REVIEW ARTICLE

Lifecycle Approach to Process Validation and Its Implementation in Pharmaceutical Industry

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ABSTRACT

Process Validation is a GMP concept and is required by the agencies to assure quality of the manufactured drug products. The need, motivation, understanding and the practices of Process validation have evolved enormously from the time of its inception. The lifecycle (modern) approach of process validation and its elements are discussed in detail here. The review article aims to provide a general understanding of the concepts of lifecycle approach of process validation. The review further provides an illustration for practical implementation of the concepts outlined for the pharmaceutical manufacturing industry through an example of a hypothetical sterile injectable product. A properly developed process/product according to principles of lifecycle approach discussed in this article should meet the expectations of majority of regulatory agencies.

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INTRODUCTION

The pharmaceutical industry was highly dependent on end-product testing and monitoring to assure the quality of the products until 1970s when outbreaks of *E. cloacae* and *Erwinia* contamination of LVP bottles claimed many human lives and resulted in significant losses to society. LVP bottles were found contaminated with microorganism even after sterilization. How come even after sterilization? The reason behind this incident was mere negligence or oversight of quality professionals. The contamination was caused by moisture seeping into a space under the screw cap of the bottles during cooling after sterilization. It could not be detected during routine testing as the cap and the septum were removed before the test. This incidence made a realization of the lacking practices of the pharmaceutical industry to assure the quality of the medicine it was delivering to the world.[1]

Later the industry learnt that merely testing the end-product quality was not enough and it was equally important to qualify the process in addition. The process of proving or providing confidence of the capability and reliability of the process to achieve desired outcomes was referred as process qualification or validation.

Evolution of Concept of Process Validation

While the pharmaceutical world was introduced to the term "validation" through GMP guidelines, expectations, or applications were not very clear at that time.[2] In 1987, the regulatory world received the first-ever guidance on process validation in the field of life sciences.[3] In this guideline FDA introduced a revolutionizing concept that "Quality cannot be tested or inspected into the finished products and quality must be designed or built into the product." It defined process validation as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics." The guideline stressed carrying out validation through designing process controls for each of the smallest steps of the manufacturing process. Process validation was used to demonstrate the effectiveness and reproducibility of the process and reduces dependence on in-process and finished product testing. However, it was understood that end-product testing could not be avoided and process validation in addition to end-product testing helped to assure that the final product with desired quality is manufactured consistently.

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The 1987 US FDA guidance laid down the fundamentals for process validation but failed to give a correct understanding of requirement and importance of process validation. Process validation was majorly seen as a documentation exercise then, that involved collection of large quantities of data from three consecutive validation batches. Further, implementation of process validation did not warrant high quality of products as expected. The quality of the products was still frequently questioned by citations of lack of robust validated process by the compliance inspectors. However today, the updated approach has shifted the focus from "documented evidence" to "scientific evidence". Based on scientific evidence, process validation is not anymore considered a one-time event but extends throughout the complete product lifecycle. This exhaustive product lifecycle approach bears its foundation in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Quality guidelines for industry, Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System.[4-6] Most regulatory authorities including USFDA,[7,8] EMA,[9,10] Health Canada[11] and India[12] have followed the approach and have published regional guidelines with a view to harmonize with current guidance from Pharmaceutical Inspection Cooperation Scheme (PIC/S),[13] ICH, and World Health Organization (WHO).[14-16] In addition, industry and agencies are aligned towards compliance with ISO 9000 standards which comprises standards concerning quality management systems (QMS). These standards help organizations to meet customer needs within statutory and regulatory requirements related to a product or service.[17-19] Thus, it is required that industry align their manufacturing and validation practices according to changing expectations.

Definition of Process Validation

The definition of Validation (or Process Validation) has evolved since its inception. The modern definition of process validation, as defined by USFDA in its 2011 guidance document – Process Validation: General Principles and Practices, states it as "the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product"**.** Now, validation is not just restricted to pre-marketing stage but involves a series of activities taking place over the complete lifecycle of the product. These activities are divided into three stages wherein each stage contributes to gain an overall confidence about the performance of the manufacturing process and the quality attributes of the product.[8]

Legal Framework

Process Validation is a requirement of regional Good Manufacturing Practices Regulations. Manufacturers seeking authorization for manufacture and sale of medicinal products are expected to comply with these regulations to assure quality of their manufactured products. Regional regulatory agencies hold the authority and responsibility to inspect and evaluate process validation performed by manufacturers. Table 1 provides the major regional regulatory bodies that are responsible for regulating pharmaceutical manufacturing and sale in different regions and also provide references to regional regulations.

Product Lifecycle Approach

Validation is an essential part of GMP and therefore, an element of quality management system.[33] The basic intent behind process validation is assurance that a particular process will deliver the desired product with expected quality consistently. Contrary to the traditional approach that was majorly dependent on testing and documentation for providing this assurance, the modern concept incorporates a more scientific lifecycle approach. This modern approach links the various stages of a product lifecycle i.e., process and product development, validation of commercial manufacturing process and maintenance of the process in a state of control during routine commercial production. The concept originated from the vision developed and adopted in an ICH meeting in Brussels in July 2003 to "develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science."[34]

The three pivotal guidance by ICH Q8, Q9 and Q10 describe the modern approach as a science and risk-based approach that employs tools like quality by design (QbD) and quality risk management (QRM), linked to an appropriate pharmaceutical quality system (PQS). QbD is defined as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" Further guidance documents were published by FDA to encourage adoption and implementation of QbD by industry.[35,36] Table 2 enlists the essential elements of QbD.

Therefore, a comprehensive pharmaceutical development approach (in combination with quality risk management principles of ICH Q9) focuses on gaining thorough knowledge of desired product and manufacturing process and to identify sources of variability. These sources of variability when identified and controlled will contribute to gaining enhanced quality assurance of the product quality and will reduce burden on end-product testing. This early understanding will also help in optimizing the process parameters to compensate for variability in material attributes. The pharmaceutical quality system (ICH Q10) further provides scope for continuous improvements that contribute to greater understanding of the product and the manufacturing process. In total, these steps will enable development of a science and risk-based approach that provides a stronger quality control strategy, improved assurance of the drug product and increased flexibility of regulatory approaches.

Stages of Process Validation

According to the modern approach, the process validation exercise is divided into 3 stages. Figure 1 illustrates the stages and sub-stages of process validation.

Table 1: Major regional regulatory bodies and applicable GMP regulations

Country/ region	*Regulator*	*Applicable GMP regulations*
India	State Drugs Control Administration (DCA) and Central Drugs Standard Control Organization (CDSCO)	WHO GMP and Indian GMP that is, Schedule M (cGMP and Requirements of Premises, Plant and Equipment for Pharmaceutical Products) and Schedule U (Manufacturing Records) of Drugs and Cosmetics Act 1940 regulate the manufacture and sale of pharmaceuticals in India.[20]
US	US Food & Drug Administration or USFDA	21 CFR Part 210 (Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs) and 211 Regulations (Current Good Manufacturing Practice for Finished Pharmaceuticals) and 21 CFR Part 820 (for Medical Devices) set the current GMP requirements.[21-23]
European Union (EU)	European Medicines Agency or EMA (coordinating/harmonizing role at EU level; coordinating GMP inspections of manufacturing sites for medicines whose marketing authorization is submitted through the centralized procedure or as part of a referral procedure). National competent authority of 31 EEA countries are responsible for inspecting manufacturing sites responsible for manufacture/import within their own territories.	Regulation No. 1252/2014 and Directive 2003/94/EC, apply to active substances and medicines for human use and Directive 91/412/ EEC applies to medicines for veterinary use. In addition, Directive 2001/83/EC and Directive 2001/82/EC lay down related provisions. Further, Regulation No. 2017/745 is applicable for Medical Devices.[24]
Australia	Therapeutic Goods Administration or TGA	Section 36 of the *Therapeutic Goods Act 1989 regulate* Medicinal products supplied in Australia and requires that manufacturers meet the PIC/S Guide to Good Manufacturing Practice (GMP) - 01 May 2021, PE009-15 issued by Pharmaceutical Inspection Co-operation Scheme, except for its Annexes 4, 5 and 14 which are not adopted by Australia.[25] The Australian Code of Good Manufacturing Practice (GMP) for Blood and Blood Components, Human Tissues and Human Cellular Therapy Products (the Code) applies to Blood, Human Tissues and Human Cellular Therapy Products manufacturers that undertake the collection, processing, testing, storage, release for supply, and quality assurance of Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products.[26]
Canada	Health Canada or HC	Part C, Division 2 of the *Food and Drug Regulations* C.02.001 to C.02.030 regulate activities of fabricators, packagers, labellers, testers, distributors, importers and wholesalers of drugs in Canada[27]
Japan	Pharmaceutical and Medical Devices Agency or PMDA	"Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs" (MHLW Ministerial Ordinance No. 179, 2004) lays down the GMP standards for manufacture and quality control of drugs and quasi-drugs in Japan. In addition, PIC/S Guide to Good Manufacturing Practice for Medicinal Products provides guidance to manufacturing sites involved in manufacture and quality control of investigational medicinal products" based on Paragraph 1, Article 17 and Article 26-3 of GMP for investigational medicinal products for MHLW Ministerial Ordinance No.28 in 1997.[28-30]
China	The National Medical Products Administration (NMPA), formerly the China Food and Drugs Administration	Good Manufacturing Practice for Drugs (2010 Revision), MOH Decree No. 79 in accordance with the Drug Administration Law of the People's Republic of China and the Regulations for Implementation of the Drug Administration Law of the People's Republic of China, regulate the manufacturing and quality management of Drugs in China.[31]

Brazil	Agência Nacional de Vigilância Sanitária - ANVISA	Following ANVISA regulations are applicable: **Drug Products (Medicines) -** Resolution RDC 658/2022 (general aspects) and Normative Instructions associated. **Radiopharmaceuticals** - Resolution RDC 658/2022 and Normative Instruction - IN 128/2022. **Medicinal Gases** - Resolution RDC 658/2022 and Normative Instruction - IN 129/2022. **Herbal products** - Resolution RDC 658/2022 and Normative Instruction - IN 130/2022. **Active Pharmaceutical Ingredients (APIs)** -Resolution RDC 654/2022 (GMP) and RDC 204/2006 (Good Distribution and Fractionating Practices for Pharmaceutical Supplies). **Pharmaceutical Excipients** - Resolution RDC 34/2015. **Medical Devices** - Resolution RDC 665/2022 (general aspects); Resolution RDC 687/2022 (administrative processes).[32]

Table 2: Essential elements of quality by design (QbD)

Element	*Description of element*
QTPP	Defining the quality target product profile (QTPP) of the desired product. QTPP is a prospective summary of the quality characteristics that need to be achieved to ensure the desired quality, considering safety and efficacy of the drug product.
CQA	Identifying the critical quality attributes (CQAs) of the drug product, that have an impact on the product quality and should be maintained within an appropriate limit or range.
CMA	Determining the critical material attributes (CMAs) of the raw materials (drug substance, excipients etc.) that have an impact on Drug Product CQAs.
CPP	Selecting an appropriate manufacturing process and determining critical process parameters (CPPs) that have an impact on Drug Product CQAs.
DESIGN SPACE	A systematic evaluation and understanding of product and manufacturing process to identify the material attributes and process parameters that impact product CQAs and determine their functional relationship. Risk Assessment tools can be used to identify and rank parameters with potential to impact product quality. These parameters that have an impact on the product quality are called variables and Risk assessment along with process development experiments can help in obtaining ranges within which consistent quality of the product can be obtained (Design space).
CONTROL STRATEGY	Establish a control strategy based on design space and/or real-time release testing.
CI	Continual improvement (CI) or management of lifecycle changes

Stage 1 – Process Design
Stage 2 – Process Qualification
Stage 3 – Continuous Process Verification

Stage 1 – Process Design

The goal of this stage is to design a commercial manufacturing process which can consistently deliver product with expected quality attributes. This stage covers all activities relating to product development including product research and development, selection of API and excipients, selection of dosage form, formulation development, manufacturing process development, pilot-scale testing and technology transfer for commercial scale manufacture. The knowledge and information obtained through this stage helps in development of a thorough master validation plan.

Process Design Components

Knowledge management (KM)

The feeder for an effective process design includes product/process knowledge gained through various sources. The knowledge regarding the product/process to be developed can be gained through:

1) Prior existing knowledge, and
2) Pharmaceutical development studies.

The prior knowledge forms the basis for commercial process design stage and could come from published literature, previous experience with similar product/process, laboratory experiments, preclinical and clinical studies, analytical characterization data, physicochemical and biological properties of drug substance, compatibility etc. The pharmaceutical development studies use the knowledge gained through experiments conducted during development of a commercial scale process.

Science and risk-based approach

Together, knowledge gained through manufacturing experience and pharmaceutical development experiments provide a scientific background for establishing a robust commercial scale manufacturing process. This scientific background for the product and process when complemented with principles of

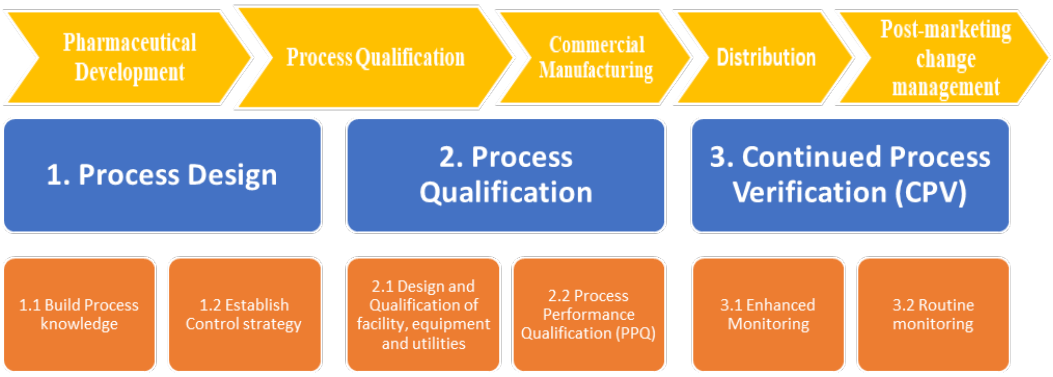

Figure 1: Stages of process validation

Table 3: QTPP Profile for a single dose vial presentation of a hypothetical drug of strength 5 mg/mL

QTPP Elements		*Target*	*Justification*
Dosage form		Lyophilized powder for injection	Pharmaceutical equivalence requirement: same dosage form as RLD.
Route of administration		I.V.	Pharmaceutical equivalence requirement: same route as RLD.
Strength		5mg /vial	Pharmaceutical equivalence requirement: same as RLD
Storage conditions		Controlled room temperature	Shelf-life storage conditions are the same as RLD
Stability		At least 24 month shelf life at controlled room temperature.	Storage conditions and shelf life are the same as RLD.
Pharmacokinetics		Matches RLD	Bioequivalence self-evident for parenteral solution intended for administration by Injection.
Drug product quality attributes	Physical Attributes		
	Identification		
	Color of solution		
	pH		
	Water content		
	Uniformity of dosage units		
	Assay	Pharmaceutical equivalence requirement: must meet compendia, ICH and other applicable quality standards such as identity, assay, purity etc.	
	Related Substances		
	Sterility		
	BET		
	Particulate matter		
	Reconstitution Time		
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure Container closure Integrity during shipping.
Administration/Concurrence with labeling		Similar food effect as RLD	Same as RLD
Alternative methods of administration		None	None listed in RLD Label

quality risk management helps to understand input variability impact and to design control strategy commensurate with the risk of impact and degree of impact. QbD approach is one approach suggested by ICH Q8 that is built on the principles of knowledge and risk management. The elements of QbD are discussed in Table 2.

Process Design Deliverables

The activities concluded in this step shall provide following major deliverables and help to transition to the next stage (Process Qualification) of process validation. Figures 2 and 3 below provides process design deliverables and an illustration of QbD concept of process design respectively.

Quality Target Product Profile (QTPP) or a prospective summary of the quality characteristics of a drug product that ideally should be achieved to ensure the desired quality, taking in account safety and efficacy of the drug product. For illustrative purposes, an example QTPP profile of a single dose vial presentation of a hypothetical drug of strength 5 mg/mL is provided in Table 3. The QTPP elements were defined based on analysis of RLD Product, RLD Label and intended patient population.

Critical Quality Attributes (CQAs) are physical, chemical, biological or microbiological properties or characteristics that are required to be within an appropriate limit, range or distribution to ensure the desired product quality. Risk assessment studies are performed to identify CQAs based on the severity of the harm to a patient resulting from failure to meet that quality attribute of the drug product. Further risk assessment studies are performed throughout the development to identify potential high risk raw material (critical material attributes or CMAs) or formulation attributes and process variables (Critical Process Parameters or CPPs) that can impact CQAs of the drug product. The CQAs that are found to be unaffected by formulation or process variables may typically be addressed through a good pharmaceutical quality system and appropriate release control strategy.

Manufacturing process design

These include flow diagrams and detailed description for the manufacturing process providing information on incoming materials, products, by-products, sequence of steps, process conditions, yields, hold times. The design document also includes specifications to qualify incoming material and intermediates and process parameters for each of the process steps. The document should also include changes to manufacturing process that may occur due to Technology Transfer or scale-up.

Analytical methods for testing of raw materials (including starting materials), intermediates and drug products and for characterization of impurities. These may be compendial or non-compendial. In case of compendial methods, a verification study and for non-compendial methods or in-house developed methods, a validation study is required to qualify that the method is suitable to use.

Risk assessment and parameter criticality designation

Parameters that have a higher risk of impacting CQAs of the Drug product are designated as critical process parameters (CPPs). Further investigations, development studies along with previous experience with these process steps are typically utilized to convert the high-risk process parameters to low-risk process parameters.

Process characterization and Product characterization testing plan

These are drug development studies aimed to study the operational parameters and its impact on the process and/or quality of the product and are governed by risk assessment studies. The final outcome of these studies help to derive a range for process parameters. Though these studies are performed in laboratories, they should be predictive of performance at commercial scales. Feasibility studies may help to obtain confidence and support PQ studies in Stage 2.

Control strategy

Control strategy is a planned set of criteria, derived from current product and process understanding obtained through previous knowledge, experience, development experiments and risk assessment studies, and assures process performance and product quality. Such controls may include parameters and attributes related to DS and DP materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. It is recommended to have control strategy as a product specific document or series of documents. An example control strategy designed for a hypothetical generic lyophilized injectable product is presented in Table 4.

Design space

The design space is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered a change. Movement out of the design space is a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Process design report

This report is an outcome of stage 1 studies as it summarizes all the design and development studies performed to gain knowledge on the dug product and the manufacturing process including all incoming raw materials, intermediates. The report details on each of the process design deliverables discussed before. The knowledge gained through the design stage is utilized to derive a Validation Master Plan for stage 2.

Validation Master Plan

Process validation master plan defines the process validation scope and rationale and that contains the list of process validation studies to be performed. This include all studies

Table 4: Sample control strategy for a hypothetical generic lyophilized Injectable product

Factors	*Attributes or parameters*	*Range Studied (Lab Scale)*	*Actual data for the exhibit batch (pilot scale)*	*Proposed range for commercial scale*
Raw material attributes				
Drug substance	Assay (%)	Range defined to assure optimum process performance and desired product quality on the basis of knowledge obtained through previous experience, development experiments and risk assessment studies. This range defines the Design Space.		
	ABC Impurity			
	DEF Impurity			
	GEH Inpurity			
	Total Impurities			
	Water content (%w/w)			
	pH			
	Microbial Load or Total Aerobic Microbial Count			
	BET (USP Endotoxin unit per mg)			
Excipients	Description			
	Assay			
	Microbial Load or Total Aerobic Microbial Count			
	BET			
Water	Description			
	Assay			
	Microbial Load or Total Aerobic Microbial Count			
	BET			
Manufacturing process parameters				
Compounding	Dissolution of API	Range defined to assure optimum process performance and desired product quality on the basis of knowledge obtained through previous experience, development experiments and risk assessment studies. This range defines the design space.		
	pH			
	Assay			
Filtration and Filling	Filter type			
	Filtration pressure			
	Bioburden			
Lyophilization	Freezing stage			
	Drying Stage			

proposed for qualification of the facility, equipment, system and utilities as well as for qualification of the process.

Stage 2 – process qualification

During this stage, the process design is evaluated in practice to determine if the process is capable of reproducible commercial manufacturing. This stage is completed before commercial distribution of the product. The stage includes following two sub-stages:

- Design and qualification of the facility, equipment, system and utilities
- Process performance qualification (PPQ)

Design and qualification of the facility, equipment, system and utilities

It is important to complete design of facility and qualification studies for equipment, systems, and utilities before performing process qualification. The purpose of qualification study is to assess if these are suitable for their intended purpose and can deliver expected output reliably. Validation master plan should provide a detail plan for qualification activities, its validity and for requalification frequency and requirements to confirm that they remain in state of control. It should also define responsibilities, expected documentation standards.

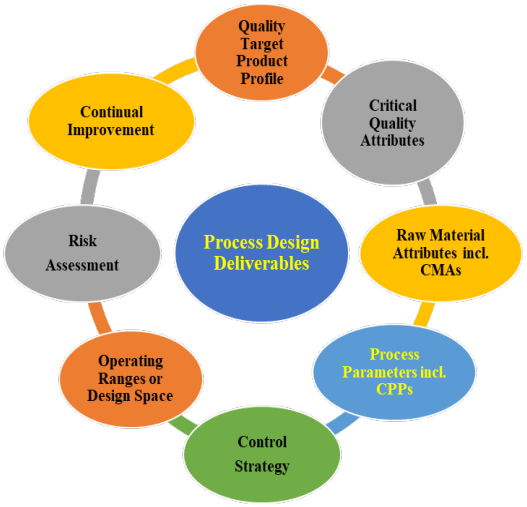

Figure 2: Process design deliverables

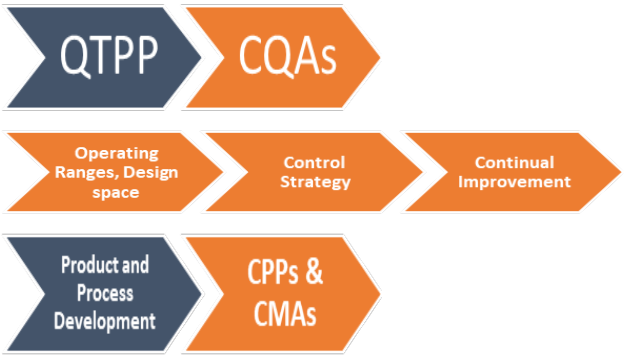

Figure 3: QbD concept of process design

Risk Assessment should be utilized to design and develop qualification plans, protocols, tests and acceptance criteria, wherever applicable.

Plan for qualification of facility, equipment, systems, and utilities generally must include the following activities:

- Verification that the equipment, systems and utilities are built as per Design specification i.e. construction of materials, operating principles and performance characteristics (Design Qualification or DQ)
- Verification of installation (Installation Qualification or IQ) and operation (Operational Qualification or OQ) of equipment, systems, and utilities in accordance with design specifications and anticipated operating ranges.
- In some cases, it may be important to verify performance (Performance Qualification or PQ) of the equipment, systems, and utilities under normal operating conditions of the specified product. These may sometimes be done using simulations or otherwise be completed along with Process Performance Qualification step.
- In case of any deviations, these need to be judiciously investigated, addressed and documented.

Process performance qualification (PPQ)

This step marks the transition from pharmaceutical development and clinical manufacturing to commercial manufacturing. The purpose of this stage is to assess the applicability of process design and the suitability of process control strategy designed in Stage 1 at the commercial manufacturing scale. A successful PPQ provides confidence over control of variability and demonstrates that the process is capable to deliver product that meets predetermined quality attributes.

A PPQ protocol is prepared, reviewed and approved before commencement of PPQ studies. The protocol is a documented plan for executing the PPQ studies and briefs PPQ Study Design (manufacturing conditions, controls, testing, and expected outcomes). A PPQ report is prepared after completing each of the study. It provides a summary of results of PPQ studies, including any deviations or protocol excursions, discussions, and conclusions. A Continued Process Verification (CPV) plan can be finalized based on the results obtained from PPQ studies. Adjustments can be made to the plan depending on study outcomes and should be handled through change control procedures. A PPQ study design consists of following major elements:

Number of batches

As against the industry norm of manufacturing three validation batches, the lifecycle approach uses statistical methods to determine the number of batches to be tested. Statistical methods in combination with other scientific, risk-based, holistic approaches provide more confidence over the state of control of the manufacturing. However, in order to gain an optimum statistical confidence on the Process Performance, it is important to consider multiple factors while determining the number of batches for PPQ Testing. These include:

- The level of process knowledge and understanding gained from Stage 1 or from previous experiences with similar processes
- The type and complexity of the manufacturing technology employed
- The inherent variability of the process resulting from raw material attributes, operating parameters, equipment, facility, systems, personnel etc.
- Bracketing, Matrixing and Family Approaches
- Sometimes, approaches where grouping is possible based on some of the process variables may be used. Examples of such variables include batch size, dosage strength, identical equipment of different size (same design or operating principle), filling line speeds etc.

Bracketing is used when only one element is variable while all others are fixed. This approach qualifies processes where the extremes of the variable represent the entire group.

In situations where the process and product design include more than one variable, *matrixing* may be used. This approach assumes that configurations utilized for PPQ testing represent the entire group.

Family grouping is utilized when multiple different but related entities can be grouped. Here again, the samples

selected for testing represent the whole group.

Sampling

In general, during PPQ, heightened sampling and analytical testing is performed. This is to assure that the process and all other variables that impact quality of the final product are in state of control. However, sampling plans may be scientifically and statistically derived, justified and approved before the commencement of testing.

Operating Conditions

It is not the intention during PPQ studies, to study extreme ranges of operation and its impact on the product. PPQ studies are carried out under normal manufacturing conditions as expected during routine manufacturing. Normal operating ranges or proven acceptable ranges (also design space, if applicable) for commercial scale manufacturing are established as part of stage 1 of process validation.

Acceptance Criteria

The acceptance criteria must be set based on the data and information obtained from process design and equipment qualification stages of the process validation. Acceptance criteria includes incoming materials attributes, process parameters (critical, key or non-key process parameters), process performance parameters (e.g. step yield), critical quality attributes and non-critical quality attributes of products, intermediates, etc.

Concurrent Approach

In ideal cases, PPQ study is completed successfully before commencement of commercial distribution of a product, so that a high degree of assurance in the process is achieved. However, in special cases, commercial distribution may happen parallel to PPQ. This is anticipated in rare exceptional cases such as where, there is an urgency due to shortage of a particular drug, in cases of frugs with short half-lives or for limited demand (Orphan designated) drugs. There is a high risk associated with drug products manufactured using such approach and in cases of unsuccessful PPQ, these may have a negative implication. Hence, a strong justification including circumstances and rationale for concurrent release should be fully described in the validation plan before commencement of such studies.

Process Analytical Technology (PAT) or Continuous Process Verification

This is an approach that provides an alternate to PPQ. PAT is designed to measure in real time the critical quality attributes of raw materials or in-process materials or the critical process parameters of manufacturing process and then adjust the process in a timely control loop so the desired quality of the output material is maintained. For successful implementation of PAT, the process design stage and the process qualification stage should focus on the design and performance of measurement system and control loop for the measured attribute. While ICH and FDA have focused more on understanding and developing PAT to ensure product quality,[37,38] a similar concept of real time release testing (RTRT) was outlined in EU GMP guidelines.[39] Here again, testing of one or more in-process material or process controls may substitute for end-product testing as part of the batch release decision. Parametric release in case of terminally sterilized products is an example of application of RTRT wherein monitoring of process parameters (e.g. temperature, pressure, time for terminal sterilization) are utilized to ensure the sterility of the product rather than performing sterility testing procedures. This method provides much more confidence over the sterility levels, is more accurate, comprehensive and also non-destructive.

Stage 3 – Continued Process Verification (CPV)

This stage is expected to provide an assurance during routine production throughout the product lifecycle that the process remains in a state of control post process qualification stage. In addition, CPV assists manufacturers to identify opportunities for process improvement. The two sub-stages in a CPV program are marked by different levels of testing. The two sub-stages of a typical CPV program are explained below.

Enhanced testing program

Following a successful PPQ, increased sampling and testing continues through CPV stage until a good understanding of the process variability is obtained. This is because unknown unanticipated incidences/issues of process variability may arise during routine manufacturing and continued monitoring can help to make adjustment to input variable via a change management process. The data collected must include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

Routine testing program

During this stage, data generated during stage 3.1 is used for routine monitoring of products and processes. The level of testing is reduced based on the level of statistical confidence obtained and the risk involved.

A CPV monitoring plan is developed based on the learnings and understanding from stage 1 and stage 2 and must include following elements:

- Roles and responsibilities
- Sampling strategy
- Data analysis methods
- Acceptance criteria
- Deviation management strategy
- Frequency of re-evaluation of CPV plan

Legacy process improvement

For application of lifecycle approach to legacy products, it is required to collect and assess large volume of historical data and an assessment of process variability. In some cases where the legacy process is well-controlled and monitored, not much action is required. But in cases where, variability

Table 5: Comparison of traditional and lifecycle approach to process validation

Concepts	*Traditional approach*	*Lifecycle approach*
process validation understanding	- One-time event - establishing documented evidence to provide assurance of quality.	- spans through lifecycle of the product - establishing scientific evidence to provide assurance of quality
stages of process validation	Focuses on validation of individual part of process. 1. Equipment – Installation qualification (includes OQ and PQ) 2. Process – performance qualification 3. Product – performance qualification	Focuses on complete product lifecycle. 1. Process Design 2. Process Qualification 3. Continued Process Verification (Or ongoing process verification)
Number of Batches	Three PV batches – golden standard	Statistical methods to provide evidence. Number of batches for testing is dependent on the risk involved.
Worst case scenario	Aims to cover conditions at lower and higher limits of processing in order to assess conditions that pose highest risk of failure.	Aims to conduct testing employing normal routine conditions. Studies at lower and higher limits to understand impact on quality is studied during process design stage.
Matrix, Bracketing etc.	Not acceptable	Grouping on the basis of justified experience level with similar products and processes is acceptable.
Revalidation	Required if any changes are introduced to the manufacturing process.	May not be required. Majority of changes can be managed through risk assessment in process design or continuous process verification stage depending on robustness of design space.
Concurrent validation	Not included	Possible for high-risk products in particular situations like drug shortage of medically necessary products or low shelf life of products. Need to be fully justified.
Retrospective validation	Validation of a product or a process already in market, on the basis of historical production and testing data	Not acceptable
Continuous process verification	Not included	Newly introduced approach wherein CPPs and/or CQAs are continuously monitored and a system to control the output variables by adjusting the input is employed.

is observed, principles of risk assessment may be helpful to understand the input variables that impact the quality of the product. These products typically enter the stage 3a of process validation. Enhanced sampling and testing may help in understanding the variability of the process and enable establishment of control strategy, acceptance criteria, and frequency of testing. Sampling plan for legacy products may also be reassessed to verify that these are well established based on scientific approaches and justified appropriately. Retrospective Validation is no more accepted by the authorities.

Revalidation

The concept and scope of revalidation is redefined under the lifecycle approach of process validation. Manufacturing changes (e.g. changes in formulation, packaging material, raw material, equipment) which previously triggered revalidation can now be managed under continued process verification. Under CPV, the assessment of ongoing process data is carried out against the variability range established under stage 1 and stage 2 of process validation and it is possible that revalidation may not be required. For situations that are not managed, all or part of stage 2 may need to be reperformed.

Benefits of Process Validation (Lifecycle Approach)

The principal idea for having a process validation exercise in a manufacturing process is to ensure that the manufacturing process will consistently produce batches with desired quality. The lifecycle approach builds this through a scientific and risk-based assessments. Thus, a robust process validation benefits the manufacturer by:

- Reducing time and money investment in R&D and improving performance/ in investigations
- Reducing regulatory actions like Warning Letters/483's/ recalls/seizures and saving cost due to minimum rejects and reworks
- Delivery of quality products
- Ensuring Patient safety
- Building the brand value

Limitations of Process Validation (Lifecycle Approach)

- Process validation is not a one-time event but spans through lifecycle of the product
- Retrospective validation cannot be performed.
- As lifecycle approach depends on statistical methods to derive confidence over the performance of validated

process, there is a known level of uncertainty or risk involved.

- The successful completion of process validation is ultimately dependent on qualified facilities, equipment, personnel and procedure. Good Documentation Practices (GDP), Good Laboratory Practices (GLP), training and development also have an important role in completion of process validation exercise.

CONCLUSION

The rise in the number of citations lacking robust manufacturing processes in facility inspections has made industry and the agencies to revisit the traditional concept of process validation. Subsequently, release of ICH (Q8, Q9 and Q10) guidelines has marked a paradigm shift from traditional to lifecycle approach in the practices of process validation. The new approach is a more holistic, scientific approach which build on a strong foundation of knowledge of product and process, gained through historic data, experiences and experimental studies. It not only provides assurance of the quality of the product and robustness of the process but also builds a system to identify and implement opportunities for continual improvement. In all, the lifecycle approach imbibes in it a model that promotes application of new technological advances, modern quality management techniques and systems and implementation of science and risk-based approaches. Table 5 presents a comparison between the traditional and the lifecycle approach. Further, a comparison of guidelines from major geographies concludes that there are not much significant differences in these guidelines as all these regional guidelines are essentially adopted from ICH concepts. Hence, it is essential that pharmaceutical manufacturers review their current validation policies and procedures against the lifecycle approach, identify any gaps and implement revisions to their current policies, documents, and system and ensure training. An integrated team approach along with a strong documentation and communication system is helpful.

REFERENCES

1. Agalloco J. Validation: an unconventional review and reinvention. PDA J Pharm Sci Technol. 1995 Jul-Aug; 49(4):175-9.
2. Food and Drug Administration. *Federal Register,* Title 21, Chapter 1, Vol. 43, #190. Human and Veterinary Drugs. Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding, 1978.
3. US Food and Drug Administration. Guideline of General Principles of Process Validation (CDER, May 1987)
4. ICH Harmonised Tripartite Guideline Pharmaceutical Development Q8(R2), Published Aug 2009.
5. ICH Harmonised Tripartite Guideline Quality Risk Management Q9, Published Nov 2005.
6. ICH Harmonised Tripartite Guideline Pharmaceutical Quality System Q10, Published Jun 2008.
7. US Food and Drug Administration. Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations. Published Oct 2006.
8. US Food and Drug Administration. Guidance for Industry Process Validation: General Principles and Practices Revision 1. Published: Jan 2011.
9. European Medicines Agency. Guideline on process validation for finished products – information and data to be provided in regulatory submissions Nov 2016
10. European Medicines Agency. Note for Guidance on Pharmaceutical Development (EMEA/CHMP/167068/2004). Published: Jun 2009.
11. Health Canada Guide to validation – drugs and supporting activities. Published: June 29, 2021.
12. Indian Pharmaceutical Alliance. Process Validation Guidelines. Published Feb 2018.
13. PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Feb 2022.
14. WHO good manufacturing practices for pharmaceutical products: Main principles *Annex 2, WHO Technical Report Series 986, 2014.*
15. WHO good manufacturing practices for active pharmaceutical ingredients (bulk drug substances) *Annex 2, WHO Technical Report Series 957, 2010.*
16. WHO good manufacturing practices: Guidelines on validation *Annex 3, WHO Technical Report Series 1019, 2019*
17. ISO 9000 Quality Management Systems – Fundamentals and Vocabulary
18. ISO 9001 Quality Management Systems - Requirements
19. ISO 9004 Managing for the sustained success of an organization – A quality Management approach
20. Government of India Ministry of Health and Family Welfare. The Drugs and Cosmetics Act, 1940 (As Amended up to the 31st December, 2016) and The Drugs and Cosmetics Rules, 1945 (As Amended up to the 31st December, 2016). (Accessed at: Acts & Rules (cdsco.gov.in))
21. 21 CFR Part 210 Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs, General (Accessed at: eCFR :: 21 CFR Part 210 -- Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General)
22. 21 CFR Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals (Accessed at: eCFR :: 21 CFR Part 211 -- Current Good Manufacturing Practice for Finished Pharmaceuticals)
23. 21 CFR Part 820 Quality System Regulation (Accessed at: eCFR :: 21 CFR Part 820 -- Quality System Regulation)
24. European Commission EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines (Accessed at: EudraLex - Volume 4 (europa.eu))
25. TGA Manufacturing principles for medicinal products PIC/S Guide to Good Manufacturing Practice for Medicinal Products, PE009-15 (01 May 2021) Published Aug 2022 (Accessed at: Manufacturing principles for medicinal products | Therapeutic Goods Administration (TGA)).
26. TGA Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products. V1.0, Apr 2013 (Accessed at: Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products | Therapeutic Goods Administration (TGA))
27. Government of Canada Food and Drug regulations. Food and Drug Regulations (justice.gc.ca)
28. Japan Ministry of Health, Labour and Welfare (MHLW)

Ministerial Ordinance No. 179, 2004 on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs (Accessed at: 000153399.pdf (pmda.go.jp))
29. Japan Ministry of Health, Labour and Welfare (MHLW) Administrative Notice on Application of PIC/S GMP Guide, Feb 2012 (Accessed at: 000153550.pdf (pmda.go.jp)) and Q and A on "Application of PIC/s GMP Guide", Feb 2012 (Accessed at: 000153339.pdf (pmda.go.jp))
30. Japan Ministry of Health, Labour and Welfare (MHLW) Ministerial Ordinance No. 28, 1997 on Good Clinical Practice for Drugs (Accessed at: 000152996.pdf (pmda.go.jp))
31. NMPA Good Manufacturing Practice for Drugs (2010 Revision) (MOH Decree No. 79) (Accessed at: Good Manufacturing Practice for Drugs (2010 Revision) (nmpa.gov.cn))
32. ANVISA Good Manufacturing Practices Applicable Regulations (Accessed at: Regulation of companies - Anvisa)
33. USFDA Pharmaceutical cGMPs for the 21st Century - A risk-based approach. Final Report Sep 2004.
34. ICH Final Concept Paper Q10: Pharmaceutical Quality Systems dated 9 September 2005.
35. US Food and Drug Administration. Guidance on Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms. April 2012.
36. US Food and Drug Administration. Guidance on Quality by Design for ANDAs: An Example for Modified Release Dosage Forms. December 2011.
37. ICH Harmonised Tripartite Guideline Continuous Manufacturing Of Drug Substances and Drug Products Q13, Published Nov 2022.
38. US Food and Drug Administration. Guidance on PAT- A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance.
39. European Commission EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines Annex 17: Real Time Release Testing and Parametric Release (Accessed at: 2018_annex17_en.pdf (gmp-compliance.org))