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Research Article

CGMP REQUIREMENTS FOR PROCESS CONTROL

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ABSTRACT

Drugs and drug products are very critical elements in Health care and they must be manufactured with highest quality levels. End-product testing is not alone sufficient to ensure the quality of the product. Therefore process control is necessary to build quality into the product at every step. Process controls are mandatory in Good Manufacturing Practice (GMP). The purpose is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it. This review presents an overview on the need and significance of process control and validation in manufacturing of pharmaceutical products.

Keywords: Process validation, Process control, Good Manufacturing Practice (GMP)

INTRODUCTION

Health Care is an area of paramount importance as it is directly related to preserving and improving the quality of life of human beings. It involves a wide spectrum of activities and disciplines, of which pharmaceutical manufacturing is an important field. Issues of quality in pharmaceutical manufacturing are of prime importance in view of the fact that an error can be detrimental to human health and life, which is why all the pharmaceutical products are required to be highly consistent in quality to maintain their safety, efficacy and stability. It is known that pharmaceutical processes and facilities have a significant impact on quality of the end product which is why all the pharmaceutical processes need to be highly controlled so that they result in same product quality always. Process control ensures that every time a process is run, it will give the desired result. It helps in significant reduction in failure, improves productivity and decreases the reliance on end product testing to determine whether the product conforms to the desired standard or not. The purpose of this work is to present an introduction and general overview on process control and validation of pharmaceutical manufacturing process with special reference to cGMP guidelines given under 21 Code of Federal Regulations(CFR) part 211(Current good manufacturing practices for finished pharmaceuticals).

Written Procedures; Deviations

This section 211.100 of 21 CFR underlines the basic concept of cGMP, that there shall be adequate written procedures that have been approved by responsible persons and it should be documented that these procedures have been followed during manufacturing. [2]

In pharmaceutical industries these written procedures are in the form of Standard Operating Procedures (SOPs). A SOP is a set of written instructions that document a routine or repetitive activity which is followed by employees in an organization. The development and use of SOPs are an integral part of a successful quality system. It provides information to perform a job properly, and consistently in order to achieve pre-determined specification and quality end-result. SOPs must contain detailed step by step instructions on how to perform a task to ensure the consistency and reliability in result whenever the task is performed by any trained personnel. A SOP must contain following details:-[3, 5]

·What is the objective of SOP (Purpose)?
·What are applicability and use of SOP (Scope)?
·Who will perform tasks (Responsibility)?
·Who will ensure implementation of procedure (Accountability)?
·How tasks will be performed (Procedure)?

Having provided written and approved procedures, the next stage is to ensure that they are followed which involves training and verification steps. Employees must be given training in all relevant procedures. This should include an understanding and awareness of the purpose of the procedures and why they need to be followed. There should be a record of the successful completion of the training. [5, 8]

On occasion, deviations from the defined procedure will occur or will be necessary. In such instances the deviation should be clearly recorded. Where the deviation was deliberate, the rationale should be explained. Whether deliberate or accidental, the responsible individuals should review the event to establish the potential impact on, and disposition of, the resulting product. If appropriate, the procedure may be resubmitted into the approval system in order to be permanently incorporated into the master documentation. [4, 6]

Charge-In of Components [1, 2]

This section gives guidelines about how the various components (raw materials etc.) are to be dispensed and added to the process to ensure that right quantity of correct material, released by QC, is added to the specified batch. The dispensing of materials is a critical step of the manufacturing operation. The labeling of the component containers (§211.101 (b) (1)–(4)) is important to avoid any confusion at later stage and makes the later checking at production usage more effective. The dispensing operation also provides an opportunity for visual examination of containers for damage, and contents for atypical appearance or foreign matter. Dispensing operators should be made aware of the importance of this role to the achievement of quality standards.

The requirement that ‘‘each container of component dispensed to manufacturing shall be examined by a second person’’ (§211.101(c)) is usually interpreted to mean that a second person should be available in the dispensary to perform this duplicate check. Several alternatives would also appear to achieve the same result. A single check could be performed in the dispensary with the second check being done on receipt by production. The dispensing label can also be removed at the production stage and it can become a part of the batch manufacturing record so that, if a problem may arise later, individual labels can be examined. Another alternative to second person check can be replacement by suitable computer system or the use of Bar Codes.

Calculation of Yield [1]

Theoretical yield is defined as the maximum quantity that could be produced, based on the quantities of components used, in the absence of any loss or error in production. Based on historical data an acceptable range for actual yield at each appropriate stage can be calculated. This range is sometimes set so that 95% of batches produced will fall within the range when the process is operating correctly. The purpose of this is to alert management of atypical situations that may require investigation. Low yields may not only signal potential problems but may also indicate opportunities to improve process with subsequent cost benefits. Process losses can

occur for a variety of reasons including dust extraction, spillage of components or product, machine losses such as in compression, machine adjustments, samples, or residue in equipment. The regulations again require that a second person verify independently the yield calculations.

Equipment Identification [1]

This regulation requires that all equipment and lines always bear a label which clearly defines there status such as: clean, to be cleaned, or with the product name and lot number and, if necessary, the phase of processing. If the individual parts of equipment tend to be cleaned separately, each part should bear the status-label to make sure that no uncleaned part is allowed to be used. These status-labels can be retained and added to the batch manufacturing record to allow back reference to the status data in event of a problem.

The intent of subsection (§211.105(b)) is to allow identification, at some future date, of the specific piece of equipment involved in the manufacturing of a certain batch. This is particularly appropriate where a manufacturer may have several different pieces of the same equipment, which may not behave identically. If the manufacturer has only one piece, then reference by name alone will suffice.

Sampling and Testing of In-Process Materials and Drug Products

In-process controls are checks that are carried out before the manufacturing process is completed. The function of in-process controls is monitoring and, if necessary, adaptation of the manufacturing process in order to comply with the specifications. This may include control of equipment and environment too. In-process controls may be performed in regular intervals during a process step (e.g. tableting, encapsulation) or at the end of a process step (e.g. granulation, blending). The objectives of in-process control are both quality control and process control. [9]

During manufacturing and packaging a lot of data are recorded which represent control factors of the manufacturing process. These data may be process parameters (e.g. outlet air temperature of a fluid bed dryer) or product attributes (e.g. hardness of tablet cores). To control the process, acceptable operational ranges for process parameters are determined to maintain product attributes within the desired specified ranges [9]. The first stage in establishing appropriate process control criteria is the identification of the key factors which impact on quality and the evaluation of acceptable operational ranges for these. This is referred to as process validation.

Process Validation

The FDA in ''Guidelines on General Principles of Process Validation'' defines process validation as ''establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics''. [13] Process validation is act of demonstrating and documenting that any procedure, process and activity will consistently lead to the expected results. The goal of the validation is to ensure that quality is built into the system at every step. The designing of quality into a product and its production processes, increases the potential for consistently achieving quality standards and reduces dependence on both in-process and end-product testing. [17]

The guidelines on general principles of process validation mentions four types of validation:

A) ***Retrospective validation*** [10, 11]

Retrospective validation involves an in-depth evaluation of a large number of consecutive batches of product to correlate processing conditions and analytical results. It is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation of these facilities, processes, and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. This kind of approach is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment. It is used only for the audit of a validated process. Satisfactory results of retrospective validation only serve as an indication that the process does not need to be subjected to validation in the immediate future

B) ***Prospective validation*** [10, 12]

Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics. It helps in establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols. In prospective validation, data from laboratory- and/or pilot-scale batches is used to identify critical quality attributes and specifications, critical steps, control ranges, and in-process tests. The number of process runs generally depends on the complexity of the process or the magnitude of the process change being considered. Although three consecutive, successful production lots are used as a guide, there could be situations where additional process runs are warranted to prove consistency of the process (e.g., complex Active Pharmaceutical Ingredient (API) processes or API processes with prolonged completion times).

C) ***Concurrent validation*** [10, 11]

In certain cases, it may be appropriate to validate a process during routine production, e.g. where the product is a different strength of a previously validated product, a different tablet shape or where the process is well understood. Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process. This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.

D) ***Revalidation*** [10, 13]

Revalidation means repeating the original validation effort or any part of it, and includes investigative review of existing performance data. A system must be established which initiates a review of the need for revalidation whenever there is a change in the equipment, facilities, process, services, formulation, or source of components. In the case of standard processes using conventional equipment, a data review similar to that which would be required for retrospective validation may provide an adequate assurance that the process continues to be under control.

Change Control [10, 16]

A consistent achievement of product quality is dependent on the availability of defined/approved/ validated procedures and the application and adherence to these procedures by trained personnel. In the event that any change is to be introduced into the production operation, it is important to evaluate its potential impact and where necessary provide appropriate evaluation and/or actions. Written procedures should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment, processing site, method of production or testing or any other change that may affect product quality or support system operations. Any proposals for changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the quality control unit.

The activities relating to validation studies may be classified into three phases: [15, 17, and 18]

Phase 1: Pre-Validation Phase or the Qualification Phase:-

This phase covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production documents, operational qualification, process capability. Process capability is defined as the studies used to determine the critical process parameters or operating variables that influence process output and the range of numerical data for critical process parameters that result in acceptable process output.

Phase 2: Process Validation Phase (Process Qualification phase):-

It is designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the "worst case" conditions**.** It represents the actual studies or trials conducted to show that all systems, subsystems, or unit operations of a manufacturing process perform as intended; that all critical process parameters operate within their assigned control limits; and that such studies and trials, which form the basis of process capability design and testing, are verifiable and certifiable through appropriate documentation.

Phase 3: Validation Maintenance Phase:-

It requires frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including Change Control procedures. At this stage the validation team also assures that there have been no changes/ deviations that should have resulted in requalification and revalidation.

Time Limitations on Production

This regulation indicates that certain processes are sufficiently sensitive that time limits need to be established for their completion. This could be especially important for: [2]

a. Material that is vulnerable microbial attack. Bulk injections are usually required to be filled into the final container within 48 hours

b. Materials subject to oxidation may be protected with nitrogen. Effective nitrogen protection may be difficult at the bulk stage; also, failure of the nitrogen system could result in batch rejection.

c. Tablet granulations or other bulk solids may absorb or release moisture on storage, making them more difficult to process or even accelerating decomposition.

Batch records should clearly indicate any time-scale restriction and dates and times should be recorded. In the event that a defined time-scale is exceeded an investigation must be initiated to identify the cause and the possible implications of the changed time-scales. Extension of established and validated time scales may be used as a basis for extending these times. In most instances data from more than one such extension will be required before a permanent change can be implemented.

Control of Microbiological Contamination

Every day the human body is invaded by countless numbers of microorganisms, which are found in the food we eat, the air we breathe, and the water we drink. Consequently, for most products other than injections, there is no need for sterility. For products that are not required to be sterile, the presence of microorganisms could still constitute a problem. Certain microorganisms are associated with human illness and should be absent. Some products may also be prone to microbial degradation resulting in loss of active ingredient or breakdown in physical characteristics, such as emulsions. In such cases it may be necessary to have a specification for total viable microorganisms. The end use of the product may also make it appropriate to have such limits: for example, for product used around the eyes or on mucous membranes. [19]

Table 1: Assignment of Microbial Count Limits for Raw Ingredients, Excipients, and Drug Substances (on the Basis of the Origins of These Materials) [21]

	Microbial alert level (X)	**Microbial action level (5X)**	**Yeast and mold count/g[b]**	**Absence of indicator organism[c]**
Material type	First-tier testing count/g	Total bacterial	Second-tier testing	
Synthetic	200	1000	100	*Escherichia coli Staphylococcus aureus Pseudomonas aeruginosa*
Natural	1000	5000	500	*Salmonella, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*
Material that can be decontaminated[a]	20	100	10	*Salmonella Escherichia coliStaphylococcus aureus Pseudomonas aeruginosa*

a Values indicated are for materials following decontamination.

b When the bacterial count is _X but _5X/g, the yeast and mold count is performed.

c Tests for the absence of indicated organisms when bacterial count is _X but _5X/g.

Table 2: Assignment of Microbial Count Limits for Nonsterile Finished Dosage Forms (by Route of Administration) [20]

Route of administration	**Bacterial count limit (cfu/g or ml)**	**Yeast or mold count (cfu/g or ml)**	**Absence of indicator organisms**
Inhalants	10	2	*Escherichia coli, Staphylococcus aureus Pseudomonas aeruginosa Salmonella*
Topical/vaginal/rectal/nasal/otic	100	10	*Escherichia coli Staphylococcus aureus Pseudomonas aeruginosa Salmonella*
Oral-liquid	500	50	*Salmonella Escherichia coli Staphylococcus aureus*
Oral-solid	1000	100	*Salmonella Escherichia coli Staphylococcus aureus*

Sterile products are manufactured using either terminal sterilization or aseptic processing. Terminal sterilization results in a significantly higher sterility assurance as autoclaving at 121°C can easily result in a microbial survivor probability of order of 10^{-6}, while this value is only 10^{-3} in case of aseptic processing. Because of these significant differences in assurance levels, terminal sterilization should be the method of choice. But some products cannot withstand the temperature conditions of autoclaving, the ingredients may be heat labile or the package maybe physically affected by the pressure changes (e.g., prefilled syringes), and aseptic processing may then be

necessary. A useful compromise situation is a combination of aseptic processing with some level of heat treatment that could effectively kill off vegetative organisms without adversely affecting chemical stability or physical integrity. [28] The possible permutations of temperature and time are almost limitless. This then places a greater emphasis on the need to validate the sterilization process and to ensure that the defined process is followed for every batch of product so that every batch falls under desired specifications. The key parameters that should be evaluated are: [2]

1. Heat distribution within the empty sterilization chamber.
2. Heat penetration within the units of product for the various loading cycles to be used.
3. Lethality calculations based on kill of known numbers of resistant bacteria or spores, usually *Bacillus stearothermophilus* spores placed in units that receive the least heat treatment.
4. Bioburden data showing the numbers and types of organisms, with particular reference to resistivity, likely to result from the components and the process prior to sterilization.
5. Perform studies outside the ranges of conditions that will routinely be used for sterilization cycles.

Validation of Aseptic Processing

We have already discussed that terminal sterilization of a product is preferable as it reduces the risk of and provides more assurance of sterility. But in parenteral manufacturing it has been recognized that many drugs and biologics would not withstand a physical sterilization process in their final container. Currently, a majority of parenterals and other products labelled sterile are manufactured using aseptic processing. In no other segment of the pharmaceutical industry is the control of manufacturing processes as critical as in the production of aseptically produced products. The recognition of the criticality of these processes has led to the continued development of advanced production and quality assurance systems. [28]

1. Environmental control and monitoring

The basic elements of an aseptic processing environmental control program consist of: [28]

- A review of environmental factors that include temperature, relative humidity, air velocity, uni-directional air flow, HEPA filtration, and pressure differentials between rooms of different classification
- An evaluation of utility services that could affect microbiological safety or product quality.
- A comprehensive microbiological and total-particulate monitoring system
- An evaluation of personnel gowning and materials transfer airlocks
- Calibration, certification and preventive maintenance on critical facility systems and processing equipment
- Training programs for personnel in both aseptic technique and standard operating procedures or work instructions.

These systems should be subject to regularly scheduled and unscheduled audits and routine supervisory oversight and evaluation.

Classification of clean areas: [25]

- Grade D (equivalent to Class 100,000, ISO 8): Clean area for carrying out less critical stages in manufacture of aseptically prepared products e.g. handling of components after washing.
- Grade C (equivalent to Class 10,000, ISO 7): Clean area for carrying out less critical stages in manufacture of aseptically prepared products e.g. preparation of solutions to be filtered.
- Grade B (equivalent to Class 100, ISO 5): Background environment for Grade A zone, e.g. cleanroom in which laminar flow workstation is housed.
- Grade A (equivalent to Class 100 (US Federal Standard 209E), ISO 5 (ISO 14644-1): Local zone for high risk operations e.g. product filling, stopper bowls, open vials, handling sterile materials, aseptic connections, transfer of partially stoppered containers to be lyophilized. Conditions usually provided by laminar air flow workstation.

Table 3: Classification of clean areas in terms of airborne particles[25]

Grade	*Maximum permitted number of particles/m3*			
	At rest		*In operation*	
	0.5 - 5.0 µm	> 5 µm	0.5 - 5.0 µm	> 5 µ
A	3 500	0	3 500	0
B	3 500	0	350 000	2 000
C	350 000	2 000	3 500 000	20 000
D	3 500 000	20 000	not defined	not defined

Table 4: Limits for viable particles (microbiological contamination) [25]

Grade	Air sample (CFU/m3)	Settle plates (90mm diameter) (CFU/4hours)	Contact plates (55mm diameter) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 3	< 3	< 3	< 3
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Other parameters typically considered in the design of an aseptic processing area are particulate matter, direction of airflow, air balance, air changes per hour, and air velocity. There are several guidelines containing sound design recommendations for aseptic processing areas: [23, 24]

- Control of Particulate is significant because they can contaminate and also carry organisms Appropriate alert and action limits should be set and corrective actions defined if limits exceeded.
- Positive pressure differential of 10-15 Pascal should be maintained between adjacent rooms of different classification (with door closed). Most critical area should have the highest pressure Pressures should be continuously monitored and frequently recorded.
- Air flow over critical areas should be uni-directional (laminar flow) at a velocity sufficient to sweep particles away from filling/closing area for B, C and D rooms at least 20 changes per hour are usually required.

– Ambient temperature and humidity should not be uncomfortably high (could cause operators to generate particles) (18°C). Laminar airflow workstation air speed should be approx. 0.45m/s ± 20% at working position.

2. Personnel requirements[22, 23, 28]

Personnel play an important part in ensuring the quality of manufacture. Only a minimum number of personnel should work in clean areas, especially during aseptic processing. As far as possible, all inspections and controls should be done from outside the production rooms. Training should be given to all including cleaning and maintenance staff, and should include initial and regular training on manufacturing, hygiene, and microbiology. In special cases, when outside staff has to enter the clean areas, they should be supervised. Personnel working in clean areas should maintain high standards of hygiene and cleanliness. They should undergo periodic health checks, wear clothing that do not shed particles, and should take care not to introduce microbiological contaminants in the areas. No outdoor clothing should be brought into clean change rooms. Personnel should follow changing and washing procedures, wear no watches, jewellery and cosmetics

3. Product filtration[23, 24]

Filter must be validated to demonstrate ability to remove bacteria. Most common method is to show that filter can retain a microbiological challenge of 10^7 CFU of *Brevundimonas diminuta* per cm^2 of the filter surface a Bioburden isolate may be more appropriate for filter retention studies than *Brevundimonas diminuta.* Challenge concentration is intended to provide a margin of safety well beyond what would be expected in production, preferably the microbial challenge is added to the fully formulated product which is then passed through the filter. If the product is bactericidal, product should be passed through the filter first followed by modified product containing the microbial challenge (after removing any bactericidal activity remaining on the filter). Filter validation should be carried out under worst case conditions e.g. maximum allowed filtration time and maximum pressure. Integrity testing specification for routine filtration should correlate with that identified during filter validation

4. Media fills[26, 27]

Process validation in aseptic processing is done by simulating the manufacturing process using microbiological growth medium (media fills). Process simulation includes formulation (compounding), filtration and filling with suitable media using the same processes involved in manufacture of the product. Modifications must be made for different dosage formats e.g. lyophilized products, ointments, sterile bulks, eye drops filled into semi-transparent/opaque containers, biological products. Media fill program should include worst case activities such as Factors associated with longest permitted run (e.g. operator fatigue), Representative number, type, and complexity of normal interventions, non-routine interventions and events (e.g. maintenance, stoppages, etc.). A minimum of 3000 units should be filled to provide a 95% probability of detecting contamination at a level of one in one thousand. Each shift and each employee used for aseptic processing should be included in the validation runs.

Reprocessing

The failure of a batch of product to meet the quality standards must be viewed as a failure of the quality control process. The main causes of failure include: [2]

1. Malfunction of equipment or services.
2. Noncompliance with defined procedures by operating personnel.
3. Atypical behavior of materials that comply with their specifications.

If none of these causes can be demonstrated, it is possible that the process had been inadequately validated and that one or more of the operating parameters are actually outside of acceptable limits. In such circumstances revalidation may be required before further lots are processed.

In addition to approving a reprocessing process, quality control should also carefully review what testing and evaluation is to be performed on the reprocessed batch. Factors to be considered would include: [2]

1. Whether any specification tests are not performed routinely, reliance being placed on validation data. Examples of this could include dissolution performed only at the uncoated stage of a film coated tablet— recoating may affect this—or content uniformity.
2. Whether the reprocessing might have affected product stability and its shelf life. This could happen for a liquid product requiring a reheat stage to fully dissolve some raw materials.

The practice of adding a small amount, say 10%, of the rejected batch to subsequent lots of product, based solely on the assumption that most tolerances are +10%, is non-valid. First, there is no evidence to indicate that the rejected processed material will not change the characteristics beyond the specifications. Second, and more important, Current Good Manufacturing Practices require that the manufacturer try to attain the product specifications; tolerances are established to take into account only unavoidable processing variation and the accuracy and reproducibility of test methods. It is not good practice to permit a lowering of target standards by adding material whose effect on the process is not known but is assumed to lower the desired quality target, even though the quality remains within specifications. If reprocessing by addition to subsequent batches is practiced, it is necessary to confirm that this does not adversely affect the target values for product quality.

CONCLUSION

From study it can be stated that Process Control is a major requirement of cGMP regulation for finished pharmaceutical products. It is a key element in assuring that the quality goals are met. Process validation is the most important and integral part of process control which makes sure that a process always leads to desired results. Equipments, facilities and raw material are equally important in maintaining the production and process under control. Finally, it can be concluded that Process control is a key element in the quality assurance of pharmaceutical product as the end product testing is not sufficient to assure quality of finished product.

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