Use of Excel Spreadsheets in a Regulated Environment

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Speakers Bio

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EXPERIENCE

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AFFILIATIONS
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PUBLISHED ARTICLES
-IT Compliance in the Life Science Industry
-Validation Management Systems
- Implementing CMMS in an FDA Regulated Environment

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Speakers Bio

Dennis Cantellops, QA Manager, FDA San Juan District

1. QA Manager for the FDA San Juan District.
2. Supports foreign inspections auditing laboratory operations, as well as API Manufacturing and Finished Products.
3. Very active in regards to the use of spreadsheets in the laboratory and has a wide variety of publications (FDA Laboratory Information Bulletins as well as Scientific Journals)
4. His articles has been referenced by international top speakers such as Dr. Ludwig Huber.

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Spreadsheets

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Spreadsheets

Pro's	Con's
Ease of Use – anybody with minimum knowledge, training and/or experience can create spreadsheets.	Potential developer/operator error, error management features.
Flexibility – Can be used to satisfy a wide range of needs	Difficult to verify the spreadsheet and the data produced. Tend to be an under-documented system because it can fly under the radar.
Accessibility – It is built-in within Microsoft Office	Inherent Security and Audit Trail deficiencies

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Spreadsheets

Two important questions to determine validation

1) Does the data involve GxP critical data that requires validation based on predicate rules?

2) Which spreadsheets within data flow should be validated?

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Spreadsheets

Typical Use of Spreadsheets

– Laboratory (Sample Results)
– Scheduling (Production / Maintenance)
– Manufacturing (Lot # Assignment)
– QA (SOP # Assignment)
– Management Review Metrics
– Other uses

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Spreadsheets

Excel Spreadsheets can fall into any of the following categories as per GaMP Model:

- Category 3 – Non Configured
- Category 4 – Configured
- Category 5 – Custom

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Typical issues found during inspections

– No validation or control procedures
– Rounding-off errors
– Conversion factors not expressed in analytical procedures.
– Formulas used for reviewing using manual calculations were not the same as those used in the spreadsheets.

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Typical issues found during inspections

- No pre-determined specifications or limits
- Spreadsheets are poorly documented. For example, the product declaration was not indicated, replaced by only a number in a cell
- Units expressed as numbers, without descriptive labels such as mg/mL or mg/g.
- No data validation used: data-entry and drop-down-list cells not color coded

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Typical issues found during inspections

- No provisions for security and data integrity
- No protection against unauthorized changes; analysts could freely change labels and formulas.
- Regression analysis calculated with the y and x axis inverted in the Excel formula, which generated erroneous slope and intercept results
- No Change Control
- Excessive use of the “Calculator Principle”
  - (a+b)*c <> a+(b*c)

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In Other Words:

Overconfidence tends to blind people to the need for taking steps to reduce risk and regulatory non compliance; the ability to catch errors instills confidence.

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Spreadsheet Design

A spreadsheet model is a set of worksheets and macro sheets designed to evaluate and organize data or to solve a particular problem. Such a model should meet two design objectives:

1. Guaranteed Correctness
2. Adaptability

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Recommendations

- Validate – Risk Based Approach
- Document spreadsheet functionality and instructions, service packs, add-ons, Operating system used, date of installation and version number etc.
- Use color-coding for data-entry
- Describe mathematical formulas used
- Document the relationship between the formulas in the analytical method and the Excel equations
- List macro programs – make sure that they are tested

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Recommendations

- Document acceptance criteria (including product declarations and specifications or USP limits)
- Test sheets with anticipated and actual results, signed and reviewed, that have been verified by manual calculations.
- Also use abnormal results (beyond boundaries, numeric/alphanumeric mix up, etc.)
- Security and password maintenance.
- Include Controls and Checks
- Use drop-down list and menus (when possible)

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Recommendations

- Introduce Units in appropriate cells
- Format Numbers
- Use supplemental cell comments
- Provide error messages
- Add validation to data-entry cells
- Establish backup/restore mechanisms
- Maintain Change Control & Configuration Management

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Upgrading to Excel 2007?

Perform testing assessment!

Excel 97 - 2003	Excel 2007
65,536 rows / worksheet	1,048,576 rows / worksheet
256 columns / worksheet	16,384 columns / worksheet
(16,777,216 cells) / worksheet	(17,179,869,184 cells) / worksheet
4 thousand types of formatting per workbook	Unlimited number of types of formatting per workbook
8 thousand cell references per cell	Cell references per cell limited by available memory per workbook
Memory management 1 GB	Memory management 2 GB
Not support multiple processors	Supports multiple processors and multithreaded chipsets - faster calculations in large, formula-intensive worksheets
	Supports up to 16 million colors

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Excel 97-2003 features that are not supported in Office Excel 2007

http://office.microsoft.com/en-us/excel/HA101988951033.aspx

- Unsupported worksheet features
- Unsupported table features
- Unsupported formula and function features
- Unsupported charting features
- Unsupported PivotTable features
- Unsupported developer features
- Unsupported file formats

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Policies on spreadsheet development

Spreadsheet Policies

When policies on analytical spreadsheet development are applied, improvement was noticed in both: formatting properties and reduced time in its development and reviewing. Additionally, the end users are more familiar with the consistency of the worksheets, reducing time in data-entry and training.

When spreadsheet software technology is improved the established policies in spreadsheet development will facilitates the application of new technology as it become available.

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Policies for Development of Spreadsheets FDA San Juan District

- Only the front side of the form will be used.
- Has exactly 18 columns (width 4.50 (37 pixels)) and 55 rows.
- Page Setup (General Continuation Sheet):
  - Page: Orientation = Portrait and Scaling = 100% normal size
  - Margins: Left: 0.75", Top & bottom = 0.2", Right = 0.2", Header & footer = 0",
  - Center on page: Horizontally & vertically. Sheet: Print = Black & white
- Custom Toolbar disabled when form 431 is active.
- Short cut menu only functions when appropriate.
- Font : Times New Roman, Size 10
- File Identification & Path as footer
- Protection attributes: Sheets are protected, as appropriate.

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Policies for Development of Spreadsheets FDA San Juan District

- New columns can not be inserted and any column present can no be deleted
  - To maintain the form's pre-set space and avoid distortion
- New rows can be inserted or deleted

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Spreadsheets in WL's

483 Items: Radio Chemical Active Pharmaceutical Ingredient Manufacturer - Nov 2007

*" Your firm **failed to validate the Excel spreadsheet** used to calculate the monthly verification of the Gamma Analyzer Spectrometry Detectors Efficiency. These Excel spreadsheets are also **used as a primary QA tool** to verify the radioactivity calculations/measurements entered in the batch production records. **Discrepancies were observed between the spreadsheets results and the calculation results manually entered in the batch records**."*

*"Failure to assure that 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, as required by 21 CFR 820 .70(i). **For example, electronic records are used, but there was no software validation. No procedures are established to validate for its intended purpose the Microsoft Word or Microsoft Excel software used in creating and maintaining nonconformance records, product return records, internal audit corrective action records, or preventive action records."***

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Good Laboratory Practice (GLP) Regulations

The use of spreadsheets by FDA regulated industries to judge the quality of a product is covered by cGMPs, GLP, regulations and ISO 17025 accreditation. The following are some of the requirements established by GLP regulations:

- **Configuration Management**
- **Written Standard Operating Procedures:** 21 CFR 58.81 (a) (2)
- **Completeness of Data:** Compliance Policy Guide (CPG) 7132a.07 (21 CFR 211.68) defines the program for input/output (I/O) checking
- **Raw/Secondary Data:** 21 CFR 58.3 (k) (2)
- **Electronic Records / Security:** 21 CFR Part 11
- **Training:** 21 CFR 58.29 (a) (2)

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CFR 21 Part 11
San Juan District Laboratory

District Lab is evaluating a paperless work environment and we are considering tools that help us use spreadsheets while complying and better understanding of 21 CFR Part 11 is achieved.

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Use of Spreadsheets at FDA Laboratory San Juan District

Some concerns we have are:

1. File accountability
2. Control of templates
3. Verification & Validation
4. Backup of data
5. File formats
6. Reviewing process
7. Time of spreadsheet development

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Spreadsheets in WL's

1999 WL-M2848N

- ***"Failure to validate*** *computer software used as part of the quality system for its intended use according to an established protocol as required by 21 CFR 820.70(i).*

  For example, the data in the ***Excel spreadsheet*** *identified as a "Hit List" of top non-conforming components contains 16 record counts for Part number 8601618 DC converter failures compared to 18 record counts for Part number 860168 DC converter failures in the dbase database. The* ***spreadsheet is used for management review*** *of component suppliers for all components."*

Spreadsheets in WL's

2004 – WL-G4601D (not excel)

- *"…your firm relied on the not yet validated system for automated calculations, obtained by using custom-made formula fields, in making release decisions without manual verification."*

Spreadsheets in WL's

2006 WL-G5699D

"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. Examples of these spreadsheets include: ***[redacted]****"*

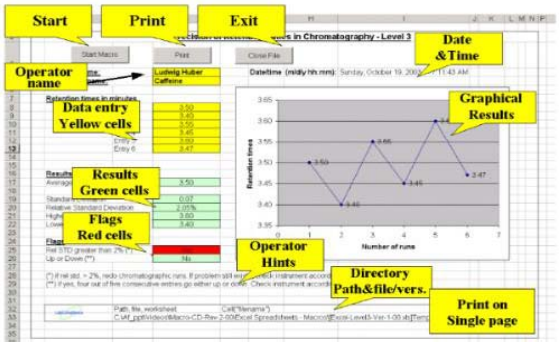
Spreadsheets in WL's

2007 WL-S6381C

"Software used as part of the production quality system was not validated for its intended use according to an established protocol [21 C.F.R. 820.70(i)]. Specifically,

(a) Spreadsheets intended to check for outliers and calculate mean, SC, % CV, value assignments for finished devices."

Validation Scope



Validation Strategy

- Define a basic documentation practice and methodology in a single document (Spreadsheet Validation Master Plan).
- Define the requirements for each sheet or chart in the workbook, then focus testing on verifying the requirements.
- Put heavy emphasis on defining and testing formulas, and also on the security for each sheet by limiting the parts of each sheet that the users are allowed to edit.
- Preferable to validate XLT's instead of XLS.

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Requirements Specifications

- List all sheets and charts in the workbook.
- For each sheet, define:
  - Data Entry Rules
  - Formulas / Calculations
  - Results
- For each chart, define properties like the title, axis labels and units, and the datasets used to create the chart.

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Design Specifications

- Describe how the requirements will be implemented.
- Break each sheet into four sections
  - Inputs
  - Processing
  - Outputs
  - Security

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Design Specifications - Inputs

- Document the cells users are expected to enter or update data.
- Document any validation rule used to enforce data entry.

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Design Specifications - Processing

- Document the formulas, custom macros and/or code used on the sheet.
- Most of the errors found while validating spreadsheets are in the formulas.

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Example: Documenting Formulas

- It may be easy to document that the range of cells F10:F20 contains the formula =(A10*$C$5)/($D$5*B10). However, it is difficult to verify if this formula is correct.
- Write the formulas out like this:

Cell $C$5:	Volume (V)
Cell $D$5:	Ideal Gas Constant (R)
Cells A10:A20	Pressure (P)
Cells B10:B20	Temperature (T)
F10:F20	Final Result (moles of gas, n)

n=(PV)/(RT)

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Example: Documenting Macros

- The other kind of processing is the validation of macros and code that is used in the spreadsheet. Here, the design specification is a good place to copy the code and annotate as needed to describe the purpose of each macro or function.
- Follow Good Coding Standards

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Design Specifications - Outputs

- Outputs usually fall under one of the following three main categories:
  - Cell or range of cells containing the final result of all previous calculations
  - Charts – sometimes printed and saved with external reports
  - Data copied into a final result sheet or exported to a separate file or database.

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Design Specifications - Security

- Examples of Security Settings
  - "All non-input cells should be locked to prevent changes."
  - "Only members of a group 'X' shall be able to open the spreadsheet for editing. All other users may open the spreadsheet in read-only mode."

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Test Protocols

- Installation Qualification (IQ) Testing - usually limited to making sure the file is in a location where users can access the file, unless the workbook is part of a larger automation project.
- Operational Qualification (OQ) Testing - mostly about verifying formulas, macros, and also to test the security of each sheet to verify that all non-input cells are locked to prevent changes.

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Input Testing

- Some examples of the types of test cases to write for input testing.
  - What data can be entered into each input cell?
  - Are validation rules being enforced?

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Process & Output Testing

- FOCUS ON TESTING THE FORMULAS! Are they correct?
  - Visual inspection of each formula or range of formulas
  - Verification of each numerical calculation using a calculator.
  - Significant Figures/Rounding

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Formula Consistency

- Testing for consistent formulas in a certain range.
- Test until all input cells have had data entered on changed, and that result has been verified.

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Testing Macros & Charts

- Macros can be tested by entering a range of data and comparing the results with a hand calculator, or by visual inspection that the function performed as expected.
- Charts can be tested by a combination of visual inspection or verification of the properties, including the dataset used as the basis for the charts.

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Security Testing

- Type and amount of security testing is largely based on how security has been implemented.
- At a bare minimum, test that users are limited to entering data into the defined input cells only, and that they do not have the ability to alter any other part of the spreadsheet.

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21 CFR Part 11

To meet 21 CFR Part 11, additional controls may need to be added

-By custom developed macros and functionality provided on a sheet by sheet basis

-Third party software packages

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Change Control

Do not forget to control changes

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Summary

- The deliverables of this methodology are:
  - User/Functional Requirements Specification
  - Software Design Specification
  - IOQ Protocol ready for approval and execution.
  - Execution Report

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Conclusion

Excel spreadsheets are a useful tool in the regulated environment. FDA Inspectors will enforce regulatory scrutiny on spreadsheet use whenever they are used for compliance with cGMP's.

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