

CALIBRATION AND QUALIFICATION OF EQUIPMENTS IN THE PHARMACEUTICAL INDUSTRY: EMPHASIS ON RADIOPHARMACEUTICALS PRODUCTION

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ABSTRACT

The calibration and qualification of equipments are listed items in RDC n° 17 of 2010 which refers about the Good Manufacturing Practice (GMP) of medicaments and RDC n° 63 of 2009 which refers about GMP of Radiopharmaceuticals. Both are essential requirements since they are involved in process control to attend the regulatory criteria and are a key part of the validation process. The aim of this work is presenting the importance of calibration and qualification, and the routine use of equipments and facilities in industrial scale production of radiopharmaceuticals in the IPEN/CNEN. The radiopharmacy of IPEN is a pharmaceutical industry that produces radiopharmaceuticals for diagnosis and therapy. It was the pioneer institute in production of radioisotopes and radiopharmaceuticals in Brazil. Currently, 38 products are distributed to the nuclear medicine centers, including primary radioisotopes, labeled molecules and lyophilized reagents for labeling with technetium-99m. To fulfill the GMP requirements for quality assurance of products, several factors must be considered including infrastructure, equipments and raw materials beyond, obviously, the whole production process should be controlled until the release of the final product. Therefore, the calibration and verification of equipments, instruments and other appliances used in the production and quality control should be performed. A program of calibration, qualification and requalification of equipments used in production and quality control of radiopharmaceuticals is necessary for the validation of production processes and analytical methods, and should be established for quality assurance of produced radiopharmaceuticals.

1. INTRODUCTION

The calibration and qualification of equipments are listed items in RDC n° 17 of 2010 (ANVISA) which refers about the Good Manufacturing Practice (GMP) of medicaments and RDC n° 63 of 2009 which refers about GMP of Radiopharmaceuticals. Both are essential requirements since they are involved in process control to attend the regulatory criteria and they are a key part of the validation process.

Calibration is defined as a set of operation that establish, under specified conditions, the relationship between values indicated by an instrument or measuring system or values represented by a materialized measure or a reference material, and the corresponding values of the quantities established by standards. The qualification is a group of procedures to certify and document that all facilities, systems and equipments are properly installed and/or have a correct performance and lead to expected results. Qualification is often a part of the validation, but the individual qualification steps are not, by themselves, a process validation.

According to GMP requirements, the company needs to identify the qualification and validation that are necessary to prove if all critical aspects of operation are under control. For

each instrument is established: full range, working range, sensibility, tolerance, and the point of calibration to use. The requalifications are made after risk analysis and the specifications are defined by change control.

Equipment

The equipments should be designed, constructed, adapted, installed, located and maintained in order to be compatible with the operations to be realized. The project, equipment localization and installation should minimize the risk of errors, allow cleaning and proper maintenance, in order to avoid the cross contamination, dust accumulation and avoid negative effect in the quality of the products.

The fixed tube line should be clearly identified, according to the current law, to indicate the content and, when applied, the flow direction. All lines of water and gases, and devices should be properly identified, preference to the use of the connections or adapters not interchangeable to gas and dangerous liquids.

The scales and measuring instruments used in production and quality control procedures should have the work range and the precision required and should be periodically calibrated. They also have to be appropriated to the methods employed. The washing of equipments, cleaning and drying should be correctly selected to do not represent a contamination source.

For this reason, the production equipments should be cleaned according to cleaning procedures approved and validated, when appropriated. They should not present any risks to the products. The parts of these equipments in direct contact with the product should not be reactive, addictive or absorptive in order to do not interfere in the quality of the product.

All equipments not in use or with defect should be removed from production and the quality control areas. When it is not possible, the equipment should be properly identified to avoid its use.

Closed equipments should be used whenever appropriated. When opened equipments are used, or when are opened during the operation, should be taken precautions to minimize contamination.

Equipments that are not dedicated should be cleaned according to validated cleaning procedures to avoid cross contamination. In the case of dedicated equipments, validated cleaning procedures should be used, considering cleaning agents waste, microbiological contamination and degradation products, when applicable.

Designs of the equipments and the systems of critical support should be kept updated.

Calibration and verification

The calibration and verification of equipments, instruments and other appliances, used in the production and quality control, should be realized in regular intervals. The people who are responsible for calibration and preventive maintenance should have appropriately training and qualification. A calibration program should be available and should provide information such as calibration patterns and limits, designated people, calibration intervals, records and actions to be adopted when problems were identified. The standards used in calibration

should be traceable to the reference calibration organization. The equipments, instruments and other appliances calibrated should be tagged, encoded or somehow identified to indicate the calibration status and the next date of recalibration. When the equipment, instrument or other appliance do not be used for certain period of time, its operation and calibration state should be checked before the use to demonstrate that the status of calibration was maintained.

Qualification

The qualification should be completed before the validation is conducted. The qualification is a systematic and logic process that starts by the project phases of the installations, equipments and utilities. Depending on the equipment function and operation, utility or system, in certain situations, only become necessary the installation qualification and the operation qualification, as well as the correct operation of the equipment, utilities or systems can be considered an enough indicator of it performance.

The equipments, utilities and systems should be monitored and calibrated periodically, besides them being submitted to preventive maintenance. The main equipments, as well as the critical utilities and systems require installation, operation and performance of qualification. The qualification must establish and provide documented evidence that equipments were projected in line with the requirements of GMP (design qualification or DQ), were constructed and installed in accordance with the project specifications (installation qualification or IQ), operate according to the planned specifications (operation qualification or OQ) and when operating are able to execute with efficacy the reproducibility, the methods and the specifications defined in protocol (performance qualification or PQ).

The radiopharmacy of IPEN is a pharmaceutical industry that produces radiopharmaceuticals for diagnosis and therapy. It was the pioneer institute in production of radioisotopes and radiopharmaceuticals in Brazil. Currently, 38 products are distributed to the nuclear medicine centers, including primary radioisotopes, labeled molecules and lyophilized reagents for labeling with technetium-99m. The challenge of the teams involved in IPEN is to distribute radiopharmaceuticals attending the requirements of GMP and radiological protection, ensuring safety and clinical efficacy of the products. To fulfill the GMP requirements for quality assurance of products, several factors must be considered including infrastructure, equipments and raw materials beyond, obviously, the whole production process should be controlled until the release of the final product. Therefore, the calibration, verification and qualification of instruments, equipments and utilities used in the production and quality control procedures should be performed at regular intervals.

2. OBJECTIVES

The objective of this work is presenting the importance of calibration and qualification, in the routine use of equipments and facilities in industrial scale production of radiopharmaceuticals.

3. DISCUSSION

3.1. Design Qualification - DQ

It consists in documented evidences that the quality is considered and constructed since its project and depends if the system or equipment is already exists or is a new one.

To installations, systems or existing equipments: it will be made directly the installation qualification that will be analyzing the specifications of the project versus the real conditions for each equipment.

To installations, systems or new equipments: it will be made the design qualification. The concept of design qualification gain more coverage when refers to installations. Before the construction of the area should be sure of the viability of the project about what will be produced and with the GMP rules. It is possible too, the realization of design qualification when it is about a related system with any utility (water, air conditioner, compressed air), the project should be verified in details evaluating the viability of the concept of utility versus installations conditions and current GMP rules. About the equipments are performing design qualification however it is very common that this stage is considered within installation qualification. Both possibilities are full possible.

3.1.1. Recommendations to design qualification

Installation, system or equipment is possible and important to the realization of design qualification. Some important recommendations can include:

- For new areas is essential to have previously planned what kind of process will be performed, which the utilities will be installed, what equipment will be purchase.
- In a new area should be defined the materials of manufacture will be use, the illumination conditions, power points and other relevant utilities.
- When is a system, being a utility or an equipment sets, should be too previously analyzed the installation/area where it will install.
- The descriptive memorials should be prepared and verified about their applicability within the installation concept.

3.1.2. Acceptance criteria for design qualification

For acceptance of design qualification should be considered:

- The project in its conception should be in accordance with GMP ideas.
- All map should be formally approved by checkers, so that, when the execution of the work you have full assurance in project conception.
- The record of each modified requested should be available in the design qualification archive.

3.2. Installation Qualification - IQ

The installation qualification is a testing procedure to assure that the parameters of installation are in accordance with the parameters defined by manufacturer. Should exist a specific protocol for each equipment or critic component of the system. These protocols, once approved, are reference material for future use. The system installation will verify by verification of the conditions the physic installation of the equipment, using test papers in the protocol. The paper will be used for document the system installation and to verify that the components of the system perform with reference specification.

3.2.1. Recommendations to installation qualification

- The installation qualification protocol should has the description of the equipment/system to be qualified following carefully the manufacturer recommendations that show too the proper utilities connection, the confirmation that the construction material is proper, if the case of surface contacts the product.
- List of system instrument, when applicable: list the instrument as critic or no critic. The critics are those whose operation affects the system operation or quality attributes. The no critics are those provided only for information purpose and label as “no require calibration”. Include as applicable: number traceable, manufacturer, location and description for each instrument.
- All installed critic instruments (accuracy and precision as process tolerance) in the equipment or system to be qualified previously should be calibrated with their respective calibration certification, properly filed and current.
- The equipment and systems should have their respective controls, a list of parts and spare components if necessary and applicable, as critical analysis in the involved area with the maintenance.
- The user requirements (UR) should be verified.
- All physic details of installation and services should be in conformity and obeying with the use purpose.
- The dimensional drawings, technical specifications and operating manuals have the purpose to document the installation and placement of each component always should be available and updated in the moment of installation qualification.
- Lubricants used, if necessary, should attend the manufacturer specifications and not adversely affect the quality of the product.
- Report qualification deviations (is necessary to open report non-compliance (RNC) in treatment of non-compliance and continuous improvement (TNCMC): document any discrepancy or variation observed during execution of the installation qualification. Include the resolution of the discrepancy and/or any detachable point that requires more effort for resolution. When all items were satisfactorily resolved or if exist an action plan developed and approved that ensure they were resolved, document that the system is ready for operation qualification.
- The GMP should follow with accuracy, so that, the involved in the qualification were properly trained within the defined concepts for this work.

3.2.2. Acceptance criteria for installation qualification

For acceptance of installation qualification should be considered:

- All relevant document of installation qualification should be completed and approved. And all supporting documentation should represent the equipment or system such as installed.
- The equipment or system should be properly identified, coinciding with the installed components.
- All recommendations for installation qualification should have been performed.
- The records and reports should coincide with specific data.

3.3. Operation Qualification - OQ

After calibration and installation qualification are necessary determine if the equipment or system works within the operation limits. For it should be realized dynamic assays, with the machine “in function”. The operation qualification evaluates each equipment function or system for ensure that will be realized the required jobs when the equipment is properly adjusted and operating within recommended operation limits and projected specifications.

3.3.1. Recommendations to operation qualification

- The operation specification of the manufacturer should be available and detailed.
- Be in conformity with the operational procedures of cleaning and maintenance of each equipment.
- Should be available in the content of the operation qualification protocol, the operational tests of the system, operation challenges, check alarms and demonstration of effectiveness of each operate component (all instrument, switches and alarms of the equipment will checked for functionally together with operational qualification).
- List of the required instruments for operational qualification should previously be calibrated with their respective calibration certification, properly filed and current.
- Report qualification deviations (is necessary to open RNC in TNCMC): document any discrepancy or variation observed during execution of the operation qualification. Include the resolution of the discrepancy and/or any detachable point that requires more effort for resolution. When all items were satisfactorily resolved or if exist an action plan developed and approved that ensure they were resolved, document that the system is ready for performance qualification.

3.3.2. Acceptance criteria for operation qualification

- All relevant document of operation qualification (monitoring and functional test of the system) should be completed and approved. The operational qualification will document that the equipment is able to operate within specified parameters.
- All use points should be installed and available for normal operation use.
- All recommendations for operation qualification should have been performed.
- The records and reports should coincide with specific data.

3.4. Performance Qualification - PQ

The performance qualification is a procedure of tests that evaluate the equipment efficiency, process and/or utilities. During this phase tests and inspections are leading to check if the

system is operational and able to perform the requirements of production of radiopharmaceuticals at IPEN.

The performance qualification approval ensures that the system is able to requirements and really provides to the product the specified qualification.

During performance qualification samples are chosen to check the quality of the product produced by the system in different points of samples. All samples should be choosing in approved containers and properly labeled. Should be handled, stored and analyzed under properly conditions according to specific procedures. The samples and assays should be performed as approved protocol.

When start the performed qualification execution, the process specifications are already defined and evaluated as able, by installation qualification, operation qualification, and equipment and installations were considered acceptable on the base of design qualification, installation qualification and operation qualification studies.

The performance qualification execution identify what the system should perform, the critics parameters of the process and demonstrate with different challenges that the operational ranges are acceptable. Additionally, the calibration of instrument, cleaning, preventive maintenance, specific procedures and the responsible operator training by using of the equipment should be documented and are reference in the moment of the qualification.

3.4.1. Recommendations to performance qualification

- Evaluation of the system operation related to quality of what is producing (intermediate) and the quality of the final product.
- Check if the variable parameters within process (defined in operation qualification) really provide the specific quality to the product.
- Samples are collected (as defined sample plan) to check the quality of the produced product by system in different points of sampling. All samples should be collected in approval containers and properly labeled, should be handled, stored and analyzed as specific procedures. The quality control section will lead the sample and the assays to selected points. The collected points will serve too as ratification test of the process measurements.
- Compile the collected data and aggregate the obtained data in laboratory, the corresponding appendix. Include the certification of analyze of all the samples to relevant appendixes, when applicable.
- The samples are analyzed physic-chemically and/or microbiologically according to protocol instruction.
- Report deviations of performance qualification (is necessary to open RNC in TNCCMC): document any discrepancy or variation observed during qualification. Include the resolution of these points and/or any pending item that require special attention to be resolved.
- The performance qualification cans available data of acceptable criteria defined by product manufacture, which can be use as base to process validation of production of a particular product.

3.4.2. Acceptance criteria for performance qualification

- All relevant document of performance qualification (sampling and tests) should be completed and approved. The performance qualification will show that equipment is able to produce a product with specific quality.
- All recommendations to performance qualification should be performed.
- The records and reports should coincide with specific data.
- All used instruments during function qualification should be calibrated and have certification of calibration (recent) and recalibration date.

The qualification should not be considered a unique exercise. After the qualification report was approved there should be a continue monitoring program, which should be grounded in a periodic review. The maintenance of qualification status should be described in relevant documents of the company, as quality manual or validation master plan. Qualification reports containing results and conclusions should be prepared and archived.

IPEN planned and executes a program for calibration and qualification of equipments as a part of a complete planning to attend GMP requirements in radiopharmaceutical production.

3. CONCLUSIONS

A program of calibration, qualification and requalification of equipments used in production and quality control of radiopharmaceuticals is necessary for the validation of production processes and analytical methods, and should be established for quality assurance of produced radiopharmaceuticals.

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