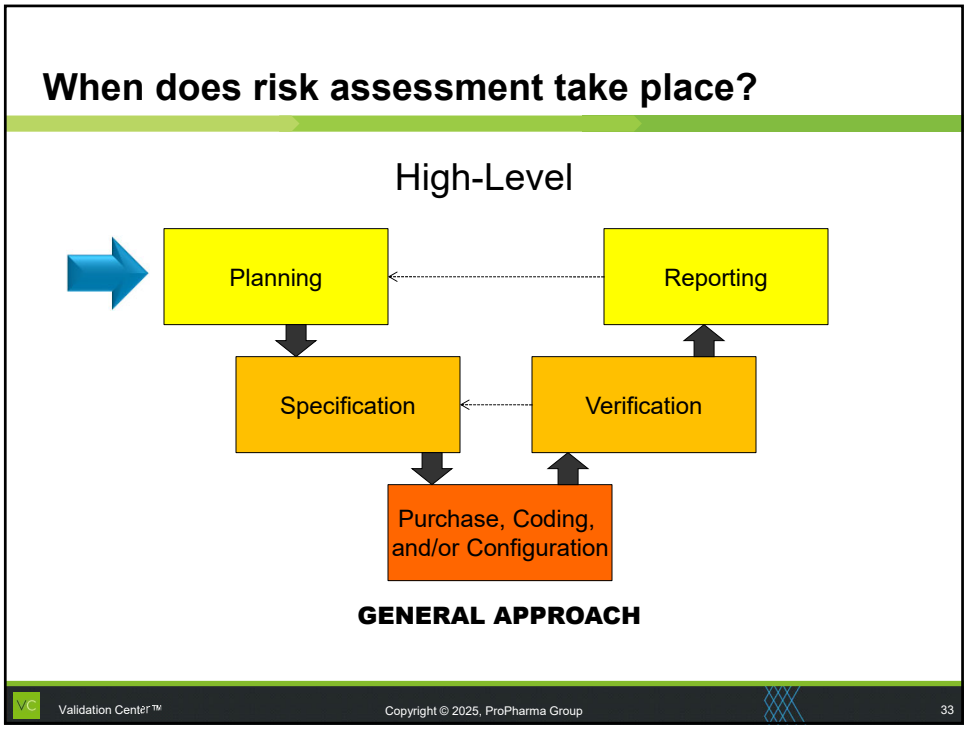

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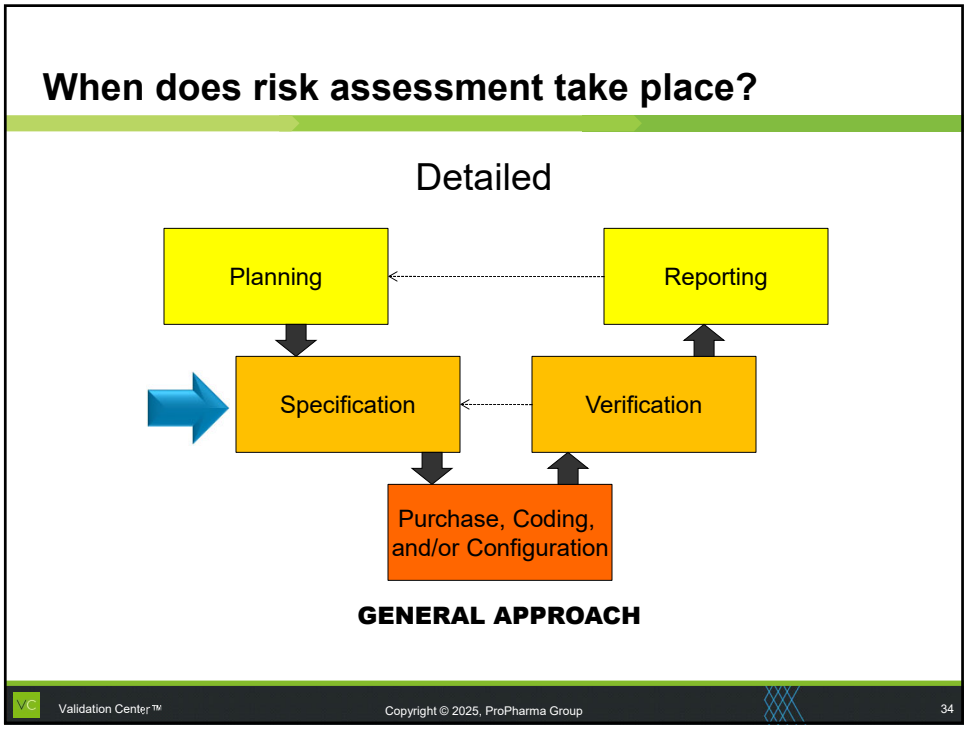

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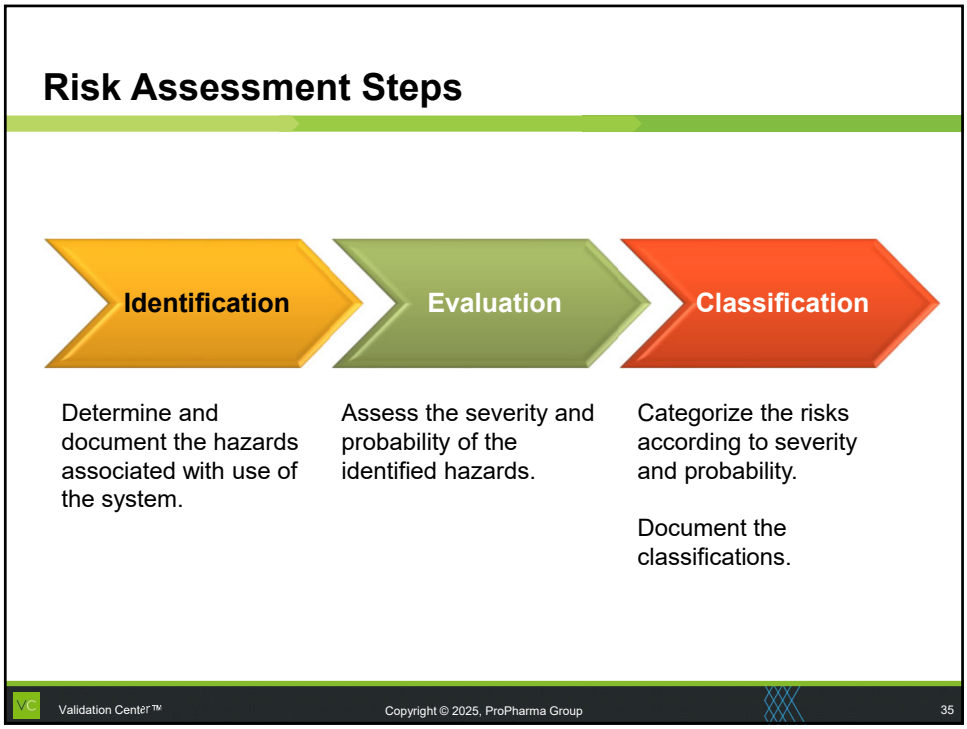

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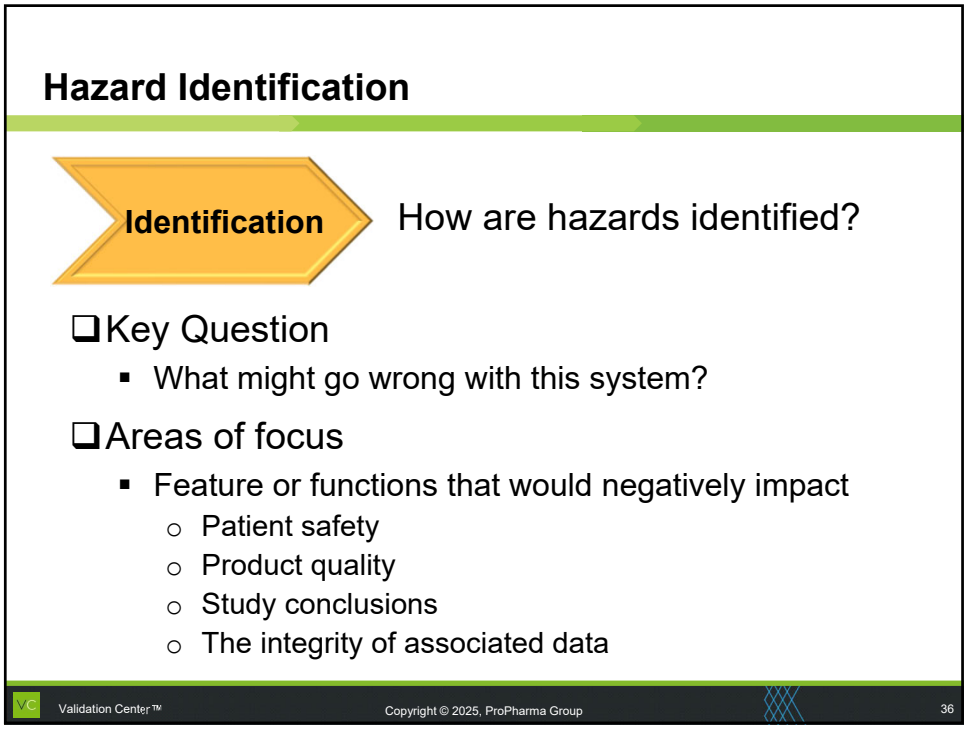

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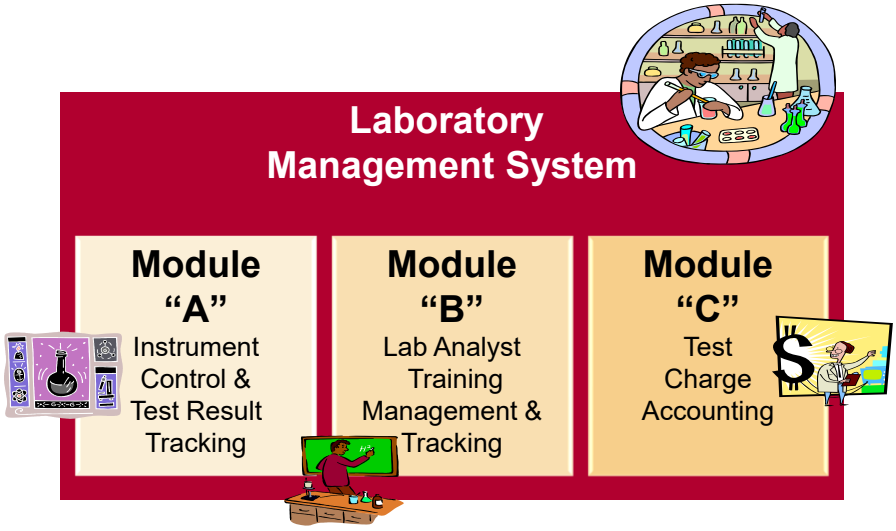
Example System



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Example Hazards

Identification What might go wrong?

User Requirement	Identified Hazard
1. Send test instructions to lab instruments and receive test result data from the instrument	An instrument interface problem could result in an incorrect reading from equipment
2. Calculate whether a test passes or fails using input from the lab instruments and analyst entries	An incorrect laboratory calculation could provide a passing test result when it should have failed
3. Assign analysts to perform tests based on training	A data integrity error in the training module could show that a lab analyst was trained when she was not
4. Calculate the charges for testing for each product line	There could be a calculation error in the Test Charge module

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Hazard Evaluation

Evaluation How are hazards evaluated?

- Key Questions
  - What are the consequences (severity) of the hazard?
  - What is the likelihood (probability) the hazard will occur?
- Areas of focus
  - Features or functions that could lead to
    - Patient death or injury
    - Product failure or quality issue
    - Study outcomes
    - Compromised integrity of the associated data

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Hazard Evaluation

Evaluation How are hazards evaluated?

Risk Definition

The combination of the probability of occurrence of a hazard and the severity of the hazard

Risk Component 1	*Risk Component 2*
Severity of Harm	**Probability of Occurrence**
Measured as Criticality	**Measured as Complexity**

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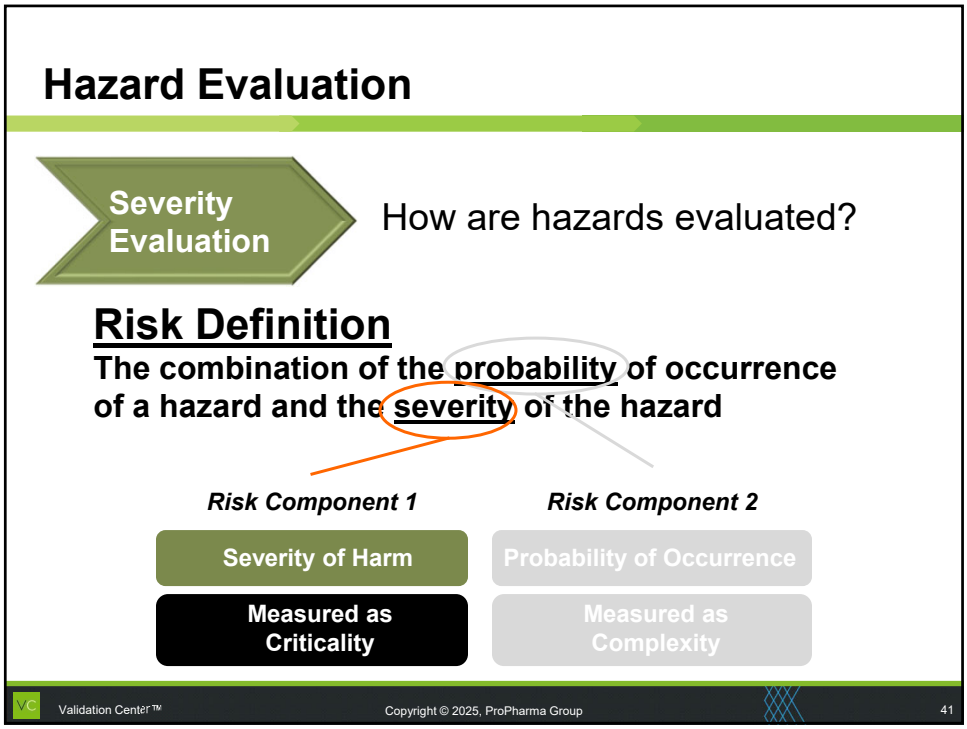

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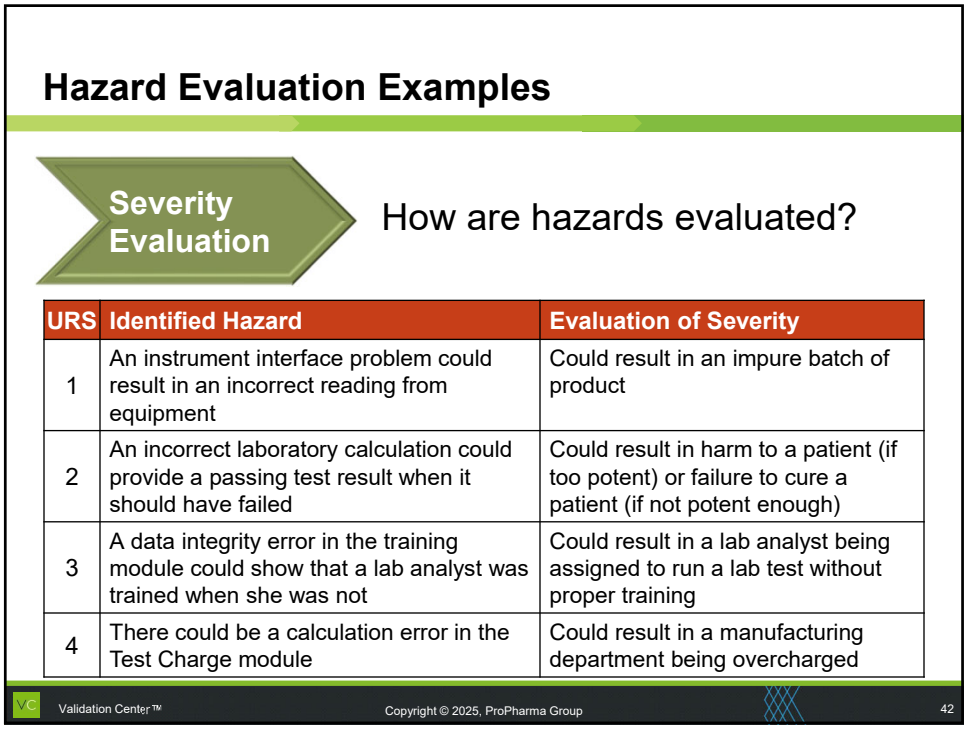

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Severity Classification

Severity Classification

How is severity classified?

- Common Classification Method
  - Classification by Criticality
  - 3 Levels

High Criticality	Direct impact on patient safety, product quality, study outcome, or the integrity of associated data
Medium Criticality	Indirect impact on patient safety, product quality, study outcome, or the integrity of associated data
Low Criticality	No impact on patient safety, product quality, study outcome, or the integrity of associated data

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Severity Classification

Level	Expanded Definition
Severity Classification **High Criticality**	Direct control of: • Manufacturing • Labeling • Distribution • Product Testing • Product Release • Clinical Trials Direct impact on: • Product Quality • Patient Safety • Study Outcomes
Medium Criticality	Indirect impact on patient safety, product quality, study outcomes, or the integrity of associated data
Low Criticality	No impact on patient safety, product quality, study outcomes, or the integrity of associated data

Examples
- Health product software
- Manufacturing controls
- Automated product inspection
- Label management & automation
- Distribution tracking to enable recalls
- Laboratory test results
- Adverse event tracking
- Clinical trial results
- Patient medical records
- GCP EDC Records

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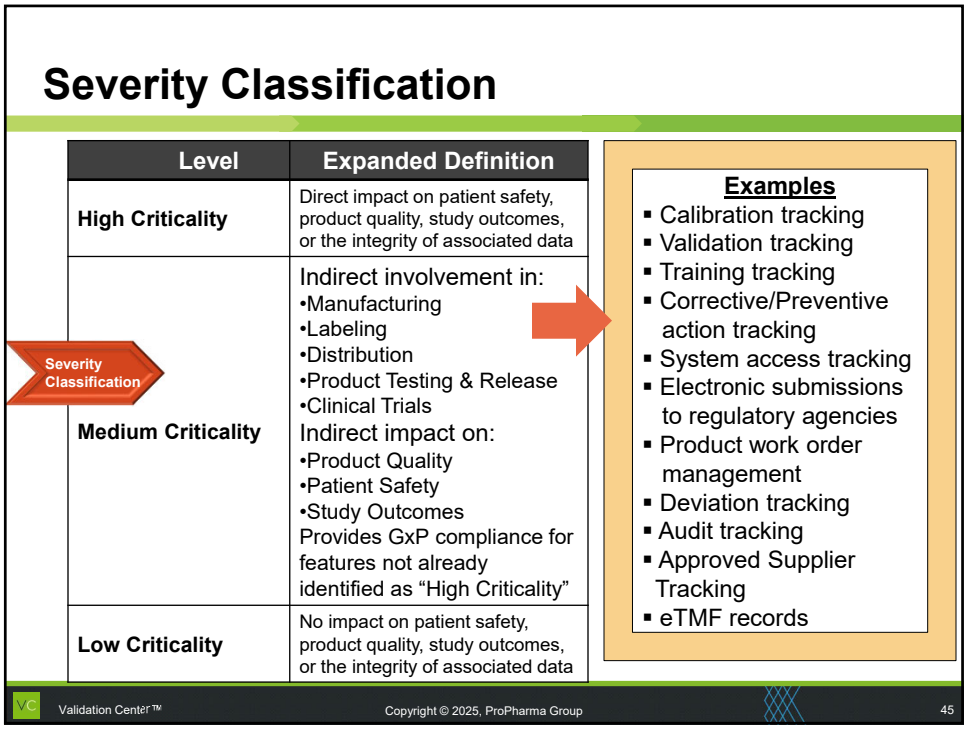

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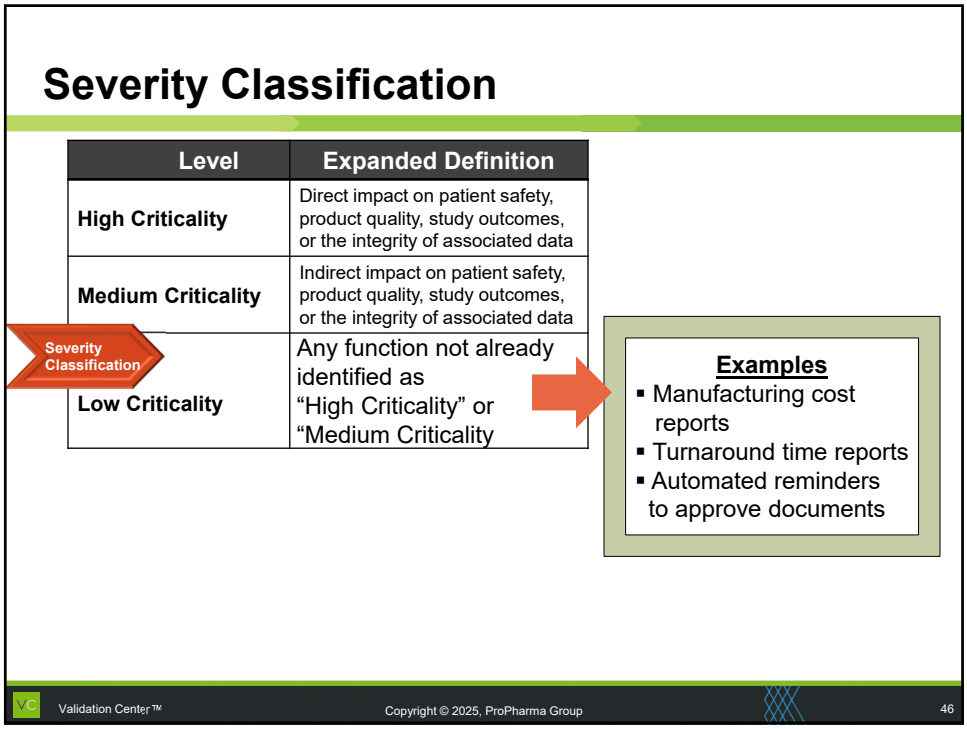

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Severity Classification Examples

Severity Classification

URS	Identified Hazard	Evaluation of Severity	Criticality
1	An instrument interface problem could result in an incorrect reading from equipment	Could result in an impure batch of product	High
2	An incorrect laboratory calculation could provide a passing test result when it should have failed	Could result in harm to a patient or failure to cure a patient	High
3	A data integrity error in the training module could show that a lab analyst was trained when she was not	Could result in a lab analyst being assigned to run a lab test without proper training	Medium
4	There could be a calculation error in the Test Charge module	Could result in a manufacturing department being overcharged	Low

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Probability Evaluation

Probability Evaluation

How are hazards evaluated?

Risk Definition

The combination of the probability of occurrence of a hazard and the severity of the hazard

Risk Component 1	*Risk Component 2*
Severity of Harm	Probability of Occurrence
Measured as Criticality	Measured as Complexity

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Probability Assessed as "Complexity"

The selection of **validation activities** should be commensurate with the **complexity** of the software and the **risk** associated with use of the software for its specific intended use

Validation **coverage** should be based on the software' **complexity** and safety **risk.**

The scope and level of **documentation** and **records** needed to formalize and satisfy basic project management requirements for **critical** systems will be dependent on the **complexity** of the system.

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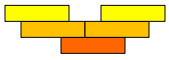
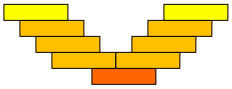
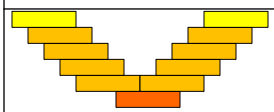
Probability Classification

Probability Classification

How can probability be classified?

Validation Approach	Complexity Level	Definition
	**Low**	Standard, non-configured functions within off-the-shelf purchased systems
	**Medium**	Configured functions within off-the-shelf purchased systems
	**High**	Custom developed functions within either purchased or custom systems

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Probability Classification

Complexity Level	Definition	Examples
Low	Standard, non-configured functions within off-the-shelf purchased systems	• Standard test result report within an off-the-shelf laboratory system • Standard data entry screen in a medical records system
Medium	Configured functions within off-the-shelf purchased systems	• Report configured with an off-the-shelf query tool • Calculation configured in a laboratory system • Calculation configured in an off-the-shelf spreadsheet tool • Product release algorithm configured in an off-the-shelf inventory control system
High	Custom developed functions within either purchased or custom systems	• Custom accounting report developed in COBOL • Custom code developed to send e-mail notification from an off-the-shelf training management system

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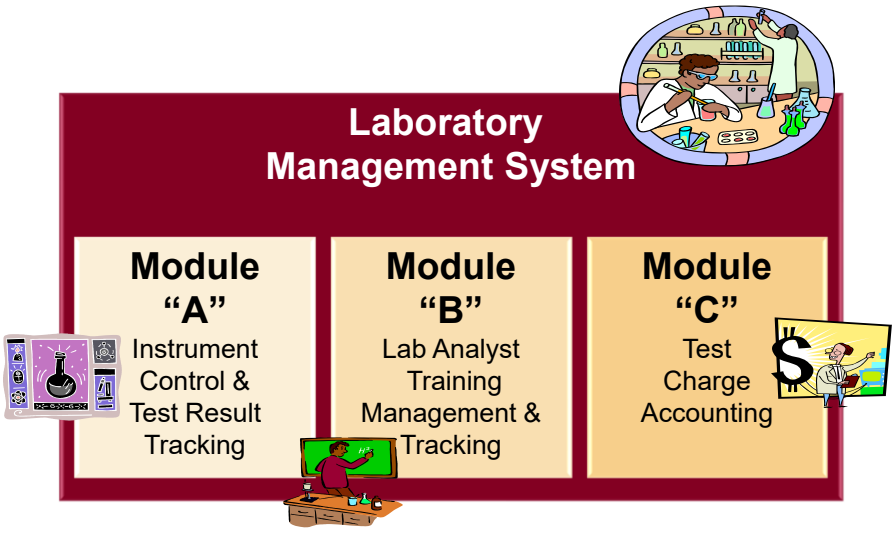
Probability Classification Example



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Probability Classification Example

Probability Classification

URS	Requirement	Criticality	Technology	Complexity
1	Send test instructions to lab instruments and receive test result data from the instrument	High	Configured using the out-of-the-box instrument interface tool	Medium
2	Calculate whether a test passes or fails using input from the lab instruments and analyst entries	High	Custom code	High
3	Assign analysts to perform tests based on training	Medium	Out-of the box functionality	Low
4	Calculate the charges for testing for each product line	Low	Custom report developed in house	High

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Classification Levels

Classification

	Requirement Level Criticality	Requirement Level Complexity
1	High	Medium
2	High	High
3	Medium	Low
4	Low	

System level criticality is the same as the highest requirement level criticality

System Level Criticality
High

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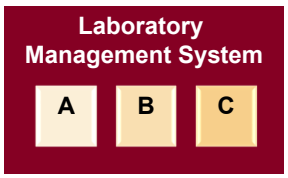
Risk Assessment Documentation

Where should the risk assessment be documented?



System Level
- Validation Master Plan (VMP)
- Stand-alone, Risk Assessment

options

Requirement Level
- Requirements Specification
- Stand-alone, Risk Assessment

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Risk Assessment Documentation

System and Requirement Risk Assessment

System Name: ABC Laboratory Management System
System Version: 1.0

System Criticality Level: ☒ High ☐ Medium ☐ Low
System Criticality Rationale: System performs functions that are critical to patient safety. See details in the analysis, below.

Requirement Criticality and Complexity Analysis

Requirement	Criticality Level	Rationale for Criticality Level	Complexity Level	Rationale for Complexity Level
Instrument control [URS 1]	High	An incorrect lab instrument reading could result in an impure batch of product.	Medium	Configured with system's instrument interface tool
Test pass/fail determination [URS 2]	High	A calculation error could result in patient harm or failure to cure a patient.	High	Custom Code
Analyst assignment based on training [URS 3]	Medium	A data integrity issue in this function could result in a lab analyst being assigned to run a lab test without proper training.	Low	Standard system functionality without modification
Testing charges for each product [URS 4]	Low	This function has no impact on patient safety or product quality.	High	Custom code

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Risk Mitigation

Part 3

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Part 3: Risk Mitigation

- Section Overview
  - Risk Mitigation Timing and Activities
  - Regulatory Guidance
  - Risk Mitigation via Risk Based Validation
  - Vendor Documentation and Testing
  - Risk Mitigation via Risk Based Software Quality Procedures

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Risk Mitigation Definition

Risk Mitigation

Actions taken to reduce the risk

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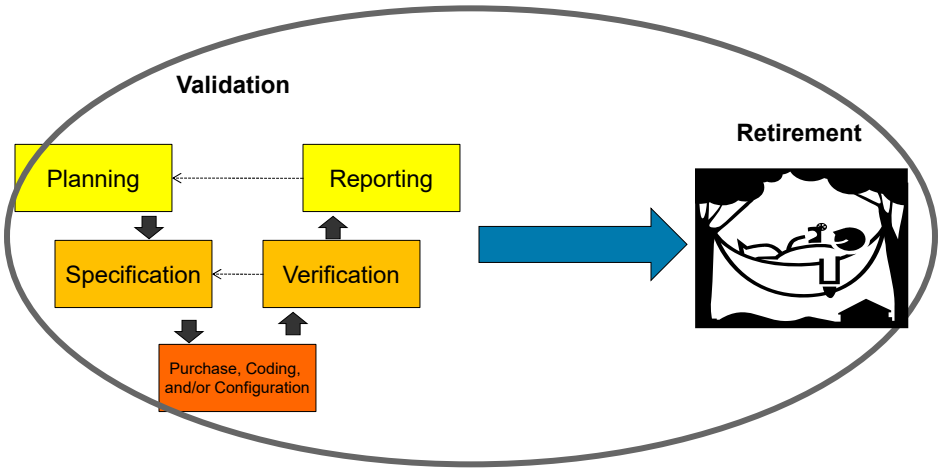
When does Risk Mitigation Take Place?



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What are Risk Mitigation Activities?

Risk Mitigation Examples

Activities that reduce the likelihood of user errors:

- 2nd person verification of data entry
- Improved user training
- Design changes for error-prone features

Activities that increase the likelihood of detection of system issues before harm:

- Audit trail reviews
- Periodic checks of back-ups
- Access reviews

Activities that reduce the likelihood of system failure:

- Design reviews
- Code walkthroughs
- Testing

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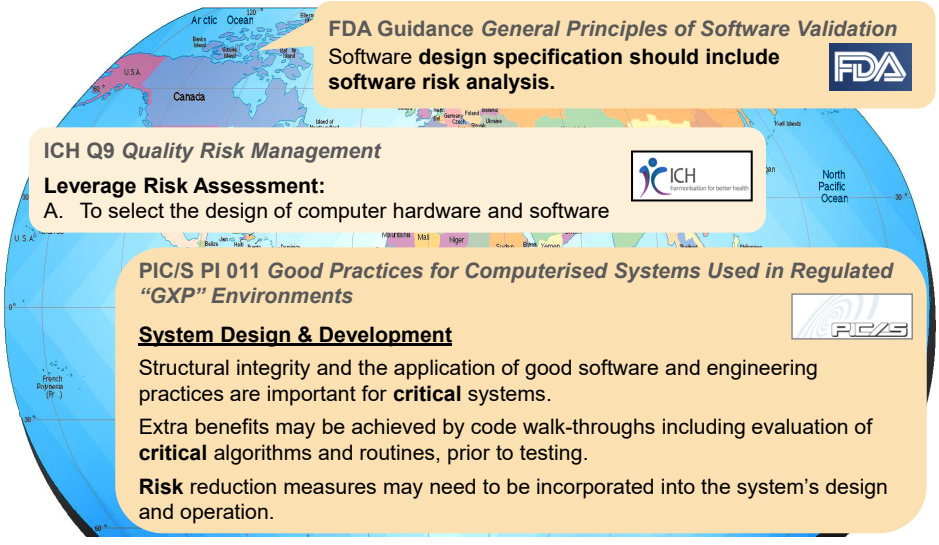
Mitigation during Design & Dev Stages



FDA Guidance *General Principles of Software Validation*

Software **design specification should include software risk analysis.**

ICH Q9 *Quality Risk Management*

Leverage Risk Assessment:

A. To select the design of computer hardware and software

PIC/S PI 011 *Good Practices for Computerised Systems Used in Regulated "GXP" Environments*

System Design & Development

Structural integrity and the application of good software and engineering practices are important for **critical** systems.

Extra benefits may be achieved by code walk-throughs including evaluation of **critical** algorithms and routines, prior to testing.

Risk reduction measures may need to be incorporated into the system's design and operation.

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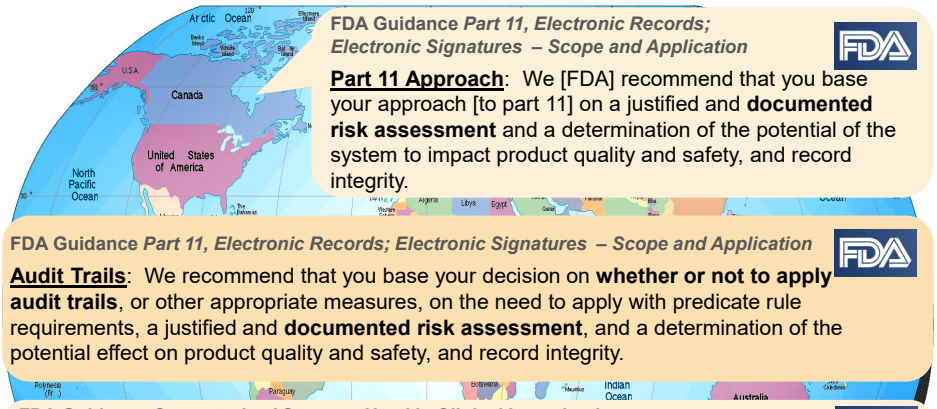
Mitigation during Design & Dev Stages



FDA Guidance *Part 11, Electronic Records; Electronic Signatures – Scope and Application*

Part 11 Approach: We [FDA] recommend that you base your approach [to part 11] on a justified and **documented risk assessment** and a determination of the potential of the system to impact product quality and safety, and record integrity.

FDA Guidance *Part 11, Electronic Records; Electronic Signatures – Scope and Application*

Audit Trails: We recommend that you base your decision on **whether or not to apply audit trails**, or other appropriate measures, on the need to apply 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.

FDA Guidance *Computerized Systems Used in Clinical Investigations*

Audit Trails: The **need for audit trails** should be determined based on a justified and **documented risk assessment** that takes into consideration circumstances surrounding system use, the likelihood that information might be compromised, and any system vulnerabilities.

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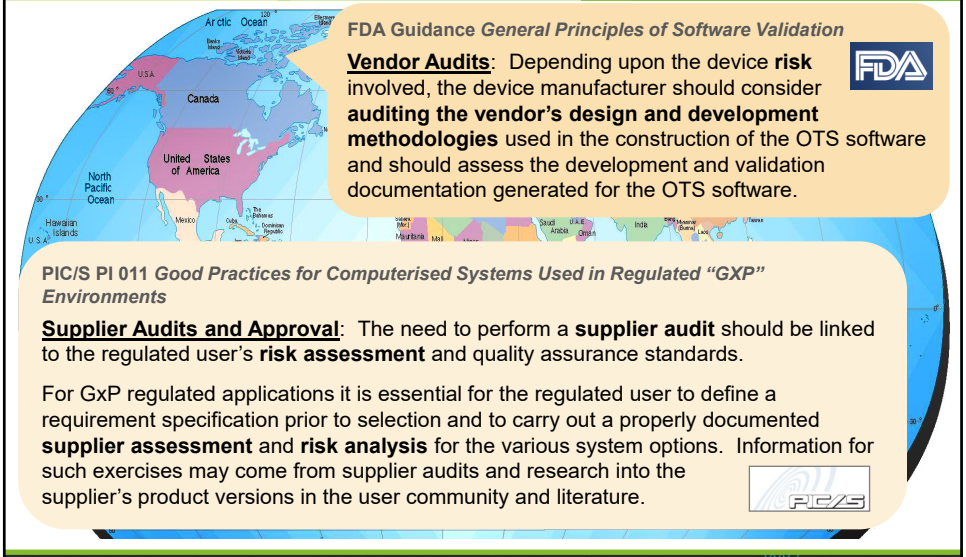
Mitigation during Vendor Selection



FDA Guidance *General Principles of Software Validation*

Vendor Audits: Depending upon the device **risk** involved, the device manufacturer should consider **auditing the vendor's design and development methodologies** used in the construction of the OTS software and should assess the development and validation documentation generated for the OTS software.

PIC/S PI 011 *Good Practices for Computerised Systems Used in Regulated "GXP" Environments*

Supplier Audits and Approval: The need to perform a **supplier audit** should be linked to the regulated user's **risk assessment** and quality assurance standards.

For GxP regulated applications it is essential for the regulated user to define a requirement specification prior to selection and to carry out a properly documented **supplier assessment** and **risk analysis** for the various system options. Information for such exercises may come from supplier audits and research into the supplier's product versions in the user community and literature.

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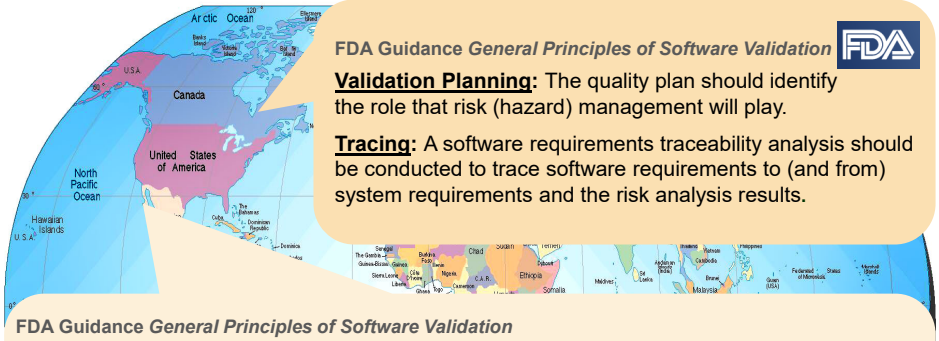
Mitigation during Validation Planning



FDA Guidance *General Principles of Software Validation*

Validation Planning: The quality plan should identify the role that risk (hazard) management will play.

Tracing: A software requirements traceability analysis should be conducted to trace software requirements to (and from) system requirements and the risk analysis results.

FDA Guidance *General Principles of Software Validation*

Validation Scope & Scale: Validation coverage should be based on the software's **complexity** and **safety risk**. The selection of validation activities should be commensurate with the **complexity** of the software design and the **risk** associated with use of the software for its specific intended use. As the **risk** increases, additional validation activities should be added to cover the additional **risk**

For **very low risk** applications, certain tasks might not be needed at all.

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Mitigation during Validation Planning

PIC/S PI 011 *Good Practices for Computerised Systems Used in Regulated "GXP" Environments*

Validation scope should include GxP compliance criteria, ranked for all product/process quality and data integrity **risk criticality**, should the system fail or malfunction.

It is essential to assign priorities and attention to those systems (and features within systems) that represent **the highest potential for disaster**, should they malfunction or become inoperative.

ICH Q9 *Quality Risk Management*

Leverage Risk Assessment to determine the **extent of validation**, e.g.,

- identification of critical performance parameters
- selection of the requirements and design
- code review
- the extent of testing and test methods
- reliability of electronic records and signatures.

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Mitigation during and after Validation

FDA Guidance *General Principles of Software Validation*

Testing: The amount of structural testing should be commensurate with the level of **risk** posed by the software. The amount of path coverage is normally established based on the **risk** or **criticality** of the software under test.

Validation Evidence: Document requirements and **risk analysis** of the automated process help to define the scope of the evidence needed to show that the software is validated for its intended use.

FDA Guidance *Computerized Systems Used in Clinical Investigations*

Validation of Changes: The effects of changes to the system should be evaluated, and some should be validated depending on **risk**

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Mitigation during the Life of the System

PIC/S PI 011 *Good Practices for Computerised Systems Used in Regulated "GXP" Environments*

Data Entry: Where applicable, there should be special procedures for **critical** data entry requiring and second check.

Back-Ups: The frequency of back-up is dependent on the computer system function and the **risk assessment** of the loss of data.

There should be procedures to assure routine back-up of data to a safe storage location, adequately separated from the primary storage location, and at a frequency based on the **analysis of risk** to GxP data.

FDA Guidance *Part 11, Electronic Records; Electronic Signatures – Scope and Application*

Record Maintenance: We [FDA] suggest 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.

FDA Guidance *Computerized Systems Used in Clinical Investigations*

Security: We [FDA] recommend that passwords or other access keys be changed at established intervals commensurate with a **documented risk assessment**

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Risk Mitigation Roles

Quality Assurance
Ensure mitigation approach meets expectations for regulatory compliance and company policies

Business Process Owner
Develop procedural mitigation approaches

Technology Owner
Develop technical mitigation approaches

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Risk Mitigation Framework

Risk Management Process					
Risk Assessment	SOP System Risk Assessment				
Risk Mitigation	SOP Risk Based Validation	SOP Audit Trails	SOP Audit Trail Review	SOP Software Vendor Assessment	
	SOP User Training	SOP Incident Management	SOP System Backup	SOP Business Continuity	Etc.

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Risk Based Approach to Validation Testing

Criticality	High	Med	Low	High	Med	Low	High	Med	Low
Complexity	**High**	**High**	**High**	**Med**	**Med**	**Med**	**Low**	**Low**	**Low**
Requirements Coverage	All require-ments, multiple data sets	All require-ments, single data set	Sampling	All require-ments, multiple data sets	All require-ments, single data set	Sampling	All require-ments, single data set	All require-ments, single data set	Sampling
Path testing	All paths, multiple scenarios	All paths, single scenario	Sampling	All paths, single scenario	All paths, single scenario	Sampling	All paths, single scenario	Sampling	Sampling
Boundary testing	✓	✓	*Optional*	✓	*Optional*	*Optional*	✓	*Optional*	*Optional*
Test case degree of detail and specificity	Specific, detailed	Medium detail	General	Specific, detailed	Medium detail	General	Specific, detailed	Medium detail	General
Test data similar to production data	✓	✓	*Optional*	✓	*Optional*	*Optional*	✓	*Optional*	*Optional*
Testing evidence	Completed protocol, Screen prints of test inputs and outputs	Completed protocol, Screen prints of test outputs	Completed protocol	Completed protocol, Screen prints of test inputs and outputs	Completed protocol, Screen prints of test outputs	Completed protocol	Completed protocol, Screen prints of test inputs and outputs	Completed protocol, Screen prints of test outputs	Completed protocol
User execution of validation tests	*OQ & PQ*	*PQ*	*Optional*	*PQ*	*Optional*	*Optional*	*PQ*	*Optional*	*Optional*

✓ Required

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Risk Based Approach to Validation Documentation

Criticality	High	Med	Low	High	Med	Low	High	Med	Low
Complexity	**High**	**High**	**High**	**Med**	**Med**	**Med**	**Low**	**Low**	**Low**
Change Request	✓	✓	✓	✓	✓	✓	✓	✓	✓
Risk Assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓
Validation Plan	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*
User Requirements (URS)	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*
Functional Specifications (FS)	✓ Highly Detailed	✓ Less Detail	*Optional*	✓ Highly Detailed	✓ Less Detail	*Optional*	✓ Medium Detail	✓ Less Detail	*Optional*
Design: Architecture	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*
Design: Software	✓ Highly Detailed	✓ Less Detail	*Optional*	n/a	n/a	n/a	n/a	n/a	n/a
Design: Configuration	n/a	n/a	n/a	✓	✓	*Optional*	n/a	n/a	n/a
Test Plan/Design	✓	✓	*Optional*	✓	*Optional*	*Optional*	*Optional*	*Optional*	*Optional*
Validation Protocols (IQ. OQ, PQ)	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*

✓ Required

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Risk Based Approach to Validation Documentation

Criticality	High	Med	Low	High	Med	Low	High	Med	Low
Complexity	**High**	**High**	**High**	**Med**	**Med**	**Med**	**Low**	**Low**	**Low**
Validation Incident Reports	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*
Trace Matrix – URS to FS	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*
Trace Matrix – FS to Design	✓	✓	*Optional*	✓	*Optional*	*Optional*	*Optional*	*Optional*	*Optional*
Trace Matrix – URS to PQ	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*
Trace Matrix – FS to OQ	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*
OQ, PQ Trace To:	Test Step	Test Step	*Optional*	Test Step	Test Case	*Optional*	Test Step	Test Case	*Optional*
Validation Summary	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*
Deployment Plan	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*
Data Conversion Plan	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*

✓ Required

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Risk Based Approach to Verification Activities

Criticality	High	Med	Low	High	Med	Low	High	Med	Low
Complexity	**High**	**High**	**High**	**Med**	**Med**	**Med**	**Low**	**Low**	**Low**
Vendor Assessment	n/a	n/a	n/a	✓	✓	*Optional*	✓	✓	*Optional*
Unit Testing	✓	✓	*Optional*	n/a	n/a	n/a	n/a	n/a	n/a
Code Review	✓	✓	*Optional*	n/a	n/a	n/a	n/a	n/a	n/a
Design Review	✓	✓	*Optional*	✓	*Optional*	*Optional*	*Optional*	*Optional*	*Optional*
Part 11 Compliance Assessment	✓	✓	n/a	✓	✓	n/a	✓	✓	n/a
Verification of System Use and Support SOPs **	✓	✓	*Optional*	✓	✓	*Optional*	✓	✓	*Optional*

✓ Required

** System Use and Support SOPs include: Back-up, Recovery, Security and Access, Training Requirements, Incident Handling, Change Management, Technical Operation and Routine Maintenance, User Operation

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Risk Based Validation Example

Examples from Laboratory Management System

	Function	Criticality	Technology	Complexity
A	Interface to a lab instrument to control instrument and read results	High	Configured using the out-of-the-box instrument interface screen	Medium

Document Requirements
- User Requirements
- Detailed Functional Specs
- Design Documentation (Architecture + Configuration)
- Test Plan/Design
- Protocols (IQ, OQ, PQ)
- Trace Matrices (URS → FS, FS → Design, URS → PQ, FS → OQ)

Testing Requirements
- All requirements, multiple data sets
- All paths, 1 scenario
- Boundaries
- Realistic test data
- Screen prints of inputs and outputs
- Users execute PQ; may delegate OQ execution

Additional Verifications
- Design Review
- Part 11 Compliance Assessment
- SOPs for system use and support

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Risk Based Validation Example

Examples from Laboratory Management System

	Function	Criticality	Technology	Complexity
B	Calculation of batch pass/fail based on lab test results	High	Custom code	High

Document Requirements
- User Requirements
- Detailed Functional Specs
- Design Documentation (Architecture + **Software**)
- Test Plan/Design
- Protocols (IQ, OQ, PQ)
- Trace Matrices (URS → FS, FS → Design, URS → PQ, FS → OQ)
- **Unit Test Report**
- **Code Review Report**

Testing Requirements
- All requirements, multiple data sets
- All paths, **multiple** scenarios
- Boundaries
- Realistic test data
- Screen prints of inputs and outputs
- **Users execute both OQ and PQ**

Additional Verifications
- Design Review
- Part 11 Compliance Assessment
- SOPs for feature use
- **Unit Testing**
- **Code Review**

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Risk Based Validation Example

Examples from Laboratory Management System

	Function	Criticality	Technology	Complexity
C	Entry of training dates	Medium	Out-of the box functionality	Low

Required Documents
- User Requirements
- Functional Specs (can be less detailed)
- Design Documentation (Architecture only)
- Protocols (IQ, OQ, PQ)
- Trace Matrices (URS → FS, URS → PQ, FS → OQ)

Optional Documents
- Test Plan/Design
- Trace from FS → Design

Testing Requirements
- All requirements, single data set
- Sample of paths
- Screen prints of outputs (no screen prints of inputs)

Testing Options
- Boundary testing
- Realistic test data
- Users may delegate both OQ & PQ execution

Additional Verifications
- Part 11 Compliance Assessment
- SOPs for feature use

Optional Verifications
- Design Review

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Risk Based Validation Example

Examples from Laboratory Management System

	Function	Criticality	Technology	Complexity
D	Reporting of test charges for a department	Low	Custom report developed in house	High

Optional Documents
- User Requirements
- Functional Specs
- Design Documentation
- Test Plan
- Protocols (IQ, OQ, PQ)
- Trace Matrices
- Unit Test Report
- Code Review Report

Testing Requirements
- Sample of requirements
- Sample of paths

Testing Options
- Boundary testing
- Realistic test data
- Screen prints
- Users may delegate both OQ & PQ execution

Optional Verifications
- Part 11 Compliance Assessment
- SOPs for feature use
- Design Review
- Code Review
- Unit Testing

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Can we leverage the vendor's work?

Criticality	High	Med	Low	High	Med	Low	High	Med	Low
Complexity	High	High	High	Med	Med	Med	Low	Low	Low
Vendor Assessment	n/a	n/a	n/a	Required	Required	Optional	Required	Required	Optional
Unit Testing	Required	Required	Optional	n/a	n/a	n/a	n/a	n/a	n/a
Code Review	Required	Optional	Optional	n/a	n/a	n/a	n/a	n/a	n/a
Part 11 Compliance Assessment	Required	Required	Optional	Required	Required	Optional	Required	Required	Optional
Verification of System Use and Support SOPs **	Required	Required	Optional	Required	Required	Optional	Required	Required	Optional

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Can we leverage the vendor's work?

Vendor Rating	Impact to Validation Approach
Full Approval	• Follow risk-based validation matrix • Internally review, approve vendor provided documents

Restricted Approval	• Use vendor documents with caution
	• Rating indicates increased risk, so additional validation required.
	• Approach validation as if 1 complexity level higher
	  • If configured, approach as "custom"
	  • If out-of-the-box, approach as "configured"

Not Approved	• Avoid reliance on vendor documents • Rating indicates increased risk, so additional validation required. • Approach validation as if "Custom"

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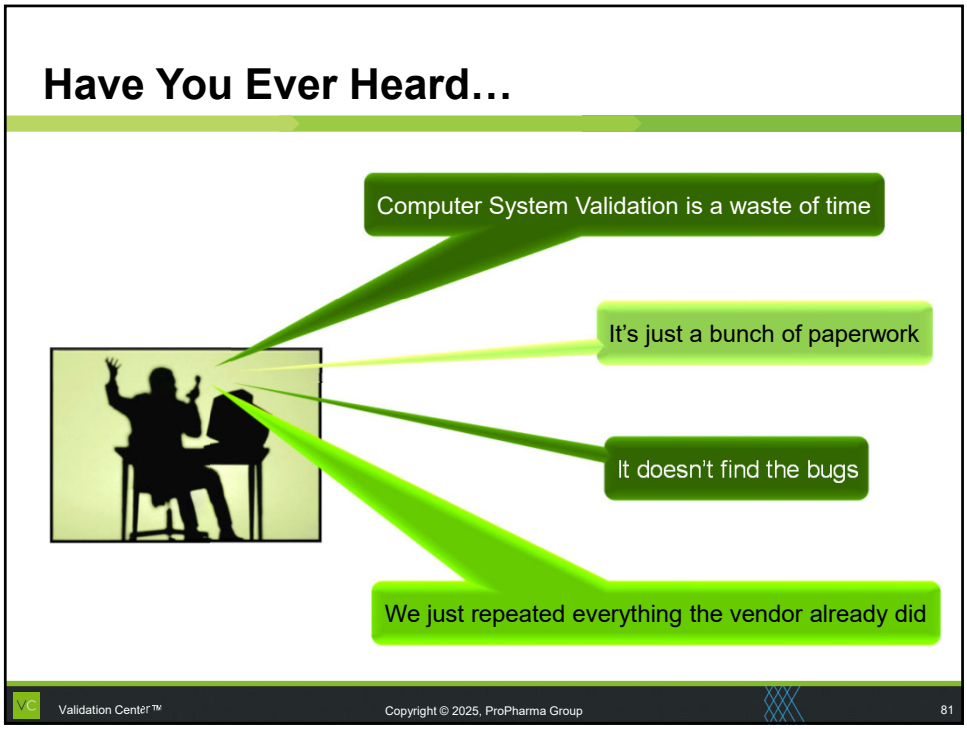

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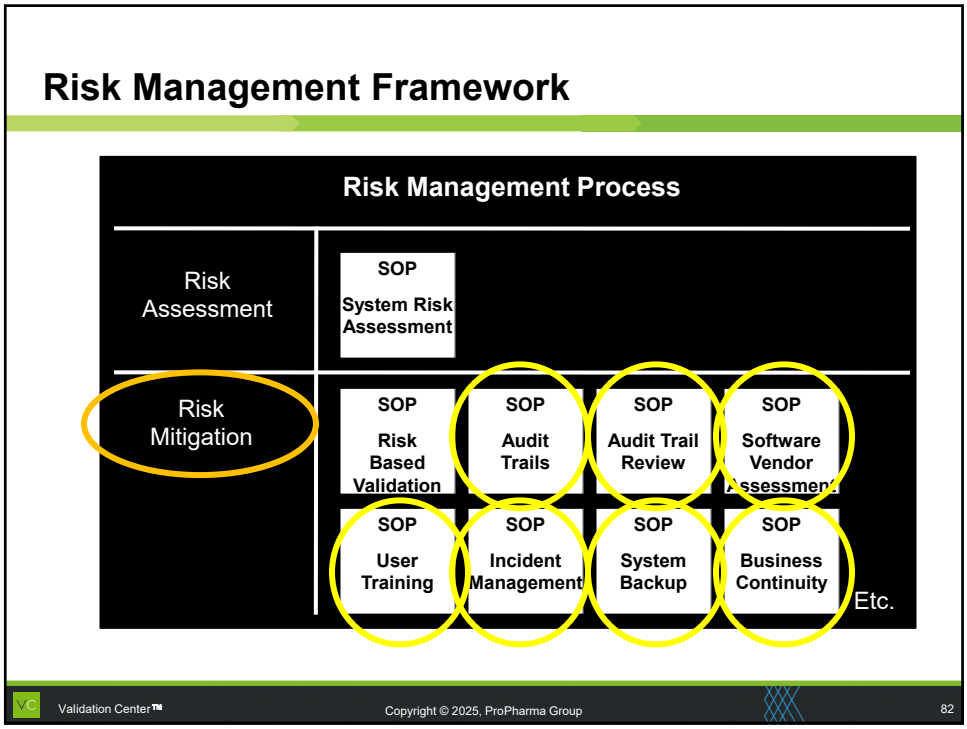

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Risk Mitigation in …

Vendor Assessment SOP *example*

SOP
Software Vendor Assessment

System Criticality Level	Vendor Assessment Method
High	An audit is the preferred method for highly critical software applications.
Medium	Questionnaire is the preferred method for medium criticality software applications.
Low	Vendors of low criticality software applications do not require assessment.

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Risk Mitigation in …

Audit Trail SOP *example*

SOP
Audit Trails

Require-ment Criticality Level	Audit Trail Requirement	Audit Trail Review
High	Audit trail is required for records associated with highly critical system functions	At the time of record approval
Medium	Audit trail is required for records associated with system functions of medium criticality	Periodically
Low	Audit trail is optional for records associated with system functions of low criticality	Optional

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Risk Mitigation in …

Audit Trail Review SOP *example*

SOP Audit Trail Review

Requirement Criticality Level	Review Timing	Audit Trail Review Scope	Audit Trail Reviewer
High	During data review and approval	Comprehensive	Independent QA Reviewer
Medium	Every 6-12 months	Targeted Scenarios	Business Process Owner
Low	Not required	Targeted Scenarios	Business Process Owner

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Risk Mitigation in …

User Training SOP *example*

SOP User Training

Requirement Criticality Level	Training Format	
	Function is not intuitive to use correctly	Function is intuitive to use correctly
High	• Instructor Led Class • Hands-on Exercises • Competency Exam	• Self-study Materials • Hands-on Exercises • Competency Exam
Medium	• Instructor Led Class • Hands-on Exercises	• Self-study Materials
Low	• Self-study Materials • Hands-on Exercises	• Self-study Materials

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Risk Mitigation in …

System Back-up SOP *example*

SOP System Back-Up

System Criticality Level	Back-up Location	Back-up Media Audit (Restoration Test) Frequency
High	Off-Site Data Center in Separate Geographic Area	Annual
Medium	Off-Site Data Center in Same Geographic Area	Every 18 months
Low	Server Room in Separate Building	Not required

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Risk Mitigation in …

Business Continuity SOP *example*

SOP Business Continuity

Requirement Criticality Level	Business Continuity Procedure (BCP) Required	BCP Testing
High	Yes – Detailed	Annual
Medium	Yes – Less Detailed	Every 2 Years
Low	No	Not Required

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Risk Mitigation in …

Incident Management SOP *example*

SOP Incident Management

Requirement Criticality Level	Resolution Priority		
	Users cannot perform job	Major Inconvenience	Minor Inconvenience
High	High	High	High
Medium	High	Medium	Medium
Low	High	Medium	Low

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FDA Leadership By Example

Part 4

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Part 4: FDA Leadership by Example

- Section Overview
  - Warning Letter Data
  - Warning Letter Examples

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FDA Warning Letter Data

- Data Source
  - FDA Warning Letters related to Software and Computers
  - 3 Year Date Range: 2022 through 2024
- Summaries
  - By system type
  - By observation topic
    - By validation observation topics

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FDA Warning Letter Example

Regulatory Reference

Summary Finding

2. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 C.F.R §211.68(b)).

Your firm failed to have adequate procedures for the use of computerized systems in the quality control (QC) laboratory. Our inspection team found that current computer users in the laboratory were able to delete data from analyses. Notably, we also found that the audit trail function for the gas chromatograph (GC) and the X-Ray Diffraction (XRD) systems was disabled at the time of the inspection. Therefore, your firm lacks records for the acquisition, or modification, of laboratory data.

Moreover, greater than **(b)(4)** QC laboratory personnel shared **(b)(4)** login IDs for **(b)(4)** high performance liquid chromatographs (HPLC) units. In addition, your laboratory staff shared one login ID for the XRD unit. Analysts also shared the username and password for the Windows operating system for the **(b)(4)** GC workstations and no computer lock mechanism had been configured to prevent unauthorized access to the operating systems. Additionally, there was no procedure for the backup and protection of data on the GC standalone workstations.

Specific Observations

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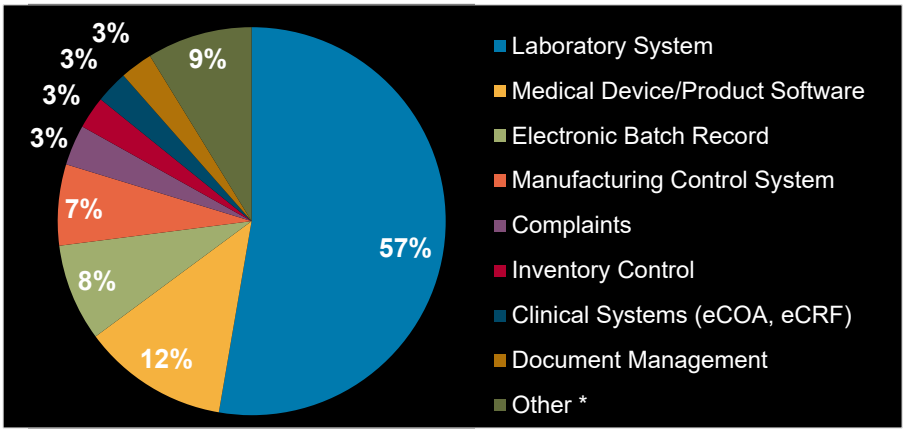
Software & Computer Warning Letters

3 Year Citation Summary by System Type



"Other" system types include systems for IRB, Calibration Management, Issue Management, Product Design, Environmental Monitoring, Stability, CoA, and Audit Management

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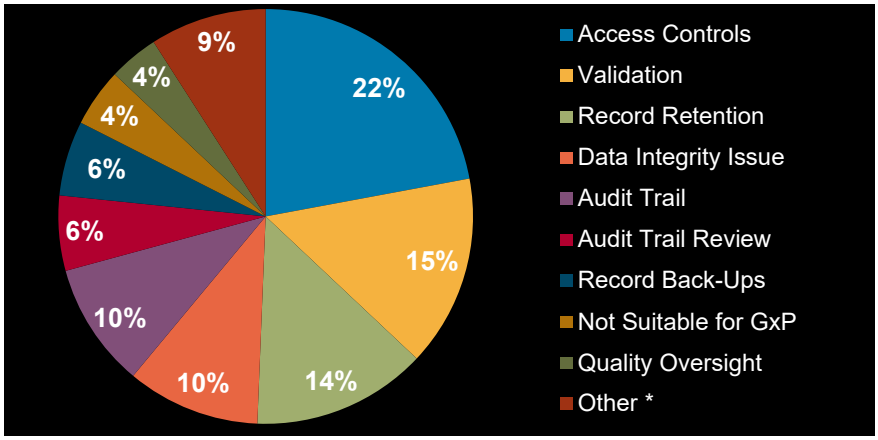
Software & Computer Warning Letters

3 Year Citation Summary by Observation Topic



"Other" observation topics include Risk Management, IT Vendor Management, Critical Defects, Change Control, System Documentation, CAPAs for device software issues, FDA registration of device software

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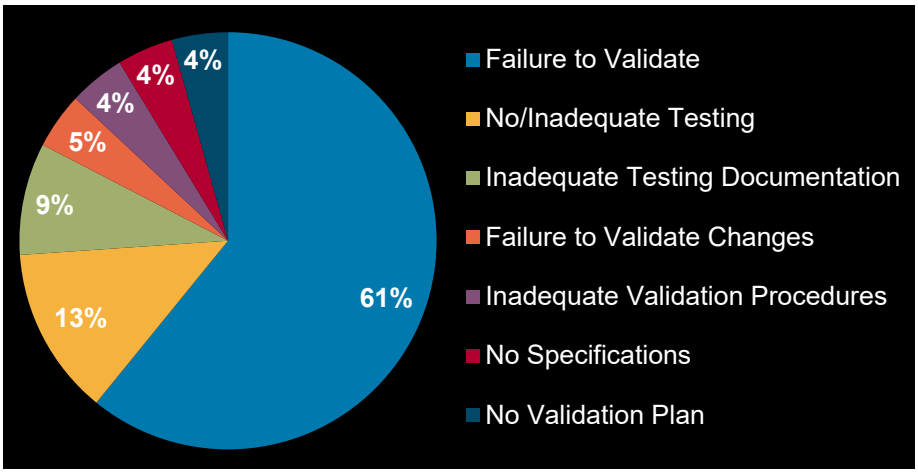
Software & Computer Warning Letters

3 Year Citation Summary by Validation Issue



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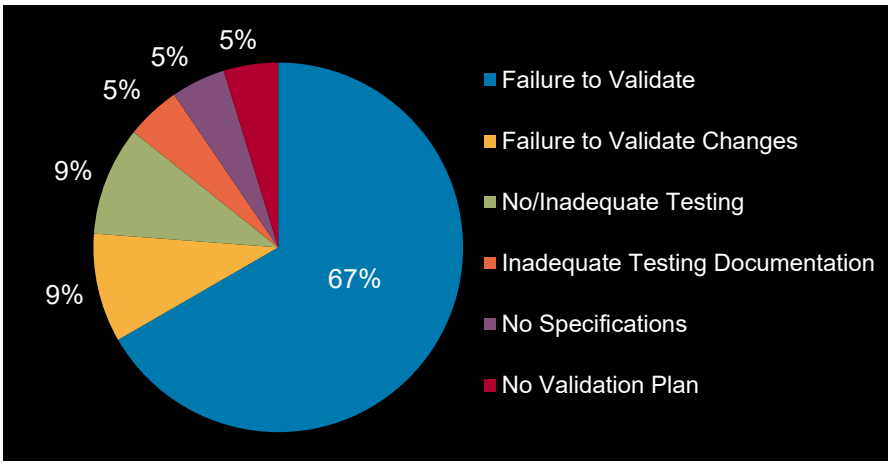
Software & Computer Warning Letters

3 Year Citation Summary by Validation Issue



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Warning Letter Examples

Regulatory Reference	21 CFR 820 (Medical Devices)
System Type	Medical Device Software
FDA Branch or District	CDRH

Failure to adequately establish and maintain procedures to control the design to ensure that requirements are met.

- *Development of Key Functionality*, requires the firm to assess risk and re-assess risk as needed. Although XXXXXX was released on November 25, Software Risk Management Summary Doc. was not completed until July 14, and did not include an analysis of the risk specific to the intended use of XXXXXX.

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Warning Letter Examples

Regulatory Reference	21 CFR 820 (Medical Devices)
System Type	Medical Device Software
FDA Branch or District	Cincinnati District

Failure to demonstrate that the device was developed in accordance with the design control requirements of the Quality System regulation.

- Failure to have complete risk analyses in that 5 versions of risk analysis were not controlled documents.
- Risk analyses were not reviewed and approved.
- Risk analyses were not updated when a software issue was discovered that resulted in a software change.

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Warning Letter Examples

Regulatory Reference	21 CFR 820 (Medical Devices)
System Type	Medical Device Software
FDA Branch or District	Florida District

Failure to adequately establish and maintain procedures for validation.

- Firm's Risk Analysis Report for software version 00, does not adequately assess the risk presented by the software controlling the X-Ray Unit XXX as a moderate risk to users and patients.
- For example, the report indicates a "No" to the questions:
  - "Could a malfunction of, or a latent design flaw in the Software Device lead to an erroneous diagnosis or a delay in delivery of appropriate medical care that would likely lead to Moderate Injury?"
  - "Does the Software Device control the delivery of potentially harmful energy that could result in death or serious injury?"

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Conclusion

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Next Steps

1. Review your regulations and guidelines
2. Identify your criticality levels and definitions
3. Define your complexity measures
4. Determine how you will apply complexity & criticality to validation and software quality practices
5. Write your policies and procedures
6. Train your staff

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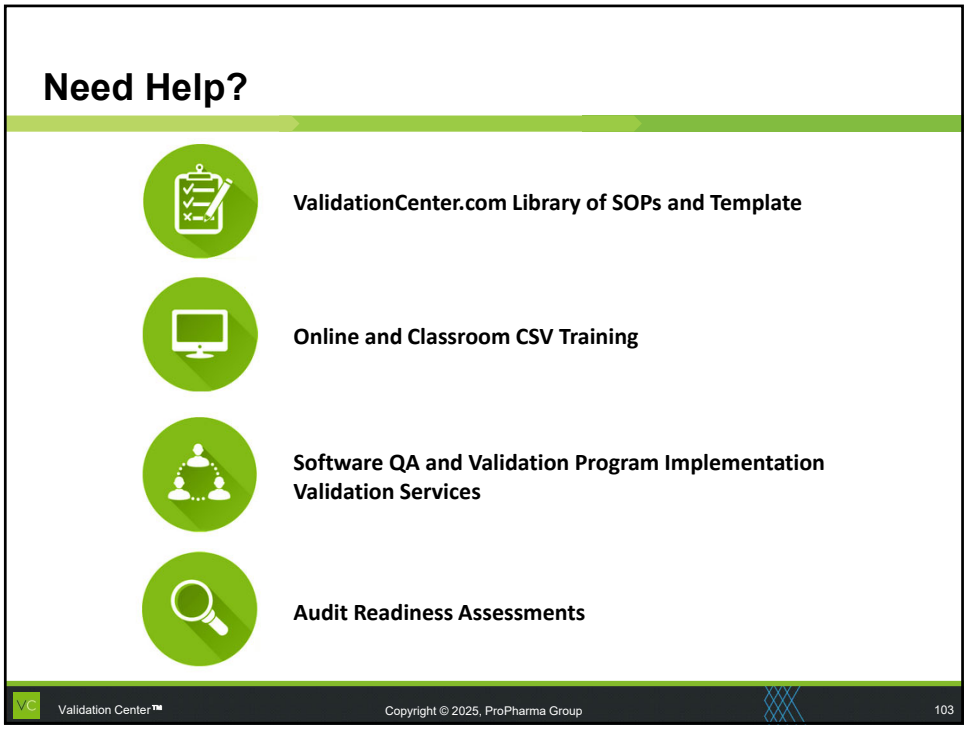

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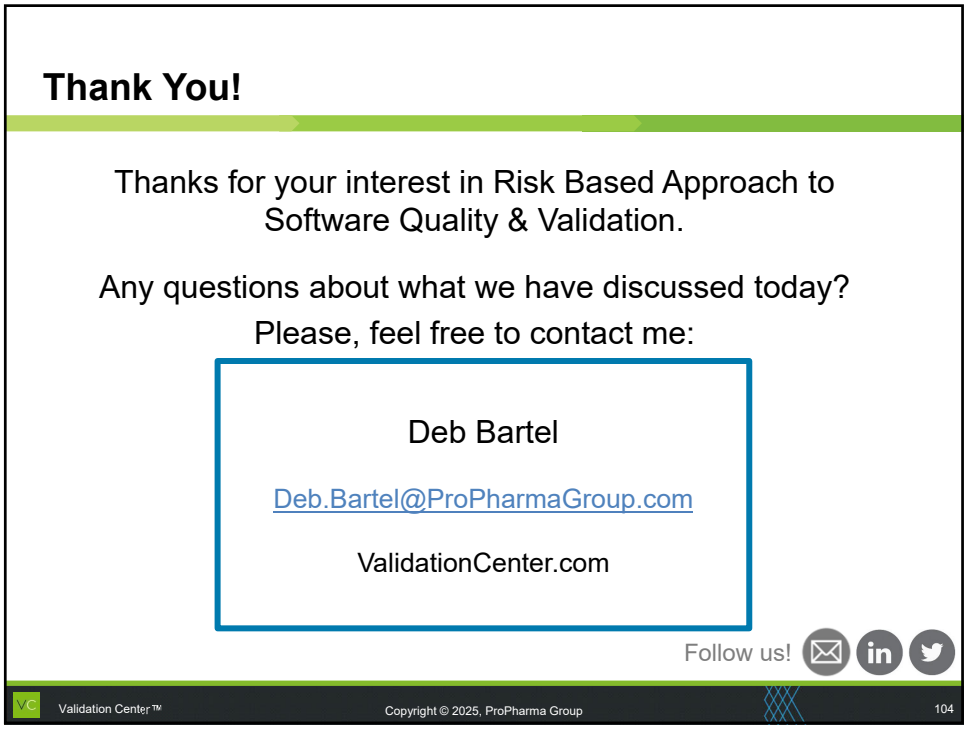

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