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A review on pharmaceutical process validation

Manish Kumar Mishra and Pooja Kumari

Abstract
The present article focus on the Introduction of Validation and common outline on process validation in pharmaceutical industry. The word validation defined as "Validation is documented evidence that provides high degree of assurance". Validation has become one of the important pharmaceutical industries accepted subjects. The process is evolved in such a way that all the given parameters are reached and it ensures that the output of the process will always meet the required parameters during regular production. Validation and quality assurance will go hand in hand, ensuring the through quality of the products. Process Validation highlight on process design elements and keeping process control during commercialization and link that process validation is a constant program and line up process validation activities with product lifecycle. The validation protocol includes inventory control and equipment inspection in the preliminary steps and in-process controls in the subsequent steps. Process validation also highlights the role of objective actions and statistical tools and examines and underlines knowledge, detection, and the control of inconsistency and gives assurance on consistent of quality throughout life cycle of product.

Keywords: Process validation, parameters, protocol, commercialization, inspection

1. Introduction [1, 2, 3]

Pharmaceutical Validation is the most significant and accepted parameters of cGMPs. The major objective of pharmaceutical industry is to manufacture products of required attribute and quality consistently, at the lowest conceivable cost. Validation is a intellection that has been developed continuously since its first formal aspect in the United States in 1978. The need of the process validation is that appears of the quality system (QS) regulation. The Aim of a quality system is to always produce result that are suitable for their wilful use. The process validation is the certification of the validation documents that must be submitted with the submission file for marketing authorization. The process validation is deliberated to assist manufacturers in tolerant quality management system (QMS) necessities concerning process validation and have common applicability to manufacturing process. Validation has become one of the Pharmaceutical industry's most familiar and discussed subjects. Its critical success factor in product support and ongoing commercialization. Quality is always an authoritative requirement when we consider any product. Therefore, the drugs must be manufactured to the highest quality levels. Finished product testing by itself does not assurance the quality of the product. A process validation procedure is required as specified by the current good manufacturing practices Regulations for Finished pharmaceuticals and is therefore applicable to manufacturing of drugs.

Validation is one of the main and essential part of cGMP. Validation is based on, FDA regulations that narrate current good manufacturing practice(cGMP) for complete pharmaceuticals that are provided in 21 CFR parts 210 & 211. The cGMP regulations need that manufacturing processes are designed and controlled to assure that the in-process materials and the finished outcome meet fixed quality requirements and do so always and reliably. Validation is therefore one the element of pharmaceutical quality assurance related with a particular process, the process vary widely, there is no universal approach to validation and regulatory bodies such as FDA and EC who have evolve general and non-mandatory guide lines. Then the word validation simply means, assessment of validity" or action of proving effectiveness. Process controls include raw materials in-process controls that targets for final products. The motive is to monitor the on-line and the off-line performance of the manufacturing process and then to validate it. After the manufacture, process is validated and current good manufacturing practice also need that their is well-written procedure for the process controls and is accepted to monitor its performance. This paper also provides an overview of the pharmaceutical validation and the process controls in drug development.

The concept of validation can be applied to the new drugs, new dosage forms and generic drug development.

2. History of validation [4]

The concept of validation was first proposed by two FDA officials, Ted Byers and Bud Loftus, in the middle of 1970's in an order to improve its quality of the pharmaceuticals (Agalloco 1995). It was proposed in direct response for several problems in the sterility of the large volume of parenteral market. The first validation task was focused on the action involved in the manufacturing of these products, but quickly spread to the associated process of pharmaceutical. U.S.F.D.A. was the colonizer to advice the concept of the process validation, but till 29th September 1978 the definition of process validation did not appear in any part of the literature of U.S.F.D.A. no cGMP regulations talked anything related to process validation [4].

3. Definitions [5, 6, 7, 8]

European commission: Validation "Act of proving, in accordance of GMPs that Any" process actually leads to expected results. 2000- "Documented evidence that the process, operated within established Parameters, can perform effectively and reproducibly to produce a Medicinal product meeting its predetermined specifications and quality attributes".

US FDA Definition

"Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

ICH Definition

"Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality."

WHO Definition

"The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to expected result."

4. Why Validation? [9, 10, 11]

- Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified.
- A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved.
- Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control adequate validation.
- The pharmaceutical industry uses expensive material, sophisticated facilities and equipment and highly qualified personals.
- Detailed study and controlled of the manufacturing process batch validation is necessary if failure cost is to be reduced and productivity is improved.
- If would not be feasible to use equipment not knowing if it will produce the product we want, not to employ the people with no assurance that they can do or fail to implement process checks or examination to assure that product meet specifications.
- The efficient use of these resources is necessary for the continued success of the industry
- Assurance of quality, cost reduction.

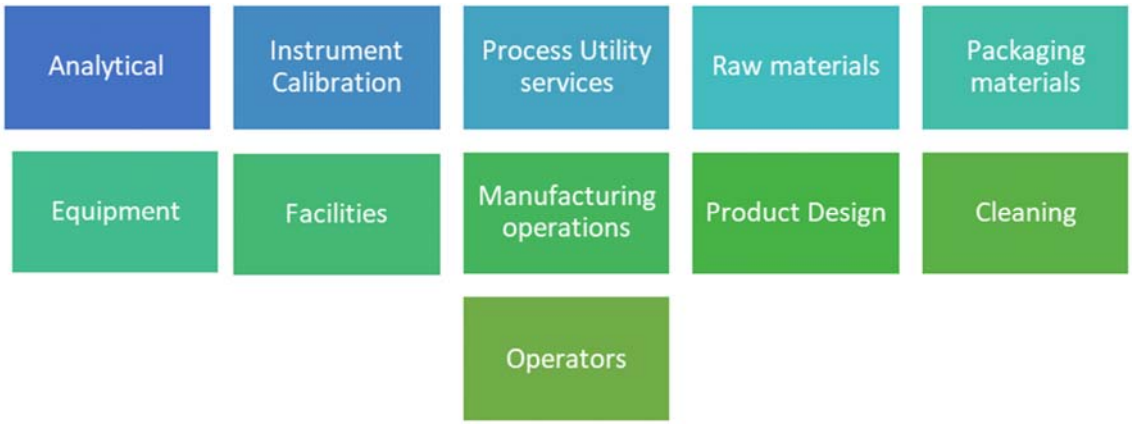
5. Validation Steps [11, 12]

Summarization of validation steps:

- As a pre-requisite, all studies should be conducted in accordance with a detailed, pre-established protocol or series of protocols, which in turn is subject to formal – change control procedures.
- Both the personnel conducting the studies and those running the process being studied should be appropriately trained and qualified and be suitable and competent to perform the task assigned to them.
- All data generated during the course of studies should be formally reviewed and certified as evaluated against pre-determined criteria.
- Suitable testing facilities, equipment, instruments and methodology should be available.
- The process should be revalidated at intervals; and Comprehensive documentation should be available to define support and record the overall validation process.

6. Scope of Validation [13]

Pharmaceutical Validation is a huge area of work and it is practically covers every aspect of the pharmaceutical processing activities, hence explaining the Scope of Validation becomes a really hard task. However, an organized look at the pharmaceutical operations will point out at least the following areas for the pharmaceutical validation:-



7. Validation Master Plan [16, 17, 18]

A Validation master plan is the document that contour the company's overall philosophy, purpose and approaches to be used for starting performance adequacy. Validation in general need careful preparation and meticulous planning of the various steps in the process. In addition, all work should be carried out in a planned way according to formally allowed standard operating procedures (SOP). All inspection must be documented and all possible observations must be recorded as actual numerical results. The validation master plan should issue an outline of the complete validation operation, its organizational structure, its content and its planning. It should be a summary document and it should therefore be brief, concise and understandable. It should not replicate the information document but should refer to existing documents such as the policy documents, SOP's and validation protocols and reports.

The format and the content should include all these things:

1. Introduction: validation policy, scope, location and schedule.
2. Organizational structure: personnel responsibilities.
3. Plant/process/product description: rational for inclusions or exclusions and extent of validation.
4. Specific process considerations that are critical and those requiring extra attention.
5. List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach.
6. Type of validation procedures employed.
7. Re-validation activities, actual status and future planning.
8. Key acceptance criteria.
9. Documentation format.
10. Reference to the required SOP's.
11. Time plans of each validation project and sub-project.

8. Phases in Validation [19, 20, 21]

It consist of three phases:

- **Phase 1:** This is the Pre-validation Qualification Phase in which it covers all the venture relating to the result research and its development, formulation, pilot batch studies, scale-up studies, and transfer of technology to commercial scale batches, begin stability conditions its storage, and handling of in-process and finished product, Equipment qualification(EQ), Installation qualification(IQ), Master production document, Operational qualification(OQ) and process capacity.
- **Phase 2:** It is designed to verify that all accepted limits of the censorious process parameter are sustainable and that adequate products can be produced even under the drub conditions.
- **Phase 3: T**hird phase is also known as the Validation Maintenance Phase, this phase requires often review of all the process related documents, including validation of audit reports, to assure that it have been no changes, deviations, failures and modifications to the production process and that all the standard operating procedures (SOPs), including change in control procedures, it have been followed. At this stage, the validation team compare each individuals representing all the major departments which assures that there have been no changes/deviations that have been resulted in re-qualification and re-validation. An alert design and validation of the systems and process controls can accept high degree of confidence that all lots or batches manufacture will encounter their particular specifications. It is supposed that through the assembling and control operations which are conducted in the accordance with the principle of Good Manufacturing Practice (GMP) both in general, in specific reference to sterile product manufacture.

9. Types of Validation [22, 23]

9.1 Analytical Validation

Analytical validation is the procedure and it is the process which is accepted by laboratory studies, that the performance characteristics of the method encounter the necessity for its deliberate use. All the Analytical methods which are intended to be used for examine any clinical samples which will need to be validated. Validation of analytical methods is an essential but it is time - consuming work for most of the analytical development laboratories. It is important to understand the need of this method in validation more detail and the options which are available to permit for optimal utilization of analytical resources in a development laboratory.

Why to Validate Analytical Procedures

Analytical Procedure is validated because, these are are regulatory requirements, good science, and the quality control requirements. The Code of Federal Regulations (CFR) 311.165c explicitly states that its accuracy, sensitivity, specificity, and reproducibility of the methods conducted by this organization must be established and documented. Management of the quality control unit would surely want to ensure that the analytical procedure that the department need to emancipate its products are properly validated for its use so that the product will be safe for the human use.

Methods should be validated when:

- It need to be established for routine use.
- The procedure is changed due to change in conditions.
- Whenever it is required to identify between new method and the standard are demonstrated.

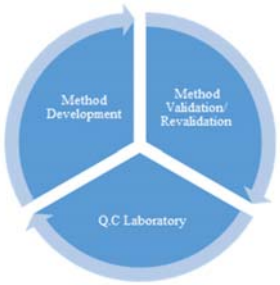


Fig 1: Life Cycle of Analytical Method

9.2 Cleaning Validation

Cleaning validation is the important process of assuring that cleaning procedures successfully remove the remaining part from manufacturing instruments, Cleaning validation is mainly applicable to the cleaning process and manufacturing equipment in the pharmaceutical industry. The term cleaning validation is used to describe that analytical examination of a cleaning procedures. It should also explain that the development of acceptance criteria, along with chemical & microbial specifications such as limit of detection & the selection of sampling methods.

The reasons for validating the cleaning procedure

1. It is a need of customer.
2. It safe guard the purity of the product.

3. It is one of the regularity requirement in active pharmaceutical ingredient for product manufacture.
4. Pharmaceutical products and API can be corrupted by other pharmaceutical products, cleaning agents & microbial contamination. The aim of the cleaning validation is to confirm the efficacy of the cleaning procedure for the eradication of product residues, degraded products, preservatives, excipients and cleaning agents as well as the control of potential microbial contamination.

9.3 Equipment Validation
Validation of the equipment is known as the qualification. Equipment validation is split into Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and the Performance Qualification (PQ). A DQ document mark the customer requirements, regulatory compliance and selection rationale of an individual supplier. An IQ documents specify static credit of a facility or an item to verify that the installation of the unit has been accurately performed and the installation specifications of the producer have been met. After installation it should be confirmed that the equipment can deliver operating ranges as given in the purchase order. This definition is called OQ. The PQ are concerned with proving that the process is being investigated and the works as it is supposed to do.

9.4 Process Validation [24, 25]
Process Validation is a documented program which provides a huge degree of assurance that a definite process will always produce a product contest its predetermined specification and quality attribute. Process validation can be split into four types:

9.4.1 Prospective Validation
It is explained as the accepted documented proof that a system does what it claims to do based on a pre-planned agreement. This validation usually carried out initial to distribution either of a new outcome or a product made under a amend manufacturing process. Performed on at least thrice successive production-sizes (Consecutive batches).

9.4.2 Retrospective Validation
It is explained as the accepted documented proof that a system does what it claims to do based on evaluation and analysis of historical data. This is attain by the review of the historical manufacturing testing data to demonstrate that the process has been always remained in control.

9.4.3 Concurrent Validation
Concurrent Validation is alike to prospective, except the operating firm would sell the product during the qualification race, to the public or at its market price. This validation require in process monitoring of critical processing steps and product testing. It is the recapitulation of a validation process or a particular part of it. This is carried out when there is some change or renewal in formulation, equipment, and plant or its site location.

9.4.4 Revalidation
Revalidation is complete when there is a change in a batch size and in the case of a sequential batches that do not connect product and process specifications. Re-validation give the proof that changes in a process and the process environment that are launch, do not adversely influence process characteristics and product quality. Documentation requirement will be same as of the initial validation of the process.

9.4.5 Change Control
Process validation of a solid dosage form will include an SOP to review a process whenever there are notable changes in the process, equipment, facilities, reactants, process materials, systems etc that may affect the critical quality assign and specification of the solid dosage forms. All changes should be formally requested, documented and suggested changes were scientifically evaluated and, depending on changes, the requirement of revalidation will be determined

10. Elements of Validation [26, 27, 28]
10.1 Design Qualification (DQ)
The design qualification figure the key features of the system draw to address the costumer requirements, regulatory compliance and the selection rationale of a specific supplier. Awareness should be taken when keeping together a design qualification since it would have major effect on installation, operation and the performance qualification. The more function which are specified in design qualification, the more work need to be included in that of the Installation, operational and the performance qualification processes.

Table 1: Important DQ Consideration Include

1	GMP and regulatory requirements
2	Performance criteria.
3	Facility air flow, movement flow & pressure regimens.
4	Reliability & efficiency.
5	Commissioning requirements.
6	Construct ability & installation of equipment .

10.2 Installation Qualification (IQ)
Begin by the objective evidence that all key feature of the process equipment and ancillary system installation stick to the manufacturer's
accepted specification and that the recommendation of the dealer of the equipment are suitably considered.

Table 2: IQ Considerations Are

1	Equipment design features (i.e. material of construction clean ability, etc.)
2	Installation conditions (wiring, utility, functionality, etc.)
3	Calibration, preventative maintenance, cleaning schedules.
4	Safety features.
5	Supplier documentation, prints, drawings and manuals.
6	Software documented.
7	Spare parts list.

10.3 Operational Qualification (OQ)
Operational qualification is a sequence of tests that estimate the performance ability of the equipment. Operational qualification focuses on every equipment, rather than indicating performance capabilities relating to producing a specific product. Confirmed by objective evidence, process control limits and action levels which result in product that of all the predetermined requirements.

Table 3: OQ Considerations Include

1	Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
2	Software parameters.
3	Raw material specifications
4	Process operating procedures.
5	Material handling requirements.
6	Process change control.
7	Training.
8	Short term stability and capability of the process, (latitude studies or control charts).
9	Potential failure modes, action levels and worst-case conditions.
10	The use of statistically valid techniques such as screening experiments to optimize the process can be used during this phase.

10.4 Performance Qualification

Performance qualification is explained as the process to prove that the system is repeatable and always producing a quality product or in the other words the process to indicate that the instrument can attain requirement given in the design qualification. Accepted by objective evidence that the process, under anticipated conditions, always produces an end product which meets all predetermined requirements of the user.

Table 4: PQ Considerations Include

1	Actual product and process parameters and procedures established in OQ.
2	Acceptability of the product
3	Assurance of the process capability as established in the OQ.
4	Process repeatability, long term process stability.

10.5 Re – Qualification

Qualification or movement of equipment should follow acceptable review and authorization of the documented which change proposal through the change in the control procedure. This formal analysis should include reflection of re-qualification of the equipment. Little changes or changes having no direct collision on final or in-process product quality need to be handled through the documentation system of the preventive maintenance program.

11. Process Validation Decision

The following model may be useful in determining whether or not a process should be validated:

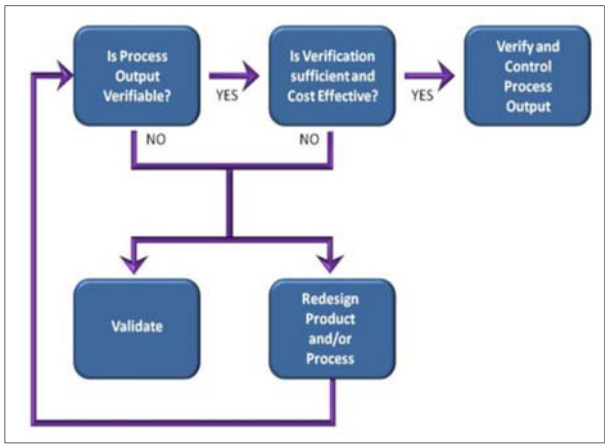


Fig 2: Process Validation Decision Tree

12. Stages of Process Validation [28, 29, 30, 31]

Process Validation is explained as the group and assessment of data, from the process design stage and between commercial production, which gives scientific confirmation that a process is capable of continually delivering quality product. Process Validation require a sequence of activities taking place over the lifecycle of the product and process. The venture relating to validation studies may be categorized into three stages:

Stage 1 – Process Design

"Focusing completely on qualification efforts without understanding the manufacturing process is explained during this stage build on knowledge obtained through development and scale-up activities. It is sees all activities understanding about product research and development formulation, scale-up studies, transfer of the technology, commercial scale batches, pilot batch studies, accepting stability conditions, storage and handling of the in-process and finished products, Equipment qualification, Installation qualification, Master production documents, operational qualification and process capability. Also this is the only stage in which the acceptance of a strategy for the process control is taking place using accumulation knowledge and also the understanding.

Stage 2 – process Qualification

During this stage, the process design is judged to determine weather the process is efficient of reproducing commercial manufacturing. It approve that all the accepted limits of the Critical Process Parameters need to be valid and that too as a satisfactory products and can be produced even under worst conditions. GMP acquiesce procedures must be followed in the particular stage and successful completion of this stage is important before any commercial distribution of the product. There are two types of process qualification:

Table 5: Design of Qualification and Facilities of Equipment and Utilities

1	Proper design of manufacturing facility is desired under 21 CFR part 211, subpart C, of the CGMP regulation on Buildings and Facilities.
2	Activities performed to assure proper facility design and that the equipment and utilities are suitable for their intended use and perform properly.

Table 6: Performance of Process Qualification

1	On the basis of process performance measure that allow for a science and risk established decision about the ability of the process to always produce quality products.
2	Part of the planning of the two stages involves interpret performance criteria and determining what data to collect when, how much data, and appropriate analysis of the data.
3	Likely consist of planned comparisons and evaluations of some combination of process measures as well as in-process and trial product attributes.
4	Manufacturer should scientifically determine acceptable criteria and justify it.
5	Objective measures, where possible.

Stage 3 – Continued Process Verification [47, 48, 49]

On-going assurance is obtained during procedure production that the process remains in the state of control. The validation of periodic repair stage needs frequent appraisal of all process related documents, as well as validation audit reports to assure that where have been no changes, deviations, failures,

modifications to the production process, and that all SOPs have been superseded, including change in control procedures. A fruitful validation program rest on the knowledge, understanding and the approach to control industrial processes. These include the source of variation, the limitation of the finding of the variation, and the qualities liable of the variation.

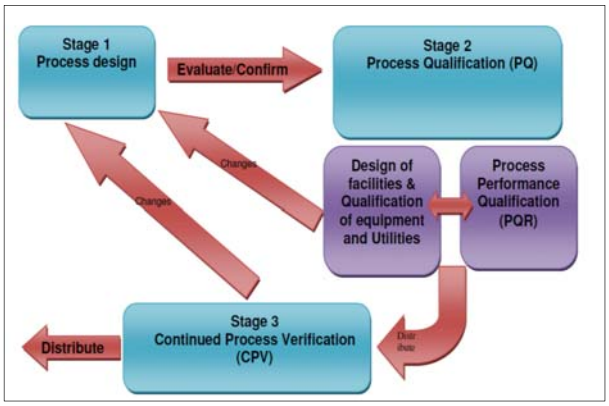


Fig 3: Three Model of Process Validation According to FDA Guidance for Industry – Process Validation

13. Reason for Process Validation [42, 43, 44]

The reason of process validation it may include:

New product or existing products as per SUPAC changes:

1. 1.Change in site of manufacturing.
2. Change in batch size.
3. Change in equipment.
4. Change in process existing products.
5. Change in composition or components.
6. Change in the critical control parameters.
7. Change in vendor of API or critical excipient.
8. Change in specification on input material.
9. Abnormal trends in quality parameters of product through review during Annual Product Review (APR).
10. Trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.

14. Advantages of process validation

1. Enlarge real time monitoring and modification of process.
2. Enlarged skill to statistically assess process performance and product variables. e.g., individuals; mean; range; control limits.
3. Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
4. Improved ability to set target parameters and control limits for routine production, correlating with validation results.
5. Enhanced reporting capability.

15. Responsibility Department and their Responsibility for Process Validation [45]

The validation working party is convened to define progress, coordinate and ultimately, approved the entire effort, including all of the documentation generated. The working party would usually include the following discipline members, preferably those with a good insight into the company's operation.

Table 7: Responsibility

Department or Designee	Responsibility
Third Level of Process Engineer	Prepare and review the validation protocol. Succeed regarding the Title, Market, Batch Size, Report no, Batch details, Product details, Reference documents.
Second Level of Process Engineer	Responsible for execution of process validation batch. Protect the information concerning reason for validation, product specification & receiving criteria, measuring device used, batch production details, in-process characteristics, validation data, results & conclusion.
First Level of Process Engineer	Review validation protocol and clarify validation report. Also ensure that batches are executed as per the plan and approved protocol. Prepare periodic revalidation calendar.
Validation	Review validation protocol and certify validation report. Review periodic revalidation calendar.
2nd level of Quality Assurance Manager	Control for withdrawing sample as explained in the validation protocol. Analysis the protocol with respect of sampling plans and procedure, validation sample Examination results. Responsible for analysing the samples as per explained in specification details in the agreement and responsible for analysis and approval of validation protocol and confirm validation report.
Head (Engineering)	Analyse the equipment and the area which is perfect for working condition as required need to certify the above in validation agreement and validation report.
Manager Operation	Analyse and safeguard that the information concerning the batch details, finished product details, pack details of the input material, equipment which are used, batch fabrication details, in-process characteristics, yield monitoring, result and conclusion.
Authorised Regulatory Person	Analyses the batch details, product details, pack details of input material with deference to the regulatory essential and accepted record in case of commercialized products in the validation agreement and certify the validation report.
Head (Quality Assurance)	Accept the validation agreement for application and attest the validation report.

16. Applications of Validation [46]

16.1 Reduction of quality cost

Through proper validation, cost of the following procedures can be optimized.

a) Preventive costs are costs incurred in order to prevent failure and reduce appraisal costs.
b) Appraisal costs of inspection, testing and quality evaluation.
c) Internal failure costs.
d) External failure costs that associated with a non-conformance condition after the product had left the company‟s ownership.

16.2 Process Optimization

The development of the facility, equipment system, closures etc. results in a product that encounter quality necessities at the lesser costs. Trained and qualified personnel's are the key elements in the process optimization that results in upgrading

efficiency and productivity.

16.3 Assurance of quality
Validation and the process control are one of the important protocol of GMPs. Without validation and controlled process it is impossible to attain quality products. Hence validation is a key element in assuring the quality of the product.

16.4 Safety
Validation can also result in increased operator safety. Properly standardized, validated instruments and devices used to reduce accidents and results in safety. Validation can also result in the increase in operation safety. e.g. instruments used on equipment that intended to operate at certain temperature and pressures must be dependable i.e. They need to be calibrated.

16.5 Better consumer quality
Through proper validation, market recall is evaded which results in better consumer care and quality of the product.
Quality costs are divided in to four categories. They are:
1. Preventive costs.
2. Appraisal costs.
3. Internal failure costs.
4. External failure costs

validated and controlled process will result in rarer internal failures like:
a) Fewer rejects
b) Reworks
c) Re-tests
d) Re-inspection

Process validation create it is likely to do the job right for the first time. Also, a systematically studied and controlled process makes it doubtful that defective products need to be dispatched to market thus no recalls or market criticisms.

17. Approaches to Validation Process [48]
There are two elementary methods to the validation of this process. These two are the experimental approach and the other approach is based on the analysis of ancient data. The experimental approach, which is applicable in both prospective and the concurrent validation, it may involve:
A) Extensive product testing,
B) Simulation process trials,
C) Challenge/worst case trials, and
D) Control of process parameters

In the method found on analysis of ancient data, no experiments are performed in the retrospective validation, but instead of all available ancient data regarding a number of groups are combined and together analysed, if production is happening easily during the period of previous validation and the data in process examination and final testing of the product are joint and preserved statistically. The consequences including the result of process ability studies, trend analysis, etc will designate whether the process is beneath control or not.

18. The Validation Report [50]
A written report need to be obtainable after conclusion of the validation. If found satisfactory, it need to be accepted and certified (signed and dated). The report need to include at least the following
1. Title and objective of study
2. Reference to protocol
3. Details of material
4. Equipment;
5. Programmes and cycles used;
6. Details of procedures and test methods;
7. Results (compared with acceptance criteria); and
8. Recommendations on the limit and criteria to be applied on future basis.

19. Conclusion
It is essential, before acceptance of a new drug, that an exact and dependable assessment for its success and safety for the future suggestion and target patient population is confirmed. This review often summaries the values and methods that is considers a suitable elements of process validation for the formation of drugs, including active pharmaceutical ingredients (APIs or drug substances), collectively mentioned to as drugs or products. The cGMP regulation needs that manufacturing processes be intended and controlled to assure that in-process resources and finished product encounter determined quality necessities and do so regularly and reliably. Quality assurance techniques need to be used to build the quality into the product in every step and not just verified at the end. Process validation includes a sequence of activities taking place over the lifecycle of the product and process. In general, pharmaceutical validation and process control provide a positive assurance of batch consistency and integrity of the product manufactured.

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