Validation and Use of Excel® Spreadsheets in Regulated Environments

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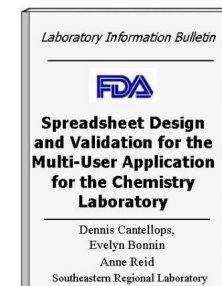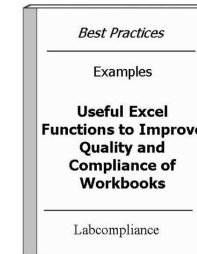E-mail:Ludwig_Huber@labcompliance.com

Today's Agenda

- Regulatory requirements/business requirements
- Recommendations from the FDA
- Design Spreadsheet for Part 11/GxP compliance
- Validation during development and installation

- How to ensure integrity&security of spreadsheets
- How the FDA is using spreadsheets
- Documentation requirements
- Case studies for Part 11 compliance

Reference material

Best Practices
Examples
Useful Excel Functions to Improve Quality and Compliance of Workbooks
Labcompliance

- Excel functions for compliance and quality
- SOPS
  - Development and use of spreadsheets for regulated environment,
  - Validation of spreadsheet applications
  - Change control of computer systems

Best Practices
Standard Operating Procedure
Validation of Spreadsheet Applications
Labcompliance

- Checklist/gap analysis
  Macros and Spreadsheets
- Two FDA Laboratory information bulletins
- FDA establishment inspection report (EIR), 483 observation with deviations related to Spreadsheets

Laboratory Information Bulletin
FDA
Spreadsheet Design and Validation for the Multi-User Application for the Chemistry Laboratory
Dennis Cantellops,
Evelyn Bonnin
Anne Reid
Southeastern Regional Laboratory

Download Reference Material
www.labcompliance.com/conferences/excel-5234.htm
(available until March 30 , 2007)

Regulations/Laws

- **Healthcare Insurance Portability and Accountability Act (HIPAA)**
  Rules governing how anyone involved in the healthcare industry should conduct business

- **Sarbanes Oxley Act**
  New regulatory controls for financial services firms (aimed at public companies)

- **21 CFR Part 11 – E-Signatures/Records**
  Defines requirements for electronic records, electronic signatures in FDA regulated industries

Common Requirements

- Strict access control to the systems and data
- Record handling and maintenance
  - Authenticity
  - Integrity
  - Confidentiality
  - Accuracy
- Tools:
  - Electronic audit trail
  - Electronic signatures
  - Digital signatures for system not under direct control
  - Validation

FDA Part 11 Validation Guidance

FDA Requirements

- Spreadsheet Calculations and Macro Programs used in GxP environments should be validated
- Testing should cover full range
- **End users should validate any program Macros and** other customizations that they prepare

Spreadsheet Calculations and Macro Programs should comply with 21 CFR Part 11 (E-records/signatures)

FDA Warning Letters

- **There is no documentation covering Excel application software**, or any procedures instituted covering the protection of electronic records or an established back-up system (069)

Validate Spreadsheets

Ref: www.fdawarningletter.com (W 069)

Warning Letter

- Failure to use **fully validated computer spreadsheets** to calculate analytical results for in-process and finished product testing [21 CFR 211.165(e)]. For example, the computer **spreadsheets used to calculate analytical results for... have not been validated**.

- QA/QC Spreadsheet Validation, is deficient in that **only a small range** of values are being used to challenge computerized spreadsheet mathematical calculations.

Validate Spreadsheets over wide range

Ref: www.fdawarningletter.com (W 063)

Verification of Corrective Actions

- These tests include the entry of the following types of data: **aberrant high findings, aberrant low findings, in-specification findings, zeros, negative numbers,** and alphanumeric combinations

- Each spreadsheet is product specific and has a separate validation package

- Each package contains the initial testing of the information as entered into the **Spreadsheet, a blank spreadsheet, and a spreadsheet showing the calculation formulas** used in the appropriate cells.

EIR = Establishment Inspection Report

Ref: www.fdawarningletter.com (W 106)

Verification of Corrective Actions

EIR

- The package contains a list of the tests conducted and the dates they were performed as well as hand calculations of some trial data for comparison

- Revised SOP "QA/QC Computer Spreadsheet Validation," contains **directions for testing new and existing spreadsheets prior to use in analytical testing**.

Validation

- The spreadsheets are **checked monthly by a familiar analyst with previously entered data**.

- The **check results are compared to the originals** to make sure that corruption of the file has not occurred

EIR = Establishment Inspection Report

Ref: www.fdawarningletter.com (W 106)

Verification of Corrective Actions

- The firm now **saves the spreadsheets in read-only form** to compact discs, specific to product.

- **Changes to spreadsheets cannot be saved in this format.**

- Two sets of CDs were made, one Set for the daily laboratory use and one master copy containing all spreadsheets kept by ….

- If **one spreadsheet an a CD is changed, then a new CD is burned and the old one is archived.**

- The spreadsheet when **printed out bears a file path** at the bottom to assure it came from the CD

.

Ref: www.fdawarningletter.com (W 106)

EIR = Establishment Inspection Report

Compliance Problems with Spreadsheets

- Easy access to programs
- Everybody (not trained on GxP validation and computer science) can write programs
- Everybody can change ==>Frequent change without control
- No validation, no documentation
- Many different environments (operating systems, PC hardware)
- Many versions in use (local PC, server, inbox, delete folders)
- No or insufficient documentation
- **Typically do not comply with regulations (e.g., Part 11), and QA Unit is not aware of this**
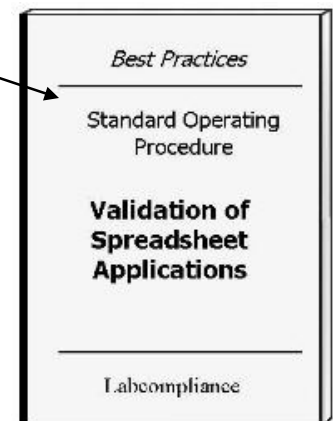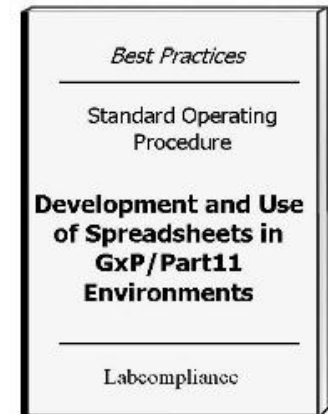
What to do for GxP/Part 11 Compliance ?

1. Use other programs
   e.g., perform calculations in **secure and validated Agilent ChemStation or Cerity** environments with functions for Part 11

2. Develop, implement, and enforce procedures for development and use of Spreadsheets with **quality, security and validation** in mind.

   Today's focus

3. Evaluate add-on software with more security and compliance functionality
   e.g., www.wimmersystems.com, www.part11solutions.com,
   or www.j-walk.com, www.prodiance.com

4. Use data management software with built-in Excel support and Part11/GxP functionality, (E.g., Agilent Cerity ECM)
   www.agilent.com/chem/cerityecm

Design Spreadsheets for Part 11/GxP

1. Follow documented procedures

2. Design for error detection

3. Design with integrity in mind
   - Don't enable users to change spreadsheets

4. Design for security

5. Validate during development, before and during use

6. Develop and apply rigorous change control procedures

Best Practices

Standard Operating Procedure

Development and Use of Spreadsheets in GxP/Part11 Environments

Labcompliance

Best Practices

Standard Operating Procedure

Validation of Spreadsheet Applications
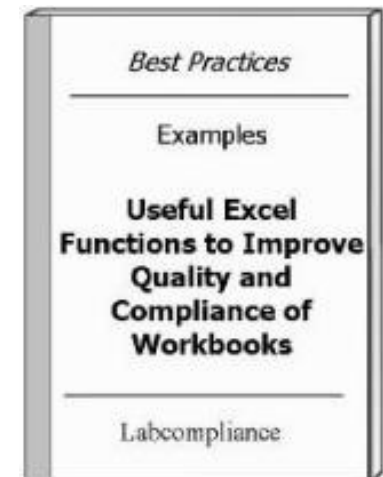
Labcompliance

Design for Error Detection

- Spreadsheet should detect errors during data entry
  - wrong type, e.g.,
    string characters instead of numbers
  - wrong sequence of entries
  - wrong data range
  - wrong format (e.g., date)

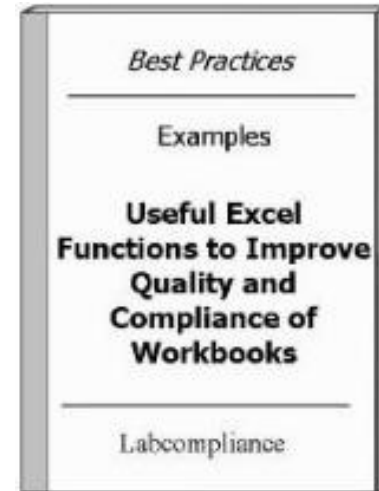- Spreadsheet should prompt the user in case of wrong entries, and not crash
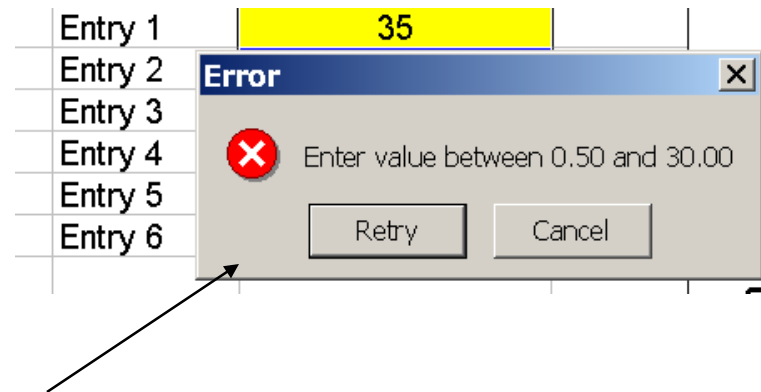
With VBA (not included in the example)

- Check and alert the user if a single data entry is 50% above average.

Entry 1	35
Entry 2	
Entry 3	
Entry 4	
Entry 5	
Entry 6	

Error

Enter value between 0.50 and 30.00

Retry   Cancel

Best Practices

Examples

Useful Excel Functions to Improve Quality and Compliance of Workbooks

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Design for Integrity and Authenticity

- Protect all cells not used for data entry
- Protect use of Excel sheet by passwords
- Store and load from write protected directory (e.g., secure server or CD)
- Display directory, subdirectories, file name and sheet name at the bottom of the spreadsheet
- Display date and time of last data entry
- Display&print operator name
- Verify file integrity with hash function

Best Practices

Examples

Useful Excel Functions to Improve Quality and Compliance of Workbooks

Labcompliance

With VBA (example 3)

- Disable menu and tool bars to limit function to the intended use
- Disable 'save' and 'save as' Disable cut/copy and paste control keys

Directory, path, file name

	Path, file, worksheet	Cell("filename")		
	C:\Ae_Winword\Book2002-Macro\Macros\RetentionTime-Macro\[Excel-Level1-0-01.xls]Template			

# Md5 Hash Calculations for File Integrity Check

- Based on security software from RSA
- Used to check accuracy or e-mail transfer
- Used for digital signatures
- Used to verify proper software installation
- Used to verify file transfer accuracy in networks

1. Calculate hash value (124 bit string)
2. Store the value
3. For verification: recalculate and compare with original value

Best Practices

Software and Validation Package

File Integrity Check with MD5 Hash Calculations

Labcompliance
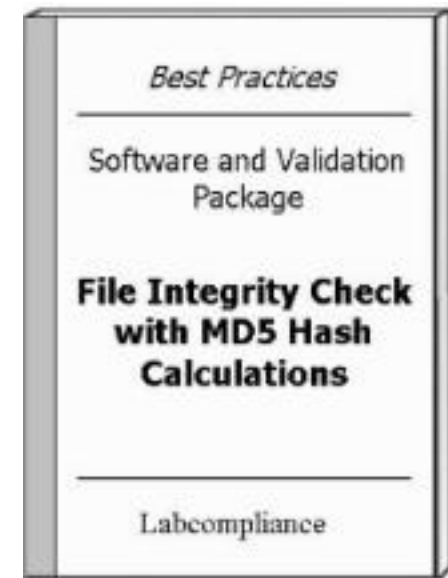
Example and validation package

Design for Security

1. Develop, implement and test procedures for limited system access to authorized users
   (e.g., through user ID/password)

2. Configure and use secure operating systems (Windows 2000, XP)

3. If available, use secure server for storage of spreadsheets and access to spreadsheets

4. Maintain user lists with authorized access

Best Practices

Template/Example

Test Protocol – Authorized System Access

Labcompliance
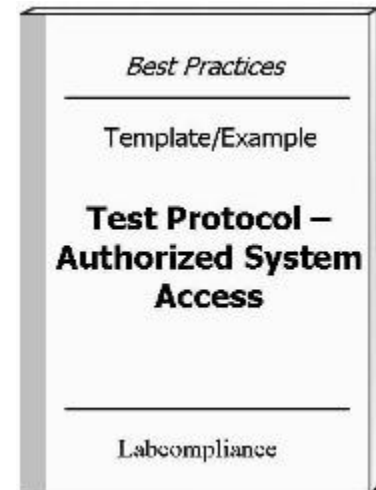
What to Validate / What not to Validate

Not to Validate

- Excel software

- Standard calculations under normal conditions (GAMP 3)

Validate

- Everything we customize, e.g.,
  - user interface (input/outputs)
  - validation functions for data entry
  - macros (VBA Scripts)

- Extreme conditions (at and above/beyond limits)

- Security functions (e.g., passwords, cell protection)

- Spreadsheet integrity (e.g., hash function)

Best Practices

Standard Operating
Procedure

**Validation of
Spreadsheet
Applications**

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What does Validation of Spreadsheets Include?

- **Planning**

- **Writing specifications**
  - functional specifications
  - computer requirements
  - user profile (skills)
  - design specifications

- **Design and code review**

- **Installation qualification/documentation**

- **Testing during development and after installation**

- **Change control/requalification**

- **Validation report**

Best Practices

Standard Operating Procedure

Validation of Spreadsheet Applications

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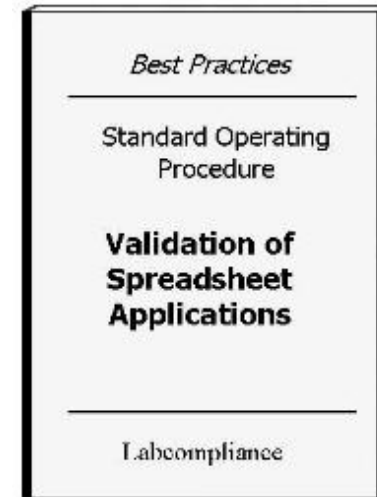
Should we Test Standard Excel Functions?

1. Standard functions used in normal operation range don't need to be verified (GAMP3)

2. Verify standard functions if used in extreme ranges (e.g., very small numbers) and if there are indications for problems with Excel

3. Use commercial calculator for verification for 2.

4. Regularly check the vendor's website for errors (need written procedure)

How to Comply with the Audit Trail Requirement

- **Procedures**
  For low risk systems

- **Print and sign**
  For low risk systems

- **Use 'Track Changes' function**
  For medium risk systems

- **Use 3rd party software**
  e.g., Agilent ECM, e-Infotree
  For high risk systems

Design for Tracking Changes (Audit Trail)

1. Click on *Tools* -select *Track Changes* -select *Highlight Changes*
2. Select **which changes you want to track and time range**
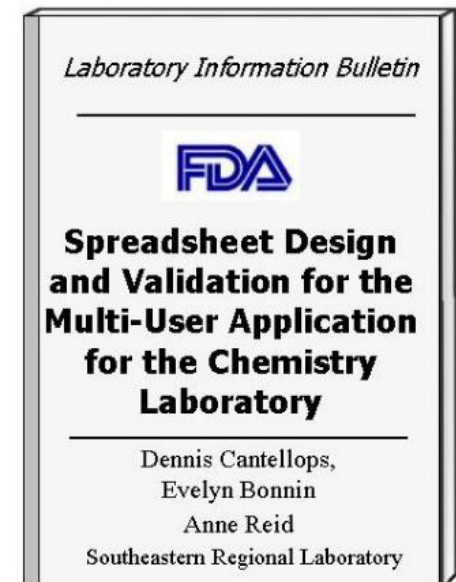3. Result: Changes can be reviewed and printed
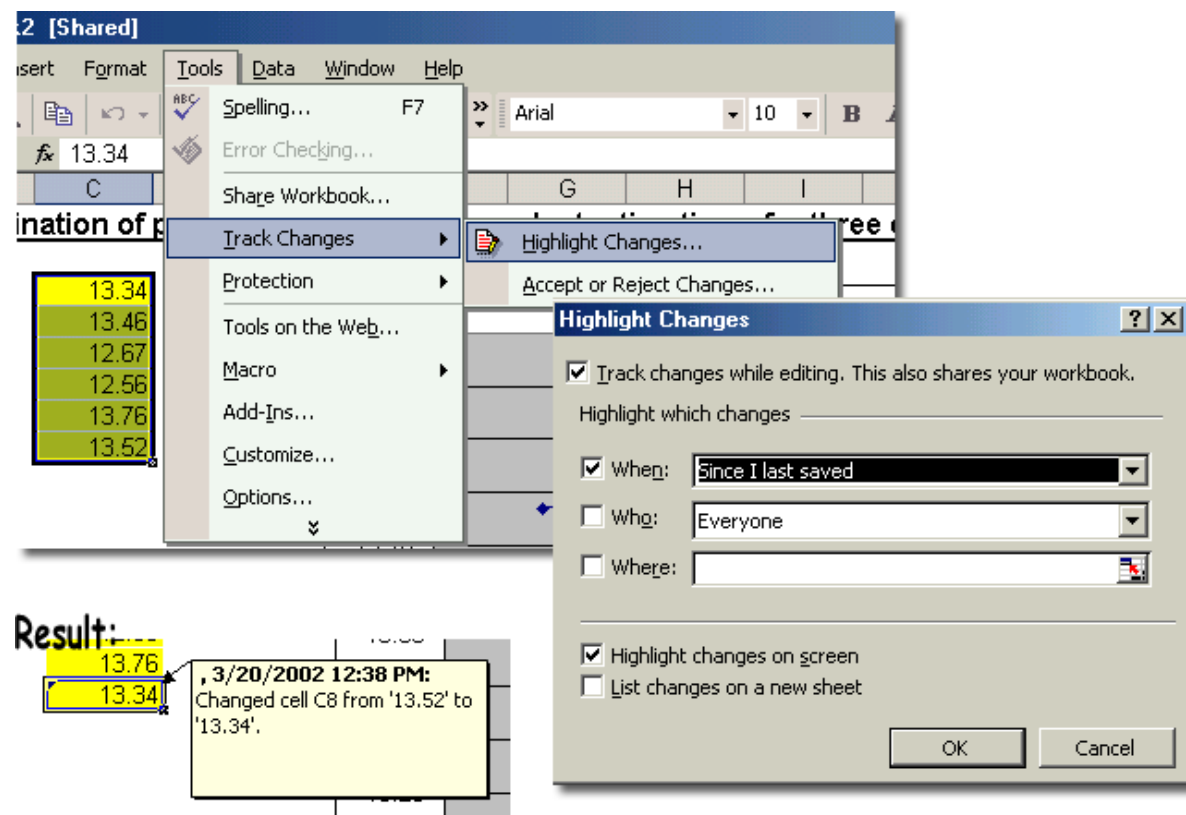
How Does the FDA Design and Use Spreadsheets

1. User ID/Password for secure log-on
2. MS NTFS to limit access to files
3. Store spreadsheets on write protected server directories
4. Validate spreadsheet applications
5. Control and archive spreadsheets for internal audits
6. Standardize design of templates (use of colors, cell protection)

Source: FDA LIB:

Spreadsheet Design and Validation for the Multi-User Application for the Chemistry Laboratory

Laboratory Information Bulletin

FDA

Spreadsheet Design and Validation for the Multi-User Application for the Chemistry Laboratory

Dennis Cantellops,
Evelyn Bonnin
Anne Reid
Southeastern Regional Laboratory

How to Validate and Use Single User Spreadsheets

- Test and document correct functioning (input/output, customized formula)

- Document used formula

- For direct input of raw data: verify data entry through second person (only for high risk records)


Laboratory Information Bulletin

FDA

Spreadsheet Design, Verification and Validation, Use and Storage of Single-User Workbook Files in the US FDA Laboratories

Part II

Dennis Cantellops
Dan Juan District

Source: FDA LIB:
Spreadsheet Design, Verification and Validation, Use and Storage of Single-User Workbook Files in the US FDA Laboratories

Documentation for Part 11

FDA Recommendation: We recommend that each study protocol identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit data.

Best Practices

Standard Operating Procedure

Part 11 Scope and Controls

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1. Document your business practices especially important: where can users change records (e.g., spreadsheet templates)
2. Define and document your rational behind part 11 controls (e.g., audit trail, archiving on paper vs. electronic, validation)
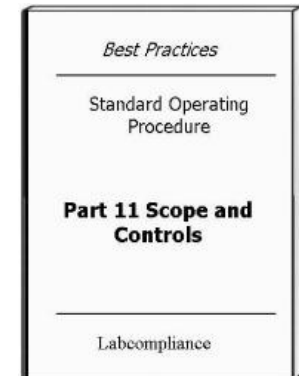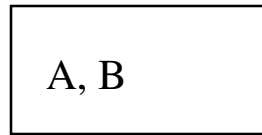
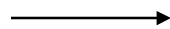# Example – Using Excel Template as Calculator

Paper
Raw data
Results

PC
Excel software
Calculates results

```
┌──────────┐         ┌──────────┐
│          │────────▶│  A, B    │
│          │         │          │
└──────────┘         └──────────┘
                          │
                          ▼
                     ┌──────────┐
                     │    C     │   Printer
                     └──────────┘
```

Events

A. Original e-record stored
B. User has authorized access to data
C. Approval

Recommendations
- No e-audit trail
- Load spreadsheet from write protected server
- Print file source with each result
- Maintain records in paper form

Business Practice - Steps
1. Spreadsheet loaded from **write-protected server**
2. Data from paper is typed into an Excel spreadsheet
   Example: weights of balance
3. Spreadsheet performs calculations and results are printed and signed
4. **All printed results are archived together with original data**
5. No electronic records stored

Records required by predicate rule
No __   Explicit _x   Implicit __
Regulated activity relies on e-records
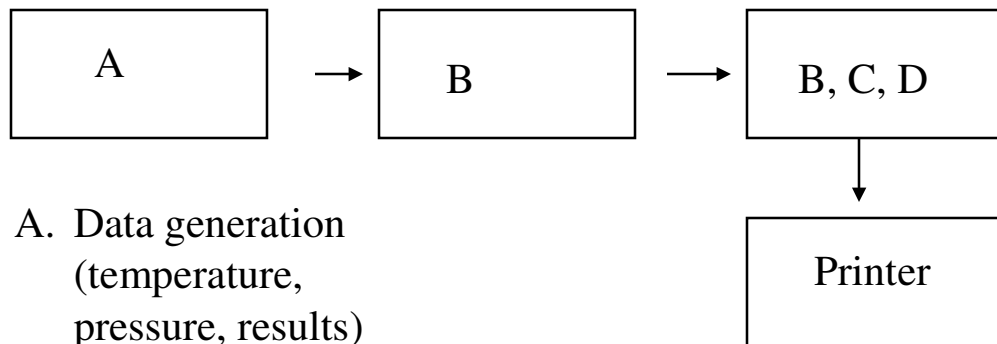Yes _x   No__
Impact on product quality
High _x   Medium __   Low __   No __

Automatic Transfer of Intermediate Data to Excel

Equipment
e.g., autoclave
or UV for
 Dissolution

Computer 1
Data acquisition
Primary data
evaluation

Computer 2
Excel software
Primary data
evaluation

| A | → | B | → | B, C, D |

                                    ↓

                              | Printer |

A. Data generation
   (temperature,
   pressure, results)
B. Data is stored
   temporarily and
   processed
C. Authorized access
    to data
D. Operators can
   manipulate data

Remark: Computer I
and II can be
combined

Recommendations

- No e-audit trail on Comp1
- E-audit trail on Comp2
- E-signature on Comp2
- Need Excel remediation
  software
- Comp1 and Comp 2 must
  be validated

Business Practice - Steps
1. Data generated by equipment
   (e.g., process parameters, signals)
2. Data transferred to computer 1 for
   primary data evaluation (no operator
   interaction)
3. Intermediate results transferred to
   computer 2 for secondary evaluation
   with operator interaction
4. Results from secondary evaluation
   are signed on computer 2 and
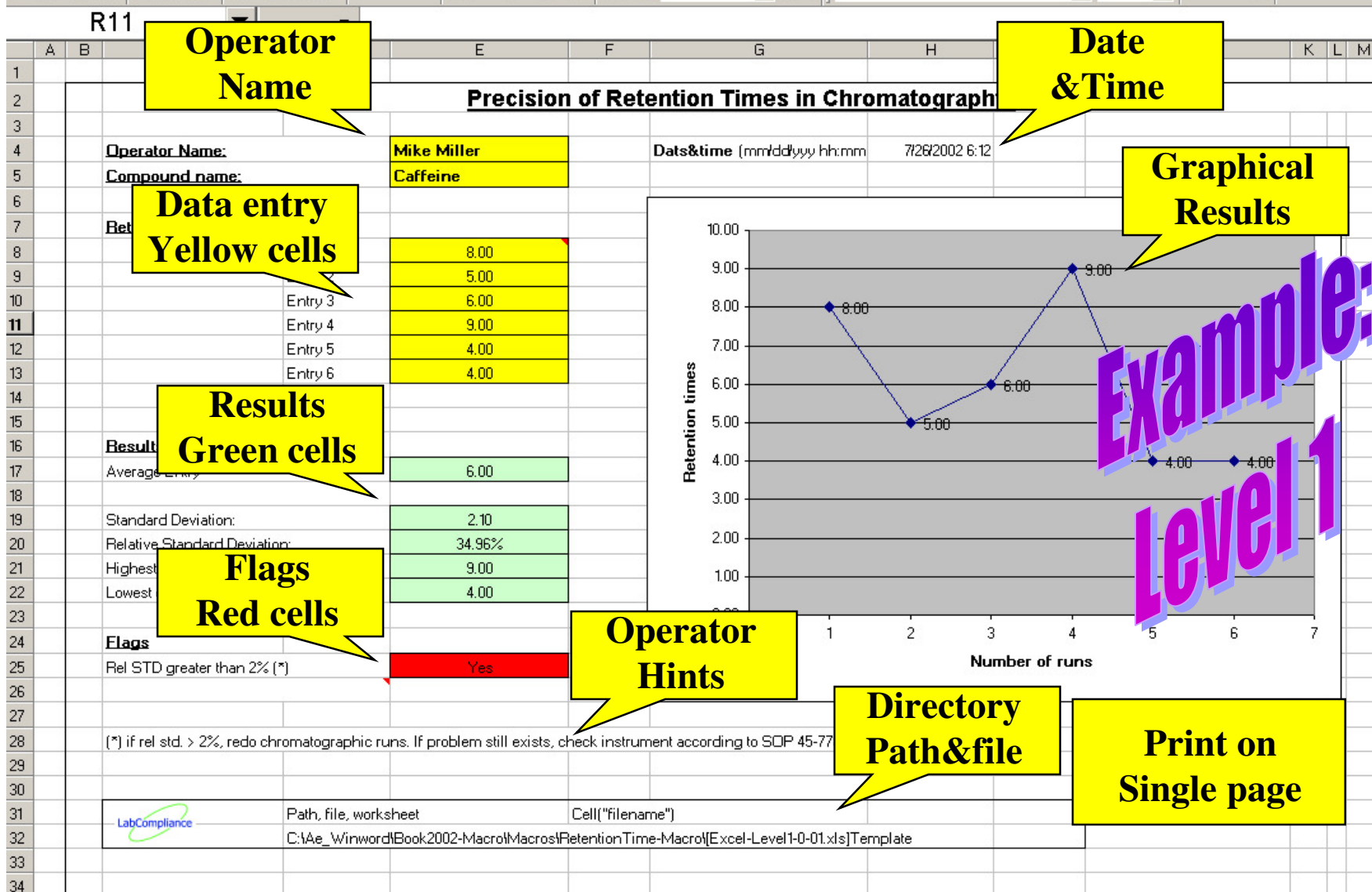   archived

Records required by predicate rule
No __   Explicit _x   Implicit __
Regulated activity relies on e-records
Yes _x   No__
Impact on product quality
High _x   Medium __   Low __   No __

Disable Menu and Tool Bars and CTRL Keys

Minimal Documentation
(equally important for new and existing spreadsheets)

1. A description of what the program does

2. Description of formulas used

3. User manual incl. description of color coded cells

4. Explanation of the relationship of formulas used in procedures to Excel equations

5. Listing of VBA Macros

6. Test sheets with anticipated results, acceptance criteria and actual results

7. Security and password maintenance, user lists

8. Documentation of operating systems, spreadsheet version, workbook version, date of installation

Thank You

I would like to thank

☞ *ComplianceOnline for the organization*

☞ *All attendees for your attention*

Ludwig Huber

Download the Reference Material from www.labcompliance.com/conferences/excel-5234.htm (available until March 30 , 2007)

Check topics and details of 60+ audio seminars on www.labcompliance.com/seminars/audio

Computer System Validation Package
Do it Right the First Time at Lowest Possible Cost

Best Practices

Computer System Validation

LabCompliance

Computer System Validation

- Primer and interactive audio seminar: requirements and strategies for implementation

- Forms, templates, examples and 22 SOPs for fast, consistent and effective implementation

- Validation master plan and project plans guide you through the complete process from writing specifications to retirement.

Users, IT and QA learn all about requirements and strategies
And get SOPs and examples for easy implementation.
More info: **www.labcompliance.com/books/computers**