Spreadsheet Validation

By Praxis Life Sciences
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
Intro to Praxis Life Sciences

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
Part 1: FDA Requirements and Guidance

Section Overview

- FDA Regulations
- FDA Guidance
- FDA Laboratory Reference Manual
Here are some key places to look for regulations and guidelines related to spreadsheets:

- Regulatory and Industry Standards
  - Software Quality Assurance, Validation, and Information Technology professionals need to be aware of many regulations and standards.
  - 21 CFR 210, 211, 820, 606 Good Manufacturing Practices
  - 21 CFR 11 Electronic Record
  - 21 CFR 50, 54, 56
  - ICH Q9 Quality Risk Management
  - 21 CFR 600 Biological Products: General
  - Eudralex V4 Chapter 4 Documentation
  - Eudralex V4 Annex 11
  - Eudralex V4 Annex 15 Qualification and Validation
  - FDA Guidance: Computerised Systems Used in Clinical Investigations
  - FDA Guidance: Computer Principles of Software Validation
  - Computerised Systems
  - Good Clinical Practices
  - Laboratory Practices
  - Signatures
  - Good Manufacturing Practice
  - Good Clinical Practice
  - 21 CFR 858 Good Clinical Practice
  - Good Clinical Practice
  - FDA Guidance & Reference Documents
  - PIC/S Guidance Documents
  - ICH Guidelines
  - FDA 21 CFR ...
  - Eudralex Volume ...
  - Regulations (Laws)
  - Guidance Documents from Regulatory Agencies
  - Best Practices from Industry Groups and Standards Bodies
  - GAMP Guides (ISPE)
  - IEEE Guides
  - ISO Standards
**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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**Framework for Regulations, Guidelines**

1. **Guidance Documents from Regulatory Agencies**
   - FDA Guidance & Reference Documents
   - PIC/S Guidance Documents
   - ICH Guidelines
   - Eudralex Volume ...
   - Regulations (Laws) FDA 21 CFR ...

2. **Best Practices from Industry Groups and Standards Bodies**
   - GAMP Guides (ISPE)
   - IEEE Guides
   - ISO Standards

3. **Company policies & procedures**

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FDA Software Validation Guidance

General Principles of Software Validation

Guidance

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.

FDA Software Validation Guidance

General Principles of Software Validation

Guidance

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.
Title: FDA Software Validation Guidance

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.

Title: Framework for Regulations, Guidelines

Guidance Documents from Regulatory Agencies
- FDA Guidance & Reference Documents
- PIC/S Guidance Documents
- ICH Guidelines

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.

etc.
FDA Spreadsheet Reference

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.

FDA Spreadsheet Reference

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).
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.
Validation and Part 11 Compliance

Part 2

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?
What Software Needs Validation?

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

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?
Which Spreadsheet Needs Validation?

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

Per FDA CSV Principles, which require validation?

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

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.
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.

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
Which Spreadsheet Needs Part 11 Compliance?

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

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

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.
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.

More Challenging Part 11 Requirements

Part 11 E-Record Requirement:
“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.

Spreadsheet Compliance Tactics

- 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
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.

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).
Difficult Part 11 Requirements

Difficult due to lack of audit trail features

Part 11 E-Record Requirement:

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.

Spreadsheet Compliance Tactics

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

Compliance Tools

Example spreadsheet tool is available at: www.ofnisystems.com
Part 3: Validation & Risk Framework

Section Overview
- Validation
  o Terminology
  o Process
- Risk
  o Terminology
  o Process
Basic Validation Terminology

**Verification**

Confirmation that specifications have been met (FDA)
- Design review
- Code inspection
- Software testing

**Qualification**

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

Validation Life Cycle

**Planning**

**Reporting**

**Specification**

**Verification**

**Purchase, Coding, and/or Configuration**

**Design Requirements Specification**

**Functional Requirements Specification**

**User Requirements Specification**

**Performance Qualification**

**Operational Qualification**

**Installation Qualification**

GENERAL APPROACH
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
Basic Risk Terminology

**Hazard**
A potential source of harm

**Risk**
Hazard probability and severity

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

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

Risk Assessment Activities

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

Spreadsheet Validation Approach

Part 4
Part 4: Spreadsheet Validation Approach

Section Overview
- Spreadsheet validation methodology
- Risk assessment and mitigation for spreadsheets

Validation Life Cycle

Planning
- User Requirement Specification
- Functional Specification
- Configuration Design Specification

Reporting
- Requirement Testing
- Functional Testing
- Configuration Testing

Configuration

CONFIGURED PRODUCT APPROACH
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Validation Life Cycle – Standard Project

- Planning
  - User Requirement Specification
  - Functional Specification
  - Configuration Design Specification

- Reporting
  - Requirement Testing
  - Functional Testing
  - Configuration Testing

- Standard Validation Project

  - Design
  - Build, Config.
  - Unit Test
  - Write IQs

- Test Plans
  - Write OQs & PQs
  - Trace Matrix

- Val. Plan

- Val. Team, Users

- TIME

- Val. Incident Report

- Val. Summary

- Run IQ

- Validated

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Validation Life Cycle – Standard Project
Validation Life Cycle – Standard Project

<table>
<thead>
<tr>
<th>Planning</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>User Requirement</td>
<td>Requirement Testing</td>
</tr>
<tr>
<td>Specification</td>
<td>Functional Testing</td>
</tr>
<tr>
<td>Functional Specification</td>
<td>Configuration Testing</td>
</tr>
<tr>
<td>Configuration Design Specification</td>
<td></td>
</tr>
<tr>
<td>Configuration</td>
<td></td>
</tr>
</tbody>
</table>

Change Request

Project Plan URS FS Val Team, Users

Val Team, Users

TIME

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Approval Points – Standard Project

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
Spreadsheet Adaptation

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

1. Eliminate the Project Plan

2. Eliminate the Unit Test
How Can the Standard Validation Project Deliverables be adapted for Spreadsheet Validation?

3. Combine the User Requirements and Functional Specifications

4. Combine the Operational and Performance Qualification Include the Trace Matrix
5. Combine the Validation and Test Plan

6. Combine the Validation and Test Summaries
Spreadsheet Adaptation

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

7. Reduce the Approval Points

Validation Life Cycle – Spreadsheets

Spreadsheet Validation Project
How are Risk Management concepts applied in Spreadsheet Validation?

**Risk Assessment Activities**

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

**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?
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?

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
### Criticality Classification

**How is risk Criticality classified?**

**Common Classification Method for Criticality**

- **3 Levels**

<table>
<thead>
<tr>
<th>Criticality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Criticality</strong></td>
<td>Direct impact on patient safety, product quality, or the integrity of associated data</td>
</tr>
<tr>
<td><strong>Medium Criticality</strong></td>
<td>Indirect impact on patient safety, product quality, or the integrity of associated data</td>
</tr>
<tr>
<td><strong>Low Criticality</strong></td>
<td>No impact on patient safety, product quality, or the integrity of associated data</td>
</tr>
</tbody>
</table>

**Examples**

- **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
Complexity Classification

How is risk Complexity classified?

Common Classification Method for Complexity – 3 Levels

<table>
<thead>
<tr>
<th>Complexity Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Complexity</td>
<td>Customization of out of the box functionality or very complex usage of out of the box functionality</td>
</tr>
<tr>
<td>Medium Complexity</td>
<td>Use of complex out of the box features</td>
</tr>
<tr>
<td>Low Complexity</td>
<td>Use of basic out of the box functionality</td>
</tr>
</tbody>
</table>

Complexity Classification

<table>
<thead>
<tr>
<th>Likelihood of Defect</th>
<th>High Complexity</th>
<th>Medium Complexity</th>
<th>Low Complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Custom Macros</td>
<td>Single Level Logical Functions</td>
<td>Standard functions, such as calculations, basic statistics (e.g., averages)</td>
</tr>
<tr>
<td></td>
<td>Sophisticated Look-up Functions</td>
<td>Advanced Statistical Functions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nested Logic Functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Look-up Functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linked Spreadsheets</td>
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</table>
### Spreadsheet Risk Assessment Examples

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

### Risk Based Approach to Validation Testing

<table>
<thead>
<tr>
<th>Criticality</th>
<th>High</th>
<th>Med</th>
<th>Low</th>
<th>High</th>
<th>Med</th>
<th>Low</th>
<th>High</th>
<th>Med</th>
<th>Low</th>
<th>High</th>
<th>Med</th>
<th>Low</th>
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<tbody>
<tr>
<td>Complexity</td>
<td>High</td>
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<tr>
<td>Path testing</td>
<td>All paths, multiple scenarios</td>
<td>All paths, single scenario</td>
<td>Sampling</td>
<td>All paths, single scenario</td>
<td>Sampling</td>
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<td>Boundary testing</td>
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<td>Test case degree of detail and specificity</td>
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<td>Medium detail</td>
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<tr>
<td>Test data similar to production data</td>
<td>Required</td>
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<td>Optional</td>
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<td>Testing evidence</td>
<td>Screen prints of inputs and outputs, signed protocol</td>
<td>Screen prints of inputs and outputs, signed protocol</td>
<td>Signed protocol</td>
<td>Screen prints of inputs and outputs, signed protocol</td>
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<td>User (vs. IT) execution of tests</td>
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### Risk Based Approach to QA Activities

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<td>High</td>
<td>Med</td>
<td>Low</td>
<td>High</td>
<td>Med</td>
<td>Low</td>
</tr>
<tr>
<td>Risk Assessment</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>Change Request</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
</tr>
<tr>
<td>Validation Documentation</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
</tr>
<tr>
<td>Design Review</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
</tr>
<tr>
<td>Part 11 Compliance for any records</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
</tr>
<tr>
<td>Verification of SOPs **</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
<td>Optional</td>
<td>Required</td>
</tr>
</tbody>
</table>

** 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

### Spreadsheet Risk Based Validation Example

<table>
<thead>
<tr>
<th>Spreadsheet Function</th>
<th>Criticality</th>
<th>Complexity</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Record of training attendance</td>
<td>Medium</td>
<td>Low</td>
<td>• Indirect impact on quality and/or safety • Basic spreadsheet functionality</td>
</tr>
</tbody>
</table>

#### 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
Spreadsheet Risk Based Validation Example

<table>
<thead>
<tr>
<th>Spreadsheet Function</th>
<th>Criticality</th>
<th>Complexity</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| 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

Spreadsheet Validation Example
Part 5
Part 5: Spreadsheet Validation Example

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

The Spreadsheet

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

1 Change Authorization

<table>
<thead>
<tr>
<th>Change Request ID</th>
<th>SS-2009-696</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spreadsheet ID</td>
<td>SS-001</td>
</tr>
<tr>
<td>Spreadsheet Title</td>
<td>Expiration Calculation</td>
</tr>
<tr>
<td>Requested By</td>
<td>M Hentschel, Sr. Lab Analyst</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Role</th>
<th>Decision</th>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Manager</td>
<td></td>
<td>Edward Grieg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT Manager</td>
<td></td>
<td>Francine Schubert</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Business Manager</td>
<td></td>
<td>Marian Pivka</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Validation Plan

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

<table>
<thead>
<tr>
<th>Risk Component</th>
<th>Category</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criticality</td>
<td>High</td>
<td>The calculations performed by this spreadsheet have direct impact on product quality</td>
</tr>
<tr>
<td>Complexity</td>
<td>Low</td>
<td>This spreadsheet uses only basic, out of the box spreadsheet features</td>
</tr>
</tbody>
</table>

Risk Mitigation:

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

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 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
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 documented and resolved; regressing testing has been completed.
- The installation qualification protocol has been written and pre-approved

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
### User and Functional Requirements

**Validation Center™ © 2016 Praxis Life Sciences**

#### 3 User and Functional Requirements

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

<table>
<thead>
<tr>
<th>User Requirement</th>
<th>1.0</th>
<th>The spreadsheet shall be secured from modification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1</td>
<td>All cells except for lot number, sample ID, drum ID, sample ID, and potency shall be secured from modification by users</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>The cells listed in requirement 1.1 shall be yellow</td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>No other cells in the spreadsheet shall be yellow</td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>There shall be a password used to lock the spreadsheet from modification by users</td>
</tr>
<tr>
<td>User Requirement</td>
<td>2.0</td>
<td>The spreadsheet shall calculate the lot potency from the potency of 3 samples</td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>The spreadsheet shall require entry of 1 digit to the right of the decimal point. An error message shall be displayed if &lt;1 digit or &gt;1 digit is entered</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>The spreadsheet shall require entry of all 3 sample potencies</td>
</tr>
<tr>
<td></td>
<td>2.3</td>
<td>The spreadsheet shall display an error message if any potency value is &lt; 0.0</td>
</tr>
<tr>
<td></td>
<td>2.4</td>
<td>The spreadsheet shall display an error message if any potency value is &gt;110.0</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>Potency shall be calculated as (1st-sample-potency + 2nd-sample-potency + 3rd-sample-potency)/3</td>
</tr>
</tbody>
</table>

#### Validation Center™ © 2016 Praxis Life Sciences

#### User and Functional Requirements

<table>
<thead>
<tr>
<th>User Requirement</th>
<th>3.0</th>
<th>The spreadsheet shall calculate the lot expiration date based on the sample date and potency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.1</td>
<td>If the lot potency is &gt;= 90, the expiration date shall be calculated as the sample date + 365 days</td>
</tr>
<tr>
<td></td>
<td>3.1.1</td>
<td>The spreadsheet shall display message “PASS – OK TO USE” in black</td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>If the lot potency is &gt;= 85 and &lt;90, the expiration date shall be calculated as the sample date + 304 days</td>
</tr>
<tr>
<td></td>
<td>3.2.1</td>
<td>The spreadsheet shall display message “PASS – OK TO USE” in black</td>
</tr>
<tr>
<td></td>
<td>3.3</td>
<td>If the lot potency is &lt; 85, no expiration date shall be calculated</td>
</tr>
<tr>
<td></td>
<td>3.3.1</td>
<td>The spreadsheet shall display message “FAIL – DO NOT USE” in red</td>
</tr>
</tbody>
</table>
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

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
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
OQ/PQ Test Design

6 Operation and Performance Qualification

6.1 Test Design

<table>
<thead>
<tr>
<th>Test Scenario(s)</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Security</td>
<td>N/A – no data needed for these tests</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Potency</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td>110.0</td>
</tr>
<tr>
<td></td>
<td>110.01</td>
</tr>
</tbody>
</table>

Average Potency

- Test the average calculation vs. the same calculation performed by a qualified calculator

<table>
<thead>
<tr>
<th>First</th>
<th>Middle</th>
<th>Last</th>
</tr>
</thead>
<tbody>
<tr>
<td>99.9</td>
<td>98.7</td>
<td>97.5</td>
</tr>
<tr>
<td>110.0</td>
<td>50.4</td>
<td>12.2</td>
</tr>
<tr>
<td>45.3</td>
<td>50.3</td>
<td>43.2</td>
</tr>
</tbody>
</table>

Expiration Date Scenario 1

- Potency >90
- Lot passes

First Sample: 90.1
Second Sample: 90.7
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

Expiration Date Scenario 3

- Potency <85
- Lot fails

First Sample: 85.0
Second Sample: 85.0
Third Sample: 79.0
Expiration Date: blank
Message: FAIL – DO NOT USE

Etc.
# OQ/PQ Test Protocol

## 6.2 Test Protocol

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

## 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: 110.3 • Second Sample: 104.1 • Third Sample: 122.2 Print screen | Average potency values is 107.5 | | |
| 2.3 | 2.5 | Enter these potencies: • First Sample: 45.9 • Second Sample: 55.3 • Third Sample: 43.2 Print screen | Average potency values is 46.6 | | |

Tester Name, Signature, and Date ____________________________
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

### 9 Installation Qualification

<table>
<thead>
<tr>
<th>Step</th>
<th>Description/Action</th>
<th>Expected Result</th>
<th>Actual Result = Expected Result (Yes/No)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Move spreadsheet SS-001 v1 to folder R:\YYXK034\Laboratory Spreadsheets\Validated Print Screen</td>
<td>File resides in folder R:\YYXK034\Laboratory Spreadsheets\Validated Print Screen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>Set spreadsheet password to LOCKED Print Screen</td>
<td>Password is set to LOCKED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>Set file permission for Users to allow “Read and Execute” only. Deny all other permissions for users. Print Screen</td>
<td>Users permissions are set to “Read and Execute” only</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Implementer Name, Signature, and Date ____________________________
Preliminary Approval

• Obtain approval of all deliverables up to this point

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

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Manager</td>
<td>Edward Grieg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT Manager</td>
<td>Francine Schubert</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Business Manager</td>
<td>Marian Pivka</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

### Issue Report

#### Appendix A - Verification Issue Report

| Issue Number | 1 |
| Test Case    | 1 |
| Test Step    | 1.2 |
| Date of Issue| 06-December-2009 |
| 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 |
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

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 error and the other was a spreadsheet functionality problem. 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 documented and resolved; regression testing has been completed
- The Installation qualification protocol has been written and pre-approved
Validation Approval

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

8 Validation Approval

The signatures below indicate:

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

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Manager</td>
<td>Edward Grieg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT Manager</td>
<td>Francine Schubert</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Business Manager</td>
<td>Marian Pivka</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Installation, Closure

Installation

• Execute the pre-approved Installation Qualification
  o Execute steps
  o Record actual results
  o Capture screen prints
  o Document steps that pass (or fail)

Closure

• Obtain signature to close validation project

Validation Closure

10 Validation Closure

The signatures below indicate:

- Completion of validation

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Manager</td>
<td>Edward Grieg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
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(e)).

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 LC, 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

Software & Computer Warning Letters

9 Year Summary by System Type

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

“Other” system types include systems for Document Management, Adverse Events, CAPAs, Distribution, Calibration, Labeling, Non-Conformance, Device History, Building Management, etc.
Spreadsheet Warning Letters

9 Year Summary by Usage

- Laboratory Calculations: 42%
- Complaint Tracking: 11%
- CAPA Tracking: 11%
- Non-Conformance Tracking: 11%
- Inventory Returns Tracking: 5%
- Calibration Tracking: 5%
- Quality Metrics Analyses: 5%

Spreadsheet Warning Letters

9 Year Summary by Topic

- Failure to Validate: 48%
- Unsecured Calculations: 21%
- Not Suitable for Intended Use: 21%
- Data Incorrect: 5%
- Lack of Audit Trails: 5%
FDA Warning Letter Examples

<table>
<thead>
<tr>
<th>Regulatory Reference</th>
<th>21 CFR 606 (Blood Products)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Office</td>
<td>Los Angeles District</td>
</tr>
<tr>
<td>Spreadsheet Usage</td>
<td>Quality Metrics Tracking &amp; Trending</td>
</tr>
<tr>
<td>Warning Topic</td>
<td>Validation</td>
</tr>
</tbody>
</table>

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.

FDA Warning Letter Examples

<table>
<thead>
<tr>
<th>Regulatory Reference</th>
<th>21 CFR 820 (Medical Devices)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Office</td>
<td>Detroit District</td>
</tr>
<tr>
<td>Spreadsheet Usage</td>
<td>Complaints Tracking</td>
</tr>
<tr>
<td>Warning Topic</td>
<td>Suitability for use</td>
</tr>
</tbody>
</table>

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.
### FDA Warning Letter Examples

<table>
<thead>
<tr>
<th>Regulatory Reference</th>
<th>21 CFR 211 (Pharmaceuticals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Office</td>
<td>Baltimore District</td>
</tr>
<tr>
<td>Spreadsheet Usage</td>
<td>Laboratory Calculation</td>
</tr>
<tr>
<td>Warning Topic</td>
<td>Security</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Regulatory Reference</th>
<th>21 CFR 820 (Medical Devices)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Office</td>
<td>CDRH</td>
</tr>
<tr>
<td>Spreadsheet Usage</td>
<td>CAPA and Non-conformance</td>
</tr>
<tr>
<td></td>
<td>Management</td>
</tr>
<tr>
<td>Warning Topic</td>
<td>Suitability for use</td>
</tr>
</tbody>
</table>

"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
## FDA Warning Letter Examples

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</tr>
<tr>
<td>Warning Topics</td>
<td>Security, Validation, Change Control</td>
</tr>
</tbody>
</table>

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

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Now You Know …

- Spreadsheets can be validated
- Spreadsheets can be compliant
- It doesn’t need to take longer to validate the spreadsheet than to build it

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
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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