Development and Validation of Calculation Data Sheets to Ensure the Accuracy and Security of Pharmaceutical Data Through Qa Procedures (Qaps)

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ABSTRACT:

Introduction: Quality stands as an essential prerequisite in the evaluation of any product and especially true for pharmaceuticals, for stringent standards of quality during their manufacturing process. In this consideration, the Food and Drug Administration introduced good manufacturing practices (GMP) and viewed validation as an integral part of cGMP. Validation studies have been conducted for a long time in industries. In recent times to better the quality of pharmaceutical products, industries emphasize quality assurance programs.

Objectives: This research has introduced a simplified and efficient method for validating Excel spreadsheets. The sheets are designed to fulfil the regulatory requirement, easy to use and developed itself by the users to assure the accuracy, integrity and quality of their data. This sheet should be validated and strictly follow the GMP and FDA 21 CFR part 11 regulations.

Methods: All the sheets are designed in Excel- 2013 following the regulatory requirements. The data is collected from the analytical laboratories following the standard procedures to perform the test.

Results: The sheets should validate and every action should be documented and all the sheets are assured to present the quality data with complete maintenance of the security, accuracy and integrity of the data. By following these principles, it is possible to fully validate and implement a standard spreadsheet in very less time.

Conclusions: The sheets provide the accuracy maintenance of data and calculations in order to protect the data from any unauthorised access. The good documentation and manufacturing practices alongwith the regulatory authorities made it important for getting regulatory compliance. Validation of process, equipment plays important role in assuring the quality of product while the excel sheets ensure the data integrity and protection from any modification. Therefore it necessary to validate the excel sheets as per the reference documents and to assure quality of the data.

1. Introduction

Quality stands as an essential prerequisite in the evaluation of any product and especially true for pharmaceuticals, for stringent standards of quality during their manufacturing process. [1]

In this consideration, the Food and Drug Administration introduced good manufacturing practices (GMP) and viewed validation as an integral part of cGMP. Validation studies have been conducted for a long time in industries. In recent times to better the quality of pharmaceutical products, industries emphasize quality assurance programs. [2]

In the mid-1970s, Ted Byers and Bud Loftus were the two FDA officials, who first proposed the concept of validation. This concept has broadened virtue to support a wide variety of activities from the quality control analytical methods of drug substances and products to computerized systems for clinical trials, research, and process control. This term is derived from the word valid or validity meaning "legally defined". [3]According to the FDA, "Validation" is characterized as the systematic procedure of gathering and analyzing data in order to establish scientific proof that equipment, utilities, or facilities can consistently produce products of high quality. [4]

COMPUTER SYSTEM VALIDATION

CSV (Computer System Validation) is synonymous with software validation. According to the FDA, validation is described as the process of verifying, through examination and presentation align with user requirements and intended

functions, and that specific requirements have been implemented accordingly.

Examination Confirmation

- Inspect the software to ensure that it meets the user requirements and that it will be suitable for the intended use.

Provision of objective evidence

- Software requirements must be identified.
- Documentation of all validated test results.

User needs and intended uses

- Software examination to ensure the fulfillment of user requirements

Particular requirements implemented through software

- Ensure that the standards can be met consistently.

In the pharmaceutical sector, validation judgment is crucial to ensuring adherence to pharmaceutical cGMP rules and assisting businesses in maintaining consistent quality. Computer systems or information technology systems can still be validated using the same basic principles. Validation of computer systems examines the efficacy and efficiency with which the system achieves there intended goals. [5]

They also provide custom support routine offering high-quality products to boost production process performance, scale back production prices, and improve product quality.

Successful validation includes:

- All standard supporting procedures are carried out satisfactorily
- Proper instructions
- Document management
- Change control
- Configuration management
- Traceability specifications
- Self-inspection and
- Deviation management

NEED OF CSV IN PHARMACEUTICAL INDUSTRY

✓ Helps in controlling different phases of development, design, testing and routine of the software life cycle.

✓ Helps deliver accuracy, security, reliability and consistency to pharmaceutical industry.

✓ Helps in finding time to time error, flaws and mistakes (software bugs) in order to minimize data integrity.

✓ Helps supports quality controls to ensure that the process is followed correctly, to reduce manual error.

✓ Helps improve product quality, to accelerate process performance, and to support high quality of product. [6]

ELEMENTS OF VALIDATION

- For quality assurance
- For time reduction
- For process optimization
- Better regulatory compliance
- Increased output
- Rapid automation [7]

QUALITY ASSURANCE

Quality Assurance (QA) is defined as all those planned actions needed to provide adequate confidence that products or services satisfy the given requirements of quality and be fit for use. It is the total of the activities aimed at achieving the required standard. [8]

Components of Quality Assurance

- Setting up the system
- The Quality Manual
- Training
- Standard Operating Procedure
- The Quality Assurance manager
- Auditing and checking compliance
- Maintaining Quality Assurance

Functions of Quality Assurance

- Ensures validation and qualification of designated formulations.
- Qualifies batches for scaling up to production batches.
- Assists in the design of validation protocols.
- Establishes clinical programs for manufacturing bio batches, aiming for FDA pre-approval clearance.
- Ensures the delivery of safe, effective, and high-quality medicines to patients.
- Encompasses technical and managerial activities necessary to fulfill all quality functions.
- Includes documentation, review of quality control laboratory tests, product performance.[9,10]

QUALITY ASSURANCE FRAMEWORK

Quality holds a significant place in the identity of the Institute and is one of the foundational elements of UNITAR's Six-Point Vision, which will guide its programming in the future. [11]

The QAF serves by incorporating these elements, the QAF ensures that the quality of UNITAR's training is upheld and provides a mechanism for continuous improvement and knowledge exchange in relation to quality matters. The Quality Assurance Committee (QAC), quality standards and guidelines, and self-assessment and review processes not only contribute to enhancing the quality of products and services offered by the Institute but also offer valuable opportunities for improvement. Additionally, they serve as a point of reference for external quality certification schemes and help facilitate the Institute's journey towards accreditation. By implementing these measures, UNITAR can ensure continuous enhancement of its offerings and align them with recognized quality benchmarks, both internally and externally. The framework in brief is shown in (Fig.1). [12]

Fig.1 Quality Assurance Framework

DATA COLLECTION AND QUALITY ASSURANCE

Data management refers to the comprehensive system that encompasses the gathering, purification, storage, oversight, analysis, and presentation of registry data. The effectiveness of this system plays a pivotal role in determining the data's suitability for achieving the registry's objectives. The database must conform to established quality standards, typically aligned with its intended functions. Additionally, specific data recipients might demand adherence to their individual guidelines or benchmarks during the data collection or validation processes. The framework of quality assurance regarding data management is shown in (Fig.2). [13]

Fig.2 Data Management System

PHARMACEUTICAL VALIDATION

In pharmaceutical industries, validation is one of the vital parts of quality assurance system; it involves the regular study of methods, equipments, facilities and processes for determining whether they produce consistent and constant results as per the pre-determined standards. To maintain the quality of system at every step and not just at the end is the main aim of doing validation. The validation activities mainly include production training, Standard Operating Procedures (SOPs), people, facilities and processes involved in that system. A process is said to be validated when it provides a high degree of assurance that uniform batches give specified results as predicted. [14]

The validated processes are helpful in understanding the Quality Management System (QMS) and also applicability of manufacturing processes. As per the FDA's perspective, ensuring the quality of a product involves meticulous and methodical focus on several crucial elements, which encompass the choice of quality processes involving both in-process and final product testing.[15]

According to the World Health Organization (WHO), validation is described as the comprehensive process of gathering and assessing data across a product's entire lifecycle, beginning from the process design phase and extending through commercial production. The goal of this process is to furnish scientific proof that a given process is capable of consistently producing a product of high quality. [16] The types of validation in pharmaceutical industries are given in (Fig.3).
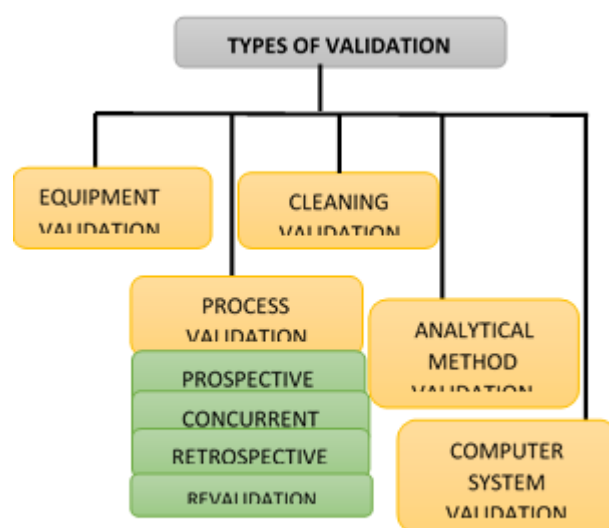

Fig. 3 Types of Pharmaceutical Validation

'V' for Validation

Good Automated Manufacturing Practice (GAMP) recommends a Software Development Life Cycle (SDLC) called the V-Model. The V-model as given in (Fig .4) in which left side gives the user demands while the right side gives the code modules.

The application of calculations within the field of pharmacy is diverse and wide-ranging. It covers a spectrum of calculations carried out by pharmacists in both conventional and specialized practice environments, spanning across operational and research domains in industries, educational institutions, and government entities. [18

Fundamentals of Pharmaceutical Calculations

Pharmaceutical calculations are the area of study that applies the basic principles of mathematics to the preparation, safe and effective use of pharmaceuticals. To have a complete understanding of various types of calculations which are involved in dispensing, it is desirable that the pharmacist should have a thorough knowledge regarding the mandatory calculations. [19]

QUALITY OF ANALYTICAL DATA AND VALIDATION [20]

- **Instrumental Signals**

- **Calibration Methods**
  - External Standard
  - One Point Calibration
  - Internal Standard
  - Standard Addition
- **Analytical Procedures**
- **Validation**
  - Specificity
  - Accuracy
  - Precision
  - Detection Limit
  - Quantitation Limit
  - Linearity and Range
  - Robustness
  - Test Methods in Ph. Eur. and USP
- **System Suitability**
  - Adjustment of Chromatographic Conditions
- **Chemical Analysis of Pharmaceutical Ingredients**
  - Pharmaceutical Ingredients, Production, and Control
  - Impurities in Pharmaceutical Ingredients
  - Impurities in Pure Chemical Ingredients
  - Impurities in Organic Multi-Chemical Ingredients
- **Identification of Pharmaceutical Ingredients**
  - IR Spectrophotometry
  - UV-Vis Spectrophotometry
  - Thin-Layer Chromatography
  - Melting Point
- **Impurity Testing of Pharmaceutical Ingredients (Pure Chemical Ingredients)**
  - Appearance of Solution
  - Absorbance
  - pH and Acidity or Alkalinity
  - Related Substances
  - Residual Solvents
- **Identification and Impurity Testing of Organic Multi-Chemical Ingredients**
  - Oxidizing Substances
  - Acid Value
  - Hydroxyl Value
  - Iodine Value
  - Peroxide Value
  - Saponification Value
  - Unsaponifiable Matter
  - Other Tests
- **Assay of Pharmaceutical Ingredients**
  - Aqueous Acid–Base Titration
  - Non-Aqueous Acid–Base Titration
  - Redox Titrations
  - Liquid Chromatography
  - UV-Vis Spectrophotometry
- **Identification of the API**
  - Identification by IR Spectrophotometry
  - Identification by Liquid Chromatography
  - Identification by UV-Vis Spectrophotometry
- **Assay of the Active Pharmaceutical Ingredient**
  - Assays Based on Liquid Chromatography
  - Assays Based on UV Spectrophotometry
- **Chemical Tests for Pharmaceutical Preparations**
  - Tests for related substances
  - Uniformity of content
  - Dissolution
- **Titration Calculations**
  - Titration of a pharmaceutical ingredient and calculation of purity (assay)
  - Preparation of primary standard (0.1 M potassium hydrogen phthalate)
  - Standardization

SPREADSHEETS

The spreadsheet is a collective computer application for analyzing and storing data in a tabular format valid for many organizations. They have replaced paper-based documentation throughout the business world. Although earlier they were used for accounting or bookkeeping tasks nowadays they are used in multiple contexts where tabular lists are built, sorted, shared, and stored. [21]

EXCEL SHEETS/ SPREADSHEETS /DATASHEETS VALIDATION

In the laboratory, various types of equipment are used to examine the quality of products. The greater challenge for analysts is the interpretation of the analysis data. Hence, Excel is the most popular software application for automatic calculation and data visualization. The use of spreadsheets in cGXP= GMP, GLP, and GDP must be controlled and validated. Spreadsheets are also used for testing acceptance criteria and as a database view tool i.e. there additional application. [22]

These sheets should strictly follow Good Manufacturing Practice and the FDA 21 CFR Part 11 electronic records and electronic signatures regulation. A comprehensive approach in the development and validation of the spreadsheets is necessary to validate the data. Spreadsheets used must be multipurpose rather than single-purpose. [23]

Eg: A spreadsheet used for more than one product or a spreadsheet producing multiple results for single data set. Like weight variation evaluation as per European Pharmacopeia (EU), British Pharmacopeia (BP), and Indian Pharmacopeia (IP). [24]

BENEFITS OF SPREADSHEETS VALIDATION

Validation is required by the FDA to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records. At Ofni Systems, we view validation as an opportunity to add value to your computer systems. Validating your spreadsheet allows you to:

- Submit data to regulatory organizations.

- Use data to make quality and GxP decisions.

- Control your data and define who has access to the data.

- Ensure your spreadsheet performs to specifications.

- Query your data to better understand your business process.

- Have documented evidence that your processes work as expected.

- Have increased confidence in your system. [24]

DEVELOPMENT OF SPREADSHEETS

Designing of the spreadsheet should be:

- In an orderly manner

- Data should be populated automatically, by a system, or manually by an operator

- It should provide a good summary concerning its objective or purpose

- It should provide well-defined operations (e.g., limit checks, transfer of data to other spreadsheets, online generation of, use of macros), and calculations.

- Results of each individual product should be easily traceable.[25]

KEY POINTS OF SPREADSHEETS

1. The spreadsheets can be used easily for other products

2. The spreadsheet shall be flexible to give results if values are changed

3. The spreadsheet should have clear visibility of data used for result calculations

4. The spreadsheet validation and revalidation should be performed easily

5. The spreadsheet cells containing critical information should be protected to avoid any changes or manipulation. [26]

CREATION OF SPREADSHEETS

The spreadsheet's design should be:

- Organized and structured

- Data entry should be done either automatically or manually by the user

- Able to summarize a clear description of its goals and objectives

- Able to include clearly defined procedures (such as limit checks, data transmission to other spreadsheets, online creation, and usage of macros), computations

- Able to provide results that are simple to track for each unique product. [27]

OBJECTIVE OF SPREADSHEETS

1. The spreadsheets are simple to utilize for different goods

2. The spreadsheet must be adaptable to produce results even if values alter.

3. The data that is utilised to calculate results should be readily visible in the spreadsheet.

4. It should be simple to validate and revalidate the spreadsheet.

5. To prevent modifications or manipulation, the spreadsheet cells holding important data should be secured. [27]

APPROACH TO SPECIFIC PART 11 REQUIREMENTS

Title 21 of the Code of Federal Regulations Part 11 (21 CFR Part 11) is a set of regulations established by the U.S. Food and Drug Administration (FDA) that specifically governs electronic records and electronic signatures in the context of pharmaceutical, biotechnology, and medical device industries. These regulations outline the requirements for the use of electronic systems in capturing, storing, and managing data that is subject to FDA regulations. Compliance with 21 CFR Part 11 is crucial for companies operating in FDA-regulated industries to ensure the integrity, confidentiality, and authenticity of electronic data and to maintain regulatory compliance. It covers aspects such as the security of electronic records, validation of computer systems, audit trails, electronic signatures, and documentation practices as shown in (Fig.1.5) .[28]
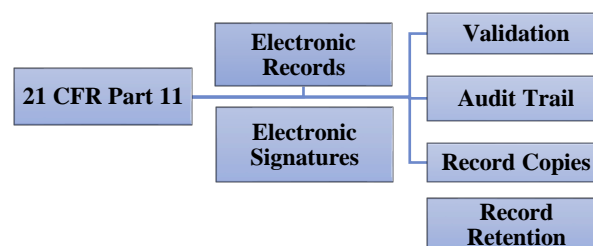

Fig. 5 Criteria for 21 CFR Part 11

OVERVIEW OF EXCEL SPREADSHEET

Spreadsheet software of today can contain numerous interconnected sheets, execute basic mathematical and arithmetic operations, and display data either graphically or as text and numbers. For typical economical and scientific activities, it offers integrated functions. In contrast, a spreadsheet manipulates numerical data, text and the formula or the information. Spreadsheet can be useful in creating budgets, data analysis, financial planning, and to perform the critical numerical operations. These sheets have tendency of automatic recalculation, self feeded formulas by the user, or by default included math functions, along with this changes in already given command or formulas could also be seen enhances the monitoring and error findings. [29]

How to start Excel

- Go to **START OPTION** on the windows taskbar

- It can be find in the search bar as well

• Click on **MS- Excel option,** the window appears as shown in (Fig.1.6). [30]
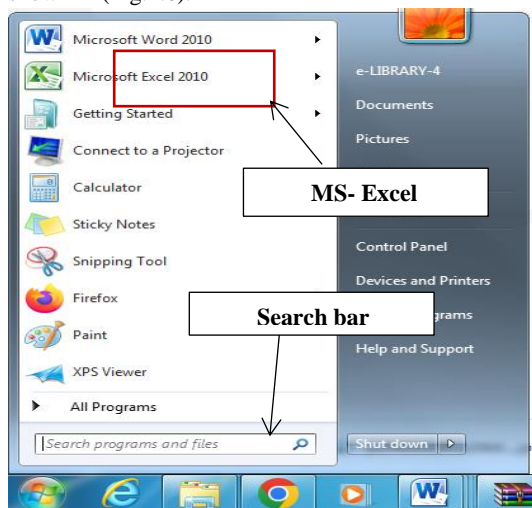

Fig. 6 MS - Excel

In the (Fig.1.7) given below the large window, labeled "Microsoft Excel" may take up the entire screen. This is referred to as the Application Window. The top line is called the Title Bar and has three buttons (Minimize, Restore, and Close) to the right. These buttons are used to size the window and close it. This title bar is standard in all Windows programs. [30] The second line is called the Menu Bar. Notice that one character of each selection is highlighted or underlined. This menu bar is also standard in all Windows programs. The next two lines contain buttons with text or images and are referred to as the Standard and Formatting Toolbars. If you have a mouse, these toolbars allow you to enhance your worksheet without accessing the menu. Keep in mind that these may not be in the exact same place as on the illustration above. All toolbars can be customized to display any buttons you desire. [31] The next line is the Formula Bar and displays the current cell address and contents. As you move from cell to cell, Excel will keep track of the current cell address for you. The Formula Bar can also be used to edit the text (contents) or formulas contained in the cell. [32]

The Excel Screen
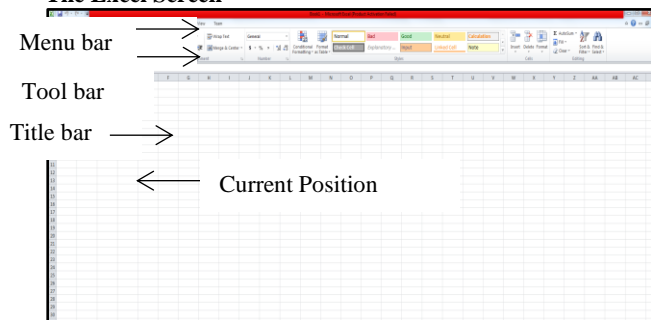
Fig.7 MS - Excel Screen

2. Objectives

NEED OF SPREADSHEET VALIDATION

During an FDA inspection of a QC analytical laboratory in a pharmaceutical firm, several spreadsheet problems were identified. These problems indicate a failure to adhere to current good manufacturing practice (cGMP) and good laboratory practice (GLP) regulations. Furthermore, the laboratory lacked proper multi-user spreadsheet design, validation, and documentation practices. Some specific problems observed in the laboratory include as described in (Fig.1.8). [33]

There are some more problems as follows:

• One specific problem identified in the QC analytical laboratory was the presence of rounding-off errors in nearly all the spreadsheets. Rounding-off errors can occur when numerical values are truncated or approximated without considering the appropriate rounding rules.

• Proper excel equations are not followed to put formulas into the sheets.

• No expressions of conversion factors in the sheets.

• Unmatched formulas used for manual calculations and excel calculations.

• The standard limits were not mentioned in the spreadsheets.

• No clear documentation of spreadsheets.

For example, No clear indication of product statement replacing it by number in a cell.

• No labels such as mg/g, mg/ml is provided for unit expressions.

• No provision to maintain data integrity and security.

• Sheets are not protected from unauthorized changes and access. [34]

Unique designing of these analytical spreadsheets by the user itself can remove these errors. A modest confirmation document must have following points:

• Properly describe the programme, its use and working.

• Entries of data should be color coded.

• Properly described calculation formulas.

• Appropriate relationship between excel equations and formulas.

• Macro functions must be listed. [35]

• Investigation sheets with projected and authentic outcomes, contracted and studied, that have been confirmed by physical calculations.

• Properly secured and password protected.

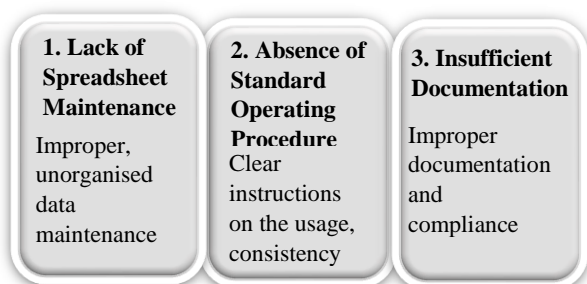• Installation date, version no. and system type.

Fig. 8 Some specific problems of spreadsheet validation

SPREADSHEET DESIGNING

The framework of an Excel spreadsheet is almost identical to that of an electronic programme. Spreadsheet formulas are essentially a type of computer code. Alternative to generate the template file and then verifying for mistakes, check for problems throughout the different phases of the creation process. A spreadsheet model is a collection of spreadsheets and custom sheets that are used to analyse and organize data or to solve a specific issue. This designing in appropriate format is shown in (Table 1.1) [18]. The sheets shall be designed in such a way that they are easy to understand and 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. [36]

Table 1 Steps of Spreadsheet Designing

S.No	STEPS	DESCRIPTION
1.	**Flexible Designing**	• Vertical calculation scheme should be promoted. • All the formulas should be written above its respective cells [19]. • Proper color formatting, border style and color should be done appropriately [20].
2.	**Typical Outline**	• **Documentation** – Must contain the title, scope, author name, list, macros and outlines. • **Menu** – A one click consist of user instructions such as drop down list, data entry location etc.
		• **Conventions** – Consist of assuming data in the sheets. • **Manuscript expectations** – Transparent documentation of assumptions made in formulas. • **Data**- This file contains raw data, such as data records from which the model will execute computations. • **Calculations** – Division of sheets into series computation stages, and the make one sheets with different series and stages. etc. • **Results** – The end part should contain the final conclusion alongwith the predictions done [22].
3.	**Clear Visibility of formulas**	• Ensures flexibility of model by reducing recalculations. • Formula shall be written into different cells instead of writing it in single cell, give cell comments wherever needed.
4.	**Control Measures**	• Checks and control measure shall be included such as "IF and ERROR conditions to avoid mistakes such as #N/A, #VALUE!, #REF!, #NUM!, #NAME?

STEPS IN PERFORMING VALIDATION

The steps followed while performing the validation are as follows:

Validation Planning

↓

A comprehensive document consisting of actions done, approaches, schedule and validation activities.

Validation procedure

↓
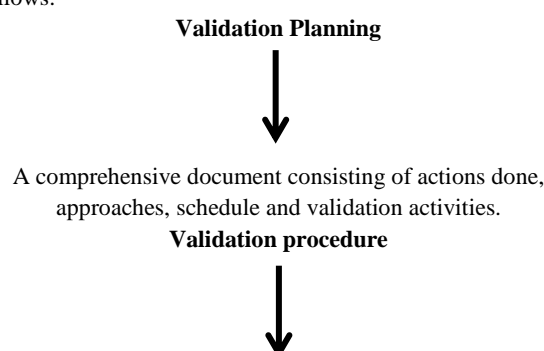
The validation procedure should be divided into an Installation Qualification (IQ) and Performance Qualification (PQ) [23].

Installation Qualification

It consists of the points to establish the confidence that the results are in compliance with the regulations.

Performance Qualification

PQ will systematically, strictly and constantly test the software by testing all involved and resultant values, records, procedure, and control flow logic [24].

Validation report

The verification report should include complete validated results, particularly the outcomes of the tests. When feasible, evaluations should be reported quantitatively rather than as "pass/fail." Qualified authority must assess and consent to the report.

Validation Lifecycle

It consists of preservation, controlling and maintenance of the validated sheets. These controls include computerized systems and it compliance with the regulations. Some controls to support the system includes

- Preventive Maintenance
- Environment Control
- Monitoring of performance
- Retention
- Recovery
- Training to users, developers and administrators

Validation Documentation

The following points should be considered while validating an excel sheet as described in (Fig 1.9). Every worksheet taken into process must be fully documented consisting of all formulas, macros, and user interface elements alongwith their copies in the validation documentation [25].

Operational Change Control

Changes to spreadsheet apps must be managed while in use. This modification management must be established from the stage in the creation life cycle where an individual begins to use the programme and will continue throughout the application's existence. [37]
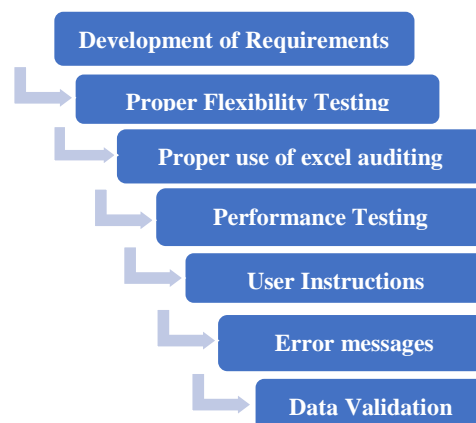
Fig. 9 Elements of Validation Documentation

DATA

Data are quantitative or qualitative facts, figures and statistics collected for reference or analysis.

Data may be captured or recorded:

- By manual recording, on paper or in an electronic system, of an observation or of an activity;

- By automatic recording, on paper or in an electronic system, using equipment that range from simple instruments through to complex highly configurable computerised systems

- Using a hybrid system where combinations of paper and electronic records constitute the raw data

- On other means of media such as photography, imaging methods and technologies, etc. could be generated manually, automatically or by hybrid system.

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. [37]

DATA VALIDATION

Data validation is the activity where one decides whether or not a particular data set is fit for a given purpose. The decision is based on testing observed data against prior expectations that a plausible dataset is assumed to satisfy. A straightforward formalization is to define it as a function from the collection of data sets that could have been observed to True or False.

DATA INTEGRITY

➢ It is done to avoid intentional, accidental falsification or deletion of data to withstand data quality during regulatory inspections

➢ Data integrity and security infractions are not only 21 (CFR) Part 11 issues, but also severe cGMP violations.

➢ It plays a very crucial role in USFDA audit. It is important to back up the data containing valid reports from the entire department.

➢ It is important to ensure the data quality in order to offer a quality product to fulfill the customers' requirements.

➢ It is a critical aspect of data management and is essential for ensuring that data is trustworthy and can be relied upon for making informed decisions, conducting research, or supporting business operations. [38]

TYPES OF DATA INTEGRITY

On the basis of mechanism and data integrity stream integrity can be divided as shown in the (Fig 1.10).
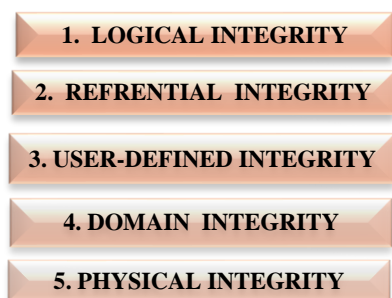
Fig. 10 Types of Data Integrity

LOGICAL INTEGRITY (LI)

It is a crucial component of DI since it involves a physical integrity procedure and safeguards data from human mistake, piracy, and data hackers. In the pharmaceutical sector, logical integrity is crucial for the preservation and processing of data collected from the appropriate department.

REFERENTIAL INTEGRITY (RI)

Integrity can take many different forms, including procedures and the application of laws related to data storage and retrieval. Foreign keys are a crucial component of referential integrity.

USER-DEFINED INTEGRITY (UDI)

Data acquired via post-marketing monitoring and information gathered from pharmacovigilance supervisors is specific to a certain group of people in the pharmaceutical sector. The process of integration requires that the data be user-defined.

DOMAIN INTEGRITY (DI)

Because the operational records of the pharmaceutical sector contain many different sets of regulations and processes, this data may be streamlined and saved by using the DOI technique.

PHYSICAL INTEGRITY (PI)

There are several ways in which different elements might impact the data integrity process and storage. One of the elements outside of one's control is one's wishes. Earthquake, flood, tsunami, tornado, and hailstorm are a few examples of natural disasters that might interfere with how data integration is stored and retrieved. Data storage and protection can greatly benefit from the application of physical integrity and its operating principles.

GOOD LABORATORY PRACTICE (GLP) ON DATA INTEGRITY [OECD, 2021]

One of the fundamental purposes of the Principles of Good Laboratory Practice (GLP) is to ensure the quality and integrity of test data. This includes the increasing use of electronic data capture, integration and automation of systems and other technologies. However, the main purpose of the requirements of the Principles of GLP remains the same in having confidence in the quality and the integrity of the data. [39]

WORLD REGULATORY GUIDANCE ON DATA INTEGRITY:

● **USFDA:** 21-CFR: The Code of Federal Regulation (CFR) is a codification of the general and permanent regulations that the executive departments and agencies of the federal government have published in the Federal Register. The Food and Drug Administration's regulations are included under Title 21 of the CFR. The CFR is updated once a year on or around April 1st of each year for each title/volume.

● **MHRA:** The MHRA's guideline on GMP data integrity requirements for the pharma sector is meant to supplement the EU's current GMP standards for dosage forms and active ingredients. The pharmaceutical quality system, which guarantees that medications are of the requisite quality, is fundamentally dependent on data integrity.

● **TGA:** The Therapeutic Goods Administration (TGA), an Australian regulatory organization, specifies the need for data integrity as a deficit. A flaw in a procedure that might lead to a considerable risk of creating a user-harmful product.

● **WHO:** Vital drugs and medical supplies, WHO releases data integrity recommendations to safeguard patients worldwide. In order to lessen instances of manufacturers providing inadequate data or purposeful data fabrication, has

WHO produced a guideline on worldwide best practices for regulatory bodies and inspectors while we are creating a medication and marketing it.

● **EME:** To guarantee the integrity of data generated during the testing, production, packaging, distribution, and monitoring of medicines, the European Medicines Agency (EMA) has published new Good Manufacturing Practice (GMP) guidelines. Effective data record management enables regulatory agencies and pharmaceutical producers to make informed decisions by ensuring that the data produced are correct and consistent.

DATA LIFECYCLE

Data life cycle management is very much useful for any enterprise or application where data is being used and processed for producing results. The lifecycle is the development phase to the release and retention of the data. It plays an important role in easy flow processes including data collection. It starts from creation, store, usability, sharing, and archive and destroy in the system and applications The different steps of data lifecycle includes data approval, Transcription, Data processing, Data migration, Computerised system transition, Data retention, Backup and Archive as shown in (Fig.1.11)
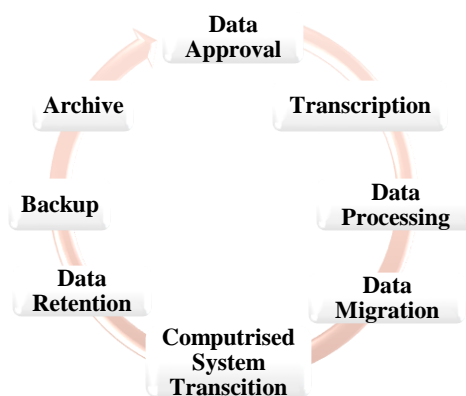
Fig. 11 Data Lifecycle

ALCOA

"ALCOA" is an acronym used in the pharmaceutical and clinical research industries, as I mentioned earlier. It is used to ensure data integrity and accuracy in the recording of data during clinical trials and research studies. Each letter in the acronym represents a fundamental principle that should be followed when collecting and documenting data: The FDA uses ALCOA to define its expectations of electronic data as shown in [Fig.1.12].

| L | **Legible:** Easy to understand, record and preserved in original form |

C	**Contemporaneous:** Data should be recorded on time
O	**Original:** Data should preserved in its original form or a certified true copy
A	**Accurate:** Data should be free from error and as per the protocol

Fig. 12 ALOCA

Attributable: All data should be attributable to the person who performed the original observation or data entry. When the record has been completed, it is advised that you use permanent ink. This method guarantees that the record remains readable. It should be persistent and readable in all scenarios.

Legible: The data of records involved in maintaining the data integrity must have appropriate accessibility during the entire duration of action. Data should be recorded in a clear and readable manner.

Contemporaneous: All the data are documented during the entire course of action. It records important information from several sources into the proper useable data in chronological series.

Original: The genuine or accurate copy of the raw data must be given. Original data should be preserved and maintained throughout the study. [52]

Accurate: Data must include complete meaning and should be correct. Use an observation check for the purpose of basic record collecting to confirm the correctness of the information. [40]

3. Methods

Validation Approach

A broad approach to spreadsheet validation has similarity to that of the computerised system validation. The process of the validation consists of same steps (user requirements, risk assessments, provisions, design, challenging, reporting), the project accountabilities, appropriate validation documents, and rules for the archival and change management processes.

Development Process

The V model is the most commonly adopted approach to develop protocol for validation. The protocol is developed for various calculations and operations involved in pharmaceutical industries. Some of the major tests includes IPQC test, Assays, Molarity, Normality etc. The sheets and the process must be easy, reliable and adaptable in order to make it easy for the developer and user to make useful to maintain data integrity and security throughout the operation.

User Requirements

The first step in the development of spreadsheet as per the User Requirements Specifications Guidelines (URS) is to capture the user's spreadsheet demands.

User Requirement Specification for Molarity and Normality determination spreadsheet:

URS-1. The spreadsheet should be applicable for all parameters.

URS-2. The spreadsheet should be easy and quick to determine the given conditions.

URS-3. The format of spreadsheet should have Test name, Sheet code, Standard taken with proper headings.

URS-4. The spreadsheet should standard reference, calculation formulas and also the instructions wherever needed.

URS-5. The spreadsheet should use the Unique ID No. for specific compound in the form of dropdown list wherever applicable.

URS-6. The spreadsheet should indicate invalid entries with error messages and numerical value entries or any specific entries.

URS-7. The spreadsheet input should only allow text, date, time and signatures as well alongwith the approval details.

Requirements concerning security, protection and GLP compliance must also be taken into account.

URS-8. The calculations in the spreadsheet should be protected against unauthorised modifications.

URS-9. The sheet should have color coding system for input, output cells and locking and unlocking system for formula cells.

URS-10. After completion of the calculation, the spreadsheet should be initialed, dated and put time electronically by the user.

URS-11. Making changes to the spreadsheet (modification/deletion) after signing off (initials/date) should not be possible.

URS-12. The spreadsheet template and completed spreadsheets should be retained in a secure location in an electronic form with access control in the form of worksheet protection.

URS-13. The sheet should consist of the macro code and audit trail.

Designing of Excel sheet
The designing of the spreadsheet is related to the system and version of the program and a worthy design ensures the:
- Reduction of mistakes while operating the sheets.
- Easily understandable, adaptable and versatile.
- Easy verification of the formulas and cells to inhibit unauthorised access.
Security, Error messages and Password

- Data entry is secured by error messages, dropdown list and for time, date entries.
- Date and time should be electronically feeded with signatures of authorized personnel's respectively.
- Error messages should be there for invalid entries into the cell.
- The template is password-protected (at sheet, workbook and VBA code level).
- Defined location to save worksheet template and to perform straightforward validation.
- All the information required for verification should be provided in the hardcopy and screenshots.

Development of Spreadsheet
- The sheets are developed based on the User Requirement Specifications (URS).
- The sheets should be designed systematically.
- The user should include all the recommendations as per URS step by step.
- In case of Macro or VBA code recording should be done by manual operations automatically.
- The code should be checked to ensure the correct cell references.
- At very first step user or the developer check the spreadsheet, cells, references and input values as per the user requirement. This is done by the set of typical data.

Review of codes
- These codes should be evaluated twice by the developer and the experienced personnel who are accustomed with the planned use and functionality.
- In excel sheets it includes inspection of cell content, especially formulas, formula locations, cell numbers and ranges, syntax of additional functionality, and VBA code.
- The content and reference of the cell can be evaluated by auditing the formula cells, dropdown list by zooming and scrolling to check mouse sensitivity.
- Formula Auditing Tools in Excel by doing following:
1. Trace Precedents.
2. Remove Arrows.
3. Trace Dependents.
4. Show Formulas.
5. Error Checking.

Trace Precedents

- The **"Trace Precedents"** command can be seen in the **"Formula Auditing"** group under the **"Formulas"** tab to trace precedents as shown in (Fig.13)
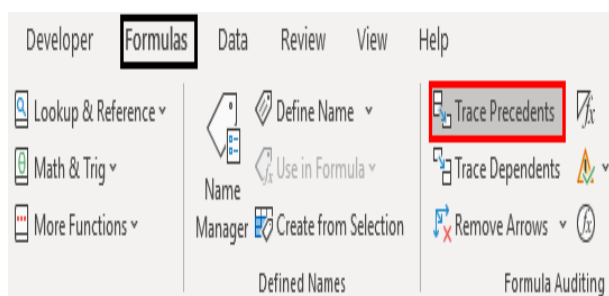
Fig. 13 Trace Precedents Command

- To select the formula cell and click on the **"Trace Precedents"** command.

- To check the formula's precedents, press F2 to get into edit mode after selecting the required cell so that precedents cells.

Remove Arrows

- We can use the **"Remove Arrows"** command in the **"Formula Auditing"** group under the **"Formulas"** tab to remove these arrows as shown below in (Fig.14).
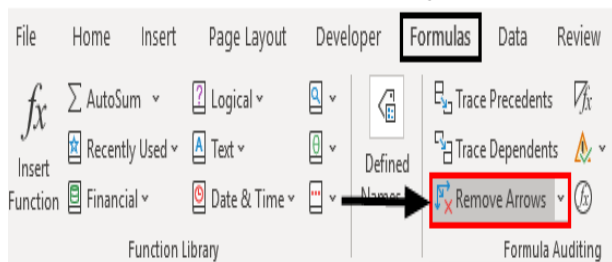
Fig. 14 Remove Arrow Command

Trace Dependents

- This command traces the cell, dependent on the selected cell.

- The **"Trace Dependents"** command can be seen in the **"Formula Auditing"** group under the **"Formulas"** tab to trace precedents as shown in (Fig.15).

- The formula weight of the compound, to know how much weight of the compound is needed.
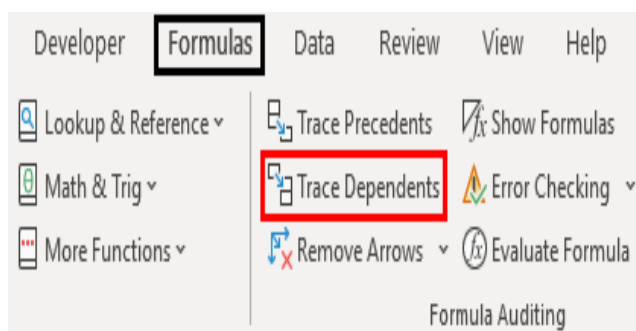
Fig.15 Trace Dependent Arrow

Show Formulas

- This command to display formulas written in the excel sheet.

- The **"Show Formulas"** command can be seen in the **"Formula Auditing"** group under the **"Formulas"** tab to trace precedents as shown in (Fig.16).
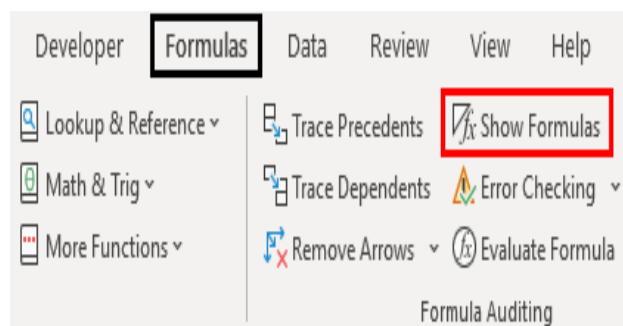
Fig.16 Show Formula Command

Error Checking

- Select the cell where the **formula or function** is written, then click **"Error Checking."** from **"Formula Auditing"** group as shown in (Fig.17).
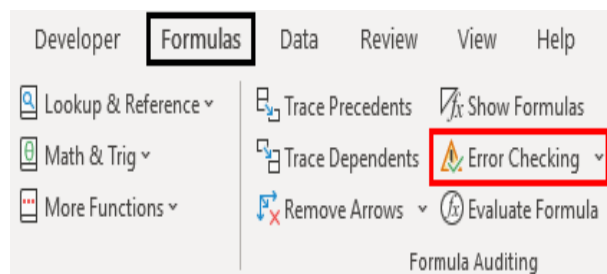
Fig.17 Error Checking Command

5.5.6. VBA Code

- To enter the code go to: **Developer tab< Record Macro< Give Macro name, Shortcut key, Destination to save and a short description of macro** as shown in (Fig. 18)
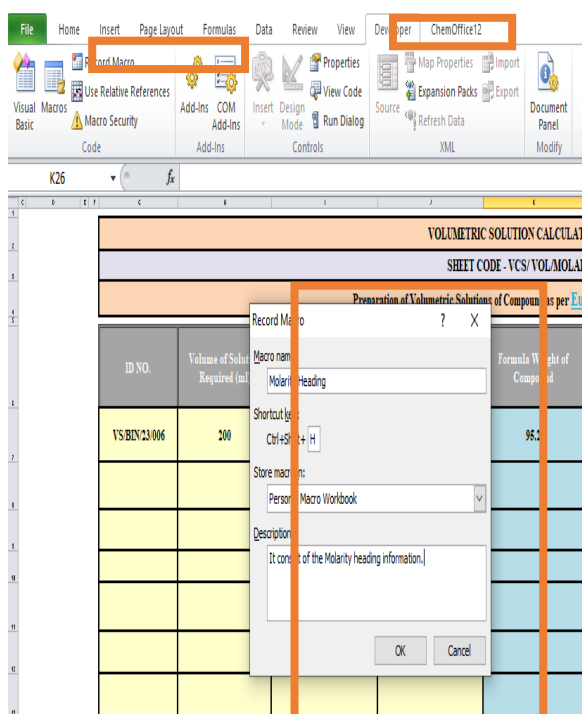
Fig.18 VBA Code Command

Qualification Process

The qualifying method's goal is to establish that the created spreadsheet is fit for its intended use. It must be proved throughout the entire procedure that the desired outcome - is, a collection of processed data that has been subjected to operations such as computations, rounding, formatting, and regrouping for presentation as a table, chart, or report - is achieved in an accurate and repeatable manner.

Installation Qualification (IQ)

A spreadsheet design is a vital document since it often contains the whole source code (VBA code and Excel functions) and may be used to run the programme.

Operational Qualification (OQ)

In the development phase user requirements are tested systematically. It is not compulsory to perform all test but some basic functions are checked. The entire test should be performed with independent data sets.

Performance Qualification (PQ)

The main purpose of this last qualification stage is demonstration of the spreadsheet by giving various commands as per the user's requirements. It is observed as the internal acceptance test. It can be done regularly by the future users.

Spreadsheet Accuracy Test
A. IPQC Test of TABLETS
Layout

- The spreadsheet is divided into an input area (yellow), an output area (green) and an area for verification of constants and specifications

- The Freeze Pane is included by: **Home > View> Freeze pane**

- The color coding of cells was done containing formulas.

- To view the formulas in Excel: **Tools > Options > Tab: View and check "Formulas" under Window options; Formulas > Formula Auditing > Show Formulas**

Security and Protection
Password Protection

- The protection of spreadsheet as well as worksheet both is important in order to avoid the unauthorised access for security purpose.

- To do any editing in the sheet the user needs password to access the sheet, these passwords are unique to individual sheets and one unique password is set to protect the worksheet containing this spreadsheets.

- **To Protect Worksheet: File > Info > Protect Worksheet > Choose option as shown in (Fig. 19)**
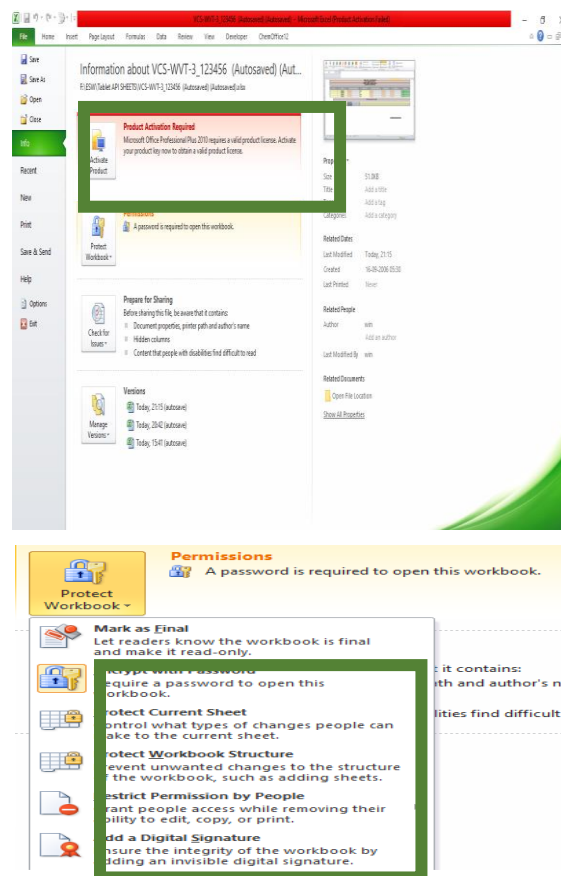
Fig.19 Worksheet Protection Window

- To protect spreadsheet go to: **Home > Format > Protect Sheet**
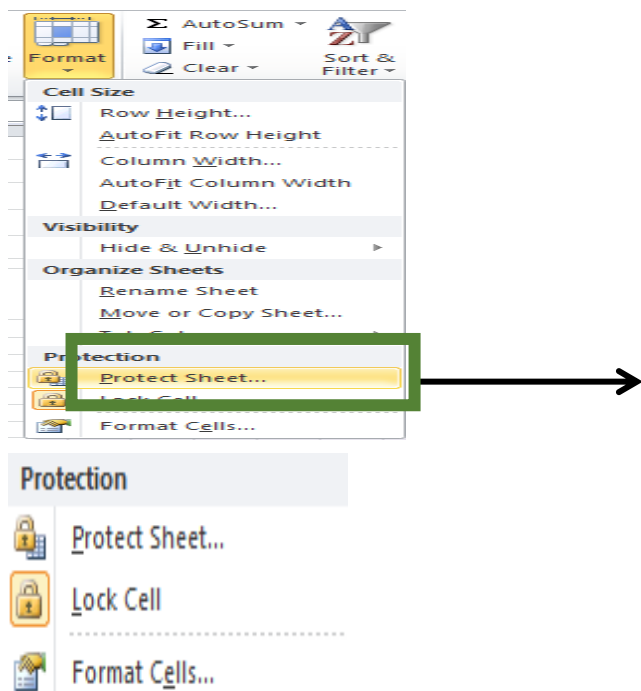
Fig.20Spreadsheet Protection Window

Cell Locking

• Cells containing formulas, sheet code, and Batch no. and test name are locked.

• To Lock Cell go to **Home > Format > Fromat Cells > Protection** as shown in (Fig.5.9)
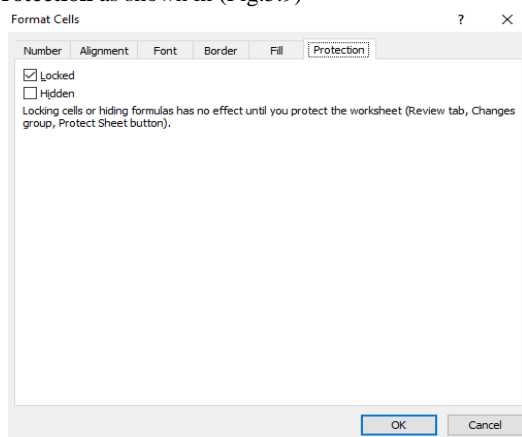
Fig.21 Cell locking Window

Logical Formula

• Microsoft Excel provides 4 logical functions to work with the logical values. The functions are AND, OR, XOR and NOT as given in (Table.5.1)

• These functions are used to compare formula or several test conditions instead of just one.

• As well as logical operators, Excel logical functions return either TRUE or FALSE when their arguments are evaluated.

• To insert it: **Home > Formulas > Insert Functions**

Table 2 Logical Formulas

Function	Description	Formula Example	Formula Description
AND	Returns TRUE if all of the arguments evaluate to TRUE.	=AND(A2>=10, B2<5)	The formula returns TRUE if a value in cell A2 is greater than or equal to 10, and a value in B2 is less than 5, FALSE otherwise.
OR	Returns TRUE if any argument evaluates to TRUE.	=OR(A2>=10, B2<5)	The formula returns TRUE if A2 is greater than or equal to 10 or B2 is less than 5, or both conditions are met. If neither of the conditions it met, the formula returns FALSE.
XOR	Returns a logical Exclusive Or of all arguments.	=XOR(A2>=10, B2<5)	The formula returns TRUE if either A2 is greater than or equal to 10 or B2 is less than 5. If neither of the conditions is met or both conditions are met, the formula returns FALSE.

	Returns the reversed logical value of its argument. I.e. If the argument is FALSE, then TRUE is returned and vice versa.	=NOT(A2 >=10)	The formula returns FALSE if a value in cell A1 is greater than or equal to 10; TRUE otherwise.
NOT			

Calculation Formula

- The formula used in these sheets as per the calculation requirements.

- The formulas used in these sheets are based on their usage in the sheets.

- In the calculation and results worksheet, each calculation should be based on the results of the previous calculation so that the calculations progress through the worksheet from top to bottom.

- They are used to make calculation easy and simple to understand

Conditional Formatting

- It consist of command where conditionally format cells in a range that have duplicate text, unique text, and text that is the same as text you specify.

- Select the cells you want to apply conditional formatting to. Click the first cell in the range, and then drag to the last cell.

- Click **HOME** > **Conditional Formatting** > **Highlight Cells Rules** > **Text that Contains**. In the **Text that Contains** box, on the left, enter the text you want highlighted.

- Select the color format for the text, and click **OK** as shown in (Fig.22)
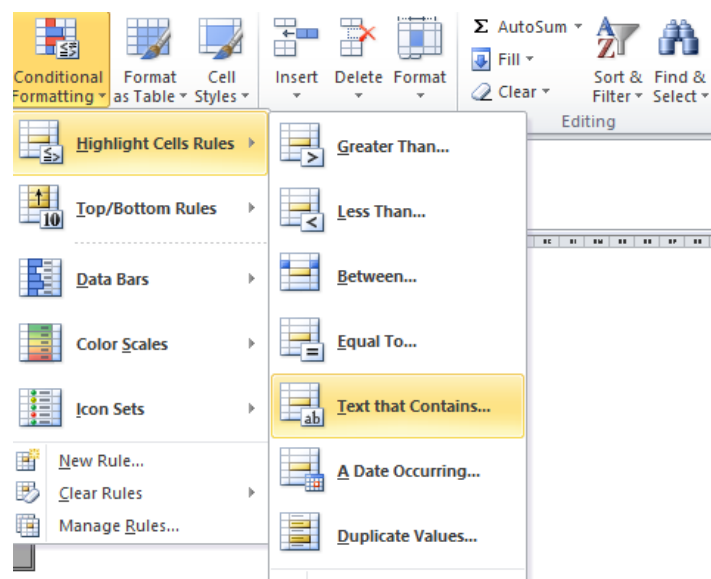
Fig. 22 Conditional Formatting Command

- Now choose the color formatting for as per the user requirement as given in the (Fig.23)
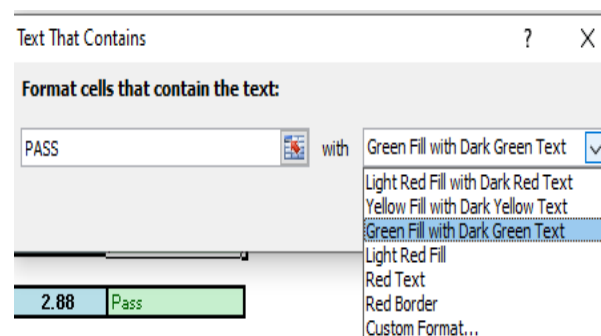
Fig.23 Cell Colour Format

DATA VALIDATION
Drop Down list menu

- For more quicker and accurate data entry dropdown list menu is useful as it can limit the entries people can make in the cell.

Steps to create a drop – down list

a. Select the cell you want to contain the lists .
b. On the ribbon, click **DATA> Data Validation** as shown below in (Fig.24)
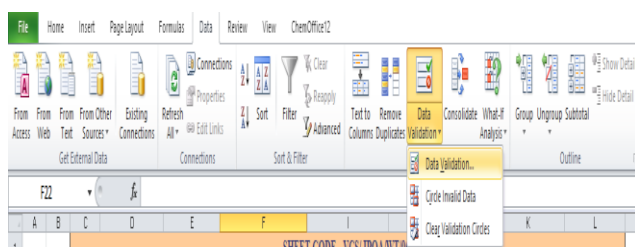
Fig.24 Data Validation Tab

c. In the dialog box, set **Allow** to **List** as given in (Fig.25)
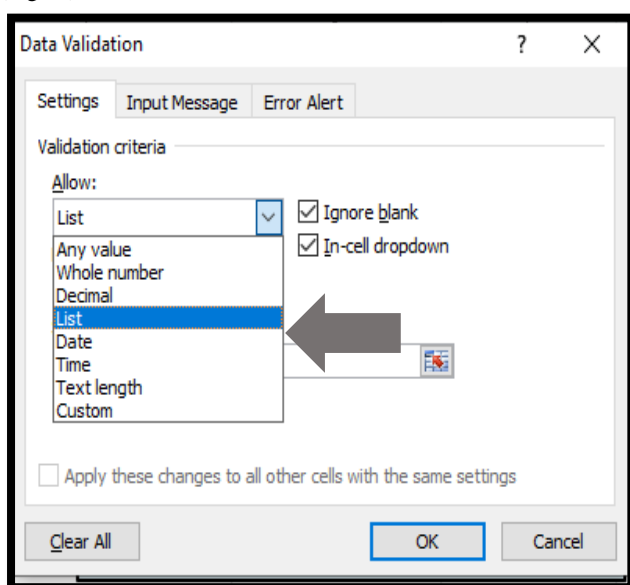
Fig.25 Validation Criteria

d. Put the data in list you want to see in drop down list as shown in (Fig. 26)
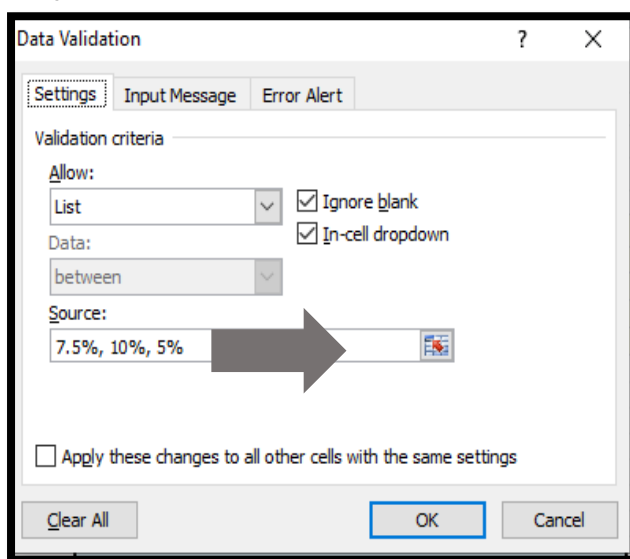
Fig.26 List Data

Data Input and Error messages

● The cells use the data validation functionality in Excel (**Data > Validation Data > Data Tools > Data Validation).**

● With this functionality, such as wrong entries of alphabets, text, decimals and so on with their respective error messages.

VBA Code

● The Office suite of applications has a rich set of features. There are many different ways to author, format, and manipulate documents, email, databases, forms, spreadsheets, and presentations.

● The great power of VBA programming in Office is that nearly every operation that you can perform with a mouse, keyboard, or a dialog box can also be done by using VBA.

● Further, if it can be done once with VBA, it can be done just as easily a hundred times. (In fact, the automation of repetitive tasks is one of the most common uses of VBA in Office.)

● Insert VBA code to Excel Workbook by following this steps

1. Open your workbook in Excel.

2. Press **Alt + F11** to open Visual Basic Editor (VBE).

3. The window appears after giving this command is described in (Fig.27).
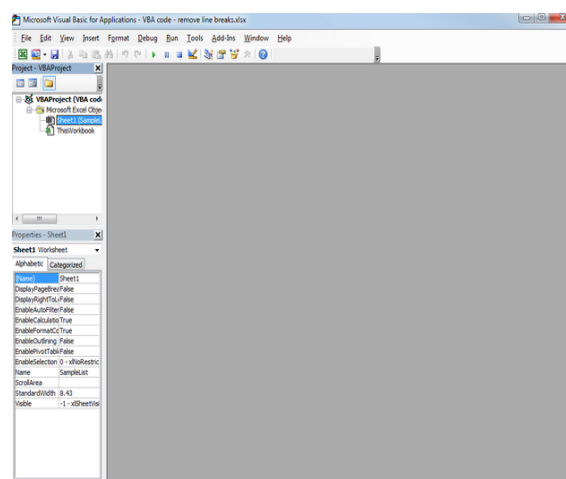
Fig. 27 VBA Window

4. Right-click on your workbook name in the "Project-VBAProject" pane (at the top left corner of the editor window) and select **Insert -> Module** from the context menu as shown in (Fig.28).
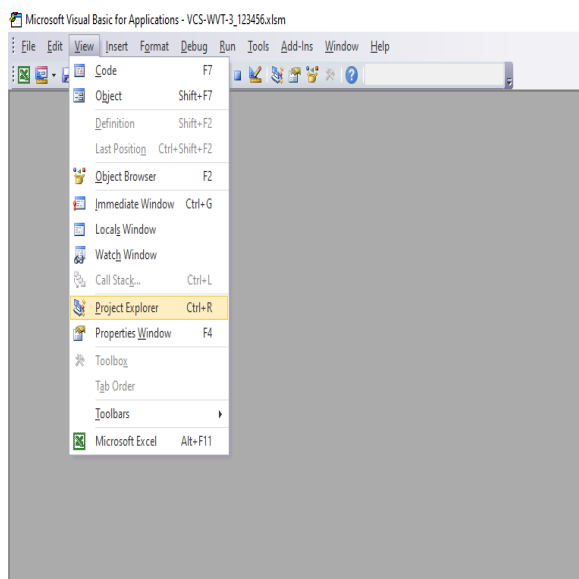
Fig.28 VBA Project Explorer

Audit Trail

Audit trails are obligatory for computerized systems falling under FDA/EU regulations. These logs are essential to document the inception, alteration, and removal of controlled digital records. During system validation, the accuracy and alignment of the audit trail with regulatory and organizational standards should be confirmed. Subsequent to successful validation and system deployment, the significance of the audit trail must not be overlooked.

To attain audit trail in spreadsheet:

1. It is important to create audit trail to track changes made to formula and data cells in the sheets.
2. To do this, go to the **"Review" menu and select "Track Changes"** as shown in (Fig.29).
3. The required changes are done for being tracked and can be assembled into the list in a new sheet.
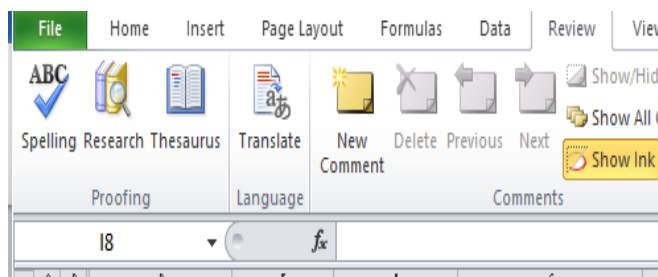
Fig.29 Track Changes Command

Excel Auditing Tool and Watch Window

1. Excel's auditing tool is used to determine the errors in formulas and data cells.
2. To do this, go to the **"Formulas" tab and select "Error Checking", "Watch Window"** as given in (Fig.30).

3. Formula auditing can be done by using the watch window as it allows the effect of change in one cell on the other.
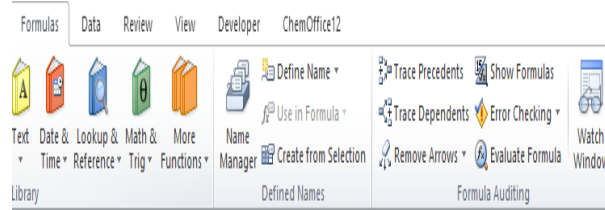
Fig.30 Excel Auditing Tools

4. To set watch window: **Click on the cell containing formula> Watch Window>Add watch to the cell** as shown in (Fig.31).
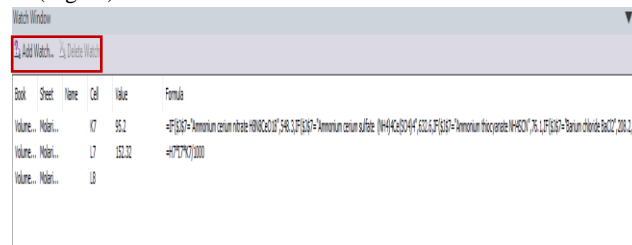
Fig.31 Add Watch Window

Addition of Hyperlink

• The hyperlinks are added to get information either from another file, web page or image. It can be inserted in a particular cell of worksheet or the chart element.

• It can be done by using **'Insert Hyperlink'** dialog box in Excel or by using Hyperlink function as shown in (Fig.32)
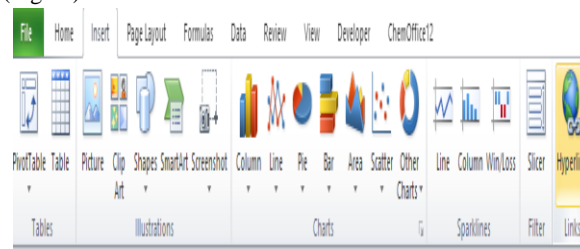
Fig.32 Hyperlink Command

• To add a hyperlink to the current file, should be selected from the list as shown in (Fig.33).
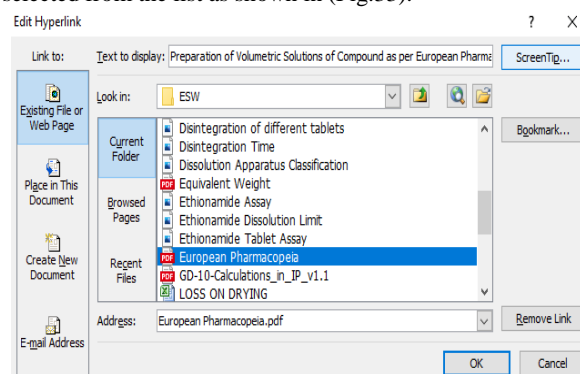
Fig.33 Hyperlink List

Validation Protocol

It is a documented plan consisting of all the experiments, their designing and the procedure to carry out the validation. This plan is a written procedure which consists of all the information such as product description, testing parameters, production process, planning and the acceptance criteria. Validation protocol consists of two major points such as:

● **Procedure:** It defines the steps involved in the procedure of the validation.

● **Form:** It is the documentation of the any change or modification done in the pre-approved validation protocols.

● **Parts of Validation Protocol**

● The important parts to be included in the protocol are described in (Table 3):

Table 3 Validation Protocol Parts

S.no	Parts	Description
1.	**Protocol Approval**	It shall be done by the concerned departments and taken for final approval from quality assurance department.
2.	**Purpose**	It includes the objective to made validation protocol.
3.	**Scope**	It includes the specific departments following this protocol
4.	**Reason of Validation**	The reason to carry out validation process either of the new, process, method or the equipment.
5.	**Revalidation Criteria**	The need of revalidation such as change to any part or step.
6.	**Responsibilities**	The responsibilities of every department should be mentioned appropriately.
7.	**Reference Documents**	All appropriate documents (BMR, BPR, SOPs) should be mentioned.
8.	**Procedure/Deviations**	Mention a stepwise procedure with required deviation.
9.	**Conclusions**	All the obtained results as per acceptance criteria or not.
10.	**Report/ Report Approval**	The report should be made with department approval

		Confirmed	Notes
1.	Whether the signature log book maintained or not	☐	
2.	Are the employees know about GMP.GDP, GAMP and 21CFR Part 11	☐	
3.	Is the all operating system update in the company?	☐	
4.	Is all the sheets used for calculation are validated or not?	☐	
5.	Is all the sheets have password protection to open the sheets or not?	☐	
6.	Is all the sheets have color coding system or not?	☐	
7.	Is the system have raw data captured	☐	
8.	All the sheets are properly named and coded	☐	
9.	Is the original data captured in readable form or not?	☐	
10.	Is the sheets follow electronic signature model or not?	☐	
11.	All information recorded both in paper and electronic form?	☐	
12.	All the sheets can be run on the entire version or not?	☐	
13.	The sheets have acceptance criteria limits or not?	☐	
14.	The sheets are provided with the VBA codes and Audit trails or not?	☐	
15.	The sheets are provided with error and warning messages or not?	☐	

16.	Sheets saved in appropriate formats as per SOPs or not?	☐	

4. Results

Validation Approach

In terms of duties, the spreadsheet designer is frequently interchangeable with the researcher who is also in charge of a certain test methods. It must be ensured in this scenario that the programmer is constantly aware of his present job and that both the creation and validation stages are clearly divided. If modifications are required during the validation process, they must be reported, assessed, and tested again. Version control may be the core in handling changes, and essential modifications may be done with fewer efforts than using CSV. At last the approach of validating a spreadsheet is to assess the risk with short and systematic procedures in order to delete some steps of the process.

Development Process

The sheets should be designed as per the user requirements or can be designed as a standard format for some common tests can be used as per the need. The key components of the sheets includes the password protection, color coding, locking and unlocking of the cell, limits as per the guidelines etc.

User Requirement Specifications

This includes calculations, formulas, layout, security and integrity of data, included in Functional Specifications.

6.4 Designing of Excel sheet

To depict a sophisticated spreadsheet design the sheet is divided into the colour coded area as shown in (Fig. 6.1) where,

• First three rows (2, 3, and 4) contain heading as Test name, Sheet code, and Standard reference.

• The next columns contains subheadings (G to P: ID No., Vol. and Strength of solution required, Name of compound, Formula Weight of compound, Weight of Compound taken and Points to remember).

• The heading and subheading cells are separated by different colours.

• The designed sheets were easy to understand and colour coded as well.

Input and output cells are separated and color coded as well:

• The first three columns (G.H, I, J, and M to P) are INPUT CELLS in YELLOW COLOUR.

• The next two columns (K and L) are OUTPUT CELLS in BLUE COLOUR.

• The input cells are UNLOCKED CELLS while the output cells are LOCKED CELLS.

• Formulas, Calculations and other parameters cannot be changed by the users in locked cells.

Fig.34 Spreadsheet Layout

Development of Spreadsheet

• Testing of spreadsheet efficiency as per User Requirement Specifications (URS)

• The spreadsheets includes the formula auditing tools namely :

1. Trace Precedents.
2. Remove Arrows.
3. Trace Dependents.
4. Show Formulas.
5. Error Checking.

• The designed sheets must have these command as described in (Fig.35)

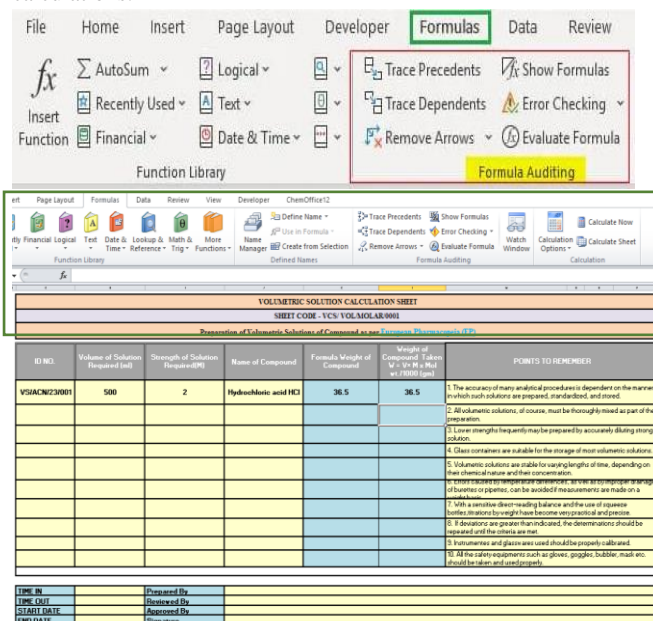• The sheets were tested for the formulas feeded for the calculations.

Fig.35 Formula Auditing Tools

Trace Precedents.

- Suppose we have the following formula in the L7 cell for calculating weight of the compound to make molar solution as shown in (Fig.36)

Fig.36 Formula Auditing Cell

- The arrows where trace precedents are highlighted with blue dots appears, as shown below in (Fig.37)

Fig.37 Trace Precedents Arrow

- The cells get bordered with various colors and written in the same color and cell reference as shown in (Fig.38).

Fig.38 Formula Precedents Check

- We can see that H7 is written with blue in the formula cell, and with the same color, the H7 cell is bordered.
- In the same way, I7cell has a green color and K7 cell has a purple color.

- This could be one of the ways including one more appropriate way to check precedents for the formula cell.

Remove Arrows

- The command was given the window appears and a click on the remove arrow just disappears the arrow seen on the sheet as given in (Fig.39).

Fig.39 Remove Arrow Cells

Trace Dependents

- Select the K7 cell and click on the **"Trace Dependents"** command as shown in (Fig.40)
- In the (Fig. 20), we can see the arrow lines where arrows indicate which cells are dependent on the cells i.e.K7 dependent on L7 cell.
- We will remove the arrow lines using the **'Remove Arrows'** command.

Fig.40 Trace Dependents Cells

Show Formulas

- In (Fig.41), the cells containing formulas in the entire sheets are shown.
- The sheet shows all the formulas from the average calculation to the every single function involved in the calculation.
- The show formulas command allows to identify the cells containing the type and cells involved in the formulas.

1607

Fig.41 Show Formula Cells

Error Checking

- Once the command is given the error checking starts and ends with a pop message as shown in (Fig.42).

Fig.42 Error Checking Popup Message

VBA Code

- The VBA codes should be should be properly reviewed line by line for the consistency, correctness, reliability and reproducibility as described in (Fig 43)

```
Sub Molarityheadings()

' Molarityheadings Macro
' information about headings.
'
' Keyboard Shortcut: Ctrl+Shift+H
'
    ActiveCell.Range("A1:J1").Select
    ActiveCell.FormulaR1C1 = "VOLUMETRIC CALCULATION SHEET"
    ActiveCell.Offset(1, 0).Range("A1:J1").Select
    ActiveCell.FormulaR1C1 = "SHEET CODE"
    ActiveCell.Offset(1, 0).Range("A1:J1").Select
    ActiveCell.FormulaR1C1 = _
        "PREPARATION OF MOLAR SOLUTIONS AS PER THE EUROPEAN PHARMACOPEIA (EP)"
    ActiveCell.Offset(-2, 0).Range("A1:J1").Select
    With Selection.Font
        .Name = "Times New Roman"
        .Size = 11
        .Strikethrough = False
        .Superscript = False
        .Subscript = False
        .OutlineFont = False
        .Shadow = False
        .Underline = xlUnderlineStyleNone
        .ThemeColor = xlThemeColorLight1
        .TintAndShade = 0
        .ThemeFont = xlThemeFontNone
    End With
    With Selection.Font
        .Name = "Times New Roman"
        .Size = 26
        .Strikethrough = False
        .Superscript = False
        .Subscript = False
        .OutlineFont = False
        .Shadow = False
        .Underline = xlUnderlineStyleNone
```

Fig.43 VBA Code

Release for Qualification

As soon as the development documentation is completed sheet and worksheet protection through password is installed and transferred for the documentation of qualification process. The recommendation of spreadsheet version is important. The sheets are than released for qualification.

Installation Qualification

To guarantee that the spreadsheet can be used across the testing facility, it may be important to verify that:

- The spreadsheet can be operated on multiple computers (either identical or varied technology configurations, user profiles, or local settings).

- The spreadsheet may be installed and operated on a variety of software platforms (Excel, OS, and, if appropriate, the data collection system).

- The sheets should be flexible so that they can be saved on the server to make it useable for many users at same time.

Operational Qualification (OQ)

The result of making wrong entries into the cell such as mistakes in date format, text instead of numbers, incorrect decimal places, and real numbers instead of integers gives the error message as described in (Table 5).

Table 5 Operational Qualification

Testing as per URS	Test	Acceptance Criteria
URS-5.	The spreadsheet should use the Unique ID No. for specific compound in the form of dropdown list wherever applicable.	The error message "Please enters code from the dropdown list".
URS-6	The spreadsheet should indicate invalid entries with error messages and numerical value entries or any specific entries.	The error message "Please enters numerical value 2, 12,4,15 only".
URS-7	The spreadsheet input should only allow text, date, time and signatures as well alongwith the approval details.	The error message "Please enter date and time as required".
URS-8	The calculations in the spreadsheet should be protected against unauthorised modifications on clicking on the cell in the sheet.	The error message "The cell or chart you are trying to change is protected and therefore read-only" appears.

Performance Qualification (OQ)

It can be done by observing the following as:

- By testing the input values in order to check the consistency by entering even the boundary values, all functional requirements and all the special and combination values .

- By testing with real data been the major part of the validation process by taking real data as the input one. This input can be done manually or by importing the files. For achieving the high level of confidence a wide variety of data is used for spreadsheet testing.

- This step makes sheets accurate, reliable so that their final copies can be tested for real data.

- The accuracy and reliability of the sheets decides their usage and compatibility with the security purpose, unauthorized access and many more.

- The qualification process is to ensure that the sheets will fulfill the predetermined standards.

Spreadsheet Accuracy Test
A. IPQC Test of TABLETS

1. Layout

- The color coding of the input and output cells are shown in (Fig. 44).

Fig.44 Test sheet Layout

- The freeze pane command can be shown in (Fig.6.12).

Fig.45Freeze Pane

- The green and blue areas contain formulas in cells as given in (Fig. 46)

Fig.46 Formulas

Security and Protection

Password Protection

• Whenever unauthorized users try to manipulated data in the sheet they will get an immediate warning to unprotect the sheet.

• The window appears as shown in (Fig.47) to enter password for opening of the sheet.

Fig.47 Worksheet Password Entry

• After the worksheet, the spreadsheet is also password protected as shown in (Fig. 48)
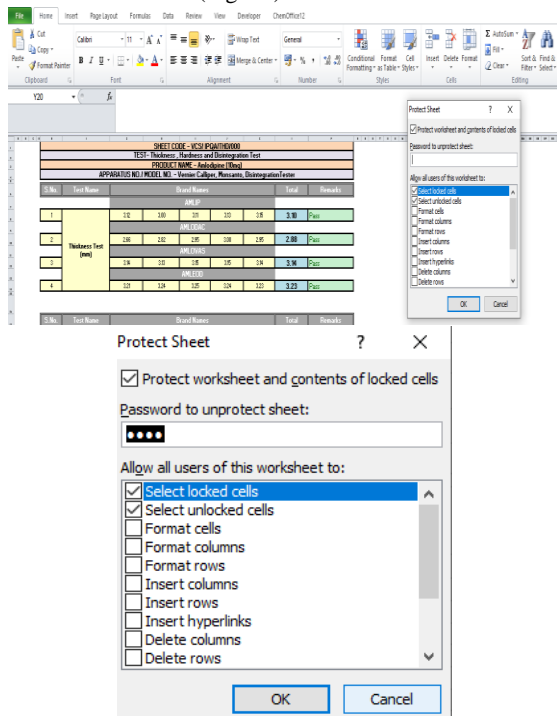
Fig. 48 Protected Spreadsheet Window

6.7.2.2 Cell Locking

• Whenever unauthorized users try to manipulated data in the sheet they will get an immediate warning to unprotect the sheet as shown below in (Fig.49)
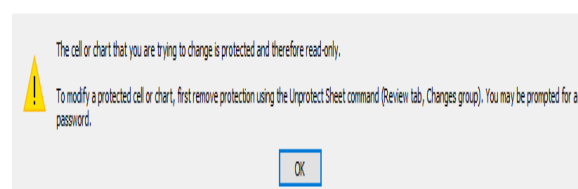
Fig.49 Warning Message

7.3 Logical Formulas

• It consist of two logical commands as shown in the dialog box as given in (Fig. 50 & 51)
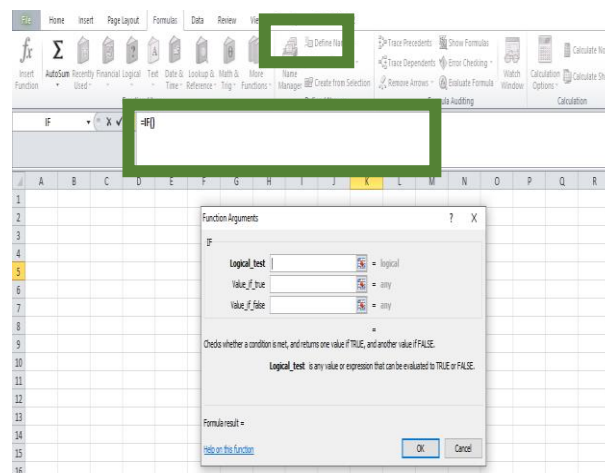
Fig.50 Logical Formula Window

• Put commands in this box and **Press ENTER**
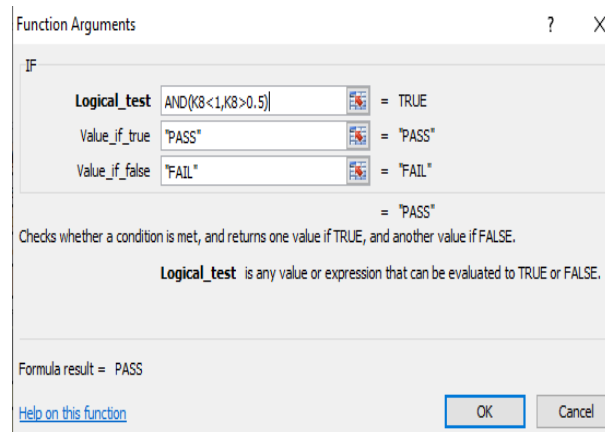
Fig. 51 Logical Formula Command

• Once the command is entered if both the command is "**True**" or "**Pass**" result displayed will also be "**True**" or "**Pass**"

-
he formula description is described in (Table.6)

Examples of Sheets containing Logical Formulas:

There are some sheets containing logical formulas as shown in (Fig. 6.19, 6.20 and 6.21)

➤

hickness, Hardness and Disintegration Sheet

=IF (AND (K8<1, K8>0.5),"PASS","FAIL")

Fig.52 IF, AND Formula

➤ **Dissolution Sheet**

=ROUND (MIN (J18:J23), 2)

Fig.53 ROUND Formula

➤ **Weight Variation Sheet**

=ROUND (SUM (F8:F27), 2)/20

T

T

Fig.54 SUM ROUND Formula

Table 6 Formula Descriptions

S.No	Formula	Description
1.	=IF (AND (K8<1, K8>0.5),"PASS", "FAIL")	Returns "PASS" if K8 contains value less than 1, greater than 0.5 and FAIL otherwise.
2.	=ROUND (MIN (J18:J23), 2)	Returns MIN value from J18 to J23 cell than round it to 2 decimal places.
3.	=ROUND (SUM (F8:F27), 2)/20	Returns MIN value from J18 to J23 cell than round it to 2 decimal places.

6.7.4 Calculation Formulas

- The formula inserted occupies one cell each for easy and clear understanding of the calculation and formulas.

- The formulas should be clear, concise and appropriately used.

- Some sheets having calculation formulas are shown in (Fig. 6.22, 6.23, & 6.24)

Fig.55 Dissolution Calculation Sheet

S.no	Tablet Batch	No. of Rotations	Time	Initial Weight (W1) (gm)	Final Weight (W2) (gm)	% Friability	No.of tablets with % friability of >1%
				SHEET CODE - VCS/ IPQA/FT/001			
				TEST - Friability Test			
				PRODUCT NAME - Amlodipine (10mg)			
				Apparatus Name/ Model No. - Roche Friabilator			
				Batch No. - PFT 01			
1	F1			3.1738	3.144	0.94	PASS
2	F2			3.523	3.468	1.56	FAIL
3	F3			3.2019	3.193	0.29	FAIL
4	F4			67544	67430	0.17	FAIL
5	F5	25 RPM/ 100 revolutions	4 min	65430	65000	0.66	PASS
6	F6			71425	71000	0.60	PASS
7	F7			68319	68219	0.15	FAIL
8	F8			66519	68000	-2.23	FAIL
9	F9			62319	62000	0.51	PASS
10	F10			52319	52219	0.19	FAIL

Calculation Formula

$$\% \text{Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Fig.56 Friability Calculation Sheet

ASSAY CALCULATION SHEET	
SHEET CODE: VCS/CAL/ASY/112	
PRODUCT NAME: TRIAMCINOLONE	
METHOD: Ultra-Violet Spectrophotometer	

Using Specific Absorbance

Specific Absorbance	389
	SET 1
Test weight (g)	0.02517
Test dilution (ml)	0.02517 g/100 ml→2 ml/50 ml
Test absorbance	0.390
Assay (%w/w) (on as is basis)	99.58
Water content/LOD (%w/w)	0.37
Assay (% w/w) (on dried /anhydrous basis)	99.95

Calculation Formula

$$\text{Assay (\%w/w) (as is basis)} = \frac{\text{Test absorbance}}{\text{Standard Absorbance}} \times \frac{\text{Standard wt.(g)}}{\text{tandard dilution}} \times \frac{\text{Test dilution}}{\text{Test weight (g)}} \times \text{Purity of Std.}$$

$$= \frac{0.390}{0.389} \times \frac{0.05}{5000} \times \frac{5000}{0.05034} \times 99.8$$

99.38

$$\text{Assay (\% w/w) (on dried /anhydrous basis)} = \frac{\text{Assay (\% w/w) (on as is basis) X 100}}{(100 - \text{Water content/LOD})}$$

$$= \frac{99.38 \times 100}{(100 - 0.37)}$$

99.75

Fig. 57 Assay Calculation Sheet

Conditional Formatting

Examples of Sheets containing Conditional Formatting

- The "Pass" result will show green colour with dark green text
- The "Fail" result will show red colour with dark red text as shown in (Fig. 6.25, 6.26 and 6.27)

S.No.	Test Name	Brand Names					Total	Remarks
				SHEET CODE - VCS/ IPQA/THD/000				
				TEST- Thickness , Hardness and Disintegration Test				
				PRODUCT NAME - Amlodipine (10mg)				
				APPARATUS NO./ MODEL NO. – Vernier Calliper, Monsanto, DisintegrationTester				
		AMLIP						
1		3.12	3.00	3.11	3.13	3.15	3.10	Pass
		AMLODAC						
2	Thickness Test (mm)	2.66	2.82	2.95	3.00	2.95	2.88	Pass
		AMLOVAS						
3		3.14	3.13	3.15	3.15	3.14	3.14	Pass
		AMLEOD						
4		3.21	3.24	3.25	3.24	3.23	3.23	Pass

S.No.	Test Name	Brand Names					Total	Remarks
		AMLIP						
1		5.00	5.40	6.00	5.50	5.80	5.54	Pass
		AMLODAC						
2	Hardness Test (Kg/cm²)	7.50	7.50	7.00	7.50	7.00	7.30	Pass
		AMLOVAS						
3		6.50	6.00	6.50	6.00	6.50	6.30	Pass
		AMLEOD						
4		3.00	3.10	3.30	3.00	3.20	3.12	Fail

S.No	Test Name	Brand Names	Type of Tablet	Disintegration Time	Observation	Temperature	Remarks
1		AMLIP	Uncoated Tablet	15min	10min 5sec	37±2°C	PASS
2	Disintegration Test	AMLODAC	Uncoated Tablet	15min	12min 5sec	37±2°C	PASS
3		AMLOVAS	Uncoated Tablet	15min	13min 2sec	37±2°C	PASS
4		AMLEOD	Uncoated Tablet	15min	14min 8sec	37±2°C	PASS

Fig.58 Thickness, Hardness and Disintegration Sheet

S.no	Brand	Average Tablet Weight	% Deviation	Limit Value (AW*%Dev.)	Upper Limit	Lower Limit	Remarks
				SHEET CODE - VCS/ IPQA/WT/005			
				TEST - Weight Variation Test			
				PRODUCT NAME - Amlodipine (10mg)			
				Cumulative Data of all Brands			
1	BRAND A	237.925	7.50%	17.84	255.77	220.08	Pass
2	BRAND B	67	10%	6.7	73.70	60.30	Pass
3	BRAND C	162.565	7.50%	12.19	174.76	150.37	Pass
4	BRAND D	134.91	7.50%	10.12	145.03	124.79	Pass

AW: Average Weight of the tablets

TIME IN		Prepared By	
TIME OUT		Reviewed By	
START DATE		Approved By	
END DATE		Signature	

Fig.59 Weight Variation Sheet

SHEET CODE - VCS/ IPQA/FT/002								
TEST - Friability Test								
PRODUCT NAME - Amlodipine (10mg)								
Cumulative Data of Brands								
S.no	Brand No.	Brand Name	No. of Rotations	Time	Initial Weight (W1) (gm)	Final Weight (W2) (gm)	% Friability	No.of tablets with % friability of >1%
1	Brand A	Amlip	25 RPM/ 100 revolutions	4 min	276	274	0.72	PASS
2	Brand B	Amlodac			668	667	0.15	FAIL
3	Brand C	Amlovas			1347	1340	0.52	PASS
4	Brand D	Amleod			1630	1620	0.61	PASS

TIME IN		Prepared By	
TIME OUT		Reviewed By	
START DATE		Approved By	
END DATE		Signature	

Fig.60 Friability Test Sheet

DATA VALIDATION
Drop Down list menu

- The dropdown list into the sheet was seen as shown in (Fig.6.28)

SHEET CODE - VCS/ IPQA/WT/005							
TEST - Weight Variation Test							
PRODUCT NAME - Amlodipine (10mg)							
Cumulative Data of all Brands							
S.no	Brand	Average Tablet Weight	% Deviation	Limit Value (AW*%Dev.)	Upper Limit	Lower Limit	Remarks
1	BRAND A	237.925	7.50%	17.84	255.77	220.08	Pass
2	BRAND B	67	10%	6.7	73.70	60.30	Pass
3	BRAND C	162.565	7.50%	12.19	174.76	150.37	Pass
4	BRAND D	134.91	7.50%	10.12	145.03	124.79	Pass

% Deviation
7.50%
10%
7.50%
7.50%

Fig.61 Drop down list

Examples of Sheets containing Drop down List

a. Molarity Sheet: It contains compounds name in drop down list as shown in (Fig. 62)

VOLUMETRIC SOLUTION CALCULATION SHEET			
SHEET CODE - VCS/ VOL/MOLAR/0001			
...tion of Volumetric Solutions of Compound as per **European Pharmacopeia (EP)**			
Iodine I Lanthanum nitrate La(NO3)3 Lead nitrate Pb(NO3)2 Lithium methoxide CH3LiO Magnesium chloride MgCl2 Nitric acid HNO3 Perchloric acid HClO4 Sulfuric acid H2SO4	Formula Weight of Compound	Weight of Compound Taken W = V× M x Mol wt./1000 (gm)	
Iodine I	126.9	50.76	1. The accuracy of ... solutions are prepar...

Iodine I
Lanthanum nitrate La(NO3)3
Lead nitrate Pb(NO3)2
Lithium methoxide CH3LiO
Magnesium chloride MgCl2
Nitric acid HNO3
Perchloric acid HClO4
Sulfuric acid H2SO4

Fig.62 List of compounds

b. Weight Variation Sheet: It contains test name in drop down list as shown in (Fig. 6.30)

SHEET CODE - VCS/ IPQA/WT/001					
TEST- Weight Variation					
TEST- Weight Variation / TEST- Uniformity of Weight					
PRODUCT NAME - Amlodipine (10mg)					
Apparatus Name/ Model No. - Weighing Balance					
BRAND NAMEA: AMLIP					
Tablet No.	Tablet Weight (W) (mg)	Limit Value (AW*7.5)	Upper Limit (AW+LV)	Lower Limit (AW - LV)	Remarks
1	237.00				Pass
2	239.00				Pass
3	240.40				Pass
4	239.80				Pass
5	237.60				Pass
6	237.40				Pass
7	238.50				Pass

TEST- Weight Variation
TEST- Uniformity of Weight

Fig.63 Test Name List

Data Input and Error messages

- The input of invalid data (e.g. alphanumerical data in numerical fields, out-of-range values) can be intercepted (Table 7).

Table 7 Data input and Error messages

6.7.6.3 VBA Code

- Click on the VBA code to open the window showing VBA codes, then click on the desired code to open the VBA code command to do this click on: **Project Explorer> VBA Project Personal> Modules> Choose the desired module** as given in (Fig.64).
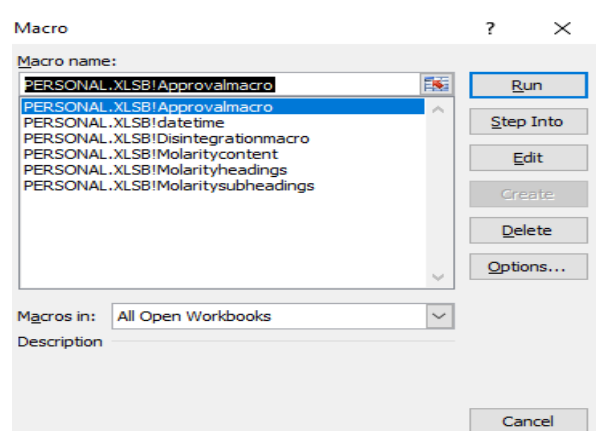

Fig. 64 VBA Code List

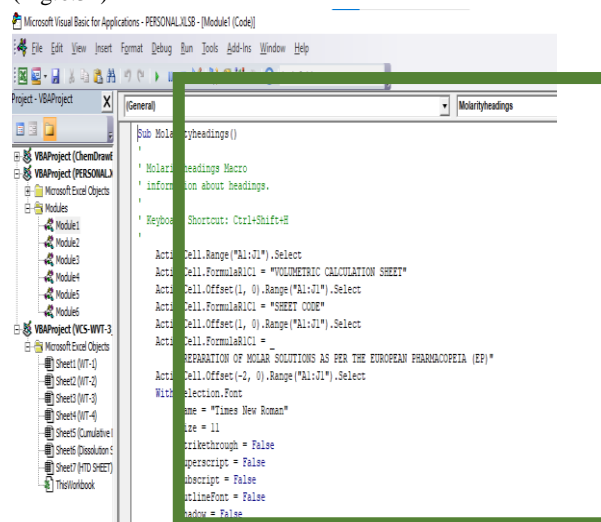- The VBA code coding can be obtain by clicking on the module than on the desired code to run it as given in (Fig.6.32)

Fig.65 VBA Code

- Save your workbook as "**Excel macro-enabled workbook**".

- Press Ctrl + S, then click the "No" button in the "The following features cannot be saved in macro free workbook" warning dialog as given in (Fig.6.33).
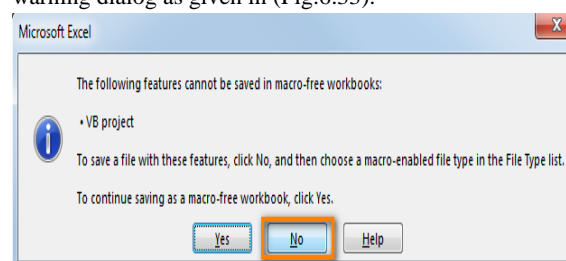
Fig.66 Macro Workbook Warning Window

- The "Save as" dialog will open as shown in (Fig.6.34). Choose "Excel macro-enabled workbook" from the "Save as type" drop-down list and click the Save button.
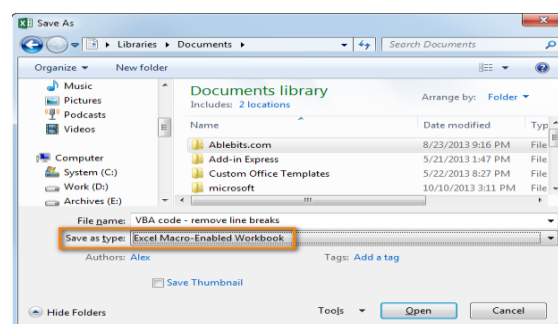
Fig.67 Macro book saving dialog box

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How to run VBA macros in Excel

When you want to run the VBA code that you added as described in the section above: press Alt+F8 to open the "Macro" dialog. Then select the wanted macro from the "Macro Name" list and click the "Run" button as shown in (Fig.68).
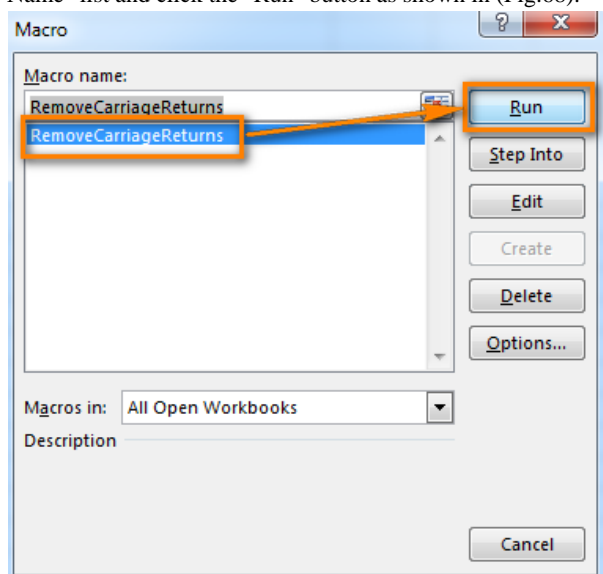
Fig.68 Macro Run dialog box

Audit Trail

- The changes done in the sheet are tracked in new sheets as shown in the (Fig.69).

Fig.69 Tracked Changes Sheet

Excel Auditing Tool and Watch Window

- The error checking can be done for the entire sheets and the message is displayed as shown in (Fig.70)
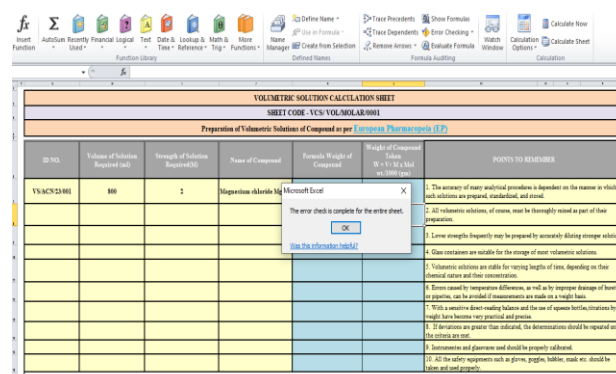

Fig.70 Error Checking Message

- The formula auditing can also be done by using watch window which shows how change into one cell brought the change into other.

- The watch window can been in (Fig.6.38).

Fig. 71 Watch Window Command

Addition of Hyperlink

- The added hyperlink can be seen on the sheet as shown in (Fig.6.39)

- One click on the hyperlink takes to the document or the image, draft from where it is inserted.

Fig.72 Hyperlink Cell

Validation Protocol

The protocol should be follow while performing the excel sheet validation:

1. Protocol Approval: Protocol should be made and approved by the QA department.

2. Purpose: The objective of this protocol is to assure the validation of excel sheets used for calculation purpose.

3. Scope: This protocol shall be followed by the QA personnel while doing the testing to assure product quality.

4. Reason of Validation: The validation of excel sheet was carried out to maintain the data security, integrity and accuracy.

5. Revalidation Criteria: The revalidation of excel sheet depends upon the change in the

- Computer Version no.
- Software Update
- Calculation, Formulas, Acceptance Criteria, color coding etc.
- Guidelines, Users and Procedures

6. Responsibilities: Following departments are responsible for the validation as follow:

- **IT Department:** Handles the password protection and any unauthorised excess.
- **Quality Control:** Prepares procedure for excel sheet validation as per SOP.
- **Quality Assurance:** QA head is responsible for the approval and implementation of protocol properly.

7. Reference Document: All the documents taken for references shall be properly checked and approved.

8. Procedure/Deviations:

- To prevent unauthorised access to the files, a file must be password protected or should be in the read-only status.
- The cell containing formulas or involved in calculation must be locked to maintain data accuracy and integrity.

- The version of the operating systems shall be fixed to prevent any problem during the change or revalidation.
- The format of the sheets should be fixed and such that it the header contains the Product name, Sheet code, Test name, Batch no. and company name , logo (if applicable)
- The middle part shall contain the calculation, where entry to be filled from Raw Data Sheet, formulas and the information needed to make results.
- The footer of the sheets must contain the in-out timing, start-end date alongwith the prepared, checked and approval information with the signature.

- The formula should be written in the corresponding cells for reference.
- The conditional formatting should be done to assure the acceptance criteria as well as the entry into the cell should also be color coded.
- The sheets should be saved with the respective name such as assay, dissolution, disintegration etc.

9. Conclusion: The sheets should be saved in ready only mode with authorized persons signature as shown in (Fig.6.40)

Fig.73 Approved Final Sheet

10. Report/ Report Approval:

The sheets should validate and every action should be documented and sent to the appropriate departments and personnel for its approval.

CONCLUSION

This research has introduced a simplified and efficient method for validating Excel spreadsheets. This method combines industry best practices into two comprehensive documents, with more specific information to follow in upcoming articles. By following these principles, it is possible to fully validate and implement a standard spreadsheet in less than four days. This approach offers a practical solution to the widespread issue of compliance, minimizing risk through an affordable and consistent process. It is adaptable to various quantities of spreadsheets and can be easily integrated into a company's computer systems validation policies.

Spreadsheet creation often point out that the process of creating spreadsheets is more casual in nature, and only a small number of organizations possess thorough guidelines for spreadsheet development. While there are instructive pieces that emphasize practices like modular design and including sections for assumptions, these might not hold as much significance as other advancements, particularly the meticulous inspection of individual cells' code following the development stage.

Acknowledgments involve the installation and checkout phase, which requires shifting the application software from the development lab to the plant site. Upon installation on-site, functional testing with the process can commence. Before this phase starts, a procedure for documented change control (defect identification, review, software and document updates) must be defined and implemented. Outputs encompass functional test results, change control reports, and a validated computer system.

The sheets provide the accuracy maintenance of data and calculations in order to protect the data from any unauthorised access. The good documentation and manufacturing practices alongwith the regulatory authorities made it important for getting regulatory compliance. Validation of process, equipment plays important role in assuring the quality of product while the excel sheets ensure the data integrity and protection from any modification. Therefore it necessary to validate the excel sheets as per the reference documents and the given guidelines to assure quality of the product as well as the generation of the quality data. The necessary steps required to validate an excel sheets are also shown here.

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