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An Effort at Improving Reliability of Laboratory Data in Titrimetric Analysis for Zinc Sulphate Tablets Using Validated Spreadsheet Calculators

M. A. Okezue, K. L. Clase, S. R. Byrn

***Abstract*—**The requirement for maintaining data integrity in laboratory operations is critical for regulatory compliance. Automation of procedures reduces incidence of human errors. Quality control laboratories located in low-income economies may face some barriers in attempts to automate their processes. Since data from quality control tests on pharmaceutical products are used in making regulatory decisions, it is important that laboratory reports are accurate and reliable. Zinc Sulphate ($ZnSO_4$) tablets is used in treatment of diarrhea in pediatric population, and as an adjunct therapy for COVID-19 regimen. Unfortunately, zinc content in these formulations is determined titrimetrically; a manual analytical procedure. The assay for ZnSO4 tablets involves time-consuming steps that contain mathematical formulae prone to calculation errors. To achieve consistency, save costs, and improve data integrity, validated spreadsheets were developed to simplify the two critical steps in the analysis of ZnSO4 tablets: standardization of 0.1M Sodium Edetate (EDTA) solution, and the complexometric titration assay procedure. The assay method in the United States Pharmacopoeia was used to create a process flow for $ZnSO_4$ tablets. For each step in the process, different formulae were input into two spreadsheets to automate calculations. Further checks were created within the automated system to ensure validity of replicate analysis in titrimetric procedures. Validations were conducted using five data sets of manually computed assay results. The acceptance criteria set for the protocol were met. Significant p-values ($p < 0.05$, $\alpha = 0.05$, at 95% Confidence Interval) were obtained from students' t-test evaluation of the mean values for manual-calculated and spreadsheet results at all levels of the analysis flow. Right-first-time analysis and principles of data integrity were enhanced by use of the validated spreadsheet calculators in titrimetric evaluations of $ZnSO_4$ tablets. Human errors were minimized in calculations when procedures were automated in quality control laboratories. The assay procedure for the formulation was achieved in a time-efficient manner with greater level of accuracy. This project is expected to promote cost savings for laboratory business models

***Keywords*—**Data integrity, spreadsheets, titrimetry, validation, zinc sulphate tablets.

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I. Introduction

PHARMACEUTICAL companies as well as regulatory authorities play important roles in ensuring the safety, efficacy and quality of medicines used for maintaining public health. However, there are instances where these institutions do not carry out their roles effectively, either intentionally or by human error. Laboratory processes which are non-automated are prone to calculation errors and the traditional wet titrimetric method of analysis falls into this category. The current method of analysis for $ZnSO_4$ tablets in many pharmacopoeias are complexometric titrimetric analysis. This method has several steps that require use of mathematical formulae which can be a challenge for many laboratory analysts. This research seeks to provide a model that can enhance the reliability of laboratory data generated from the titrimetric analysis of $ZnSO_4$ tablets.

Inaccurate laboratory data may lead to supply of poor-quality medicines, which elicit deleterious impact on the entire population. To mitigate this undesirable outcome, there are guidelines, required within the pharmaceutical space to ensure that medicines are consistently manufactured to produce the intended quality. In recent years, pharmaceutical inspections reveal that there is increasing amount of non-compliance with reliability of data submitted for regulatory decisions [1]. The WHO guideline for computer systems validation stipulates that data generated during manufacture of pharmaceutical products should meet the principles governing data integrity. Such records should satisfy the "ALCOA" (attributable, legible, contemporaneous, original and accurate) values for assuring data integrity [2]. In advanced economies, many laboratories automate their procedures to minimize human errors and improve data integrity. For low-and medium income countries, the cost of automating laboratory processes should not cause a barrier to comply with the requirements for maintaining data integrity. The use of alternative procedures, with sound scientific backgrounds can be employed to achieve the objectives of ALCOA. To demonstrate one of such mechanisms, this research automated the calculations for $ZnSO_4$ tablets assay which is prone to human errors inevitable in manual titrimetric analysis.

A. Use of $ZnSO_4$ Tablets in Vulnerable Populations

$ZnSO_4$ tablets are an essential medicine commodity in maintaining the health of children under five years of age. The World Health Organization (WHO) reported that over 155 million children, especially in Africa and Asia suffered stunted

growth as a result of zinc deficiency [3]. Important for cell growth and differentiation, a deficiency of this element in children impaired growth and increased risk of other infections [3]. Another report from the WHO recognized diarrhea to be the leading cause of death in under-fives, but supplementing dietary zinc was shown to be effective in controlling duration and severity of fluid loss in children that experienced episodes of the disease [4]. Furthermore, $ZnSO_4$ tablets was used in the treatment of viral pneumonia, which is reported to be common in low- and medium-income countries, with an incidence rate of 0.22 episodes per child-year [5]. Pediatric zinc prevented the disease occurrence when administered for over three months in children five years and younger [6]. The WHO recommended dose for in children is "20 mg per day of zinc supplementation for 10-14 days (10 mg per day for infants under the age of six months)" [4]. Zinc formulations were also found to be effective in inhibiting viral replication first in animal models [7], and later in management of patients infected with coronaviruses, SARS-CoV, MERS-CoV, and 2019-nCoV [8]-[10].

B. Instrumentation and Errors for Titrimetric Analysis

The encyclopedia of analytical chemistry describes titrimetry as a quantitative method that evaluates a compound through its reaction with a standardized titrant of known concentration. The end of the reaction is determined visually with the use of an appropriate indicator or instrumentally, using potentiometers, turbidimeters, Karl-Fischer titrators and other instruments [11]. Though one of the oldest analytical techniques, titrimetry is still widely applicable due to the simplicity of the equipment and skilled execution of the procedure, results in high precision of less than 0.2% at 0.01 moles/liter level. However, manual titrations are time consuming and the accuracy of the results depends on the analyst's skills and the ability to execute the somewhat complex calculations [12]. Furthermore, there are random and systematic errors associated with this method of analysis. Typical systematic titration errors include the use of in accurate titrants or indicators, use of incorrect calculation formulas, and other process mistakes that yield incorrect endpoint in analysis [13], [14].

The official method of analysis for $ZnSO_4$ tablets uses complexometric tritimetry to quantify the amount of elemental zinc in the formulation. This study introduces validated spreadsheet calculators for assay of $ZnSO_4$ tablets. The model provides a means for quality control laboratories to ensure consistency in the calculations associated with the manual titrimetric analysis, reduce human errors, and improve data integrity.

C. Objectives

1. Develop and validate spreadsheet calculators for the critical steps in the analysis of $ZnSO_4$ tablets
2. Provide a means for quality control laboratories to ensure consistency in the calculations associated with manual titrimetric analysis of $ZnSO_4$ tablets

II. METHOD

A. Research Design

In this quantitative study, two spreadsheet calculators were developed for $ZnSo_4$ tablets assay. And then we randomly selected five manually generated analytical data results for the tablets to validate the data generated from the spreadsheet calculators.

B. Research Question

For low-income economies, will spreadsheet automation for USP method of ZnSO4 tablets assay save costs and improve laboratory compliance to principles of data integrity?

C. Hypothesis for Spreadsheet Validation

To test for a significant difference between the means of values obtained by manual calculations and those generated using the validated spreadsheet: H_0: $H_M \neq H_S$

1. Alternative Hypothesis for Spreadsheet Validation

There is no significant difference between the means of values obtained by manual calculations and those generated using the validated spreadsheet: H_1: $H_M = H_S$ (H_0 = null hypothesis, H_1= alternate hypothesis, H_M = manually calculated replicate analysis values, H_S = validated spreadsheet generated replicate analysis values, $\alpha = 0.05$).

D. Process Flow in Spreadsheets

The spreadsheet calculators were designed from a flow chart of the USP assay method for $ZnSO_4$ tablets. The mathematical formulae at various stages of the analysis were input into various cells in the spreadsheets to perform the calculations. Two spreadsheets were developed for the procedure, the first was for the standardization process for the titrant, 0.1M EDTA, while the second handled the assay for $ZnSO_4$ tablets.

The first part of both spreadsheets was designed to acquire data that aid process traceability and control of document. The attributable data requirements included documented analyst-sample identification parameters, reagents and equipment information.

1. Spreadsheet Components - Standardization of 0.1M EDTA

The second section in the spreadsheet contains the determination of titrant volume used for blank and primary standard Calcium Carbonate ($CaCO_3$). The third part contains calculations for the actual molarity of the 0.1M EDTA solution. The spreadsheet was designed to generate a relative standard deviation (RSD) verification to assess repeatability of result obtained. If the RSD of the triplicate molarity results obtained is greater than 0.2%, there will be a prompt for a fourth replicate determination to be performed to attain the RSD limit. Subsequent failure to comply will be considered an analyst error in procedural accuracy. However, if the RSD criteria are met, the last section in the spreadsheet calculator leads to the final output for factor of the 0.1M EDTA volumetric solution.

2. Spreadsheet Components - $ZnSO_4$ Quantitation

The second section in the spreadsheet contains the assay procedure for tablet weights, and determination of volumes of titrants used for blank and samples. The third part contains calculations for $ZnSO_4$ concentration. The spreadsheet was designed to generate an RSD verification to assess repeatability of result obtained. If the RSD of the triplicate assay results obtained is greater than 1.0%, there will be a prompt for a fourth replicate determination to be performed to attain the RSD limit. Subsequent failure to comply will be considered an analyst error in procedural accuracy. However, if the RSD criteria are met, the last section in the spreadsheet calculator leads to the final output for percentage label claim for content of ZnSo4 per tablet.

3. Spreadsheet Validation and Acceptance Criteria

A protocol of validation was prepared, and the following acceptance criteria were set for validation: the result of the manual calculation shall match the result performed by the spreadsheet for each set of data entered. Standard Deviation and Variance not more than (NMT) 0.001 were established for results with single data output. However, for replicate data endpoints, the difference between mean values had significant p-value < 0.05 with alpha = 0.05 at 95% confidence interval.

To verify if the acceptance criteria were met, five sets of data were manually computed with a scientific calculator, and the results were compared to the spreadsheets' data.

4. Assumptions

To ensure proper audit trail, the validated $ZnSO_4$ calculators were intended to be integrated into a laboratory Information management system (LIMS). Through this or other secured mechanisms, only trained and authorized laboratory personnel can gain access to use of the spreadsheets using personal login credentials.

5. Control of Spreadsheets

The spreadsheets were designed to have a colored background for the areas where human interactions were not required; and white contrast reflected sections that could be manipulated.

III. Results

A flow chart adapted from the USP assay method for $ZnSO_4$ tablets was used to develop two spreadsheet calculators with three major sections illustrated in Table I. The flow chart, see Fig. 1, depicts the various steps and sub-procedures in the USP Monograph. There are 7-steps in the preparation and standardization of the Titrant (0.1M EDTA), which serves as the reference standard for the analysis. Additional 5-steps are required in the prepare other reagent solutions needed to complete the assay for $ZnSO_4$ tablet, see Fig. 1.

The first sections of the validated spreadsheet calculators, see Table I, contained details to identify 'who' did 'what', 'when' and 'how'. This gave information that ensured sample traceability or chain of custody and enforced good documentation practices. Please note the assumption that the calculators will be integrated into LIMS or computerized systems with access controls. Thereafter, the titrimetric analysis data are traceable and details of the tests are available for reviews and audits.

The second sections of the spreadsheets, see Table I, handled weights and titer determinations. Precision in replicate weights for titrimetric analysis is vital for $ZnSO_4$ tablets determination. Failure to achieve lower than 0.2% difference between replicate weights taken, will generally result in unacceptable molarity and concentration errors. This precision requirement was built into the spreadsheets to ensure analysts met that critical step when they take replicate weights and determine end titer volumes. Moreover, the procedure would only progress after the molarity criteria were satisfied. This feature ensured right-first time analysis; which otherwise would have been an error carried over to the end-point of the ZnSO4 tablets assays, with attendant wastes of laboratory reagents and manhour.

Calculations for average molarities and nominal concentrations, see Table I, were evaluated in the third sections of the spreadsheets. Here, the nominal concentration for the molarity of the 0.1M EDTA standard solution is maintained within 10% of the prescribed value, to ensure titrimetric accuracy is achieved.

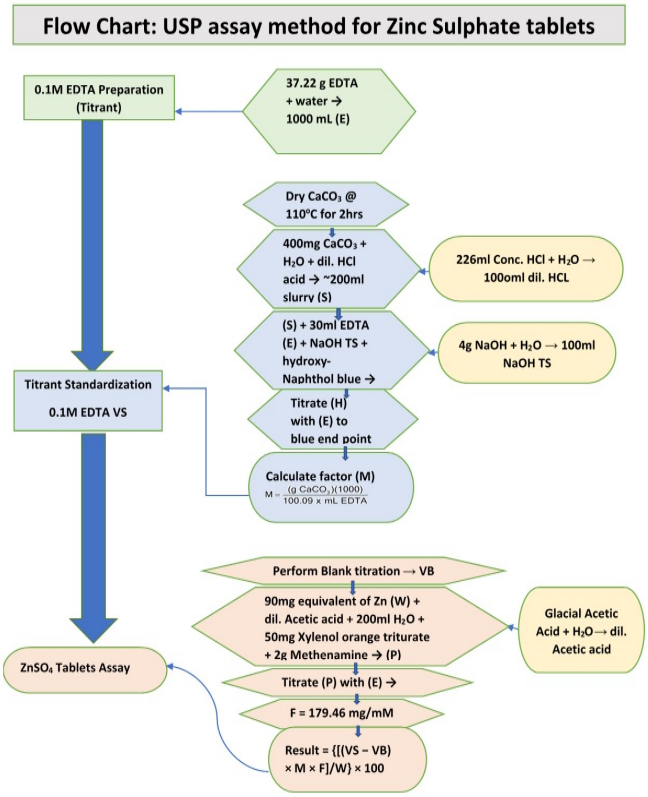


Fig. 1 Flowchart of USP method for $ZnSO_4$ assay showing the 12 major steps and sub-sections for the procedure

TABLE I
DIFFERENT SECTIONS OF THE SPREADSHEET CALCULATORS DEVELOPED FOR THE TWO-STEP ASSAY OF $ZnSO_4$ TABLETS

Section 1 — 0.1M EDTA solution standardization

STANDERDISATION OF VOLUMETRIC SOLUTIONS			
NAME OF SOLUTION	0.1M EDTA	Doc. Ref.	
DATE OF PREPATION	19/12/2016	Num	yyy-320-02
DATE OF STANDERDISATION	19/12/2019	Annexture	
LAB. NUM AWARDED SOLUTION	L2-VS-16-09-004		
BALANCE USED ID/CAL DUE	xx-AB-04 (12/2019)		
BURRETE ID	P19088 93sec		
STIRRER ID	xx-MS-02		
OVEN (DRYING CaCO3) ID /cal due	xx-OV-02 (12/2019)	DATE DRIED	9/9/2019
REAGENTS USED / ID			
EDTA	RGT-16-1485 (99+%)		
WATER	PW-1609-15		
CaCO3	ST-L2-1502-224		
PURITY FOR CaCO3 (e.g 0.9995)	0.9995		

Section 1 — ZnSO4 Assay

Document Reference #	xxxx-320-02
Annexture	1
ANALYST NAME /ID	STELLA
LAB (UNIT) / TEMP (°C)	AC1 / 23
DATE OF ANALYSIS	20/12/2019
NAME OF SAMPLE	Zinc Sulphate tablets
LAB . NUMBER	xx/yyy/2376/2019
BATCH NUMBER	
METHOD USED	USP 42
REAGENTS INFORMATION	
TITRANT: 0.1M Edetate disodium (Sodium edetate) VS	
DATE OF PREPATION	15/12/2019
DATE OF STANDERDISATION	15/12/2019
LAB. NUM AWARDED SOLUTION	L2-VS-19-12-003
FACTOR OF EDTA SOLUTION (M = actual molarity of titrant mM/mL)	0.1012
EQUIVALENCY FACTOR (mg /mM)	179.46

Section 2

METHOD USED	USP 42			
WEIGHING OF CaCO3				
	A	B	C	D
INITAL WEIGHT (g)	0.4005	0.4006	0.4006	0
FINAL WEIGHT (g)	0	0	0.001	0
WEIGTH TAKEN (g)	0.4005	0.4006	0.3996	0
TITRE DETERMINATION (EDTA SOLUTION)				
	A	B	C	D
INITIAL VOLUME (ml)	50	50	50	0
FINAL VOLUME (ml)	11.2	11.2	11.3	0
VOL. USED (ml)	38.8	38.8	38.7	0

BLANK DETERMINATION (V_B = Titrant volume consumed by blank)				
	A	B	C	D
INITIAL VOLUME (ml)	10	10	10	NA
FINAL VOLUME (ml)	10	10	10	NA
VOL. USED (ml)	0	0	0	NA
SAMPLE DETERMINATION (V_S = Titrant volume consumed by sample)				
	A	B	C	D
INITIAL VOLUME (ml)	10	10	10	NA
FINAL VOLUME (ml)	4.4	4.4	4.6	NA
VOL. USED (ml)	5.6	5.6	5.4	NA

Section 3

MOLARITY CALCULATION (M)				
FORMULA USED	A	B	C	D
WT. (g) * 1000*CaCO3 Purity / 100.09 * VOL USED (EDTA)	0.10308	0.10310	0.10311	0*D13)/(10
AVERAGE MOLARITY (M)	0.10310			
REPEATABILITY FOR MOLARITY				
FORMULA USED	A	B	C	D
AVE.MOLARITY(M) - M * 100 / AVE. MOLARITY (M)	0.02	-0.01	-0.01	7-G34)/E3
LIMIT	NMT 0.2%			

$ZnSO_4.H_2O$ CONC. CALCULATION (mg)				
FORMULA USED	A	B	C	D
[(VS − VB) × M × F]/W} × 100	20.3366	20.3407	19.6103	NA
AVE. $ZnSO_4.H_2O$ CONC.(mg)	20.0959			
RSD FOR CONC.				
FORMULA USED	A	B	C	D
STANDARD DEVIATION (S)	0.4205			
AVERAGE (AV)	20.0959			
RSD = (S/AV)*100	2.0925			
LIMIT	NMT 1.0 %			
COMMENT	satisfactory			
if RSD is greater than 1.0% repeat analysis using additional replicate WT (D) below				

The colored sections of the spreadsheets, see Table I, were secured and could not be manipulated, while the others were accessible to change entries made in them. Thereby, the users were only allowed to enter data into the fields which were non-colored but could not alter formulae and other information in fields that were colored.

Validation established consistency of the mathematical calculations controlled in the spreadsheets developed for the titrimetric analysis for $ZnSO_4$ tablets.

Two acceptance criteria were stipulated for the validation. Namely, for cells with single data output, a standard deviation and variance of not more than 0.001 will establish the results. And for cells with replicate data endpoints, the difference between the mean values should have significant *p*-value (< 0.05), at alpha = 0.05.

The results of five datasets generated by the spreadsheets, when compared to manually calculated data, met these acceptance criteria.

Results obtained from Fig. 2 and Table II indicated 100% validation compliance for weights and titer determinations in the second sections of the spreadsheet. Five sets of data manually determined with a scientific calculator, when compared to output from the spreadsheets gave significant *p*-values (minimum = 0, maximum = 0.0059) α = 0.05.

TABLE II
WEIGHTS AND TITER DETERMINATIONS OBTAINED FROM ALL DATASETS USED FOR VALIDATION IN SECOND SECTION OF SPREADSHEET

Dataset #	Max. *p*-value	Min. *p*- value	Acceptance Criteria (*p*-value < 0.05) for t-test satisfied, Yes =1, No = 0
1	3.51E-31	0	1
2	0	0	1
3	0	0	1
4	0.0059	0	1
5	0.00045	0	1

Acceptance criteria set for t-test was $p < 0.05$

All validation data sets had *p*-values less than 0.05, which provided the evidence needed to reject the null hypothesis that there was a significant difference between the manual and spreadsheet generated data. The alternative hypothesis was retained as all sets of validation data gave similar results. The validated $ZnSO_4$ spreadsheet calculators yield similar results to manually calculated process. Though manual computation is prone to human errors, the validated calculators are automated and error-free.

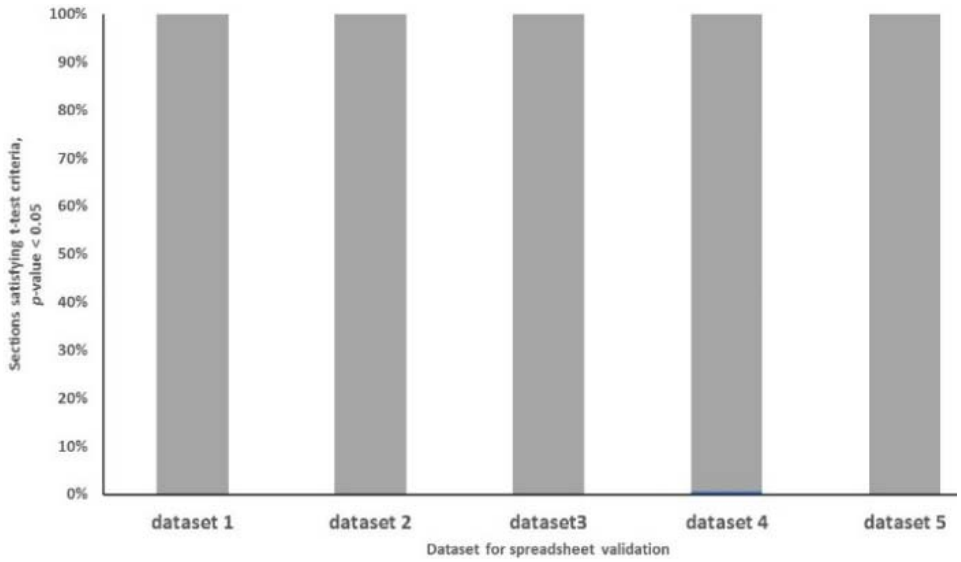


Fig. 2 Percentage of all validation dataset in second section of spreadsheet that satisfied acceptance criteria set for t-test, $p < 0.05$, for weights and titer determinations.

TABLE III
AVERAGE MOLARITY AND CONCENTRATION VALUES OBTAINED FROM ALL DATASET USED FOR VALIDATION IN THIRD SECTION OF SPREADSHEET

Dataset #	Max. SD & VAR	Min. SD & VAR	Acceptance Criteria (NMT 0.001) for SD & VAR. satisfied, Yes = 1, No = 0
1	0.000157	0	1
2	2.97E-06	0	1
3	2.04E-06	0	1
4	3.19E-07	9.91E-14	1
5	2.35E-06	0	1

Acceptance criteria set for standard deviation and variance NMT 0.001.

A similar 100% compliance to validation acceptance criteria were obtained for the third sections of the spreadsheet, which compared results of data with single output. Examples of these were in the results' output for molarity and concentrations, see Fig. 3 and Table III. All manually derived datasets, compared to spreadsheet generated results, gave standard deviations and variance not more than 0.001 (minimum = 0, maximum = 0.000157). This provided further evidence that the validated spreadsheet yielded similar results which would have been obtained by an error-free manual evaluation.

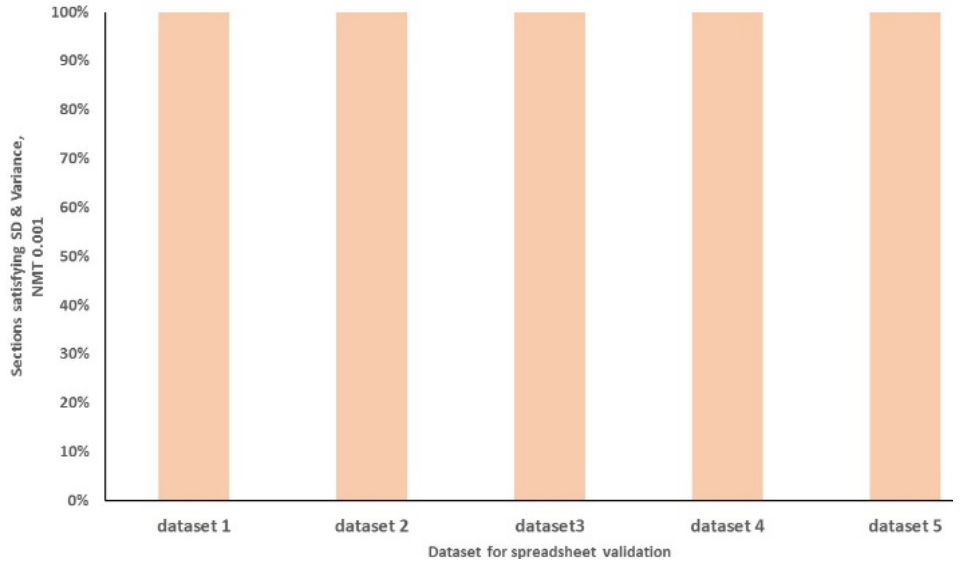


Fig. 3 Percentage of all validation dataset that satisfied acceptance criteria set for standard deviation and variance, NMT 0.001 in Average Molarity & Concentrations determinations, third part of spreadsheet.

Boxplots were used to further establish statistical relationship. The one-way analysis of the manual and spreadsheet results generated boxplots that indicated their average, and other percentile values, were statistically similar, see Figs. 4 (a)-(d).

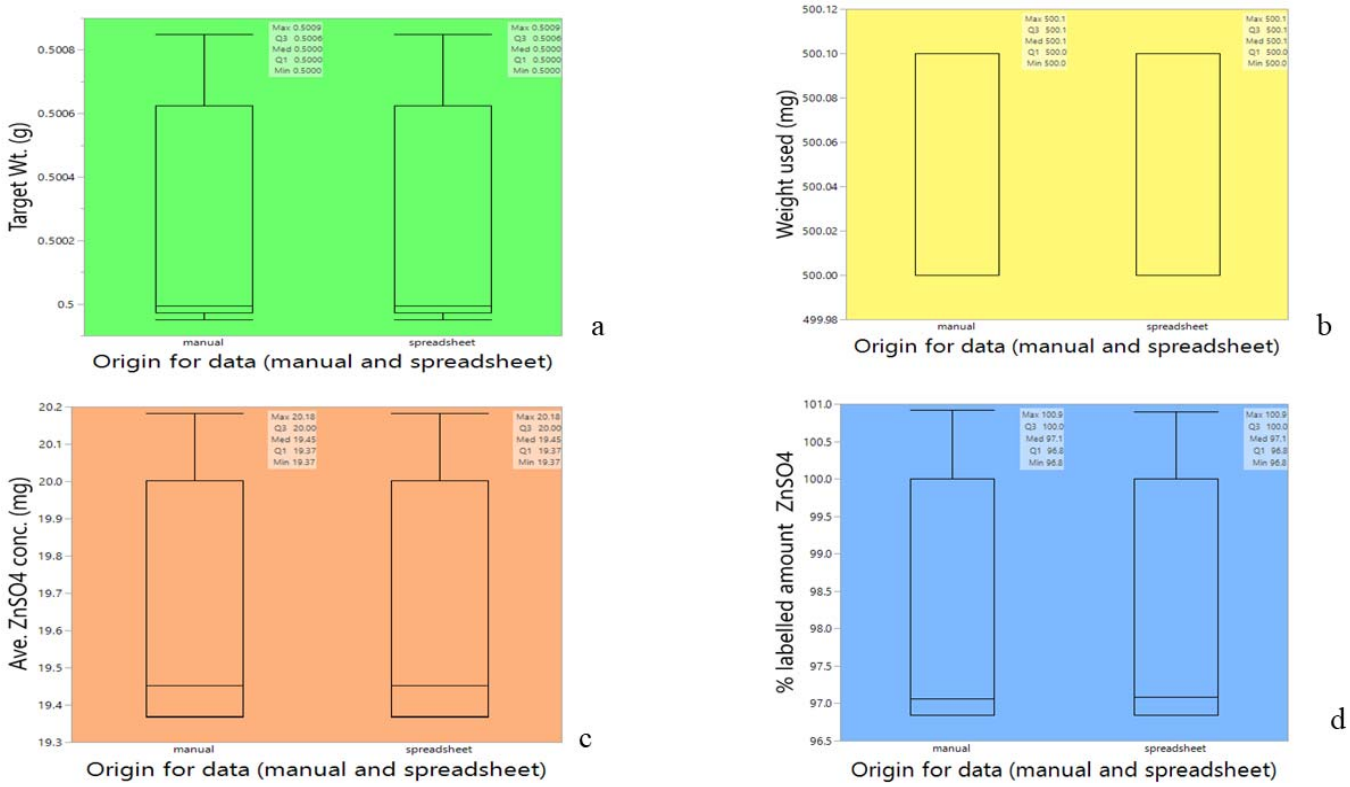


Fig. 4 (a) Box-plot for One-way Analysis of all data for Target Wt. (g) (manual = Spreadsheet), (b) Box-plot for One-way Analysis of all data for Weight used (mg) (manual = spreadsheet), (c) Box-plot for One-way Analysis of all data for Ave. ZnSO4 conc. (mg) (manual = spreadsheet), (d) Box-plot for One-way Analysis of all data for % labelled amount ZnSO4 (manual = spreadsheet)

The components of the spreadsheet calculator were designed to satisfy the requirements for data integrity contained in the WHO guidance for Good Data and Record Management Practices (GDRP). The design of the segments of the calculator engendered ALCOA principles, see Fig. 5 Furthermore, the laboratory reports for $ZnSO_4$ tablet assay will be non-amendable PDF formats in the LIMs system.

IV. Discussions

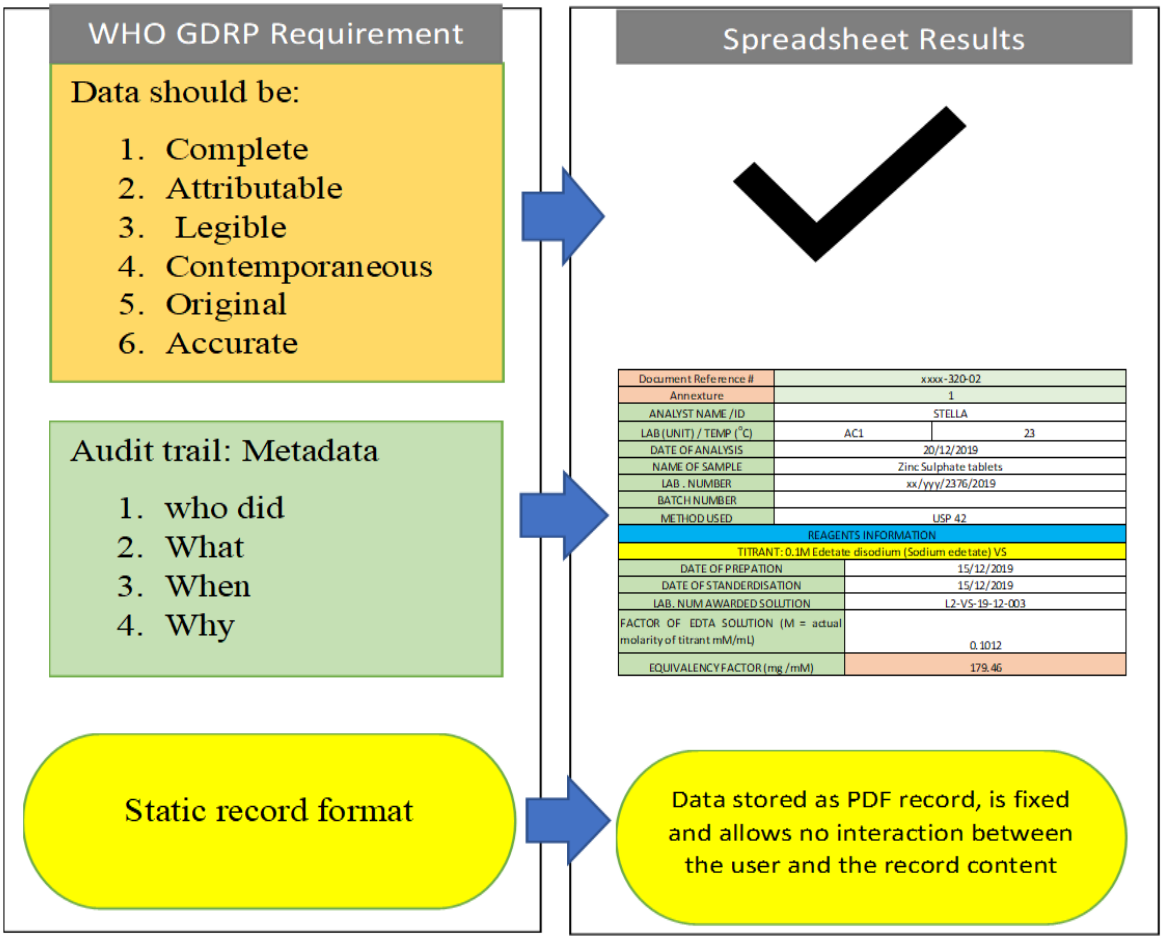
Titrimetric analytical procedure is used as the official method for quantitative determinations of some medicines used for life threatening conditions in vulnerable patient groups. Examples of these products include magnesium sulphate and calcium gluconate injections used in maternal health. The former is used in management of seizures in pregnant women with high blood pressure [15], [16], while the latter is used in the treatment of hypocalcemia [17]. Titrimetric analysis is also used for $ZnSO_4$, a life-saving medication for children losing body fluid through vomiting and diarrhea [18]. Due to several non-automated steps in the pharmacopoeia method for assay of $ZnSO_4$ tablets, it is prone to errors.

This work adds to the body of knowledge on the use of validated spreadsheets to improve reliability and accuracy of laboratory data, similar to other procedures that involve the use of validated spreadsheet calculators in laboratory processes [19]. Some authors also reported greater efficiencies in laboratory operations after they introduced spreadsheet calculators in their procedures, and minimized errors [20], [21].

A. Complexities in Evaluating $ZnSO_4$ Tablets

The official method of analysis for zinc, formulated as pediatric $ZnSO_4$ dispersible tablets in the United States Pharmacopoeia [22], British Pharmacopoeia and the International Pharmacopoeia [23] are titrimetric assays. $ZnSO_4$ tablets for pediatrics' use are formulated as dispersible tablets which is expected to dissolve in water within 1 minute [22]. From the IUPAC definition "…. titration is the process of determining the quantity of a substance A by adding measured increments of substance B, with which it reacts…." [24]. And, though there are modern methods for assay of medicines, classical titrimetry is an analytical method that involves various manual steps and little computerizations. Deployment of this method of analysis has associated uncertainties. A classic example includes difficulties in the visual detection of an end-point; as documented for volumetric measurements of hardness in water samples [25]. This error-prone end-point assessment is also needed for complexometric assays required in the evaluation of $ZnSO_4$ tablets [22]. Under similar complexometric determinations, Kimaru and his colleagues used classical titrimetric methods to evaluate the potency of calcium and magnesium injections [26]. Similar to the narrative behind the rationale for this current validation effort, the Kimaru et al. study equally elaborated the complex steps

needed to verify the products' label claims [26].



Document Reference #	xxxx-320-02	
Annexture	1	
ANALYST NAME /ID	STELLA	
LAB (UNIT) / TEMP (°C)	AC1	23
DATE OF ANALYSIS	20/12/2019	
NAME OF SAMPLE	Zinc Sulphate tablets	
LAB . NUMBER	xx/yyy/2376/2019	
BATCH NUMBER		
METHOD USED	USP 42	
REAGENTS INFORMATION		
TITRANT: 0.1M Edetate disodium (Sodium edetate) VS		
DATE OF PREPATION	15/12/2019	
DATE OF STANDERDISATION	15/12/2019	
LAB. NUM AWARDED SOLUTION	L2-VS-19-12-003	
FACTOR OF EDTA SOLUTION (M = actual molarity of titrant mM/mL)	0.1012	
EQUIVALENCY FACTOR (mg /mM)	179.46	

Fig. 5 Elements of the ZnSO4 Spreadsheet that met requirements for WHO guidance on Good Data and Record Management Practices (GDRP) for data integrity

B. Challenges of Laboratory Automation for Low-Income Economies

The costs for modern titrators range from $570s for automatic burettes (50 ml capacity) to $17,600 for Karl-Fischer equipment; these do not include other costs associated with maintenance and use of these automated systems [27]. Many laboratories in low- and medium-income economies cannot afford these costs, but they are still required to conduct analyses that meet international standards for accuracy of test results and data integrity. The $ZnSO_4$ validated spreadsheet calculators developed in this study offer an alternative affordable mechanism for these quality control laboratories to achieve reliable data for this convoluted method.

C. Regulatory Compliance for the Validated $ZnSO_4$ Spreadsheet

Similar to other laboratory processes, the ALCOA principles are important for maintain integrity of data generated in titrimetric analysis. The first section of the spreadsheet, together with access control in LIMS or computer systems hosting the calculators, have features that uniquely identify the originator of the tests. The other sections also capture samples, reagents and test details, as permanent data; which the analyst inputs at various steps in the assay procedure. Therefore, the records generated using the $ZnSO_4$ tablets spreadsheets will meet the regulatory requirements for ALCOA.

To improve accuracy of tests results, the intricate processes in titrimetric analysis of $ZnSO_4$ tablets, were simplified by the spreadsheet calculator. These included analytical steps where precision in weights and volumetric measurements were critical. At these points, the analyst must achieve the required repeatability between measurements, to proceed to the next steps. The validated $ZnSO_4$ calculator was designed to enforce the 0.2% repeatability for molarity between replicate determinations. Also, it ensured the difference between concentrations of prepared and prescribed solutions were less than 10%; a pharmacopoeia requirement for titrimetric analysis. These components in the spreadsheet ensure accuracy; the data are correct, truthful, complete, valid and reliable. These attributes are all part of WHO GDRP requirements for data integrity [2].

The final data generated are saved as non-amendable PDF formats in a repository with access control mechanisms which

ensures that the data cannot be retrieved without authorization. Thereby a data trail is available for audit reviews. By these attributes the spreadsheet met the WHO GDRP guidance requirements, which stipulate development of a data management program for electronic and paper records to have audit trails and preferably, results be stored in a static record format that restricts interaction between user and the record content

D. Proposed Impact from the Validated Spreadsheet

Use of the validated spreadsheets will improve laboratory efficiency and save costs. These will include expenses related to re-analysis due to out-of-specification (OOS) results from human error in calculations and time- costs of OOS investigations. Other cost benefits will include right-first-time analysis and regulatory conformance to requirements of data integrity.

V. Conclusions

Use of validated spreadsheets to accomplish assay of $ZnSO_4$ tablets ensured measures that improved data integrity. Laboratory data generated using this automated calculator removed human error and increased accuracy of titrimetric assay of tablets using the USP method of analysis. Furthermore, the validation effort enhanced compliance to requirements for WHO guidance on Good Data and Record Management Practices (GDRP). Data generated using the automated spreadsheets, combined with other laboratory quality management systems, were attributable, legible, contemporaneous, original and accurate, and thus met "ALCOA" principles.

Ultimately, the validation effort yielded improved reliability of laboratory data in titrimetric analysis for $ZnSO_4$ tablets. The Calculator is integrated as part of a LIMS, to meet regulatory requirement for data integrity.

Acknowledgment

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