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QUALIFICATION AND COMPUTER SYSTEM VALIDATION OF PHARMACEUTICAL INSTRUMENT: CRITICAL QUALITY ATTRIBUTES IN PHARMACEUTICAL INDUSTRY

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ABSTRACT: Quality is the most important requirement in the manufacturing process for every pharmaceutical and healthcare industry. All the drugs must be manufactured to the highest quality level. Quality cannot be guaranteed just by end-product testing, but we have to control each critical step carefully during the manufacturing process. This qualification and computer system validation plays an important role in controlling each critical step of application in order to maintain the quality of the final product. Computer system validation involves a series of activities that are taking place during the life cycle of processes. It also involves careful planning of various stages in the qualification and validation of application/software used in the manufacturing process, and all the work should be carried out in a structured way according to standardized working procedures. The objective of this work is to overview the qualification and computer system validation of instrument/equipment used in the pharmaceutical industry.

INTRODUCTION: In any pharmaceutical industry, validation and qualification of instrument/ equipment is a basic segment that supports company commitment to quality assurance. Validation/ Computer system validation is a tool of quality assurance that provides confirmation of the quality in equipment systems, manufacturing processes, software, and testing methods. Two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid-1970s introduced the concept of validation in order to improve the quality of pharmaceuticals products.

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The first validation activities were focused on the processes involved in making pharmaceutical products but quickly spread to associated processes including environmental control; media fill, equipment sanitization, and purified water production [1].

Computer system validation encompasses computers, which directly control the process or system or collect analytical data. Computer system validation includes the qualification of all software and hardware, which has an impact, direct or indirect, on the quality of a product. The validation approach for the programmable logic controller (PLC) hardware and personal computers (PCs) is almost similar in many ways, both to one another and to the general overall approach top validation, in that the end-user should define each requirement. The field of computer technology is used to

develop considerable speed, and the regulated user has to ensure that the software and systems have been developed to best engineering practices in a quality assured manner. It will be for regulated users to define relevant applications, impacted business units, and corresponding deliverables for such applications [2]. Validation in itself does not improve processes, but it gives the assurance of the processes that have been properly developed and are under control. Adequate validation/qualification is beneficial to the manufacturer in many ways like It helps to the understanding of processes; decreases the risk of preventing problems, defect costs, regulatory non-compliances and thus assures the smooth running of the process. The regulations also set out an expectation that the different parts of the manufacturing and analysis process are well defined and controlled, such that the results of that production will not substantially change over time [3-4]. Nowadays, there is an increasing trend to integrate electronic records and business management systems across all operational areas. In the future, it is expected that our dependency on computer systems will continue to grow. The use of validated, effective, GxP controlled computerized systems provide enhancements in the quality assurance of regulated materials/products and associated data/information management. The extent of the validation effort and control arrangements should not be underestimated, and a harmonized approach by industry and regulators is beneficial [5-6].

Goal of Qualification and Validation: The main aim of any regulatory agencies is to ensure that quality is built into the system at every step, and not just tested for at the end, as such validation activities will commonly include training on the production process and operating procedures, training of people involved and monitoring of the system whilst in production. In general, an entire process should be validated or verified, for a particular object within that process is verified. The regulations also set out an expectation that the different parts of the manufacturing process are well defined and controlled, such that the results of that production will not substantially change over time. This also extends to include the development and implementation and the use and maintenance of computer systems [7]. The software validation guideline (GAMP-5) states: "The software development and validation process should be sufficiently well planned, controlled, and documented to detect and correct unexpected results from software changes."

Verification and Validation of Instrument: There is a difference between 'Verification' and 'Validation' activities. 'Verification' is referring the evaluation of the software with respect to the given set of requirements and specifications, which is done in-house at the software development site by the developers and testers. In contrast, **'**Validation**'** is a set of quality assurance checks which are carried out by the external agencies, owners, vendors on the product being delivered to them, to check the suitability before accepting or purchasing the product. Validation activities are mostly carried out in the production environment.

TABLE 1: DIFFERENCE BETWEEN VERIFICATION AND VALIDATION

Verification	Validation
Done- in house	Done at the Production site
Done by Developer and testers	Done by customers, owners, vendors, and operation team
Includes unit, integration, and system testing	Includes Installation, Operations, and performance suitability

Hence, in the case of Application Development, it is the Operations Team who is carrying out the Validation activities for the software.

Phases of Validation Process: Generally, the Validation Process of any product refers to the complete life cycle of a product from the development through use and maintenance. And hence the validation process is broken down into 5 Phases, 5 Phases of Validation Process are:

This 5 phase approach of the Validation process is being followed in many Industries like Manufacturing, Medical, and Pharmaceuticals, *etc*. At this end, Computer system validation and qualification will be performed by the end customer before buying the software, instrument/equipment, or the product [8-10].

Analytical Instrument Qualification (AIQ) and Computer System Validation (CSV): Analytical instrument qualification (AIQ), previously known as equipment qualification (EQ), it is the process by which an apparatus is demonstrated to be fit for its intended use. All the instrument/equipment calibration parameters such as temperature accuracy, linearity, pressure, flow rate, which are used by the techniques for which the machine is used, are then expected to be within acceptable limits. In the ideal case, these parameters follow international/recognized or regulatory standards, though this is not always so in real life. The instrument parameters which are to be qualified may vary between industry to industry because many laboratories use their own specific methods. EQ is important for every equipment which is used in a controlled environment and forms the foundation for any other validation of analytical methods. Analytical instrument qualification (AIQ) term used by the Pharmaceutical Manufacturers Association (PMA). It has four phases, and every phase user was having different responsibilities [11-12]. The user's role is shown in **Table 2** below.

TABLE 2: OVERVIEW OF THE DIFFERENT PHASES RELEVANT FOR THE USER IN THE QUALIFICATION OF AN INSTRUMENT

Qualification	Phase	Responsibility of	Activities
Design Qualification	Evaluation of the instrument	User	Document evidence that proves that the instrument meets the requirement with regards to functional and operational specification
Installation Qualification	Installation of the instrument	User	Documented evidence that verifies that the instrument has been properly installed in the selected environment. Functional check
Operational Qualification	Putting the instrument into operation	User	Documented evidence that verifies that the instrument functions according to operational specifications in the selected environment. Performance check.
Performance Qualification	Check the performance of the instrument for its intended uses	user	Documented evidence that verifies that the instrument performs consistently as intended in routine use in a normal operating environment. Periodic checks of: • Specification • Specific system suitability tests • Analysis of control samples

Computerized System Validation (CSV): As with other equipment, CSV is meant to demonstrate that the system operates in a way that is appropriate for its use. As with Analytical Instrument Qualification, IQ, OQ, and PQ are different, but their actual meaning in this context is slightly different, which may confuse the understanding of these terms, as recognized by the regulatory agencies like USFDA, which has led to its exclusion from the Guidance for Industry on the "general principles of software validation document". A special problem, in this case, is that the computerized system which is being validated is part of the measuring instrument, and therefore needs to be qualified as well. The user will therefore carry out analytical instrument qualification on the instrument *via* installation qualification and operational qualification and validated the software/application via IQ, OQ and PQ as well. Any validation plan must include how this is to be achieved, whether the software and instrument qualification will be separate or as part of the same approach. In the case of thermal analysis, most instruments require the computerized system for data processing and acquisition, making the second option the only feasible one. **Table 3** below compares the qualification steps in AIQ and CSV, and **Fig. 1** shows more differences in the way these three terms are used in the two procedures.

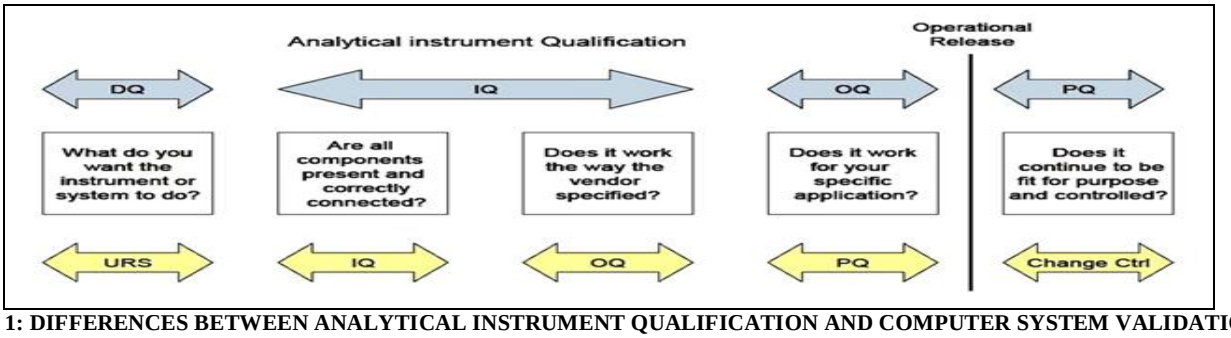

FIG. 1: DIFFERENCES BETWEEN ANALYTICAL INSTRUMENT QUALIFICATION AND COMPUTER SYSTEM VALIDATION

TABLE 3: DIFFERENCES IN QUALIFICATION TERMINOLOGY BETWEEN ANALYTICAL INSTRUMENT QUALIFICATION AND COMPUTERIZED SYSTEM VALIDATION

Term	Analytical Instrument Qualification	Computerized system validation
Design Qualification (DQ)	DQ or user requirement specification that documents the functional requirement of the instrument and any software features including 21 CFR part 11 and predicate rule compliance.	
Installation Qualification (IQ)	Assurance that indented equipment is received as designed and specified	Documented evidence that all key aspect of hardware and software installation adhere to appropriate codes and the computerized system specification
Operational Qualification (OQ)	Confirmation that the equipment functions as specified and operates correctly (Operational Release of Equipment)	Documented evidence that the system or subsystem operates as intended in the computerized system specifications throughout representative or anticipated operating ranges.
Performance Qualification (PQ)	Confirmation that the equipment consistently to continue to perform as required. (requires periodic testing and calibration)	Documented evidence that the integrated computerized system performs as intended in its normal operating environment (Operational Release of System)
On-going validation Activities	Change control and configuration management (Maintenance)	Periodic reviews to ensure that the system is still validated and under control.

Reconciling AIQ and CSV: There is an essential similarity between the (Design qualification) DQ and IQ stages in computer system validation and analytical instrument qualification (**Table 3** shows). Both of these expose whether the system is qualified and installed properly. The main difference in the operation and performance stages (OQ&PQ), partly due to the increased complexity of a computerized system compared to an analytical instrument. During Operational qualification, it ensures the fitness of the item for its intended objective and should be carried out by the laboratory, as only then is the instrument permitted to be put into operation. Computer system validation, having added two more stages, the OQ, which confirms that the system works according to the vendor's claimed operating ranges, and the PQ to show that application/ software works in the actual operating environment defined by the user. This last stage is to be done by the laboratory and is the last step before the computerized system can be used in a regulatory environment. In real life, this means that systems which are assembled with a computer must always undergo testing of the CSV. These are so closely connected that EQ and CSV are performed at the same time [13-15].

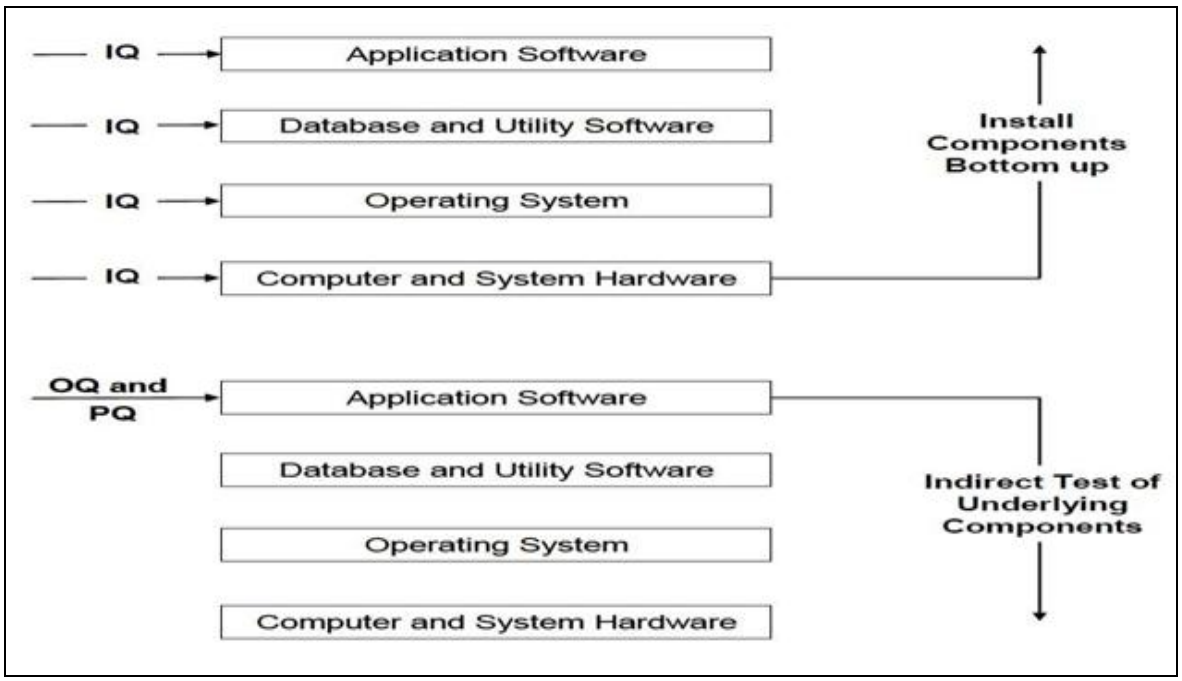

FIG. 2: DIFFERENCES BETWEEN INSTALLATION QUALIFICATION AND OPERATIONAL AND PERFORMANCE QUALIFICATION

Differing Objectives of Computer System Validation: The aims of these two phases of computer system validation are shown in **Fig. 2**, which shows the IQ of the computerized system at the top and the IQ of each layer of the system from the bottom upwards. Computer hardware, configuration, installation, and qualification of the operating system, such as putting the Internet protocol address of the computer on the computer network and turning operating system functions off and on as is required, installation and qualification of the database as well as software. The concept of this type of testing is that each layer can be reached only by the successful termination of the one just below it.

The Relationships between AIQ, CSV, and AMV: The Relationship between analytical instrument qualification, computer system validation and analytical method validation is given in **Fig. 3**. The first three are to be done by the equipment vendor, while the rest should be done by the end-user or laboratory.

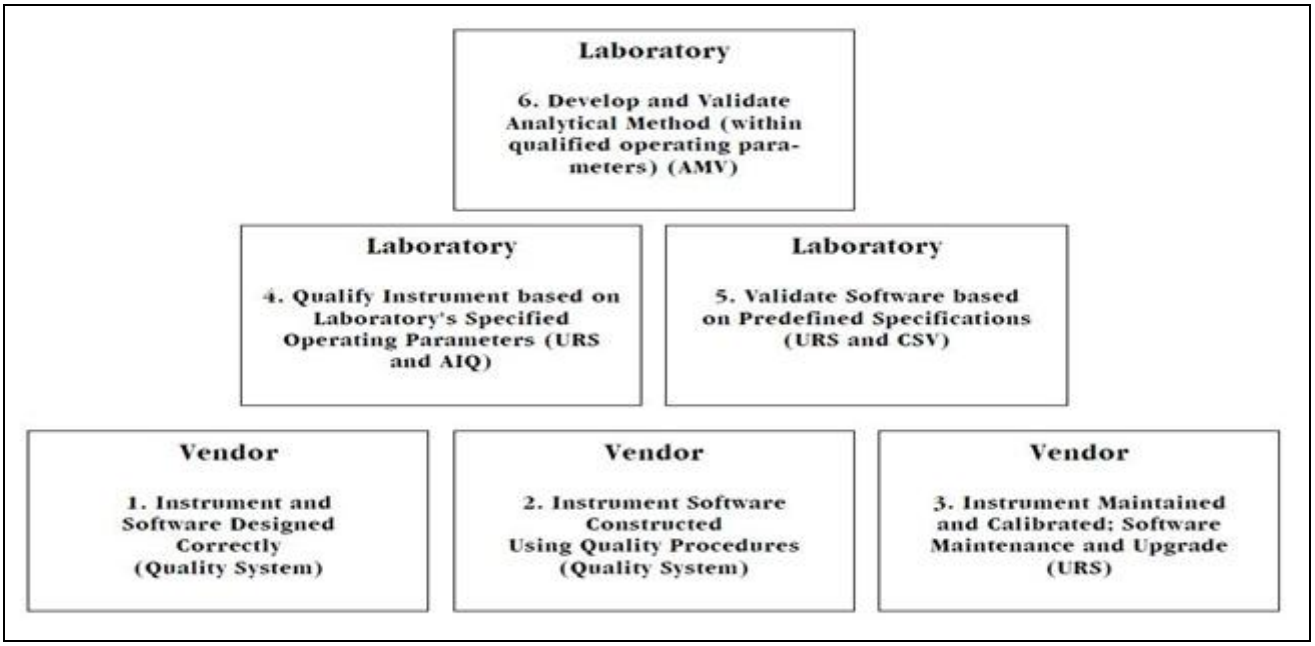

FIG. 3: RELATIONSHIP BETWEEN ANALYTICAL INSTRUMENT QUALIFICATION, COMPUTER SYSTEM VALIDATION, AND ANALYTICAL METHOD VALIDATION

The foundation of the whole structure is to test that the analytical system or instrument has been designed and maintained properly. This is the responsibility of the vendor/supplier who builds and tests it, including the software, and thereafter maintains and upgrades it as required. The user should, of course, choose the right kind of instrument and software for the analytical activity. This is the job of the laboratory, which should have a clear specification for the functions to be carried out by the instrument as well as the requirements for the software. Healthy authority regulatory agencies such as GAMP or 21 CFR part 11 guidelines need to follow for compliance during qualification and validation. The next step is the responsibility of the lab user for AIQ and CSV. The user requirement specification (URS) defines the operating parameter range against which the instrument is qualified, such as using a digital thermometer that is calibrated to national standards to measure the set temperature of the instrument, and ensuring the actual temperature is the one that is set. After instrument qualification and software validation, the next step is the validation of each analytical method, which is used for the analysis of products/compounds [16-18].

Installation Qualification (IQ): IQ is a short form of Installation qualification; it is the process of validating the supplied software installed on the specified environment with the specified configurations, and verification of installation steps recorded in the document called 'Installation Guide'. Installation Qualification of Software is the most crucial phase, and typically many issues open up during this phase. These include: a)

Development environment will not have a 100% real-time environment available to verify the installation issues, and hence a difference in the environment contributes to several issues. b) There could be some documenting issues while recording the actual installation steps in the document, which may not exactly match the production environment.

To overcome these issues nowadays, the entire software installation procedure will be automated as much as possible via a series of scripts. If there are any issues with the installation, then the automated installation fails due to any miss-match in the configurations, and manual intervention to fix those issues is required. If any issues are found during the installation qualification validation phase, then it will be reported to the concerned department, upon fixing of which, the smoke testing and build verification tests will be carried out to check the success of the software installation. So, the successful completion of the Installation phase is very important as a successful and right installation of software ensures that most of the issues related to functionality failures are negated. Below mentioned test script are typical test executed during installation qualification:

TABLE 4: STANDARD TEST SCRIPT OF INSTALLATION QUALIFICATION

Test Case ID	Test Title
IQT.001	Documentation Verification
IQT.002	Hardware Configuration Verification
IQT.003	Software Configuration Verification
IQT.004	Controlled Equipment Verification
IQT.005	Data Security Verification
IQT.006	Password Settings Verification
IQT.007	User profile and related privileges Verification

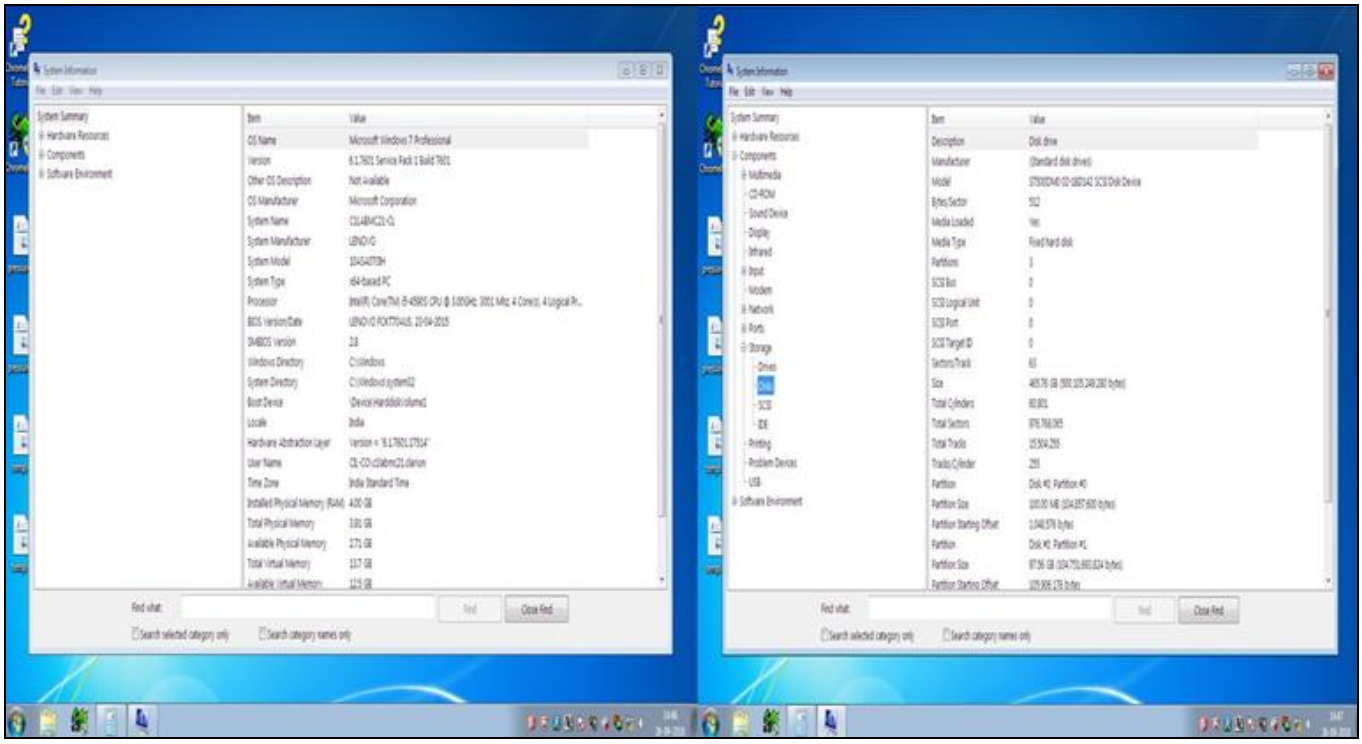

FIG. 4: TYPICAL HARDWARE AND SOFTWARE VERIFICATION EVIDENCE

Operational Qualification (OQ): After Installation qualification, the second stage is Operational qualification, which is also known as OQ. This qualification activity includes the tests to be run in order to verify that the software is operationally fit to be deployed to the consumers. Normally, the key functionalities of the software are verified as part of this qualification process. Operation qualification cover all the aspects of OQ testing that need to be carried out, including details like no. of tests, test schedule, methodology, tools, impact on the service, test execution sequence, method of reporting issues, and Defect Triage approach, *etc*. The Operational Qualification tests are a collection of important tests that are designed based on the 'Functional Requirements Specification or user requirement specification' document to ensure that the entire software system

functions as per the expectation. This OQ Test Specification Document is generally prepared by the Test Engineers/software validation analyst against the Functional Requirements Specification document. Generally, this document will be the subset of the system test specification document prepared and verified during the system testing phase of the software development life cycle (SDLC). The tests may be altered or updated to suit the operational team requirements and the conditions of the environment where execution activity is performed. During OQ activity, it is necessary to check all the key functionalities, and the main business workflows are included as a part of this verification. Successful completion of OQ demonstrates that the software will function according to its operational specifications in the selected environment, and it is the stage-gate in moving the software towards its production and is the signal to go ahead with the next activity of the Validation process, which is known as Performance qualification.

TABLE 5: STANDARD TEST SCRIPT OF OPERATIONAL QUALIFICATION

Test Case ID	Test Title
OQT.001	Backup & Restore of data
OQT.002	Access Control
OQT.003	Authority Check – User Profiles
OQT.004	Device Check
OQT.005	Record Inspectability
OQT.006	Altered and modified Record
OQT.007	Invalid Entry
OQT.008	Time Reference Control
OQT.009	Audit Trail

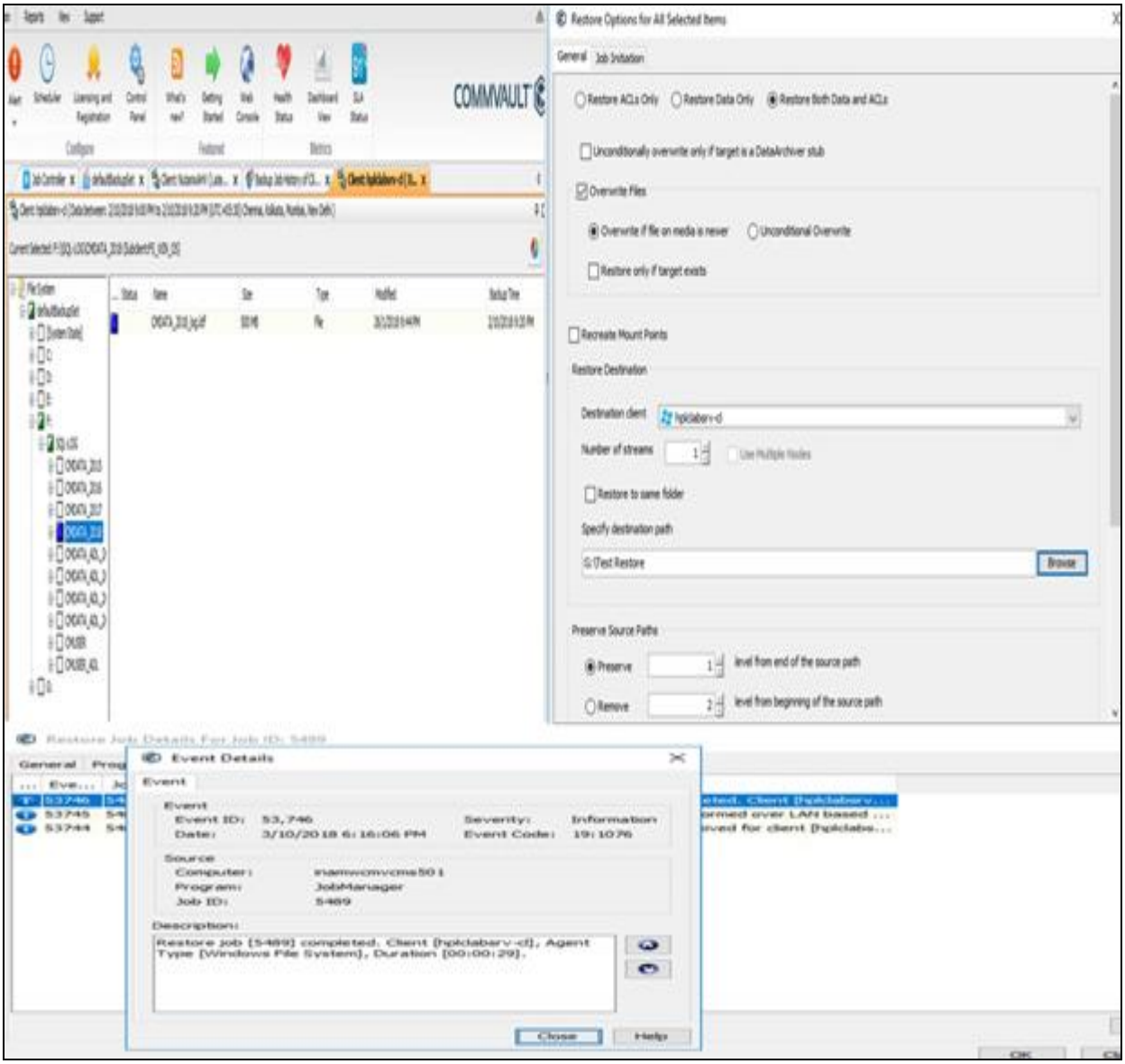

FIG. 5: BACKUP AND RESTORE VERIFICATION EVIDENCE

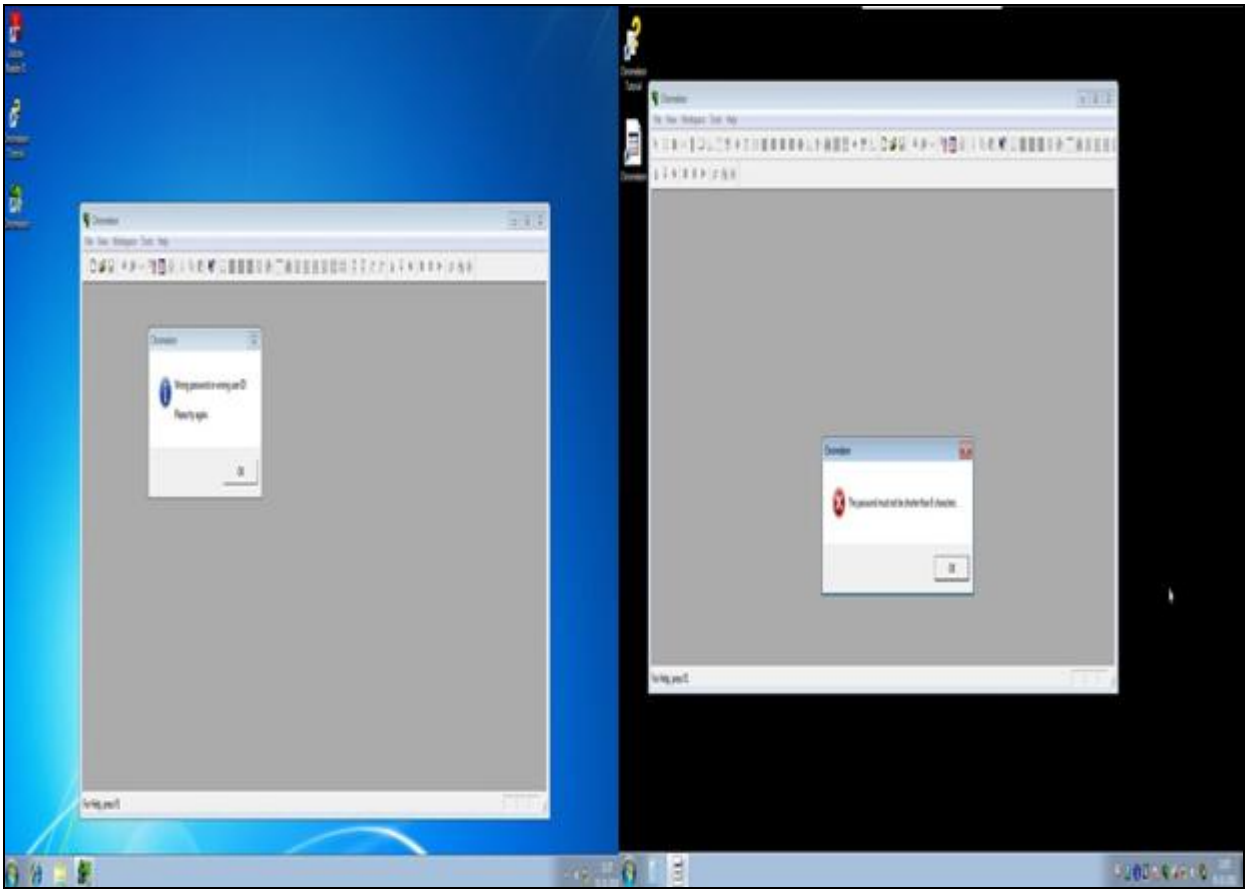

FIG. 6: ACCESS CONTROL AND PASSWORD VERIFICATION EVIDENCE

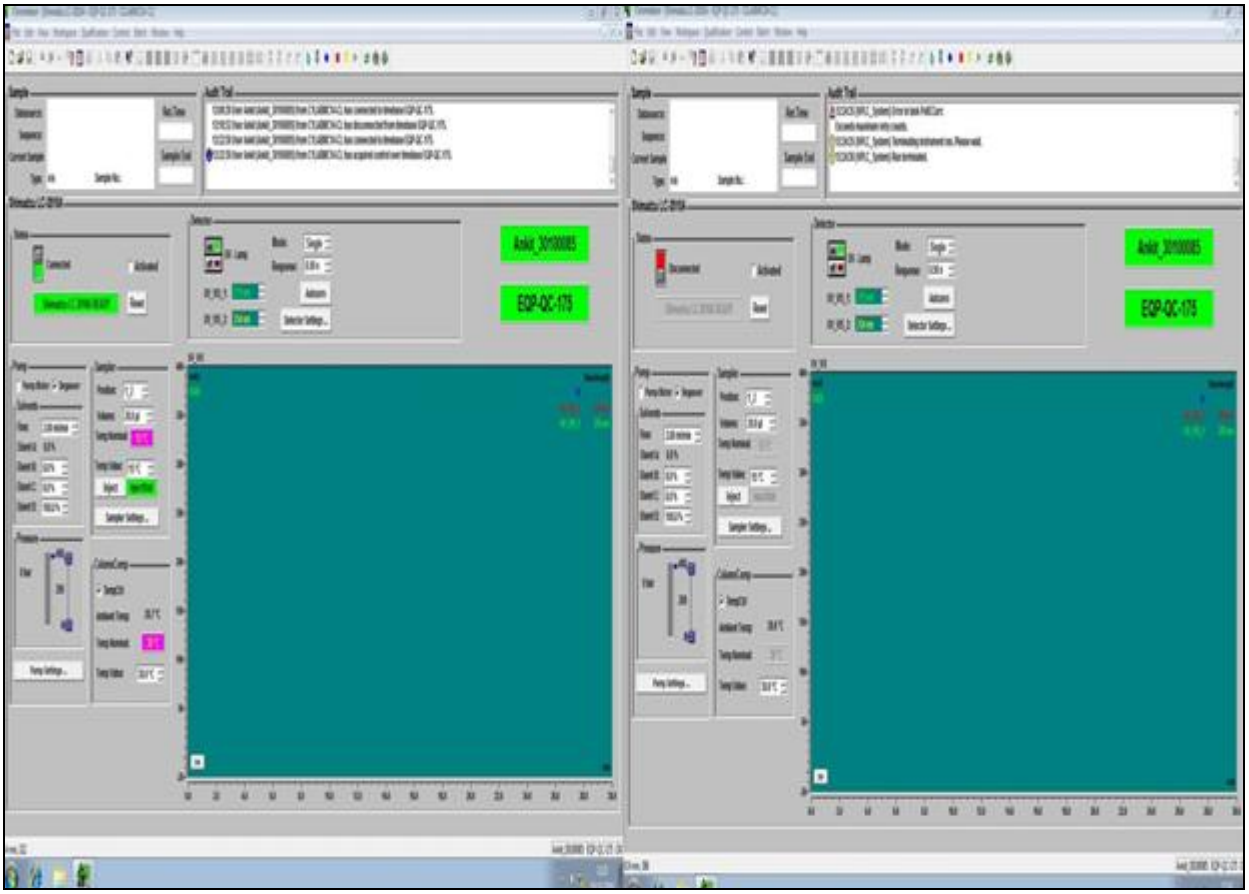

FIG. 7: DEVICE CHECK TYPICAL EVIDENCE

Performance Qualification (PQ): Once the installation & operational qualification activity is completed successfully, the next activity in the validation process is to ensure if the product/ software meets the specified Performance aspects under the expected load consistently without causing any bottleneck in the production environment. The main aim of performance qualification is to ensure that software when installed on the expected system. Performance qualification is performed to ensure the specified performance criteria for software are achieved over a period of time on a reliable basis with varying load conditions, as is the pattern in the live. Hence these tests have to be run every day to monitor the software system behavior and hence PQ will take a while to complete until it is ensured that the system is proved for its performance. Ideally, PQ Validation is carried out post the completion of OQ, where the functionality of the software is ensured and can go ahead with verifying the performance aspect of the product or software. Sometimes due to time constraints, PQ can start in parallel to the OQ, based on the confidence on the percentage of OQ completion. The following tests are generally run as part of the Performance Qualification. And the choice of the tests varies from software to software.

TABLE 6: STANDARD TEST SCRIPT OF INSTALLATION QUALIFICATION

Test Case ID	Test Title
PQT.001	SOPs Verification
PQT.002	Data Acquisition and Report Printing

Component Qualification (CQ): It is a relatively new term developed in 2005. This term refers to the manufacturing of auxiliary components to ensure that they are manufactured to the correct design criteria. This could include packaging components such as folding cartons, shipping cases, labels or even phase change material. All of these components must have some type of random inspection to ensure that the third party manufacturer's process is consistently producing components that are used in the world of GMP at drug or biologic manufacturers.

CONCLUSION: Even if the product/software has passed all the verification stages and fails to prove any one of the Qualification (IQ-OQ-PQ) and validation stage, the result can be disastrous and will incur a huge cost. Hence successful completion of Installation, Operation, and Performance alone is the successful transfer of the product from the development site to the production site. Overall, the successful completion of the qualification and validation process not only gives them confidence in the software but also gives peace of mind to the Client, Owner, Software Developers, and the Testers. Running installation, operational, and performance qualification also reduces the risk of deploying it to live, without carrying out testing and reduces the cost of failure and mitigates the risk of recall of the products.

From the above qualification and validation point of view, we can conclude that instrument qualification and software validation is a critical quality attribute for any manufacturing industry where instrument/ equipment used for continuous, uninterrupted process.

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