Validation and Use of Excel® Spreadsheets in Regulated Environments

For Compliance with FDA Part 11 EU Annex 11.

27 Novembre, Moscou

Today's Agenda

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

Part 1

Q&A'S

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

Part 2

Q&A'S

Regulations/Guidelines

- **GxPs**
Systems should be suitable for intended use

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

- **EU Annex 11 to GMPs**
Defines requirements for software and computer systems in EU GMP regulated environments

- **PIC/S Good Practice Guide**
Has lots of good recommendations on using computers in regulated environments

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

- **No procedures are established to validate for its intended purpose the Microsoft Excel software** used in creating and maintaining nonconformance records, product return records, internal audit corrective records, or corrective action records**. (189)

- In addition, you continued to release products based on assay results generated by the **spreadsheet that have not been verified for accuracy** (W-237)

- **Spreadsheets** intended to check for outliers and calculate mean, SC, % CV, not validated (W-201)

Validate Spreadsheets

Ref: www.fdawarningletter.com

FDA Warning Letters

- Failure to validate computer software for its intended use according to an established protocol. For example; the Microsoft Excel **spreadsheet software program was not validated for formulation of reagents and was seen to give incorrect data** (W-125)

- Microsoft Excel **spreadsheet software** used manufacturing **has not been validated** for the purpose of generating a worksheet for formulation of reagents.

- **No documentation** was found to establish or verify **corrections** made to the program. (W-125)

Validate Spreadsheets

Ref: www.fdawarningletter.com

FDA Warning Letters

- "Your laboratory records did not include a record of all calculations performed in connection with laboratory tests as required by 21 CFR §211.194(a).

- For example, the notebook does not document reference to the spreadsheet calculation used to generate the results.

- Your SOP omits instructions to include in the notebook the reference to the spreadsheet calculation used to generate the results, as well as the raw data and calculations."

Record Spreadsheet Calculations

Ref: www.fdawarningletter.com (W-237)

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

EIR

- 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

Validation

- 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

EIR

- 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 ….

Integrity

- 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

European Medicines Agency GMP-Q&A

- Q: Which type of accuracy checks (Annex 11 p 6) are expected for use of spreadsheets?

- A: Data integrity should be ensured by suitably implemented and **risk assessed controls**.
  The calculations and the files should be secured in such a way that **formulations are not accidentally overwritten**.
  Accidental input of an inappropriate data type **should be prevented or result in an error message** (e.g. text in a numeric field and or a decimal format into integer field) - so called boundary checks are encouraged.

European Medicines Agency GMP-Q&A

- Q: Are there any specific considerations for the validation of spreadsheets?

- A: Validation according to paragraph 4 of Annex 11 is required at least for **Spread-sheets that contain custom code (e.g. Visual basic for applications**). Formulas or other types of algorithms should be verified for correctness..

Ref: EMA Website

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** environments with functions for Part 11, e.g., chromatographic data systems, LIMS etc

2. Use document management software with built-in Excel support and Part11/GxP functionality, (E.g., Agilent OpenLab)

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

4. Evaluate and use add-on software with more security and compliance functionality, e.g., e-audit trail, e-signatures
   Examples: e-Infotree from Cimcon, www.part11solutions.com, ExcelSafe from Ofnisystems, *www.ofnisystems.com/ExcelSafe*

Today's focus

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

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
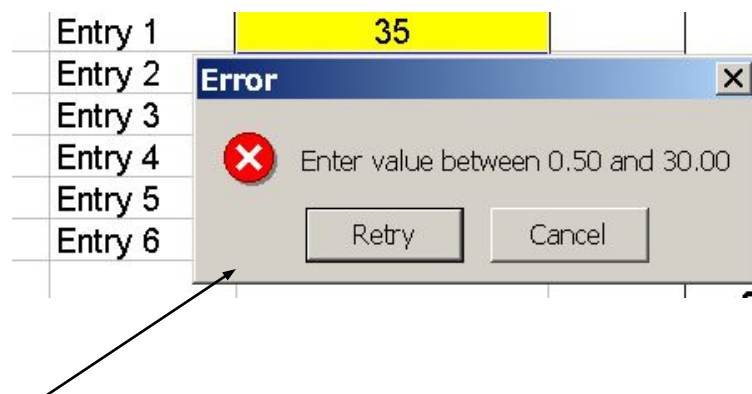
With VBA

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

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

   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

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 7, XP, VISTA)
3. If available, use secure server for storage of spreadsheets and access to spreadsheets
4. Maintain user lists with authorized access

What to Validate / What not to Validate

Not to Validate

- Excel software
- Standard calculations under normal conditions (GAMP Category 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)

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**

Should we Test Standard Excel Functions?

1. Standard functions used in normal operation range don't need to be verified (GAMP category 3)

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)

Recommendations from GAMP

- Document the purpose of the spreadsheet
- Verify that the correct calculations have been used, e.g., (a+b)*c can be easily mixed up with a + (b*c)
- Document formula
- Verify any cell links
- Protect the spreadsheet
- Strict access controls
- Validate data input of critical data
- Ensure integrity of electronic data

No need to verify accuracy of native functions
Ref: (GAMP 5, Page 294)

Excel Spreadsheet Validation from Beginning to End (1)

1. New spreadsheet proposed
2. Proposal approved
3. Establish validation team
4. Develop preliminary project plan
5. Interview anticipated user departments about use of the SS
6. Update project plan and distribute to QA and operation manager
7. Interview anticipated users for intended use and requirements
8. Interview anticipated users about required functions
9. Draft of requirement specifications
10. Conduct risk assessment
11. Qualify developer/supplier
12. Develop template for design specification and review
13. Develp and review design specification

# Excel Spreadsheet Validation from Beginning to End (2)

14.   Develop functional specification test plan

15.   Distribute test plan to test persons (user representatives)

16.   Test functional specifications

17.   Evaluate test results (and correct deficiencies, if there are any)

18.   Develop a list with anticipated users

19.   Distribute spreadsheet to anticipated users

20.   Install and document spreadsheet

21.   Test spreadsheet in the user's environment

22.   Add the spreadsheet to the company's spreadsheet data base

23.   Write the validation report

24.   Repeat tests from (21) every quarter

25.   Follow documented procedures for any changes and record changes in the change history

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., ExcelSafe, 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**
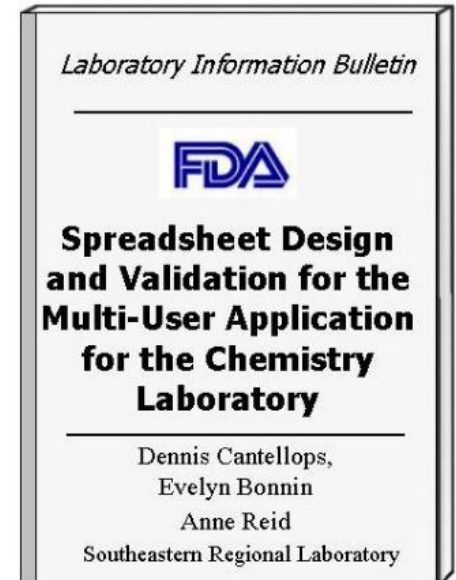3. Result: Changes can be reviewed and printed
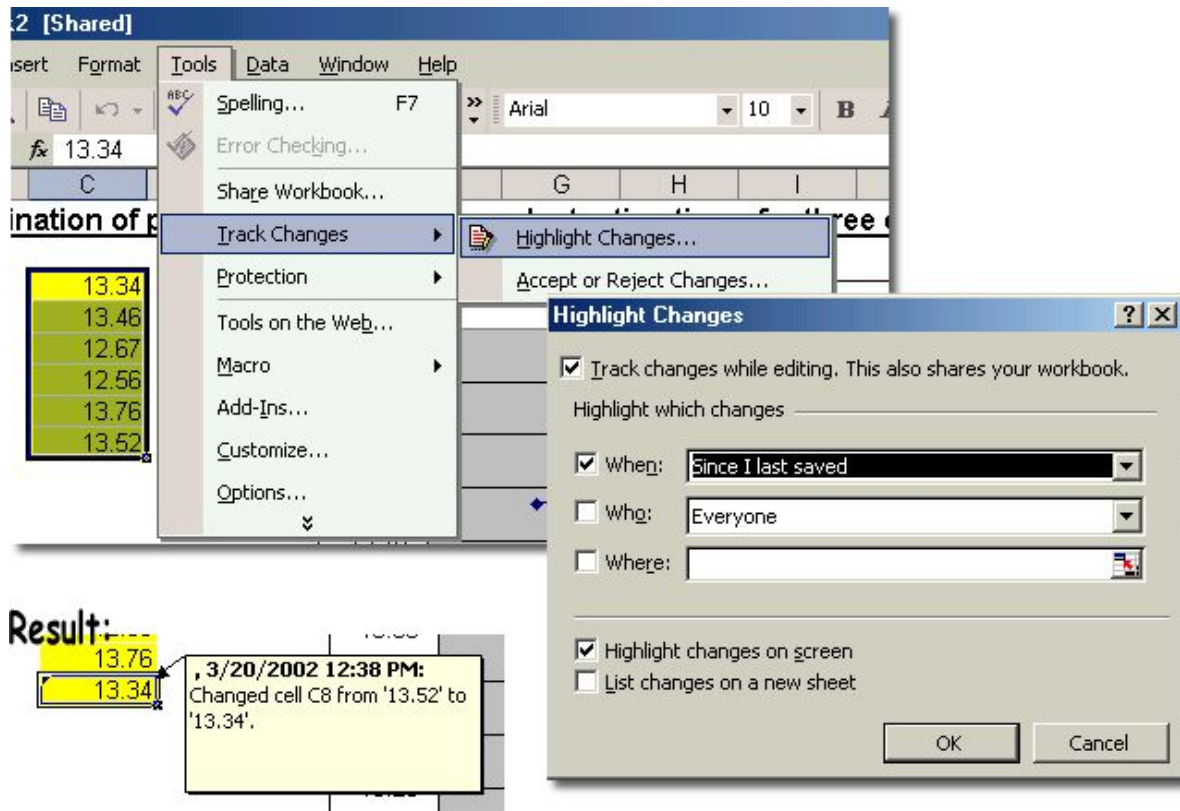
Multi-User Excel Spreadsheets in FDA Laboratories

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

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Evelyn Bonnin
Anne Reid
Southeastern Regional Laboratory

Single-User Excel Spreadsheets in FDA Laboratories

- 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)

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

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

Documentation for Part 11

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

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)
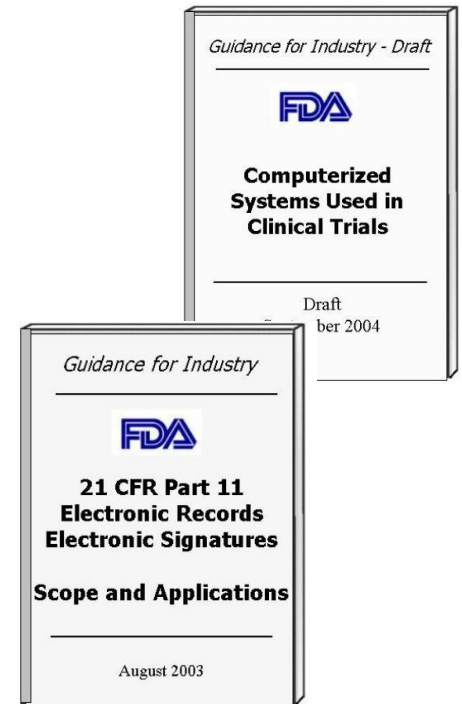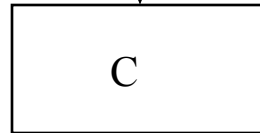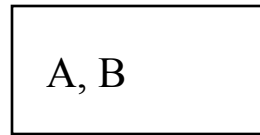
Example – Using Excel Template as Calculator

Paper
Raw data
Results

PC
Excel software
Calculates results

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

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

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

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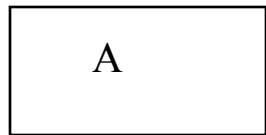Yes _x   No__
Impact on product quality
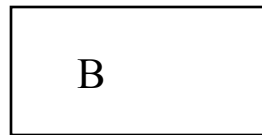High _x   Medium __   Low __   No __

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

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

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

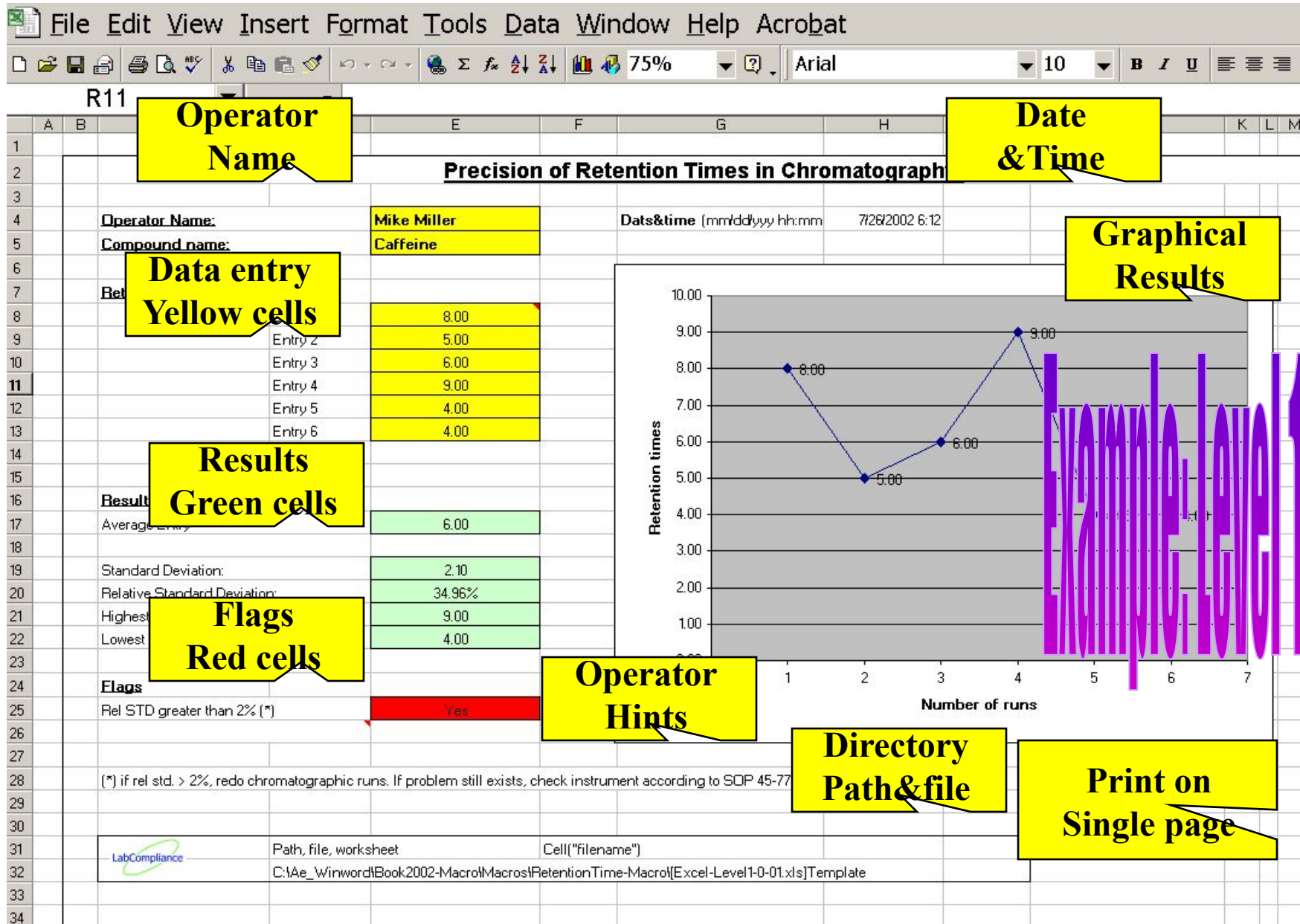**Records required by predicate rule**
No __   Explicit _x_   Implicit __
Regulated activity relies on e-records
Yes _x_   No __
Impact on product quality
High _x_   Medium __   Low __   No __

Disable Menu and Tool Bars and CTRL Keys

Start

Print

Exit

Date &Time

Operator name

Graphical Results

Data entry Yellow cells

Results Green cells

Flags Red cells

Operator Hints

Directory Path&file/vers.

Print on Single page

Precision of Retention Times in Chromatography - Level 3

Start Macro | Print | Close File

Name: **Ludwig Huber**
name: **Caffeine**

Date/time (m/d/y hh:mm): Sunday, October 19, 2003 --- 7:11:43 AM

Entry	Value
	3.50
	3.40
	3.55
Entry 4	3.45
Entry 5	3.60
Entry 6	3.47

Results
Average: 3.50

Standard Deviation: 0.07
Relative Standard Deviation: 2.05%
Highe: 3.60
Lowe: 3.40

Flags
Rel STD greater than 2% (*): Yes
Up or Down (**): No

(*) if rel std. > 2%, redo chromatographic runs. If problem still exists, check instrument accordi
(**) if yes, four out of five consecutive entries go either up or down. Check instrument accordi

LabCompliance | Path, file, worksheet | Cell("filename")
C:\Af_ppt\Videos\Macro-CD-Rev-2-00\Excel Spreadsheets - Macros\[Excel-Level3-Ver-1-00.xls]Temp

Retention times graph (3.65 to 3.35, Number of runs 1-5): 3.50, 3.40, 3.55, 3.45, 3.60

Example: Level 3

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