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VALIDATION

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ABSTRACT

Validation is the process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in testing and then production maintains the desired level of compliance at all stages. Validation has been proven assurance for the process efficiency and sturdiness and it is the full-fledged quality attributing tool for the pharmaceutical industries and making different type dosage form and solution. Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked with process monitoring, sampling and testing.

INTRODUCTION

Validation is the process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in testing and then production maintains the desired level of compliance at all stages. Validation is a tool for total quality management and ensures always product of best quality. The validation in case of sterile product monitors safety and efficiency of the product.[1]

In the pharmaceutical industry, it is very important that in addition to final testing and compliance of products, it is also assured that the process will consistently produce the expected results. The desired results are established in terms of specifications for outcome of the process. Qualification of systems and equipment is therefore a part of the process of validation. Validation is a requirement of food, drug and pharmaceutical regulating agencies such as the US FDA and their good manufacturing practices guidelines. Since a wide variety of procedures, processes, and activities need to be validated, the field of validation is divided into a number of subsections including the following: Equipment validation, Facilities validation, HVAC system validation, Cleaning validation, Process Validation, Analytical method validation, Computer system validation.[1]

The validation scope, boundaries and responsibilities for each process or groups of similar processes or similar equipment's must be documented and approved in a validation plan. These documents, terms and references for the protocol authors are for use in setting the scope of their protocols. It must be based on a Validation Risk Assessment (VRA) to ensure that the scope of validation being authorized is appropriate for the complexity and importance of the equipment or process under validation. Within the references given in the Validation Protocol (VP), the protocol authors must ensure that all aspects of the process or equipment under qualification; that may affect the efficacy, quality and or records of the product are properly qualified.[2]

The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in 1979 in USA, to improve the quality of pharmaceuticals. It was proposed in direct response to several problems in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes including environmental control, media fill, equipment, and sanitization and purified water production.[2]

FDA, or any other food and drugs regulatory agency around the globe not only ask for a product that meets its specification but also require a process, procedures, intermediate stages of inspections, and testing adopted during manufacturing are designed such that when they are adopted they produce consistently similar, reproducible, desired results which meet the quality standard of product being manufactured and complies the Regulatory and Security Aspects. Such procedures are developed through the process of validation. This is to maintain and assure a higher degree of quality of food and drug products.[3]

Importance of validation [4]

- Quality assurance and cost reduction
- Validation produces a product fit for intended use

- Key element in assuming the quality of the product
- Determine the worst case and risks that may arise during manufacturing of product
- Helps to investigate the deviations caused during the process
- Deep study and understanding of the system and equipment are made possible
- The risk of regulatory non-compliance is minimized
- Batch to batch variation is minimized
- Reduces production cost of the product
- Increases the production of manufacturing facility due to the minimized rework and rejection
- Decreases the chances of the failure of batches
- Regulation of all raw materials and production procedures as well as testing of final product
- Process parameters and controls are determined

Types of validation[2,5,6,7]

1. Prospective Validation
2. Retrospective Validation
3. Concurrent Validation
4. Re-Validation

❖ **Prospective validation**

Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps. These are then evaluated on the basis of past experience to determine whether they might lead to critical situations. Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. Prospective validation includes the division of the production process into separate steps, and the analysis of potentially critical points in the manufacturing process. Example: mixing times, or temperature. Before prospective validation can take place, the following requirements are need to be satisfied:

- The facilities and equipment must be qualified.
- The operators running must have an understanding of the process.
- The design and optimization must be completed.
- The pilot laboratory batches must be completed.
- Product stability information is available.
- At least one pilot batch has been completed which shows no significant deviations from the expected performance of the process.

Retrospective validation

Retrospective validation is establishing documented evidence that a process does what it is supposed to do based on review and analysis of historic information.

Retrospective validation is the validation of older/legacy products, processes, or equipment's.
Steps require for validation:

- Protocol preparation
- Validation reports
- Data analysis
- Conclusion
- Recommendations

Retrospective validation is conducted for a product already being marketed and is based on extensive data accumulated over several lots and over time.

Retrospective validation is used for facilities, processes and process control parameters used in operation that have not undergone in documented validation process. Validation of these facilities, processes and process control parameters is possible using historical data (Quality Assurance/Quality Control records) to provide the necessary documented evidence that the process is doping what is believed to do.

❖ **Concurrent validation**

Concurrent validation is a process where current production batches are used to monitor processing parameters. Concurrent validation gives of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch.

The first three production-scale batches must be monitored as comprehensively as possible. The nature and specifications of subsequent in-process and final tests are based on the evaluation of the results of such monitoring. Concurrent validation together with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product.

Concurrent validation is used to establish documented evidence that a facility and process will perform as they are intended, based on information generated during actual use of the process.

Extensive testing and monitoring ensure the desired quality characteristics of product with high degree of confidence.

Revalidation

Revalidation is needed to ensure that the changes in the process and/or in the process environment, whether intentional or unintentional, do not adversely affect the process characteristics and product quality.
Revalidation is divided into two broad categories:

- Revalidation after any change having a bearing on product quality.
- Periodic evaluation carried out at scheduled intervals.

❖ **Equipment validation**[8]

Whenever new equipment is procured the Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Quality (PQ) is done by QA to establish that the equipment does what it is supposed to do. All the equipment's are

validated as per the pre-determined schedule for validation.

❖ **Cleaning validation**[8]

The objective is to minimize the possibility of significant cross contamination.

The three sampling methods are in general use and they are:

1. Swabs
2. Rinses
3. Placebos

This is establishing documented evidence that the cleaning procedure does what it is supposed to do based on the analysis of the rinse/swab sample. The equipment is cleaned as per the SOP. The rinse samples are collected and analyzed as per validated QC procedure. The experiments are carried out on three product changeovers.

❖ **Personnel validation**[8]

This is documented evidence to show that no contamination occur due to a person.

The source of particulate matter and microbial contamination is due to the personnel involved. The personnel should be validated in the following:

1. Growing validation
2. Medical examination
3. Personnel concerned are trained

Process validation protocol[9]

According to WHO, process validation is defined 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 **Process validation requirements**

A manufacture should evaluate all the factors that affect product quality when designing and undertaking a process validation style. These factors may vary considerably among different products and manufacturing technologies and could include, for example, component specification, air and water handling systems, environmental controls, equipment functions and process control operations. No single approach to process validation will be appropriate and complete in all cases; however, the following quality activities should be undertaken in most situations. [9]

During the research and development phase, the desired product should be carefully defined in terms of its characteristics, such as physical and chemical characteristics and in terms of its performance. It is important to translate the product characteristics into specifications as a basis for description and control of the product. [9]

Process validation protocol[10]

(Reference: SOP_____)

Note 1: The initial mixing time of granulations must be 5 minutes. Rotation speed is not variable.

Note 2: Pre-blending time of raw materials must be 10 minutes. Rotation speed is not variable.

Note 3: Blending mixing time must be 30 minutes. Rotation speed is not variable. Note 4: The mixing time of blend must be 10 minutes. Rotation speed is not variable. Note 5: The mixing time of blend must be 20 minutes. Rotation speed is not variable. Note 6: Ensure that Talc and Magnesium stearate are sieved just prior to addition to blender 1.

Note 7: The final mixing time of blend must be 5 minutes. Rotation speed is not variable.

Approaches to process validation[11]

- Process validation involves a series of activities taking place over the lifecycle of the product and process. Process validation activities are described in three stages.

Stage 1 – Process design

Process Design stage is the research and development phase and involves defining a process for manufacturing the product. It usually includes the following:

- Creation of a Quality Target Product Profile (QTPP)
- Identifying Critical Quality Attributes (CQAs) Defining Critical Process Parameters (CPPs)
- Conducting risk assessments

Stage 2 – Process validation or process qualification

Process Validation or Process Qualification stage evaluates/qualifies the process designed earlier to ensure it can reproduce consistent and reliable levels of quality. Process Validation or Process Qualification involves collecting and evaluating data on all aspects and stages of the manufacturing process. This includes:

- The building and facilities, i.e. ensuring they adhere to local regulations as well as pharmaceutical manufacturing regulations
- The transportation and storage of raw materials
- The knowledge, training, and working practices of production line employees
- Every step of the process to turn raw materials into the finished product. This includes having pre-defined sampling points at various stages of the process.
- Finished product packaging, storage, and distribution. Another useful component of this stage of Process Validation is to develop contingency plans for situations where things go wrong.

Stage 3 – Continued process verification

Continued Process Verification involves on-going validation during production of the commercial product to ensure the process designed and qualified in the previous stages continues to deliver consistent quality. One of the main aims of this stage is to detect and resolve process drift. The stage involves product

sampling, analysis, and verification at various points in the manufacturing process, and requires the involvement of employees with quality control training. Again, comprehensive record-keeping is required at this stage, including logging anomalies and issues with product quality.

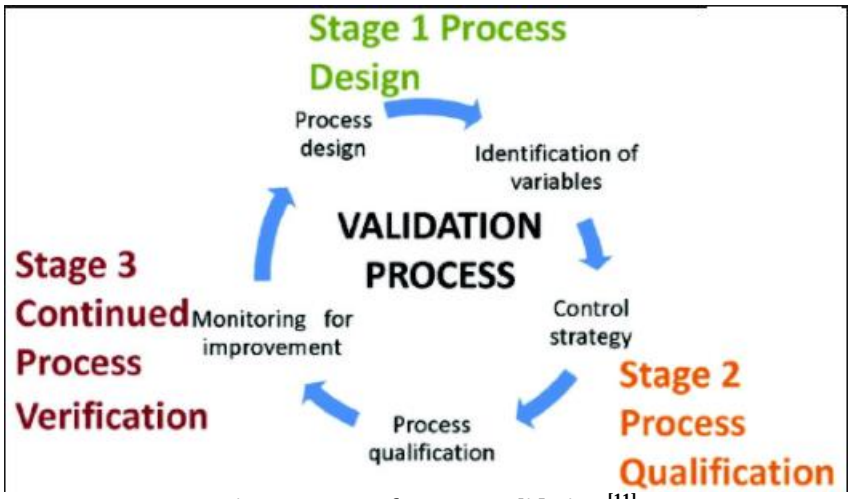

Fig. 1: Stages of process validation. [11]

Process validation of tablet and critical parameters [12]

Table 1: Identification of Critical Tableting steps.

Process step	Physical/Chemical step	Parameters	Criticality
Tableting	Compression of blend into tablets	Machine speed	Critical
		Main compression force	Critical *Note 1
		Pre-compression force-Bottom	Critical *Note 1
		Pre-compression force-Top	Critical *Note 1
		Thickness setting	Critical *Note 1
		Fill Depth setting	Critical *Note 1
		Feeder speed	Critical *Note 1

Table 2: Identification of critical coating steps.

Process / Step	Physical/Chemical step	Parameters	Criticality
Table coating	Coating of tablet with specified coating solution	Machine speed	Critical
		Spray rate	Critical
		Spray pressure	Critical
		Gun to bed distance	Critical
		Gun to gun distance	Critical
		Temperature	Critical
		Air volumes	Critical

Regulatory requirement for the processvalidation [13]

- The first current Good Manufacturing Practices (cGMP) regulations based largely on the Pharmaceutical Manufacturers Association's manufacturing control guidelines.
- Validation under document cGMP covers procedure, process qualification, equipment and facilities.
- According to WHO (World Health Organization) cGMP guidelines, validation studies are an essential part of current good manufacturing practice (cGMP) and should be conducted in accordance with predefined protocols.

As per WHO, validation is defined as the documented act of proving any procedure, process, equipment, material, activity or system which actually lead to the expected results. [13]

According to EU, Validation is a 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.[13]

EU (European Union) and PIC (Pharmaceutical Inspection Convention) GMP guidelines: - Formally authorised Manufacturing Formula and Processing Instructions should exist for each product and batch size

to be manufactured. They are often combined in one document. [13]

Health Canada GMP guidelines:- MASTER FORMULA (formula-type) – A document or set of documents specifying the raw materials with their quantities and the packaging materials, together with a detailed description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls. [13]

US CFR(United States Code of Federal Regulations): - To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person.

Master manufacturing documents[14]

- Master manufacturing record is also called as master formula record (MFR) or master production record.
- Master manufacturing record is a master document for any pharmaceutical product contains all information about the manufacturing process for the product.
- Master manufacturing record is a document or set of documents specifying the starting material with their quantities and packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including in- process controls.[14]

MFR should include

- Product details
  - Name, logo and address of the manufacturing company
  - Dosage form name
  - Brand name
  - Generic name
  - Product code
  - Label claim of all ingredients
  - Product description
  - Batch size
  - Pack size and packing style
  - Shelf life
  - Storage conditions
  - MFR number and date
  - Supersede MFR number and date
  - Effective batch number
  - Authorisation by the production and Quality Assurance head
  - Flow chart
- API/Excipient Details
  - A list of all starting materials to be used [if applicable, with the INN**s** **(**International Nonproprietary Names)]
- Equipment
  - A statement of the processing location and the principal equipment to be used
  - The methods
  - Reference to the methods
  - To be used for preparing and operating the critical equipment
  - E.g. cleaning (especially after a change in product)
  - Assembling
    Calibrating
  - Sterilizing
  - Use
  - Yield

SOP for preparation of master formula record[15]

Objective

To describe the procedure for preparation of Master Formula Record.

Scope

This SOP applies to the preparation of Master Formula Record.

Responsibility

Production Pharmacist
Quality Assurance Officer

Accountability

Production Pharmacist
Manager Quality Control
Manager Quality Assurance

Procedure

Production Department in association with F&D, shall prepare Master Formula Record (MFR).
Master Formula Record (MFR) shall be divided into two parts

- Manufacturing part
- Packaging part
  The first page of both Manufacturing part and Packaging part shall have following details:
- Name, Address and Logo of the Company
- Dosage Form
- Brand Name
- Generic Name
- Product Code
- Label claim
- Product description
- Batch Size
- Pack size
- Shelf life
- Storage condition
- Drug schedule: Whether schedule "H" or schedule "G" drug
- Reference of change control number
  There shall be authorization on all pages of Master Formula Record (MFR) by three persons:
- Production Pharmacist Production Manager
- Quality Assurance Manager

All the three persons will sign off all the pages. Their designation and their name will be printed below their signatures along with the date of signing the document.

The second page of manufacturing section shall include:

- Subsequent pages shall include the processes to be monitored
- The stage-wise movement of the material in a form of flowchart
- The flow chart shall cover all activities beginning from the dispensing of the materials and ending at the transfer of a batch to finished stores
- The list of equipment, machines, utensils to be used, shall be described
- The subsequent page shall include any special precautions to be taken for the product during manufacturing and packing. The same page should also include Batch Manufacturing Formula.

The batch formula should have following columns:

- Serial number
- Name of ingredients
- Reference of the specification of ingredients
- Quantity to be added
- Overages to be added (in %)
- Quantity to be added per batch or per lot
- Calculation steps for every active material, ensuring that the active materials shall be compensated for assay values less than 100 % which could be due to less potency or higher moisture content
- Written process stage wise and stepwise. At the end of every important stage, calculate yield with acceptable limits
- In-process quality checks at every important step with their limits
- The process shall include the process equipment's, methods or the reference of the methods/ procedures to be employed for preparing, cleaning, assembling, operating the various equipment shall be given:

✓ Detailed stepwise processing instructions
✓ Checks on materials
✓ Pre-treatments
✓ The sequence for adding materials
✓ Mixing times
✓ Temperatures and humidity etc.
✓ Requirements for storage conditions of the products

The packing part of Master Formula Record (MFR) should include:

- A complete list of all the packaging materials required for a standard batch size including quantities, sizes and types.
- Line clearance checking during batch coding and batch packing operations
- Reconciliation of printed and unprinted packing materials with acceptable limits
- Destruction of excess or rejected printed packing materials
- Description of packaging operation including any significant subsidiary operations and equipment to be used
- Details of in-process controls with instructions for sampling and acceptance limits.
- Reconciliation of the packing yield with acceptable limits.
- Finally include batch release procedure.

Validation master plan[16]

- Validation master plan is a document, which describes a company's intentions and the method which are related with validation of the equipment's, instruments, systems, utilities, facilities, materials, analytical methods and processes.
- Validation program is designed to demonstrate that the facility for the production up to final stage of production of different dosage forms is capable of meeting the process parameters in a repeatable and controllable manner.
- Validation Master Plan ensure that validation activities are carried out a per respective protocols and after completion will determine whether the equipment, system, process and methods:

➢ Meets the specifications of its design.
➢ Suitable for its intended applications.
➢ Confirm to the basic cGMP design criteria.
➢ Will satisfy the regulatory requirements.
➢ Meets safety requirements as applicable.
➢ Is capable of consistently producing a product that is fit for use.

The critical utilities, equipment & process validation program are established in accordance with the methods and procedures maintained by the product requirements which are based on the currently available product information and the Current Good Manufacturing Practices, guidelines and other regulations.

Scope of validation master plan[17]

- The scope of this document is to describe the systems and methodology used to execute the various phases of the validation program.
- Validation Master Plan applies to all critical equipment's, instruments, procedures, utilities, facilities and other quality supporting systems used for manufacturing, processing, testing, labelling, and packaging which may affect the quality of product directly or indirectly.
- Validation master plan applies methodology of validation program of following,

➢ Facilities
➢ Equipment / Instruments system {Qualification}
➢ Utilities (eg: HVAC, water system, pure steam and compressed air)
➢ Control systems (eg: computer hardware and software)
➢ Manufacturing processes
➢ Cleaning processes
➢ Analytical methods

- Environmental (physical & microbiological)
- Personnel (eg: analysts, checkers on inspection or packing line).

Importance of validation master plan[17]

- Validation Master Plan is not a requirement of the Food and Drug Administration (FDA), but it has become almost an industry standard.
- It is important to include such a document, as it sets the overall goals and limits that will be followed during validation, and can be referred to throughout the project.
- As a reference document, the plan permits the reviewer immediately to understand the scope of the validation and so avoid misconceptions.
- The validation plan is thus used to set the limits of the validation, to define the scope of the project, the systems included and not included in the qualifications, and what the project will attempt to prove.

Contents of validation master plan[18]

1. Introduction
2. Methodology
3. Qualification- DQ IQ OQ PQ
4. Personnel
5. Schedule
6. Preventative maintenance
7. Change control.
8. Procedure
9. Documentation

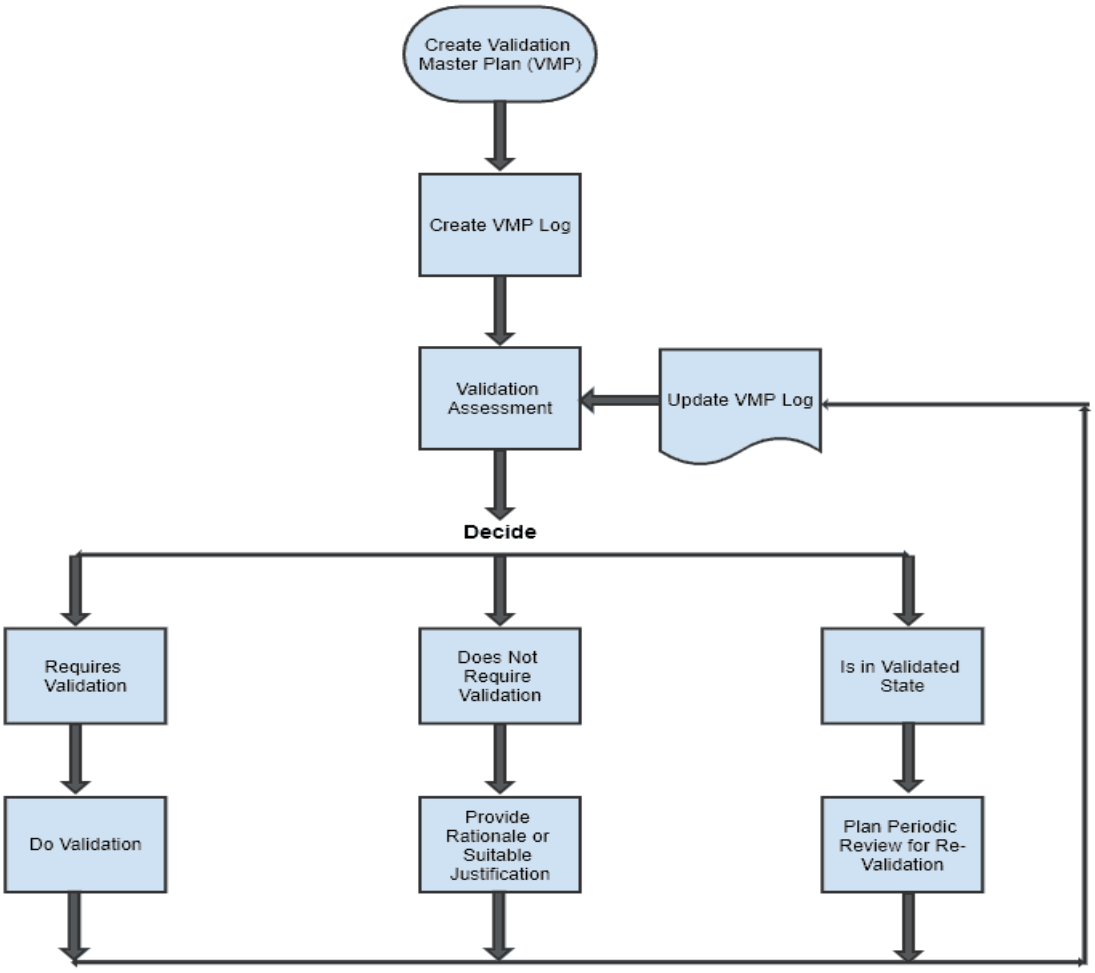

Fig. 2: Process validation master plan.[19]

ICH AND Who guidelines for validation of equipment[20]

Equipment

- Equipment may be defined as a physical entity which is used to carry out a general or specific activity in the plant.
- Equipment can be;

-Single piece, for example; tablet compression machine, HPLC, FTIR, weighing balance.

-Integrated system for example; water demineralizing plant, an air handling system.

ICH guidelines for validation of equipment's

- 1 meter distance from walls and other obstacles.
- Easy to operate, clean and maintainable
- Working should be at proper commissioned position

- Certification of equipment
- Checking of overhead heights
- Proper source of light
- Drop down utility system
- Design of equipment
- Layout of equipment
- Marking of pipe lines as per their flow of direction
- SOP of equipment
- Tracing of equipment
- Identification marking for equipment
- Cleaning of equipment
- Distinguishing between the equipment
- Record of each processing

WHO guidelines for validation of equipment's[21]

- Equipment must be located, designed, constructed, adapted and maintained to suit the operation
- Layout and design of equipment
- Cleaning of equipment
- Labelling of equipment
- Establishment of written procedures for each operation
- Record keeping

Process validation of ibuprofen tablet

Ibuprofen is a NSAID that is used for treating pain, fever, and inflammation.

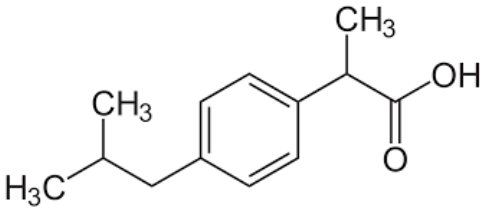

***Fig. 3: Structure of Ibuprofen.*[22]**

Materialsand methods[23]

Prospective process validation was performed on the three batches of Ibuprofen film coated tablet.

The three consecutive batches were labeled as (Batch A, Batch B, Batch C)

Materials used	Equipment's and Instruments
Ibuprofen	Vibratory sifter with 20 & 40 sieves
Lactose	High shear rapid mixer granulator
Maize starch	Octagonal blender
Sodium methyl paraben	Double rotary tablet
Sodium propyl paraben	Compression machine with punches
Magnesium stearate	Coating pan
Talcum powder	Blister packing machine
Colloidal silicone dioxide	Moisture analyzer
Stearic acid	Weighing balance

Methods

Validation Procedure

i. Three batches of 5, 15,000 tablets to be manufactured as described in the batch manufacturing record.
ii. Current version of standard operating procedures needs to be followed.
iii. Record the observations at compression stage in the data sheets.
iv. Record the yield after coating.

- Manufacturing Process
- Sifting
  - Ibuprofen is sifted using 20# sieve while lactose, maize starch is sifted using 40# sieve.
- Dry Mixing
  - Mixture of above ingredients are allowed for mixing for 15 minutes at slow speed.
  - Binder preparation and addition
  - Add purified water in paste preparation kettle and boil it up to 90-100 ºC.
  - Dissolve Sodium Methyl Paraben and Propyl Paraben in it.
  - Dissolve Maize starch in purified water and make slurry.
  - Add this slurry into paste vessel with constant stirring and make lump free paste.
  - Allow paste to cool at room temperature
- Drying
  - Dry the whole batch in FBD at 45-55 ºC temperature for 60-80 min.
- Dry Milling
  - Check the integrity of 1.5 mm multi mill screen.
  - Pass the retained granules at medium speed and collect in double polybag placed in a container.
- Lubrication:
  - Sift Talcum powder, Colloidal silicone dioxide and stearic acid through 40# sieve and collect in a poly bag Then load the sifted materials into Octagonal Blender.
  - Load the milled granules into octagonal blender then after operate the blender for 30 min.

- Collect the lubricated granules in double poly bag in polyethylene lined containers.

➢ Compression

- Compress the granules as per following specifications. :

- Machine: rotary compression machine
- Punch: standard plain
- Diameter: 10.0 mm.

➢ Packaging

- Print batch no., mfg. date, exp. date
- Set roller temperature at 130-160 ºC and sealing temperature at 140-210 ºC
- Pack the tablets in foil, blister of 10 tablets by blister pack machine.
- Pack 10 tablets in overprinted carton.

Stages	Test to be performed
Dry mixing	Blend uniformity
Lubrication	%LOD
	Bulk density
	Tapped density
	Angle of repose
	Blend uniformity
	Assay for blend uniformity
Compression	Average weight
	Weight uniformity
	Thickness
	Disintegration time
	Friability
Packaging	Appearance of tablet
	Overprinting quality

REVIEW AND CONCLUSION

Validation is a preeminent constituent of quality assurance scheme of a particular process. Validation is regarded as the requisite component of Good Manufacturing Practices (cGMP).When such a technique is employed in examining each step of manufacturing process; it is referred to as Process Validation. It allows us to ensure that a given pharmaceutical process will produce quality products that meet its predetermined specifications. Process Validation focuses on process design elements and maintaining control over process during commercialization and communicates that process validation is an on-going program and align process validation activities with product lifecycle. Process Validation also accentuates understanding, identifying and control of variability.[2, 24]

The Pharmaceutical Process Validation is the most important and recognized parameters for in-process materials and finished product. The product should be designed robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Process validation involves a series of activities taking place over the lifecycle of the product and process.[11, 24]

Validation has been proven assurance for the process efficiency and sturdiness and it is the full-fledged quality attributing tool for the pharmaceutical industries and making different type dosage form and solution. Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked with process monitoring, sampling and testing. Apart from all the consistency and reliability of a validated process to produce a quality product is the very important for an industry. [25]

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