INTRODUCTION
The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus in the mid 1970’s in order to improve the quality of pharmaceuticals. Validation is the act of demonstrating and documenting that a procedure operates effectively. The U.S Food and Drug Administration (FDA) guidelines state that the process validation is the established documented evidence which provides a high degree of assurance that specific process. The validation protocol includes inventory control and equipment inspection in preliminary steps and in-process controls in subsequent steps. The purpose of setting validation parameters is to monitor the on-line and off-line performance of manufacturing process. Thus Validation is an integral part of quality assurance. Validation has become one of the pharmaceutical industry’s most recognized and discussed subjects. It is a critical success factor in product approval and ongoing commercialization. This review focus on need of validation, elements of validation, principles of Validation, types of validation, brief introduction on MDI includes uses, components, materials and manufacturing. Inhalation aerosols have been used for the delivery of drugs to the respiratory system since the mid-1950s. The most common dosage form for inhalation is the metered-dose inhaler (MDI), by which the drug is delivered from a pressurized container using a liquefied gas propellant. Inhalation is the convenient way to deliver drugs to respiratory tract in treatment of respiratory disease like ASTHMA. The process validation process parameters are derived from the specifications for the device, component or other entity to be produced by the process. The process is developed in such a way that the required parameters are achieved and it ensures that the output of the process will consistently meet the required parameters during routine production, the process is validated. A manufacturer can assure through careful design of the device, processes, process controls and packaging that all manufactured units will meet specifications and have uniform quality. However, in-process and finished product testing still play an important role in assuring that products meet specifications. Validation is defined as a 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. MDI is pocket-sized, hand-held, pressure multiple-dose inhalation delivery system. It delivers small, precisely measured therapeutic doses, greatly minimizing the risk of adverse side effects. A metered dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs in the form of a short burst of aerosolized medicine that is inhaled by the patient. Three consecutive batches of metered dose inhaler shall be taken up for process validation. Based on the results of all the 3 batches, suitable conclusions will be drawn with respect to the suitability of proposed method of manufacture for metered dose inhaler. This review covers need of validation, elements of validation, principles of Validation, Types of validation; brief introduction on MDI includes uses, components, materials and manufacturing.

KEYWORDS: Validation, Metered dose inhaler, Aerosols, consistent, Inhalation.

ABSTRACT
The purpose of this work is to present an introduction and general overview on process validation of Metered dose inhaler. The word validation simply means, “Assessment of validation or action of proving effectiveness”. The most common dosage form for inhalation is the metered-dose inhaler (MDI), by which the drug is delivered from a pressurized container using a liquefied gas propellant. Inhalation is the convenient way to deliver drugs to respiratory tract in treatment of respiratory disease like ASTHMA. The process validation process parameters are derived from the specifications for the device, component or other entity to be produced by the process. The process is developed in such a way that the required parameters are achieved and it ensures that the output of the process will consistently meet the required parameters during routine production, the process is validated. A manufacturer can assure through careful design of the device, processes, process controls and packaging that all manufactured units will meet specifications and have uniform quality. However, in-process and finished product testing still play an important role in assuring that products meet specifications. Validation is defined as a 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. MDI is pocket-sized, hand-held, pressure multiple-dose inhalation delivery system. It delivers small, precisely measured therapeutic doses, greatly minimizing the risk of adverse side effects. A metered dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs in the form of a short burst of aerosolized medicine that is inhaled by the patient. Three consecutive batches of metered dose inhaler shall be taken up for process validation. Based on the results of all the 3 batches, suitable conclusions will be drawn with respect to the suitability of proposed method of manufacture for metered dose inhaler. This review covers need of validation, elements of validation, principles of Validation, Types of validation; brief introduction on MDI includes uses, components, materials and manufacturing.

INTRODUCTION
The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus in the mid 1970’s in order to improve the quality of pharmaceuticals. Validation is the act of demonstrating and documenting that a procedure operates effectively. The U.S Food and Drug Administration (FDA) guidelines state that the process validation is the established documented evidence which provides a high degree of assurance that specific process. The validation protocol includes inventory control and equipment inspection in preliminary steps and in-process controls in subsequent steps. The purpose of setting validation parameters is to monitor the on-line and off-line performance of manufacturing process. Thus Validation is an integral part of quality assurance. Validation has become one of the pharmaceutical industry’s most recognized and discussed subjects. It is a critical success factor in product approval and ongoing commercialization. This review focus on need of validation, elements of validation, principles of Validation, types of validation, brief introduction on MDI includes uses, components, materials and manufacturing. Inhalation aerosols have been used for the delivery of drugs to the respiratory system since the mid-1950s. The most common dosage form for inhalation is the metered-dose inhaler (MDI), by which the drug is delivered from a pressurized container using a liquefied gas propellant. Quality is always an imperative prerequisite when we consider any product. Therefore, drugs must be manufactured to the highest quality levels. End-product testing by itself does not guarantee the quality of the product. A process validation protocol is a requirement as stipulated by the Current Good Manufacturing Practices Regulations for Finished Pharmaceuticals and is therefore applicable to manufacturing of drugs.

Validation should be considered in the following situation
- Totally new process
- New equipment
- Process and equipment which have been altered to suit changing priorities.
- Process where the end–product test is poor and an unreliable indication of product quality

Process validation is a establishing documented evidence, which provide a high degree of assurance that a specific process will consistently produce a product meeting its predefined specification and quality characterstics.

METERED DOSE INHALERS (MDI’S)
A metered dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs in the form of a short burst of aerosolized medicine that is inhaled by the patient. In MDIs, medication is most commonly stored in solution in a pressurized canister that contains a propellant, although it may also be a suspension. The MDI canister is attached to a plastic, hand-operated actuator Fig.1. On activation, the metered-dose inhaler releases a fixed dose of medication in aerosol form.

HOW TO USE METERED DOSE INHALER
The MDI is a pressurized canister of medicine in a plastic holder with a mouthpiece. When sprayed, it gives a reliable, consistent dose of medication.

When using a metered dose inhaler for the first time (with or without a spacer), prepare the inhaler first:
(a) Shake the inhaler for five seconds.
(b) Prime the inhaler by pressing down the canister with the index finger to release the medication. Hold the inhaler away from your face to prevent medication from getting into your
eyes. Press the canister down again 3 times. After an inhaler is used for the first time, it does not need to be primed again unless you do not use it for 2 weeks or more.

**ADVANTAGES**
- Portable and Compact
- Treatment time is short
- No drug preparation required
- No contamination of content
- Dose-dose reproducibility high
- Some can be used with breath actuated mouth-piece

**NEED OF VALIDATION**
- To reduce batch to batch variation
- To achieve reproducible products of same quality, purity & strength

**RESPONSIBLE AUTHORITIES FOR VALIDATION**

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

- Head of quality assurance
- Head of engineering
- Validation manager
- Production manager
- Specialist validation discipline (s)-all areas

**TYPES OF PROCESS VALIDATION**

**Prospective Validation**

This approach to validation is normally undertaken whenever the process for new formula must be validated before routine pharmaceutical production commences. It’s based upon existing & historical process data. Some of the essential elements for retrospective validation are:

- Batches manufactured for a defined period (minimum of 10 last consecutive batches)
- Number of lots released per year
- Batch size/strength/manufacturer/year/period
- Master manufacturing/packaging documents
- Current specifications for active materials/finished products
- List of process deviations, corrective actions and changes to manufacturing documents
- Data for stability testing for several batches

**Retrospective Validation**

It deals with performing the validation after production is already in market place. It’s based upon existing & historical process data.

**Concurrent Validation**

It’s nothing more than requalifying, revalidating or even recertification an ongoing process in response to a significant change in product components manufacturing, equipments, facilities, batch size or manufacturing procedure.

**Revalidation**

It means repeating the original validation effort or any part of it and includes investigation review of existing performance data. Revalidation criteria are given below:

- Major changes in the manufacturing process which may affect the quality of the product.
- Change in the Batch Size
- Change in the Batch Formula
- Change in manufacturing Location

**ELEMENTS OF VALIDATION**

**Design Qualification (DQ)**

It is documented review of the design, at an appropriate stage of stages in the project, for conformance to operational and regulatory expectations.

**Installation Qualification (IQ)**

It is documented verification that all aspects of a facility, utility or equipment that can affect product quality operate to approved specifications and are correctly installed.

**Operational Qualification (OQ)**

It is documented verification that all aspects of a facility, utility or equipment that can affect product quality operate to Intend throughout all anticipated ranges.

**Performance Qualification (PQ)**

It is documented verification that all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria.

**TYPE OF DOCUMENTATION FOR VALIDATION**

Validation Master Plan (VMP)
Validation Protocol (VP)
Validation Reports (VR)
Standard Operating Procedures (SOP)

**Validation Master Plan**

A validation master plan is a document that summarizes the company’s overall philosophy, intentions and approaches to be used for establishing performance adequacy. The validation master plan should be agreed upon by management. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements include the list/inventory of the items to be validated and planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan as shown below fig 2. It should comprise all prospective, concurrent and retrospective validations as well as re-validation. The validation master plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP’s and validation protocols and reports.

**Validation Protocol**

A written plan stating how validation will be conducted, including test parameters, product characteristics, production and packaging equipment, and decision points on what constitutes acceptable test results. This document should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested. The validation protocol provides a synopsis of what is hoped to be accomplished. The protocol should list the selected process and control parameters, state the number of batches to be included in the study, and specify how the data, once assembled, will be treated for relevance. The date of approval by the validation team should also be noted.

**Validation Report**

The validation report should contain the approved validation protocol, tabulated or graphical results, process monitoring
(forms), and all analytical results of the validation batches. The validation report should have a conclusion that explains the manufacturing specialist’s (preparer’s) statement and opinion Stability testing on all validation batches must be performed according to the protocol, according to the NDA/ANDA stability plan. The delivery of drugs to the respiratory system via an MDI has been the dosage form of choice for over 50 years. Propelled with CFCs, they have had a remarkable safety record and acceptance by both patient and physician. The development, production, and marketing of this dosage form have resided in very limited number of pharmaceutical companies.

**IMPORTANCE OF VALIDATION**

The most compelling reasons to optimize and validate pharmaceutical productions and supporting processes are quality assurance and cost reduction. The basic principles of quality assurance have their goal and the production of articles that are fit for their intended use. These principles are Quality, safety, and effectiveness must be designed and built in to the product, quality cannot be inspected or tested in the finished products and each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specification. The relationship of quality assurance and process validation goes well beyond the responsibility of any quality assurance functions, nevertheless it is fair to say that process validation is a quality assurance tool because it is establishes a quality standard for the specific process.

**CONCLUSION**

Three batches of metered dose inhaler are taken for performing concurrent validation of the process. All the three batches were found within the specifications by following predetermined Critical Process Parameters, in process Tests and by Raw materials. Therefore, the process for manufacturing metered dose inhaler considered to be validated. From the compiled data it was concluded that process of manufacturing and filling of product metered dose inhaler meets the acceptance criteria for its designed parameters and quality attributes and hence concluded that process followed confirms its capability of producing the product in consistent manner.

**ACKNOWLEDGMENT**

I am very thankful to Rayat Educational and Research Trust for supporting me at each and every step of my work.

**REFERENCES**


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**TABLE 1: MAIN INGREDIENTS USED IN MDI FORMULATION**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>Co-solvent</td>
<td>Stabilize suspension formulation</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Propellant suspends the drug substance and provides energy</td>
</tr>
</tbody>
</table>

**Table 2: Process Critical Parameters During Process Validation Of Metered Dose Inhaler Manufacturing Procedure**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Process Stage</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Environmental Conditions</td>
<td>15-40%</td>
</tr>
<tr>
<td></td>
<td>(a) Relative Humidity</td>
<td>20-25°C</td>
</tr>
<tr>
<td></td>
<td>(b) Temperature</td>
<td>2°C-8°C</td>
</tr>
<tr>
<td></td>
<td>(c) Compressor Air Drier Dew Point</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Mixing</td>
<td>30 min</td>
</tr>
<tr>
<td></td>
<td>(a) Stirrer time (in min.)</td>
<td>200-300</td>
</tr>
<tr>
<td></td>
<td>(b) Speed (rpm)</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Recirculation</td>
<td>100-150</td>
</tr>
<tr>
<td></td>
<td>(a) Speed (in rpm)</td>
<td>10 min.</td>
</tr>
<tr>
<td></td>
<td>(b) Recirculation Time</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Filling Stage</td>
<td>11.40-12.00g</td>
</tr>
<tr>
<td></td>
<td>(a) Weight of suspension per canister</td>
<td>18.50-19.10g</td>
</tr>
<tr>
<td></td>
<td>(b) Gross weight of filled canister</td>
<td>Diameter: 17.80±0.1 mm</td>
</tr>
<tr>
<td></td>
<td>(c) Crimp parameters</td>
<td>Height: 5.70±0.1 mm, Total Height: 56.00-57.00</td>
</tr>
<tr>
<td></td>
<td>(d) Leak Test</td>
<td>Bubble should not observed</td>
</tr>
</tbody>
</table>
Drug Development Phase

Optimization

Scale-up

Process Qualification

Pivotal Batch

Validation

3 Full Size Batches

Marketed Product

Major Changes

Validation-Protocol

Sampling Plan

Testing Plan

Validation Report

Re-Validation of Commercial product after (a) New process equipment introduced (b) Major Process Change

Intra-Batch Variability
(Reproducibility of the 3 validation lots) via
(a) Content Per Can (b) content Uniformity (c) Water Content

Inter-Batch Equivalency
(equivalency of three validation lots) and the biostudy batch Content Per Can

Critical Stages (a) Fill weight of Suspension (b) Content Uniformity

Control Limits (a) UCL (b) LCL

Fig 1 SCHEMATIC OF TYPICAL PRESSURIZED METERED-DOSE INHALER

Fig 2 PROCESS VALIDATION MASTER PLAN OF METERED DOSE INHALER
Fig 3. Manufacturing Procedure For MDI