WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 9, 501-517. Review Article ISSN 2277– 7105

PROCESS PERFORMANANCE QUALIFICATION (AN EFFECTIVE TOOL TO ENSURE PRODUCT QUALITY AND PATIENT SAFETY)

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Article Received on
11 May 2022,

Revised on 01 June 2022,
Accepted on 22 June 2022

DOI: 10.20959/wjpr20229-24675

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ABSTRACT

Pharmaceutical Process Performance Qualification is establishing documented tool of quality assurance which delivers high level of confidence and assurance of that a products meeting its standard specifications and predetermined quality attributes. Process Performance Qualification is mainly emphasise on quality in Pharmaceutical manufacturing process, Equipment system, software and analytical testing methods. According to FDA guideline Process Validation is essential approach to transfer a product from development to commercialization. Process Validation is moreover emphasizes on study of Critical quality attribute, Critical process parameter, objective measures, statistical tool, and graphical method, cleaning protocol, risk assessment and control variability to gives assurance on quality compliance to consistent productivity throughout the product lifecycle. This article represent a basic fundamental concept of Process performance qualification, approaches for validation, general outline and overview on Pharmaceuticals Process Performance Qualification of Products.

KEYWORDS: FDA, GMPs, Quality Assurance, Process Performance Qualification, Control variables.

INTRODUCTION

Process Performance Qualification is establishes documentary evidence that gives a high level of confidence and assurance of that a particular procedure or process constantly

produces a products that meeting its pre-determined standard specification and quality features.

In pharmaceuticals industry Process Performance Qualification is the utmost significant as well as well-known parameter for Current Good Manufacturing process (cGMPs). The main aim of process verification is always produced high-quality products that are suitable for target use. It is an effective tools for ensuring that terms and conditions are met related to quality of products.

Process Performance Qualification and process controls are two important parameters that can ensure the various parameter in the production of dosage units – Verification is a quality assurance tool that provides quality assurance in machine system, production process, software and analytical testing methods.

In Pharmaceutical industry Validation is an important component that supports an organisation's commitment to regulatory agency to ensure quality of product and patient safety. Pharmaceutical Process Validation is a quality assurance tool that provides quality assurance in machine systems, process in development & manufacturing of drug at each step, software and analysis of drug and its testing procedures.

Process validation is done by collection of sufficient data and assessment of data, from the process knowledge gained from product development stage through commercial manufacturing of batches, which establishes scientific evidence that a process is capable of consistently delivering high-quality product.[1, 2, 3, 4]

Fig 1.

HISTORY

The basic fundamental of Process Validation as first recommended by both Food and Drug Administration (FDA) administrators, Ted Byers and Bud Loftus, in 1979 in United States, to improvement of the pharmaceutical products in quality with low risk, it was offered in main reaction to a number of sterility issues in the bulk parenteral market.

1978: Good Manufacturing Process includes validation.

1987: Guideline for the first validation i.e. on equipment (installation qualification)

2000: A new approach or documented presentation.

2008: Daft guidelines for validating new processes which is implemented on equipment and analytical test validation

2011: A new guideline for process validation issued.[5]

DEFINITION BY REGULATORY AUTHORITIES

1991 European Commission – The Process Validation is "Laws to confirm in accordance with GMP" essentially wants to predictable outcomes meeting its standard specifications.[2]

In 2000: "Documentary confirmation that processes carried out with in its specified limits could be performed efficiently and reproducible to manufacturing of drug products which meetings standard specification as well as quality characteristics."[2]

US Food and Drug Administration (USFDA): "Pharmaceutical Process Validation stands the establishment of documentary proof that delivers a high level of assertion to particular process would continuously manufacture a product that meets pre-determined specification as well as quality attributes."[1]

ICH: "Process Validation is the certifying and documenting the process can repeat and reliably produce an end product (Bulk finish) with essential quality within specified design parameter."[4]

WHO: "Documented form of evidence that any method, process, equipment, approved material, action related to manufacturing process or system actually its intended outcomes."[6]

AIM OF PROCESS PERFORMANCE QUALIFICATION:

1. The manufacturing process must be validating with individual equipment
2. The aim of Process Performance Qualification activities are to performing a robustness manufacturing activity such a constantly produces medicinal product having minimum

inconsistency that meeting its quality standard for pureness, identification and effectiveness.

3. The qualification and validation of equipment, major changes after primary qualification require concurrent validation or verification batch.

Ultimately process validation will provide reliable products with high reproducibility over time and more confidence on the product which confirm predicated quality, assurance as well as efficiency of the drug product and patient safety.[5,7]

PURPOSE FOR PROCESS PERFORMANCE QUALIFICATION

Probable reason to execute Process Qualification activities:-

- Newest Products (Exhibit batches) or current product due to Scale-up and the post approval modifications.
- Location variation products.
- Updating size of batch.
- Updation of any manufacturing formulation like unit formula i.e. composition or components.
- Alternate use of vendor (Alternate vendor as for active pharmaceutical ingredients & Excipients).
- Updation of specifications or standard test procedure for analysis of drug products.
- Change in critical process parameter and critical quality attribute (Measured Response).
- Change in building/manufacturing area within the premises
- As required by regulatory bodies or customers.
- Atypical trend in product quality parameters as a result of identification during Annual Product Review (APR).
- Revalidation as necessary based on annual product quality review that include checking for factors such as deviations, Out of specification, Out of trend, Market complaints.[8]

IMPORTANCE OF PROCESS PERFORMANCE QUALIFICATION

- Assurity on quality of products.
- Time limit
- Process optimization
- Quality cost reduction.
- Nominal confusions and bottlenecks.
- Minimum batch failure/error improved efficiency and productivity.

- Reduction in batch rejection.
- Production increases to gives higher output.
- Avoid investment on process optimization.
- Minor comments regarding process related errors.
- Reduction testing of finish product and in process checks.
- Faster and more reliable test run for new plant.
- Easy to scale up in development work.
- Easy to maintain equipment.
- Raising employee awareness related to process activities.
- Faster implementation or automation.
- Government's regulations (Compliance with standard procedure of validation requirements is required to obtain approval for the manufacture and introduction of new products).[9]

REGULORY DEMAND FOR PROCESS PERFORMANCE QUALIFICATION

- Pharmaceutical validation is playing an essential role in GMP's (Good Manufacturing Practices).Global complaisance beside validation requirement is required to gained agreement for manufacturing as well as introduction of newest product.
- Current Good Manufacturing Practices (cGMP) FDA refers to the validation concept in validation unit 211.110,211.113 & unit 211.110 claimed in this way i.e. these standard procedure has been proved to be ensure such effectiveness of that process involve in manufacturing of dosage form should be accountable to variations in critical quality attributes for processed material and dosage forms.
- The accurate, sensitive, specific as well as reproducible of the method used in manufacturing site. It should recognized as well as documentary.
- The basic requirements intended for Process validation are :
- It was included that cGMP regulation for medicinal devices, Sections 820.110 (b) (1) states-Deviation from medical devices specification can occur as the final outcome for the pharmaceutical manufactured practice by itself, here would be a standard procedure that explains all processing controls as required to ensure compliance with specifications.[1,2,3,9]

VARIOUS STAGE OF PROCESS VALIDATION

- Process Validation includes a sequence of events come across the life cycle as for process & products which involves 3 phases. It links Product, Product development and Qualification of commercial manufacturing process.
- **Stage 1- Process design (Pre-verification/Certification):** This includes whole activity associated with products research as well as developments, formulation, trial batch release, scale up research, technologies transmission to marketable production batches, establishment of stale conditions, storage and handling at Pharma Times Vol.46 – No.04 – April 2014 13 Processes and Completed dosage forms, Device certification, Installation certifications, Master formula and records, Operational certification and Process capabilities.
- **Stage 2- Process Qualifications (Process evaluation phase):** In this phase, the process design is estimated to define if the process of manufacturing are effective to reproduce marketable production. This phase have two parts:
- To designed the manufacturing site as well as qualifications of the equipments and also utility: It was necessary to ensure the activity performed for Premise's layout compliance to standard procedure as per the PPQ. The terminology qualifications stand for activity accepted to established the utility as well as equipments appropriate for their proposed application and performed appropriately.
- **Process Performance Qualifications (PPQ):** PPQ is combination of the definite premises, utility, equipments also with skilled recruits for the marketable production, standard procedure and component for the commercialization of marketed batches.
- **Stage 3- Continuous Process Verification (Maintenance phase of validation):** verification is done for continuous monitoring of commercial batches for evaluation of life-threatening process parameter as well as life-threatening quality characteristics.
- Validated Excel spreadsheet, that is located in access restricted folder on common server and password protected is used for monitoring of CPP's (Critical process parameter) and CQA's (Critical quality attributes) for complete product life cycle.[10]

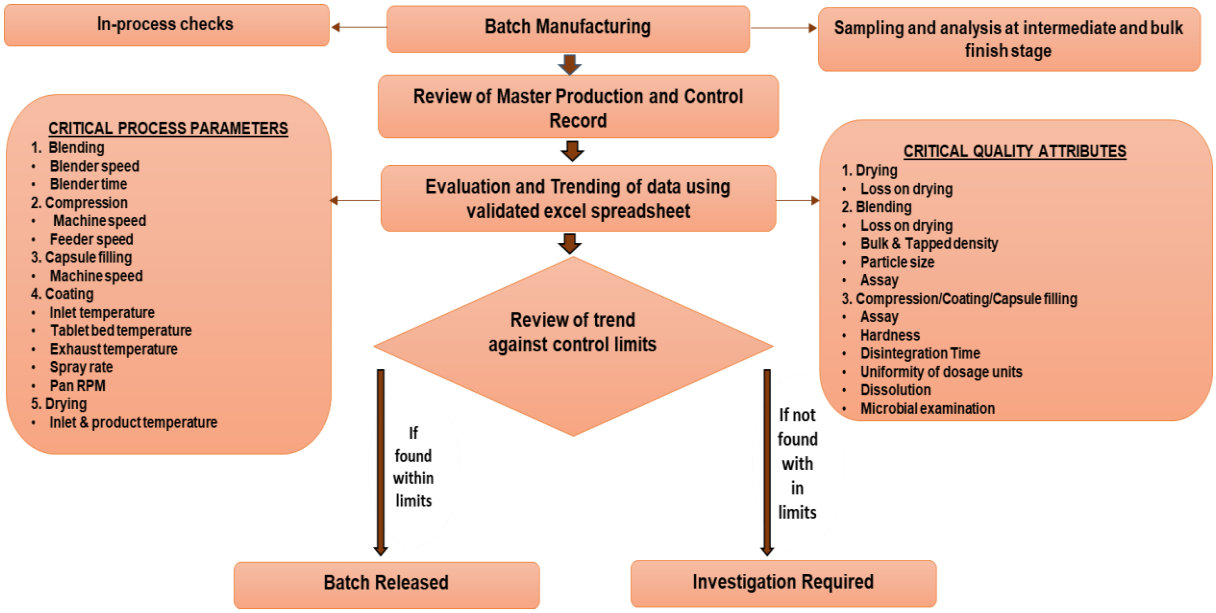

Fig 2.

PRINCIPLE OF PROCEES PERFORMANACE QUALIFICATION

The basic principle of validation can be formulated as follows.

User Requirement Specification (URS)

Users' requirement specification (URS), which contains the requirement of the user on behalf of output and quality of product. The specifications used for equipments, facility, utility otherwise system must be well-defined in URS otherwise in a functioning specifications. This is the important element of quality necessity to be build-up at that phase & whichever GMP risk moderated towards an acceptance levels.

1. Design Qualifications (DQ): Establishment by back-ground data and descriptions of equipment application. Select the techniques and also types of equipments, utility, applicable measuring devices with appropriate rationale or justification. Design Qualification (DQ) shall be provided by the vendor. The necessities of that user requirement specifications must be certified for the duration of this design qualifications.

DQ Proposal are.

- Description of that purpose and intended use of the equipment.
- Descriptions of that proposed environment.
- Description for usage of that equipments into the designated atmospheres / process.
- Primary selectivity of that function as well as performance specification (high-technical, surroundings, protection, security access, compatibility with existing / future systems.

- Consultation and documents of contract, accommodation, trainings and supplementary supplier (vendor) facilities.
- Verification for Material of Construction (MOC).

Factory acceptance test [FAT] and Site acceptance test [SAT]:

- Factory acceptance tests [FAT] and Site acceptance tests [SAT] which containing verification for following with respect to. Design Qualification. FAT might be accompanied by the performance of an SAT subsequent the receipts of equipments at that industrial location.

2. **Installation Qualification (IQ):** Establishment of purposes confirmation with all major features for the installation of process equipments as well as auxiliary systems are consistent with the manufacturers authorized specifications and that the equipment supplier's recommendations have been adequately measured.

IQ Proposal are:-

- Equipments designed characteristics [that is construction of materials, cleaning condition like easy to clean or hard to clean etc.]
- Installment condition [writing, utilities, functionally etc.]
- Calibrations, preventive maintenances, cleaning and washing period.
- Security characteristics.
- Vendor's documents, design, diagrams and instruction booklet.
- Soft copy that is in software documentation.
- List of replacement part.
- Environment condition such as [Requirement of sanitized areas, temperature, relative humidity etc...]

3. **Operational Qualification (OQ):** Established through demonstrative or direct evidence of process measurable limit and actions level that outcomes which is products meets completely specified requirements.

OQ Proposal are.

- Process measurable parameters like [Temperature, pressure, time interval, speed of line, operation condition etc...]
- Limits of software systems.
- Specification and standard test procedure for analysis of raw material.
- Standard operating procedure for manufacturing process

- Requirement of handling of the material.
- Change control associated with process.
- Trainings or self-training through E-learning system.
- Short-range stabilities and capabilities [extensive study method as well as control chart.]
- Possible (i.e. potential) failures mode, action plan and worst case condition.
- At this stage, you can optimize the process using a statistically valid method, such as a selection of experiments design.

4. Performance Qualification (PQ)

After successfully completion of OQ, PQ should be started. An objective proof that the process constantly delivers a products that meeting its pre-determined specified necessities under expected condition.

PQ Proposal are:

- Authentic products, all parameter of process and procedures are recognized into the PQ. All test, via formulating raw-materials, eligible alternatives otherwise simulated products proved that having comparable performance beneath standard operational condition as in worst-case batch proportions. The confirmed process must be justify via frequency of sampling methods.
- All the tests must be covered in that operative tentative limit for that proposed process, if documentary confirmation of that development stages assuring to the operating ranges are obtainable.
- Repeatable process, long- term process stability.[6,11,12]

TYPE OF PROCESS VALIDATION

1. **Prospective Validation: -** This is well-defined as recognized, documentary confirmation that the method which is proposed to a pre-approved protocols. The verification is typically performed before distributing either introduction of new products as well as products manufactured using a updated production process executed in minimum three consecutively production lot or batches.
2. **Concurrent Validation: -** This is called verification, which is performed during normal production and this method only succeeds if you gone through perpetually understanding of the basics about the process during the development phase. It also consists of nearby as well as extremely observing of the critical step as such a key observations for the initially three consecutively manufacturing batches.

3. **Retrospective Validation: -** This is a well-firmed and documentary confirmation for the systems make sure of what its claims to doing when it reviews as well as analyzes chronological figures. This can be accomplished by reviewing previous manufacturing test documents directed towards the process is constantly within the acceptances limits. The present indication of the validation is to take responsibility that the configuration, procedures and equipment have not changed.
4. **Revalidation: -** Revalidation is the repetitions of a process and its parts. This process is performed when recipes, equipment, plant location or replaced and subsequent batches do not meet the quality characteristics and product quality. Revalidation is maintaining the Process qualification status of the facility and if major changes have been made related facility, system, equipment in that case process will meet certain requirements and it is necessary to revalidate requirements.[13]

PROCESS PERFORMANACE QUALIFICATION STATREGY

Fig 3.

- Defines the objective as well as scope for the process.
- Development of protocol for validation otherwise operating method of validation.
- Defines performance parameter as well as specification limits.
- Defines experiment on validation.
- Validates the significant performances characteristic as for device.
- Selection of high quality material such as standard as well as reagent.
- Execute pre-verification experiment.
- Adjustment of method parameter and specification limits as needed.
- Complete in-house and external validation set-up.

- Developed an SOP that executes method on a regular basis
- System Compliance test.
- Routine analytical quality control type and frequency of sampling
- Evolution of quality risk assessments.
- Defines the stability batches.
- Identify the critical process parameter as well as critical quality attribute throughout manufacturing activity.[14]

Critical process parameter {CPPs} and Critical quality Attribute {CQAs}

- Stage wise critical process parameters as well as critical quality attributes has been identified as follows for significant manufacturing steps:
- CPPs and CQAs are only for guidance it can be vary based on product/process knowledge gained from design/development studies.
- The major role of process performances qualification of manufacturing process is identified and evaluation of CPPs and CQAs.
- From this evaluation, generation of reports of the process performances qualification as for established documentary proof that validated process is capable for the production of marketed dosage form pertaining quality product having minimum side effects.[15]

Table No.1.

Sr. No.	Process Stage	Critical Process Parameters	Critical Quality Attributes
1.	Dry Mixing	• Dry mixing time • Dry mixing speed	• Blend uniformity
2.	Drying	• Machine air temperature • Exhaust air Temperature, • Product Temperature	• Loss on drying
3.	Pre-lubrication/Lubrication	• Blending Time, • Blender speed	• Assay, • Blend uniformity
4.	Compression	• Machine speed, • Feeder speed	• Assay, • Dissolution, • Uniformity of dosage units by weight variation
5.	Coating	• RPM of coating pan, • Machine air temperature, • Outlet temperature, • Tablet bed Temperature, • Spraying rate	• Assay, • Dissolution, • Uniformity of dosage units by weight variation
6.	Primary packaging (Blister packing)	• Induction sealer • Sealing Temperature • Machine Temperature	• Related substances

DOCUMENT REQUIRED IN THE VALIDATION PROCESS

1) Validation Master Plan (VMP)
2) Process Qualification Protocol (PQP)
3) Process Qualifications Report (PQR)
4) Standard Operating Procedure (SOPs)

1. Validation Master Plan (VMP)

- Validation master plan (VMP) is a documents that outlines a facility's whole viewpoint, intent, & approaches that should be utilize to establish the acceptability of work.
- Altogether validation activity should be properly scheduled. The significant element of the verification activity must be evidently well-defined as well as recognized in the validation master plan. All validation activities related to dosage form and process control must be incorporated in the VMP.[13,16]

Basic Requirements for the VMP: Validation policies, over-all descriptions as far the scope of work enclosed in the VMP, site and scheduled (enclosing priority).

Lists of Products, Equipment, Process and System should be validated

All the validation activities shall be summarized and compiled in a matrix format. Such matrix shall provide an overview and contain

- All elements covered by the VMP that are subject to validation describing the extended phase of validation required [i.e. DQ, IQ, OQ and PQ]. This should include the validation of analytical methods which are to be used in defining the validation status of other processes or system.
- Validation Stages i.e. Process design, Process Qualification and Continuous Process Verification.
- Re-Validation activities.
- Actual status and future planning.[15,16]

2. Process Qualification Protocol

- Process Qualification Protocol shall cover the critical process parameters and Critical Quality attributes during granulation, compression, Capsule filling, coating and packaging procedures.

Following prerequisite at the minimum shall be fulfilled before initiating the process qualification study

- A well-defined process should be available prior to the initiating process qualification activities.
- Approved Master Production and Control Record and process qualification protocol must be available.
- A clear and brief sampling plan shall be provided and clarified.
- Samples shall be of an appropriate size, taken at a sufficient time interval and tested to provide high level of assurance that the entire batch will meet with its specifications.
- Validated analytical methods/ compendia analytical methods shall be used. Approved Product specifications (Raw material, packaging material, and In-process and Finished product specification) and standard testing procedures shall be used.
- Verify process qualification study are in calibrated condition at the time of the study. Process qualification study are in calibrated condition at the time of the study.
- Where necessary, a risk assessment based on knowledge of the product and process should be performed.[17]

3. Process Qualification Report (PQR)

- Process Qualification report shall be prepared after the completion of the process Qualification activity.
- Process Qualification report shall cover the critical process parameters and Critical Quality attributes during granulation, compression, Capsule filling, coating and packaging procedures
- Qualification batches data should be reviewed and recommendation shall be made based on the observed values of the parameters on which the batches are executed
- A process shall be considered validated, when three consecutive validation batches give consistent results within the established acceptance criteria however, same may be extended incase recommended in Risk Assessment of respective Product.[18]

4. Standard Operating Procedure (SOPs)

- Write SOP in present tense and verb shall be in active voice.
- Write SOP in a clear (informative, consecutive and error less), easy to understand and easy to follow language.

- Keep the content of the SOP in chronological order, practical and easy to implement on routine basis.
- Use simple sentences and avoid using adjectives viz. proper, adequate and satisfactory.
- Instructions/Procedures shall be written in unmistakable and imperative mandatory style'[19]

Table No.2.

SECTION OF SOP's	FORMAT OF SOP's
Objective	Logo
Scope	Department
Responsibility	Area
Accountability	SOP numbering
References	Format/Annexure numbering
Procedure	Title
Cross-references	Effective date, Review date
Abbreviation / Definition	Signature, Date, Designation and Department
Revision history	Issuance of SOP's

RESPONSIBILITIES OF DESIGNATED DEPARTMENT

Various responsibility of designated person or department to prepare, review and approve process qualification protocol and report and also ensure that critical manufacturing steps identified and are validated with cGMP compliance during execution of process performance activity.[20]

Table No.3

Departments	Responsibilities
Formulation and development	To prepare Process Performance Protocol(PPQ), to demonstrate and supervise the process qualification activities
Quality Assurance	To prepare, review and approve PPQ & compilation of validation report and evaluate the data generated during process qualification, asses change control and authorize deviation (if any) during execution of protocol and compilation of Process qualification report
Quality Control	To carry out testing in-process, intermediate and finished samples as per standard procedure
Production	To review and approve PPQ carry out manufacturing of the qualification batches.
Engineering	To ensue availability of qualified facilities, equipment's of the manufacturing for the qualification activities.
Regulatory Affairs	To review the PPQ and ensure that all the compliance as per regulatory commitments.

STEPS INVOLVED IN PROCESSS VALIDATION

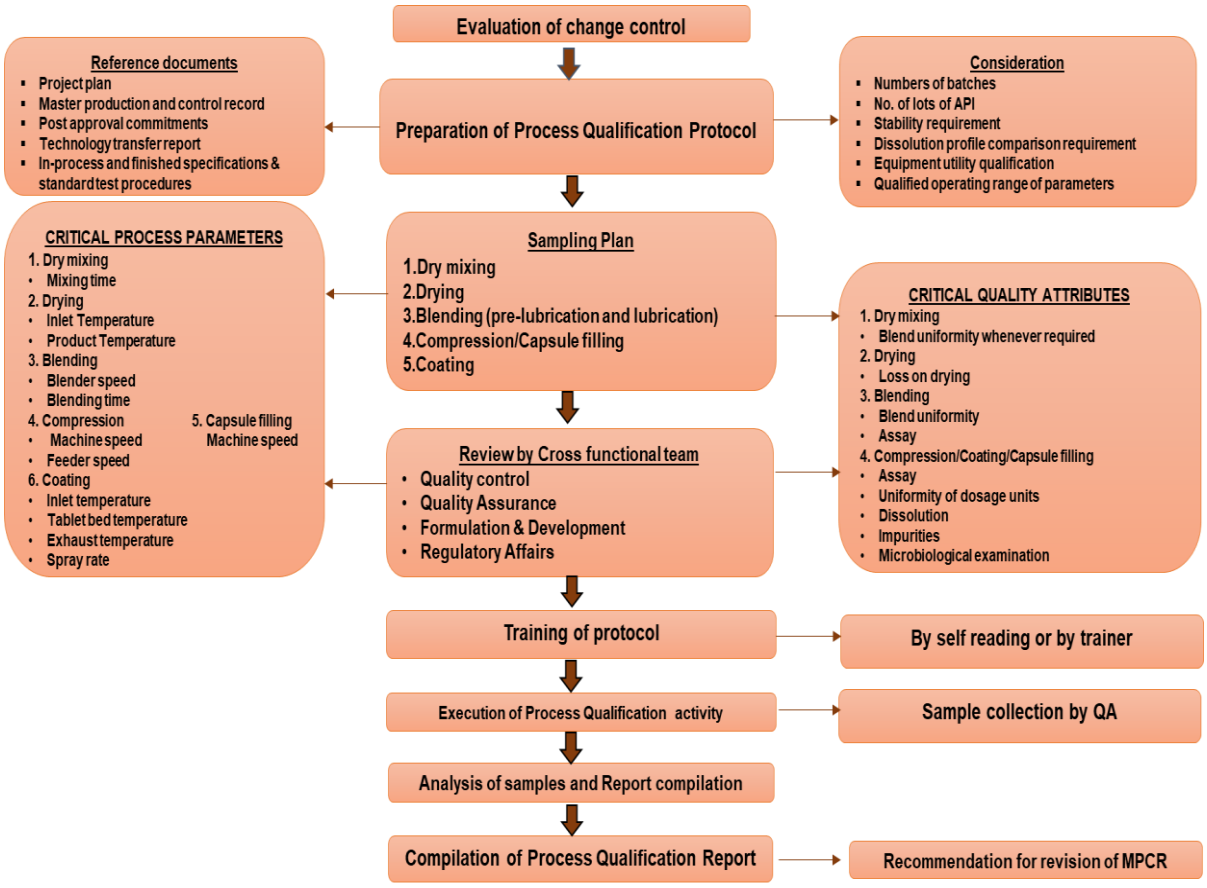

Fig 4.

CONCLUSION

In pharmaceutical industry Process Performance Qualification is the very essential as well as acknowledged Current Good Manufacturing Practices (cGMP) criteria, according to a regulatory requirements. All the critical manufacturing steps should be identified and validated. From manufacturing of drug and its process should be developed and measured to ensure that in process parameters are in place to support process qualification activities and product after execution result of all analytical test must be observed and evaluate with standard specification that product meeting its quality as per regulatory requirements and delivers with patient safety.

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