Evaluation of ExcelSafe to Implement Part 11 Rules in FDA Analyst Workbook Files

by

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Abstract
The FDA is responsible for a wide variety of sample testing and data reporting tasks, and many sites have chosen to use MS Excel spreadsheets and templates to help automate these tasks. We wanted to make this a paperless environment with the help of the ExcelSafe software to add audit trails and electronic signatures as required in 21 CFR Part 11. Existing spreadsheet templates are being checked into ExcelSafe so eventually all new spreadsheets would be covered by the security controls. We also modified our existing templates to allow lab analysts to be able to create any kind of sample testing workbook that they needed by selecting from a large library of existing test worksheets. We found that by going paperless, we will be able to realize that cost and time savings will be significantly greater than the cost of the software. In addition we are streamlining our testing procedures to be able to process samples faster and shorten the review process as well. We have concluded that this approach can be easily implemented, and are planning on continuing with this system to process and report sample testing results, and upload this data into the LIMS system when it goes online in the future.

Introduction
The Microsoft Excel spreadsheet program has become the software of choice in FDA laboratories for processing results and analyzing and presenting scientific data in the chemical as well as the microbiological laboratories. Those not familiar with conventional programming can often develop their own solutions using this spreadsheet software without help. Additional controls and policies must be implemented by the agency in order to bring uniformity, security, and data protection to worksheets where complex sample are being analyzed. Analytical chemists and microbiologists need more effective data analysis tools for rapid formatting of documentation and data processing addressed in this article.

Spreadsheets are recognized as powerful tools for data handling, report generation and routine data analysis of analytical results. In addition to their strength for calculations and presentation, the capability of spreadsheet programs to perform logical operations and calculations is critical for the generation of effective reports. The spreadsheet approach is efficient in terms of development costs, flexibility, and allowing modification of calculations in an interactive environment. The flexibility required in a research environment and the rigid demands for reporting in a regulatory analytical environment provides for a continuous spectrum of applications. Spreadsheet software can be applied throughout this spectrum including interactive model development in a research environment.

Background
Previously, two Laboratory Information Bulletins were written on the subject of the single-user and multi-user analytical spreadsheet applications (Microsoft Excel program) for reporting in a regulatory environment (1, 2). For multi-user applications, the requirements were established and implemented for use in San Juan District Laboratory. The single-user workbook files (which have been enhanced and renamed as the Starter template in this article), which are the most used in the San Juan District Laboratory, (used for varying sample matrixes, such as drugs, food chemistry, microbiology and others such as newly developed methods and data gathered from research in all areas of FDA analyses), have triggered further research due to their complexity.

Goals of the Project
The goal of this project was to transform the analytical laboratory by combining new and existing technology in order to enhance laboratory performance and at the same time save money, for example a paperless environment utilizing electronic signatures and audit trails. In order to improve the capabilities of Microsoft Excel security and data integrity for our sample testing worksheets, ExcelSafe is being used. ExcelSafe can provide spreadsheet security which protects data integrity and provides controls for all templates and spreadsheets used in the analytical laboratory.

The San Juan District Laboratory is improving our analytical spreadsheet templates in order to provide all analysts with a tool that can reduce the time spent completing sample worksheets. The new template facilitates the development of the sample analyses worksheets including a reduced time in formatting, as well as enhancing the review process by a second analyst. The review time is reduced because the reviewing analyst has a well organized sample worksheet package similar in formatting properties and printing capabilities. These workbooks help to maintain a controlled environment while still providing the flexibility needed to analyze any sample or type of testing. ExcelSafe by having a better security and data integrity, enhances the quality control of the data analyzed.

ExcelSafe Use in the Laboratory
To further enhance the security and protect data integrity for all analytical spreadsheet workbook files in the San Juan Laboratory, a new software named ExcelSafe from Ofni Systems (www.OfniSystems.com/ExcelSafe/index.htm), is being implemented. ExcelSafe tracks changes, controls system access and prevents unauthorized changes automatically through password protection, audit trails, and electronic signatures. ExcelSafe can provide the spreadsheet security which protects data integrity and controls all templates used in the analytical laboratory.

Additionally, ExcelSafe facilitates generation of validation documentation thru a standard feature called FastVal. Templates are edited using ExcelSafe for change control in order to maintain the validated status of the spreadsheets.

ExcelSafe can meet the requirements of 21 CFR Part 11.10.d for limiting system access to authorized users, administrators can add and remove users from security groups as well as to reset passwords. Additionally, ExcelSafe includes a search engine that allows users to search for any audit trail or other information about the spreadsheets. The Search Engine includes the ability to view search results in any number of customized reports.

It is important to mention that at present FDA does not have a Laboratory Information Management System (LIMS) to process the raw data that is generated from balances and other laboratory instrumentation. LIMS can send the raw data to the spreadsheet applications for the calculation of the results as well as acquire entered raw data and the results calculated from the spreadsheet. These are stored in the ExcelSafe database which can be sent to the LIMS for reporting results.

Another advantage is that raw data can be collected using the Tablet PC or workstation directly onto the analytical spreadsheets since ExcelSafe generates audit trails, records the date and time of the cell entry and by whom. These can be printed when needed. The raw data collection can be accomplished by using the analyst's PC deployed in the laboratory areas of analyses, such as the balance room, instrument room or any other area where raw data is collected. Raw data can be entered directly to the cells eliminating transcription errors.

When all analyses are completed, the analytical workbook file is reviewed by a second analyst. If needed, errors found by the second analyst are then corrected by the original analyst. When all errors are corrected, the original analyst implements the electronic signature followed by the second reviewing analyst on the FDA form 431. After the reviewing process all the worksheets in the workbook file are converted to a PDF file while maintaining all the audit trails and electronic signatures in the ExcelSafe database. Then the original analyst includes the PDF file from the analytical instrumentation in a single report (the "PDF" file from the analytical workbook file combined with the "PDF" file from the analytical instrumentation).

Advantages of Using ExcelSafe

1. Integrity of the analytical data (ExcelSafe audit trails, password security for each user and electronic signatures).
2. Reduced errors related to transcribing raw data
3. All analytical template files can be stored in ExcelSafe improving accountability and security of the files.
4. Improved efficiency, including:
   - analytical worksheet packages can be sent as a CD (or in the future by email) instead of a block of paper (FedEx or UPS), saving money and paper.
   - review time of worksheet packages is reduced since Excel formulas and all of the formatting properties can be validated
5. Supervisors and directors can see data in real time as it is being generated to make urgent decisions when needed

6. Analysts could monitor their analysis (example: HPLC runs) remotely to assure no technical problems have arisen (future functionality)
7. Using fully electronic data recording systems is improving the reliability and credibility of the laboratory operations

Important Information about ExcelSafe Audit Trails
1. All changes to spreadsheets are recorded, including who edited the spreadsheet, the previous and new value of the cell and the date/time of the change.
2. Audit trails also record key sheet events, including opening and closing spreadsheets and applications and applying or removal of electronic signatures.
3. Audit trails are automatic, unalterable and secure. They are retained for deleted items.
4. A copy of the audit trail can be exported to the spreadsheet automatically or upon demand.
5. All electronic signatures are recorded, including the original analyst as well as the reviewer or any other analysts that works in the sample analysis.
6. Should be able to meet the requirements of 21 CFR Part 11.10.e for audit trails.

Return on Investment Calculations
Calculations of the potential benefits of the ExcelSafe software were included in the report "E-431 Spreadsheets under 21 CFR Part 11 Rules using ExcelSafe" that was sent to the Division of Field Science as part of the pilot project Return on Investment (ROI) report. Savings are realized by going paperless in the form of reduced time to complete the sample testing reporting requirements and also by being able to send reports as CD (or in the future via email rather than shipping via commercial transit services) rather than printing blocks of paper.

ROI calculations are shown in the table below and are based on the following observations using electronic worksheet processing using MS Excel with ExcelSafe:
- Decrease in the amount of time needed to generate the worksheets
- Decrease in the verification of calculations, corrections and review time, decreasing the turn-around time between sample assignment and sample completion.
- Reduction in the frequency that data is transcribed (manually) from one place to another (e.g. from equipment to worksheet)
- Support for multiple concurrent users
- Uses existing software (MS Excel and Access or Oracle databases) that are already available to FDA at no additional cost
- Can be used by drug laboratories as well as any laboratory that uses analytical spreadsheets.

Table 1. San Juan Laboratory Return on Investment Calculations when fully implemented

Description	Amount
Number of labs	1
Number of analysts GS-12	11
Number of Specialists GS-13	3
GS-12 average annual salary (approximately, $30.75 per hr)	$77,546.51
GS-13 average annual salary (approximately, $38.75 per hr)	$89,443.64

Weighted average hourly salary per analysts GS- 12, GS-13 (average 14 analysts per hr)	$((11*30.75)+(3*38.75))/14 = \$32.46$
Average worksheet package preparation time per sample before ExcelSafe - 1 worksheet package in approximately 20 hours	20 hrs per worksheet package
Average worksheet package preparation time per sample after ExcelSafe (validated analytical template (only data-entry)) 10 worksheet packages in approximately 8 hours (8 hrs / 10 worksheet packages)	0.8 hrs per worksheet package
Average time saved with ExcelSafe	19.2 hrs per worksheet package
289 sample worksheet packages per year x 19.2 hrs saved per worksheet package	5548.8 hrs saved
5548.8 hrs saved x $32.46	$180,114 per year
Amount of paper used will be considerably reduced from 5 reams per project to about 2.5 reams per project. 12 reams used (12 x 3.5 = 42.00) $3.50 per ream.	$42.00 per year
Toner used before ExcelSafe: Average toner used per printer: 3 per year. There were 12 printers in the lab. Each toner at $80.00. (80 x 12 x 3) = 2880.00	$2880.00 per year
Mail (for example: FedEx or UPS) expenses (sending heavier analytical package to other district, region, etc.) Average Mail expense per year (289 samples x $15.00 = now $19)	4,335.00 per year
Total saved per year for one lab (San Juan Drug Lab)	$187,371 per year
*13 labs Total saved per year (Example) $187,371 per year x 13 Labs	$2,435,823 per year
*13 labs Total saved per 4 year (Example) $2,435,823 per year x 4	$9,743,292 per 4 year

ROI for the investment was obtained in less than 1 year. These savings were evidenced in the amount of samples received vs. the amount of samples completed. The turn around time was decreased to a degree that eventually the amount of samples analyzed can be doubled.

Because ExcelSafe can meet the security and Part 11 requirements for Microsoft Excel, the analytical applications are used as an electronic laboratory notebook (managing original raw data at actual time 100% of the analyst data-entry) saving printing and reviewing time.

Although this pilot project is performed in the San Juan drug laboratory using Microsoft Excel drug analytical applications, any laboratory using Microsoft Excel analytical applications can use ExcelSafe, saving considerable time and money from the very first time the analytical application are used with ExcelSafe. With these increases in laboratory automation, time consuming laboratory data entry operations will be reduced or eliminated.

The goal of this pilot project was to combine new technology with existing and currently used technology to enhance laboratory operations in a rapid and effective way and at the same time save considerable amount of money. Additionally, ExcelSafe application database can be integrated with a LIMS to complement the security and integrity of our Excel analytical applications allowing a paperless environment and using the powerful Excel calculations allowing enough flexibility to the analysts to finalize the worksheet package.

Enforcement of Spreadsheet Policies in the FDA San Juan Laboratory
Currently the analytical spreadsheet developers (analysts, microbiologists, etc.) tend to be overconfident in the development of spreadsheets where controls and policies are deficient. This publication recommends the use of spreadsheet policies in order to improve our capabilities in the development of analytical spreadsheet design, including its consistency in the reviewing process.

Reducing Errors
Dr. Panko (University of Hawaii) has compiled a large amount of data about the high rate of errors found in spreadsheets (4, 5). He concluded that spreadsheet errors are very common and widely reported, with the results from these errors costing millions of dollars per year. It is logical then that companies would implement strong policies for spreadsheet development and testing. However, this is rarely the case. Most studies (4, 5) that have audited spreadsheets or surveyed users, have reported poor development practices. In addition, studies that looked at corporate controls also found a general pattern of little control, and the controls that did exist were largely informal. One reason for this lack of disciplined development practices and policies may be that spreadsheet developers and their management are overconfident in the accuracy of their spreadsheets.

Additionally, spreadsheet errors have been shown to be almost exactly like software development errors in terms of type, frequency, and detectability. This similarity suggests that spreadsheet developers need to use the traditional system development life cycle (SDLC) used in software development or some modification of the SDLC for rapid application development, agile development methods, test-driven development, or other new development methods.

Our proposed development procedure is to apply strong policies (see section "Spreadsheet Template Design and its Policies" below) in the development of our analytical spreadsheet applications. During the research we found that a large number of our analytical spreadsheet errors were due to the lack of spreadsheet policies. This was evident in the additional time needed for the review process by a second analyst. For example, analytical spreadsheets were not consistent (formatting properties) and the development or modifications of formulas were not standardized.

Quality Standards and Guidelines (ISO/IEC 17025:2005 Standard)
The "General Requirements for the Competence of Testing and Calibration Laboratories", (International Organization for Standardization ISO 17025). Sections 4.3: Document Control, 4.12: Control of Records, and 5.4.7: Control Data, includes requirements on the handling of quality and technical records and the use of computers. Where computers or automated equipment are used for the capture, processing, manipulation, recording, storage or retrieval of calibration or test data, the laboratory shall ensure that:

a. Computer software is documented and suitably validated as being adequate for use.
b. Procedures are established for protecting the integrity of data; such procedures shall include, but not be limited to, integrity of data entry or capture, data storage, data transmission and data processing.
c. Computer and automated equipment are maintained to ensure proper functioning and are provided with the environmental and operating conditions necessary to maintain the integrity of test and calibration data.
d. It establishes and implements appropriate procedures for the maintenance of security of data, including the prevention of unauthorized access and/or amendment of computer records.
e. Procedures are established to describe how changes in documents maintained in computerized systems are made and controlled.

ExcelSafe complies with all the integrity, security processes and data handling requirements specified in the ISO 17025, as in the sections mentioned above.

Notes:
1. Testing and calibration laboratories that comply with this International Standard will also operate in accordance with ISO 9001:2000 and ISO 9001:2008
2. For cGMPs, see below in section "Spreadsheet from a Compliance Perspective (cGMP's)"

Spreadsheet Template Design and its Policies
The purpose of standardizing worksheets is to format results for printing and to normalize where information is located on the worksheets. This also led to reduced time required for training and review, and will assist later to format data for uploading into a LIMS system. During the research process, it was found that when policies on analytical spreadsheet development were applied, the analytical spreadsheets were improved in both formatting properties and a reduction in the amount of time required to complete, review and approve assay worksheets.

How to Put ExcelSafe to Work in FDA Labs

Currently, analytical spreadsheets are used to assess the product quality in a regulated environment across all areas of analytical work. There are several ways that analytical spreadsheets are used in FDA laboratories such as:

- Validated templates (XLT, saved in network hard drives) to be accessible to the users
- Spreadsheets files (XLS) generated from the validated templates (saved in local employee hard drives)
- Un-validated templates (needs 100% verification of manual calculations) (sometimes located in network or employees local drives)
- Spreadsheets created by the employee or a personal workbook file are saved in a local employee hard drive

In some laboratories the analytical templates are saved in a network drive in order to be accessible to all analysts. The analytical spreadsheet files created with the templates are saved in the analysts local drives, with no access to the supervisor or other analyst that may need to verify the workbook file to assure compliance with test methods and product specifications. Additionally, these files are

often lost since analysts do not use a standardized saving file pattern and / or forget the location of the same. This is due to a lack of an SOP for analytical spreadsheets.

Here is where ExcelSafe (Figure 8) has an advantage. ExcelSafe has an area where all validated templates are stored for ease of access to the analysts when needed. All the analytical templates used in the laboratory are organized for rapid access to the files and for template accountability.

When the analytical spreadsheets files are created from the template files, they will be available in the list of ExcelSafe active workbooks ("All Sheets" section) where the users can access and track them. Other analysts working with the same sample can access the sample workbook at the same time and add their electronic signature to indicate the review and / or approval of the same.

The advantages of this process are that all analytical spreadsheet files generated from the analytical templates or existing workbooks that have been added to ExcelSafe are accessible in the network drive and files accountability will be maintained. All sample files stored in ExcelSafe can be searched with the ExcelSafe search engine for fast file retrieval.

Quality managers can access ExcelSafe to see the sample results or raw data generated by any analyst in order to verify and / or review the analytical workbook files before their completion. Using ExcelSafe we can save paper since the review can be performed and the print out will be done at the end. Also, electronic file back-up of analytical work is kept in the network drive.

Quality Managers, Lab Supervisors or Lab Directors can access ExcelSafe and review any analytical spreadsheet files created by the analysts for their review, modification or corrections before printing the workbook file. Currently, any spreadsheet used by FDA laboratories can be loaded into ExcelSafe with no additional modifications or changes.

Spreadsheet Settings Used (Some of the spreadsheet policies)
The following are spreadsheet policies and settings for the San Juan District Laboratory:
1. Our FDA Form 431 (Analyst Worksheet) and the FDA Form 431a (General Continuation Sheet) template specifications are:
   a. FDA Form 431 has exactly 18 columns (width 5.00 (35 pixels)) and approximately 52 to 55 rows.
   b. FDA Form 431a Continuation Sheet has a total of twenty columns. Two narrow columns (0.64 (7 pixels)) to the left and right of the sheet, and 18 columns (width 4.83 (34 pixels)) in between the two narrow columns. The sheet has approximately 52 rows (modifying area of the sheet).
   c. Page Setup for FDA Forms 431 & 431a:
      o Page: Orientation = Portrait and Scaling = 100% normal size
      o Margins: Left: 0.75", Top & bottom = 0.25", Right = 0.2", Header & footer = 0", Center on page: Horizontally & vertically.
      o Sheet: Print = Black & white
   d. Cell merging (flexibility): If a cell needs to be wider to accommodate a long number or text, the cell is merged according to the size of the data. Columns are always the same width (4.83 / 34 pixels)

   e. Excel file: FDA Form 431 Analyst Worksheet.xls, includes both FDA forms (431 & 431a and examples of analytical worksheets already developed).

   f. Additional policies on spreadsheet development were defined in the San Juan District Laboratory in several SOP documents.

2. Use the equation editor to describe the formulas in the analytical procedure.

   a. Use the equation editor to describe the formulas in the analytical procedure: The formula in the procedure as well as in the Excel formula bar must resemble the formula description using the equation editor.

   b. Use the Round function in the Excel formula when appropriate.

3. The house style and formatting properties are:

   a. Every worksheet is protected as needed.

   b. Data-entry cells are unprotected and have a light yellow background.

   c. Drop-down-lists are unprotected and have a blue background.

   d. Headings are bold and justified as appropriate over numerical data.

   e. Red font or background is reserved for error messages or results out of specifications.

Starter Template and Individual Assay Worksheet Templates (San Juan Drug Lab)

Once the spreadsheet policies were defined and implemented, standardization of many of the analytical spreadsheet templates was achieved and others are in process. During our research we found that for the drug laboratory where all types of drug sample matrixes are analyzed, a flexible template is necessary in order to accommodate the changes or modifications between different sample matrixes (Tablets, Capsules, liquids, suspensions, injections, etc.).

The introduction of a unique template named the **Starter** template (see Figure 7) was used for the generation of analytical workbooks. The Starter template allows the selections and importing of the individual testing worksheets from separate templates. The templates are used as follows:

- The **Starter template** contains the e431 form the e431 abbreviated as well as the "Worksheet Review Checklist" and the functionality to import individual testing worksheets (import templates)
- A library of individual **Import templates** is used to select a specific template (Assay, content uniformity, dissolution test and many other tests) using the Starter template to develop the analytical package. Each template contains specific analysis where formulas, specification limits and instructions for processing any single test is included.

The starter template is used as the basis for creating all new sample workbooks by allowing the analysts to create any combination of individual testing worksheets that is needed to properly analyze any analytical sample package. This Starter template provides the following enhancements and capabilities to our analytical spreadsheet templates:

   a. The capability to insert any pre-validated assay template, including:

- Assay module (raw data worksheet, calculation results, instrument parameters, QC form for reporting, etc.)
- Content Uniformity (raw data, calculation and results with USP criteria

- Dissolution test (raw data, calculation and results (stages 1, 2 and 3)

b. The capability to insert a single worksheet when needed. For example, if an assay needs to be repeated, the template for that assay can be re-imported without overwriting the existing information.

c. The Starter template provides an automatic page numbering system and will automatically reference the sample name and sample number being tested for all imported assay worksheets.

The imported templates all come with the instructions for use embedded within each template. The Starter template also has built-in instructions for use. A continuous on-going process to improve the development of the individual test templates has become a research interest in the San Juan District Laboratory.

Template Use, Completion and Approval

If one uses a verified template to develop a spreadsheet, attention should be given to identifying the raw data and secondary data used in the analytical method. Once the analyst identifies the raw data required for the procedure, then they use the appropriate template or modify an existing template to meet the requirements of the analytical procedure. This raw data page becomes an official document when the weights and dilutions are entered. The procedure may be more complicated if multiple active ingredients are tested within the same workbook.

When ExcelSafe is used, there is no need to print the raw data page since ExcelSafe keeps track of all changes and saves the audit trail in a separate secured database. When this type of spreadsheet is developed, the creator performs an in-process verification of the analytical data and when completed, a second analyst will verify the formulas, calculations and data integrity.

After the workbook is completed and verified by a second analyst, the supervisor will perform a final review of all data and work done. The worksheets are then electronically signed and printed into an official PDF report. During this pilot we printed the weights using a small printer connected to the balances, and attached the printout to the analytical package to verify the weights manually typed into the cell. This process was performed to verify the data-entry in the ExcelSafe audit trails. Additionally, the printed weights were scanned and converted to a "PDF" file.

Designing Spreadsheet Templates for Multiple Users

If you are creating templates that will be used by multiple users, more attention needs to be given to minor details. Such a spreadsheet therefore takes longer to create. The amount of extra effort depends, on large part, on the experience level of the other users. A spreadsheet that will be utilized by an inexperienced user is often the most difficult to develop, simply because you need to make sure that it is "bulletproof." In other words, you do not want the user to be allowed to tamper or accidentally edit formulas, constants, etc. In addition, you have to make it perfectly clear how the spreadsheet is to be used. This often means providing additional formatting and instructional elements, such as including instructions on each worksheet.

Spreadsheet from a Compliance Perspective (cGMP's)

The topic of spreadsheets and traceability of records and/or laboratory activities is not new for FDA Investigators and Compliance Officers, whom among other responsibilities are required to review and determine a firm's adherence to GMPs. Much has been written about the need to comply with 21 CFR Parts 210 and 211, 58 /GLP) and 820 /QSR), but unfortunately, as reviewers, we are consistently surprised with many incidents of poor documentation and GMP practices when working with spreadsheets. This includes from maintaining records and tracing records, to verifying calculations and assuring that the information saved as the official batch production or analytical results are adequate and representative of the true quality of the product. As a Field Investigator (Carmelo Rosa) for approximately 13 years and a Compliance Officer for the last 5 years, and as we move to a more computerized and highly technical environment, we still are seeing more examples of firms not understanding the basic regulatory expectations related to spreadsheets. For example: a citation such as "the failure to validate your excel spreadsheet used for the calculation of the analytical data input or obtained from your HPLC Chromatographic run for batch XXX" may be basic to many computer experts. Nevertheless, if the wrong formula is established or the results involve incorrect entries for a narrow therapeutic product, the consequences can pose a significant risk to the consumers taking a particular product. What is expected from a regulatory perspective?

Perhaps it may be simple, but also complicated. How does a firm demonstrate that they have a clear understanding of the intention of the spreadsheet and the way it operates? How are worst case scenarios or conditions challenged or verified? Who has the proper training on the spreadsheet? How do you demonstrate traceability and that the system is robust and reliable? How and where is the supporting data maintained? How do we demonstrate that we have a secure system and different levels of access? The list can go on. The point I am trying to convey, is that it all goes back to basic GMPs/GLPs. For many, gaps or flaws are discovered the hard way, during an inspection or when someone discovers that no backup has been maintained when the power was lost. Having spreadsheets may facilitate an operation, but if incorrectly designed, can turn into a firm's worst nightmare.

Part 11 is the other perspective to be implemented in order to increase the integrity, accountability and security of the spreadsheets used during the manufacturing as well as during the gathering of the analytical raw data when assessing the product quality in the analytical laboratory.

Results of Our Findings

We found that when enhancing the design, applying controls, macro automation of format or functions, a more homogeneous spreadsheet development system among the analysts was achieved, assuring the integrity of the data. Additionally, when applying specific policies in the development of the Starter template, analytical applications were improved, saving time in the development and reviewing stages of the life cycle of the analytical spreadsheets.

The design aspects of the Starter template have been improved in order to achieve homogeneous workbook files among all analysts developing the sample workbooks. Training is necessary in order to normalize the process, as well as the specific details on using the "Starter Template". Additionally the use of ExcelSafe database application which provides extra security (audit trails, password protections, and electronic signatures) to our analytical spreadsheets was introduced.

During this process, an improvement in the development of the workbook files among all analysts was evident. This was reflected in enhanced worksheet formatting, less time on spreadsheet development, less errors and less review time. Therefore, we are proposing that the Starter template (FDA Form431 Starter.xlt) as well as the individual test Import templates as a viable alternative to FDA laboratories.

Pending Issues

Currently, all our analytical spreadsheets can be converted from the Excel file format "xls" to the "PDF" format with no problems. The issue appears when the instrument output such as the GC/HPLC chromatograms and other analytical raw data are generated. These laboratory equipments are stand alone and a LIMS is needed in order to generate the output in the "PDF" file format. Another approach is that analysts save the "PDF" data files in a "CD" or "Pen drive" and combines it with the analytical spreadsheets in "PDF" format. At present we are still printing the final analytical reports, however since it is stored electronically, you have the option of not having to print.

Conclusions

Our research in analytical spreadsheet applications shows that when using spreadsheet policies along with Part 11 requirements, the analytical spreadsheet applications are enhanced in the following areas: data integrity, security, templates accountability as well as their validation / verification process along with its documentation.

ExcelSafe can be an efficient tool to implement Part 11 requirements in spreadsheet applications, increasing data integrity thru audit trails and electronic signatures. Additionally, accountability of all samples analyzed is well maintained and organized which enhances access capabilities by the analysts, supervisors, and the Quality System Managers (QSM).

ExcelSafe improves our laboratory efficiency since printing of worksheets is not always necessary during the reviewing stages of the analytical packages. The analysts can verify the workbook files generated in the laboratory at any time, through ExcelSafe, decreasing the reviewing time and enhancing our laboratory capability. Finally, it is important to note that these tools can be used for any spreadsheet used by the agency, not just for sample testing. This is important as the agency comes under increased scrutiny.

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Special Dedication of the Article
In memoriam of our late Science Advisor, Basil Vassos Ph.D., who inspired this work and gave great motivation to the author and many others in the development of publications in the field of computer science and analytical chemistry. His research and teaching in the area of software programming and analytical chemistry touched several minds and guided our first steps.

Figures

Figure 1. Example of a completed Form FDA 431 Analyst Worksheet. This workbook file is used in the Drug Laboratory. Pale yellow cells are unlocked to allow data entry, and drop-down lists are blue. The electronic signature at the bottom includes the meaning and date/time of the signing, and signing the sheet will protect all cells from further editing. (A generic login 'ESAdmin' was used for this article, printed full names are used in normal lab operations.)

Flag: Original Analysis

Analyst Worksheet		1. Product Glycerin		2. Sample Number 123456
3. Seals ☐ Intact ☑ None ☐ Broken		4. Date Rec'd 8/9/2009	5. Received From Samuel Guzman	6. District/Laboratory SJN-SB

7. Description of Sample

8. Net Contents
☑ Not Applicable   Declared/Unit _____
☐ Not Determined   Amount Found _____
Units Examined ____   % of Declared _____

9. Labeling
Original (s) Submitted _____ ☑ None
Copies Submitted _____

10. Summary of Analysis

Container:
Clear glass jar with approximate measures of 140 mm in height (with screw-on green plastic cap) X 79 mm diameter at the center of glass jar.

Labeling:
None

Code:
None

Product:
Clear viscous liquid.

Method:
USP 31 under Glycerin, section "Diethylene glycol and Ethylene glycol impurities" by GC, Electronic Version.

Analysis:
Diethylene Glycol and Ethylene Glycol Impurities by GC

Results: See continuation sheet, page 2.

11. Reserve Sample

12. a. Analyst Signature ☐ Broken Seal Electronic Signature - Authored by Esadmin on 8/9/2009 6:34:53 PM	13. Work - Sheet Check	a. By Electronic Signature - Verified by Esadmin on 8/9/2009 6:39:51 PM
b.		
c.		
14. a. QA Approval Signature (SB-QAT) Electronic Signature - Verified by Esadmin on 8/9/2009 6:37:23 PM		15. Date Reported 8/9/2009

SJN Form FDA 431 Version 2.07   Attachment (s): A-   Page 1   of _____ Page (s)

Figure 2. Audit trails from e-431 sheet shown above. All audit trails from analytical spreadsheets are automatically saved in the ExcelSafe database including all sample data entered to the spreadsheets (weights, dilution calculations, etc.). This data can be searched, exported or uploaded into LIMS.

Book or Sheet	Action or Range	Edit Type	Original Value	New Value	Changed By (ID)	Date	Reason
FDA 431	$P$60:$S$60	Added		8/9/2009	ExcelSafe Administrator (Esadmin)	8/9/2009 6:40:48 PM	
123456-0-DC.xls	N/A	Added		Passwords viewed	ExcelSafe Administrator (Esadmin)	8/9/2009 6:40:20 PM	
FDA 431	$P$54:$S$58	Added		Electronic Signature - Verified by Esadmin on	ExcelSafe Administrator (Esadmin)	8/9/2009 6:39:53 PM	
FDA 431	$B$60:$O$60	Added		Electronic Signature - Verified by Esadmin on	ExcelSafe Administrator (Esadmin)	8/9/2009 6:37:25 PM	
FDA 431	$B$54:$M$54	Added		Electronic Signature -	ExcelSafe Administrator	8/9/2009	

Show Audit Trail for...
 ● Current Sheet   ○ All Sheets

□ Auto-refresh every 0 ▾ seconds.

Refresh   Report   Close

123456-0-DC.xls

Figure 3. Example of raw Data worksheet. The electronic signature from the form 431a is applied for all of the 431a worksheets used by the analysts.

General Continuation Sheet	Product	Sample No.
	Glycerin	123456

Method: USP 31 under Glycerin, section "Diethylene glycol and Ethylene glycol impurities", Electronic Version.

Standard's Used:
1. Diethylene Glycol, FLUKA Lot. 1290160 13206104, Lab ID # 6293B used "as is".
2. Glycerin Lot # 086K00441, Purity: 99.9%, Lab Id: 6293A used "as is".
3. Ethylene Glycol, Sigma Batch #: 04258J6, Purity: 99% used "as is".
4. Internal Standard: 2,2,2-trichloroethanol, Lot #: 138951534708265

DG Purity: 0.99
Glycerin Purity: 0.999
EG Purity: 0.99

Standard's 1 & 2 Preps.: **Stds. Wt. Date:** 8/9/2009   **Balance #:** 7   **Cal. Due Date:** 8/2009
Standard 1 Preparation:

	Diethylene Glycol	Ethylene Glycol	Glyceryn	Internal Standard Soln.
Net wt. (mg):	105.24	120.57	114.78	202.29
Stk. Std. Dilution:	200.0 mL	200.0 mL	200.0 mL	200.0 mL
*Conc. (mg/mL):	0.5209	0.5968		
Aliquot:		10.0 mL		
Int. Std. Aliquot:		10.0 mL		Internal Std.
Dilution:		200.0 mL		
*Conc. (mg/mL):	0.02605	0.02984	0.57333	

Note: *Stds corrected for purity

Standard 2 Preparation:

Resolution Soln.:

	Diethylene Glycol	Ethylene Glycol	Glycerin
Net wt. (mg):	102.40	117.45	567.48
Dilution:	200.0 mL	200.0 mL	
*Conc. (mg/mL):	0.5069	0.5814	Aliquot: 0.5 mL Stk-Aliquot: Std 1 + Std 2
Aliquot:		10.0 mL	10.0 mL
Int. Std. Aliquot:		10.0 mL	Internal Std.
Dilution:		200.0 mL	
*Conc. (mg/mL):	0.02534	0.02907	56.748

Note: *Stds corrected for purity

Diluent: Stds, sample and spike diluted with Methanol

Analyst (s)		
Electronic Signature - Authored by Esadmin on 8/9/2009 6:34:53 PM	Page 3 of X Page(s)	

Form FDA 431a

Figure 4. Example of audit trails from raw-data worksheet. All Audit trails from raw-data entry (weights and dilutions) are saved. If changes to the raw data are necessary, the audit trails will record all changes including the "Reason" for change which is recorded on the audit trails.

Book or Sheet	Action or Range	Edit Type	Original Value	New Value	Changed By (ID)	Date	Reason
ExcelSafe Audit Trail	Updated Data	Default			ExcelSafe Administrator (Esadmin)	8/9/2009 6:06:02 PM	
AssayRawData1	$F$19:$G$19	Changed	108.25	105.24	ExcelSafe Administrator (Esadmin)	8/9/2009 12:38:01 PM	wrong data-entry
AssayRawData1	$F$19:$G$19	Changed	105.24	108.25	ExcelSafe Administrator (Esadmin)	8/9/2009 12:37:13 PM	Correction: sample vial broken
DG-EG Determ	$P$22:$S$22	Added		A	ExcelSafe Administrator (Esadmin)	8/9/2009 12:35:19 PM	
DG-EG Determ	$L$43:$N$43	Added		0.00968	ExcelSafe Administrator	8/9/2009	

Figure 5. Example of secondary data worksheet (calculations & results). All the raw data from the raw data sheet are re-entered in this form for subsequent calculations. A copy of the electronic signature from form 431 is displayed in all the 431a worksheets.

General Continuation Sheet	Product		Sample No.
	Glycerin		123456

Date: 8/9/2009

Method: USP 31 under Glycerin, section "Diethylene glycol and Ethylene glycol impurities", Electronic Version.

Std. Conc. for DG (Cs) = 0.02605 mg/mL   Std. Conc. for EG (Cs) = 0.02535 mg/mL
Resp. (DG) in Std. Soln. (Rs) = 1.00317   Resp. (EG) in Std. Soln. (Rs) = 0.99684611
                                              Glycerin in Test Soln. Conc. (Cu) = 11.94 mg/mL

Formula Used:

$$\% \ wt/wt = \left(\frac{C_s}{C_u} \right) x \left(\frac{R_u}{R_s} \right) x \ 100 \qquad Respose = Area$$

Where:
Cs = Conc. (mg/mL) of DG (or EG) in Std. solution.   Ru = Response for DG (or EG) in Test solution.
Cu = Conc. (mg/mL) of Glycerin in Test solution.   Rs = Response for DG (or EG) in Standard solution.

Sub 1   Attachment: A

Compound	RT Spl, Sub 1	Impurity Area, Ru	% Impurity	
Diethylene Glycol	ND	0.0	0	ND = Not Detected
Ethylene Glycol	ND	0.0	0	
Unknown 1	9.312	16.45007	0.00083	
Unknown 2	12.328	193.8252	0.00974	

Sub 2

Compound	RT Spl, Sub 1	Impurity Area, Ru	% Impurity
Diethylene Glycol	ND	0.0	0
Ethylene Glycol	ND	0.0	0
Unknown 1	9.317	16.92272	0.00085
Unknown 2	12.336	193.15273	0.00968

Sub 3

Compound	RT Spl, Sub 1	Impurity Area	% Impurity
Diethylene Glycol	ND	0.0	0
Ethylene Glycol	ND	0.0	0
Unknown 1	9.317	16.92272	0.00085
Unknown 2	12.336	193.15273	0.00968

USP Limits: NMT the limit of quantitation (0.025%) for diethylene glycol and ethylene glycol is found.

Note (s):

1) For unknow 1, the peak area is lower than the limit of quantitation (0.025%) for diethylene glycol and ethylene glycol. The % impurity is lower than 0.1% of the total detected area (% TDA).

2) For unknow 2, the peak area is higher than the limit of quantitation (0.025%) for diethylene glycol and ethylene glycol. The % impurity is lower than 0.1% of the total detected area (% TDA).

Analyst (s)			
Electronic Signature - Authored by Esadmin on 8/9/2009 6:34:53 PM	Page _____	of _____	Page(s)

Form FDA 431a

Figure 6. Checklist of tasks that must be completed in the review process before the analytical package can be completed. The checklist is contained within the workbook as a protected sheet. Depicted is the first page of the checklist.

	Food and Drug Administration San Juan District Laboratory Worksheet Review Checklist	Form #: **WRC.1.3**	Version #: 1.8
			Page 1 of 3
SOP Title: **SJN-QMS.015 Internal Audits**			Effective Date:
Form Title: Worksheet Review Checklist, **Attachment D**			11/22/2011

Analyst Name		Date:		Sample #: <Enter Sample #>
Sample Receipt/Storage/Transfer			**Spl. Classification:**	
Analyst: ☐ Yes ☐ No ☐ NA		Worksheet clearly describes the sample and condition when received by the analyst.		
Reviewer: ☐ Yes ☐ No ☐ NA		(Reference – LM, Vol. III, 3.3.2)		
Analyst: ☐ Yes ☐ No ☐ NA		Worksheet fully and accurately reflects continuity of sample accountability and		
Reviewer: ☐ Yes ☐ No ☐ NA		integrity. (Reference – LM, Vol. III, 3.3.2)		
Analyst: ☐ Yes ☐ No ☐ NA		Worksheet documents any sample or sample portions transferred among analysts within the laboratory noting what was provided, to whom, date, and reason for transfer.		
Reviewer: ☐ Yes ☐ No ☐ NA		(Reference – LM, Vol. III, 3.3.2)		
Analyst: ☐ Yes ☐ No ☐ NA		Information on the worksheet is compatible with C/R and other supporting		
Reviewer: ☐ Yes ☐ No ☐ NA		documentation. Any discrepancies are explained. (Reference – LM, Vol. III, 3.3.2)		
Analyst: ☐ Yes ☐ No ☐ NA		Reserve sample description is complete and accurately maintains sample accountability.		
Reviewer: ☐ Yes ☐ No ☐ NA		(Reference – LM, Vol. III, 3.3.2 Block 11)		
Sample Analysis				
Analyst: ☐ Yes ☐ No ☐ NA Reviewer: ☐ Yes ☐ No ☐ NA		The method used as reference in the worksheet is approved. Analyses performed and methods used are consistent with appropriate Compliance Program, assignment or documented instructions from laboratory Supervisor.(Reference – LM, Vol. III, 3.3.2 Method)		
Analyst: ☐ Yes ☐ No ☐ NA		Deviations from the reference method are explained on the worksheet (Reference – LM, Vol. III, 3.3.2 Method)		
Reviewer: ☐ Yes ☐ No ☐ NA				
Analyst: ☐ Yes ☐ No ☐ NA Reviewer: ☐ Yes ☐ No ☐ NA		If an analyst/technician develops a method or uses a non-standard method, it must have been validated. For violative samples, the method used is attached to the analytical package. The worksheet references the memo as "attached memo of…" For non-violative samples; the method is referenced and kept on file with analyzing laboratory. (Reference – LM, Vol. III, 3.3.2 Method)		
Analyst: ☐ Yes ☐ No ☐ NA		The use of appropriate standards, reagents, media containing name, must have supplier or type (USP, NIST, working), lot number or local reference control number as		
Reviewer: ☐ Yes ☐ No ☐ NA		applicable. (Reference – LM, Vol. III, 3.3.4)		
Analyst: ☐ Yes ☐ No ☐ NA Reviewer: ☐ Yes ☐ No ☐ NA		Instrument (FDA number and calibration due date) and instrument settings are listed on the worksheet or attached printouts containing this information. (Reference – LM, Vol. III, 3.3.3)		
Analyst: ☐ Yes ☐ No ☐ NA Reviewer: ☐ Yes ☐ No ☐ NA		If selection and preparation of the analytical sample is not described in the method or applicable compliance program, this information is described in the analytical package (Reference – LM, Vol. III, 3.3.2)		
Analyst: ☐ Yes ☐ No ☐ NA Reviewer: ☐ Yes ☐ No ☐ NA		Calculations are accurate, easy to follow, and a calculation / method check is performed. This includes checking of conversion factors, normality factor, significant figures, etc for accuracy of recording. (Reference – LM, Vol. III, 3.3.2). Note: Raw data and secondary data (calculations & results) are properly identified. Example, for an assay determination the raw data page goes before the secondary data page.		
Analyst: ☐ Yes ☐ No ☐ NA		If applicable, chromatograms and spectra are clear, easy to follow, accurate and		
Reviewer: ☐ Yes ☐ No ☐ NA		adequate to obtain stated or calculated results.		

Figure 7. Starter template being used to create a new sample workbook. All individual assay templates are saved as separate templates, and can be imported into the testing workbook at any time. In this example, the user has selected three dissolution assays to import from the list. The arrow shows the folder selection choices that are available to populate the list of available assays.
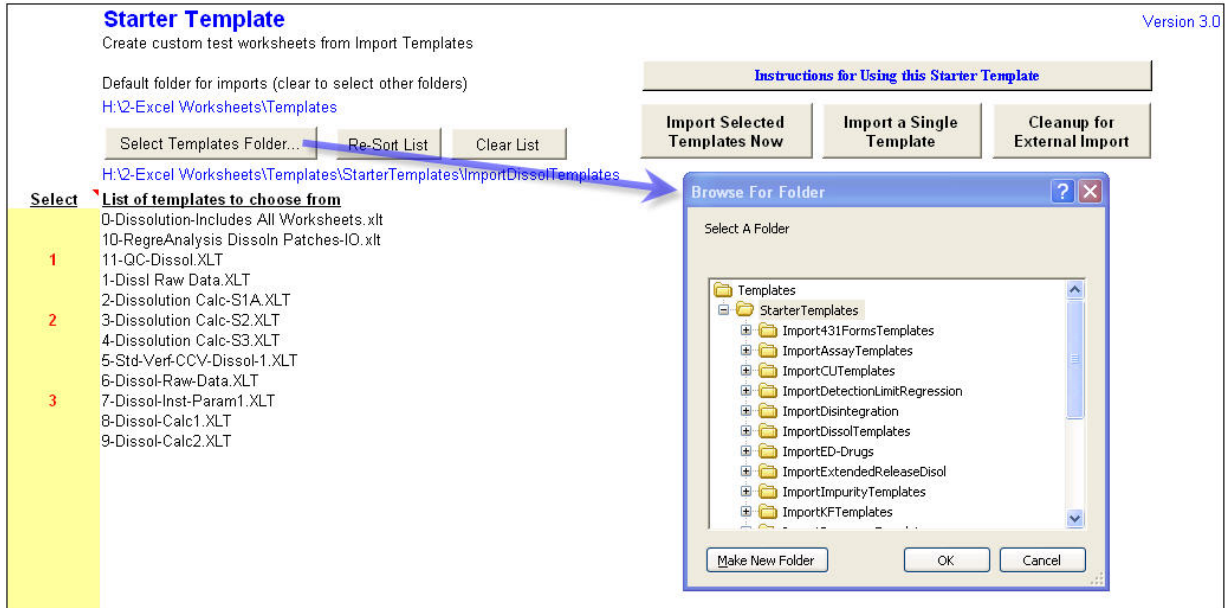
Figure 8. The ExcelSafe Main Screen has six main sections:

1. **Show Spreadsheets** allows the user to choose how to display the list of available spreadsheets. Available Spreadsheets displays the list of spreadsheets. The following is a description of each section under "Show Spreadsheets":
   - **"Templates"** is a list of available spreadsheets that displays all spreadsheets identified as Templates (XLT).
   - **"All Sheets"** depicts a list of available spreadsheets that displays all spreadsheets except Templates. The list is sorted by date opened.
   - **"My Recent Spreadsheets"** depicts a list of available spreadsheets that displays all spreadsheets recently opened by the user except Templates. The list is sorted by date opened.
   - **"Find"** is used to enter the desired search criteria in the Find field. The list of available spreadsheets will filter based on the search criteria. The Name, File Name, Location, Notes, Department and Project or Area fields can all be searched using Find.
2. **Spreadsheet Details** displays information about the spreadsheet, opens the spreadsheets and provides access to the audit trail.
3. **Add New Spreadsheets** allows users to add spreadsheets to ExcelSafe.
4. **Active Sheet Tools** provides access to program utilities. Sheet Tools include adding and removing electronic signatures and exporting the audit trail to the spreadsheet.
5. **Settings** provides access to system configuration, including security settings and migration settings.
6. **Management** provides access to Spreadsheet management tools.