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# Spreadsheet Validation

By Praxis Life Sciences

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## Spreadsheet Validation

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## Your Praxis Facilitator

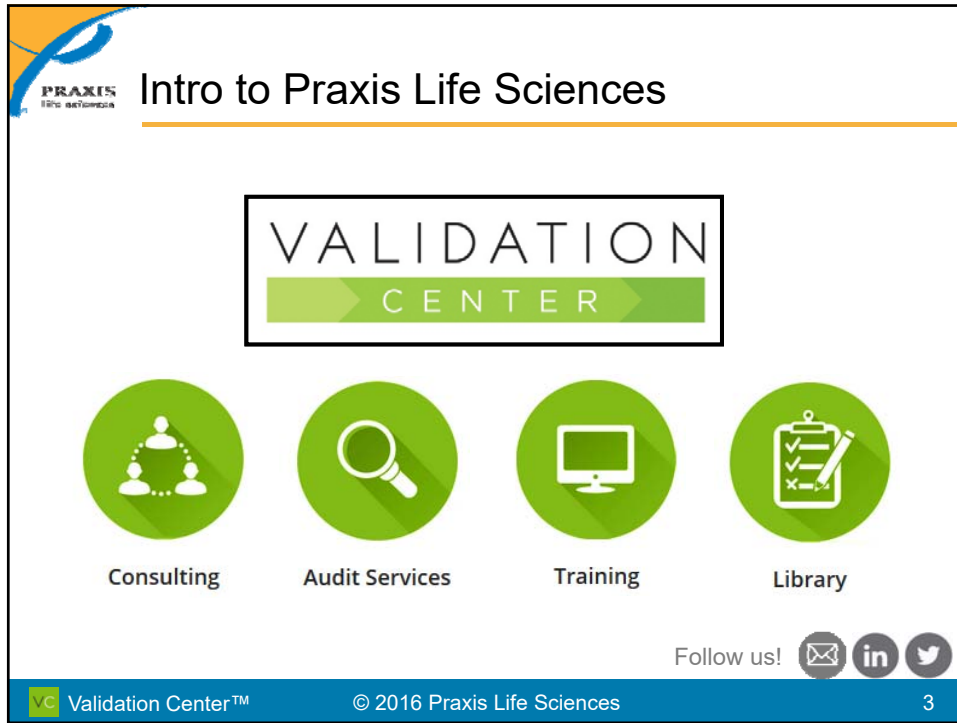
- Debra Bartel, MBA, CQA, PMP
- Principal, Praxis Life Sciences
- 25+ years experience specializing in software quality assurance, validation and regulatory compliance, Information Systems project management, and process design.
- Prior to joining Praxis, held management positions in the pharmaceutical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



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## Intro to Praxis Life Sciences




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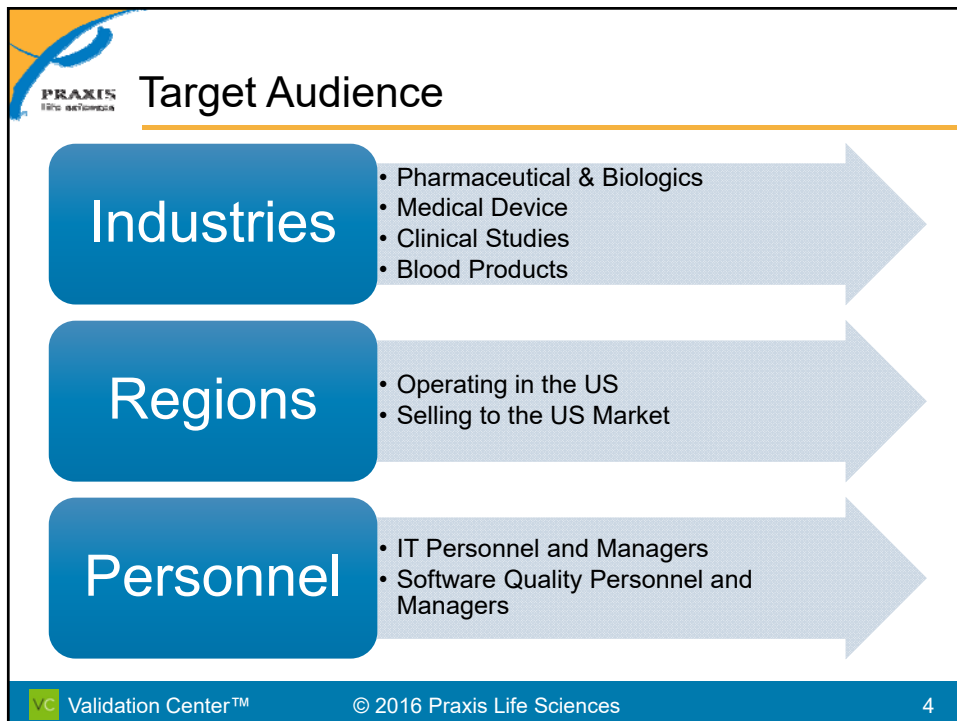
Audit Services

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Follow us!   

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## Target Audience

**Industries**


- Pharmaceutical & Biologics
- Medical Device
- Clinical Studies
- Blood Products

**Regions**

- Operating in the US
- Selling to the US Market

**Personnel**

- IT Personnel and Managers
- Software Quality Personnel and Managers

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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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## Webinar Outline

- 1 • FDA Guidance
- 2 • Validation and Part 11 Compliance
- 3 • Validation & Risk Framework
- 4 • Spreadsheet Validation Approach
- 5 • Spreadsheet Validation Example
- 6 • FDA Warning Letter Examples

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# FDA Requirements and Guidance

Part 1



## Part 1: FDA Requirements and Guidance

### Section Overview

- FDA Regulations
- FDA Guidance
- FDA Laboratory Reference Manual

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## Framework for Regulations, Guidelines

21 CFR 210,211, 820, 606 Good Manufacturing Practices FDA Guidance: General  
Good Clinical Practices FDA Guidance: Computerized Systems Used in Clinical Investigations  
& Signatures ICH Q9 Quality Risk Management 21 CFR 600 Biological Products: General

**Regulatory and Industry Standards**

Software Quality Assurance, Validation, and Information  
Technology professionals need to be aware of many  
regulations and standards.



Here are some **key places** to look for  
regulations and guidelines related to  
spreadsheets

21 CFR 50, 54, 56  
Eudralex V4 Chapter 4 Documentation 21 CFR 11 Electronic Record  
Laboratory Practices 21 CFR 11 Electronic Record

21 CFR 58 Good  
FDA Guidance: Validation of Blood Establishment Computer Systems ICH Q7A Good Manufacturing Practice ICH E6 Good Clinical Practice

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## Framework for Regulations, Guidelines

Guidance Documents from Regulatory Agencies


FDA Guidance & Reference Documents PIC/S Guidance Documents ICH Guidelines etc.

**Regulations (Laws)**  
FDA 21 CFR ....  
Eudralex Volume ...

Company policies & procedures

Best Practices from Industry Groups and Standards Bodies

GAMP Guides (ISPE) IEEE Guides ISO Standards etc.



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## FDA Regulations for Validation

**21 CFR 11**

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.

**21 CFR 211**

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.

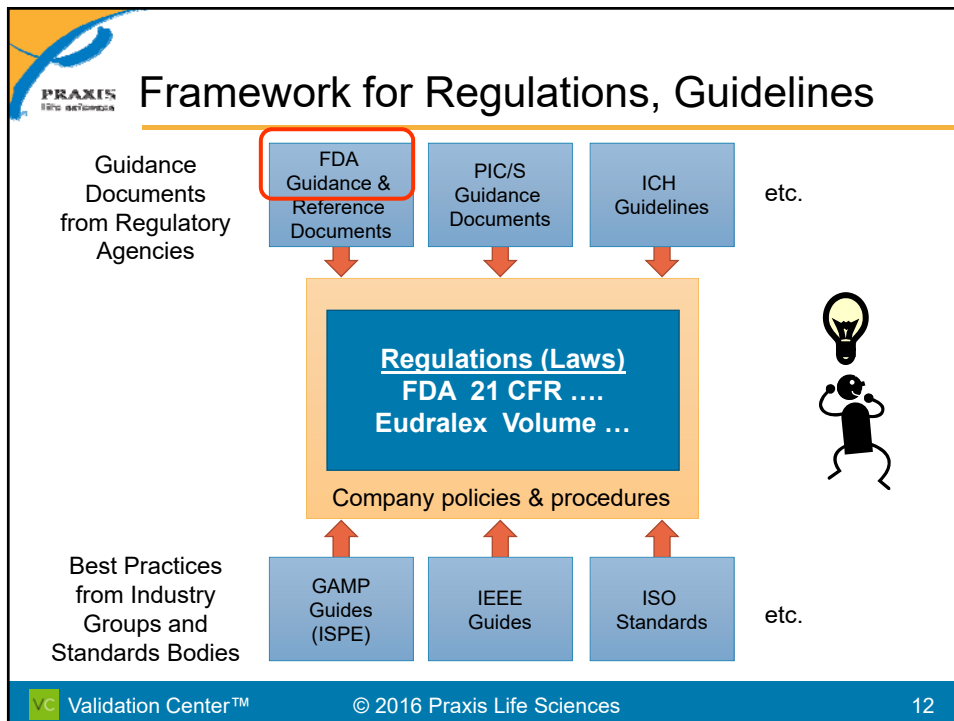
**21 CFR 820**

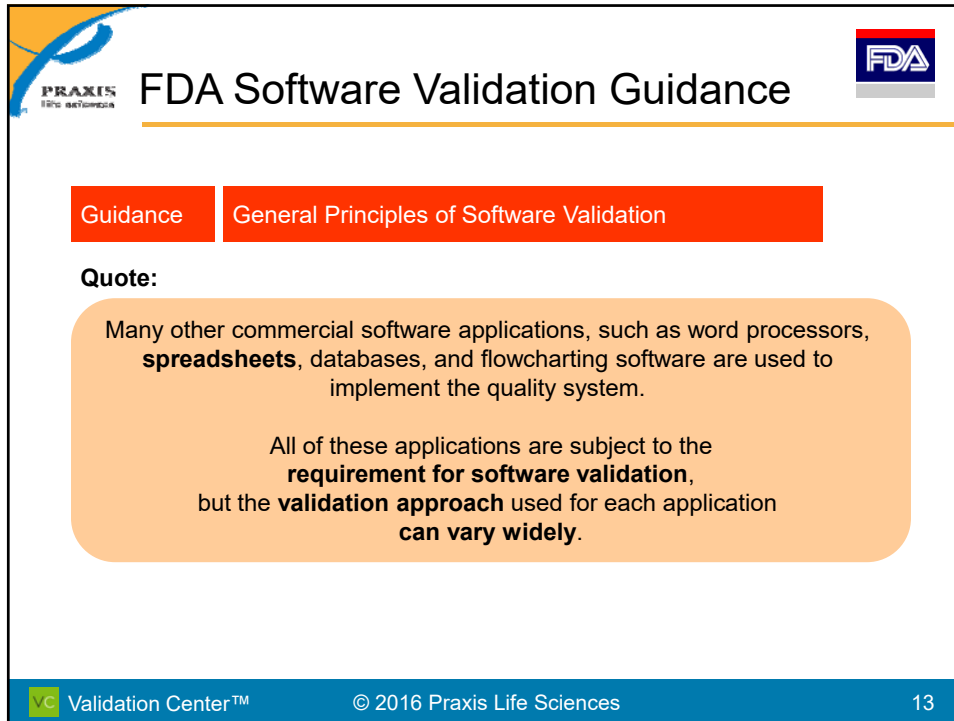
When computers or automated data processing systems are used as part of the production or quality system, the manufacturer shall **validate computer software for its intended use** according to an established protocol.

All software **changes shall be validated** before approval and issuance.

These **validation activities shall be documented.**

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**FDA**

## FDA Software Validation Guidance

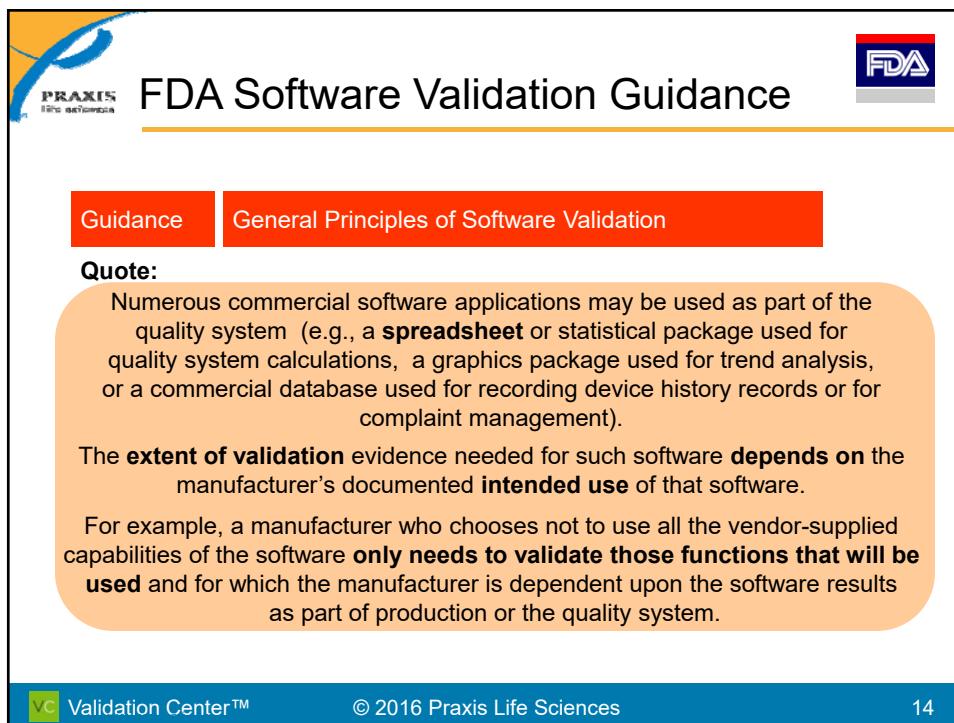
Guidance | General Principles of Software Validation

**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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**FDA**

## FDA Software Validation Guidance

Guidance | General Principles of Software Validation

**Quote:**



Numerous commercial software applications may be used as part of the quality system (e.g., a **spreadsheet** or statistical package used for quality system calculations, a graphics package used for trend analysis, or a commercial database used for recording device history records or for complaint management).

The **extent of validation** evidence needed for such software **depends on** the manufacturer's documented **intended use** of that software.

For example, a manufacturer who chooses not to use all the vendor-supplied capabilities of the software **only needs to validate those functions that will be used** and for which the manufacturer is dependent upon the software results as part of production or the quality system.

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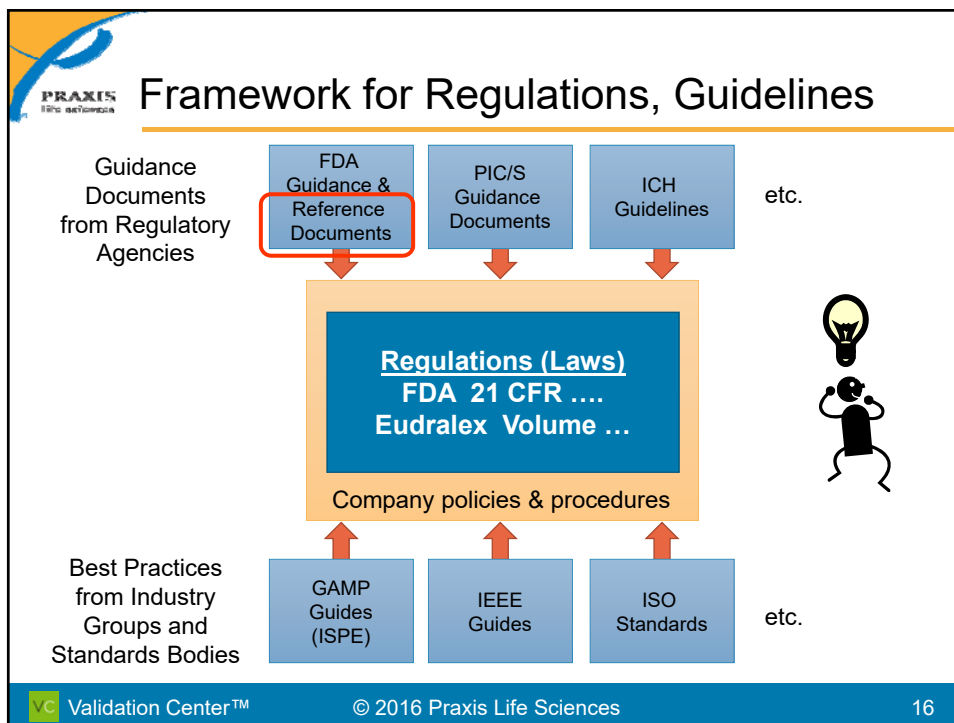
 **FDA Software Validation Guidance** 



Guidance | General Principles of Software Validation

**Quote:**

When software is upgraded or any changes are made to the software, the manufacturer should consider how those changes may **impact** the “used portions” of the software and must reconfirm the validation of those portions of the software that are used.

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## 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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## FDA Spreadsheet Reference

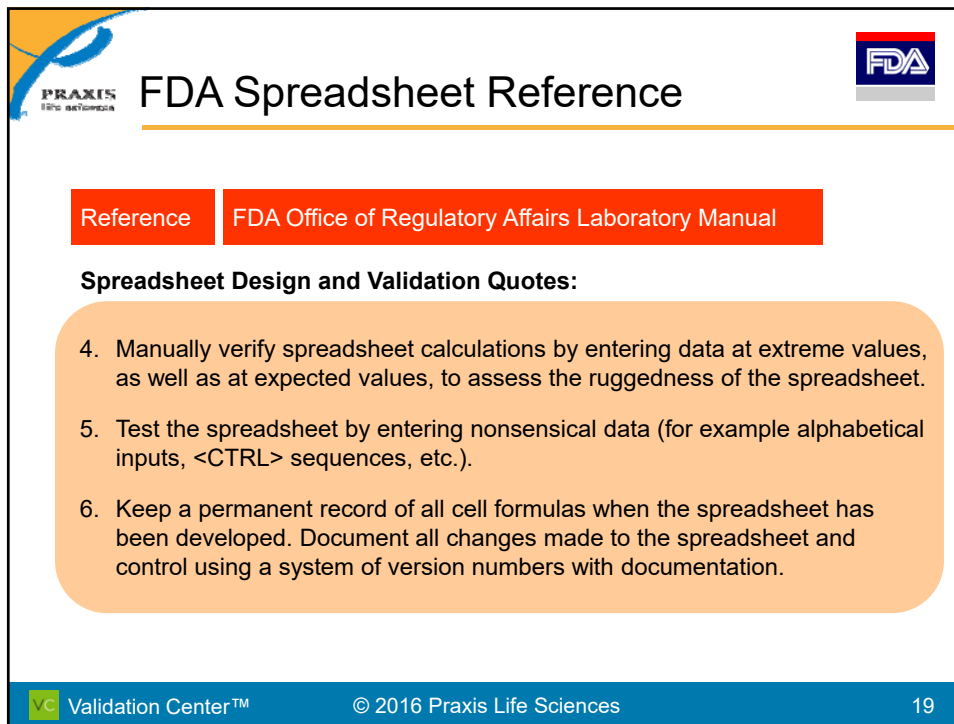
Reference | FDA Office of Regulatory Affairs Laboratory Manual

**Spreadsheet Design and Validation Quotes:**

General guidance for design and validation of in-house spreadsheets and other numerical calculation programs includes the following considerations:

1. Lock all cells of a spreadsheet, except those needed by the user to input data.
2. Make spreadsheets read-only, with password protection, so that only authorized users can alter the spreadsheet.
3. Design the spreadsheet so that data outside acceptable conditions is rejected (for example, reject non-numerical inputs).

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**PRAXIS** life sciences **FDA**

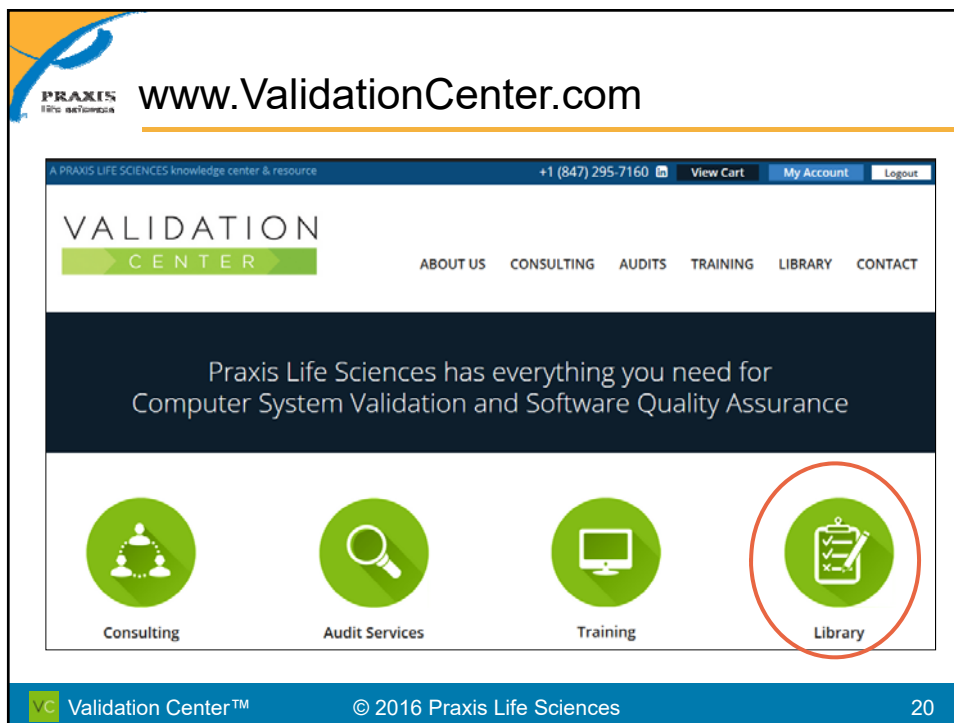
## FDA Spreadsheet Reference

Reference FDA Office of Regulatory Affairs Laboratory Manual

**Spreadsheet Design and Validation Quotes:**

4. Manually verify spreadsheet calculations by entering data at extreme values, as well as at expected values, to assess the ruggedness of the spreadsheet.
5. Test the spreadsheet by entering nonsensical data (for example alphabetical inputs, <CTRL> sequences, etc.).
6. Keep a permanent record of all cell formulas when the spreadsheet has been developed. Document all changes made to the spreadsheet and control using a system of version numbers with documentation.

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# Validation and Part 11 Compliance

Part 2




## Part 2: Validation and Part 11 Compliance

### Section Overview

- Does my spreadsheet need to be validated?
- Does my spreadsheet need to be 21 CFR Part 11 compliant?
- What is Part 11 compliance?


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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


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 **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?



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## 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

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## What Records Need Part 11 Compliance?


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



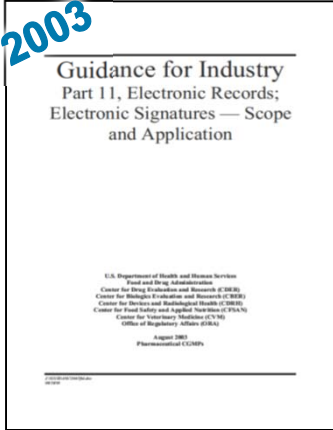
Part 11 applies to:

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.

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 **What Records Need Part 11 Compliance?**


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



Part 11 Scope Clarification:

- When persons choose to use records in electronic format in place of paper format, Part 11 would apply.
- When persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be "using electronic records in lieu of paper records". In these instances, the use of computer systems in the generation of paper records would not trigger Part 11.

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 **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



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## 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


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## 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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 **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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 **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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 **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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 **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).

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## 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



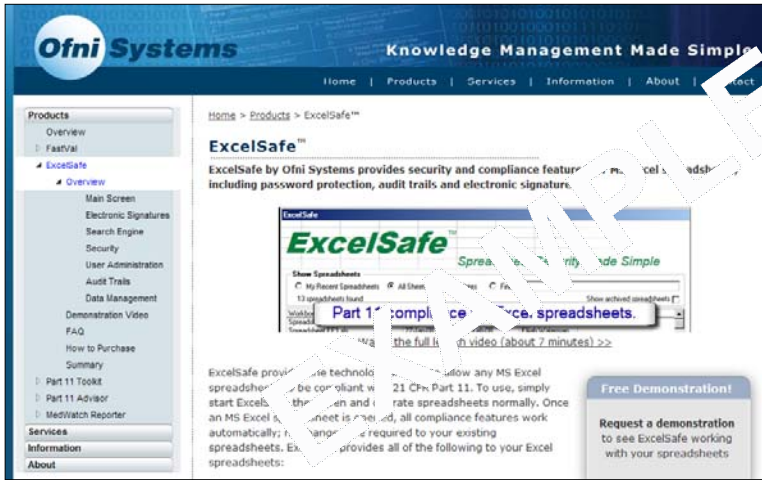
- Very difficult requirement for spreadsheets – no audit trails
- For very simple (single record) spreadsheets, could use a document management system with versioning

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## Compliance Tools

Example spreadsheet tool is available at: [www.ofnissystems.com](http://www.ofnissystems.com)



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Products

- Overview
- FastVal
- ExcelSafe

ExcelSafe™

ExcelSafe by Ofni Systems provides security and compliance features including password protection, audit trails and electronic signatures.

ExcelSafe

Show Spreadsheets

My Recent Spreadsheets All Spreadsheets

Part 11 compliance for Excel spreadsheets

ExcelSafe provides the technology to allow any MS Excel spreadsheet to be compliant with 21 CFR Part 11. To use, simply start ExcelSafe, then open and edit spreadsheets normally. Once an MS Excel spreadsheet is loaded, all compliance features work automatically; no changes are required to your existing spreadsheets. ExcelSafe provides all of the following to your Excel spreadsheets:

Free Demonstration!


Request a demonstration to see ExcelSafe working with your spreadsheets

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# Validation & Risk Framework

Part 3




## Part 3: Validation & Risk Framework

### Section Overview

- Validation
  - o Terminology
  - o Process
- Risk
  - o Terminology
  - o Process

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## Basic Validation Terminology

### Verification

**Confirmation that specifications have been met (FDA)**

- Design review
- Code inspection
- Software testing

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## Basic Validation Terminology

**Verification** Confirmation of specifications

### Qualification

**Verification of**

- Design (DQ)
- Installation & Configuration (IQ)
- Operation vs. specification (OQ)
- Performance for intended use (PQ)

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## Basic Validation Terminology

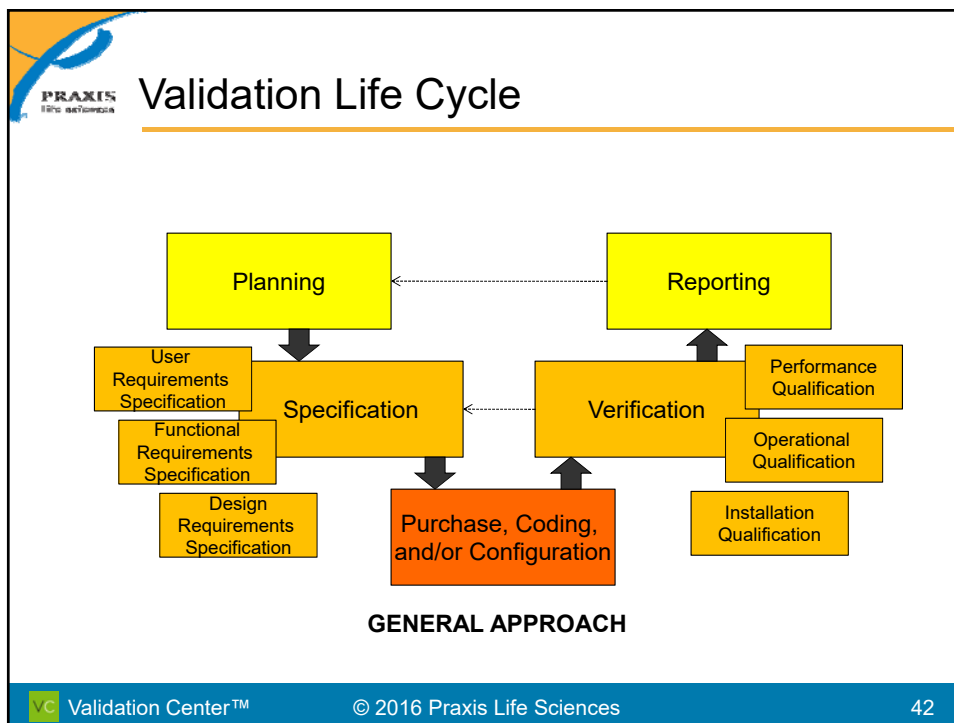
**Verification** Confirmation of specifications


**Qualification** Verification

**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. (FDA)**

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**Basic Risk Terminology**

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**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 hazard and the severity of the harm

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## Basic Risk Terminology

**Hazard** A potential source of harm

**Risk** Hazard probability and severity

**Risk Assessment**  
A comprehensive evaluation of risks and associated impacts

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## Basic Risk Terminology

**Hazard** A potential source of harm

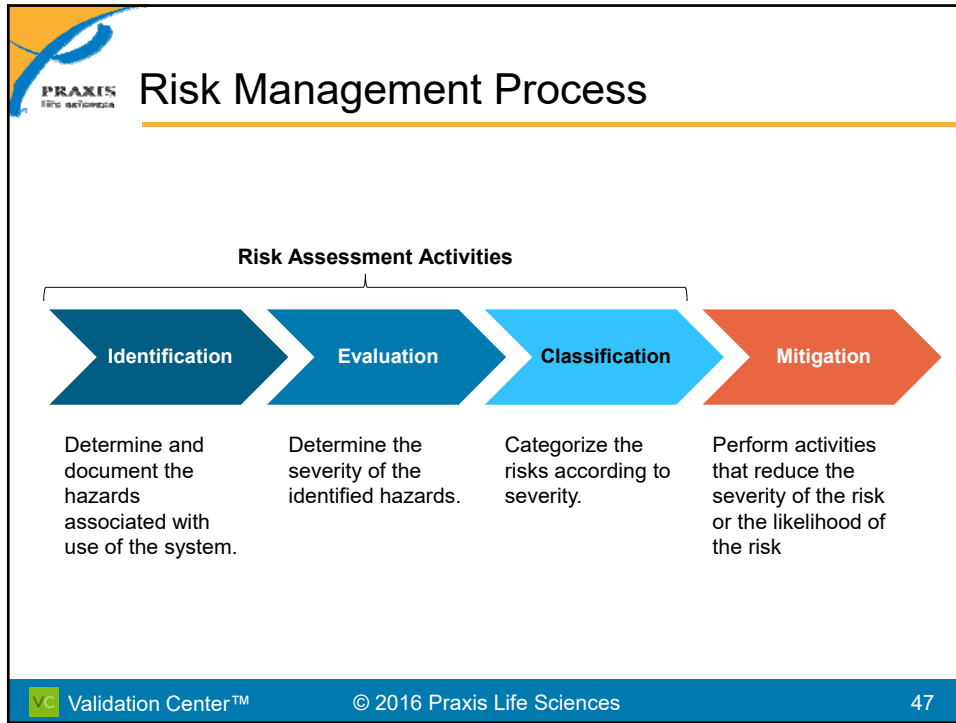
**Risk** Hazard probability and severity

**Risk Assessment** Evaluation of risk and impact

**Risk Mitigation**  
Actions taken to reduce the impacts of risks

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**Spreadsheet Validation Approach**  
Part 4

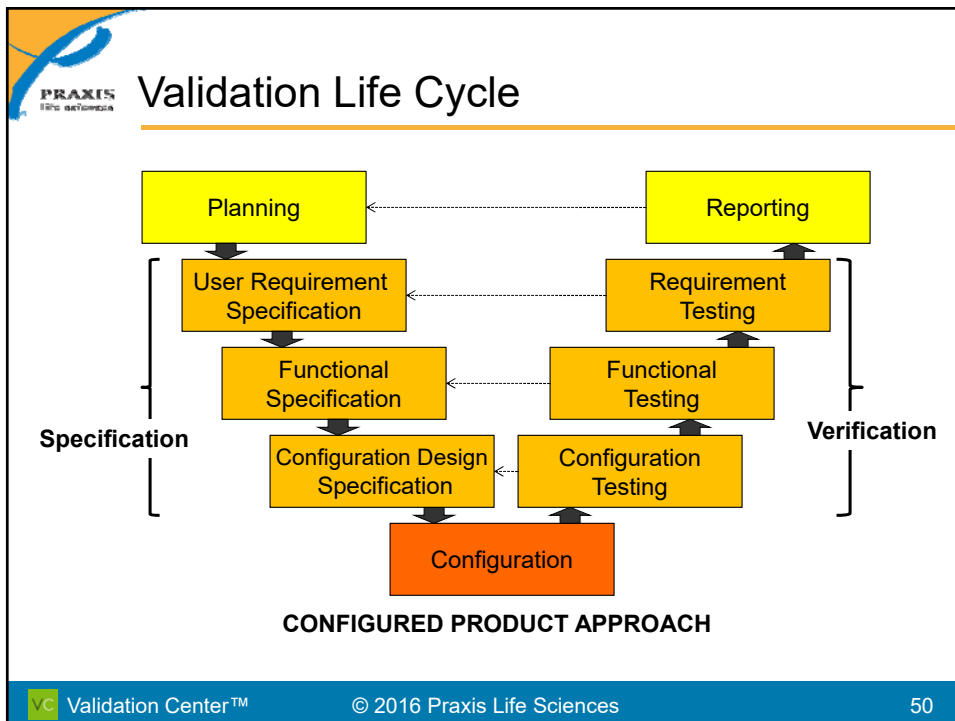
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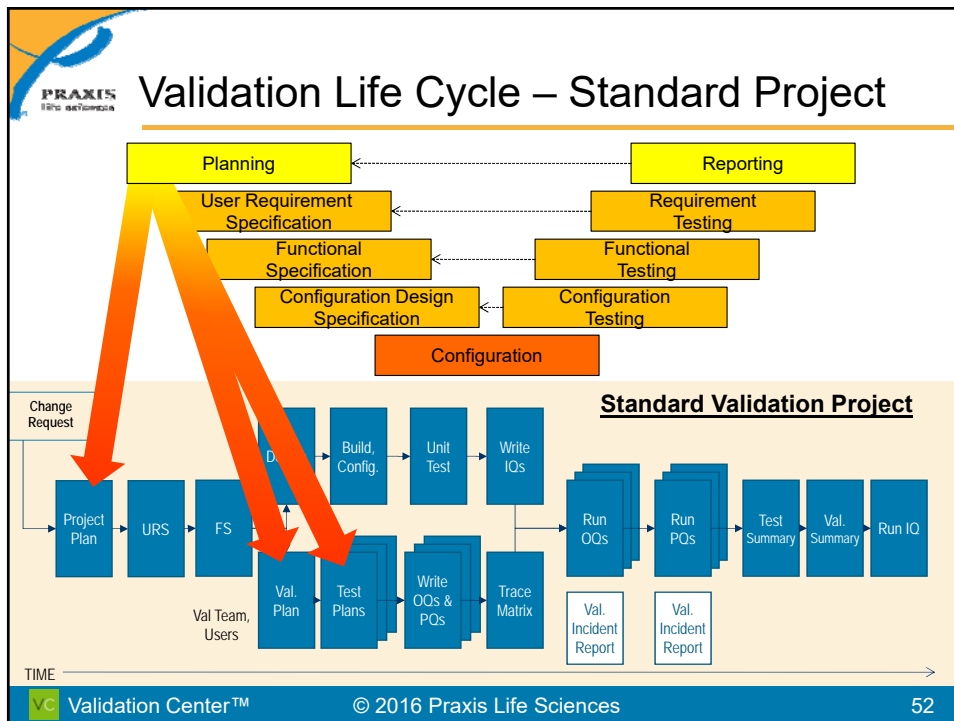
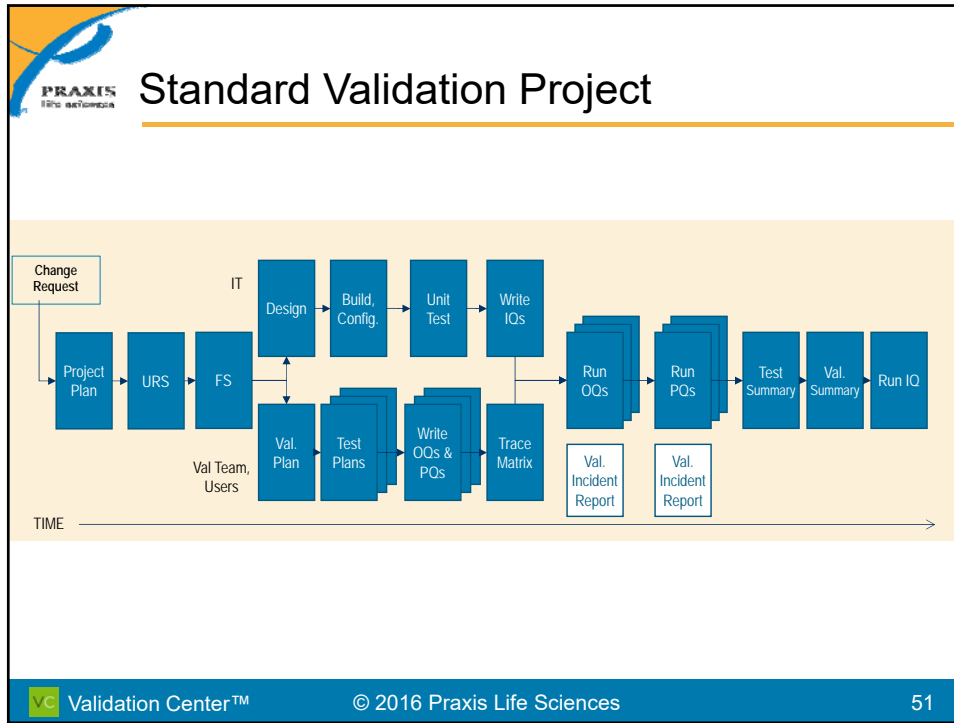
## Part 4: Spreadsheet Validation Approach

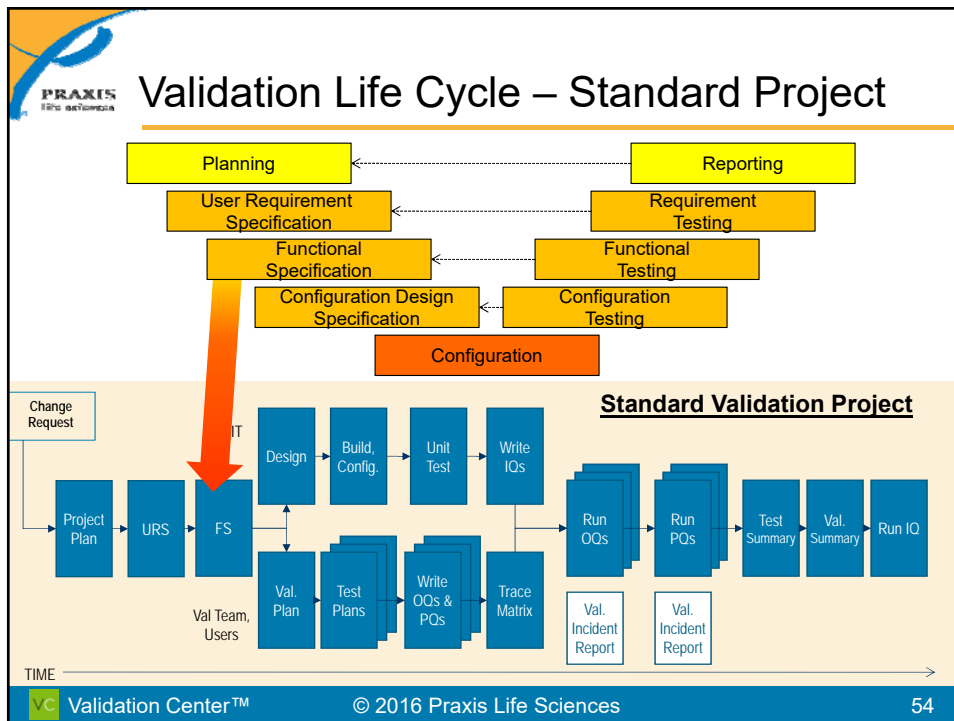
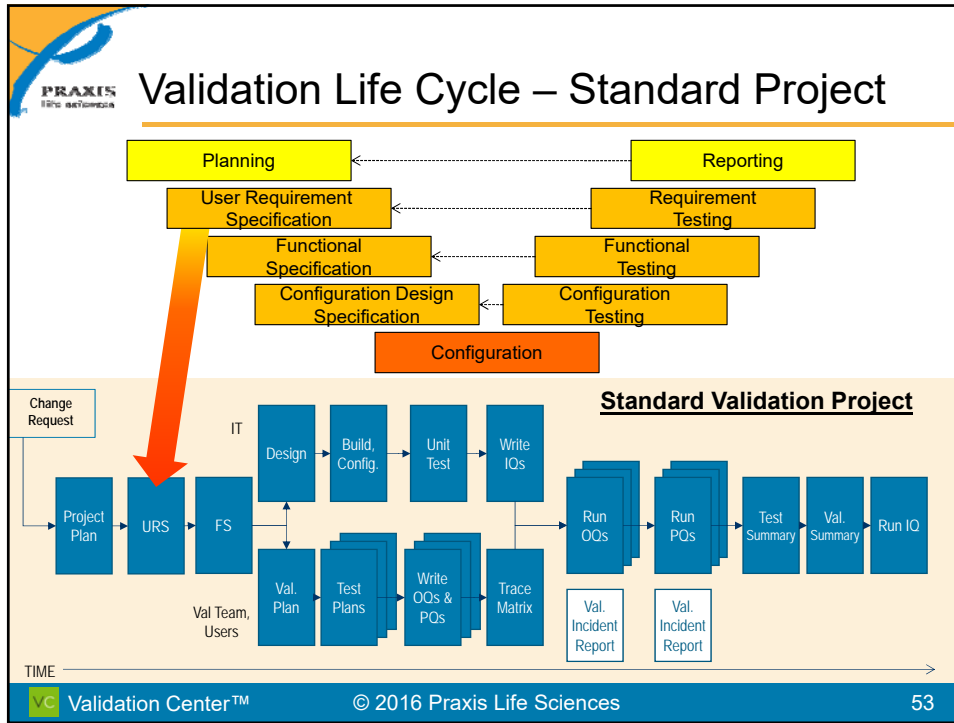
### Section Overview

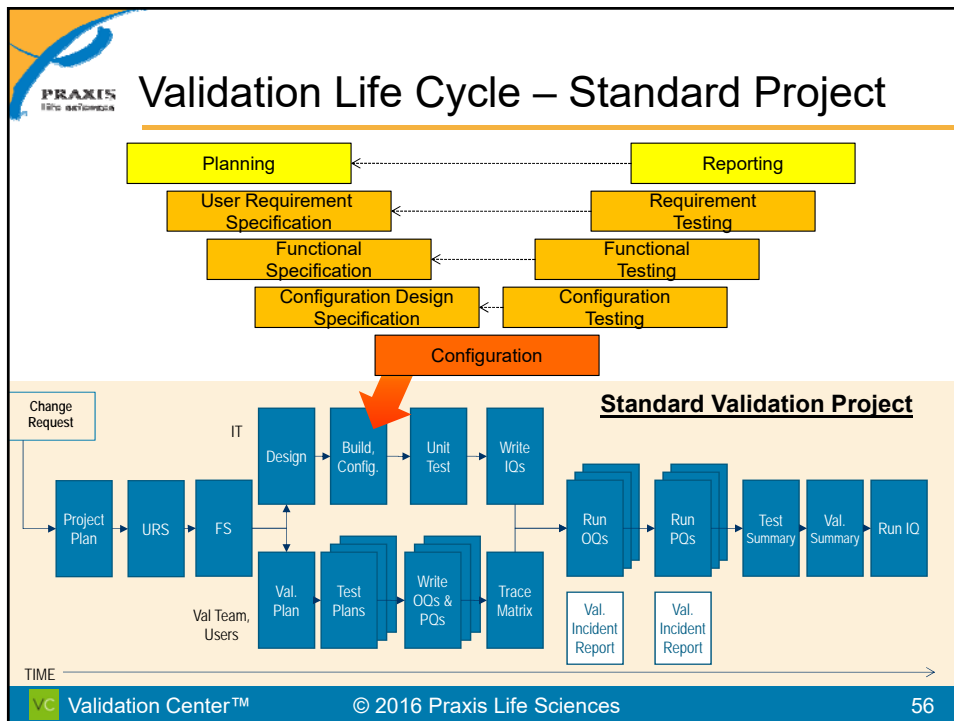
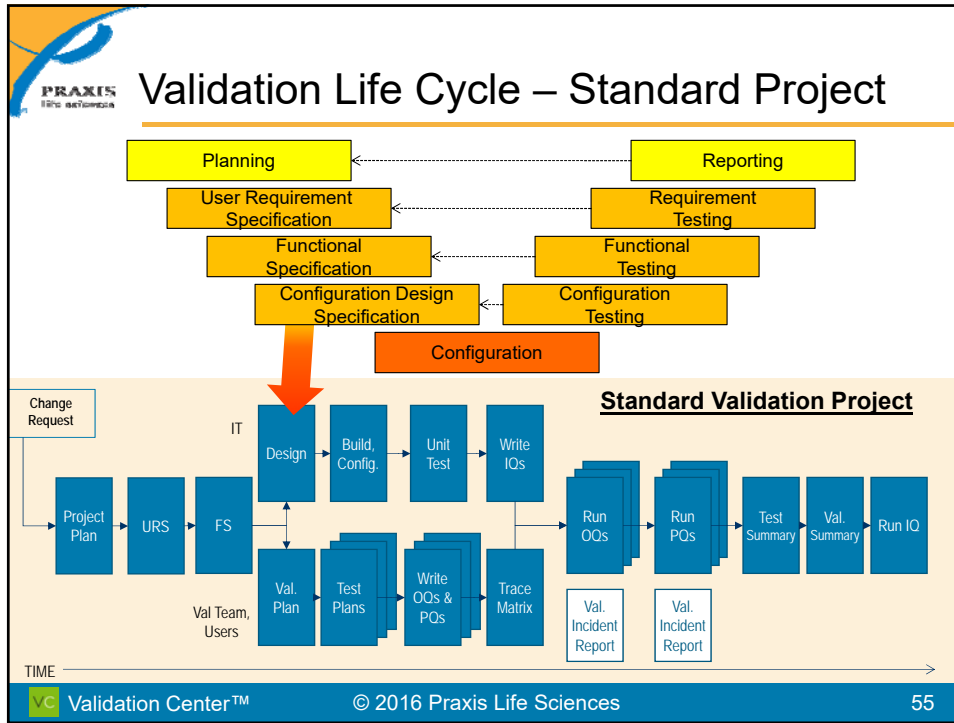
- Spreadsheet validation methodology
- Risk assessment and mitigation for spreadsheets

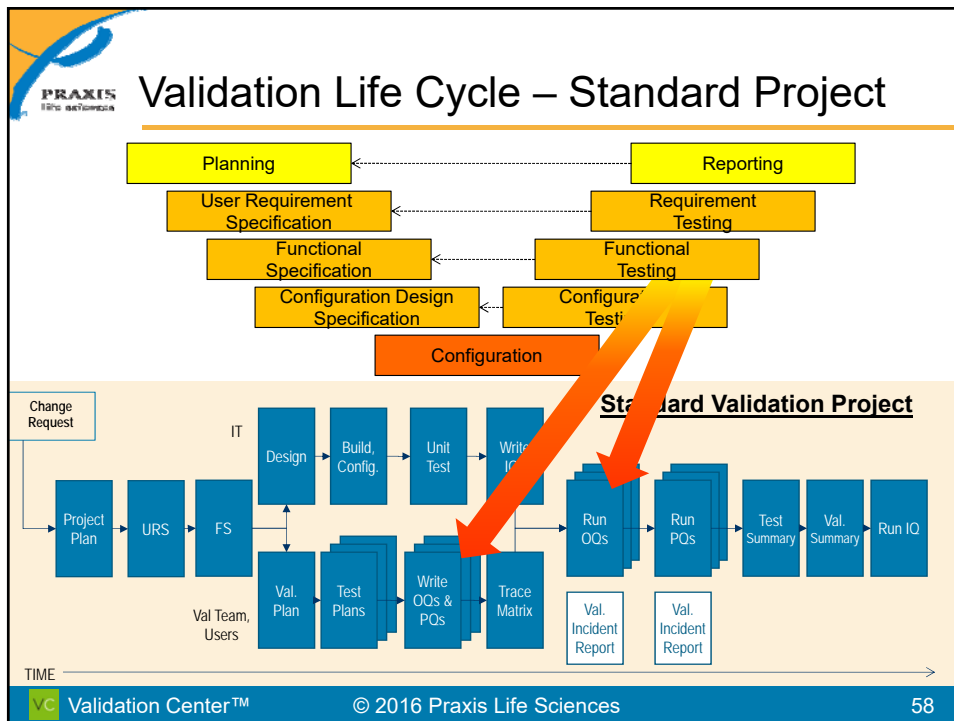
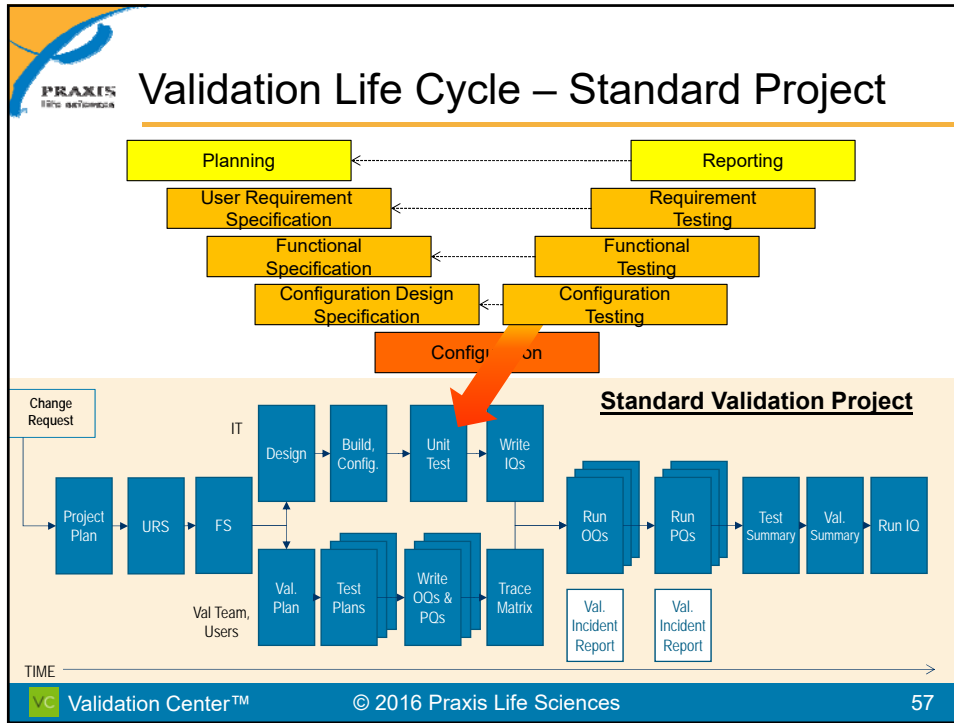
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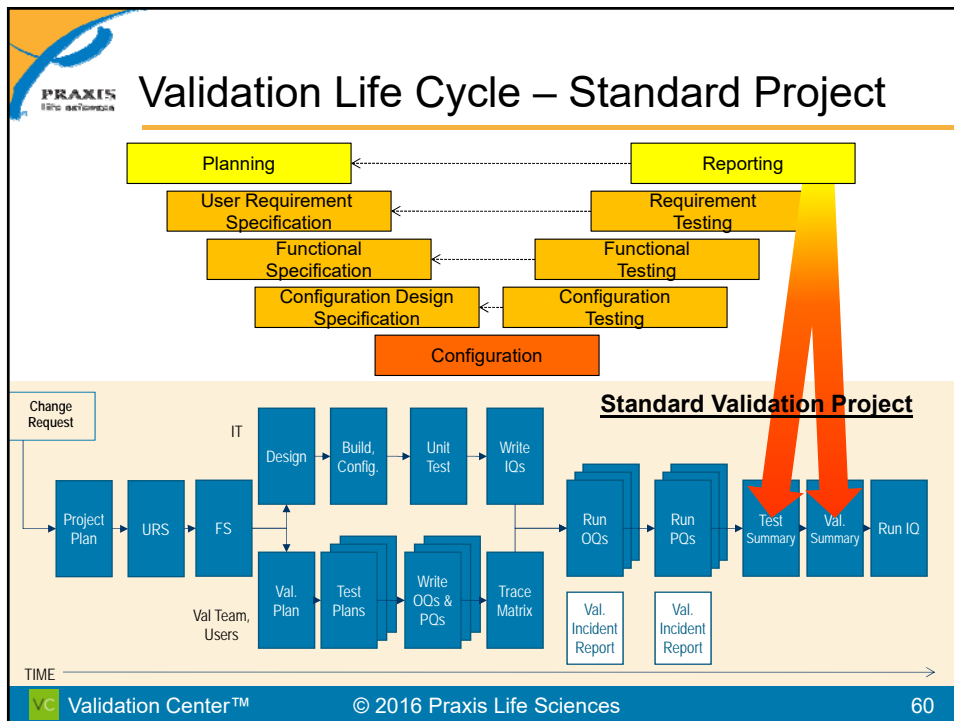
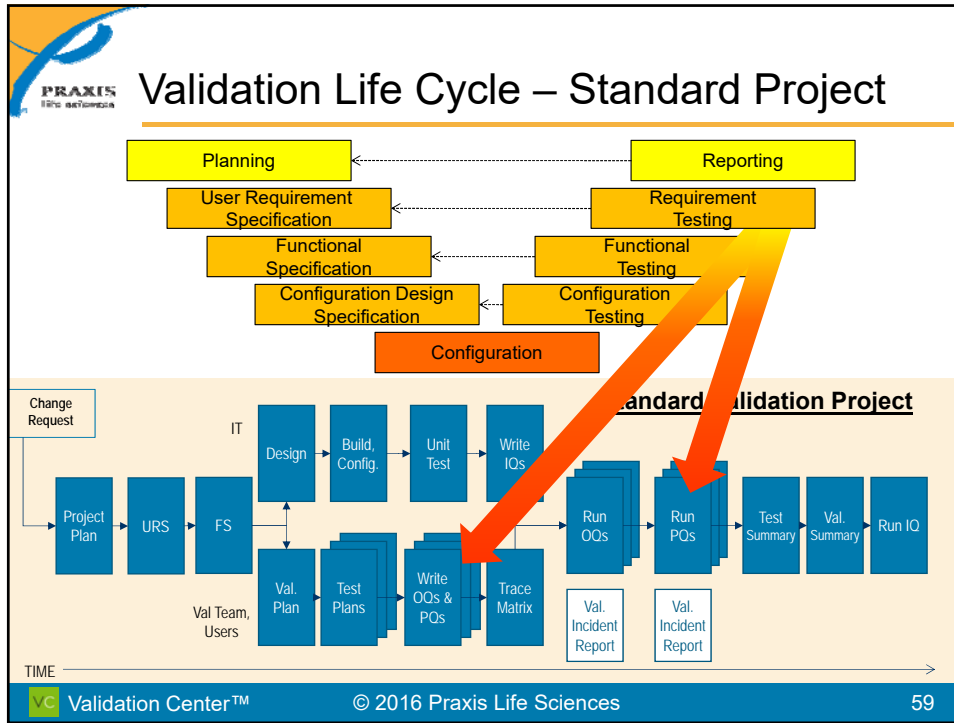


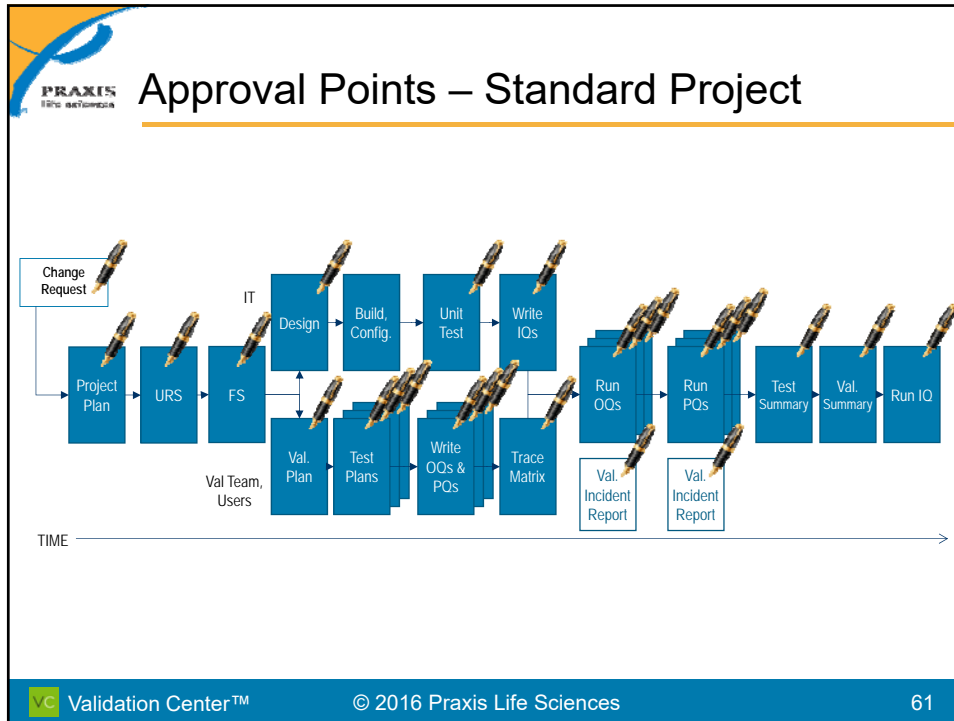












The slide compares two types of spreadsheets. On the left, a single slice of bread is shown, representing a 'much smaller scope'. On the right, a large table set for a formal dinner is shown, representing a 'much larger scope'. The text 'vs.' is placed between the two images.

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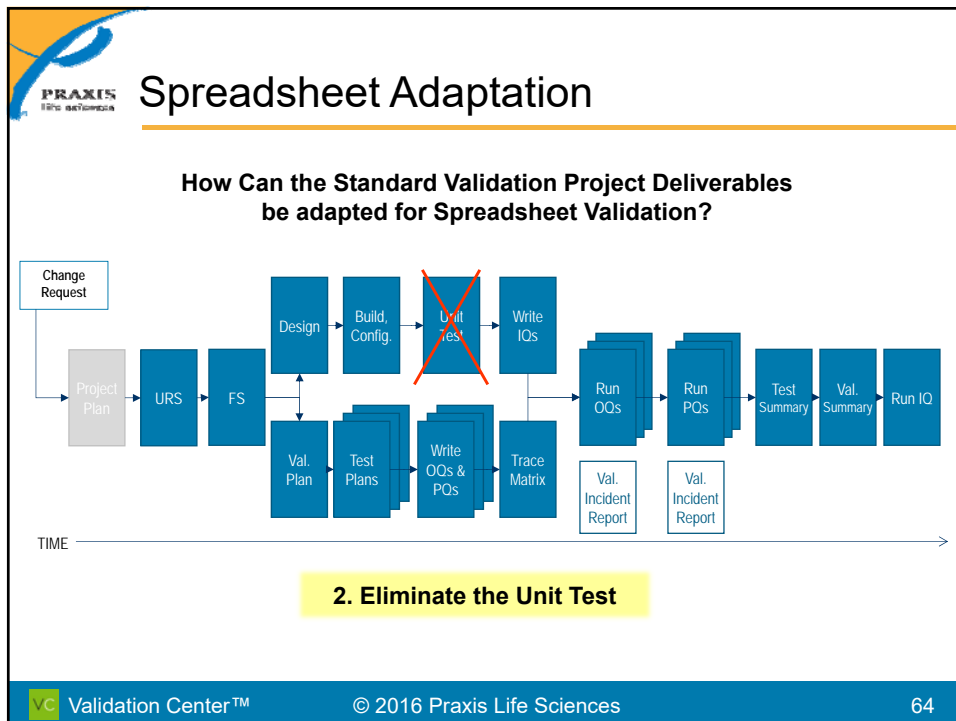
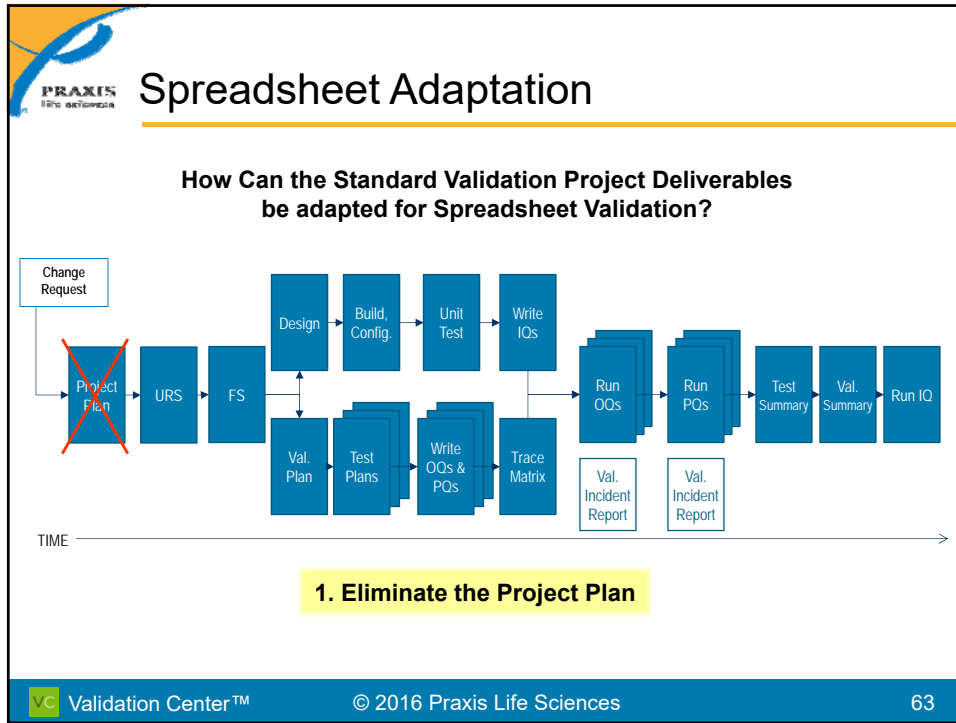
## Spreadsheets Are Different

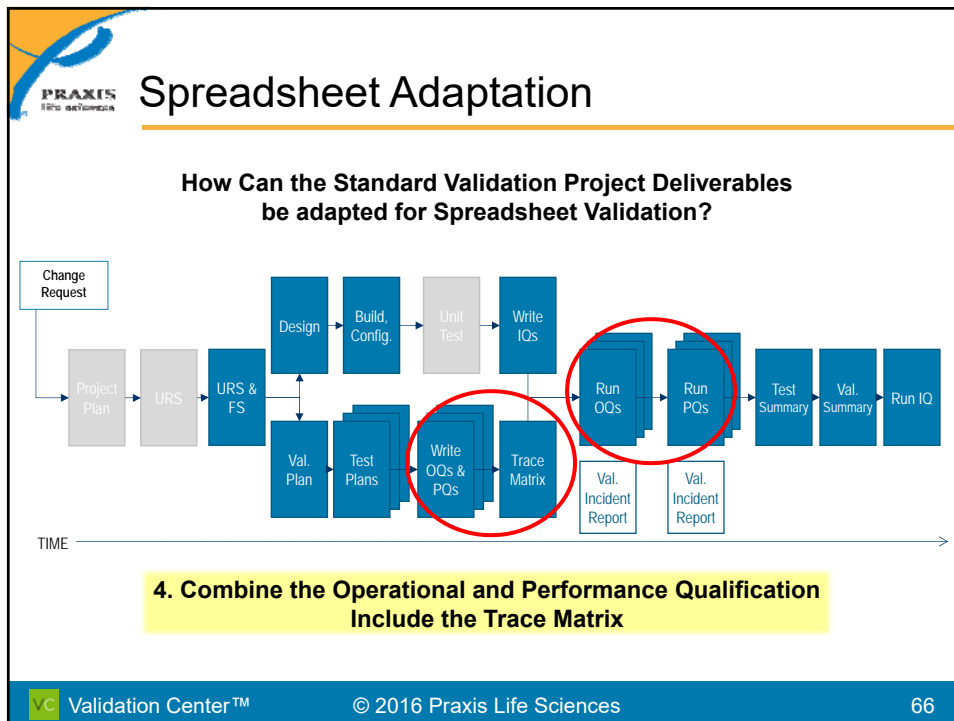
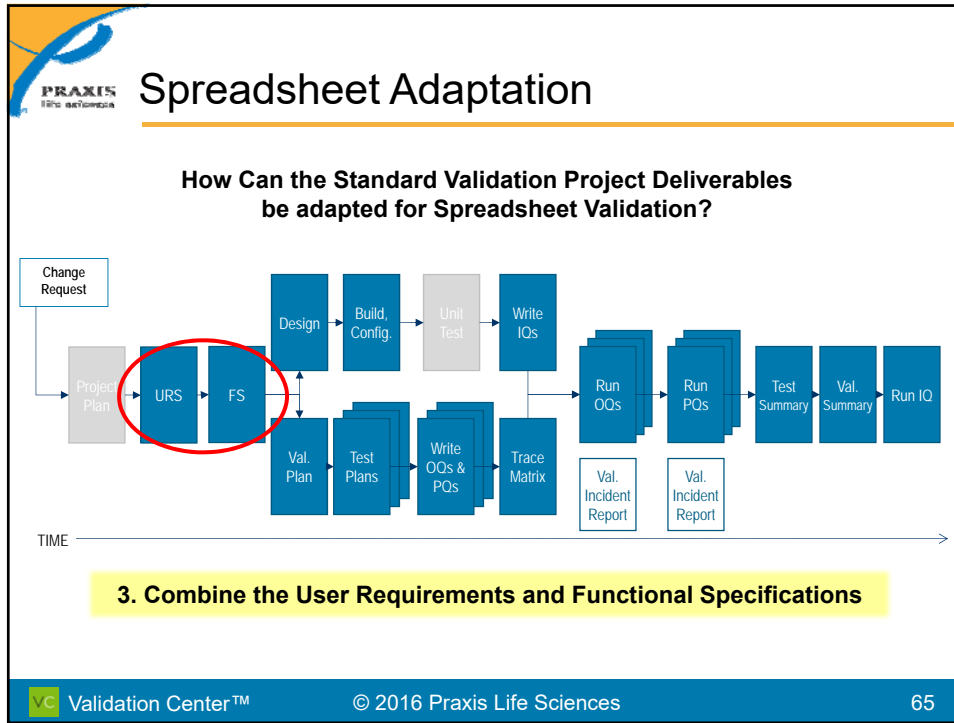
- 1. Much smaller scope**
- 2. Much shorter timeline**
- 3. Usually less complex**
  - Single technology
  - Single function
  - Little or no programming
  - Single programmer/developer
  - Well understood technology

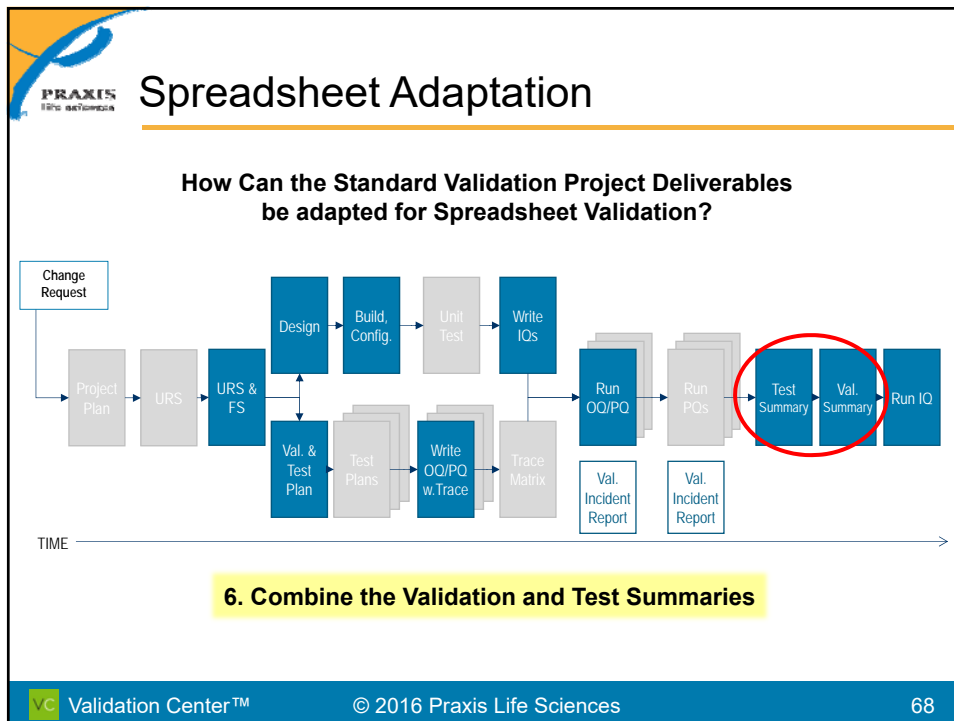
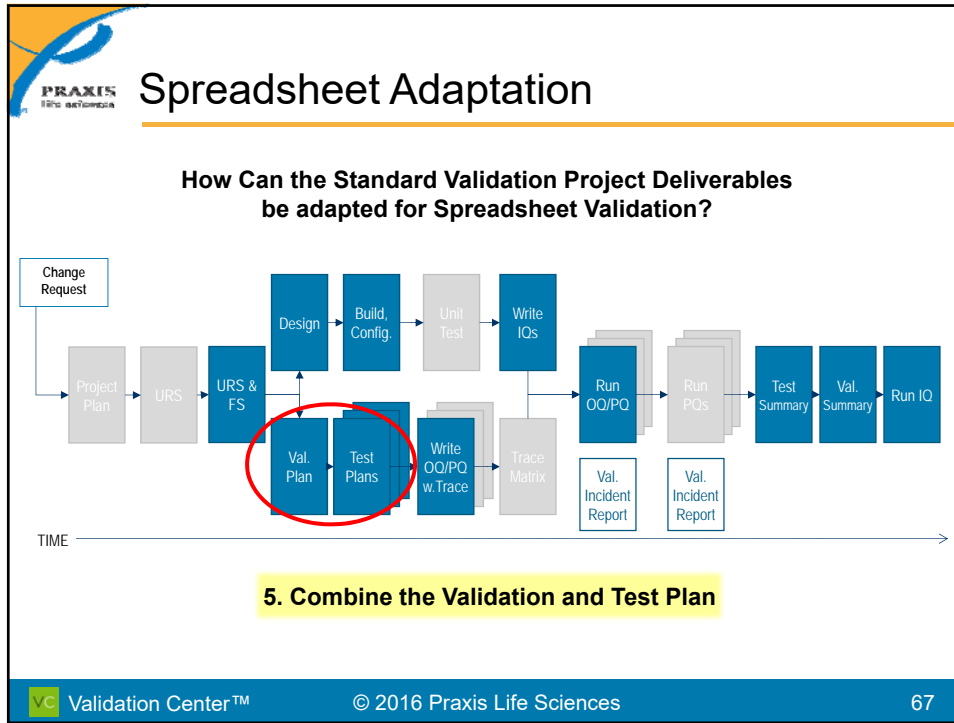
vs.

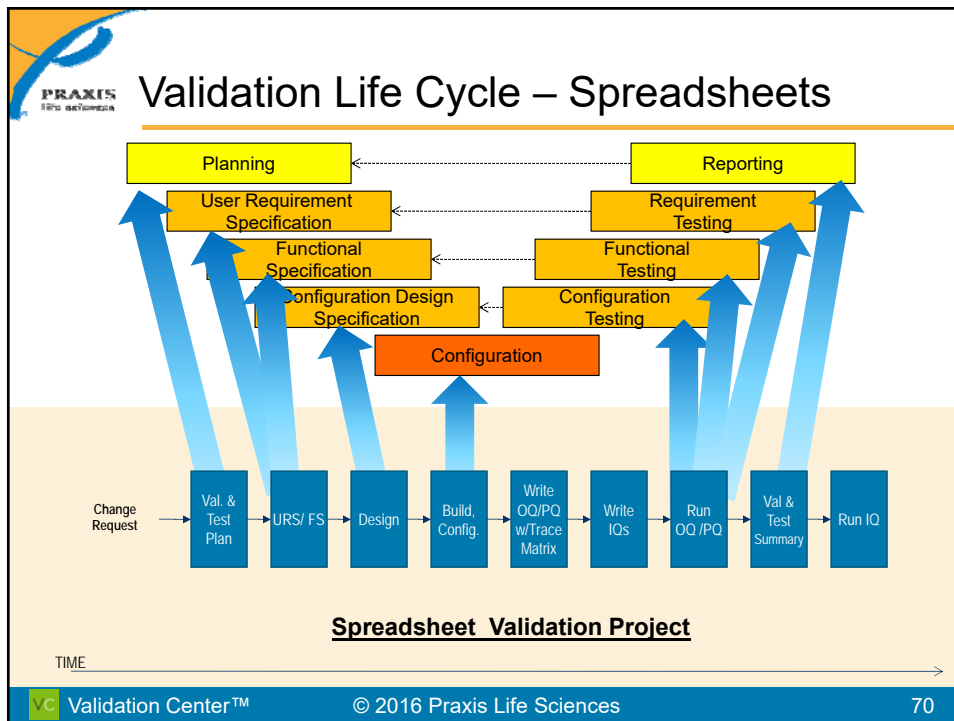
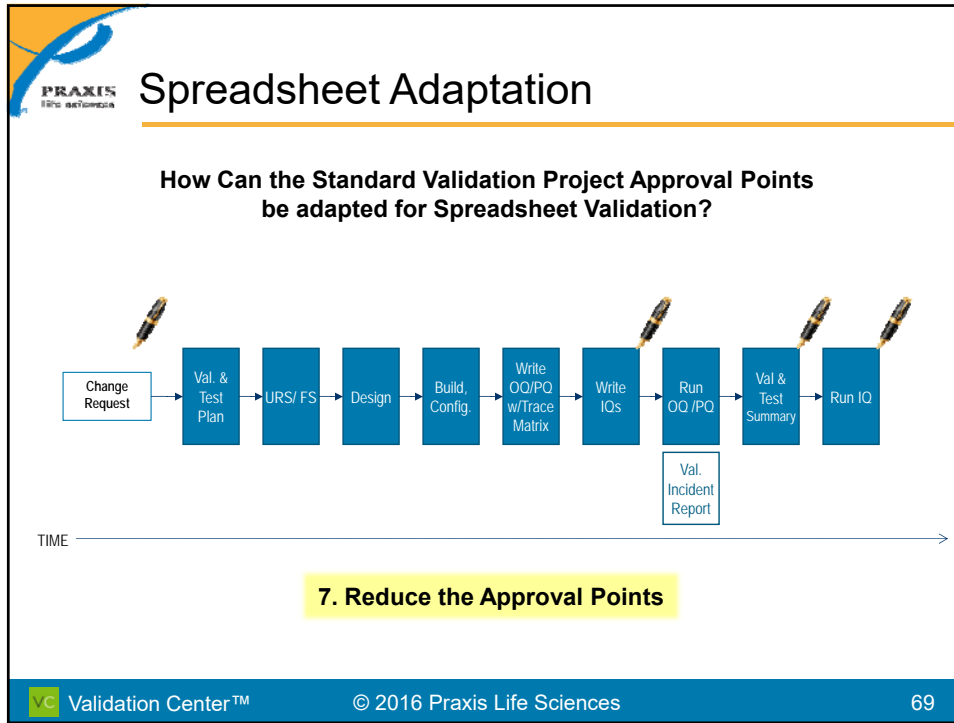
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## Risk Management - Spreadsheets

How are Risk Management concepts applied in Spreadsheet Validation?

**Risk Assessment Activities** | **Risk Mitigation**

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

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## Hazard Identification


### Identification

### How are hazards identified?

#### 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?

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## Hazard Evaluation

**Evaluation** How are hazards evaluated?

### Key Questions

- If this hazard occurred what would be the consequence?
- Could this hazard lead to:
  - » Patient death or injury?
  - » Product failure or waste?

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## Risk Classification


**Classification** How are risks classified?

**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

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## Criticality Classification


**Classification** → How is risk Criticality classified?

### Common Classification Method for Criticality

– 3 Levels

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

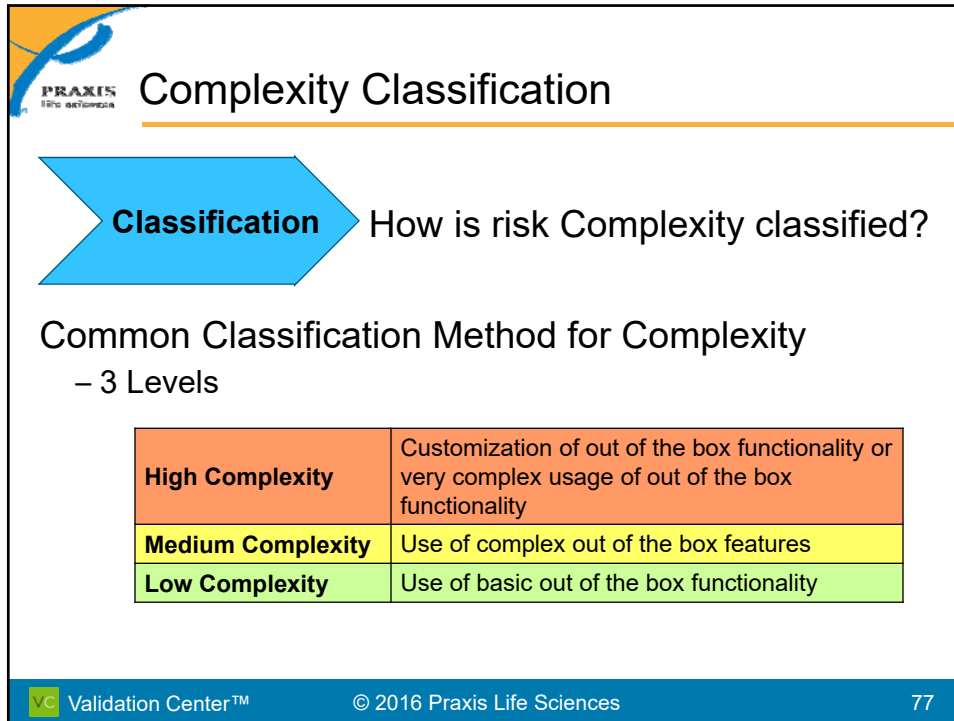
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## Criticality Classification

Classification	High Criticality	Medium Criticality	Low Criticality
<b>Quality/Safety Impact</b>	Direct	Indirect	None
<b>Examples</b>	<ul style="list-style-type: none"> <li>Health product software</li> <li>Manufacturing controls</li> <li>Automated product inspection</li> <li>Label management &amp; automation</li> <li>Distribution tracking to enable recalls</li> <li>Laboratory test calculations</li> <li>Adverse event tracking</li> <li>Clinical trial results</li> <li>Patient medical records</li> <li>Product quality status management</li> </ul>	<ul style="list-style-type: none"> <li>Calibration tracking</li> <li>Validation tracking</li> <li>Document management</li> <li>Training tracking</li> <li>Corrective/Preventive action tracking</li> <li>System access tracking</li> <li>Electronic submissions to regulatory agencies</li> <li>Product work order management</li> <li>Deviation tracking</li> <li>Audit tracking</li> </ul>	<ul style="list-style-type: none"> <li>Manufacturing cost reports</li> <li>Turnaround time reports</li> </ul>

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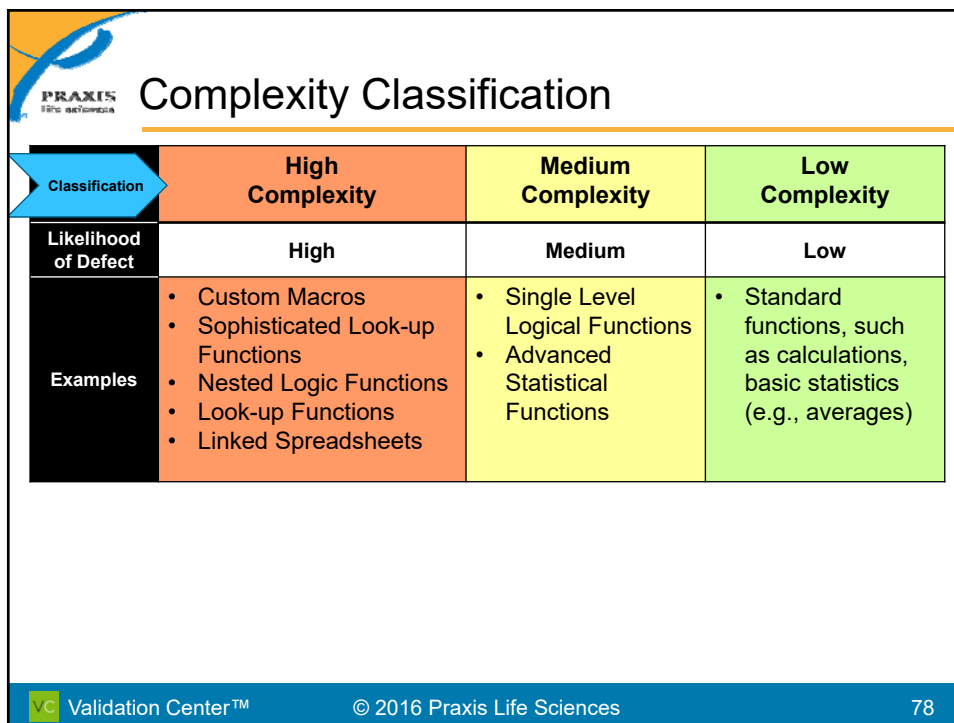
## Complexity Classification

**Classification** → How is risk Complexity classified?

Common Classification Method for Complexity  
– 3 Levels

<b>High Complexity</b>	Customization of out of the box functionality or very complex usage of out of the box functionality
<b>Medium Complexity</b>	Use of complex out of the box features
<b>Low Complexity</b>	Use of basic out of the box functionality

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## Complexity Classification

Classification	High Complexity	Medium Complexity	Low Complexity
<b>Likelihood of Defect</b>	High	Medium	Low
<b>Examples</b>	<ul style="list-style-type: none"> <li>• Custom Macros</li> <li>• Sophisticated Look-up Functions</li> <li>• Nested Logic Functions</li> <li>• Look-up Functions</li> <li>• Linked Spreadsheets</li> </ul>	<ul style="list-style-type: none"> <li>• Single Level Logical Functions</li> <li>• Advanced Statistical Functions</li> </ul>	<ul style="list-style-type: none"> <li>• Standard functions, such as calculations, basic statistics (e.g., averages)</li> </ul>

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## Spreadsheet Risk Assessment Examples

Spreadsheet Function		Criticality	Complexity	Rationale
<b>A</b>	Simple arithmetic calculation for content uniformity	High	Low	<ul style="list-style-type: none"> <li>Direct impact on product quality</li> <li>Basic spreadsheet functionality</li> </ul>
<b>B</b>	Record of training attendance	Medium	Low	<ul style="list-style-type: none"> <li>Indirect impact on quality and/or safety</li> <li>Basic spreadsheet functionality</li> </ul>
<b>C</b>	Statistical analysis of clinical study data with VB macros	High	High	<ul style="list-style-type: none"> <li>Direct impact on patient safety</li> <li>Custom Macros</li> </ul>
<b>D</b>	Statistical analysis of manufacturing data for process control	High	Medium	<ul style="list-style-type: none"> <li>Direct impact on product quality</li> <li>Complex logic and look-up functions</li> </ul>


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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
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

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## 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

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## Spreadsheet Risk Based Validation Example

Spreadsheet Function	Criticality	Complexity	Rationale
1 Record of training attendance	Medium	Low	<ul style="list-style-type: none"> <li>Indirect impact on quality and/or safety</li> <li>Basic spreadsheet functionality</li> </ul>

**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

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## Spreadsheet Risk Based Validation Example

	Spreadsheet Function	Criticality	Complexity	Rationale
2	Statistical analysis of clinical study data with VB macros	High	High	<ul style="list-style-type: none"><li>• Direct impact on patient safety</li><li>• Custom Macros</li></ul>

**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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# Spreadsheet Validation Example


Part 5


 **Part 5: Spreadsheet Validation Example**

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**Section Overview**

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

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 **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:  %  
Expiration Date:  **FAIL - DO NOT USE**


Analyst:  
Name (Print) \_\_\_\_\_  
Signature \_\_\_\_\_ Date \_\_\_\_\_

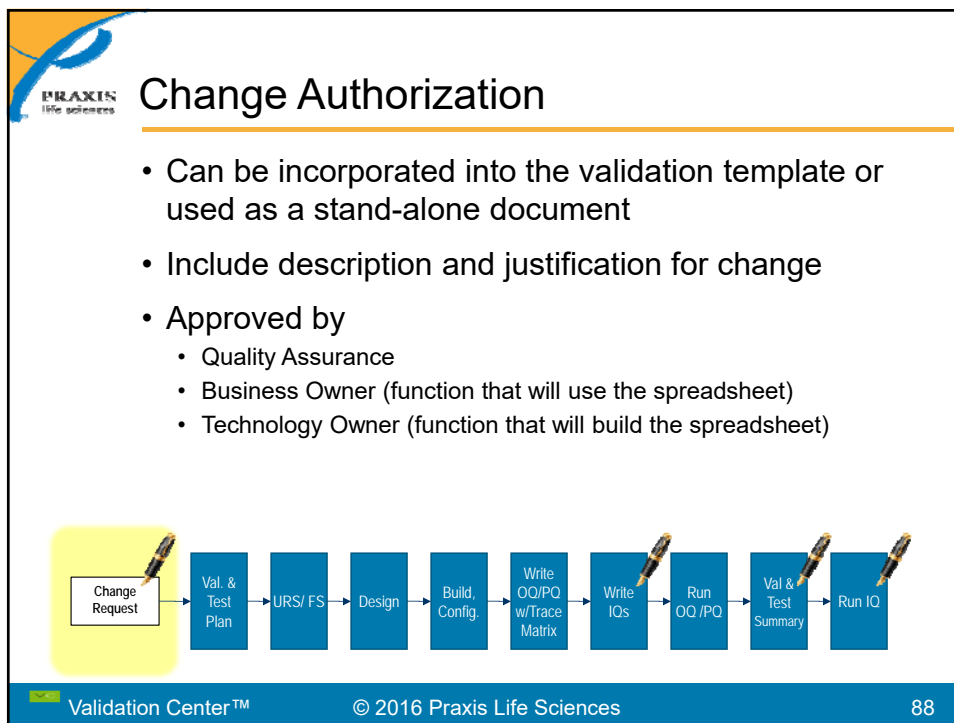
**Purpose:** Calculate the expiration date of a batch of active pharmaceutical ingredients based on the potency of 3 samples


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## Change Request

### 1 Change Authorization

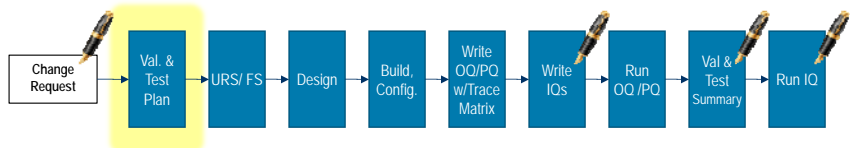
<b>Change Request ID</b>	CR-SS-2009-056			
<b>Spreadsheet ID</b>	SS-001			
<b>Spreadsheet Title</b>	Expiration Calculation			
<b>Requested By</b>	M Hentschel, Sr. Lab Analyst			
<b>Change Request Description</b>				
<b>Change Description</b>	Create a new spreadsheet to calculate the expiration date of a batch of pharmaceutical ingredients from the average potency of 3 samples.			
<b>Change Rationale</b>	A validated spreadsheet will ensure accurate calculations and reduce the effort needed by laboratory personnel.			
<b>Authorization of Change</b>				
<b>Role</b>	<b>Decision</b>	<b>Name</b>	<b>Signature</b>	<b>Date</b>
Quality Manager	<input type="checkbox"/> Approve <input type="checkbox"/> Reject	Edward Grieg		
IT Manager	<input type="checkbox"/> Approve <input type="checkbox"/> Reject	Francine Schubert		
Business Manager	<input type="checkbox"/> Approve <input type="checkbox"/> Reject	Marian Pivka		

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## Validation Plan

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



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## Validation Plan

### 2 Validation Plan

#### 2.1 Validation Scope

Spreadsheet SS-001 is a new spreadsheet to calculate the expiration date of a batch of active pharmaceutical ingredient (API) from the potency of 3 samples. All functionality will be validated.

#### 2.2 Risk Assessment and Mitigation


**Risk Assessment:**

Risk Component	Category	Rationale
Criticality	High	The calculations performed by this spreadsheet have direct impact on product quality
Complexity	Low	This spreadsheet uses only basic, out of the box spreadsheet features

**Risk Mitigation:**

To control quality risk, the criticality and complexity levels of spreadsheet have been utilized in determining the validation strategy, below.

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## Validation Plan

### 2.3 Validation Strategy

The following strategy will be followed for validation of spreadsheet SS-001.


- Documentation of User and Functional Requirements
- Spreadsheet design per established Spreadsheet Design Standards, and documentation of design
- Documentation of an Operational and Performance Qualification protocol
- Approval of requirements, design documentation, and protocols
- Execution of the Operational and Performance Qualification protocols, and if needed:
  - Documentation of testing failures
  - Regression testing of corrections
- Documentation of Installation Qualification protocol
- Approval of executed the Operational and Performance Qualification protocol, test failures (if any), regression tests (if any) and the Installation Qualification protocol
- Execution of the Installation Qualification protocol
- Approval of the executed Installation Qualification protocol

#### 2.4 Test Plan

Testing of spreadsheet SS-001 will include:

- Verification of all user and functional requirements
- Tracing of Requirements to verification tests
- Path, stress, and boundary testing with multiple data sets
- Utilization of data and scenarios similar to production data


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 **Validation Plan**

**2.5 Acceptance Criteria**

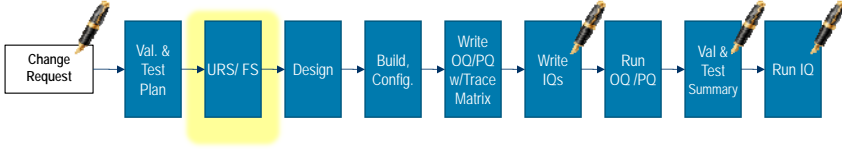
The following acceptance criteria must be met to certify spreadsheet SS-001 for production use.


- 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

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 **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



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## 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 users
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



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## 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.

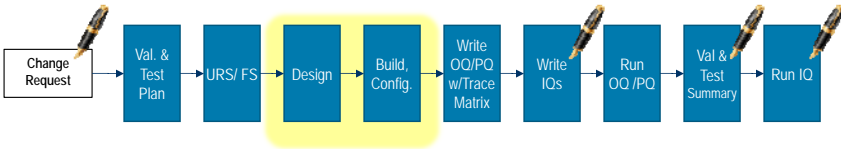

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 **Build and Document Design**


- 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



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 **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

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## Formula Printing

Example Spreadsheet.xls [Compatibility Mode] - Microsoft Excel

Home Insert Page Layout Formulas Data Review View

fx AutoSum Recently Used Insert Function Financial Date & Time More Functions

Logical Lookup & Reference Math & Trig

Define Name Use in Formula Name Manager Create from Selection Defined Names

Trace Precedents Trace Dependents Remove Arrows Evaluate Formula Formula Auditing

Show Formulas

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

Average Potency: 0.0 %

Expiration Date: FAIL - DO NOT USE

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## 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

```
graph LR; A[Change Request] --> B[Val. & Test Plan]; B --> C[URS/ FS]; C --> D[Design]; D --> E[Build, Config.]; E --> F[Write OQ/PO w/Trace Matrix]; F --> G[Write IQs]; G --> H[Run OQ/PO]; H --> I[Val & Test Summary]; I --> J[Run IQ]
```

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## OO/PQ Test Design


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### 6 Operation and Performance Qualification

#### 6.1 Test Design

Test Scenario(s)	Data												
<b>Security</b> <ul style="list-style-type: none"> <li>Test that all cells are locked from user modification except for lot#, sample date, drum ID, sample ID, and potency</li> <li>Verify that the unlocked cells are yellow and that no other cells are yellow</li> </ul>	<ul style="list-style-type: none"> <li>N/A – no data needed for these tests</li> </ul>												
<b>Potency</b> <ul style="list-style-type: none"> <li>For all 3 potency fields, verify that users can only enter values between 0 and 110</li> <li>Numbers outside this range should receive an error message</li> </ul>	<ul style="list-style-type: none"> <li>0.0</li> <li>0.01</li> <li>30.0</li> <li>99.9</li> <li>110.0</li> <li>110.01</li> </ul>												
<b>Average Potency</b> <ul style="list-style-type: none"> <li>Test the average calculation vs. the same calculation performed by a qualified calculator</li> </ul>	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr style="background-color: #f2f2f2;"> <th style="padding: 2px 5px;">First</th> <th style="padding: 2px 5px;">Middle</th> <th style="padding: 2px 5px;">Last</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px 5px;">99.9</td> <td style="padding: 2px 5px;">98.7</td> <td style="padding: 2px 5px;">97.5</td> </tr> <tr> <td style="padding: 2px 5px;">110.0</td> <td style="padding: 2px 5px;">50.4</td> <td style="padding: 2px 5px;">12.2</td> </tr> <tr> <td style="padding: 2px 5px;">45.9</td> <td style="padding: 2px 5px;">56.3</td> <td style="padding: 2px 5px;">43.2</td> </tr> </tbody> </table>	First	Middle	Last	99.9	98.7	97.5	110.0	50.4	12.2	45.9	56.3	43.2
First	Middle	Last											
99.9	98.7	97.5											
110.0	50.4	12.2											
45.9	56.3	43.2											

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## OO/PQ Test Design

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<b>Expiration Date Scenario 1</b> <ul style="list-style-type: none"> <li>Potency &gt;=90</li> <li>Lot passes</li> </ul>	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
<b>Expiration Date Scenario 2</b> <ul style="list-style-type: none"> <li>Potency &gt;=85 but &lt;90</li> <li>Lot passes</li> </ul>	First Sample: 90.0 Second Sample: 90.0 Third Sample: 89.9 Expiration Date: 304 days after Sample Date Message: PASS – OK TO USE
<b>Expiration Date Scenario 3</b> <ul style="list-style-type: none"> <li>Potency &lt;85</li> <li>Lot fails</li> </ul>	First Sample: 85.0 Second Sample: 85.0 Third Sample: 79.9 Expiration Date: blank Message: FAIL – DO NOT USE

Etc.

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## OQ/PQ Test Protocol

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**6.2 Test Protocol**

Step	Req.	Description/Action	Expected Result	Actual Result = Expected Result (Yes/No)	Comment
<b>Test Case 1: Security</b>					
1.1	1.1	Attempt to enter data into the following cells: <ul style="list-style-type: none"> <li>• lot#</li> <li>• sample date</li> <li>• drum ID – 1st, 2nd , 3rd</li> <li>• sample ID</li> <li>• potency – 1st, 2nd, 3rd</li> </ul> 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	<ul style="list-style-type: none"> <li>• Cells listed in Step 1.1 are yellow.</li> <li>• Average potency and Expiration date cells are blue</li> <li>• All other cells are white</li> </ul>		


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## OQ/PQ Test Protocol

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<b>Test Case 2: Average Potency Calculation</b>					
2.1	2.5	Enter these potencies <ul style="list-style-type: none"> <li>• First Sample: <b>99.9</b></li> <li>• Second Sample: <b>98.7</b></li> <li>• Third Sample: <b>97.5</b></li> </ul> Print screen	Average potency values is <b>98.7</b>		
2.2	2.5	Enter these potencies <ul style="list-style-type: none"> <li>• First Sample: <b>110.0</b></li> <li>• Second Sample: <b>50.4</b></li> <li>• Third Sample: <b>12.2</b></li> </ul> Print screen	Average potency values is <b>57.5</b>		
2.3	2.5	Enter these potencies <ul style="list-style-type: none"> <li>• First Sample: <b>45.9</b></li> <li>• Second Sample: <b>56.3</b></li> <li>• Third Sample: <b>43.2</b></li> </ul> Print screen	Average potency values is <b>48.6</b>		

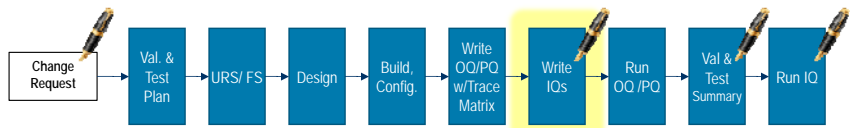
Tester Name, Signature, and Date \_\_\_\_\_


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## 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



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## Installation Qualification

### 9 Installation Qualification

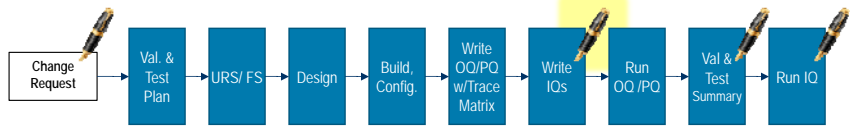
Step	Description/Action	Expected Result	Actual Result = Expected Result (Yes/No)	Comment
1.1	Move spreadsheet SS-001 v1 to folder R:\YXK034\Laboratory Spreadsheets\Validated Print Screen	File resides in folder R:\YXK034\Laboratory Spreadsheets\Validated		
1.2	Set spreadsheet password to LOCKED Print 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 \_\_\_\_\_


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 **Preliminary Approval**

- Obtain approval of all deliverables up to this point



Change Request → Val. & Test Plan → URS/ FS → Design → Build, Config. → Write OQ/PO w/Trace Matrix → Write IQs → Run OO /PO → Val & Test Summary → Run IQ

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 **Preliminary Approval**


### 5 Preliminary Approval

The signatures below indicate:

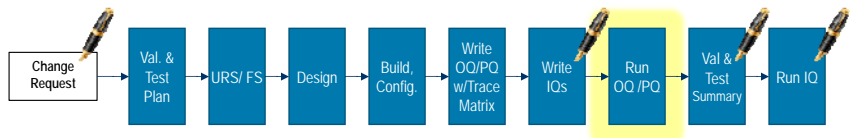
- Approval of the Validation Plan, User and Functional Requirements, and Design Documentation
- Pre-approval of Operational and Performance Qualification protocol
- Pre-approval of the Installation Qualification protocol

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


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 **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



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 **Issue Report**

**Appendix A - Verification Issue Report**

<b>Issue Number</b>	1
<b>Test Case</b>	1
<b>Test Step</b>	1.2
<b>Date of Issue</b>	06-December-2009
<b>Description of Issue</b>	Tester was able to enter data into cells H11, I11, and J11. These cells should have been protected from entry.
<b>Issue Type</b>	Functionality Error
<b>Steps for Issue Correction</b>	IT Spreadsheet configuration analyst will turn on protection for these cells
<b>Regression Testing Required</b>	Rerun Test Case 1, steps 1.1 and 1.2

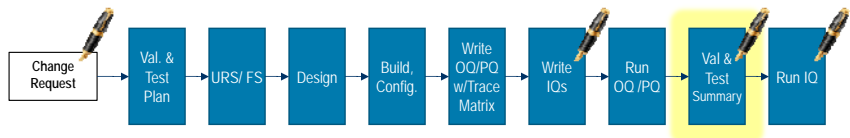
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## Summary Reports

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



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## 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

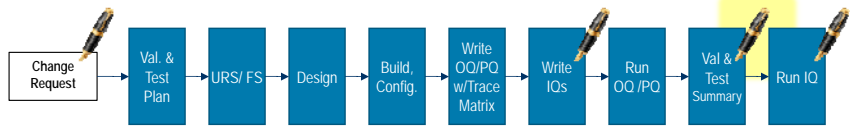
The following acceptance criteria have been met, and therefore this spreadsheet can be implemented for production use

- 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


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 **Validation Approval**

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



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 **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		

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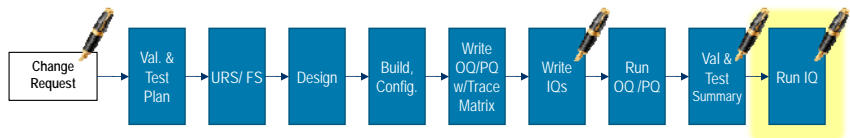
 **Installation, Closure**


### 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



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 **Validation Closure**


### 10 Validation Closure



The signatures below indicate:

- Completion of validation

Role	Name	Signature	Date
Quality Manager	Edward Grieg		




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# FDA Warning Letter Examples

Part 6




## 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
- 9 Year Range: 2007-2015



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## 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**

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Life Sciences

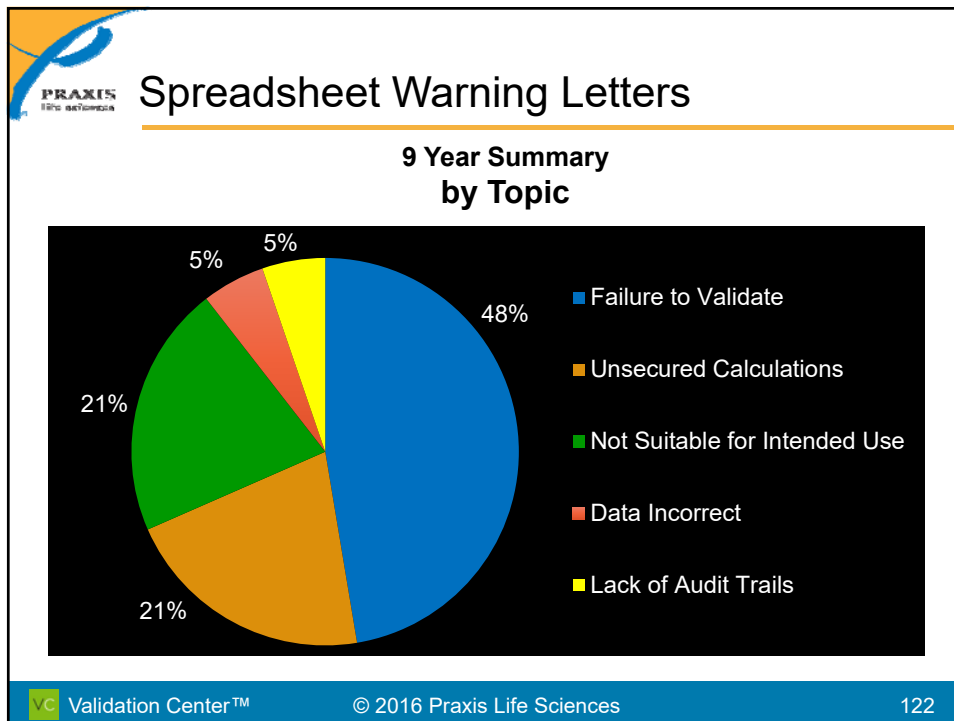
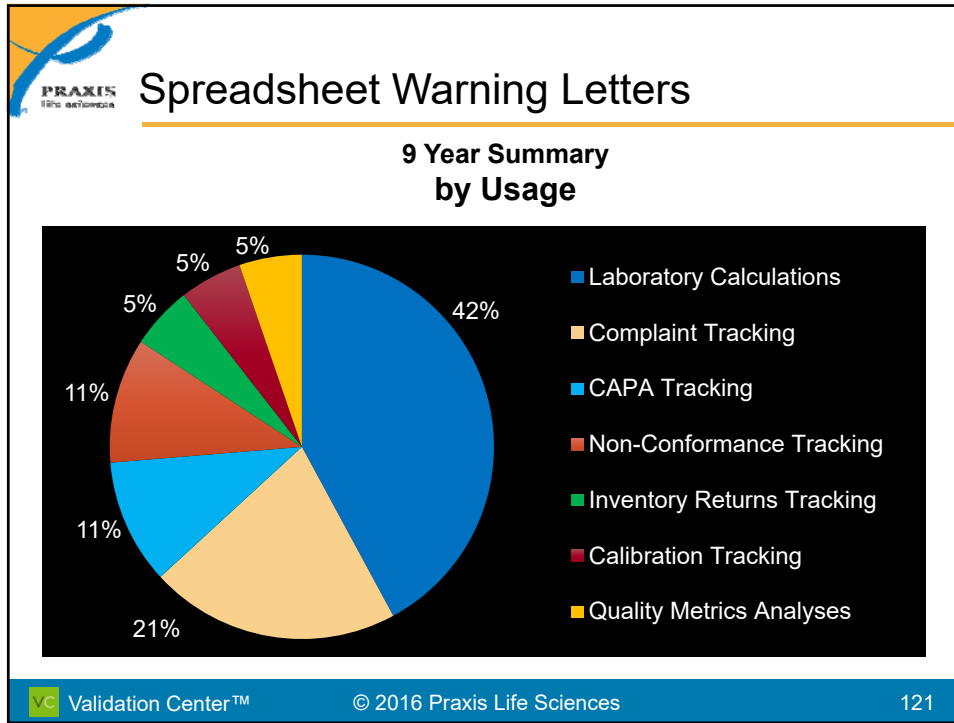
## Software & Computer Warning Letters


### 9 Year Summary by System Type

System Type	Percentage
Device/product Software	35%
Laboratory Systems	25%
Manufacturing Control Software	7%
Complaint Systems	4%
Blood Management Systems	4%
Clinical Study Systems	4%
SPREADSHEETS	4%
Inventory Control Systems	4%
Others (< 4% each)	13%

"Other" system types include systems for Document Management, Adverse Events, CAPAs, Distribution, Calibration, Labeling, Non-Conformance, Device History, Building Management, etc.

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## FDA Warning Letter Examples


<b>Regulatory Reference</b>	21 CFR 606 (Blood Products)
<b>FDA Office</b>	Los Angeles District
<b>Spreadsheet Usage</b>	Quality Metrics Tracking & Trending
<b>Warning Topic</b>	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.

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## FDA Warning Letter Examples


<b>Regulatory Reference</b>	21 CFR 820 (Medical Devices)
<b>FDA Office</b>	Detroit District
<b>Spreadsheet Usage</b>	Complaints Tracking
<b>Warning Topic</b>	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.

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## 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.

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## 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

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## FDA Warning Letter Examples

<b>Regulatory Reference</b>	21 CFR 211 (Pharmaceuticals)
<b>FDA Office</b>	CDER
<b>Spreadsheet Usage</b>	Laboratory Calculation
<b>Warning Topics</b>	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.

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## Conclusion





 **Now You Know ...**




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

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 **Need Help?**

-  **ValidationCenter.com Library of SOPs and CSV templates**
-  **Online and Classroom CSV Training**
-  **Software QA and Validation Program Implementation  
Validation Services**
-  **Audit Readiness Assessments**

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## Thank You!

Thanks for your interest in Spreadsheet Validation




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


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