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

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## Introduction

Two Laboratory Information Bulletins (LIBs)* covering the design, testing, verification and validation of spreadsheets have been prepared. Part I covers the general principles of spreadsheet application to be employed by several users (multi-users). This document (Part II) covers the spreadsheets to be used by single-users. It includes the use and storage of single-user spreadsheet files, the design aspects of spreadsheets and the verification and validation documentation for reporting in a regulatory environment. The discussion pertains to applications of the Microsoft Excel spreadsheet program.

Due to the variability and complexity of sample analyses in FDA laboratories, analytical spreadsheet applications are often modified or created in actual time, as an analyst performs the analytical procedure.

This paper relates to a single-user spreadsheet which is intended to be used by a single analyst, its creator, at one specific point in time for one time use depending of the type (single-user template or module). The single user spreadsheet can take various forms, but in general it is a single workbook file which is relatively simple because it is based on uncomplicated formula construction and does not contain macros, color-coding, cells protection or instruction worksheets. These features are not needed when the spreadsheet is intended for personal use, since the developer knows how to identify the raw data, cell locations of formulas, data-entry cells and cell addresses.

The single user spreadsheet usually follows one of two basic options:

A) A single-user workbook file can be created from a pre-developed single user template, which can contain approved and protected FDA forms (e.g. forms 431, 431a, and nutrition sample transfer form) and worksheet examples to aid the analyst in undertaking the sample analysis with the spreadsheet. The single user template is installed in a shared network location for use by the analysts. After the single user template is opened, it is saved as a single-user workbook file in a designated folder on a personal drive for

personal use. The individual analyst can perform data entries and modifications to handle raw and secondary data. This single-user workbook file will increase in file size because the analyst will add the additional data including formula construction and additional formatting to complete the sample analyses.

B) Another way to implement the single-user workbook file is to develop it from an empty workbook i.e. the analyst opens an empty workbook with unpopulated worksheets (or opens a previously used version from the local drive for use in the development of the necessary worksheets). For this article we shall refer to this process as using a single user module. During the creation and data population (data-entry) stages of the single-user workbook files, the analyst uses the same formatting practices as if it was a hand-written worksheet. The creator should perform in-process verification of any formulas by manual calculations during the developmental stage of the workbook file. These verifications should be documented and the evidence of correct operation should be attached with the future workbook results, either in paper form or as a separate worksheet if the verification is performed electronically using one of the referenced auditing tools. After completion, but prior to data use or approval, a second analyst verifies the calculations and data integrity of the printed sample worksheet using the visible data and the formulas displayed by the auditing tools. Therefore, the degree of the verification depends on the module complexity.

In either of the two options mentioned, whether the single user workbook is created from a single user template or a single user module, the workbook file must not be transferred between the analysts. This is explained on section under “Managing Single-User Workbook Files”, page 14. In addition, a copy of the completed, verified and printed sample worksheet shall be maintained for documentation in the laboratory for future worksheet audits against the saved single user workbook file.

The Power Pak Utility-PUP v5.0 (1) mentioned in Part I (2), or the ABB Spreadsheet Specification and Reporting Tool (3), can be used to audit the single-user workbook file templates during the testing and verification stages. It is important that effective and appropriate principles and procedures be applied to all stages of producing analytical spreadsheets. At the design stage, such principles include design standards, clarity of formulas, documentation, and user-friendliness. Furthermore, when the basic principles of software engineering techniques are applied to the construction of spreadsheet models, many errors are reduced or eliminated.

**Notes:**

1. Excel documents are called workbook files. Each workbook is made up of individual spreadsheets called worksheets and sheets containing charts called chart sheets.
2. In summary “spreadsheet” is only really used as a generic term whereas “single-user template”, is the read only template, “single-user module” is the empty file ready for development and “single-user workbook”, is a saved analyst file (it can be created from either the template or a module).

Below there is a table describing the differences between the Single-User Template[1], Single-User Modules[2], Single-User Workbooks[3], and Multi-User application.

**Table 1** – Differences between analytical spreadsheets (Single-User Template[1], Single-User Modules[2], Single-User Workbooks[3], and Multi-User)

| Spreadsheet Attributes | Single [1] User Template | Single [2] User Module | Single [3] User Workbook | Multi-user |
|---|---|---|---|---|
| Created from empty spreadsheet | | ✓ | | |
| Designed for use by one analyst | ✓ | ✓ | ✓ | |
| Can be opened by more than one analyst | ✓ | ✓ | | ✓ |
| Can be populated by more than one analyst | | | | ✓ |
| May contain complex formulas | | | | ✓ |
| May contain macros | ✓ | | | ✓ |
| May contain color coded data-entry | ✓ | | ✓ | ✓ |
| Should protect cells, whenever possible | ✓ | | ✓ | ✓ |
| May contain instruction worksheets | ✓ | | ✓ | ✓ |
| May contain protected forms (e.g., 431 and 431a) | ✓ | | ✓ | ✓ |
| During population, formulas checked by calculator | | | ✓ | |
| Second analyst verifies raw data entry | | | ✓ | ✓ |
| Second analyst verifies calculations integrity | | | ✓ | |
| Electronic workbook file is saved | | | ✓ | ✓ |
| Contains unprotected worksheets | ✓ | ✓ | ✓ | |
| May insert worksheets | ✓ | ✓ | ✓ | |
| Needs validation documentation | ✓ | | | ✓ |
| Needs in-process verification of formulas during the population stage | | | ✓ | |
| Should verify data-entry | | | ✓ | ✓ |

**Notes:**

1) The Single User Template[1] and the Single User Module[2] only exist prior to use. Once they are opened and saved, they become a Single User Workbook[3]. The differences between single and multi-user spreadsheets are summarized in Table 1 above.
2) For single-user workbook files standard formulas (such as “Round” and statistical functions) need to be verified for accuracy by the creator and by the reviewer (second check analyst). For multi-user workbook file applications the standard formulas (such as “Round” and statistical functions) need to be verified for accuracy by the developer during the testing and validation of the application. After the validation the reviewer only needs to verify data-entry entered by the end user.

**Analytical Spreadsheets and Hand-Written Worksheets; a Comparison**

When only hand-written paper worksheets (e.g. FDA forms 431, 431a and calculation of results worksheets) are used, a hand electronic calculator is used to calculate sample results. Microsoft Excel single user workbook files can be created in a similar manner, as a simple reporting method, which includes an integrated calculator. For example, when using Excel to implement a simple calculation, the formula is entered into a cell, which will display the formula result. When using the paper or electronic process, the creator should perform in-process verification of formulas using an electronic calculator (hand electronic calculator or Windows Accessory calculator).

Single-user workbook templates should be kept very simple. For example, they may involve the FDA form 431 and its general continuation form 431a for describing the sample. The template may also include other worksheets to aid the analyst in the population of raw data forms (fill-in-the-blank form) and development of secondary data forms (calculations and results) including the option to insert worksheets to create personal formatting capabilities. The equation editor (Microsoft Equation v3.0) can be used to describe the formulas in the analytical procedure. We can visualize the spreadsheet worksheet as an integrated electronic calculator in the background of the worksheet.

In normal use, calculations are performed in the background of the spreadsheet, due to formulas inserted in the cells and the Excel formulas will reference other cells in the workbook to display the correct result. To aid the user (and the verifier) in the visualization and traceability of such formulas standard, Excel tools can give visual presentation (draws lines to the respective relative active cells) of the relationships between the cells that provide values to the formulas or the cells that depend on the formulas. Similar commands in the Auditing toolbar can locate the cells that provide data to the formula in the active cell and find the cells that depend on the value in the active cell.

It is important to mention that both systems (paper hand-written worksheets and analytical spreadsheets) are developed in a similar manner according to the FDA Laboratory Manual of Quality Policies for ORA Regulatory Laboratories, the Good Laboratory Practices Manual in conjunction with any FDA worksheet-training module. The analytical spreadsheet construction mimics the paper hand-written worksheet. Labels (sample number, method reference, description of formulas) and formulas are located in comparable places to where they are situated on the paper hand-written worksheets. Therefore, when viewed on screen or printed the analytical spreadsheet should look similar to the paper hand-written worksheet.

**Types of Single-User Workbook Files**

There are several ways to implement single-user workbooks:

a. *Exclusive use Single-user Template.* The analyst opens a read-only template file (usually saved as an XLT file), which may include protected forms (e.g. *FDA 431* and *FDA 431a* continuation sheet) and other forms verified by the creator of the single-

user template and approved by the management for sample documentation. This read-only template file should be installed in a shared or network drive. Also, this template is likely to contain unprotected forms to aid the analyst in the population and/or development of the analytical worksheets. Analysts can create raw data worksheets (fill-in-the-blank forms) and secondary data worksheets (calculation and results) for a particular analysis such as a USP drug assays or for a vitamin determination. This single-user template can vary in complexity depending on the number of tests required for completion of sample analysis. Once in use, this template would be saved with a unique name and would become a single-user workbook.

b. *Portion of work (*single-user module*).* The analyst creates a module for a specific type of analysis. Creation may begin from a blank workbook, or from a workbook already populated with data from another source. Examples of single-user modules include workbook files with data on content uniformity for a drug or the calculations required for various assays. Also, a single-user module can consist of one or a combination of the following:

   1) Raw data and secondary data worksheets including supporting documentation (system suitability results, instrument parameters, HPLC/GC chromatograms).
   2) Secondary data only combined with other forms (for example Microsoft Word or Excel fill-in-the-blanks forms). Once in use, this module would be saved with a unique name and would become a single-user workbook.

c. *Fill-in-the-blank form (with no formulas).* In this case, the analyst creates a workbook for a specific analysis: a fill-in-the-blank form with no formulas being used within the workbook. Usually these forms are used to enter hand-written raw data such as standard and sample weights, sample dilution factors and their aliquots and dilutions. The creator may use the workbook to simply create table headings and formatting.

d. *Fill-in-the-blank form with formulas.* In this case, the analyst creates a workbook for a specific analysis: a fill-in-the-blank form with formulas being used in the population of tables or associated worksheets. Usually these forms with formulas utilize the raw data (standard and sample weights, sample dilution factors and their aliquots and dilutions) which were hand-written on the fill-in-the-blank form with no formulas and then this form with formulas automatically calculates the results using standard Excel functions such as SUM, AVERAGE, STDEV etc.

An example familiar to FDA staff of an "*Exclusive use Single-user Template"* is the spreadsheet which includes forms FDA 431 and 431a, along with other forms used to aid the analyst to create or modify raw data and secondary data worksheets for specific assays. Single-user modules are also widely used in FDA laboratories and include a combination of one or more of Microsoft Office Programs such as Word, fill-in-the-blanks forms, Excel analytical applications and Excel fill-in-the-blanks forms.

**Good Laboratory Practice (GLP) Regulations**

The use of spreadsheets by FDA regulated establishments to judge the quality of a product is covered by cGMPs (4), GLP (5), regulations and ISO 17025 accreditation. The following are some of the requirements established by GLP regulations:

- **Configuration Management.**
- **Written Standard Operating Procedures (SOPs).**
- **Completeness of Data.**
- **Raw Data.**
- **Security.**
- **Training.**

**Note:** For more detail on the requirement definitions, see Part I (2) of this series.

**Quality Standards and Guidelines (See ISO/IEC 17025 Guideline)**

The "General Requirements for the Competence of Testing and Calibration Laboratories", (International Organization for Standardization ISO 17025) (6). Sections 4.3 Document Control, 4.12 Control of Records, and 5.10 Reporting the Results include several paragraphs on the manipulation of quality and technical records and the use of computers. For details, see Part I (2).

**General Spreadsheet Design (Single-user and Multi-User Spreadsheets)**

Spreadsheet structure is fundamentally similar to a computer program (7). Formula construction in a spreadsheet is essentially a form of computer programming. Therefore, it is important to apply basic software engineering techniques and quality assurance principles in the construction and use of spreadsheets. For spreadsheets this means the following:

- Following a structured and documented approach to design, develop, and specify the spreadsheet.
- Apply security principles to access the workbooks and data and the environment in which they are housed.
- Thoroughly test the spreadsheet applications: considering correct cell inputs-outputs, correct cell and worksheets links, user defined formulas.
- Fully document the above process using a comprehensive validation approach
- Use the spreadsheets in a controlled and consistent manner, operated and maintained by trained individuals, with appropriate procedures.
- Apply the principles of change control when spreadsheets are updated (multi-user applications and single-user template)

Despite the controls needed to validate a spreadsheet it is important to remember the goal of the spreadsheet and the flexibility the analysts may require in its routine use. A spreadsheet is

usually a set of worksheets and macro sheets designed to evaluate and organize data or to solve a particular problem (8). Such a solution should meet two design objectives:

- ***Guaranteed correctness.*** If you cannot guarantee that your solution always yields the right answers, it is not effective and is dangerous. Design your solution to make errors immediately apparent.
- ***Adaptability***. Most likely, the task you want your solution to perform will change with time. Design the solution so that it is flexible and can be easily modified.

**Note:** For more detail on "General Spreadsheet Design", see Part I (2).

**Safety Design Procedures (Single and Multi-User Spreadsheets)**

The following are safety features for developing an analytical spreadsheet (9):

- **Separate primary (raw data) from secondary data.** Identify and separate all raw data (Fig. 3) and secondary data (Fig. 4) from the analytical procedure. Provide a separate sheet for the raw data. All the calculations, results, and graphs should be in the Secondary Sheets 2, 3, etc. If needed, add sheets with *Insert → Worksheet*. Protect the secondary sheets (see below). For very small or simple spreadsheets the separation can be done using clearly headed tables for raw data and secondary data.

- **Use drop-down-lists whenever possible.** This feature restricts the user to valid entries, when they are known beforehand. It is created by the sequence: *Data → Validation →* Choose *"Setting"* Tab → in *"Allow"* choose *"List"* → in *"Source"*. Give the cell range where the allowed choices will be written. A message will be activated when the cell is addressed. For setting up the message, select *Data → Validation →* choose *Input Message →* and enter short instructions in the window *Title*. Optionally, choose: *Error Alert* and write the correction instructions in the window: *Error Message*. For example, in single-user the drop-down-list can be used for titles in front of the continuation sheet (431a). Example of titles are; Raw Data for Assay, Assay Calculation and Results, Content Uniformity Raw Data, Content Uniformity Calculations and Results, Dissolution Test Raw Data, Dissolution Test Calculations and Results, etc.. The continuation sheet (431a) is printed with the title for each analysis performed and in the back of the continuation sheet the raw-data or the secondary data worksheet is printed.

- **Introduce the units in all appropriate cells.** This feature allows creation of new number formats. For example, the units (e.g. mg/mL) used in the analytical methods can be added by selecting from the Excel main menu bar: *Format → Format Cells →* Choose *"Number" →* Choose *Category "Custom" →:* Type: *General*. In the window where General is typed, type the entry: "mg/mL" just after General and click *OK*.

- **Format numbers.** Use the *Round* function and specify the number of decimal places to which the value should be rounded-off. For example, a formula to calculate an average with two decimal places would be:

  =ROUND(AVERAGE(Range), 2)

  Never round to less than a total of five places (including decimal places). For example, it is permissible to round the average to 87.333 but not to 87.33. This criterion is used for rounding-off the values of intermediate calculations. The weights and chromatographic peak areas should be reported with all their digits. The final results should be rounded to the least significant digit (LSD), using the appropriate official guidance. For example, the USP 28 / NF 23 page 4 provides the following rules:

  - ✓ Establish the position of the LSD.
  - ✓ If the digit to the right of the LSD is less than 5, eliminate all remaining digits after the LSD.
  - ✓ If the next digit is larger than or equal to 5, increase the LSD by one and eliminate all the digits beyond the LSD.

  The calculations always must be done with an excess of digits over the significant ones. Rounding off should be done only on the final results, intermediate data steps should be left without rounding and Excel should then be allowed to managed the calculation to its maximum available decimal places (this is generally far more accurate than hand calculators). *Excel* will not automatically round-off. The Round function should be included in the formula verification where rounding is performed. When considering the impact of rounding on calculations, always remain pragmatic and refer back to the assay accuracy and a comparison to a paper based method. Often calculators and manual calculation will give a different result to one performed by Excel as calculators can not handle as many significant figures as Excel can.

- **Calculations.** In the calculation and results worksheet (secondary data, attachment B3), each result should be based on the results of the previous calculation so that the calculations progresses through the worksheet from top to bottom.

- **Statistics.** Use the following *Excel* formulas when necessary (use *Excel 2002* Office Assistant for *Excel 2002* formula definitions):

  - ✓ **Equations for calculating trendlines**

    The equation for the straight line: $y = mx + b$
    where:
    m is the slope
    b is the intercept

Once the slope and intercept are known, if one of the dependent variables is known, a value for the other dependent variable x' or y' can be calculated through the formulas:

$$x' = \frac{(y - b)}{m} \qquad y' = mx + b$$

Example
Use: =(Sample Response - INTERCEPT)/SLOPE.
This formula gives the sample concentration as found by regression.

- ✓ **Equation for calculating the intercept**

  Use: =INTERCEPT(Response range of cells, Concentration range of cells). For example, INTERCEPT(A1:A6, B1:B6).

- ✓ **Equation for calculating the slope**

  Use: =SLOPE(Response range of cells, Concentration range of cells). For example, SLOPE(A1:A6, B1:B6).

- ✓ **Equation for calculating the correlation coefficient**

  Use: =CORREL(Concentration range of cells, Response range of cells). This is the correlation coefficient. For example, CORREL(A1:A6, B1:B6).

- ✓ **Equation for calculating the average**

  Use: =AVERAGE(Range of cells). For example, AVERAGE(A1:A6).

- ✓ **Equation for calculating the standard deviation**

  Use: =STDEV(Range of cells).

  For example, STDEV(A1:A6).

  For the % RSD: =(STDEV/AVERAGE)*100.

**Note:** For more detail on "Safety Design Procedures", see Part I (2) of this series.

**Design and Verification/Validation of Analyst Single-user Templates and Workbooks**

The design (follow above sections "General Spreadsheet Design and Safety Design Procedures") of the single-user workbook must be performed by an analyst experienced in the used of

analytical spreadsheets. For example, FDA forms 431 and 431a are developed and followed by any other forms that a particular laboratory section may need. The forms or worksheets to be included in this workbook file are selected by the creators (or analysts) and management of the particular laboratory section. Second, after compilation, the protected and read-only workbook file is installed as a template (XLT) in a shared or network drive with controlled access. In addition, this workbook file is flexible, allowing the analyst to create raw data (fill-in-the-blank forms) and secondary data (calculation and results) worksheets for a particular analysis such as a drug or vitamin assay. Also, the worksheet examples that are included in the template can be modified as per analyst needs.

Therefore, when the analyst opens this protected and read-only single-user template from the shared or network drive the analyst must save the template in a designated protected folder in their private network drive directory with the sample number and abbreviated product name. From this stage on, the analyst will personalize this single-user workbook with new sample description data in the FDA forms (431, 431a) including new data from the analytical method in the subsequent worksheets.

Protect cells when developing a form or formulas that should not change. Unprotect data-entry cells and color code for easy identification. Apply protection as follows: By default, *Excel* has all cells locked. First, unlock all data-entry cells in each worksheet by using the *Format* → *Cells* → *Protection* tab and remove both checkmarks. Next, apply protection to each of **the other** worksheets in the workbook file by selecting from the *Excel* main menu bar: *Tools* → *Protection* → *Protect Sheet* and, optionally, entering a password. This protects the secondary calculated data from unintentional changes.

The verification or validation of the single-user template is performed according to the complexity of the workbook file. This may involve following the advice in this article or for more complex spreadsheets consider the Validation for Multi-User Applications in Part I (2). Follow the instructions below:

- If the template contains only protected forms and example worksheets, perform 100% verification.
- If the template contains protected formulas, validation should be performed (see multi-user validation procedure, Part I) and appropriate documentation produced. The workbook template can include examples of unprotected analytical worksheets that demonstrate the use of *Excel* formulas and functions.

Figure 1a we can observe an analyst spreadsheet flow chart displaying the sequence of events as the worksheets are developed. Figure 1b displays a brief description of the differences between the single-user template and the single-user module. Figures 2, 3, and 4 show examples of the analyst spreadsheet (single-user) which include the “Analyst Worksheet” form FDA 431 (Fig. 2) and the raw data worksheet for an assay of Baclofen tablets (Fig. 3). Also, Figure 2 (FDA form 431) item “10. Summary of Analysis” under “Notes:” includes the software name and version (Microsoft Excel 2002) along with any upgrades or add-ins used to create the workbook file. Figure 4 shows a secondary data worksheet (calculation and results), which summarizes the raw

data for the calculations and results. Figure 5 shows an Analyst Spreadsheet / Worksheet Review which is used by the check analyst to review the completed printed worksheets.

**How to Use the Single-User Template**

The analyst will open a single-user template previously verified or validated. FDA forms 431 and 431a used for sample description along with other necessary forms to describe the sample are completed. The analyst will identify the first method to be used for the sample analysis along with the raw data and secondary data from the analytical procedure. If the template does not include the forms for raw data and secondary data (calculations and results) the analyst proceeds to create them following the formatting properties identified in the template. Then save the file template to create a single-user workbook in a designated protected folder located in a network drive for personal use, with the sample number and abbreviated product name.

The analyst workbook files should flow logically with raw data first followed by the secondary data (calculation and results) plus system suitability results if a liquid or gas chromatographic assay was performed. All steps should be followed in a chronological order. A logical progression diminishes confusion when a second analyst is checking the workbook file.

Verification of data integrity, raw data and calculation of results (secondary data) are in-process activities performed concurrently with the spreadsheet population. With single-user workbook files, it is seldom necessary to apply color-coding or cell protection. Specific instructions might be useful for seldom-used worksheets. On single-user templates, official FDA forms are protected and data-entry cells are color coded along with any specific raw data and secondary data worksheets for a particular analysis. Therefore, when analysts use a template with protected FDA forms and containing protected worksheets for any previously identified sample analysis (for example assay or dissolution test), and if other analyses are need to be included in the workbook file, the creation of additional raw data and secondary data worksheets do not need to apply color-coding or cell protection because the creator knows where the formulas and data-entry cells are located.

Manually verify the calculations and results reported on the spreadsheet. This in-process verification must initially be done by the spreadsheet creator, then by the check analyst who verifies the calculations and sample integrity. The spreadsheet creator should consider the impact of rounding in the manual calculation, and attempt to minimize the chance of minor numerical discrepancies due to manual calculation rounding.

After completion, any unused worksheet examples and dummy data included in the template should be deleted, maintaining only the data necessary for regulatory purposes.

**Design and Verification of Single-user Modules**

Single-user modules are the most commonly used form of spreadsheet in FDA laboratories. Analysts should follow the guidance given above in “General Spreadsheet Design and Safety Design Procedures” for the design of the single-user modules. This type of workbook file is

created if no other spreadsheet application (single-user template or validated multi-user application) is available for the sample calculations of the results. In this scenario, the analyst reads the method, identifies the raw and secondary data (Figures 3 and 4), opens a blank workbook (spreadsheet) and creates the module, which may consist of 1 or more worksheets. The analyst proceeds to create any raw data (fill-in-the-blank-form) and secondary data (calculation and results) worksheets for a specific assay determination. When the raw data (fill-in-the-blank-form, see figure 3) is completed, is it printed, and the analyst, in this example, proceeds to weigh the standard and sample (hand written on the created fill-in-the-blank-form) following the analytical procedure. After completion of the assay, the analyst completes the secondary data worksheet. The standard and sample weights and dilution factor, which are in the raw data worksheet, are entered in the secondary data worksheet to calculate the results.

The verification of the single-user module is performed according to the complexity, the risk or impact the results have on product quality and the level of customization of the workbook file, following the section below "Verification of Single-User Workbooks Files".

When generating a single-user module from a workbook used in a previous analysis, verify all compound names, data and values pertinent to the current sample by using the *Edit → Replace* to pick up the elements needed to be verified or changed. This verification diminishes the chances of carrying over compound names or data from previous sample assays.

The single-user workbook files (templates/modules) should be developed and formatted according to the FDA Laboratory Manual of Quality Policies for ORA Regulatory Laboratories, the Good Laboratory Practices Manual in conjunction with any FDA worksheet training modules. The above sources should be consulted if additional information is required for the development of the single-user workbook files.

**Spreadsheet Verification**

Verification is defined as "The process of evaluating the spreadsheet application for consistency and correctness of the software at each stage and between each stage of the development life cycle to ensure compliance with the analytical method. Verification activities are in-process activities (testing and measurement) performed concurrently with spreadsheet (workbook file) development and population".

When constructing the single-user workbook, the creator performs in-process testing. Then, a second analyst verifies the completed printed report. A copy of the completed printed report is maintained for future audits. The electronic workbook file should be reviewed against the completed printed sample report copy, then maintained, preserved and controlled for future audits. The electronic workbook file and validation documentation are kept for future auditing. For more detail on "Spreadsheet Verification and Validation; a Comparison", see Part I (2).

**Verification of Single-User Workbook Files** (Figures 2, 3 and 4)

Any single-user workbook file that will be independently and 100% re-verified by a second analyst, team leader, supervisor, etc. does not require validation documentation. The printed report is the official regulatory document. The single-user workbook file (templates or modules) normally is very simple, contains fill-in-the-blank forms and no macros, and has very easy formula construction. In addition, the creator performs in-process verification of the formulas by manual calculations during the development stage of the workbook file. After completion, a second analyst verifies the calculations and the sample integrity of the printed worksheets. A copy of the completed verified printed sample worksheets should be maintained as documented evidence in the laboratory for future audits against the saved workbook file. The workbook file is saved for future audits against the finished printed sample worksheets. Care is needed to ensure unique identification and naming of both paper worksheets and electronic workbook to ensure they can be compared by an auditor.

**Spreadsheet Security, Storage and Use**

Each analyst must maintain a protected folder in a secure network drive for the storage of all completed single-user workbook files. The use of network drives allows centralized backup of all files and ensures backup routines are performed regularly and in a controlled manner. Back-up routines are normally managed centrally under an appropriate IT procedure. The access to the analyst folder must be granted only to those analysts that will maintain the workbook files such as the supervisor or other authorized personnel. These personnel should have appropriate training records to confirm they understand the processes for use and maintenance of the workbook files.

The analyst can not re-use any completed filled-in spreadsheets stored in the protected folder for subsequent analyses. The analyst can use an example template of a completed sample file for a similar sample under a different sample file number in a local or different folder.

Under FDA's internal policy, after one year, the completed single-user workbooks are removed and archived in a protected location. Other organization should have their own policy on archiving electronic files that ensure all data is adequately protected throughout its required lifetime.

**On-going Control of the Single-User Workbook**

When the single-user workbook files are verified, they should be preserved, controlled and maintained. These controls are fundamental to the operation of the equipment and process in a regulatory environment. Control of supporting systems for software and computerized systems include (10):

- Preventive maintenance.
- Environmental control.
- Performance monitoring.
- Backup.

- Recovery.
- Security controls
- Training.

**Note:** For more detail on on-going control consider the guidance given in Part I (2).

**Managing Single-User Workbook Files**

Single-user workbook files should not be transferred among analysts because the creator is the only person who knows how the workbook file was created (where text, formulas, data-entry cells are located). In addition, the level of expertise using electronic spreadsheets varies among analysts. For example, some analysts use more formatting or more complex formula constructions than others. Because single-user workbook files do not include security, instructions for the user or color coding for data-entry, other users may not know where data-entry cells or formulas are located. Therefore, someone who did not author the spreadsheet might inadvertently modify the workbook file in a way that complicates the operation and introduces errors. If many analysts introduce changes to the same workbook file, the file might become a "spaghetti spreadsheet", which is very difficult to verify or follow by others.

It is important to mention that a verified and management approved read-only single-user template should be installed on a shared drive. In our example this single-user template would include protected FDA forms 431 and 431a (protected color coded data-entry cells containing no data from previous samples) and other forms that analysts must use. Also, the single-user template should include worksheet examples to help analysts prepare sample worksheets. During the implementation phase, all analysts should be trained on how to use this approved template. Analysts should be trained on the templates drive location, how to open and close the file and where to save it. In addition, training should cover how to format the workbook files. Formatting is very important because if all analysts used similar formatting properties, the analytical worksheets will look similar which makes the worksheets easier to review as well as easier to detect errors. Another advantage is that the time to review the workbook will be less due to the same formatting properties used among all analysts. Also, if a validated multi-user application (e.g. dissolution test, content uniformity, FAME calculations, regression analysis, etc.) is available in the laboratory, this multi-user application should be used, printed, and added to the printed single-user worksheets for the completion of the sample.

**Summary**

Currently, spreadsheets for analytical applications such as the single-user workbook files are widely used in FDA analytical laboratories, including other laboratory areas such as microbiology. For these reasons, Excel workbook file applications need to be standardized within all FDA laboratories through standard operation procedures (SOPs) to minimize design and verification discrepancies. Basic principles of software engineering techniques must be applied to construction of spreadsheet applications. If spreadsheet applications are used without proper control (SOPs, training), the operation may go out of control, creating the potential for serious errors.

Single-user templates to be used for more than one analyst should be designed by experienced analysts and verified and approved by the creators, analysts and project managers. After the single-user template is approved, the read-only template is installed in a shared drive. A read-only single-user template should include protected forms and should include worksheet examples to help analysts prepare sample analysis worksheets controlling the homogeneity of worksheet formatting among different analysts.

Single-user modules are widely used in FDA laboratories. This type of workbook file is created if no other spreadsheet application (single-user template or validated multi-user application, Part I (2)) is available for the sample calculations of the results. In this scenario, the analyst reads the method, identifies the raw and secondary data, opens a blank workbook (spreadsheet) and creates the module, which may consist of one or more worksheets. A saved module from a previous analysis developed by the same creator can be used for the development of the raw and secondary data of the new analysis as long as the necessary precautions are taken to ensure that no old previous data are used with the new analysis.

A *single-user* workbook file (whether created from a template or module), which is only used by its creator, needs in-process verification by the creator. A copy of the completed sample report should be maintained and filed for future audits. After completion, the printed sample report needs to be checked by a second analyst to verify the formulas and sample integrity. In addition, the completed printed sample report should be checked against the maintained workbook file. A copy of the completed sample report should be maintained in the laboratory along with any associated instrument files and Excel workbook files, for future audits. Workbook files need to be saved, maintained, preserved and controlled for future audits against the printed sample report. Therefore, this document is a hybrid system, based on electronic and paper records. For example, when a workbook file is completed and printed by the original analyst and verified by the second analyst, the verified printed sample worksheets are used for regulatory documentation and not the electronic workbook file, which is saved and maintained in the laboratory where the sample analysis was performed. This saved workbook file should be made available for future audits against the completed printed worksheets. (This procedure applies to the single-user workbooks as well as the multi-user applications, which was described in Part I (2)).

Each laboratory must train analysts to design and verify single-user spreadsheets. Trained analysts can, in turn, train other analysts in how to use single-user spreadsheets. The advantage of training analysts in creating spreadsheet applications is definitely positive for the FDA, as demonstrated by the Atlanta Center for Nutrient Analysis (ACNA), in which all analysts are using *single-user* spreadsheets as well as multi-user applications. All analysts cooperate to improve *multi-user* applications and *single-user* workbook files. Standardization of ACNA analytical spreadsheets improved reports and saved considerable analyst time. The authors currently maintain and upgrade the multi-user applications (method changes, errors, method reference changes and improvement of the instructions for the users as requested by the analysts) and revalidations.

Management commitment is needed in order to implement policies and SOPs necessary for laboratory accreditation. Implementing controls over the design and development of analytical spreadsheets (such as the single-user as well as multi-user) applications serves to protect the integrity of data reporting and offers assurance regarding the usefulness of the information generated by the applications. We found that spreadsheet error rates are consistent with error rates found in other human activities (speech, typing, programming, driving, industrial accidents, even commercial aircraft disasters) (13). Overconfidence tends to blind people of the need to take steps to reduce risk. In "spreadsheeting", formal testing and adherence to tedious disciplines (such as training and SOPs) can save time and avoid errors. Ability to find errors instills confidence.

In addition, because single-user spreadsheets are a hybrid system (first the electronic file and last the completed printed sample report which is use for regulatory documentation) the completed Excel workbook file can be converted to a PDF file using Adobe Acrobat Writer or Distiller in which this file can be used electronically within the agency. Another approach to use the single-user workbook file is to add extra security, such as audit trails, and true electronic signatures which can be implemented by software and services such as that available from the company Wimmer Systems (24), for example:

- For single-user workbook files the audit trails would allow full traceability of the analyst's development process, aiding in the verification activities.
- The use of true electronic signatures would remove the need for paper output from the system and a paperless business flow can be designed.
- It is important to mention that multi-user analytical application files (2) can be used with these types of software, adding extra security, audit trails, and true electronic signatures and ease the validation burden on each spreadsheet as the additional security removes the need for repeated validation around the spreadsheets security and audit trail capability.

In summary the use of spreadsheets (single-user template and module) is a very helpful tool for data-organization, data-entry and data-calculations. We hope that this LIB serves as a tool to increase the knowledge for beginners as well as advance regular users and open many windows to continue research and learn more on spreadsheet based analytical applications. As new software technology continues to increase in sophistication, chemists in US FDA need to maintain their high level of expertise in the development of analytical spreadsheet applications, which will save time and reduce errors.

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**Note:** For detail on references 11 to 27 see Part I (2) of this study under "Literature review".

## Additional Useful Information

1. **Spreadsheet Research** (SSR) (1997b) is a repository for research on spreadsheet development, testing, use, and technology. The Web site (http://panko.cba.hawaii.edu/) includes the research on Human Error, especially Spreadsheet Error. Dr. Raymond Panko (http://panko.net/), from the University of Hawaii, Honolulu.

2. **The spreadsheet validation Web Site** (www.spreadsheetvalidation.com) is a complete location for understanding and solving your spreadsheet validation concerns and hosted by ABB Process Solutions. Wimmer Systems (www.wimmersystems.com) also includes many references about the latest news on spreadsheet validation issues, including Part 11 implementation on electronic spreadsheet applications.

3. **Laboratory Compliance Web** site (http://www.labcompliance.com), maintained by Huber, Ludwig, Ph.D, is private organization that provides the regulated Bio/Pharmaceutical industry with information on how to improve quality and comply with FDA and other regulations. The information is provided through, Books, videos on CD, reference papers for basic understanding of regulations, quality principles and standards and guidelines, interactive on-line audio seminars with extensive hand-outs to provide information and tools for specific topics, free Newsletter to keep visitors up-to-date with ever changing regulations, links to other internet sites, e.g., FDA and other authorities. Efficient tools like SOPs, checklists and examples for convenient cost-effective implementation. While some information is available for free, for example the newsletter, others are available for a fee. Also, a Users Club is available to members which can access protected sites and download more than 300 documents. They include selected SOPs and other compliance tools but also information that is not available otherwise, e.g., interviews, video clips and presentations with FDA officials.

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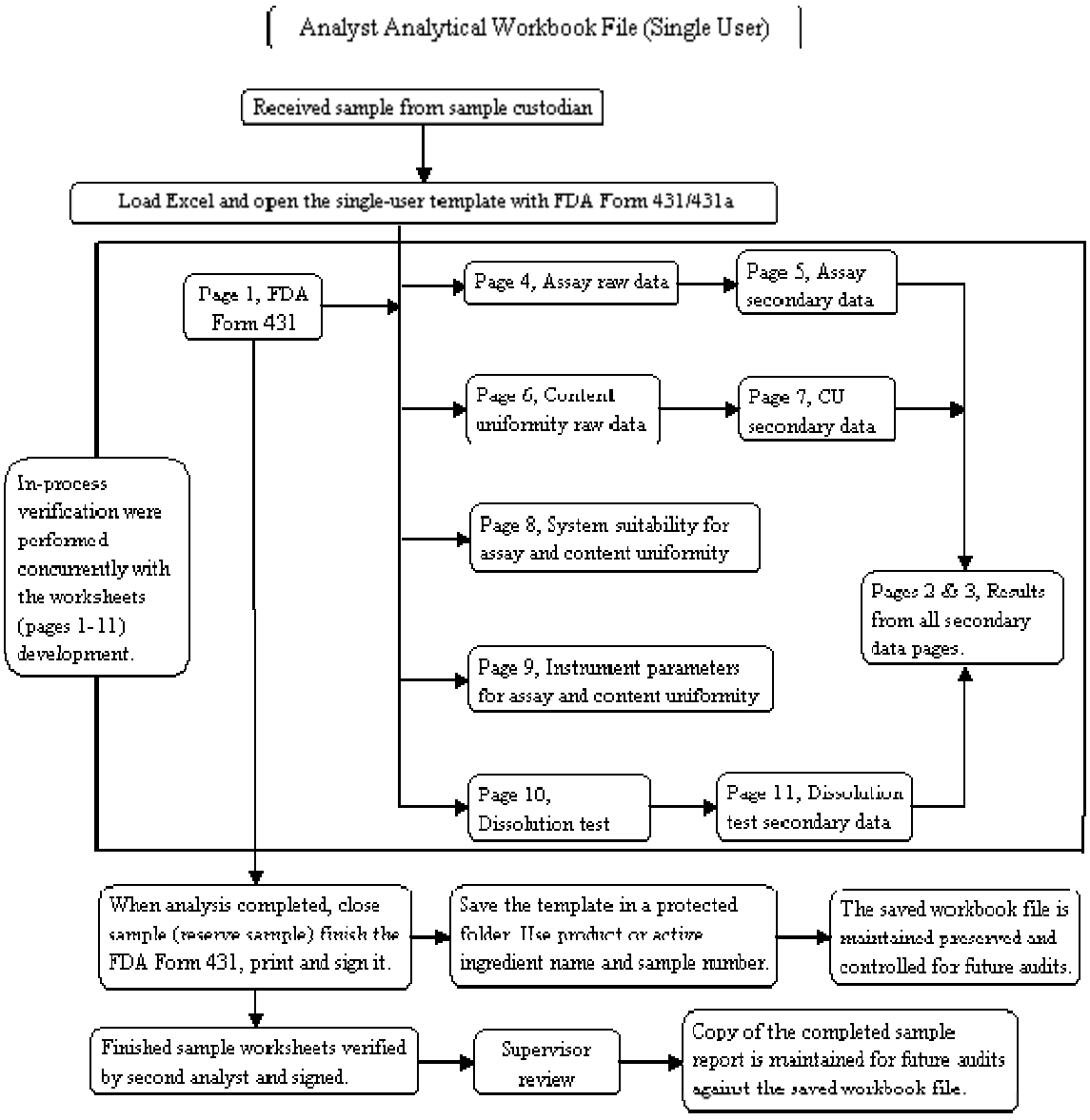



**Figure 1a.** Flow chart for an Excel Single-user template used in the drug lab, containing eleven worksheets for the analytical report / results and documentation in a regulatory environment (assay, uniformity of dosage units, dissolution test, system suitability, etc.). This workbook template can be adapted to other drug analysis samples, maintaining the original file unchanged. The sequence of the worksheet pages numbers (1 to 11) follows a logical organization for the completion of sample analysis.

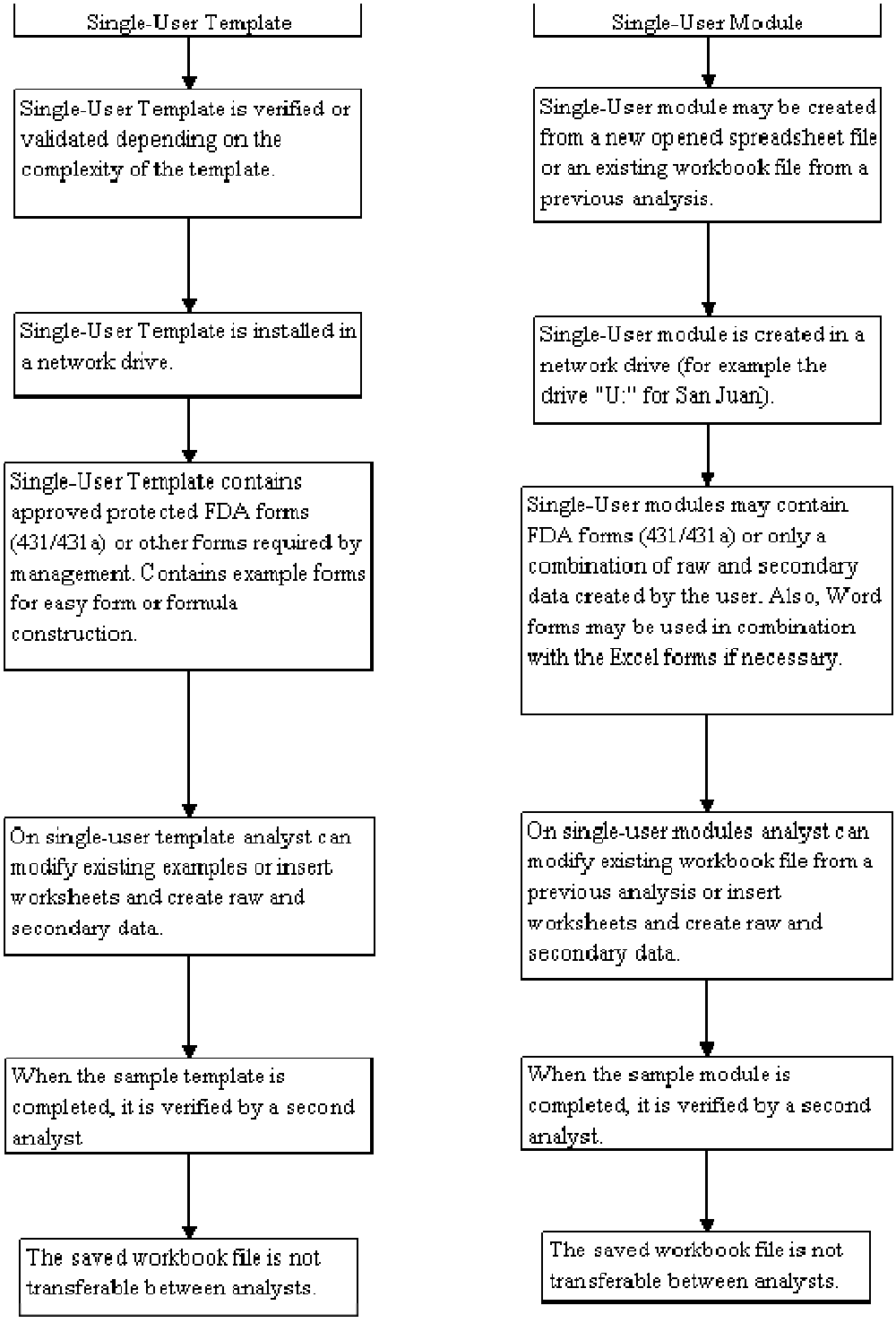



**Figure 1b.** A brief description flow chart of the differences between the single-user template and single-user module, both become single-user workbook files when saved.

Flag **Periodic Survey 02**

| **Analyst Worksheet** | 1. Product: Baclofen Tablets | | 2. Sample Number: **123456** |
|---|---|---|---|
| 3. Seals: ☐ None ☑ Intact ☐ Broken | 4. Date Rec'd: 7/12/02 | 5. Received From: Dexter Smith | 6. District or Laboratory: SRL |

7. Description of Sample

| 8. Net Contents | | 9. Labeling |
|---|---|---|
| ☐ Not Applicable | Declared/Unit 100 Tabs. | Original (s) Submitted |
| ☑ Not Determined | Amount Found | Copies Submitted ☐ None |
| Units Examined | % of Declared | |

10. Summary of Analysis

**Container:** Matches description on CR-FDA Form 464

**Labeling:** Matches description on CR-FDA Form 464

**Code:** "XXXX Jan 00" NDC 0364-2312-01

**Product:** Matches description on CR-FDA Form 464

**Method:** Baclofen Tablets, USP 23, p. 163 & 5th Supplement, p. 3383

**Analysis:** Assay, Identification, Dissolution <711>, and Uniformity of Dosage Units <905>

**Results:** **Assay Determination**

Found: It contains, 9.79 mg / Tab Baclofen or 97.9% of Declared

**Limit:** 90.0% to 110.0%

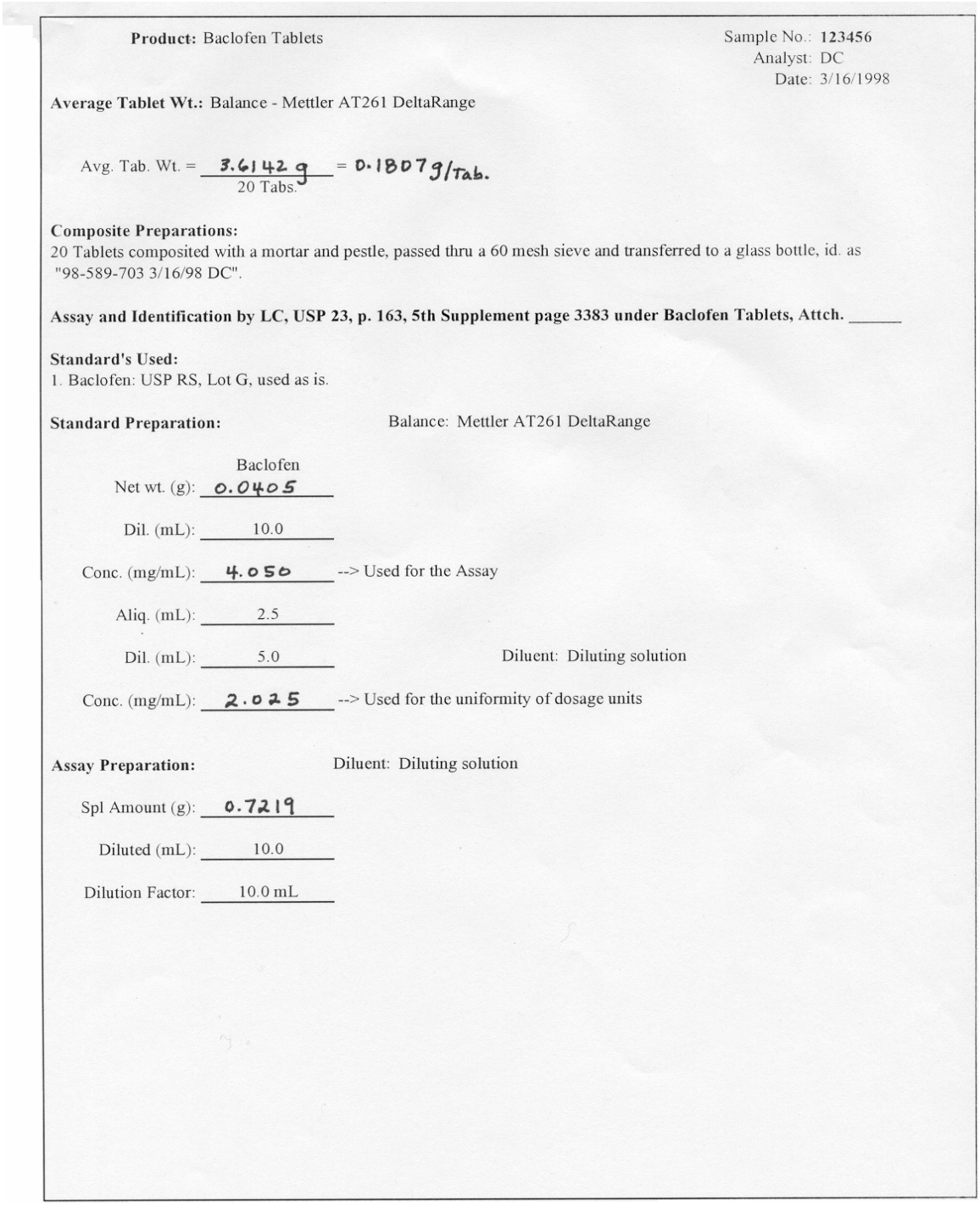
**Notes:**
1. Microsoft Excel 2002 computerized spreadsheet program was used to developed this worksheet application.
2. Sample was kept in a locked cabinet while not analyzed.

11. Reserve Sample

| 12. a. Analyst Signature ☐ Broken Seal | **13. Work - Sheet Check** | a. By |
|---|---|---|
| b. | | b. Date |
| c. | 14. Date Reported: 7/16/2002 | |

**Form FDA 431** Attachment (s) Page 1 of Pages

**Figure 2.** The Single-User Analyst Spreadsheet Form FDA 431. This workbook file is used in the Drug Laboratory.



**Product:** Baclofen Tablets

Sample No.: **123456**
Analyst: DC
Date: 3/16/1998

**Average Tablet Wt.:** Balance - Mettler AT261 DeltaRange

Avg. Tab. Wt. = 3.6142 g / 20 Tabs. = 0.1807 g/Tab.

**Composite Preparations:**
20 Tablets composited with a mortar and pestle, passed thru a 60 mesh sieve and transferred to a glass bottle, id. as "98-589-703 3/16/98 DC".

**Assay and Identification by LC, USP 23, p. 163, 5th Supplement page 3383 under Baclofen Tablets, Attch. _____**

**Standard's Used:**
1. Baclofen: USP RS, Lot G, used as is.

**Standard Preparation:** Balance: Mettler AT261 DeltaRange

| | Baclofen | |
|---|---|---|
| Net wt. (g): | 0.0405 | |
| Dil. (mL): | 10.0 | |
| Conc. (mg/mL): | 4.050 | --> Used for the Assay |
| Aliq. (mL): | 2.5 | |
| Dil. (mL): | 5.0 | Diluent: Diluting solution |
| Conc. (mg/mL): | 2.025 | --> Used for the uniformity of dosage units |

**Assay Preparation:** Diluent: Diluting solution

| | | |
|---|---|---|
| Spl Amount (g): | 0.7219 | |
| Diluted (mL): | 10.0 | |
| Dilution Factor: | 10.0 mL | |

**Figure 3.** Raw data worksheet. This form is used after the analyst has identified all the raw data. It is printed and used as a fill-in-the-blanks-form. When this worksheet is printed, the analyst proceeds to enter data in the empty blanks by hand writing.

**Product:** Baclofen Tablets
Declaration: 10 mg Baclofen

Sample No.: **123456**
Analyst: DC
Date: 7/16/02

**Assay and Identification by LC, USP 23, p. 163, 5th Supplement page 3383 under Baclofen Tablets, Attch. _____**

LC Data - See Attach. _____ Response = **height**

| Sample | | | Standard | | |
|---|---|---|---|---|---|
| **Run #** | **RT** | **Peak Response** | **Run #** | **RT** | **Peak Response** |
| 168 | 5.00 | 900284 | 167 | 4.99 | 927315 |
| | | | 173 | 4.97 | 938094 |
| | | | Avg. (2) | 4.98 | 932704.5 |

**Sample determination for Baclofen:**

Spl. Wt.: 0.7219 g
Avg. Tab. Wt.: 0.1807 g/Tab.

Dil. Factor: 10.0 mL
Wkg. Std. Conc.: 4.05 mg/mL

Formula used for Baclofen:

$$\text{mg Baclofen per Tab.} = \frac{\text{Spl. response}}{\text{Std. response}} \text{ x } \frac{\text{Std., mg/mL}}{\text{Spl. Wt., g}} \text{ x Dilution Factor, mL x Avg. Tab. Wt., g/Tab.}$$

Baclofen found = 9.79 mg/Tab.

$$\text{\% of Declared} = \frac{\text{Amount Found}}{\text{Amount Declared}} \text{ x } 100$$

% of Declared = 97.9 %

**USP Limits: 90.0 % to 110.0 %**

**Figure 4.** Secondary data worksheet. All the raw data from the raw data sheet are re-entered in this form for subsequent calculation.

**Single-User Analyst Spreadsheet / Worksheet Review**

Used to determine if the spreadsheet / worksheet presents a complete and legible picture of what was done and ensure that the worksheets are understandable by other reviewers.

Enter Y or N (Yes / No) for each factor, or N/A if the factor does not apply.

**A. General Considerations**

| Analyst | Reviewer | |
|---|---|---|
| _____ | _____ | Worksheet is legible and in black ink, where necessary. |
| _____ | _____ | Margins are clear (0.5 inch left on front pages and right on back pages). |
| _____ | _____ | Sample number is present on all worksheets (front and back). |
| _____ | _____ | If more than one person participated in the analysis, the worksheet includes all signatures. |
| _____ | _____ | All pages are numbered in the correct sequence. |
| _____ | _____ | Attachments (and mounting, if used) are identified. |
| _____ | _____ | Disposition of sample and / or reserve portion is accurately described. |
| _____ | _____ | Laboratory conclusions are supported by analytical results and consistent with guidelines. |
| _____ | _____ | 704 (d) letter or complaint letter is issued as appropriate. |
| _____ | _____ | Single-user workbook file is saved in a protected folder for future audits against the completed printed sample report. |

**B. Accuracy and Completeness of Spreadsheet / Worksheet**

| Analyst | Reviewer | |
|---|---|---|
| _____ | _____ | Sample and condition when received by the analyst are clearly described, documenting continuity and integrity. |
| _____ | _____ | Worksheet is compatible with the collection report with discrepancies noted. |
| _____ | _____ | Accurate descriptions are recorded of sample, container, label, code, product, net contents in proper units. |
| _____ | _____ | Appropriate method was performed. |
| _____ | _____ | Any modifications to the method are stated. |
| _____ | _____ | Any modifications to the method are validated (recoveries). |
| _____ | _____ | Method of sample preparation is shown. |
| _____ | _____ | Raw data and secondary data are properly identified (spreadsheet). |
| _____ | _____ | Dilution factors are shown for all methods. |
| _____ | _____ | Results are described by subsample. |
| _____ | _____ | Calculations are correct with correct precision being expressed (using adequate rounding). |
| _____ | _____ | Original data are reported, including chromatograms, spectra, etc., showing operating parameters. |
| _____ | _____ | Name, model, FDA number of instrument, accessories used are reported. |
| _____ | _____ | Work is dated and initialed by analyst, where more than one analyst was involved (this includes back pages which reflect the work of a single analyst). |
| _____ | _____ | Errors are corrected by striking through the incorrect entry, inserting and initialing the new entry. (Note: It is not necessary to initial spelling corrections) |
| _____ | _____ | Discarded data and results are explained. |
| _____ | _____ | No unresolved analytical problems are evident. |
| _____ | _____ | Carry over of compound names or data from previous samples is checked. |

**C. Standard Data**

| Analyst | Reviewer | |
|---|---|---|
| _____ | _____ | Source of standard (s) is cited. |
| _____ | _____ | Preparation dates and preparer of primary & working standard are cited. |
| _____ | _____ | Weights, dilutions & concentrations of standard materials are documented. |
| _____ | _____ | Standard curve has adequate number of points; sample results are within the limits of the standard curve. |

**Figure 5.** Single-User Workbook review using *Excel 2002* spreadsheet program.