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Use of Excel Spreadsheet Calculators in Handling Data Generated From UV- Spectrometer

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ABSTRACT

Various laboratory equipment is used in assessing the quality of pharmaceutical products. It is one thing to generate data, but the greater challenge lies in the ability of different analysts handling equipment to consistently use the data generated to obtain valid results.

From my experience as a Quality Control Analyst, a common error I observed when reviewing analytical notebooks was variation in the way calculations of concentration, for example, is handled by different analysts, largely due to their different ways of interpreting basic mathematical formulae.

To ease the complexities of handling data generated from different analytical procedures, validated excel spreadsheets containing relevant formulas are developed to ensure the process of data handling will consistently produce the expected results. There will be greater assurance on the integrity of data generated from these processes since the calculations will be done electronically using validated Excel spread sheets. Thus, this paper introduces the use of Excel spreadsheets in handling data generated from using a UV- Spectrometer in determination of analyte concentration in various dosage forms.

KEYWORDS

UV- Spectrometer, Data handling, Quality Control (QC), Quality Control Analyst, Excel Spreadsheets, Validation, Acceptance Criteria.

INTRODUCTION

To ensure that the medicines being used in a country are effective, safe and of good quality, it is necessary for the countries to have drug regulatory authorities supported by quality control laboratories (Africa, 1999) . The term "quality control" refers to the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical product. Such procedures may range from the performance of simple chemical experiments which determine the identity and screening for the presence of particular pharmaceutical substance to more complicated requirements of pharmacopoeial monographs (Shiham, 2014). One of the pieces of equipment used in the QC lab is Ultraviolet/Visible (UV/Vis) Spectrometer. UV/Vis spectroscopy is routinely used in analytical chemistry for the quantitative determination of different analytes. It uses the principle of Beer-Lambert law; that the absorbance of a solution is directly proportional to

the concentration of the absorbing species in the solution and the path length. Thus, for a fixed path length, UV/Vis Spectroscopy can be used to determine the concentration of the absorber in a solution (Mehta, 2012). The basic parts of a Spectrometer are: a light source, holder for the sample, diffraction grating in a monochromator or a prism to separate the different wavelengths of light and a detector.

Pharmacopeias contain monographs which are referenced work for pharmaceutical drug specifications. Some of these monographs have assay methods which employ UV-Spectrophotometer as the equipment in determining the concentration of analyte in different pharmaceutical dosage forms.

In conducting quality control tests on medicines using monographs from the United States, Pharmacopeia usually involves the concomitant use of Reference Standards at the same time as assay of the analyte of interest; whereas monographs from

the British Pharmacopeia may provide Relative absorptivity values, A^{11} , which precludes the concomitant use of Reference Standards.

Pharmacopoeia, pharmacopeia, or pharmacopoea (literally, "drug-making"), in its modern technical sense, is a book containing directions for the identification of compound medicines, and published by the authority of a government or a medical or pharmaceutical society.

Descriptions of preparations are called monographs. In a broader sense it is a reference work for pharmaceutical drug specifications (contributors, 2014)

The Problem

Handling data generated from equipment used for medicines analysis in a Quality Control (QC) laboratory is subject to some degree of variability. This may arise as a result of variations in the way QC analysts interpret mathematical manipulations of data. As a Technical Manager in a National Regulatory QC laboratory, I found some discrepancies the way different analysts handled quantitative data generated from the UV Spectrometer.

Project Purpose

- I. Ease the complexities of handling data generated by use of validated excel spreadsheet containing relevant formulas
- II. Ensure the process of data handling will consistently produce the expected results
- III. Greater assurance on the integrity of data generated from these processes since the calculations will be done electronically using validated Excel spreadsheets
- IV. Demonstrate that the results emanating from the National Agency for Food and Drug administration and Control (NAFDAC) QC Laboratory are accurate and reliable

Assumptions

- I. NAFDAC QC laboratory top management will play a vital role in reviewing the document generated while performing this project and they will be involved (especially the Deputy Director/Head of lab) in the various stages of this project to ensure they give the needed support.
- II. All needed documents can be generated and all relevant training can be conducted by the project leader.

- III. All unit staff will follow relevant SOPs to perform UV-Spectrometric analysis.

Delimitations

- I. Records of Equipment Qualification and Calibration/Verification, though very key in equipment performance, will not be included in this study.
- II. Analysts competency records for the various procedures will not be captured in the study.
- III. Individual SOPs for operating the UV-Spectrometer equipment under consideration will be omitted.
- IV. Protocol and results data for the validation of the UV-Spectrometer Excel Spreadsheet Calculator, though available in the NAFDAC QC lab, will not be included.
- V. The controlled UV-Spectrometer Excel Spreadsheet Calculator (currently in use) will be omitted.
- VI. Data integrity, which is a key concept in laboratory management, will not be covered under this study.

Limitations

The various excel sheet validation meeting set acceptance criteria

Summary

The excel spreadsheets developed for use in handling data from the UV Spectrometer were shown to have valid formulas. The validation results met the acceptance criteria stipulated in the protocols.

REVIEW OF LITERATURE

Covered topics on the use of spreadsheet for analytical work and problems encountered when using them. There were some discussions on the concept of Good laboratory Practices with some insight on the need for data integrity.

Methodology Of The Review

The following databases were used to search for relevant literature

- I. Purdue Library database
- II. Google scholar
- III. www.ICH.org
- IV. www.pharmamedtechbi.com
- V. Other data bases as outlined in reference section

Use of Spreadsheets for Analytical Work

Although spreadsheet programs are used for small "scratchpad" applications, they are also used to develop many large applications. In recent years, we have learned a good deal about the errors that people make when they develop spreadsheets. In general, errors seem to occur in a few percent of all cells, meaning that for large spreadsheets, the issue is how many errors there are, not whether an error exists. These error rates, although troubling, are in line with those in programming and other human cognitive domains. In programming, we have learned to follow strict development disciplines to eliminate most errors. Surveys of spreadsheet developers indicate that spreadsheet creation, in contrast, is informal, and few organizations have comprehensive policies for spreadsheet development. Although prescriptive articles have focused on such disciplines as modularization and having assumptions sections, these may be far less important than other innovations, especially cell-by-cell code inspection after the development phase (Panko, Revised 2008)

Good laboratory practice (Glp) regulations

The use of spreadsheets to judge the quality of a product is controlled by cGMP's, Glp regulations and ISO 17025 standards. The following are some of the requirements established by Glp regulations:

- **Configuration Management:** Quality assurance for managing software addresses all documentation associated with the system and is applied during all operational phases of software use, including the development and maintenance phases. It includes identification of changes, implementation of changes as reported and revalidation of formulas and workbook files at specified times or when the developer introduces a new version of the spreadsheet. If modifications upgrade or changes to the software have been implemented, one should perform regression analysis to determine what portions of the software that had not been changed might have been adversely affected by changes elsewhere in the software. In addition, conduct regression testing on those portions to determine if any new errors or problems were introduced.
- **Written Standard Operating Procedures (SOPs):** SOPs are defined at 21 CFR 58.81 (a) (2), as "A testing facility shall have standard operating procedures in writing, setting forth non-clinical laboratory study methods that management is satisfied are adequate to ensure the quality and integrity of the data generated in the course of a

study. All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management." (Regulations, 2014a)

- **Completeness of Data:** Validated analytical applications need a performance-monitoring program to establish data integrity and completeness. Compliance Policy Guide (CPG) 7132a.07 (21 CFR 211.68) defines the program for input/output (I/O) checking. The I/O test involves inputting a set of data packages that have an accurately known solution and checking this known solution against the result given by the software application. In addition, all workbook files should be preserved, controlled and maintained for future audits against the reviewed printed sample reports. A backup-and-restore system should be in place to ensure data completeness and security. A backup-and-restore SOP provides detailed instructions as to how to recover the spreadsheet files after a system failure, designate the backup location and define the schedule-and-restore methodology. The SOP should identify the person responsible for retaining backup records, including schedules or logs, the type and storage location of the media used, system failures and recovery logs.
- **Raw Data:** Raw data is defined at 21 CFR 58.3 (k) (2), as "any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observation and activities of a non-clinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study." In addition to hand written observations in ink on paper, "raw data may include photographs, microfilm, or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments." In the chemistry laboratory, the raw data from notebooks or paper worksheets can be entered manually into the computer spreadsheet program or can be directly collected (from balances, GC, LC, etc.) into the spreadsheet program, by means of an interface or a Laboratory Information Management System (LIMS). Under those circumstances, the spreadsheet becomes raw data. A worksheet generated by a spreadsheet program can be designed to be used as a fill-in-the-blanks worksheet for raw data. After the raw data is entered manually into the paper worksheet (fill-in-the-blanks worksheet), the worksheet becomes original data, which is the result of original observations. The raw data worksheet cannot be remade if errors are found. Errors cannot be erased or overwritten; a line

must be drawn through an incorrect entry and the correct figure or word written nearby and initialed. Also, significant data must not be discarded without explanation. Discarded analytical data must be crossed out, initialed, and the reason for discarding the data explained. (Regulations, 2014b)

- **Secondary Data:** The secondary data worksheet is used for the calculations and results, which utilize the data from the raw data worksheet (standard and sample weights and dilutions, sample dilution factor, etc.) previously developed and printed, which included the original observations. It can be remade if errors are found. To verify the secondary data spreadsheet (calculation and results sheet), data in the spreadsheet are checked against the printed and used raw data sheet (fill-in-the-blanks Excel Worksheet in which the blanks had been manually written). The results of the verification must be documented and the check analyst must sign for approval. A laboratory notebook in which raw data is entered manually also becomes original data and copies can be attached to the spreadsheet printout. The workbook files containing the raw data (fill-in-the-blank form) and secondary data worksheets should be preserved, controlled and maintained for future audits of the electronic file. In addition, a copy of the completed sample printout should include the name and "saved" date for the workbook file, and the software name, version and upgrade designations. (McCulloch, Woodson, & Long, 2014)

What is Data Integrity?

Data integrity is the assurance that data records are accurate, complete, intact and maintained within their original context, including their relationship to other data records. This definition applies to data recorded in electronic and paper formats or a hybrid of both. A good way to understand data integrity is through an analogy from the legal world. A data record is similar to a contract. A contract is valid only if all the pages of the document are complete and legible, contain the required, authentic signatures and properly state the terms and conditions. In this sense, integrity denotes validity.

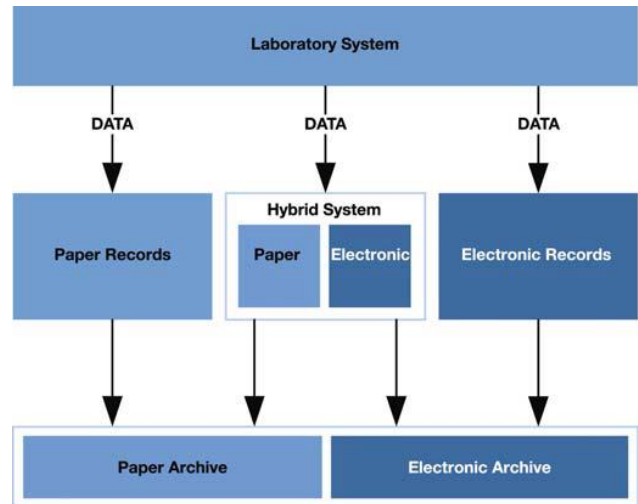
Ensuring data integrity means protecting original data from accidental or intentional modification, falsification or even deletion, which is the key to reliable and trustworthy records that will withstand scrutiny during regulatory inspections. (McCulloch et al., 2014)

To assure the quality of raw materials, in process materials and finished goods, laboratory data integrity is assuming greater importance in current Good Manufacturing Practices (CGMP) for US Food and Drug Administration (FDA)-regulated industry. Data integrity and security infractions are not only 21 Code of Federal Regulations (CFR) Part 11 issues, but also severe CGMP violations. The reasoning behind this complex issue is quite simple: if the integrity of laboratory data is compromised, batches of finished goods may not comply with regulatory authorization terms and, consequently, will not be released for sale.

As FDA increases its focus on data integrity and reliability, inspectors are examining data based on multiple regulations and standards including CGMP, Good Laboratory Practices (GLP), Good Clinical Practices (GCP) and the Application Integrity Policy (AIP), in addition to FDA-recognized consensus standards.

Challenges of Maintaining Laboratory Data Integrity

The first challenge in ensuring the integrity of laboratory data involves utilization of hybrid systems (See Figure 1) (McCulloch et al., 2014). If both are used, paper and electronic records need to be synchronized.



Not 21 CFR part 11 relevant

21 CFR part 11 relevant

Figure 1: Data Handling Alternatives

Computerized systems add a second challenge to laboratory data integrity due to the potential for electronic data manipulation. Such manipulation can include human errors when data are entered by mistake or intentionally falsified, and selection of

good or passing results to the exclusion of those that are poor or failing.

One example of how to overcome some of the challenges of managing data integrity is in the manual entry of critical data. After manual entry of the critical data is complete, a verification of the data entry can be performed by a second person or can be verified with the use of a validated computerized verification process.

The third challenge comes from system interfaces. If interfaces are used to transfer data from instrument to system or between systems, such as between the chromatography data system (CDS) and laboratory information management system (LIMS), the probability of data integrity issues due to human error is decreased but the validation burden and effort to maintain a validated state are higher due to the increased amount of validation testing needed when transferring data from one computer system to another.

Accreditation to the International Standard ISO/IEC 17025: 2005 General Requirements for Competence of Testing and Calibration Laboratories is an advantage to maintaining data integrity. The main difference between good analytical practices and accreditation is the amount of documentation produced. Although any good analytical laboratory uses qualified analysts, checks the performance of equipment used for testing and validates analytical methods, many times the outcome of the tests is not fully documented.

ISO/IEC 17025 accreditation requires formal documentation for nearly everything in the laboratory workflow (McCulloch et al., 2014)

Data integrity matters because properly recorded information is the basis for manufacturers to assure product identity, strength, purity and safety. Inaccurate manufacturing data, moreover, threatens to undermine FDA efforts to streamline regulatory processes, which is of particular concern to agency leaders. The aim is to focus agency resources on the greatest sources of risk to patients, while also reducing oversight of firms with "robust quality systems," which may benefit from "less interference from FDA" (Wechsler, 2014)

The concept of data integrity will be an area for future expansion of this current study.

FINDINGS PERTAINING TO THE METHODOLOGY OF CITED STUDIES & PROPOSED METHODOLOGY

Observed Spreadsheet Application Problems

The following spreadsheet problems were discovered during an FDA inspection of a QC analytical laboratory in a pharmaceutical firm. The QC laboratory failed to follow current good manufacturing practice (cGMP) (1) and good laboratory practice (GLP) (2) regulations. Also, basic principles of multi-user spreadsheet design, validation and documentation were not apparent. Spreadsheet files were not maintained and many were deleted. The SOPs for the spreadsheets were absent and validation and documentation procedures were not in use. These spreadsheet problems can also be present in FDA laboratories. Specific problems included the following:

- Nearly all of the spreadsheets in the laboratory showed rounding-off errors and none used the Excel rounding function when needed; this is to avoid rounding-off discrepancies between the original(spread sheet values) and check (e.g. manual calculations) performed by the second analyst.
- Formulas in the analytical procedures did not follow the Excel equations.
- Conversion factors were not expressed in the analytical procedures.
- The formulas used by the check analyst for manual calculations were not the same as those used in the Excel spreadsheets.
- The pre-determined specifications or limits were not shown in the spreadsheets.
- Spreadsheets were not clearly documented. For example, the product declaration was not indicated, replaced by only a number in a cell.
- Units were expressed as numbers without descriptive labels such as mg/mL or mg/g.
- Sample weights were described as sample volume and areas as ratios.
- Spreadsheets did not contain provisions for security and integrity of data.
- Spreadsheet applications were not protected from changes, meaning analysts could freely change labels and formulas.

- Regression analysis was calculated with the y and x axis inverted in the Excel formula, which generated erroneous slope and intercept results.

These analytical spreadsheet mistakes can be eliminated if the analyst (developer) ensures that each element in the spreadsheet application is uniquely and unambiguously defined.

As a minimum, simple spreadsheet validation documentation should include the following items:

- A description of what the program does and proper instructions
- Use of color-coding for data-entry
- A description of the mathematical formulas used
- An explanation of the relationship of the formulas in the analytical method to the Excel equations
- Listings for any macro programs (Cantellops, Bonnin, & Reid, 2002)

METHODOLOGY

Data Collection and Analysis

The use of UV-Spectrometer as a means of determining concentration of an analyte in different dosage forms is largely dependent on the monograph specification.

The sequence for sample preparation is described in individual drug monograph, but summarily it involves taking an equivalent weight of the analyte from a sample matrix, dissolving in a solvent, making dilutions and reading the absorbance of the resulting solutions.

Excel sheets were developed for the following dosage forms:

1. Tablet or capsule, containing calculators for the following parameters
 - a. Dilution factor for RS and Sample
 - b. Absorptivity, E^{1}_{1} or A^{1}_{1} value from Working and Control standards
 - c. Concentration of API (analyte) in drug sample
 - d. Calculation of Percentage Label claim
 - e. Conversion from salt to Base form
 - f. Calculating using purity factor
2. Syrups and Liquids, containing calculators for the calculation of Weight / ml, in addition to the parameters for tablets
3. Injections, containing calculators for the following parameters the calculation of Net

Weight, in addition to the parameters for tablets

4. Tablets or Capsules with A^{1}_{1} value, containing calculators for the following parameters
 - a. Dilution factor Sample
 - b. Concentration of API (analyte) in drug sample
 - c. Calculation of Percentage Label claim
 - d. Conversion from salt to Base form
 - e. Calculating using purity factor.
5. Syrups and Liquids with A^{1}_{1} value, containing calculators for the following parameters
 - a. Calculation of Weight / ml, in addition to the parameters for tablets with A^{1}_{1} value
 - b. Injections powder with A^{1}_{1} value, containing calculators for the following parameters
 - c. Calculation of Net Weight, in addition to the parameters for tablets with A^{1}_{1} value

In using the excel spreadsheet, a Standard Operating Procedure was developed to ease understanding of the use of the UV-Spreadsheet.

Validation of Spreadsheets

The validation protocol for a spreadsheet included the following information:

- Purpose
- Scope
- Responsibilities
- Formulas included in spreadsheet
- Location of formulas in spreadsheet
- Procedure
- Acceptance Criteria

1) The validation ensured that all standard application formulas contained in the spreadsheet produce the correct value.

2) The validation tested the formulas with data to prove that the spreadsheets produce the expected results.

3) The formulas were tested by performing the calculations by hand or calculator, comparing the output from the spreadsheet to a known and tested formula, or other means that can be substantiated with evidence.

4) The formulas in the spreadsheet were identified in the validation; the location of the formula were identified within the spreadsheet in the validation.

5) Acceptance Criteria were specified in the protocol. If the acceptance criteria are not met during the execution of the validation, the failure must be discussed in the final report.

6) All spreadsheet validation final reports were contained in an electronic copy of the spreadsheet. This electronic copy was placed on flash drive/disk.

7) All original testing of formulas were retained in the validation package.

After completion of the validation activities, a final report was documented.

Validation Protocol

A protocol was then written and executed for the validation of the UV Excel spreadsheets developed.

A summary of the protocol for validation of spreadsheet document involves:

- I. Obtain five (5) sets of data to be entered in the formula
- II. Enter each set of data into the spreadsheet
- III. Print copies of the spreadsheet with each set of data entered; the printed copy shall show the data entered as well as the result of the calculation performed by the formula in designated cells
- IV. Perform the calculation of the formula by first principle manual calculation; the formula shall be recorded on paper along with the data to be entered in the formula; a scientific calculator may be used, but the calculations shall be recorded on paper as well

Acceptance Criteria: The result of the calculation performed manually (scientific calculator) shall match the result of the calculation performed by the spreadsheet for each set of data entered.

RESULTS AND REPORTS

The UV- Vis Spectrometer excel spreadsheet calculator developed for handling data has different segments for data generated from analyses of various dosage forms; oral solid, liquid dosage forms as well as injectables.

The spreadsheet is color-coded to indicate cells that can be manipulated and others are 'locked' so that the mathematical formulae contained in them cannot be altered.

During UV-spectrometric analyses, weighed samples dissolved in specified solvents, produce

peak absorbancies proportional to the concentration of analyte (active pharmaceutical ingredient), at specific wavelenghts. The figures (2 & 3) below are representative sections of the UV-spreadsheet calculators. Figures 4 & 5 are representative sections of results showing the standard deviation and variance between manual and excel calculations.

8.1.1 CALCULATION OF DILUTION FACTOR FOR REFERENCE STANDARD									
			VOLUME TRANSFERED	VOLUME TRANSFERED					
VOL. OF 1ST	VOL. OF 2ND	VOL. OF 1ST	VOL. OF 3RD	VOL. OF 2ND	DILUTION				
ETRIC	ETRIC	ETRIC	ETRIC	ETRIC	FACTO R				
FLASK (ml)	CONST ANT	FLASK (ml)	FLASK (ML)	FLASK (ml)	FLASK (ML)	REF. ST D			
100	100	100	10	100	10	100			
8.1.2a ABSORBTVITY OR E11 CALCULATED FROM WORKING STANDARD(W/S) AND CONTROL STANDARD (CS) BEFORE SAMPLE RUNS									
NAME OF REF. ST D.	SAMPL E ID	WEIGH T OF WS(g)	WEIGH T OF CS(g)	ABS. OF WS	ABS. O F CS	DILUTI ON FACTO R	E11 FROM WS	E11 FROM CS	RSD(NM T 2%)
metfor min	530131	4	0.1007	0.1007	0.78125	0.7812	776.19	775.94	20.023223
				0.7824		0.7814			
				0.78124		0.7813			
				0.78163		0.0001			
				AVERAGE ABSORBANCE	0.78163	0.0001			
				STANDARD DEVIATION	0.00067	1			
				RELATIVE STD.DEVIATION (NMT 1%)	0.0140	0.08532	4		
8.1.2b ABSORBTVITY OR E11 CALCULATED FROM WORKING STANDARD(W/S) AFTER SP RUNS									
				ABS. OF WS (after runs)		E11 OF WS (after)		E11 OF WS B/4 AND AFTER RUNS (NMT 1.5%)	
				0.7845		777.2724263		0.097936601	
				0.7824					
				0.78124					
				AVERAGE ABSORBANCE	0.78271				
				STANDARD DEVIATION	0.00165				
				RELATIVE STD.DEVIATION (NMT 1%)	0.21112				

Figure 2: Section of the UV-Spreadsheet calculators.

8.3.1 CALCULATION OF DILUTION FACTOR FOR SAMPLE (POWDER INJECTIONS)

VOL. OF 1ST FLASK (ml)	VOL OF 2ND FLASK (ml)	VOLUM FROM 1ST (ML)	VOL OF 3RD FLASK (ml)	VOLUM FROM 2ND (ML)	DILUTION FACTOR FOR SAMPLE
100	100	50	1	1	50

8.3.2 CALCULATION FOR DETERMINATION OF NET WEIGHT

VIAL GROSS WEIGHT (g)	VIAL EMPTY WEIGHT (g)	NET WEIGHT (g)	% NET WEIGHT CLAIM
26.11	25.0572	1.0528	105.28

8.3.3 CALCULATION OF CONCENTRATION OF API IN SAMPLE(SP)

SAMPL E ID	WEIGH T OF SP(1)(g)	WEIGH T OF SP(2)(g)	WEIGH T OF SP(3)(g)	WEIGH T OF SP(1)	WEIGH T OF SP(2)	WEIGH T OF SP(3)	DILUTIO N FACTOR	NET WT. (g)
711851	4	0.0316	0.032	0.0321	0.29523	0.29924	0.2992	50
								CO NC. (1)(g)
								CO NC. (2)(g)
								CO NC. (3)(g)
								AVERAGE CO NC (1,2,3) (g)
								ST D. DEV.
								RSD (NMT 1%)

8.3.4 CALCULATION OF PERCENTAGE LABEL CLAIM

CONC. (1)(g)	CONC. (2)(g)	CONC. (3)(g)	LABEL CLAIM (mg)	% LABEL CLAIM (1)(mg)	% LABEL CLAIM (2)(mg)	% LABEL CLAIM (3)(mg)
1.00542	1.00634	1.003068	1000	100.542	100.634	100.307
				AVERAGE % LABEL CLAIM (mg)	100.4941482	
				ST D. DEV.	0.168612341	
				RSD (NMT 1%)	0.167783243	
				SPECIFICATION / LIMIT	90.0% - 110.0%	
				% LABEL CLAIM (mg) (Rounded up)	100.5%	
				COMMENT	SATISFACTORY	

Figure 3: Section of UV-Spreadsheet calculator

1.3.1 Calculation Of Concentration of API in sample (SP). (For All Dosage Forms).

1.3.1.1 Absorbance (SP) $E_1^1 * DF * AW/WT$

Data set S/N	STD between Excel and manual calculation	Variance between Excel and manual calculation	Comment (Acceptance Criteria- STD and Variance NMT 0.001)
1	6.823E-11 0.0007817	4.65476E-21 6.10998E-07	Meets Acceptance criteria
2	6.63E-12 3.11E-11	4.39E-23 9.66E-22	Meets Acceptance criteria
3	3.175E-08 1.947E-06	1.008E-15 3.79226E-12	Meets Acceptance criteria
4	3.037E-06 3.386E-06	9.22394E-12 6.07376E-14	Meets Acceptance criteria
5	1.318E-08 1.318E-08	2.05012E-16 2.05012E-16	Meets Acceptance criteria

Figure 4: section of results showing the standard deviation and variance between manual and excel calculations

1.11.1 Calculation of Rel.Std.Dev. of Concentration of API in sample (For All Dosage Forms).

1.11.1.1 $RSD = \text{STD.DEV} / \text{Mean (X)} * 100$

Data set S/N	STD between Excel and manual calculation	Variance between Excel and manual calculation	Comment (Acceptance Criteria- STD and Variance NMT 0.001)
1	2.6811E-06	7.18813E-12	Meets Acceptance criteria
2	0.00011995	1.43887E-08	Meets Acceptance criteria
3	1.9199E-09	3.686E-18	Meets Acceptance criteria
4	3.2713E-05	1.07014E-09	Meets Acceptance criteria
5	1.0504E-06	1.10341E-12	Meets Acceptance criteria

Figure 5: section of results showing the standard deviation and variance between manual and excel calculations

Validation Protocol parameters

The acceptance criteria was that 'the result of the calculation performed by hand shall match the result of the calculation performed by the spreadsheet for each set of data entered; Standard Deviation and Variance NMT 0.001 or using t-test, the t Stat (calculated) is less than t Critical and P is > 0.05'.

RESEARCH APPROACH

The study consisted quantitative experiments involving collecting quantitative data from the UV-Spectrometer.

Quantitative data was also employed in the creation and validation of the excel spreadsheet used in handling data generated from use of the equipment in quality control activities within the medicine laboratory. (Creswell, 2014)

Sampling method

Non-random/non-probability Convenience Sampling was used to choose data sets used for the validation of the excel spreadsheet developed.

Parameters

The general requirements used for validation of spreadsheets as outlined in Table 1.

Table 1

The validation protocol for a spreadsheet shall include the following information:

- a. Purpose
 - b. Scope
 - c. Responsibilities
 - d. Formulas included in spreadsheet
 - e. Location of formulas in spreadsheet
 - f. Procedure
 - g. Acceptance Criteria
1. The validation shall ensure that all standard application formulas contained in the spreadsheet produce the correct value. The validation shall test the formulas with data to prove that the spreadsheets produce the expected results. The formulas may be tested by performing the calculations by hand or calculator, comparing the output from the spreadsheet to a known and tested formula, or other means that can be substantiated with evidence.

2. The formulas in the spreadsheet shall be identified in the validation. The location of the formula shall be identified within the spreadsheet in the validation.
3. Acceptance Criteria shall be specified in the protocol. If the acceptance criteria are not met during the execution of the validation, the failure must be discussed in the final report.
4. All spreadsheet validation final reports shall contain an electronic copy of the spreadsheet. This electronic copy shall be placed on flash drive/disk.
5. All original testing of formulas shall be retained in the validation package.
6. After completion of the validation activities, a final report shall be documented.

Sample size

The validation of the spreadsheets involved (comparing results) between not less than five (5) data sets of manual calculations against Excel spreadsheet results.

Variables

Independent Variables

- Formulae and equations in the excel spreadsheets used for data processing.
- Protocols for excel sheets validation

Dependent Variables

- Excel spreadsheets for UV calculations
- Reports of validations

Instrumentation

The brand of equipment used to generate data for this study was a double beam spaced Perkin-Elmer UV-Spectrometer using 2cm quartz cells (cuvettes).

Data Analysis

Data generated for this study includes primary data from direct observations made by the analysts assigned to analyze the various samples on the UV-Spectrometer.

Data Conditioning

Microsoft Office Excel 2010 was used Spreadsheet calculators and results of validation. The Spreadsheets used for calculations are controlled. The cells that cannot be altered are colored while the

others can be manipulated. Microsoft Office word 2010 was used for all data that were recorded as word document. All data were periodically backed up using external hard drives dedicated to the equipment. The computer systems were adequately protected with up-to-date antivirus software. The computer systems were also Pass Worded to prevent un-authorized access.

DATA ANALYSIS

The under listed Procedure is outlined in the validation of spreadsheet document:

- I. Obtain five (5) sets of data to be entered in the formula.
- II. Enter each set of data into the spreadsheet.
- III. Print copies of the spreadsheet with each set of data entered. The printed copy shall show the data entered as well as the result of the calculation performed by the formula in designated cells.
- IV. Perform the calculation of the formula by hand. The formula shall be recorded on paper along with the data to be entered in the formula. A calculator may be used, but the calculations shall be recorded on paper as well.

Acceptance Criteria: The result of the calculation performed by hand shall match the result of the calculation performed by the spreadsheet for each set of data entered.

Results of excel spreadsheet validation

The reports of Excel vs Manual calculation: Comparison met the acceptance criteria stated in the protocol for validation of UV spreadsheets [The result of the calculation performed by hand shall match the result of the calculation performed by the spreadsheet for each set of data entered. Standard Deviation and Variance NMT 0.001].

The excel spreadsheets used for handling data from the various processes were shown to have valid formulas, the validation results met the acceptance criteria stipulated in the protocols

SUMMARY

The results obtained when the protocol for validation was executed showed that the manual calculations performed using mathematical first principles, were not significantly different from the data set handled using the excel spreadsheet.

The use of validated excel spreadsheets in handling data generated in quality control procedures,

reduced analyst errors and variabilities in data processing; ultimately leading to greater assurance in data quality and integrity

FINDINGS

The Excel spreadsheets developed for use in handling data from the UV Spectrometer were shown to have valid formulas, the validation results met the acceptance criteria stipulated in the protocols.

Thus, the validated spreadsheets can serve as reliable means for handling data when using the UV Spectrometer to ensure better accuracy and eliminate errors due to variations in analysts' understanding of operational mathematical formulae.

CONCLUSIONS

All the Excel spreadsheets developed met the requirements for validation and were thus suitable to be used to ease the complexities of handling data generated from the use of the UV-Spectrometer equipment.

The Validated Spreadsheets Calculators served as reliable means for handling data to ensure better accuracy and eliminate analysts' errors.

There was greater assurance on data integrity generated from these processes since the calculations were performed electronically using controlled spreadsheets.

What was the impact on the organization?

- I. Demonstrated accuracy and reliability of results emanating from NAFDAC QC lab
- II. Eased the complexities of handling data generated
- III. Validated excel sheet calculators for UV analysis
- IV. Culture of continuous improvement instituted; other Excel Spreadsheet Calculators have been developed for other procedures

What is the broader impact on the organization?

- I. Recognition as an ISO17025 Accredited Facility on ANSI website
- II. Model can be adapted by other Quality Control laboratories

Future Opportunities and Recommendations for Next Steps

- I. Develop additional procedures for new scope extension for the laboratory
- II. More emphasis on data integrity;
- III. a new focus of regulatory requirements for good laboratory practices

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