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Development and Validation of Electronic Data Recording System, Integratable with all Other Systems to Create Complete Electronic Documentation

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ABSTRACT

As per the current expectation USFDA, MHRA and other major Regulatory Authorities, especially with respect to the Data Integrity policies, the Sponsor has decided to implement e-BMR project by end of 2020. However considering the current state of our different Electronic Records, and the complexity of the e-BMR project, this project cannot be achieved directly. A multitude of different systems has to be converted to 'Electronic Records'. A number of other Systems and Equipments, which has Electronic Records, works in isolation and don't interact with others. The systems which are to be converted to 'Electronic Records' includes different logs, like 'Area and Equipment Usage Logs', 'Calibration Logs', 'Weighing Balance Verification Logs', 'Temperature and Relative Humidity Logs'. All these logs are to be converted to electronic records, before the next stage i.e. Integrating all Equipments and Instruments to the Central Server. Only after these two major system, along with other standalone systems like Bar Code Enabled Dispensing and Intermediate Storage Records are Online, that the main project e-BMR can be implemented, as it will require data from all other systems. This project is aimed for the 'Development and Validation of Electronic Data Recording System, Integra table with all Other Systems to create Complete Electronic Documentation'. There are no computerized systems available in Market which can meets this requirement. So a new computerized systems was configured and validated, which will later be integrated with other systems so smooth flow of data between all systems.

Keywords: Data Integrity, Electronic Records, e-BMR

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INTRODUCTION

Documents and Document Control

The Good Manufacturing Practices is the integral part of the Pharmaceutical Industry. In recent times, a few branches of it have also become prominent, like Good Documentation Practices, Good Laboratory Practices, Good Engineering Practices.

Documents have always been an important part of Pharmaceutical Industry. So have been its retention and its retrieval. A wide range of documents are used in this industry, which are Operating Instructions (SOP, specification), Operating Record (Forms, Checklist) and both (Batch Records). Documents, in form of Technical Documents are routinely submitted for regulatory approval. Documentation is also in prime focus of all Regulatory Audits. It is warranted that any data it has should always be Correct and Reliable.

Lately, however, there is a growing concern on Data Integrity and hence Data Reliability. About all Warning Letters and Import Alerts issued today contains these concerns.

The causes of Data Integrity can be both Intentional and Unintentional. Training, counselling, supervision and other means have proven to be insufficient to completely remove these issues. Moreover, as per USFDA, lack of training only constitutes for 10% of the mistakes. The causes for remaining 90%, are both difficult at accurately identify and removed.[1]

Data Integrity and Data Reliability[2,3]

Data Integrity is a Data which has not been tampered with. USFDA defines Data Integrity as Completeness, Consistency, and Accuracy of data. Complete, consistent, and accurate data should be Attributable, Legible, Contemporaneously recorded, Original or a true copy, and Accurate (ALCOA).

Data Integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

A: Attributable to the person generating the data, with Date & if applicable, Time.

L: Legible and Permanent. Should be easy to read. Entries should only be made by Non Erasing Pen. Correcting / Erasable Ink should not be used. For electronic records, an correction should be captured in Audit Trail.

C: Contemporaneous, that is entries should be done at time of activity.

O: Original record (or certified true copy). Entry should be made on original record directly. It shouldn't be written and then copied from any Scrap Paper.

A: Accurate

Data integrity requirements apply equally to manual (paper) and electronic data. We should be aware that reverting from automated / computerised to manual / paper-based systems will not in itself remove the need for data integrity controls. This may also constitute a failure to comply with Article 23 of Directive 2001/83/EC, which requires an authorization holder to take account of scientific and technical progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Systems should be designed in a way that encourages compliance with the principles of data integrity. Examples include:

- Access to clocks for recording timed events.
- Accessibility of batch records at locations where activities take place so that ad hoc data recording and later transcription to official records is not necessary.
- Control over blank paper templates for data recording.
- User access rights which prevent (or audit trail) data amendments.
- Automated data capture or printers attached to equipment such as balances.
- Proximity of printers to relevant activities.
- Access to sampling points (e.g. for water systems).
- Access to raw data for staff performing data checking activities

The Reaction of The Pharmaceutical Industry [(4)]

With the increased vigilance of the local and international Regulatory Authorities, the industry faced years of turmoil. However, but slowly, rather been looked as 'The Threat', it was perceived as an 'Opportunity'. Companies which already had received the feedback, like 'Establishment Inspection Reports' for USFDA, had taken appropriate (Reactive) Actions. Others started to monitor the Industry and the USFDA databases for Warning Letters, reviewed their internal processes, and took Proactive Actions.

Future Expectation

Similar to the expectations of cGMP, the expectation of Regulatory Authorities is not only the compliance with the current guideline and trends, but to proactively explore the current technological advancements and to develop new technology which ensures a greater Data Integrity, and hence Data Reliability, than today.

USFDA expectation for Paperless Documentation in near future. However considering the complexity and individuality of each process, it is understood to be Work in Progress. The comparison between the Paper Records and the Electronic Records is given in Table 1.

Table 1 The comparisons between The Paper Records and The Electronic Records

Paper Records	Electronic Records
Easy to create records. Also records are easy to review	Knowledge about the Computer System is required for creating and reviewing any records.
The possibility of accidental entry on wrong records (like records of adjacent instruments) is rare.	The possibility of accidental entry on wrong records is considerably higher than Paper Records, as all records are accessed by same system, and there could error in selection of records from a long list.
To ensure Data Integrity, these have to be issued through audit trail enabled systems (Batch Records through SAP) or issued in Bound Book method.	No such requirement, as the entire record is electronic.
Usage copy of paper records are issued (Request is to be raised by user to QA, printed, and then issued by QA to user)	Issuance activity is not required.
Bound Books are difficult to manage, as all records are handled through QA, and is a huge monthly activity.	Issuance activity is not required.
In case, where a single record need entry / approval at different locations, physical movement of record is done.	Relevant entries can be done on any user terminal. Record is automatically routed for approval.
Data entries on all records, with same data, have to be done on individually.	Data entries on all records, with same data, can be interlinked such that, data entry will be done only on the primary record, and automatically copied on all secondary records.
To review these records, all related records have to be cross verified.	All related records, are interlinked, with necessary interlocks which makes cross verification easy, and sometimes redundant.
Uses lots of paper, burden to environment.	Paperless, Environment friendly.
Is costly method, due to paper cost, binding cost and heavy duty printer cost.	Have only one time installation and a minor service cost.
Has Data Integrity and Data Reliability concerns.	Is Data Integrity and Data Reliability complaint. Entries once made, can only be changed by Admin, and the changes are visible in Audit Trail
Date and Time is manually written.	Date and time, is auto entered, from the system time, which is synchronized with server and cannot be altered.

The Way Forward (Need For Work)

For all the reasons discussed previously, to improve the current process of data capture, and to comply with the regulatory requirements and USFDA expectation for Paperless Documentation,

each company in the industry is gradually moving towards the electronic records for each of its documents.

The pharmaceutical industry uses different unique and unrelated processes, where output of one process becomes input of another. This however requires human intervention. Same is the case of data generated through these system.

But the future will be different. Each process will still be unique and unrelated. But the data generated through these will be like that of a single process. Like the Material on receipt will be weighed, however its weight will be automatically recorded by an Online Balance. An online printer will automatically print the label, which will also have barcode / 2d matrix, which whenever scanned in future will give information like the current status (Quarantined, Passed, Rejected, Under Reanalysis etc.) and current remaining weight in the container. Similarly, location of storage of Raw Material and Inprocess Containers can be easily made by scanning the location tags and the material tags.

Similarly, the equipment will be so linked that all its process parameters will be automatically linked with the BMR. The machine can only be operated as per the pre-approved and validated settings for the product. All the usage history will be automatically entered in the Usage Logs, with the applicable records copied in eBMR. And all this can be controlled by the Bar Code which would be generated during Work order / Process Order creation.

As mentioned earlier, all these individual processes are currently not interlinked. These are currently interlinked with human input. And the vastness of the processes, gives us immense opportunity to automate the Operations and the Data Capture.

However the types of documents will dictate the nature of solution that would work.

- Operating Instructions[5], which includes Standard Operation Instructions (SOPs) and Specification. These instructions are for Operators to read and execute. They should always be readily available and referred. These documents are most easy to be converted to electronic records, as these are only referred during work and no information is recorded here. Enterprise Content Management Software[6] are the type of solutions available in market which are used to review, approve and refer Operation Instructions.
- Operation Records[5], includes Forms (Like Change Request Forms, Deviation Approval Forms, etc), Checklist for review of Process like ‘Line Clearance’, ‘Maintenance’ and ‘Review of Documents’, and Logs (Change Request, Deviations, Investigation, and for any other process like ‘Equipment Usage’, ‘Calibration Records’, ‘Maintenance Records’).

Enterprise Quality Management Software[7] are the type of available solutions which converts all Quality Management System (QMS) Forms and Logs to electronic records.

- Documents which are Both Operating Instructions and Operation Records : These documents are both instruction and records, and are the most complex types of documents, and so each has to be handled separately. These includes, Batch Manufacturing Records (BMR), Batch Packing Records (BPR), and Test Data Sheet (TDS). All these documents contain instruction and records of multiple complex process, and each such process has to be handled solely, with solutions which can be integrated together.

There are multiple solutions available in market, but none is suitable for rest of the Operation Records, giving an opportunity to develop one solution.

The Ultimate Aim : Electronic Batch Records

The ultimate aim of the Paperless / Electronic Documentation is the 'Electronic Batch Records'. But the complexity and varied nature of each processes involved from the procurement of raw materials to the release of finished goods makes it an insurmountable task. The best way to achieve this, is by targeting each process individually, with provision to integrate it with other processes at latter stages

Today many of processes like those dealing with procurement raw materials and the release of finished goods, some processes in between performed electronically, by systems like SAP. Many of these systems are interlinked, like interlinking of SAP and LIMS, in such a way the relevant information. Whenever a raw material is received, the Good Receipt Note (GRN) is prepared for the same, the Material Batch No. is automatically created and Sampling request is generated in LIMS. Similarly once analysis is completed, its results is auto-populated in SAP from LIMS. Interlinking controls are also available, where usage of 'Under test' and 'Rejected Materials' in LIMS, is not allowed by SAP. Such interlinking provisions are available in all major systems available in market, but these has to be done during customization.

The next stage is targeting other manual systems, and convert them to electronic systems. The sponsor of this project has already identified three different independent process which are being developed at its different sites, which after satisfactory and complete installation will be initiated at all sites globally and will be integrated with other existing systems. These are

- Integration of all Equipment and Instruments to the Supervisory Control And Data Acquisition (SCADA), where all Equipment and Instruments data will be uploaded and stored in SCADA servers. As the configuration specification of each model of Equipment

and Instruments is different and will also necessitate input from the Manufacturers, this project will be approached in a phased manner.

- Material Management through Bar Coding, where Physical Material, Balances and Inventory Management Systems (SAP) will be integrated to eliminate all manual entries.
- Conversion of all Log Books and other forms, where every activity performed will be recorded electronically instead of paper records. Due to the varied nature and flow of different Log Books and other forms, this project will be approached in a phased manner.

E-Logbook System Components

- E-Logbook System Server
- Mint Matrix Client Terminal
- E-Logbook User Terminals

Figure 1 gives the Systematic Diagram for E-Logbook System Components

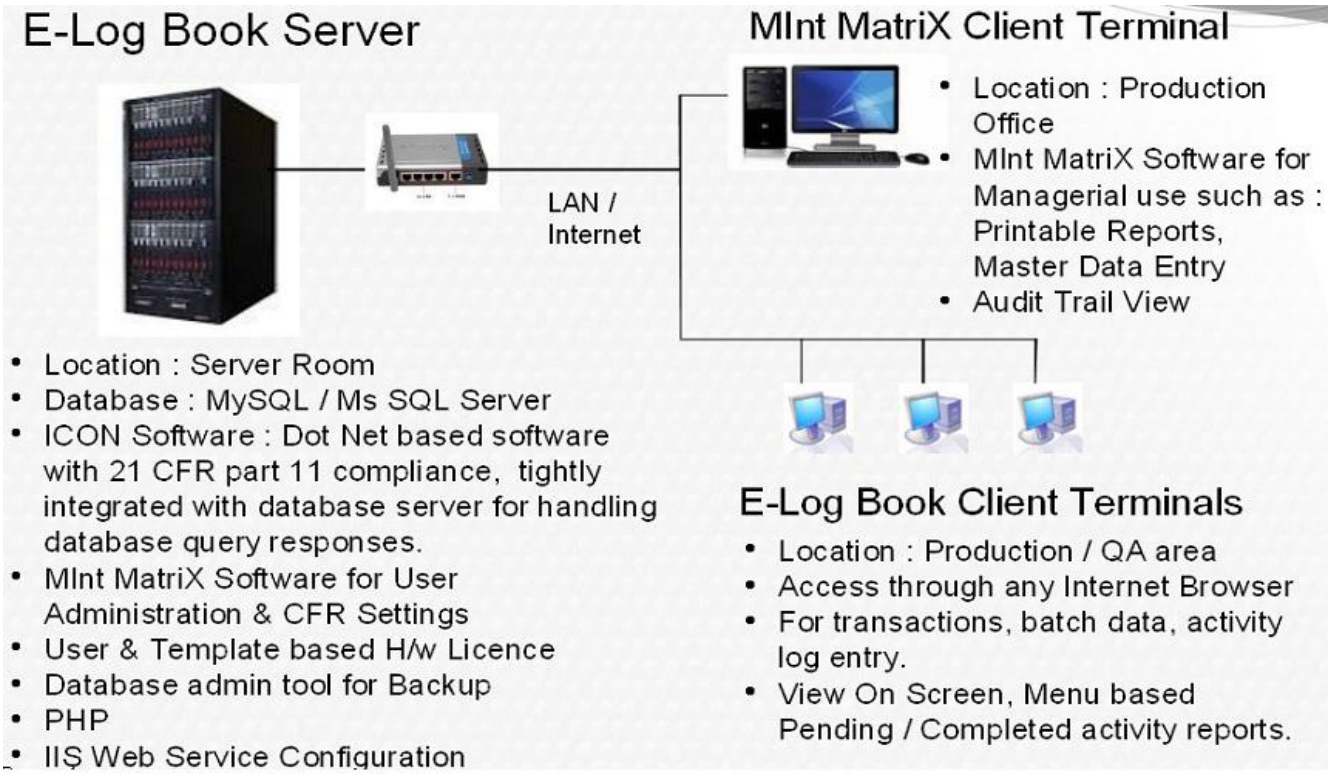

Figure 1 Systematic Diagram for E-Logbook System Components

Other Requirements for Implementation of E-Logbook System

- Portable recording device for recording balance calibration reading.
    - Laptop
    - Tablet
    - Touch Screen

- Network Connectivity in the area for on line data entry
    - LAN connection
    - Wi-Fi connectivity

Table 2 gives the E-Logbook System Software Details.

Table 2 E-Logbook System Software Details

Heading	Details
Software Name	PRAMAAN
Version No. / Release No.	1.1.5519.21451
Classification of Software as per GAMP 5	Custom development / GAMP category 5
Vendor	Autovue Electronics (Pune) Pvt. Ltd.
Language	
Server :	JavaScript
User Terminal :	PHP (Hypertext Preprocessor)
Market Release	Not yet. The vendor is free to do so, provided he maintains the Sponsor's Confidentiality Agreements
Server, Minimum Configuration	
Operating System for PC	Windows (Server2003/2008)
RAM	2 GB
Hard Disk	80 GB

Change Request describing the rational for change and implementation plan was initiated and approved by all stakeholders.

- The change proposal document had details including problem with current system and the advantages of the proposed system.
- Implementation Plan was the part of Change Request, and same was approved.

High Level Risk Assessment (HLRA)[2, 8, 9, 10, 11, 12]

High Level Risk Assessment (HLRA) was performed to determine relevance of system with respect to GxP, Electronic Records and Electronic Signature. Based on the same, it was concluded that the Computerised System (PRAMAAN) is 'GxP Relevant', 'ER Relevant' and 'ES Relevant'

User Requirement Specification (URS)[2, 8, 9, 10, 11, 12]

User Requirement Specification (URS) was prepared considering the below requirements.

- Operational and Design Requirements : The main functionality in regard to the supported processes and analysis including
    - Modes and Ranges of Operations
    - Performance Requirements
    - Output Requirements e.g. Reports / Emails, Safety

- Environment Requirements : The main functionality in regard to the design and environment including
    - Components,
    - Interfaces,
    - Location,
    - Environment,
    - Availability,
    - Integration into IT Infrastructure
- Regulatory Requirements : There are no Regulatory Requirements for conversion of these records from Paper Based to Electronic Records (e.g. Pharmacopoeial requirement).
- Regulatory Requirements for Electronic Record (ER) / Electronic Signature (ES)
    - Service Requirements : The requirement towards the supplier, e.g.
        - Required Maintenance Services
        - Required Documentation
        - Training Support

Vendor Assessment[10]

Vendor Assessment was performed to identify the appropriate vendor for the 'E-Log Book (Electronic Data Recording System) (PRAMAAN)'. Existing vendors were shortlisted for configuration of the software, based on their previous performance and service.

The User Requirement Specification was shared with interested the parties and were invited (individually) to discuss the project and to submit initial proposal. The vendor 'Autovue Electronics (Pune) Private Limited, Pune, India' was selected because of they had already developed similar program, which could be used a template for this project. The Human Machine Interface (HMI) of this program was mostly consistent with the Sponsor's need, and can be customized.

As this was an existing vendor and was currently approved, the previous On Site (Vendor) Audit was valid.

Validation Plan[2, 8, 9, 10, 11, 12]

The validation plan was prepared detailing activities that would be performed for validation of E-Log Book (Electronic Data Recording System) (PRAMAAN). It had a list of system life cycle documentation items and defines the testing strategy. A rationale for any deviation was documented.

Functional Design Specification (FDS)[2, 8, 9, 10, 11, 12]

'Functional Design Specification (FDS)' was obtained from the selected vendor 'Autovue Electronics Private Limited, Pune, India' and was compared against the User Requirement Specification (URS). The 'Functional Design Specification (FDS)' was then approved.

Reference Traceability Matrix (RTM)[2, 8, 9, 10, 11, 12]

As this is a 'Customized Applications', Reference Traceability Matrix (RTM) was prepared during the design stage to ensure that the requirements from the URS are verified to be available in the design.

The requirements as mentioned in the User Requirements Specifications are to be tested and verified post validation and documented in the Reference Traceability Matrix. The reference of the documents is provided to ensure the computerized system is validated as per the URS and can be released for intended use.

The Reference Traceability Matrix was prepared wherein the each requirement from User Requirement Specification was listed along with the corresponding functionalities from Functional specification. For each requirement – functionalities, thus mentioned column to record the corresponding document in validation, where this check was performed was included.

For ease of preparation, Reference Traceability Matrix was updated periodically to include information e.g. inclusion of details of configuration specification, mapping of validation tests with the individual requirements during the course of validation.

Failure Mode Effect And Criticality Analysis (FMECA)[13]

Failure Mode Effect and Criticality Analysis (FMECA) as a risk management tool was used to identify each 'Potential Failure Mode' along with its 'Potential Effect', and then rated on its 'Severity Level'.

Functional Risk Assessment (FRA)[2, 8, 9, 10, 11, 12]

Risk assessment for system functionality i.e. Functional Risk Assessment (FRA) identified in the URS and/or the FS is performed for all 'Customized Applications'. This helped to decide the scope of the validation testing.

Functionalities listed in the functional specifications were classified as GxP or Business relevant (or both or non-relevant). Based on this assessment determine the extent of testing to be performed for the individual functionality.

Risk Assessment (for each Functionalities) was done under GxP, Business, Risk Scenarios, Probability of Occurrence, Severity, Risk Class, Detectability and Priority. Based on above Risk Assessment, Extent of Testing was given for each Functionalities, as Low, Medium or High.

Design Qualification (DQ)[2, 8, 9, 10, 11, 12]

Design Qualification is the documented evidence that the proposed design of the facilities, systems and equipment are suitable for intended purpose. The compliance of the design with various standards like cGMP and safety, was demonstrated and documented.

Availability of following documents was checked to provide documented evidence that all the documents required for commencing the validation of 'E-Log Book (Electronic Data Recording System) (PRAMAAN)' are available.

- User Requirement Specification
- Vendor audit / assessment documentation
- Functional Specifications
- Risk Assessment (FMECA)
- Functional Risk Assessment
- Configuration / Design Specifications
- Reference Traceability Matrix
- List of components
- System / Electrical Diagrams / Network / IT Infrastructure
- Brochures / Discussions / Meetings
- Comparison of Requirement Specification
- Purchase Order Copy
- Invoice Copy

There was no design related pending items and no deviation was observed during Design Qualification.

Installation Qualification (IQ)[2, 8, 9, 10, 11, 12]

Installation Qualification provides the documented evidence that the computerized system has been successfully installed in the selected (validation) environment.

During Installation Qualification, installation checks for the computerized system in the validation environment was performed. It was ensured that the site pre-requisites are fulfilled and the site is ready for the installation of the computerized system.

Installation Qualification was performed by the designees from 'Vendor`s representative', 'System User', 'IT' and 'Quality Assurance'.

User Requirements Specification (URS), Validation Plan (VP), Functional Design Specification (FDS) and Functional Risk Assessment (FRA) were taken into account for the Installation qualification of the computerized system are,

Pre-Installation Checks including Delivery Inspection, Documentation (Installation procedure, user manuals, certificates (FAT), etc.), and work place and location check as per site prerequisites was performed. After Pre-Installation Checks, Installation Qualification Checks were performed, and evidence (Screenshots) (Wherever applicable) for the same were appended. There was no installation related pending items and no deviation was observed during Installation Qualification.

Operation Qualification (OQ)[2, 8, 9, 10, 11, 12]

Operation Qualification is the documented evidence that the computerized system is will function according to its operational specifications in the selected (validation) environment.

During Operation Qualification, operation checks for the computerized system in the test / validation environment was performed. It was ensured that prior to Operation Qualification, Operation Training is completed. Operation Qualification was performed by the designees from 'Vendor`s representative', 'System User', 'IT' and 'Quality Assurance'.

User Requirements Specification (URS), Validation Plan (VP), Functional Design Specification (FDS) and Functional Risk Assessment (FRA) were taken into account for the Operation qualification of the computerized system are,

Operation Checks were performed as per the preapproved Operation Qualification protocol and Test Scripts. Evidence (Screenshots) for the same were appended to the applicable Operational Qualification Report and or Test Scripts. There was no operation related pending items and no deviation was observed during Operation Qualification.

Performance Qualification (PQ)[2, 8, 9, 10, 11, 12]

The Performance Qualification is the documented evidence that the computerized system meet user requirement specification in the selected (production) environment. It is the evidence that the system is accepted by the system owner and / or process owner by ensuring that the system is validated for its intended use by testing end to end workflow.

During Performance Qualification, performance checks for the computerized system in the production environment was performed. Installation Qualification was performed by the designees from 'Vendor`s representative', 'System User', 'IT' and 'Quality Assurance'.

User Requirements Specification (URS), Validation Plan (VP), Functional Design Specification (FDS) and Functional Risk Assessment (FRA) were taken into account for the Installation qualification of the computerized system

Performance Checks were performed as per the preapproved Performance Qualification protocol and Validation Protocol. Simultaneous entries were done in Pramaan and Manual Logs, for one month. On completion of review period, System Generated Logs and Manual Logs were compared and same were appended to the Performance Qualification Report. There was no performance related pending items and no deviation was observed during Performance Qualification.

User Creation and User Privileges

After completion of Installation Qualification, training program for of all end users was initiated, and before commencing the Operation Qualification training was imparted to the end users on the operational part.

Only after completion of training and successfull evaluation of the trainee, users were created in the system. The User Privileges in the system is as below,

- Operator : Performing Activity
- Production Officer : Checking
- Department Head : Review of Audit Trail
- QA Officer : Verification
- Administrator : Addition / Modification / Deactivation of users, areas, equipment, products and other masters; Generation of reports; Review of Audit Trail
- Administrators are the non-system user from Information Technology, Quality Assurance and / or Vendor.

Whenever required, new users will be created after completion of training and successfull evaluation of the trainee.

Standard Operation Procedure (SOP)

The draft Standard Operation Procedure ‘Operation of Pramaan (E- log book) system’ was prepared prior to Operation Qualification and approved after Operation Qualification

The Followed Workflow is given in Figure 2.

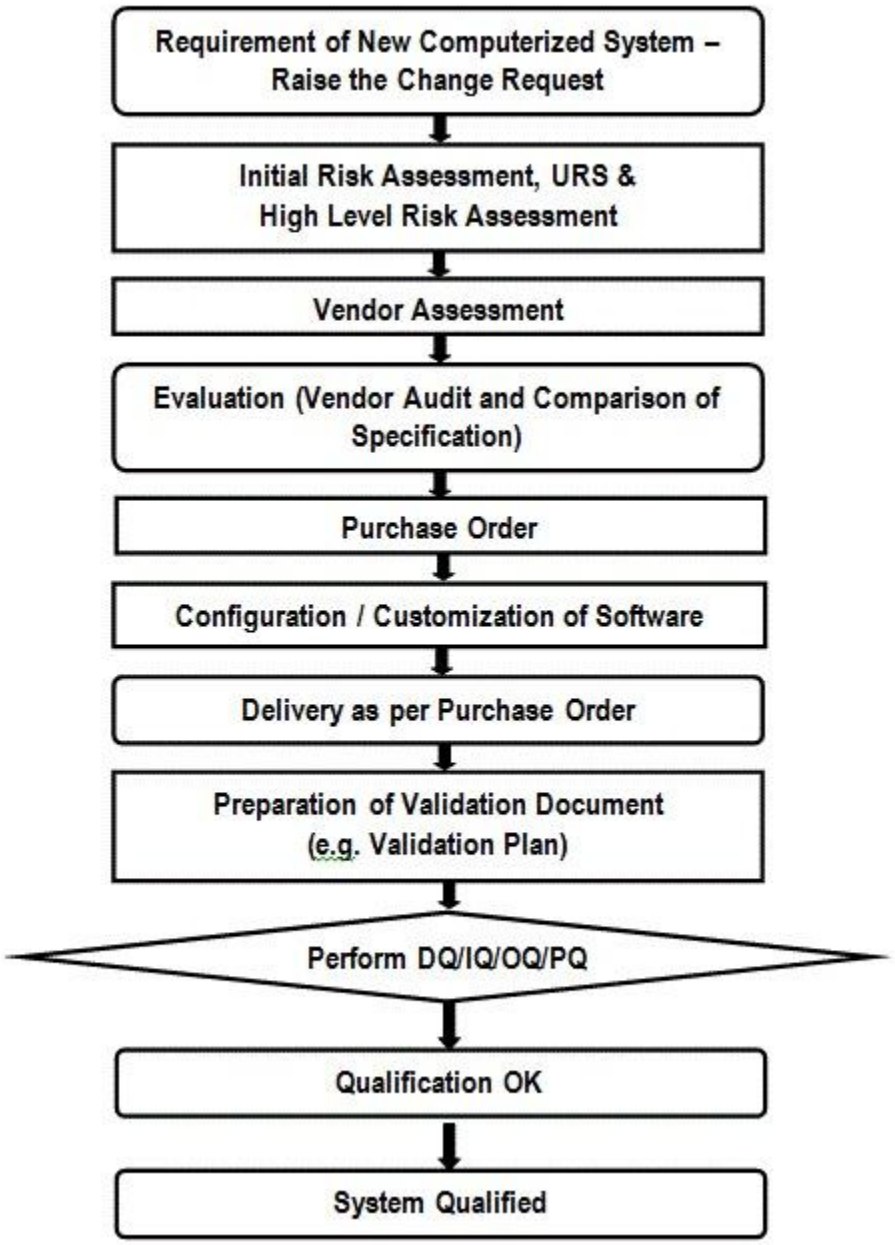

Figure 2: Followed Work Flow

Validation Summary Report (VSR)

The validation has been performed following the validation plan. All activities have been executed as planned and fully meet the requirements as defined in the plan.

- Deviation from the Validation Plan : No Deviation
- Deviation observed during Validation : No Deviation
- Follow-up Actions : No follow-up actions

Summery and Assessment of System Life Cycle Documentation:

- As planned in the validation plan, User Requirements Specification, High Level Risk Assessment, Validation Plan, Function Specification, Reference Traceability Matrix, Risk Assessment (FMECA), Functional Risk Assessment, Vendor Assessment / Audit, Comparison of Requirement Specification, Configuration Specification / Design Specification, Design Qualification, Installation Qualification, Operational Qualification, Performance Qualification, Validation Report and SOPs were created in scope of the project.
- raining : Initially after completion of the IQ and before commencing the OQ and PQ training imparted to the end users on the operational part. When new user required access to software then the training shall be imparted to the new user and then access shall be provided. Any updates in the SOP and functional change in the software shall be intimated to the user by conducting formal training session.
- Design Qualification, Installation Qualification, Operational Qualification and Performance Qualification was successfully completed.

System Acceptance and Release:

Validation activities related to PRAMAAN system are executed as defined in the SOP and have been completed successfully.

Based on the results of validation activities PRAMAAN system was released for operational use without limitations.

Post Implementation Review:

After Go live of the software, post implementation review shall be performed yearly. Post implementation review shall include the following, but not limited to,

- Review of validation documents to ensure it is complete, up-to-date, and correct.
- Incidence management
- System security and access control
- Review of audit trail
- Change management
- Software and data backups
- Training
- Availability of Standard Operating Procedures / User manuals.
- Outstanding actions required by a Validation Report

- That any controls implemented to manage risk are in place.

Incidence Management

- Post go live malfunctions shall be handled as per the Incidence Management Procedure. These malfunctions or issues shall be categorised as,
- Software Issues - Issues observed in software
- Training Issues - Issues observed due to in adequate training
- Procedural Issues - Issues observed due to deficient procedure
- Other Issues - Issues observed due to reasons like LAN, Server, Human Error, etc.

CONCLUSION:

- An Electronic Data Recording System' was developed which meets the 'User Requirement Specification', is 21-CFR complaint.
- Training was given to all concerned staff.
- Administrator role was assigned to Non-System users from QA.
- Validation activities related to PRAMAAN system are executed as defined in the SOP and have been completed successfully.
- Based on the results of validation activities PRAMAAN system was released for operational use without limitations.
- The Post Implementation Review (PIR) will be performed yearly.

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