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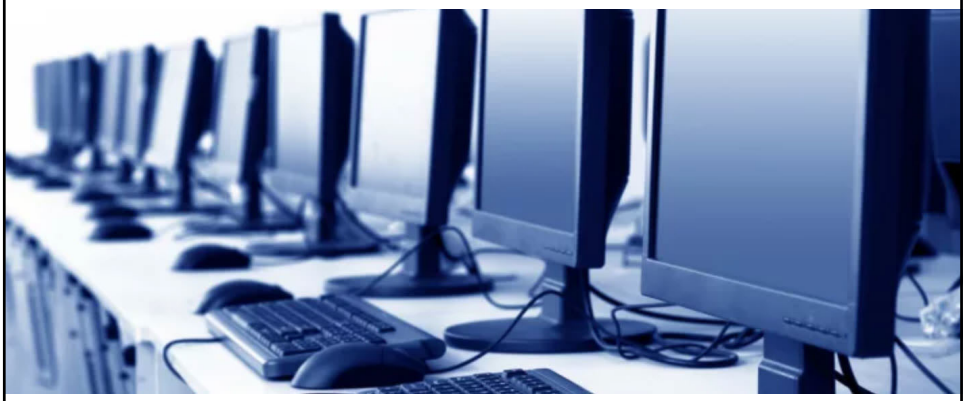
VALIDATION CENTER



Spreadsheet Validation

v.24-03

1

Your Presenter

- Debra Bartel, MBA, CQA, PMP
- VP, Life Sciences QA
- 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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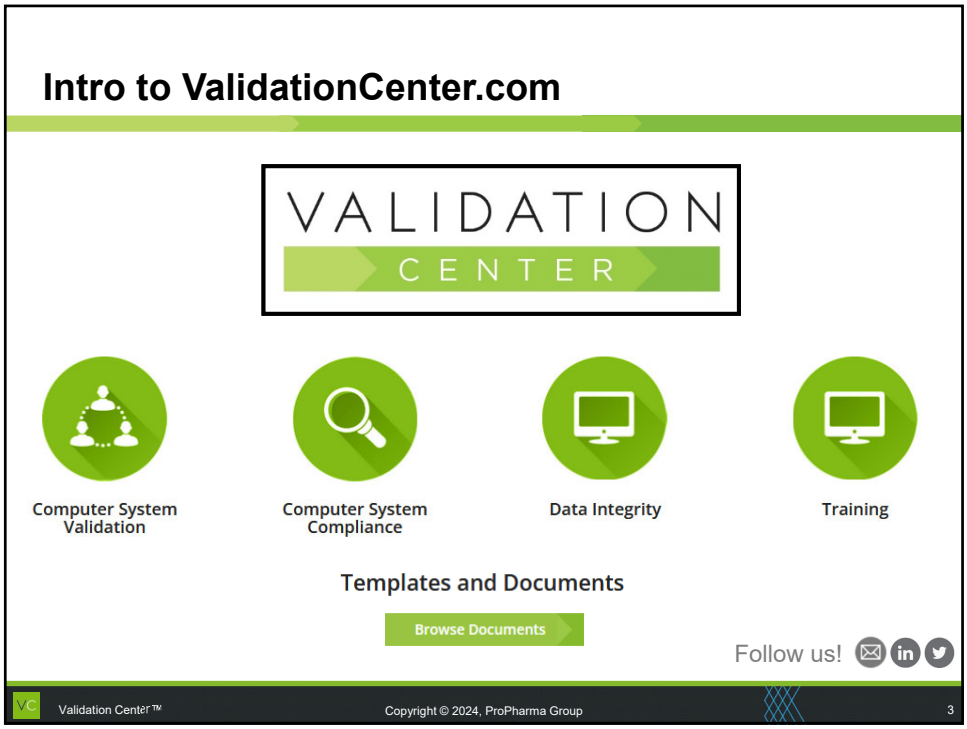

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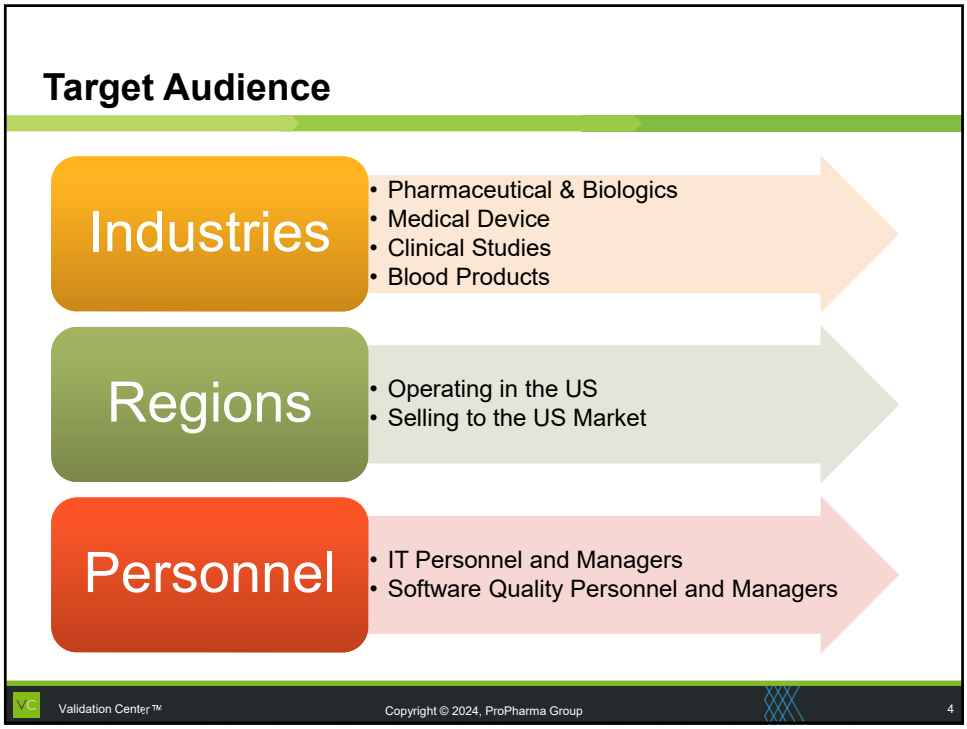

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Have you ever heard…

- Spreadsheets can't be used when FDA regulated
- Spreadsheets can't be validated
- Spreadsheets can't be compliant
- It takes longer to validate the spreadsheet than it did to build it

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5

Webinar Outline

1. FDA Guidance
2. Validation and Part 11 Compliance
3. Risk Assessment & Mitigation Approach
4. Spreadsheet Validation Approach
5. Spreadsheet Validation Example
6. FDA Warning Letter Examples

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6

FDA Requirements and Guidance

Part 1

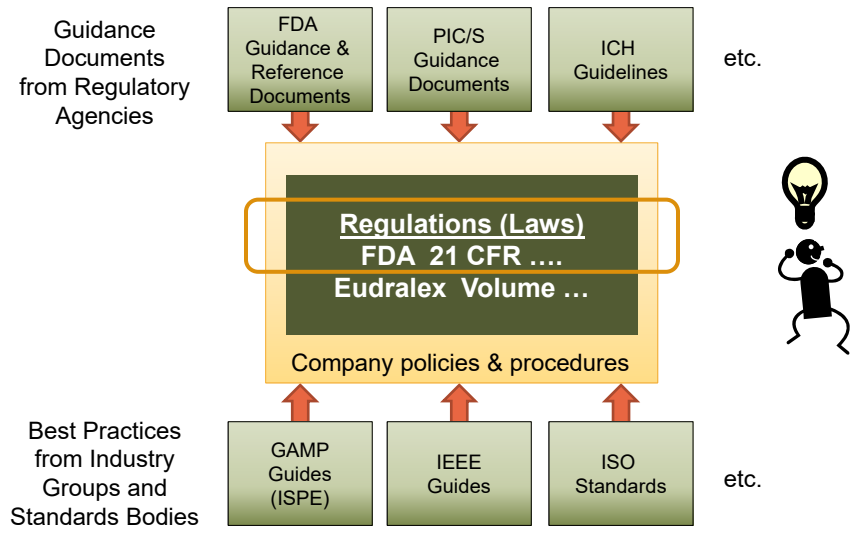
7

Part 1: FDA Requirements and Guidance

- Section Overview
  - FDA Regulations
  - FDA Guidance
  - FDA Laboratory Reference Manual

8

Framework for Regulations, Guidelines



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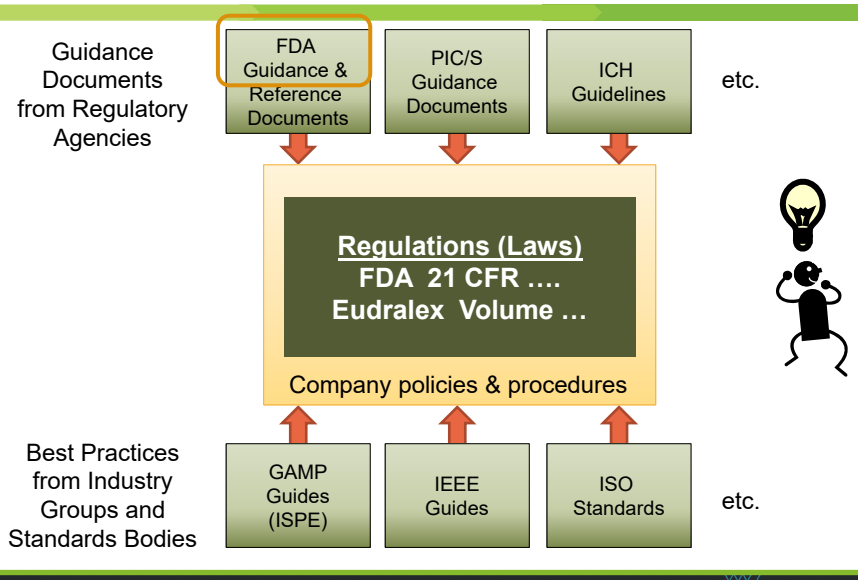
FDA Regulations for Validation

21 CFR 11	21 CFR 211	21 CFR 820
Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls to designed to ensure the authenticity, integrity, and … the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record ... Procedures and controls shall include **validation of systems to ensure accuracy, reliability, consistent intended performance**, and the ability to discern invalid or altered records.	Input to and output from the computer or related system or formulas …. shall be **checked for accuracy**. The **degree and frequency** of input/output verification shall be **based on the complexity and reliability** of the computer or related system. A **written record** of the program shall be maintained along with validation data.	When computers or automated data processing systems are used as part of the production or quality system, the manufacturer shall **validate computer software for its intended use** according to an established protocol. All software **changes shall be validated** before approval and issuance. These **validation activities shall be documented**.

10

Framework for Regulations, Guidelines



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FDA Software Validation Guidance

Guidance	General Principles of Software Validation

Quote:

Many other commercial software applications, such as word processors, **spreadsheets**, databases, and flowcharting software are used to implement the quality system.

All of these applications are subject to the **requirement for software validation**, but the **validation approach** used for each application **can vary widely**.

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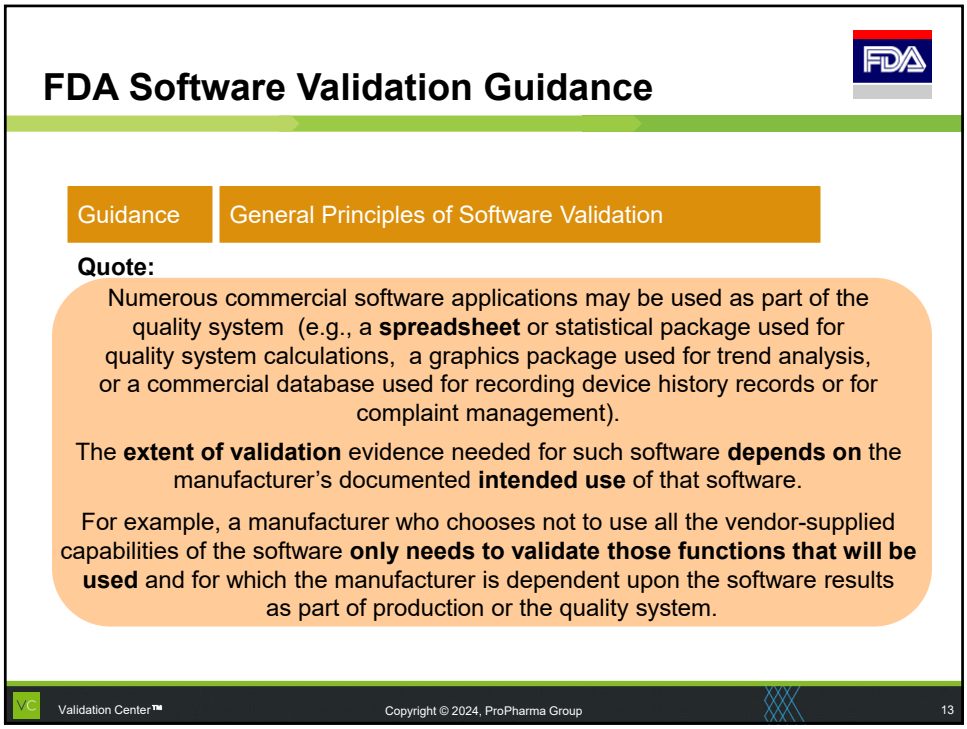

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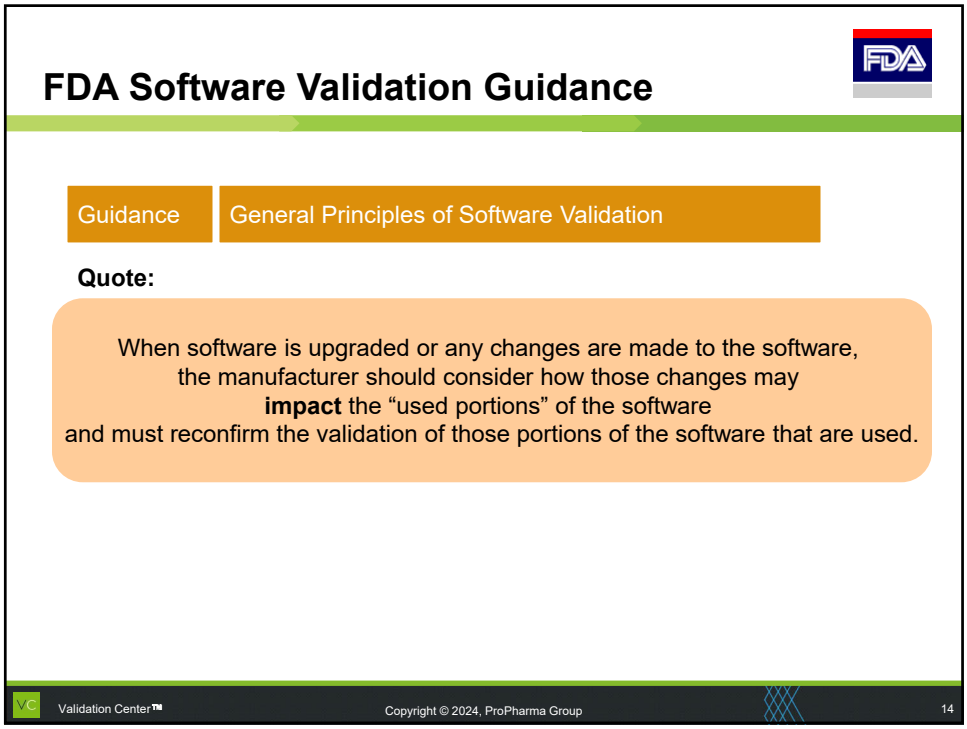

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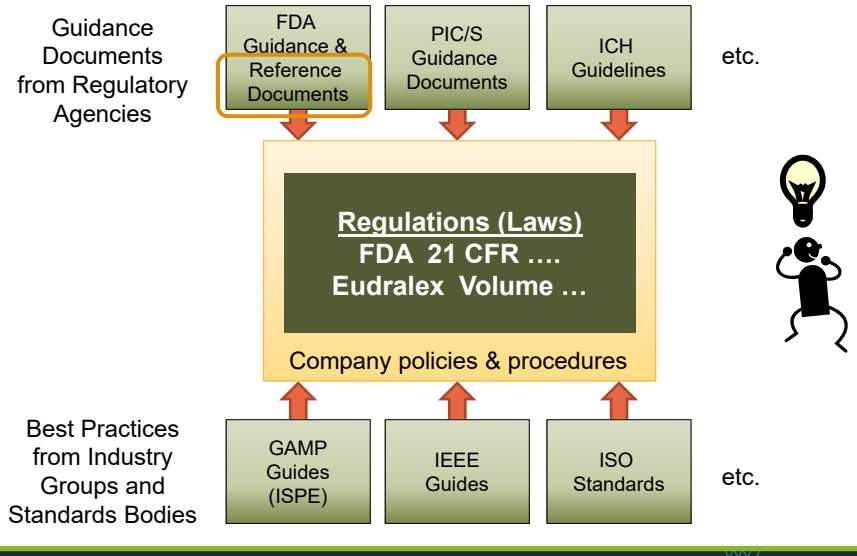
Framework for Regulations, Guidelines



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15

FDA Spreadsheet Reference

Reference	FDA Office of Regulatory Affairs Laboratory Manual

Spreadsheet Development Quote:

Although individual spreadsheet functions can be considered as reliable, it is important to make sure that data is presented to the spreadsheet with the proper syntax.

Also, when spreadsheets are used for multiple numerical calculations in the form of in-house developed templates, it is important to

1. **protect the spreadsheet from inadvertent changes**,
2. **verify the reliability** of the spreadsheet by comparison with known results from known data, and to
3. **ensure that the spreadsheet can handle unforeseen data** input needs.

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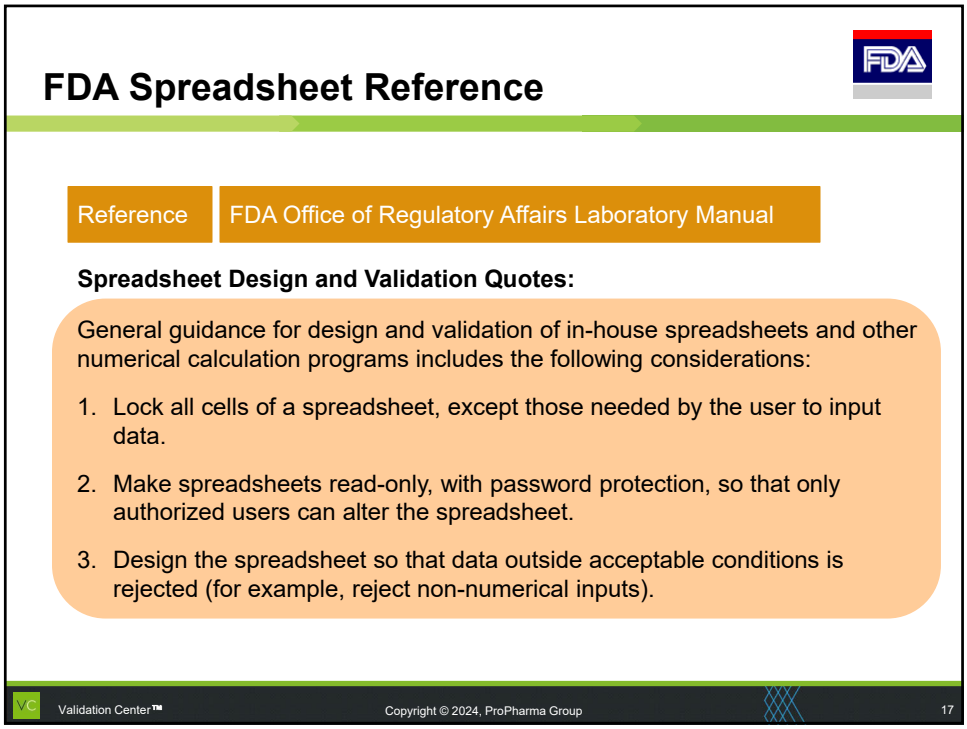
16



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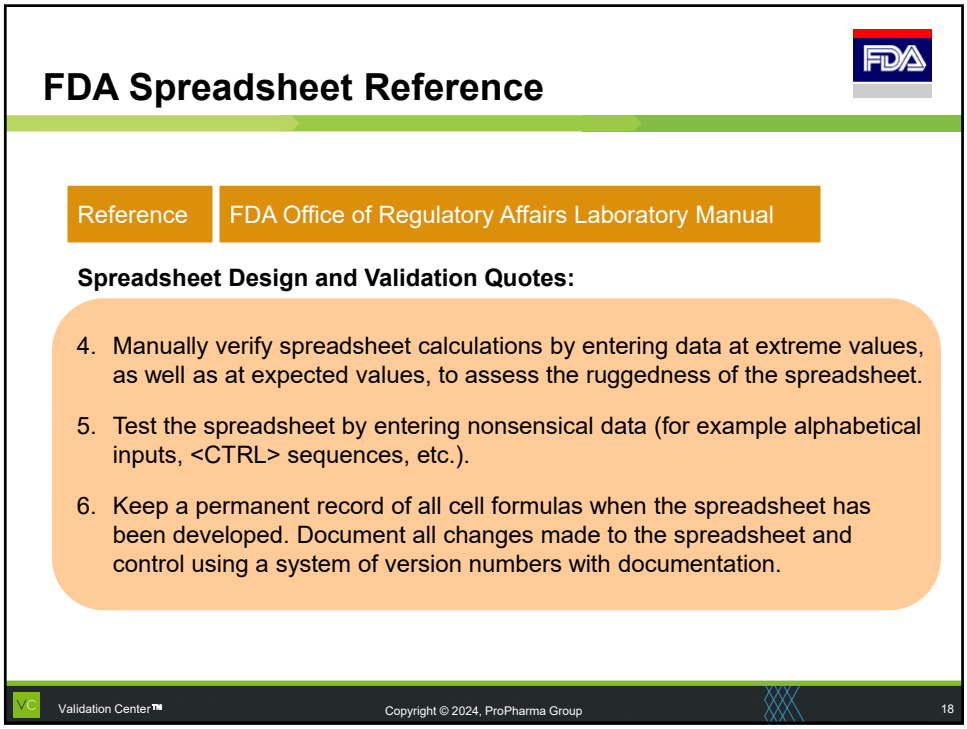

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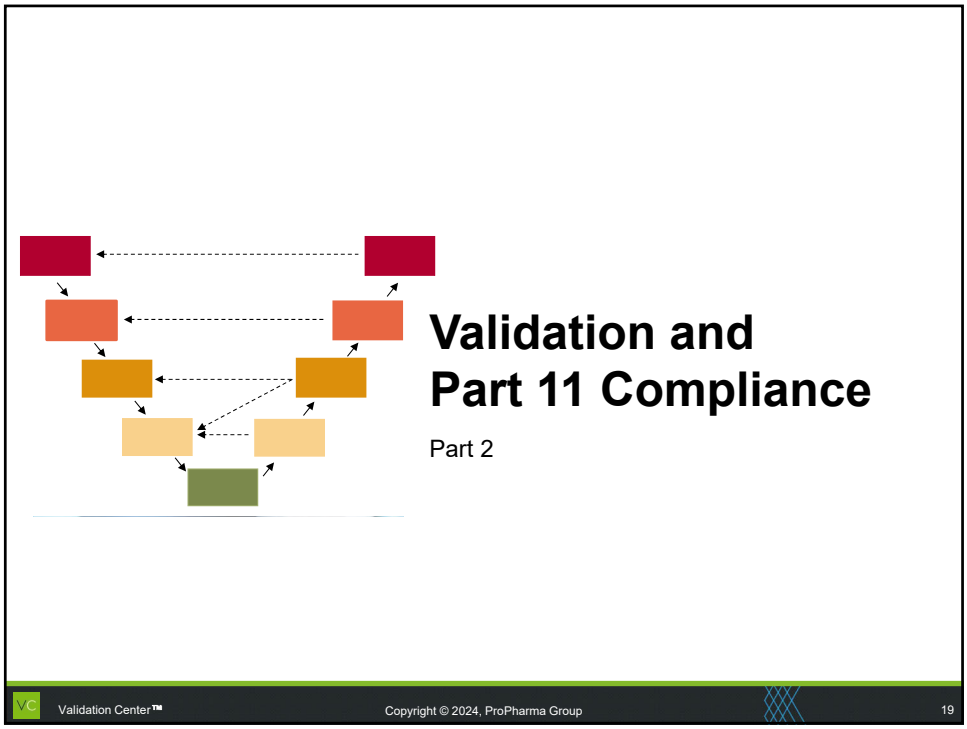

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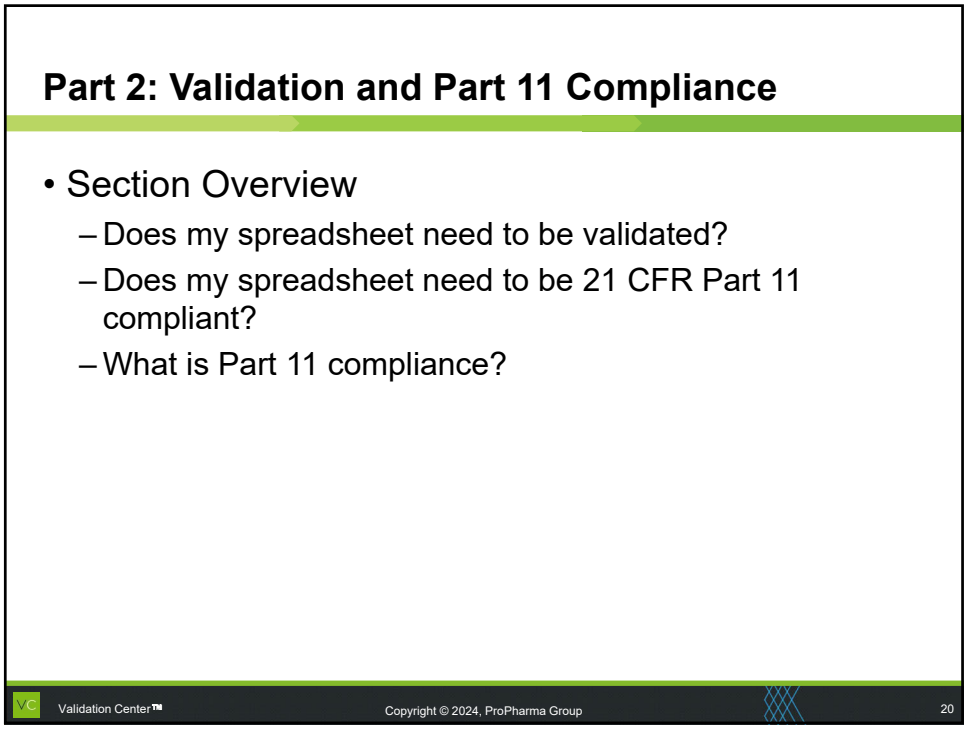

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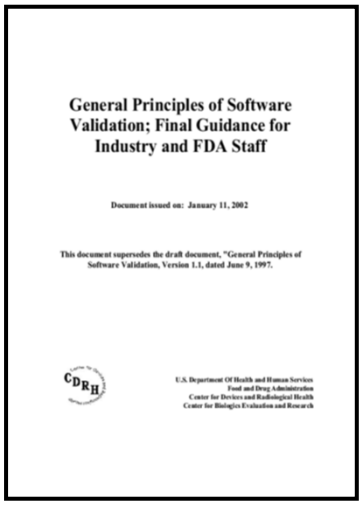
What Software Needs Validation?


General Principles of Software Validation; Final Guidance for Industry and FDA Staff

Document issued on: January 11, 2002

This document supersedes the draft document, "General Principles of Software Validation, Version 1.1, dated June 9, 1997.

U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

FDA CSV Principles on what software needs validation:

1. Software used as a component, part, or accessory of a medical device
2. Software that is itself a medical device
3. Software used in the production of the product
4. Software used in implementation of the quality system

21

Does My Spreadsheet Need Validation?

Questions to Ask

Could the spreadsheet impact:

- Patient Health? Public Safety?
- Product Quality?
- The integrity of the data and records associated with either of the above?

22

Which Spreadsheet Needs Validation?

Per FDA CSV Principles, which require validation?

A. The spreadsheet that computes the potency of the raw material

B. The product complaint tracking spreadsheet

C. The spreadsheet that tracks which donors are (and are not) eligible to donate plasma

D. An accounting spreadsheet that also tracks the quality status of each lot

E. The spreadsheet that calculates how long to dry a batch of active ingredient

23

What Records Need Part 11 Compliance?

FDA Electronic Records & Signatures Regulation on what records need to comply with Part 11:

Part 11 applies to:

1. Records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency [FDA] regulations.
2. Electronic records submitted to the agency under requirements of the *Federal Food, Drug, and Cosmetic Act and the Public Health Service Act,* even if such records are not specifically identified in agency regulations.

24

Does My Spreadsheet Need Part 11 Compliance?

Questions to Ask

1. Could the spreadsheet impact:
   - Patient Health? Public Safety?
   - Product Quality?
   - The integrity of the data and records associated with either of the above?

AND

2. Will the spreadsheet be used as an electronic record

25

Which Spreadsheet Needs Part 11 Compliance?

Per FDA 21 CFR Part 11, which spreadsheets would be in scope?

A. Spreadsheet of training on QA SOPs

B. Spreadsheet of lab test results

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

D. Spreadsheets of manufacturing schedules

E. Spreadsheets used to calculate lab results

26

Easy to Meet Part 11 Requirements

Part 11 E-Record Requirement:

" Controls shall include…

- Validation

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

- Documentation

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

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

- Record Protection

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

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27

Easy to Meet Part 11 Requirements

Part 11 E-Record Requirement:

" Controls shall include…

- Sequencing Functionality

  11.10(f) Use of operational system checks to enforce permitted sequencing of steps and events.

- Training

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

- Copies

  11.10(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the [FDA] agency.

- Accountability

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

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28

More Challenging Part 11 Requirements

Part 11 E-Record Requirement:

Spreadsheet Compliance Tactics

" Controls shall include…

11.10(d) Limiting system access to authorized individuals.

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

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

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29

Difficult Part 11 Requirements

Difficult due to lack of security features

Part 11 E-Record Requirement:

" Controls shall include…

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

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

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

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

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

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30

Difficult Part 11 Requirements

Difficult due to lack of security features

Part 11 E-Record Requirement:

" Controls shall include…

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

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

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

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

31

Difficult Part 11 Requirements

Difficult due to lack of audit trail features

Part 11 E-Record Requirement: **Spreadsheet Compliance Tactics**

" Controls shall include…

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

Record changes shall not obscure previously recorded information.

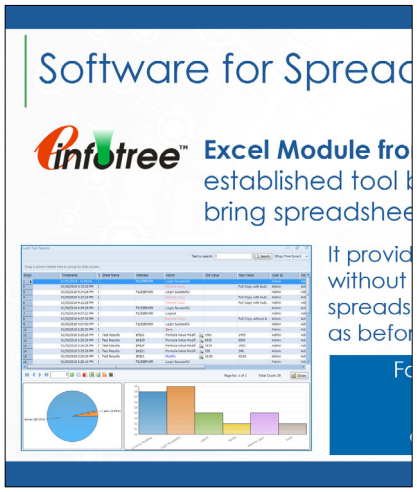
Audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copy

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

32

Compliance Tool Examples

For more information: www.part11solutions.com



For more information: www.ofnisystems.com

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33

Spreadsheet Risk Assessment & Mitigation

Part 3

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34

Part 3: Risk Assessment & Mitigation

- Section Overview
  - Risk Terminology
  - Risk-Based Spreadsheet Validation

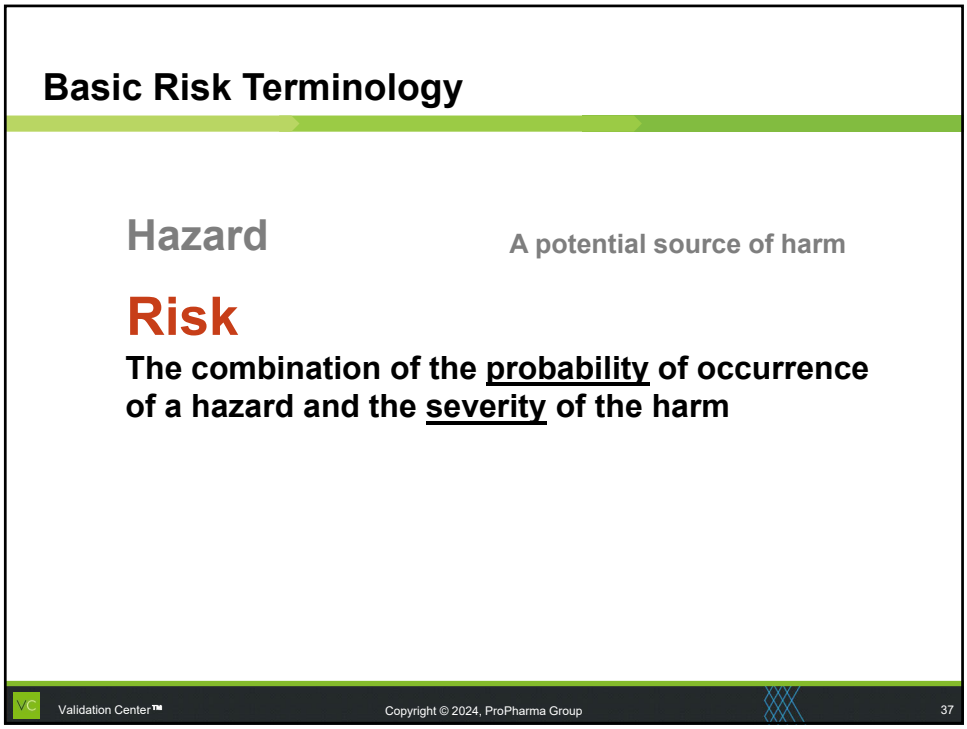
35

Basic Risk Terminology

Hazard

A potential source of harm

36



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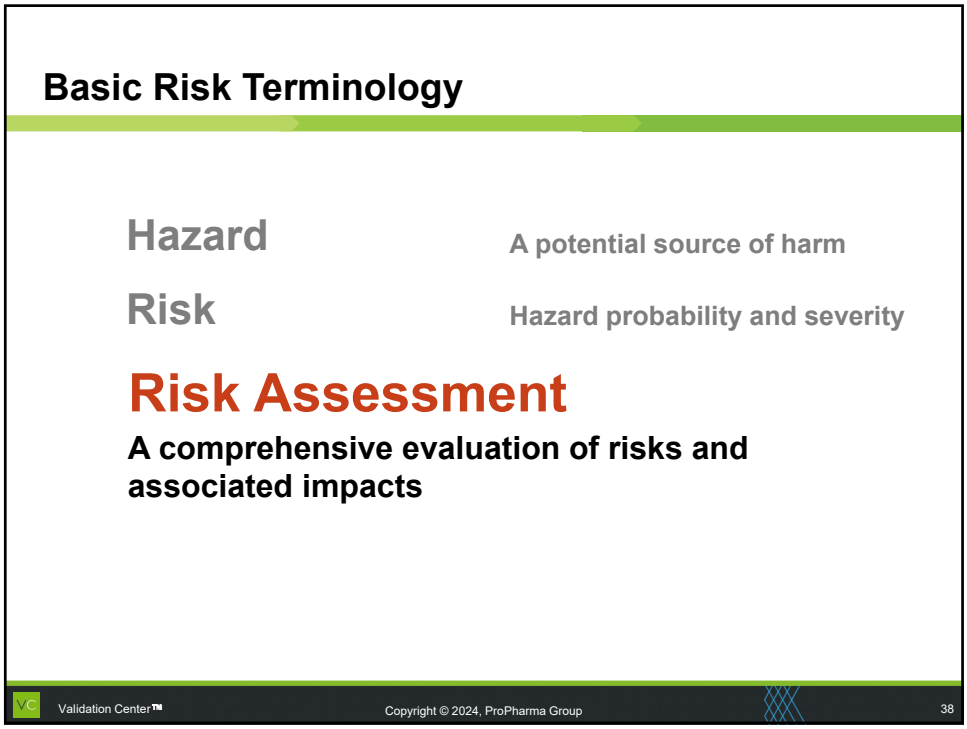


38

Basic Risk Terminology

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

Risk Mitigation

Actions taken to reduce the impacts of risks

39

Risk Management Process

Risk Assessment Activities

Identification	Evaluation	Classification	Mitigation
Determine and document the hazards associated with use of the system.	Determine the severity of the identified hazards.	Categorize the risks according to severity.	Perform activities that reduce the severity of the risk or the likelihood of the risk

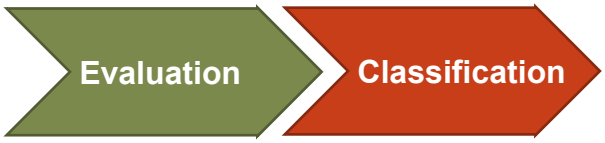
40

Hazard Identification

- Key Questions
  - What could go wrong with this spreadsheet?
  - How would this impact business operations?
  - Would this negatively affect:
    - Patient safety?
    - Product quality?
    - The Integrity of associated data?

41

Risk Classification



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

"Criticality" measures The safety severity of the hazard

"**Complexity**" is used to predict "probability of occurrence" for software hazards

42

Criticality Classification

Common Classification Method for Criticality

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

43

Criticality Classification, *examples*

	High Criticality	Medium Criticality	Low Criticality
Quality/ Safety Impact	**Direct**	**Indirect**	**None**
Examples	• Health product software • Manufacturing controls • Automated product inspection • Label management & automation • Distribution tracking to enable recalls • Laboratory test calculations • Adverse event tracking • Clinical trial results • Patient medical records • Product quality status management	• Calibration tracking • Validation tracking • Document management • Training tracking • Corrective/Preventive action tracking • System access tracking • Electronic submissions to regulatory agencies • Product work order management • Deviation tracking • Audit tracking	• Manufacturing cost reports • Turnaround time reports • Out of office calendars

44

Complexity Classification

Classification Method for Complexity (likelihood of failure)

	High Complexity	Medium Complexity	Low Complexity
Likelihood of Defect	High	Medium	Low
Examples	• Custom Macros • Sophisticated Look-up Functions • Nested Logic Functions • Look-up Functions • Linked Spreadsheets	• Single Level Logical Functions • Advanced Statistical Functions	• Standard functions, such as calculations, basic statistics (e.g., averages)

45

Spreadsheet Risk Assessment Examples

	Spreadsheet Function	Criticality	Complexity	Rationale
A	Simple arithmetic calculation for content uniformity	High	Low	• Direct impact on product quality • Basic spreadsheet functionality
B	Record of training attendance	Medium	Low	• Indirect impact on quality and/or safety • Basic spreadsheet functionality
C	Statistical analysis of clinical study data with VB macros	High	High	• Direct impact on patient safety • Custom Macros
D	Statistical analysis of manufacturing data for process control	High	Medium	• Direct impact on product quality • Complex logic and look-up functions

46

Risk Mitigation via Testing

Criticality	High	Med	Low	High	Med	Low	High	Med	Low
Complexity	**High**	**High**	**High**	**Med**	**Med**	**Med**	**Low**	**Low**	**Low**
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	Required	Required	Optional	Required	Optional	Optional	Required	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	Required	Required	Optional	Required	Optional	Optional	Required	Optional	Optional
Testing evidence	Screen prints of inputs and outputs, signed protocol	Screen prints of outputs, signed protocol	Signed protocol	Screen prints of inputs and outputs, signed protocol	Screen prints of outputs, signed protocol	Signed protocol	Screen prints of inputs and outputs, signed protocol	Screen prints of outputs, signed protocol	Signed protocol
User (vs. IT) execution of tests	Required	Required	Optional	Required	Optional	Optional	Required	Optional	Optional

47

Risk Based Approach to QA Activities

Criticality	High	Med	Low	High	Med	Low	High	Med	Low
Complexity	**High**	**High**	**High**	**Med**	**Med**	**Med**	**Low**	**Low**	**Low**
Risk Assessment	Required	Required	Required	Required	Required	Required	Required	Required	Required
Change Request	Required	Required	Optional	Required	Required	Optional	Required	Required	Optional
Validation Documentation	Required	Required	Optional	Required	Required	Optional	Required	Required	Optional
Design Review	Required	Required	Optional	Required	Optional	Optional	Optional	Optional	Optional
Part 11 Compliance for any records	Required	Required	Optional	Required	Required	Optional	Required	Required	Optional
Verification of SOPs **	Required	Required	Optional	Required	Required	Optional	Required	Required	Optional

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

48

Spreadsheet Risk Based Validation Example

	Spreadsheet Function	Criticality	Complexity	Rationale
1	Record of training attendance	**Medium**	**Low**	• Indirect impact on quality and/or safety • Basic spreadsheet functionality

Documentation Requirements
- Change Request
- Risk Assessment
- Validation Documentation

Testing Requirements
- Sampling of logic paths
- Screen prints of outputs

Testing Options
- Boundaries
- Realistic Test Data
- User execution of tests

Other Requirements
- SOPs Verification
- Part 11 compliance

Optional
- Design Review

49

Spreadsheet Risk Based Validation Example

	Spreadsheet Function	Criticality	Complexity	Rationale
2	Statistical analysis of clinical study data with VB macros	**High**	**High**	• Direct impact on patient safety • Custom Macros

Documentation Requirements
- Change Request
- Risk Assessment
- Validation Documentation

Testing Requirements
- All logic paths using multiple scenarios
- Boundaries
- Realistic test data
- Screen prints of inputs and outputs
- User execution of tests

Other Requirements
- SOPs Verification
- Part 11 compliance
- Design Review

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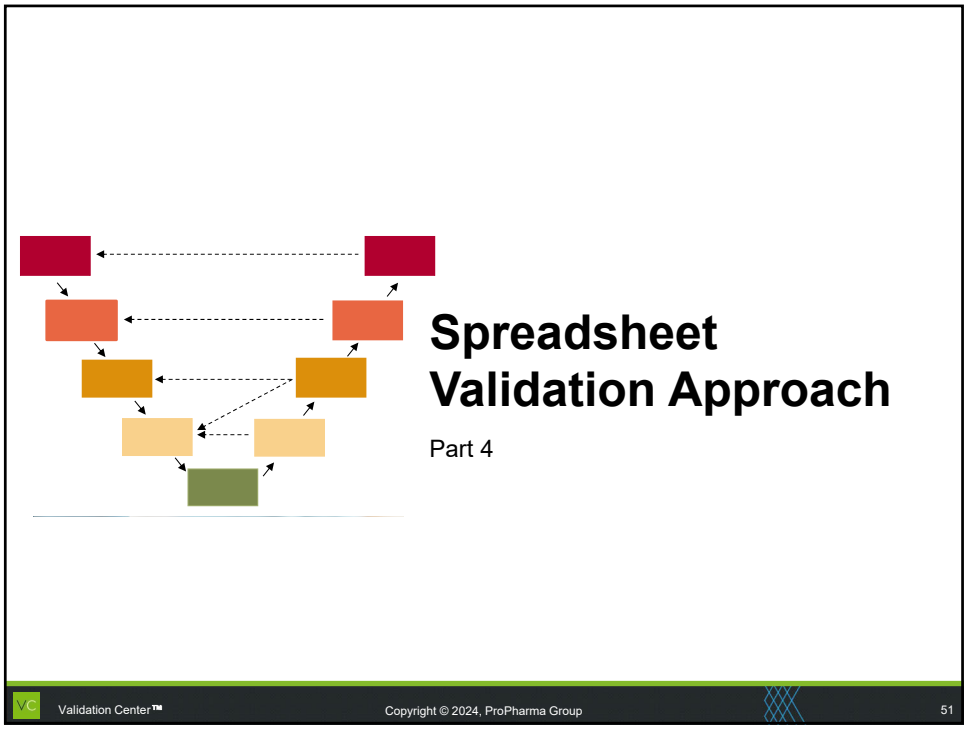

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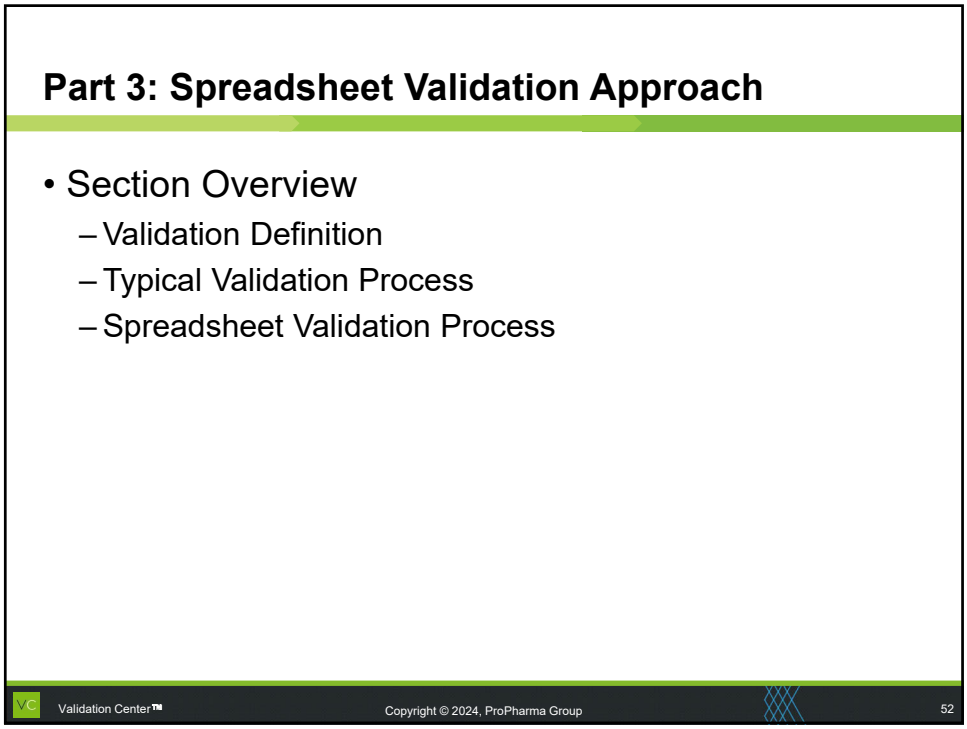


52

FDA Definitions

The FDA defines software validation as…

Document all validation activities and test results

Define what the user needs to do with the software and how they will use the software

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

Examine the software to confirm that it functions as defined in requirements and it will be suitable for the intended use

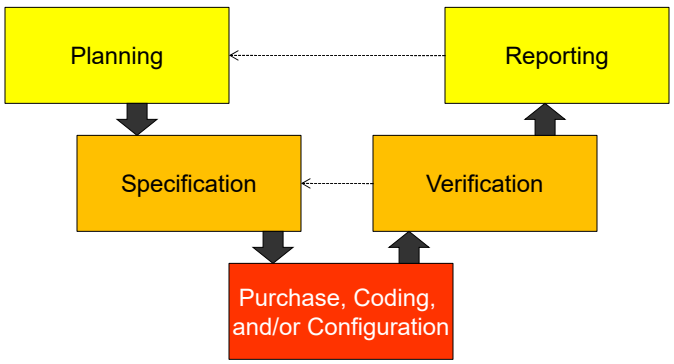
Define how the software needs to work to enable the intended use

The examination needs to confirm that the software will work in all anticipated situations

Source: General Principles of Software Validation: Final Guidance for Industry and FDA Staff

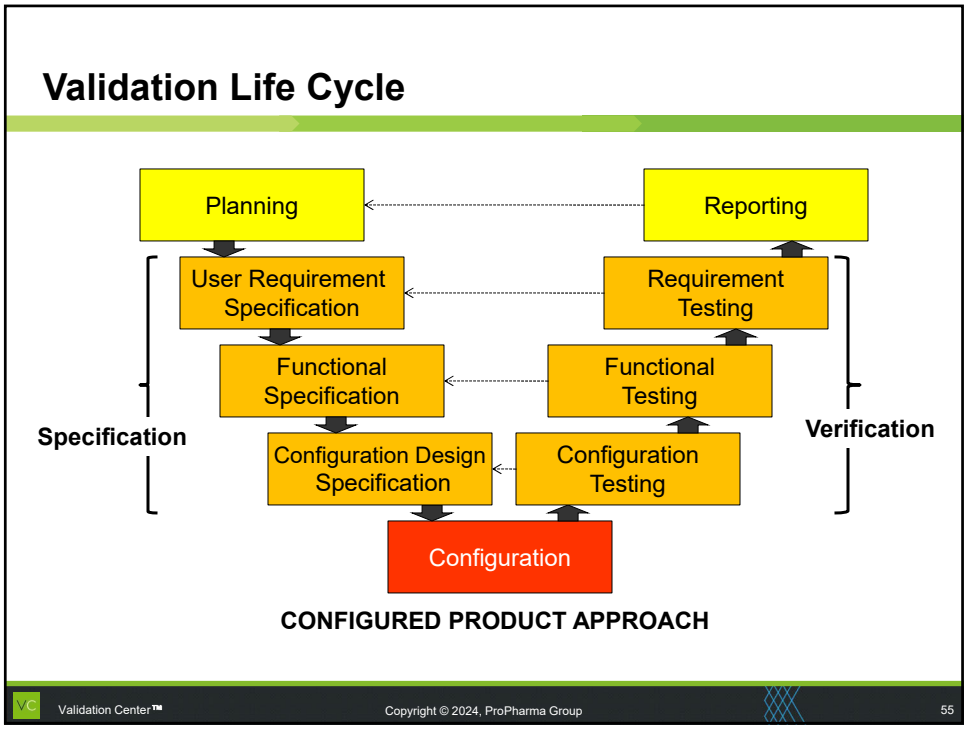
53

Validation Life Cycle



GENERAL APPROACH

54



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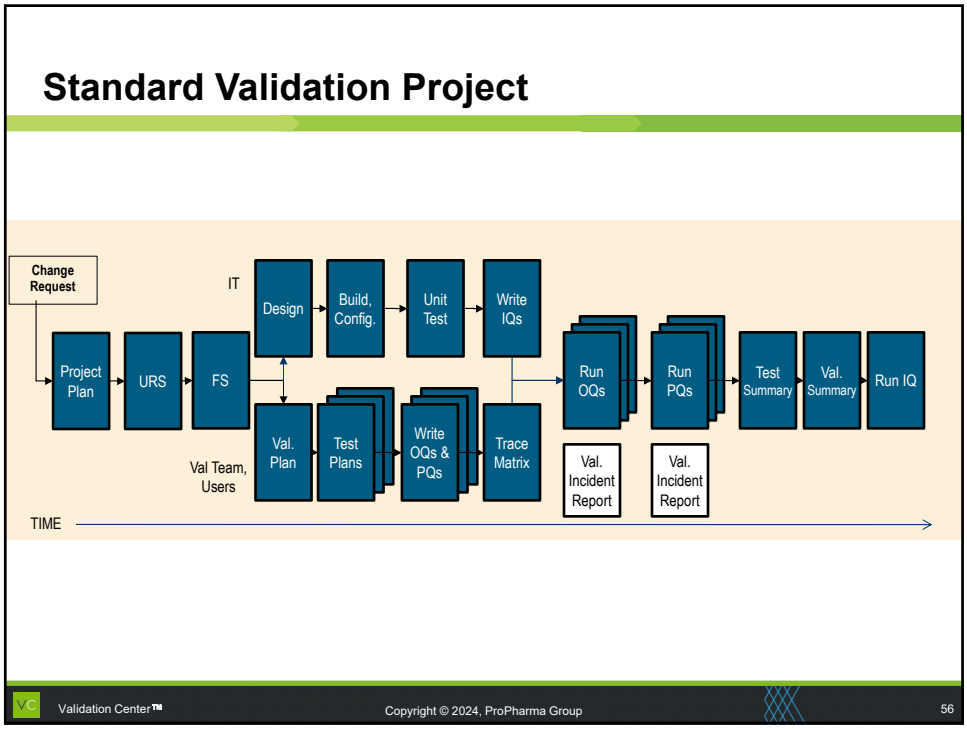

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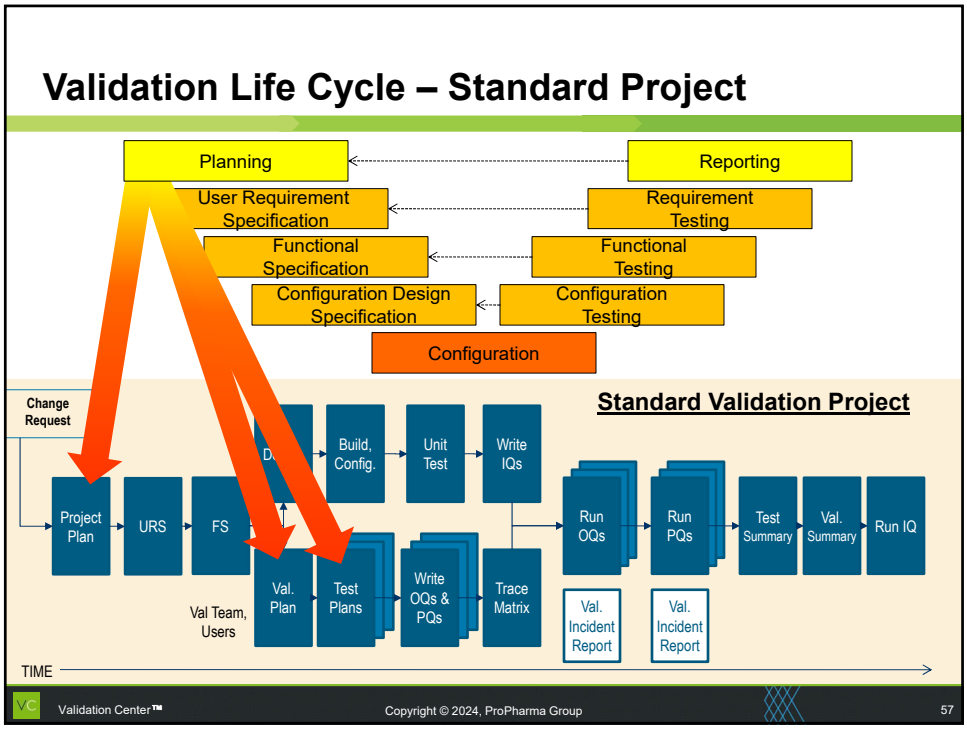

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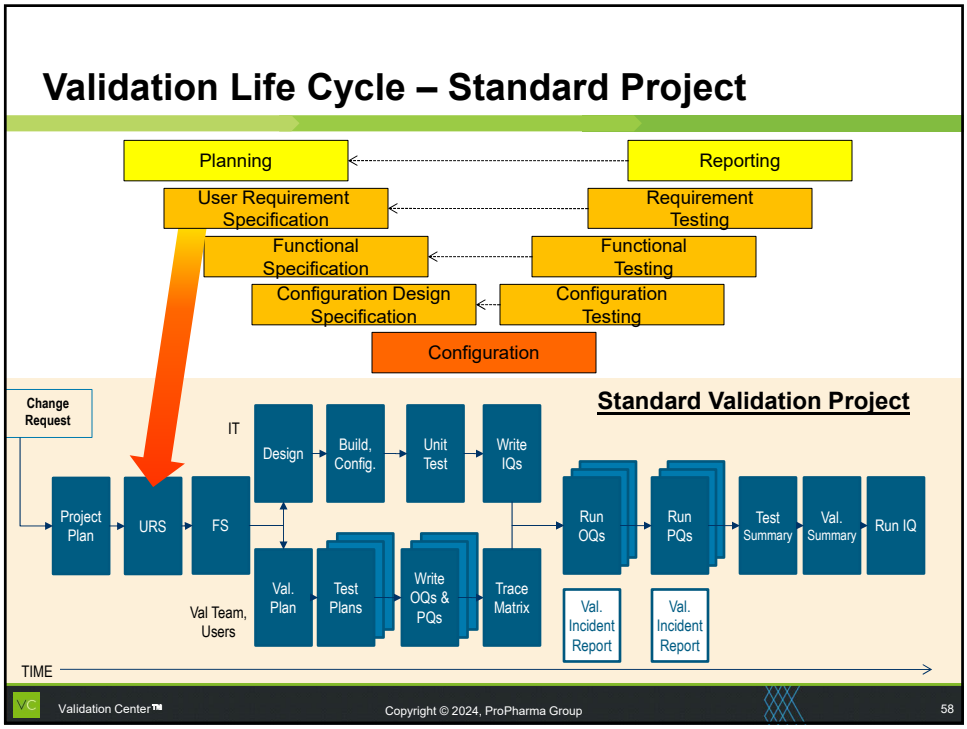

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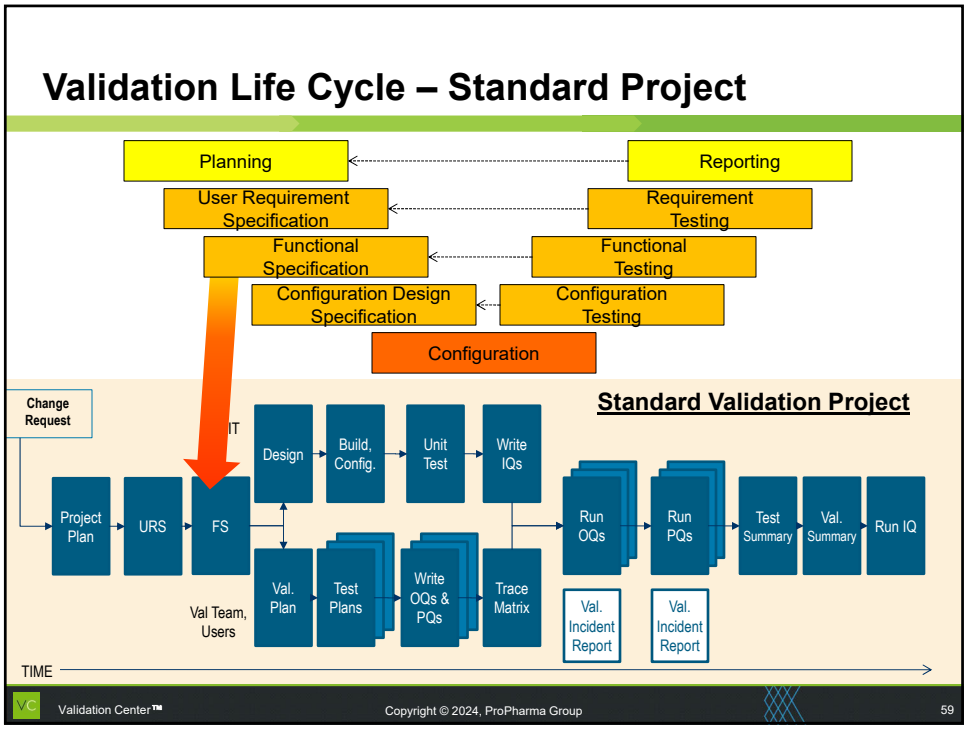

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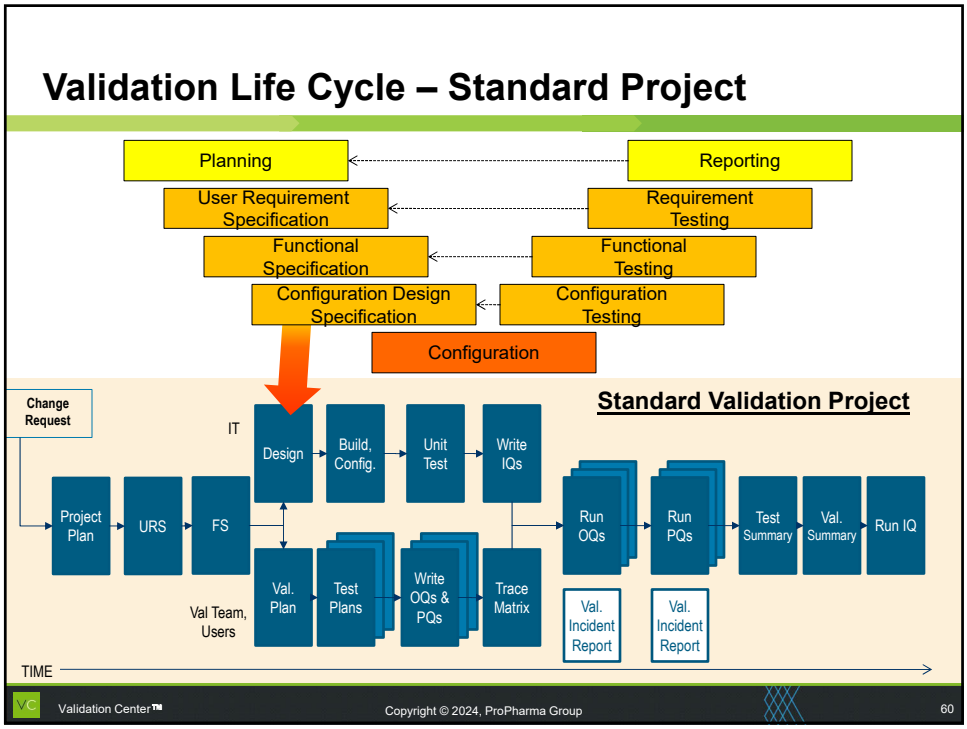

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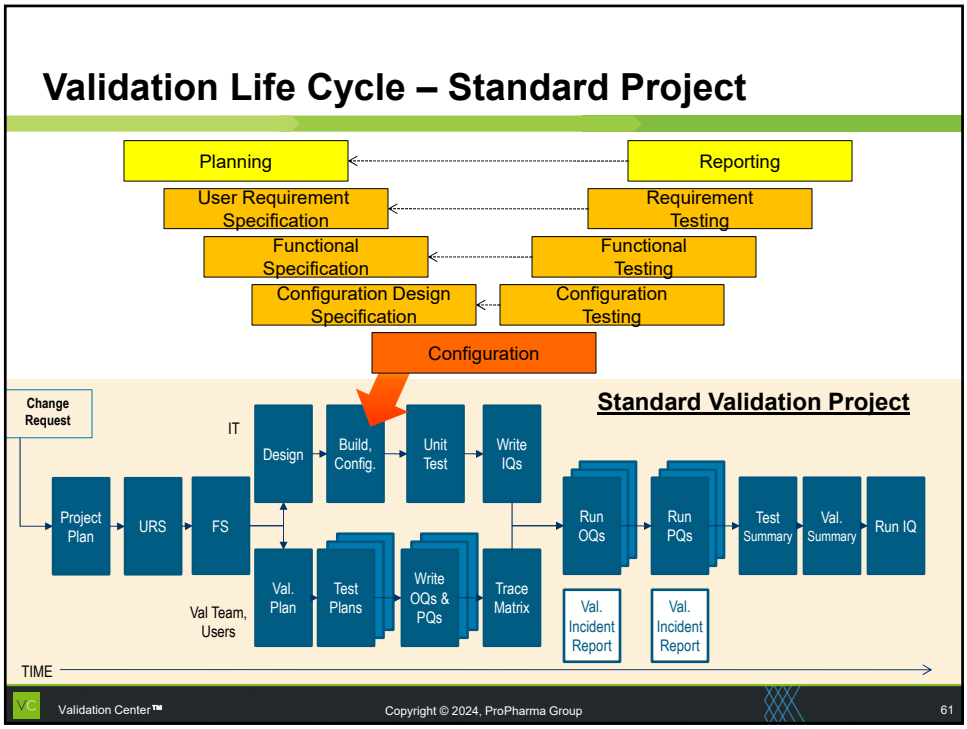

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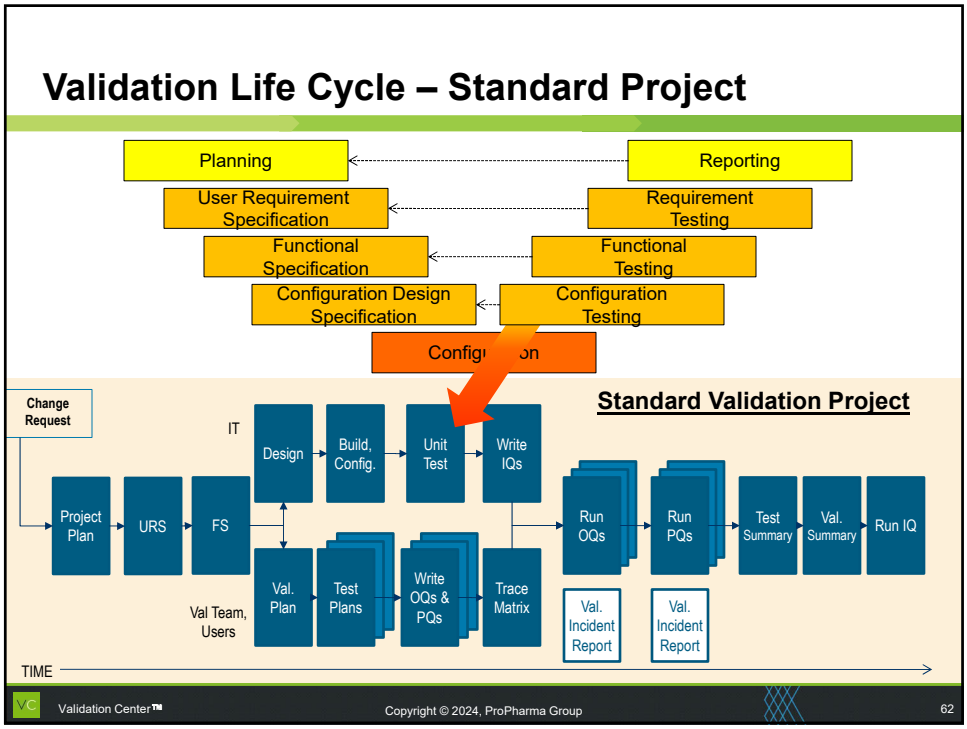

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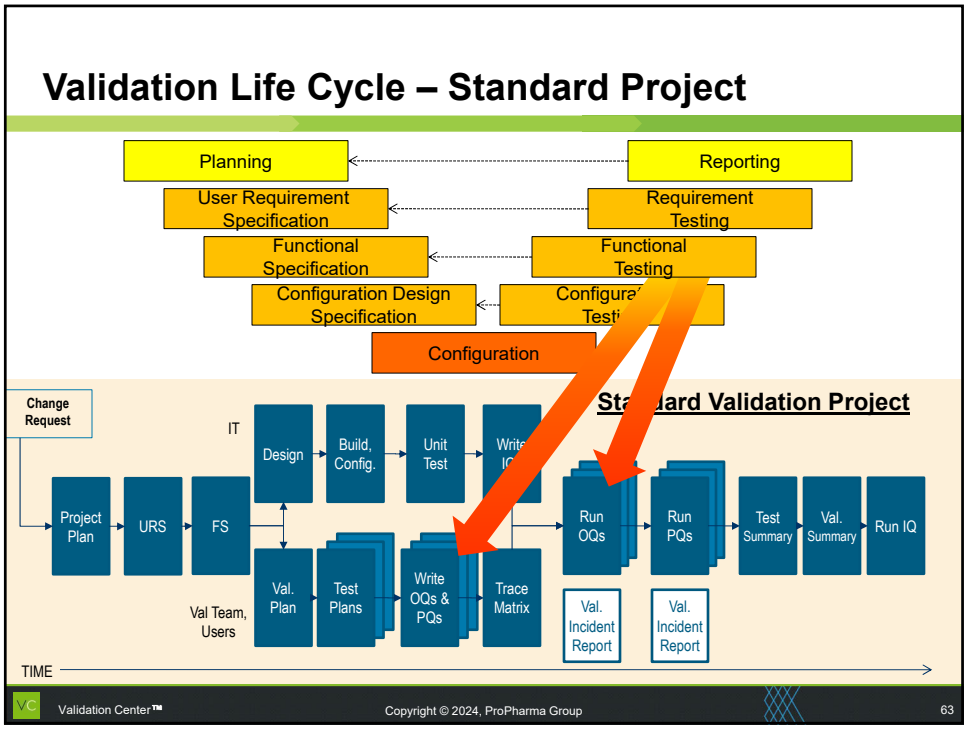

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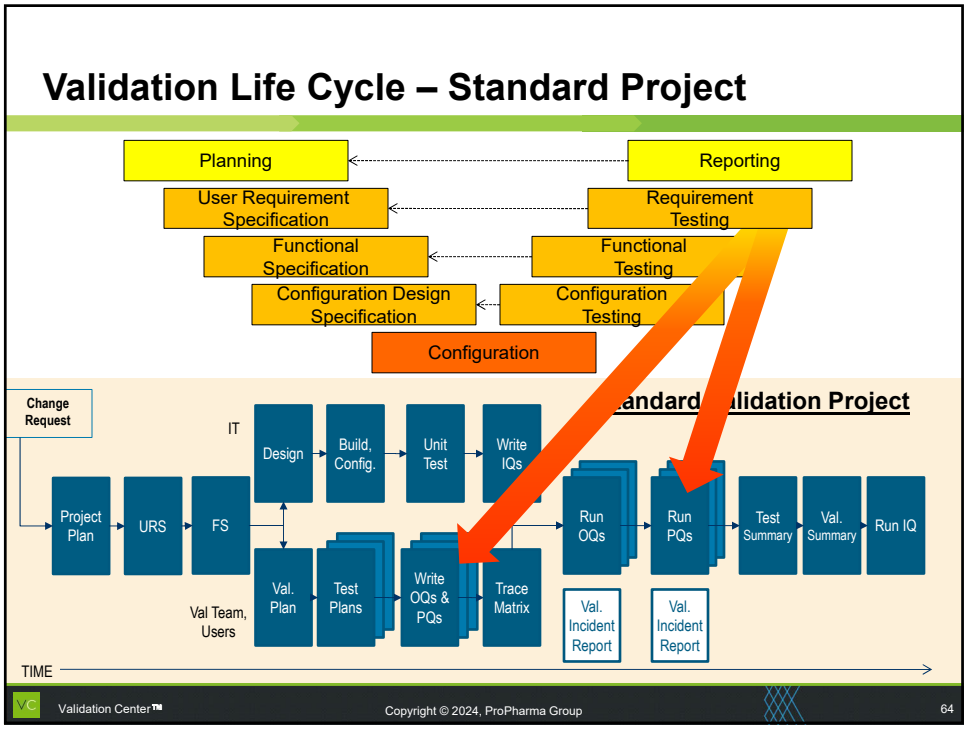

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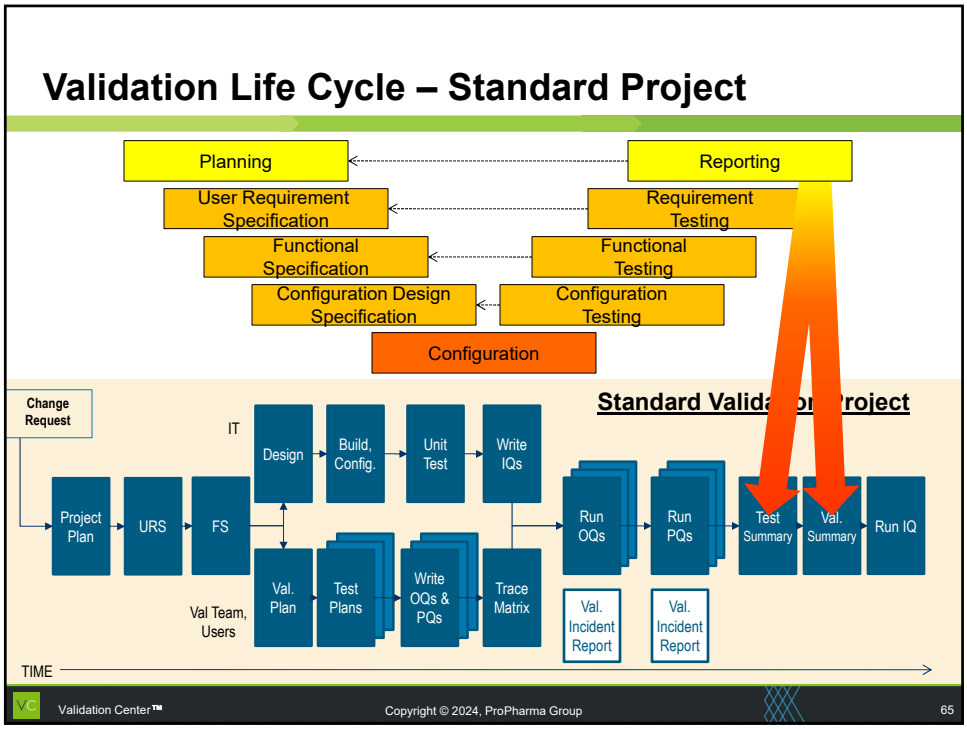

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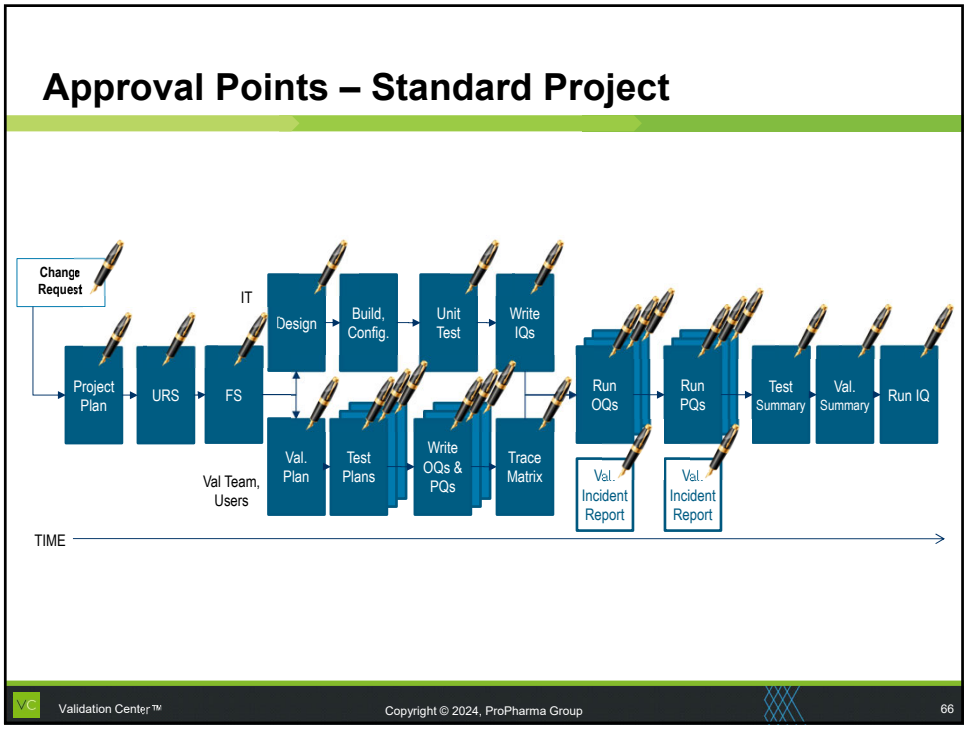


66

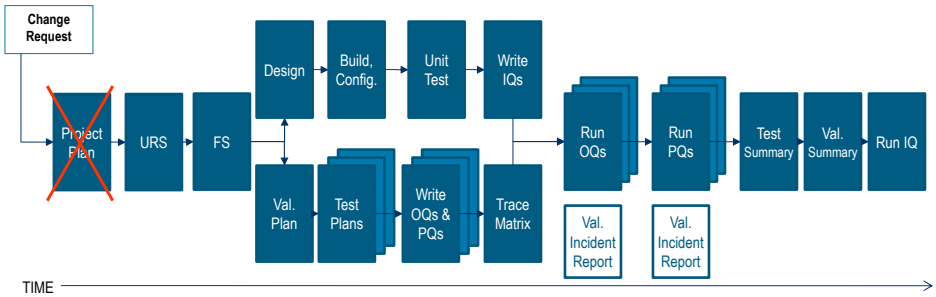
Spreadsheets Are Different

1. **Much smaller scope**
2. **Much shorter timeline**
3. **Usually less complex**
   - Single technology
   - Single function
   - Little or no programming
   - Single programmer/developer
   - Well-understood technology

67

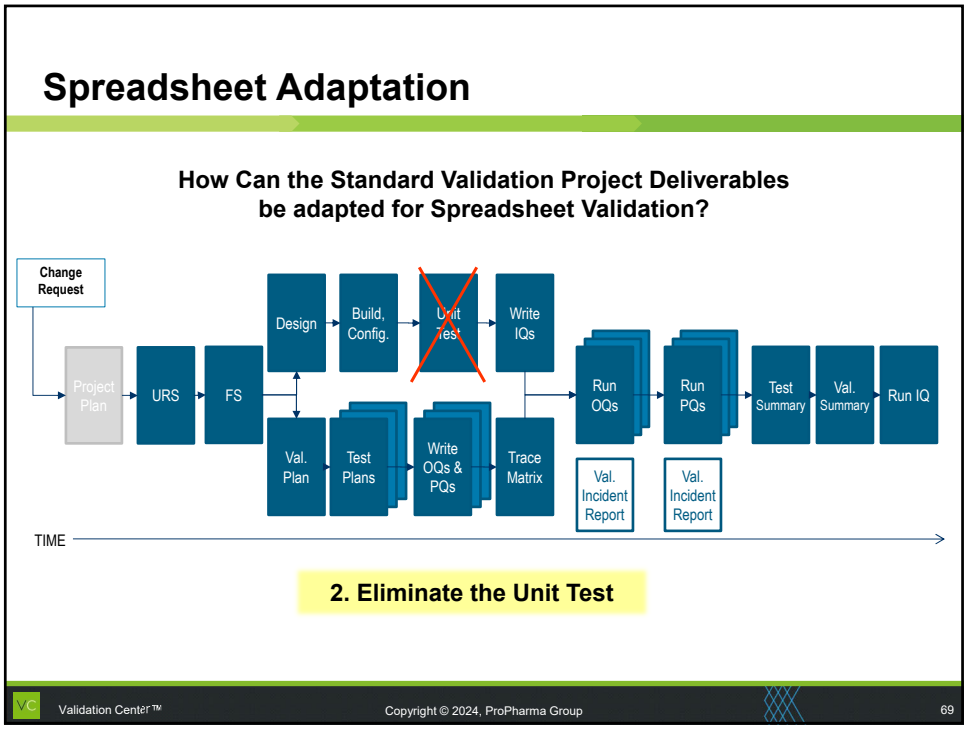
Spreadsheet Adaptation

How Can the Standard Validation Project Deliverables be adapted for Spreadsheet Validation?



1. Eliminate the Project Plan

68



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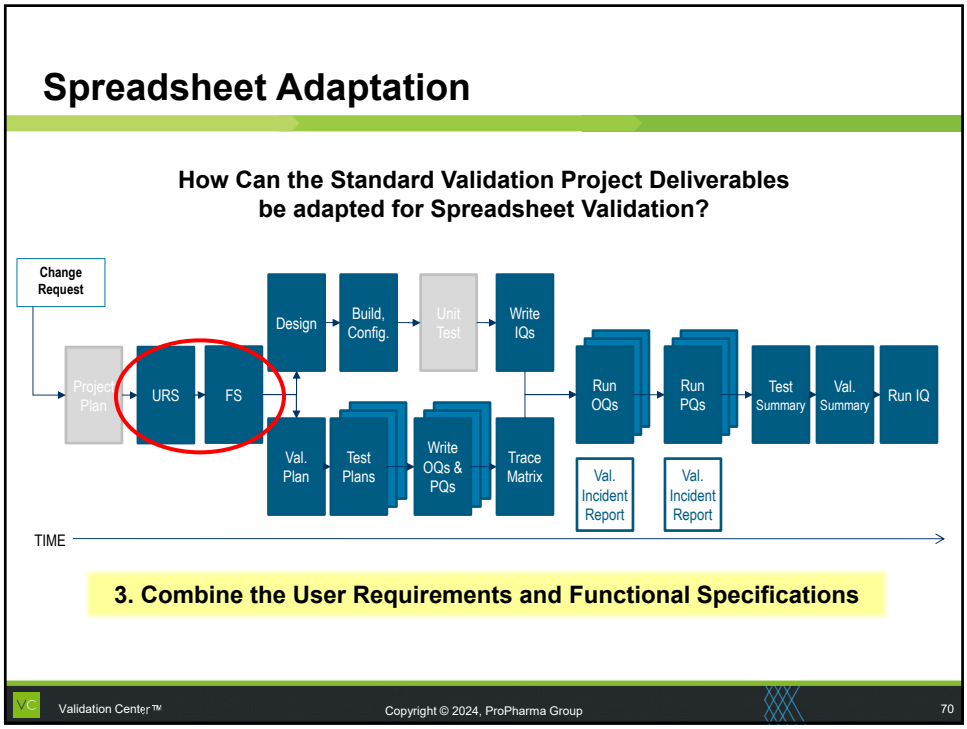
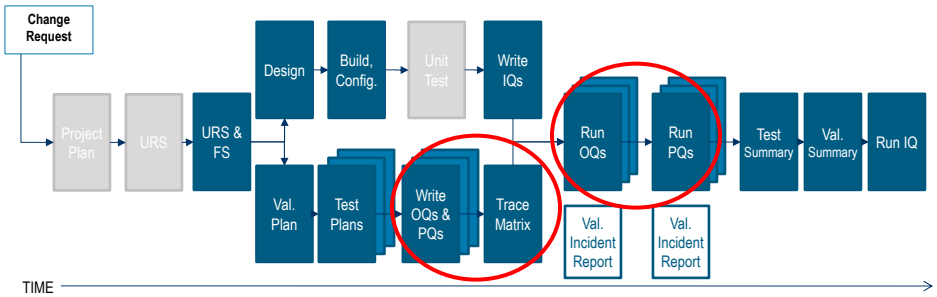


70

Spreadsheet Adaptation

How Can the Standard Validation Project Deliverables be adapted for Spreadsheet Validation?

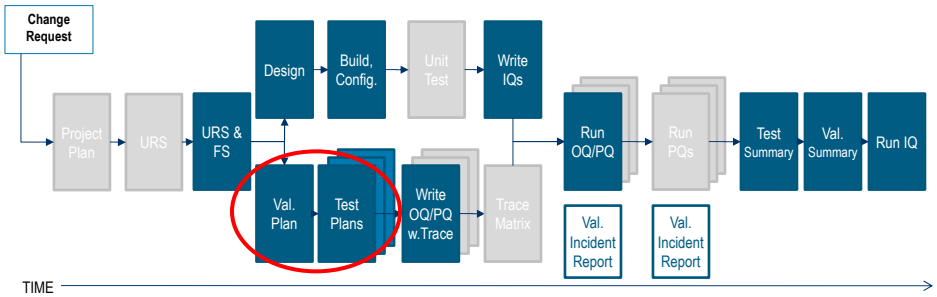


4. Combine the Operational and Performance Qualification Include the Trace Matrix

71

Spreadsheet Adaptation

How Can the Standard Validation Project Deliverables be adapted for Spreadsheet Validation?

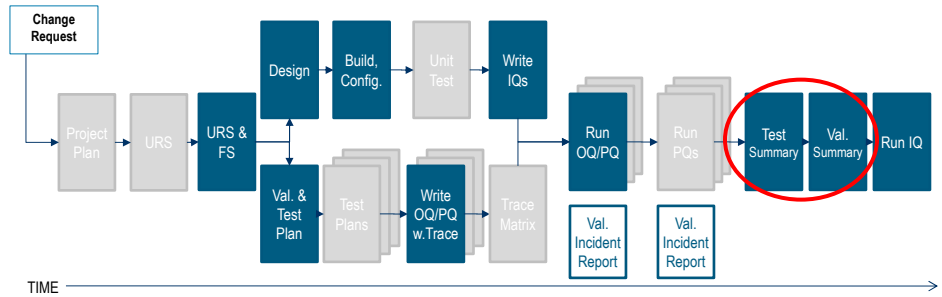


5. Combine the Validation and Test Plan

72

Spreadsheet Adaptation

How Can the Standard Validation Project Deliverables be adapted for Spreadsheet Validation?

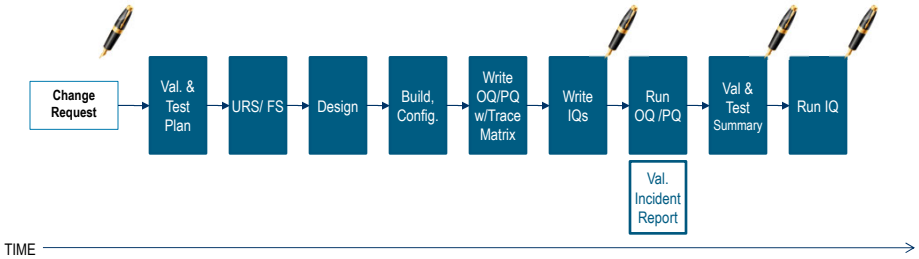


6. Combine the Validation and Test Summaries

73

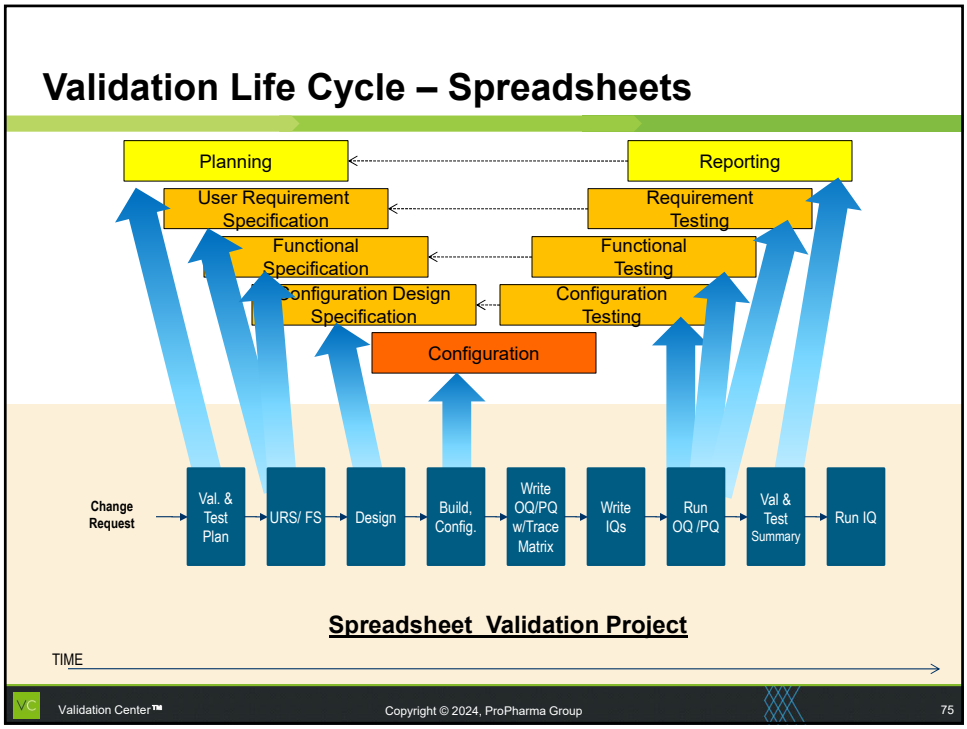
Spreadsheet Adaptation

How Can the Standard Validation Project Approval Points be adapted for Spreadsheet Validation?



7. Reduce the Approval Points

74



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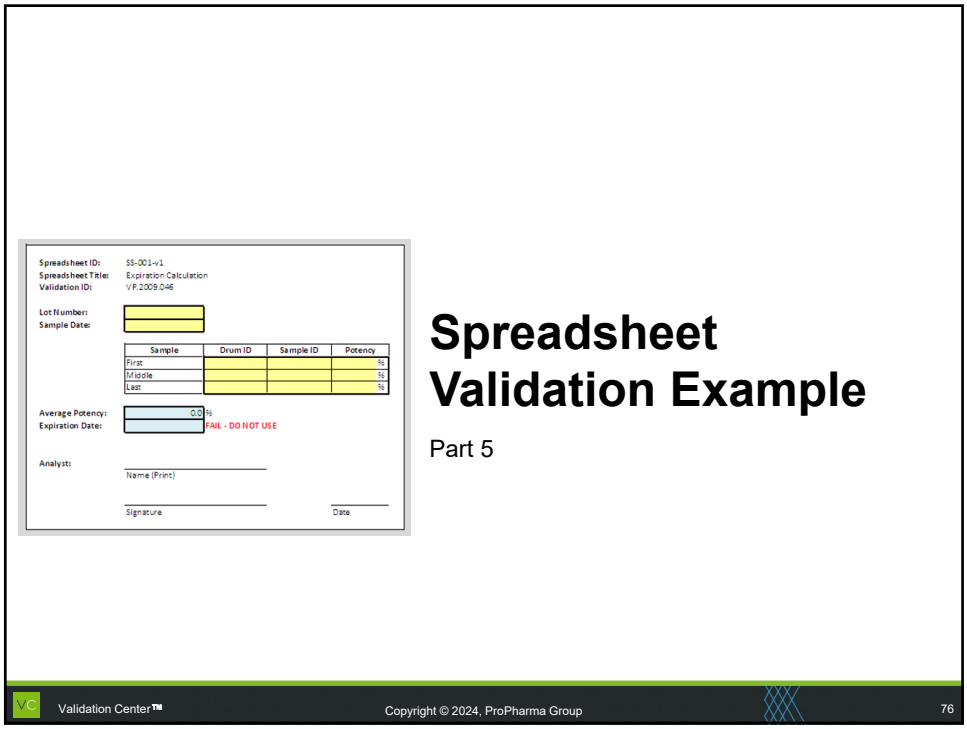


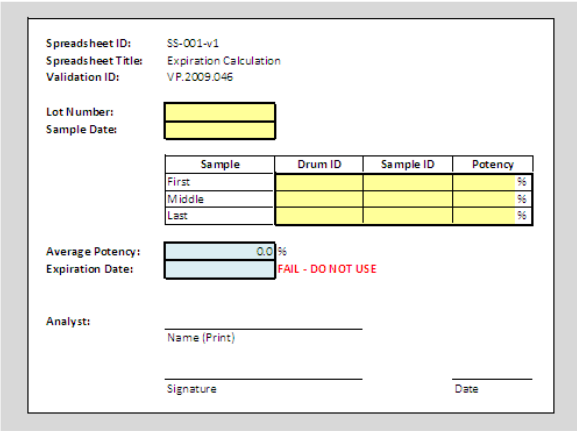
76

Part 5: Spreadsheet Validation Example

- Section Overview
  - Walkthrough example of validation for a small spreadsheet application using a condensed validation template

77

The Spreadsheet



Spreadsheet ID: SS-001-v1
Spreadsheet Title: Expiration Calculation
Validation ID: VP.2009.046

Lot Number:
Sample Date:

Sample	Drum ID	Sample ID	Potency
First			%
Middle			%
Last			%

Average Potency: 0.0 %
Expiration Date: FAIL - DO NOT USE

Analyst:
Name (Print)
Signature
Date

Purpose: Calculate the expiration date of a batch of active pharmaceutical ingredients based on the potency of 3 samples

78

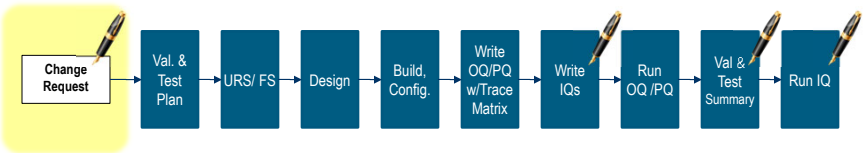
Validation Table of Contents

CONTENTS

79

Change Authorization

- Can be incorporated into the validation template or used as a stand-alone document
- Include description and justification for change
- Approved by
  - Quality Assurance
  - Business Owner (function that will use the spreadsheet)
  - Technology Owner (function that will build the spreadsheet)



80

Change Request

1 Change Authorization

Change Request ID	CR-SS-2009-056
Spreadsheet ID	SS-001
Spreadsheet Title	Expiration Calculation
Requested By	M Hentschel, Sr. Lab Analyst
Change Request Description	
Change Description	Create a new spreadsheet to calculate the expiration date of a batch of pharmaceutical ingredients from the average potency of 3 samples.
Change Rationale	A validated spreadsheet will ensure accurate calculations and reduce the effort needed by laboratory personnel.

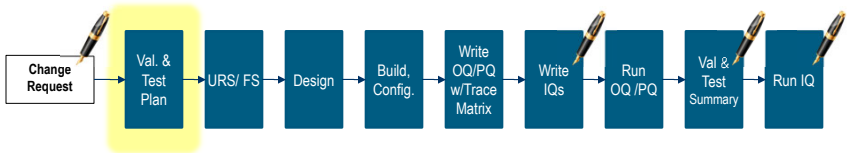
Authorization of Change

Role	Decision	Name	Signature	Date
Quality Manager	☐ Approve ☐ Reject	Edward Grieg		
IT Manager	☐ Approve ☐ Reject	Francine Schubert		
Business Manager	☐ Approve ☐ Reject	Marian Pivka		

81

Validation Plan

- Validation Scope
- Risk Assessment and Mitigation
- Validation Strategy
- Test Plan
- Acceptance Criteria



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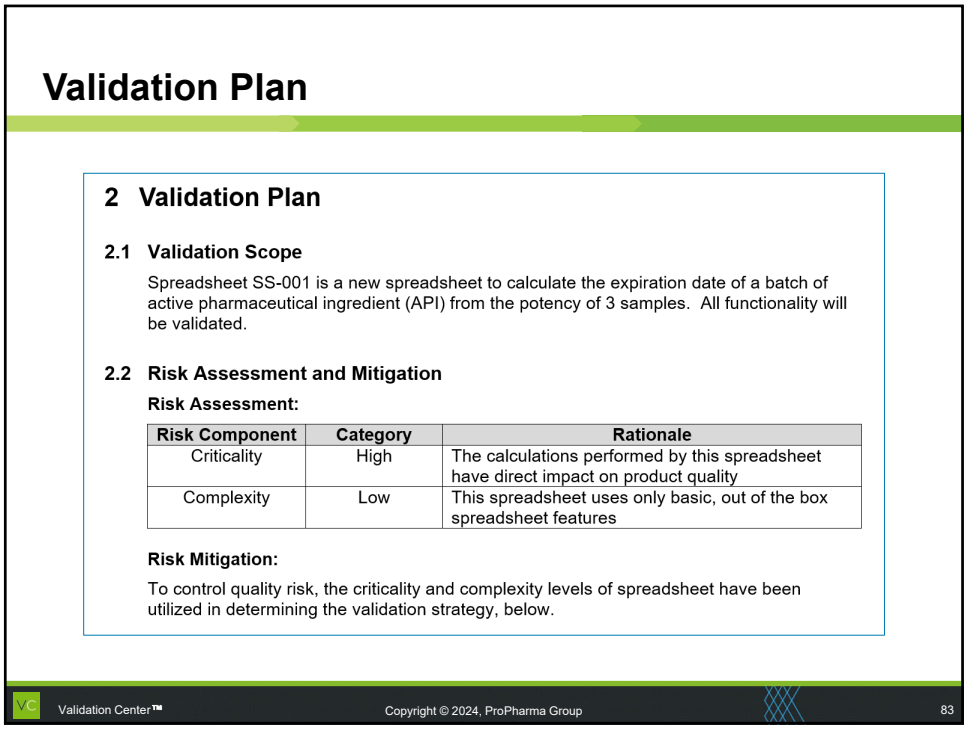

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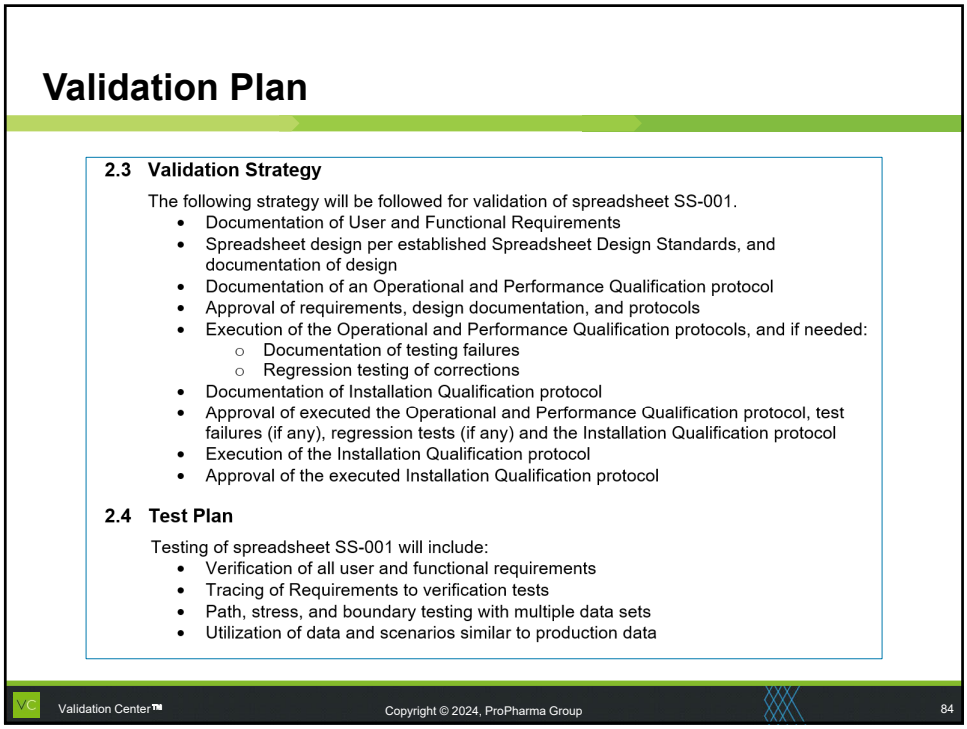


84

Validation Plan

2.5 Acceptance Criteria

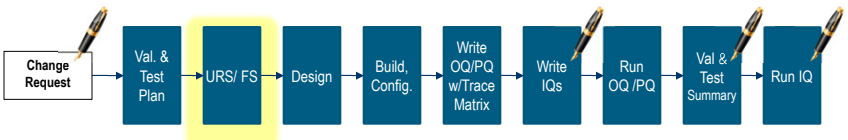
The following acceptance criteria must be met to certify spreadsheet SS-001 for production use.

- User and functional requirements have been approved
- Design has been documented
- The Operational and Performance qualification protocol has been executed and approved
- Any incidents detected during testing have been document and resolved; regressing testing has been completed.
- The Installation qualification protocol has been written and pre-approved

85

User and Functional Requirements

- Combine into single set of requirements
  - High Level = User Requirements
  - Details = Functional Requirements
- Document the features needed for
  - Intended business use
  - FDA compliance
- Key areas:
  - Calculations, statistical functions
  - Logic
  - Security



86

User and Functional Requirements

3 User and Functional Requirements

This functionality must be available in the spreadsheet to meet the intended business use.

User Requirement	**1.0**	The spreadsheet shall be secured from modification	
Functional Requirements		1.1	All cells except for lot number, sample date, drum ID, sample ID, and potency shall be secured from modification by users
		1.2	The cells listed in requirement 1.1 shall be yellow
		1.3	No other cells in the spreadsheet shall be yellow
		1.4	There shall be a password used to lock the spreadsheet from modification by uses
User Requirement	**2.0**	The spreadsheet shall calculate the lot potency from the potency of 3 samples	
Functional Requirements		2.1	The spreadsheet shall require entry of 1 digit to the right of the decimal point. An error message shall be displayed if <1 digit or >1 digit is entered.
		2.2	The spreadsheet shall require entry of all 3 sample potencies
		2.3	The spreadsheet shall display an error message if any potency value is < 0.0
		2.4	The spreadsheet shall display an error message if any potency value is >110.0
		2.5	Potency shall be calculated as (first-sample-potency + second-sample-potency +third-sample-potency) / 3

87

User and Functional Requirements

User Requirement	**3.0**	The spreadsheet shall calculate the lot expiration date based on the sample date and potency	
Functional Requirements		3.1	If the lot potency is >= 90, the expiration date shall be calculated as the sample date + 365 days
		3.1.1	The spreadsheet shall display message “PASS – OK TO USE” in black
		3.2	If the lot potency is >= 85 and <90, the expiration date shall be calculated as the sample date + 304 days
		3.2.1	The spreadsheet shall display message “PASS – OK TO USE” in black
		3.3	If the lot potency is < 85, no expiration date shall be calculated
		3.3.1	The spreadsheet shall display message “FAIL – DO NOT USE” in red

Etc.

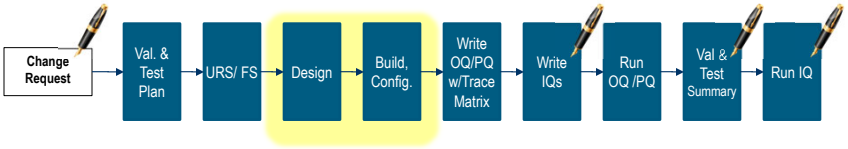
88

Build and Document Design

- Document the design of the spreadsheet

For Example…

- Reference any design standards followed
- Insert or attach an image of the spreadsheet
- Insert or attach a view of the spreadsheet showing the formulas in each cell
- Insert or attach images of configurations, macros, security settings, and any other design elements



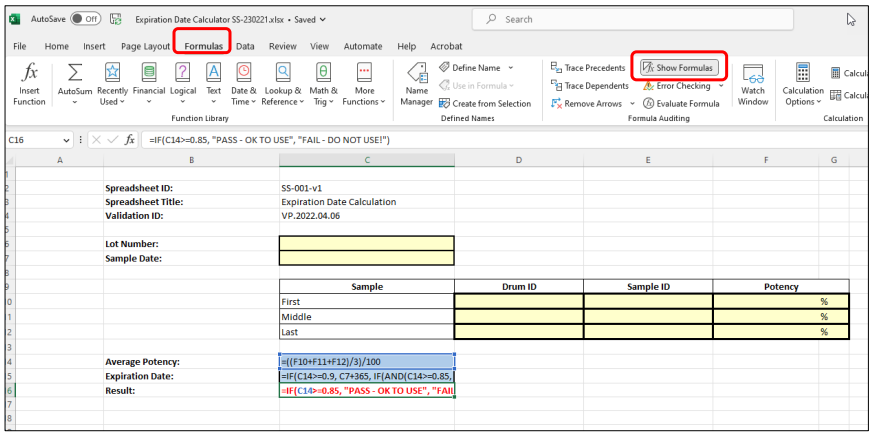
89

Design Standards, Example

- Password protection on non-data entry cells
- Formatting standards, such as inclusion of spreadsheet ID, version number, and validation reference (e.g., validation ID and/or date) on spreadsheet
- Standard number of decimal points to use
- Standard for rounding rules
- Standard date formats
- Standard colors for data entry cells and calculated cells
- Standard file naming conventions
- Standard error message formats

90

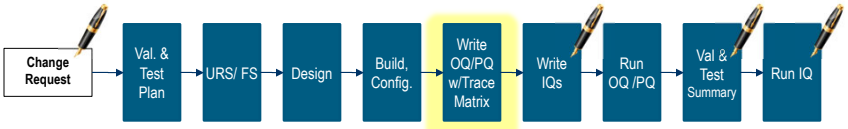
Formula Printing



91

Operational and Performance Qualification

- Combine into single set of tests
- Follow approved test plan
  - Scope of requirements to test
  - Documentation requirements
- Document Test Design (scenarios & data) for high criticality / high complexity features
- Cross-reference (trace) each step to the requirement tested
- Leave space for
  - Entry of actual results
  - Name, signature, and date of tester



92

OQ/PQ Test Design

6 Operation and Performance Qualification

6.1 Test Design

Test Scenario(s)	Data
Security • Test that all cells are locked from user modification except for lot#, sample date, drum ID, sample ID, and potency • Verify that the unlocked cells are yellow and that no other cells are yellow	• N/A – no data needed for these tests
Potency • For all 3 potency fields, verify that users can only enter values between 0 and 110 • Numbers outside this range should receive an error message	• 0.0 • 0.01 • 30.0 • 99.9 • 110.0 • 110.01
Average Potency • Test the average calculation vs. the same calculation performed by a qualified calculator	First / Middle / Last 99.9 / 98.7 / 97.5 110.0 / 50.4 / 12.2 45.9 / 56.3 / 43.2

93

OQ/PQ Test Design

Expiration Date Scenario 1 • Potency >=90 • Lot passes	First Sample: 90.1 Second Sample: 88.7 Third Sample: 99.9 Expiration Date: 365 days after Sample Date Message: PASS – OK TO USE First Sample: 90.0 Second Sample: 90.0 Third Sample: 90.0 Expiration Date: 365 days after Sample Date Message: PASS – OK TO USE
Expiration Date Scenario 2 • Potency >=85 but <90 • Lot passes	First Sample: 90.0 Second Sample: 90.0 Third Sample: 89.9 Expiration Date: 304 days after Sample Date Message: PASS – OK TO USE
Expiration Date Scenario 3 • Potency <85 • Lot fails	First Sample: 85.0 Second Sample: 85.0 Third Sample: 79.9 Expiration Date: blank Message: FAIL – DO NOT USE

Etc.

94

OQ/PQ Test Protocol

6.2 Test Protocol

Step	Req.	Description/Action	Expected Result	Actual Result = Expected Result (Yes/No)	Comment
Test Case 1: Security					
1.1	1.1	Attempt to enter data into the following cells: • lot#, • sample date • drum ID – 1st, 2nd , 3rd • sample ID • potency – 1st, 2nd, 3rd Print screen	Tester is able to enter values into the cells listed		
1.2	1.1	Attempt to enter data into all other cells. Print error message	Tester is unable to enter data and receives an error message stating that the cell is protected		
1.3	1.2 1.3	Visually inspect cell colors	• Cells listed in Step 1.1 are yellow. • Average potency and Expiration date cells are blue • All other cells are white		

95

OQ/PQ Test Protocol

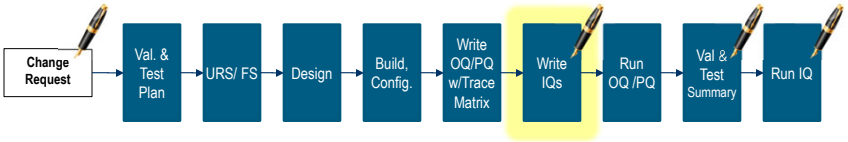
Test Case 2: Average Potency Calculation					
2.1	2.5	Enter these potencies • First Sample: **99.9** • Second Sample: **98.7** • Third Sample: **97.5** Print screen	Average potency values is **98.7**		
2.2	2.5	Enter these potencies • First Sample: **110.0** • Second Sample: **50.4** • Third Sample: **12.2** Print screen	Average potency values is **57.5**		
2.3	2.5	Enter these potencies • First Sample: **45.9** • Second Sample: **56.3** • Third Sample: **43.2** Print screen	Average potency values is **48.6**		

Tester Name, Signature, and Date _____

96

Installation Qualification

- Describe the steps to install the spreadsheet into production
  - Location
  - File security
  - Password protection
- Include space for
  - Entry of actual results
  - Name, signature, and date of tester



97

Installation Qualification

9 Installation Qualification

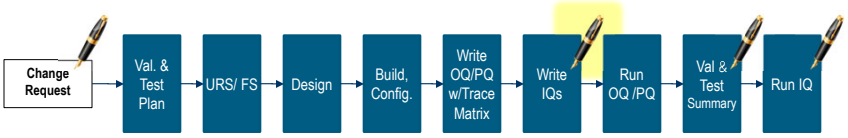
Step	Description/Action	Expected Result	Actual Result = Expected Result (Yes/No)	Comment
1,1	Move spreadsheet SS-001 v1 to folder R:\YXK034\Laboratory Spreadsheets\Validated Print Screen	File resides in folder R:\YXK034\Laboratory Spreadsheets\Validated		
1.2	Set spreadsheet password to LOCKED Print Screen	Password is set to LOCKED		
1.3	Set file permission for Users to allow "Read and Execute" only. Deny all other permissions for users. Print Screen	Users permissions are set to "Read and Execute" only		

Implementer Name, Signature, and Date _____

98

Preliminary Approval

- Obtain approval of all deliverables up to this point



99

Preliminary Approval

5 Preliminary Approval

The signatures below indicate:

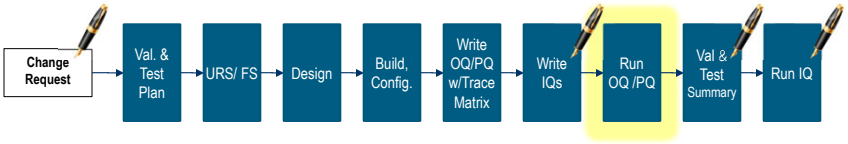
- Approval of the Validation Plan, User and Functional Requirements, and Design Documentation
- Pre-approval of Operational and Performance Qualification protocol
- Pre-approval of the Installation Qualification protocol

Role	Name	Signature	Date
Quality Manager	Edward Grieg		
IT Manager	Francine Schubert		
Business Manager	Marian Pivka		

100

Run OQ and PQ

- Follow the approved test protocol
  - Execute steps
  - Record actual results
  - Capture screen prints
  - Document steps that pass (or fail)
- Create a Verification Issue Report for any failing tests
  - Describe failure
  - Determine error type (e.g., test error, tester error, functionality error)
  - Describe resolution
  - Describe re-testing and regression testing required



101

Issue Report

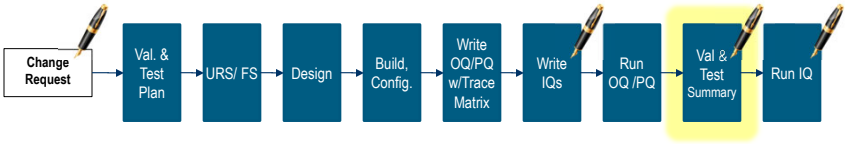
Appendix A - Verification Issue Report

Issue Number	1
Test Case	1
Test Step	1.2
Date of Issue	06-December-2022
Description of Issue	Tester was able to enter data into cells H11, I11, and J11. These cells should have been protected from entry.
Issue Type	Functionality Error
Steps for Issue Correction	IT Spreadsheet configuration analyst will turn on protection for these cells
Regression Testing Required	Rerun Test Case 1, steps 1.1 and 1.2

102

Summary Reports

- Testing Summary
  - Summarize the results of the verification (testing) activities
- Validation Summary
  - Compare current state vs. acceptance criteria identified in the approved Validation Plan



103

Summary Reports

7 Testing Summary and Validation Summary

7.1 Testing Summary

During execution of OQ/PQ testing, a total of 2 issues were identified. Of these issues, 1 was a test protocol errors and the other was a spreadsheet functionality problems. Both issues have been resolved. See Appendix A for test issue details.

7.2 Validation Summary

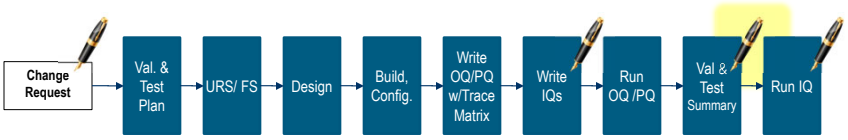
The following acceptance criteria have been met, and therefore this spreadsheet can be implemented for production use

- User and functional requirements have been approved
- Spreadsheet design has been documented
- The Operational and Performance qualification protocol has been executed and approved
- Incidents detected during testing have been document and resolved; regressing testing has been completed
- The Installation qualification protocol has been written and pre-approved

104

Validation Approval

- Approve the validation deliverables and authorize the production use of the spreadsheet



105

Validation Approval

8 Validation Approval

The signatures below indicate:

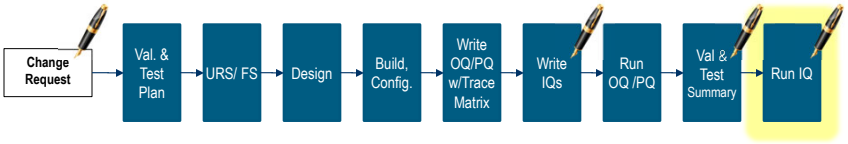
- Approval of the Operational and Performance Qualification test results, the Verification Summary, and the Validation Conclusion
- Authorization to move the spreadsheet into production use

Role	Name	Signature	Date
Quality Manager	Edward Grieg		
IT Manager	Francine Schubert		
Business Manager	Marian Pivka		

106

Installation, Closure

- Installation
  - Execute the pre-approved Installation Qualification
    - Execute steps
    - Record actual results
    - Capture screen prints
    - Document steps that pass (or fail)
- Closure
  - Obtain signature to close validation project



107

Validation Closure

10 Validation Closure

The signatures below indicate: • Completion of validation			
Role	**Name**	**Signature**	**Date**
Quality Manager	Edward Grieg		

108

FDA Warning Letter Examples

Part 6

109

Part 6: FDA Warning Letter Examples

- Section Overview
  - Warning Letter Data
  - Warning Letter Examples
- Data Source
  - FDA Warning Letters related to Software and Computer Systems
  - 14 Year Range: 2010-2023

110

FDA Warning Letter Example

Audit Finding

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

For example:

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

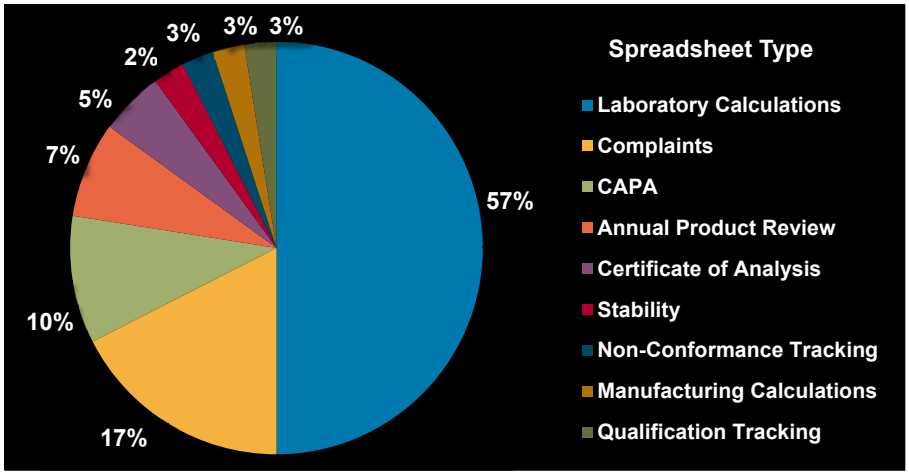
b. Your firm had no system in place to ensure appropriate backup of electronic raw data and no standard procedure for naming and saving data for retrieval at a later date.

Observations

111

Spreadsheet Warning Letters

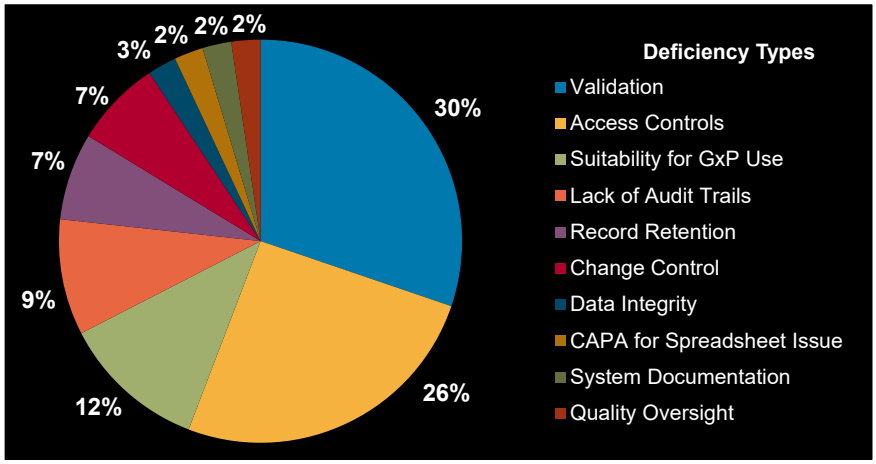
by Spreadsheet Use



112

Spreadsheet Warning Letters

by Topic



113

FDA Warning Letter Examples

Regulatory Reference	21 CFR 606 (Blood Products)
FDA Office	Los Angeles District
Spreadsheet Usage	Quality Metrics Tracking & Trending
Warning Topic	Validation

There are no data to demonstrate that the quality control/quality assurance spreadsheets used for tracking and trending various quality metrics have been properly validated (installation qualification, operational qualification, and performance qualification) and are performing as intended.

The percent Average and percent Standard Deviation results did not change from month to month on the Aberrant Controls, Failed Run or Failed Runs/Aberrant Controls spreadsheets. The error was due to failure to use the current rolling 12-month formula in the spreadsheet calculations.

When a recalculation was performed, an alert level for HIV was identified.

114

FDA Warning Letter Examples

Regulatory Reference	21 CFR 820 (Medical Devices)
FDA Office	Detroit District
Spreadsheet Usage	Complaints Tracking
Warning Topic	Suitability for use

Firm tracks complaint data on a spreadsheet that contains free form text fields that are not standardized, resulting in an **inability to adequately trend the data**.

For example,

when using complaint data for part "6090," 14 complaints are shown. However, the spreadsheet contains several different descriptions of the same part failure that when totaled resulted in a total count of 40 complaints related to part #6090.

115

FDA Warning Letter Examples

Regulatory Reference	21 CFR 211 (Pharmaceuticals)
FDA Office	Baltimore District
Spreadsheet Usage	Laboratory Calculation
Warning Topic	Security

Your firm failed to exercise appropriate controls over computer or related systems to ensure that changes are instituted only by authorized personnel.

Specifically

Your firm's **laboratory analysts have the ability to access and modify the formulas in the Excel spreadsheets** used to calculate assay results for drug products. Due to the unrestrictive access, there is no assurance that the formulas in the Excel spreadsheets are accurate and valid.

116

FDA Warning Letter Examples

Regulatory Reference	21 CFR 820 (Medical Devices)
FDA Office	CDRH
Spreadsheet Usage	CAPA and Non-conformance Management
Warning Topic	Suitability for use

"Task Force Meeting" spreadsheets are used to review all non-conformances.

However, these spreadsheet records do not document:

- Investigation of the cause of nonconformities
- Implementation of action plans needed to correct and prevent identified quality problems,
- Whether corrective actions were verified or validated as effective, or that the actions do not adversely affect the finished device

117

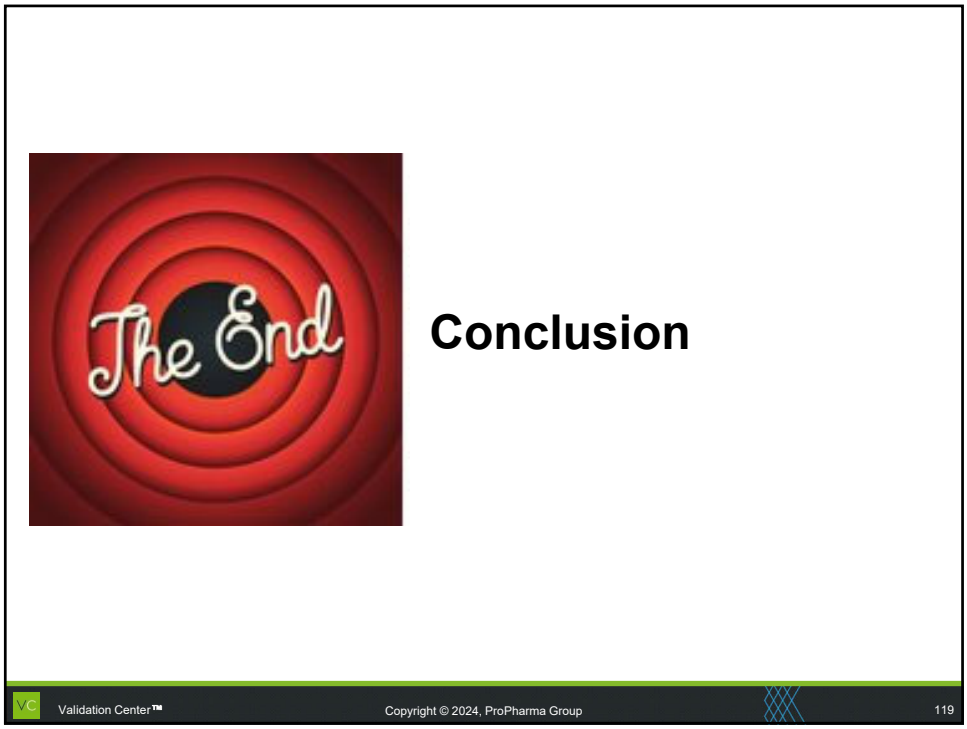
FDA Warning Letter Examples

Regulatory Reference	21 CFR 211 (Pharmaceuticals)
FDA Office	CDER
Spreadsheet Usage	Laboratory Calculation
Warning Topics	Security, Validation, Change Control

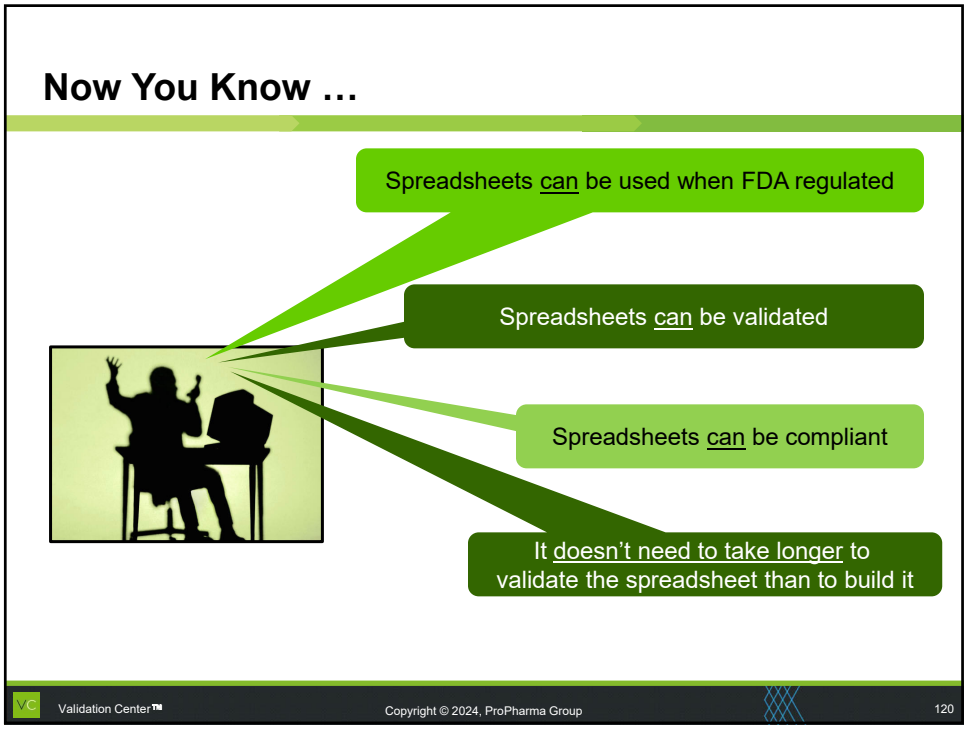
At the drug facility, the investigator noticed that the use of the Excel spreadsheets in analytical calculations are neither controlled nor protected from modifications or deletion.

The investigator noticed that the calculation for residual solvent uses an Excel spreadsheet that has not been qualified. We are concerned about the data generated by your QC laboratory from non-qualified and uncontrolled Excel spreadsheets.

118



119



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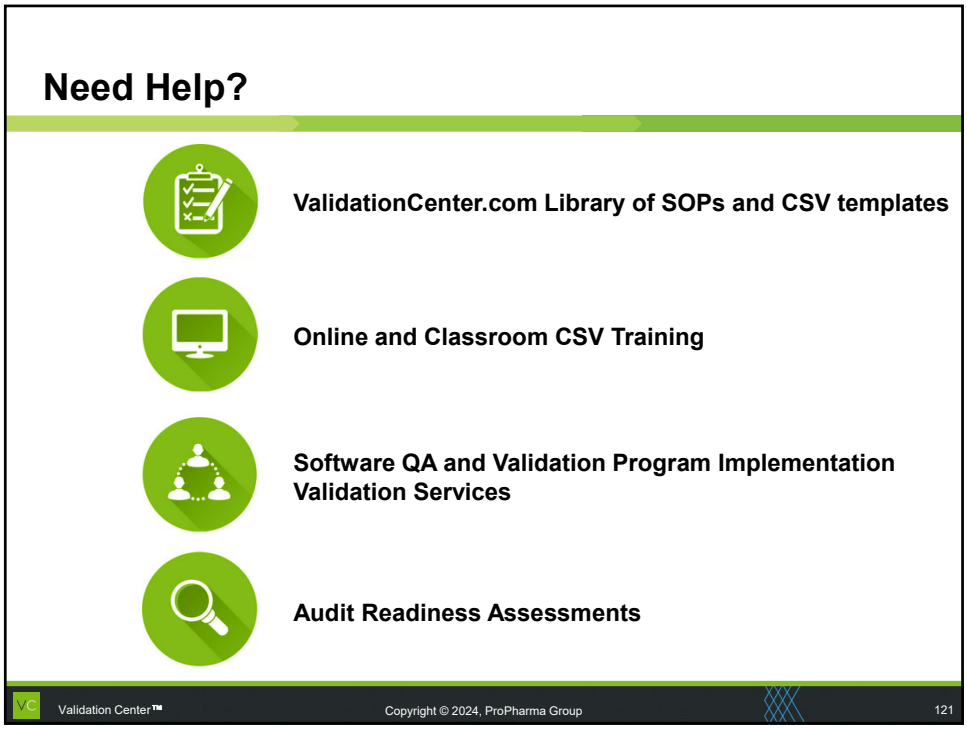

121

122