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Review Article

A REVIEW ON VALIDATION OF PHARMACEUTICAL INHALATION AEROSOLS-PRESSURIZED METERED DOSE INHALER(pMDI)

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ABSTRACT

The purpose and interest of this overview on process validation of Pharmaceutical Inhalation/Aerosols, is to highlight the critical process parameters to be validate during the activity of validation of Pressurised Metered Dose Inhaler (pMDI). It is the most common dosage form for inhalation by which the micronized drug is delivered from a pressurized container suspended in a liquefied gas (Propellant- HFA134a/HFA 227ea). Inhalation is the convenient way to deliver drugs to respiratory tract in treatment of respiratory disease like Asthma & Chronic Obstructive Pulmonary Diseases (COPD). The Process validation should confirm that the control strategy is sufficient to support the process design and the quality of the product. This validation review covers the aspects of MDI process validation for all verities of Metered Dose inhalers with different strengths. 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. This review covers need of process validation, Approach of validation, Bracketing Approach, types of validation; brief introduction on MDI includes the materials, manufacturing & filling process along with schematic flow of all the operations of the metered dose inhaler process.

Keywords: Process Validation, Concurrent Validation, Metered Dose Inhalers (MDI), Re-validation.

INTRODUCTION

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. Medication delivered via this dosage form has allowed for a quick therapeutic response to the symptoms of asthma, emphysema, and chronic obstructive pulmonary disease (COPD), and has resulted in an improvement in the quality of life for millions of asthma sufferers.[1]

In Pharmaceutical organizations, validation is a fundamental segment that supports a company commitment to quality assurance. Validation is a tool of quality assurance which provides confirmation of the quality in equipment systems, manufacturing processes, software and testing methods.[2]

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. 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[3].

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.[4]

USFDA defines validation as: "Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics. According to European commission: Validation is defined as "Action providing in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually lead to the expected results.[5]

Validation is defined as the collection and evaluation of data, from the process design stages through commercial production, which establishes scientific evidences that a process is capable of consistently delivering quality product. The purpose of setting validation parameters is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it.[6,7]

Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties. This is an important concept, since it serves to support the underlying definition of validation, which is a systematic approach to identifying, measuring, evaluating, documenting, and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.[8]

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that result in products with the desired quality attributes.

Manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes.
- Control the variation in a manner commensurate with the risk it represents to the process and product.[9]

Pressurized Metered Dose Inhalers (pMDI)[13]

These are the mostcommon device for administration of aerosolizeddrugs.In this technique, a medication is mixed in acanister with a propellant, and the preformed mixtureis expelled in exact measured amounts uponactuation of the device**Fig.01**. Correct use of MDIs requires that patients learn how to organize exhalation and inhalation with actuation of the device. By using the spacer device it may solve the problem moderately the bulky size of the device can be prevention for patients who have need of use of MDIs outside their homes.

In near the beginning 1990, attempts were actively made to reformulate MDIs as a result of the mandatory ban on the use of propellant chlorofluorocarbons (CFCs), which have been concerned in the depletion of the Earth's ozone layer. Optional propellants, such as hydrofluoroalkane 134a/227ea, have been extensively investigated for their potentials to change CFCs since 1990.

During pressure filling, the propellant or propellant blend may be pressure filledalone or in combination. Pressure filling can be filled by single step or two filling steps, drug concentrate and propellant filling **Fig. 03** (Courtesy of Ellis Horwood Publishers)[19] shows a schematic sequence of MDI manufacture.[1]

General Considerations for Process Validation[10, 11]

1.0 Manufacturing processes may be developed using a traditional approach or a continuous verification approach. However, irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market.

2.0 Process validation of new products should cover all intended marketed

strengths and sites of manufacture. Bracketing could be justified for new products based on extensive process knowledge from the development stage in conjunction with an appropriate ongoing verification programme.

3.0 For process validation of products which are transferred from one site to another or within the same site, the number of validation batches could be reduced by the use of a bracketing approach.[10]
However, existing product knowledge, including the content of the previous validation, should be available. Different strengths, batch sizes and pack sizes/container types may also use a bracketing approach, if justified.
A science and risk based validation approach such that only batches on the extremes of certain predetermined and justified design factors;
E.g. Strength, batch size and/or pack size, are tested during process validation. The design assumes that validation of any intermediate levels is represented by validation of the extremes. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition, e.g. for a inhaler range made with different pack size in number of metered doses of a similar by filling different strengths of same basic composition into different size aluminium containers.

4.0 Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified (E.g. Stability, Trail/Development batches etc).

5.0 Equipments, facilities, utilities and systems especially compressed air and HVAC systems used for process validation should be qualified.

6.0 The suppliers/Vendors of critical starting (raw materials) and primary packaging materials should be qualified prior to the manufacture of validation batches.

VALIDATION APPROACH[11]

Two basic approaches to the validation of the process itself exist (apart from the qualification of equipment used in production, the calibration of control and measurement instruments, the evaluation of environmental factors, etc.), namely the experimental approach and the approach based on the analysis of historical data.

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.
- Extensive product testing.
- Simulation process trials.
- Challenge/worst case trials.
- Controls of process parameters (mostly physical).

Validation Team[4, 15]

A multidisciplinary team is primarily responsible for conducting and supervising validation studies. Personnel qualified by training and experience in a relevant discipline may conduct such studies. The working party would usually include the following staff members such as;

- Head of quality assurance.
- Head of engineering.
- Validation manager.
- Production manager.
- Specialist validation discipline: all areas.

The validation team must beprepared the site validation master plan with the specific requirements as per the company policy.

- Meet regularly, In accordance with a defined schedule, to discuss the progress and compliance with the validation plan and schedule.
- Determine the systems / equipment to be qualified / validated and the extent of validation to be carried out.
- Determine the frequency of validation.
- Prepare and evaluate the suitability of the protocols.
- Verify the adequacy of the tests used for proving that the objectives are achieved.
- Complied reports should be checked and approved by validation teammembers.
- Assurance of progress in terms of validation plan and schedule.

TYPES OF PROCESS VALIDATION[3,11,12,15,18]

1.0 Prospective Validation: This approach to validation is normally undertaken whenever the process for new formula must be validated before routine pharmaceutical production commences.In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase the production process should be broken down into

individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product.

2.0 Retrospective Validation: It deals with performing the validation after production is already in market place. It is based upon existing & historical process data.

Retrospective validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analysed to determine the limits of process parameters. A trend analysis may be conducted to determine the extent to which the process parameters are within the permissible range.

Some of the essential elements for the retrospective validation are;

- Batches manufactured for 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 specification of active materials/Finished products.
- List of deviations, corrective actions and Changes to manufacturing documents.
- Data for stability testing of several batches.

3.0 Concurrent validation: It's nothing more than requalification, revalidating or even recertification an ongoing process in response to a significant change in product component, manufacturing, equipments, facilities, batch size or manufacturing procedure.In using this approach there is always the risk of having to modify process parameters or specifications over a period of time.

Concurrent validation may be the practical approach under certain circumstances. Examples of these may be:

- When a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site.
- Where the product is a different strength of a previously validated product with the same ratio of active / inactive ingredients.
- When the number of lots evaluated under the Retrospective Validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control.
- When the numbers of batches produced are limited. It is important in these cases however, that the systems and equipment to be used have been fully validated previously.
- The justification for conducting concurrent validation must be documented and the protocol must be approved by the Validation Team.
- A report should be prepared and approved prior to the sale of each batch and a final report should be prepared and approved after the completion of all concurrent batches. It is generally considered acceptable that a minimum of three consecutive batches within the finally agreed parameters, giving the product the desired quality would constitute a proper validation of the process.

4.0 Revalidation.*Revalidation* is needed to ensure that changes in the process and/or in the process environment, whether intentional or unintentional, do not adversely affect process characteristics and product quality.

Revalidation may be divided into two broad categories:

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

Revalidation after changes, some typical changes which require revalidation include the following:

- Changes in the starting material(s). Changes in the physical properties, such as density, viscosity, particle size distribution, and crystal type and modification, of the active ingredients or Excipients may affect the mechanical properties of the material; as a consequence, they may adversely affect the process or the product.
- Changes in the packaging material, e.g. replacing plastics by glass, may require changes in the packaging procedure and therefore affect product stability.
- Changes in the process, e.g. changes in mixing time, drying temperature and

cooling regime, may affect subsequent process steps and product quality.

- Changes in equipment, including measuring instruments, may affect both the process and the product; repair and maintenance work, such as the replacement of major equipment components, may affect the process.
- Changes in the production area and support system, e.g. the rearrangement of manufacturing areas and/or support systems, may result in changes in the process. The repair and maintenance of support systems, such as ventilation, may change the environmental conditions and, as a consequence,

revalidation/requalification may be necessary, mainly in the manufacture of sterile products.

Sampling Plan(Process Validation)

Validation sampling plan is more rigorous in nature than the plan developed for routine quality monitoring. Sampling shall be done by the Quality Assurance or by production personnel in presence of Quality Assurance. Samples needs to be withdrawn from different stages of filling like initial, and then after the specific interval till the completion of filling processof MDI inhalers.The drawn samples should be analysed for specific product quality characteristics.

Challenge Test / Worst Case[1]

Meaningful process limits on conditions will need to be established if not done during the development. Operating outside the set limits may or may not lead to failure of the process or product specifications. The limits may also be used to demonstrate that process conditions are under consistent control.

Examples may be;

- Humidity range (e.g., 30-45%) in the manufacturing room.
- Mixing Stirrer Speed ranges (100-250 RPM).
- Mixing Vessel Jacket Temperature (18-25°C).
- Product Suspension/Solution Temperature (10-16°C).

An alternative and preferable procedure would be to test these conditions during development. For Example; Drug uniformity might be verified by using lowest mixing speed (100 RPM), Lowest Temperature (18°C & 10°C) of Vessel Jacket and Product respectively.

Documentation[18]

A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria. A report that cross-references the qualification and/or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification. After completion of a satisfactory qualification, a format release for the next step in qualification and validation should be made as a written authorization.

Validation Master Plan[3, 16, 17]

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 manufacturing process flow &controls of pMDIwithin a firm should be included in the validation master plan as shown below **Fig 02**. It should comprise all prospective, concurrent and retrospective validations as well as revalidation.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.

Contents of Validation Protocol and Report[3]

Validation Protocol; A written plan of actions stating how process validation will be conducted, it will specify who will conduct the various tasks and define testing parameters, sampling plans, testing methods and specifications, will specify product characteristics, and equipment to be used. It must be specify the minimum number of batches to be used for validation studies, it must specify the acceptance criteria and who will sign \ approve \ disapprove the

conclusions derived from such a scientific study.
The validation protocol should contain the following elements;

- Short description of the process.
- Summary of critical processing steps to be investigated.
- In process, finished product specification for release.
- Sampling plans.
- Departmental responsibility.
- Proposed timetable.
- Approval of protocol.

Validation Report; A written report should be available after completion of the validation, if found acceptable it should be approved and authorized.
The report should include at least the following;

- Title and objective of study.
- Reference to protocol.
- Details of material.
- Equipment.
- Programs and cycles used.
- Details of procedures and test methods.
- Result.
- Recommendations on the limit and criteria to be applied on future basis.

Importance of Process Validation[15]
Assurance of Quality Validation is an extension of the concepts of quality assurance since close control of the process is necessary to assure product quality and it is not possible to control a process properly without thorough knowledge of the capabilities of that process without validated and controlled processes, it is impossible to produce quality products consistently. End product testing, in the absence of validation, gives little assurance of quality for variety reasons, among which are.

1. Very limited sample size.
2. The limited number of tests performed on a sample. For example, it is impractical to test for all potential impurities or contaminants.
3. The limited sensitivity of the test.

Process Optimization The optimization of a process for maximum efficiency, while maintaining quality standards, is a consequence of validation. Literal meaning of word to optimize is “To make as effective, perfect or useful as possible”. The optimization of the facility, equipment, systems, and processes results in a product that meets quality requirements at the lowest cost.

Reduction of Quality Costs; Quality costs are divided in to four categories.
They are: a) Preventive costs, b) Appraisal costs, c) Internal failure costs and
d) External failure costs.
E.g. of internal failure costs: Any validated and controlled process will result in fewer internal failures like; fewer rejects, reworks, re-tests and re-inspection[14]

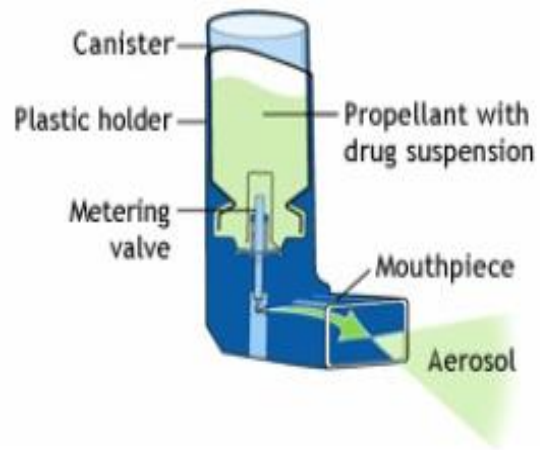

Fig. 01. Metered Dose Inhaler (MDI)

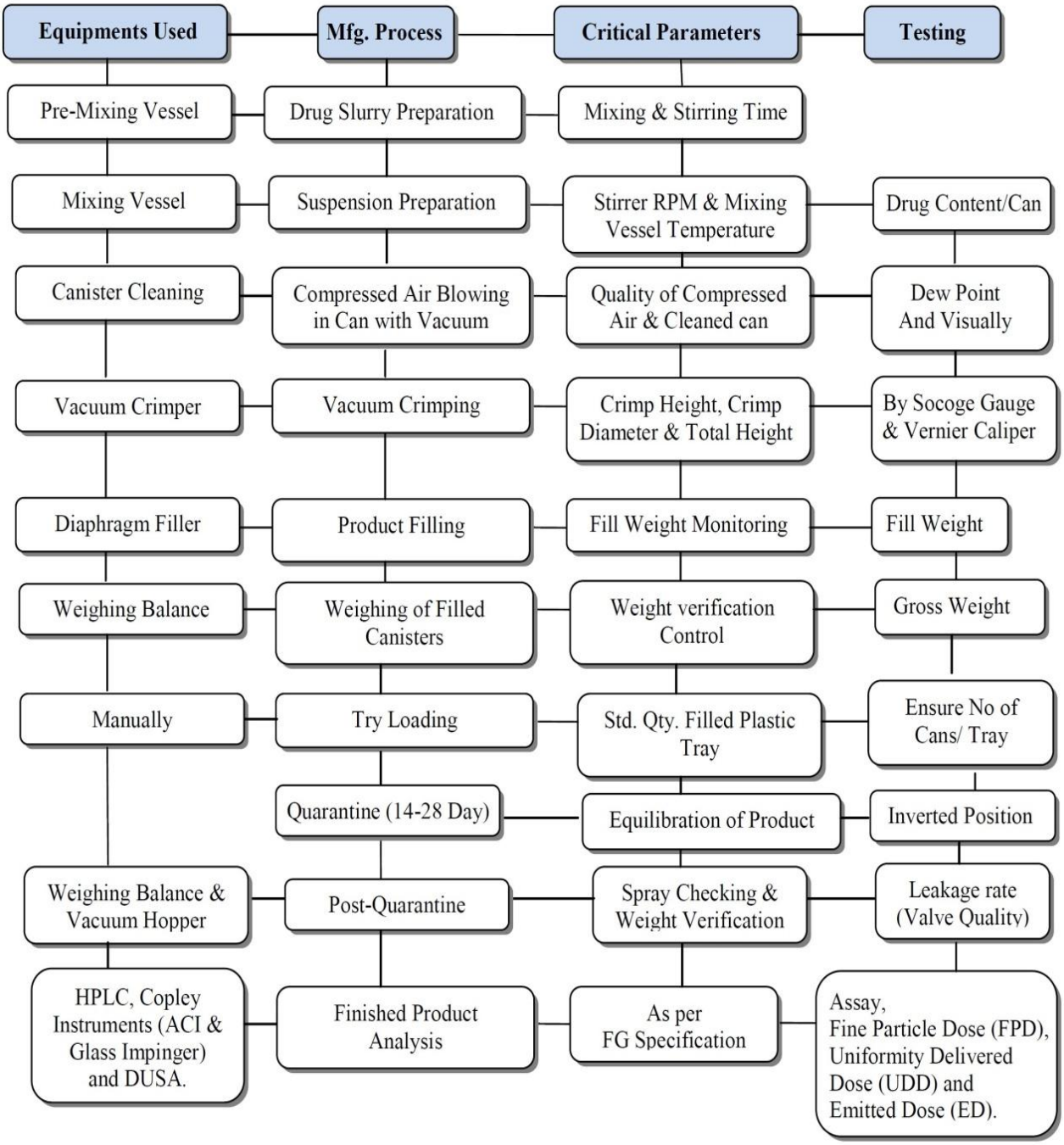

Fig. 02 Manufacturing Process Flow of (pMDI)

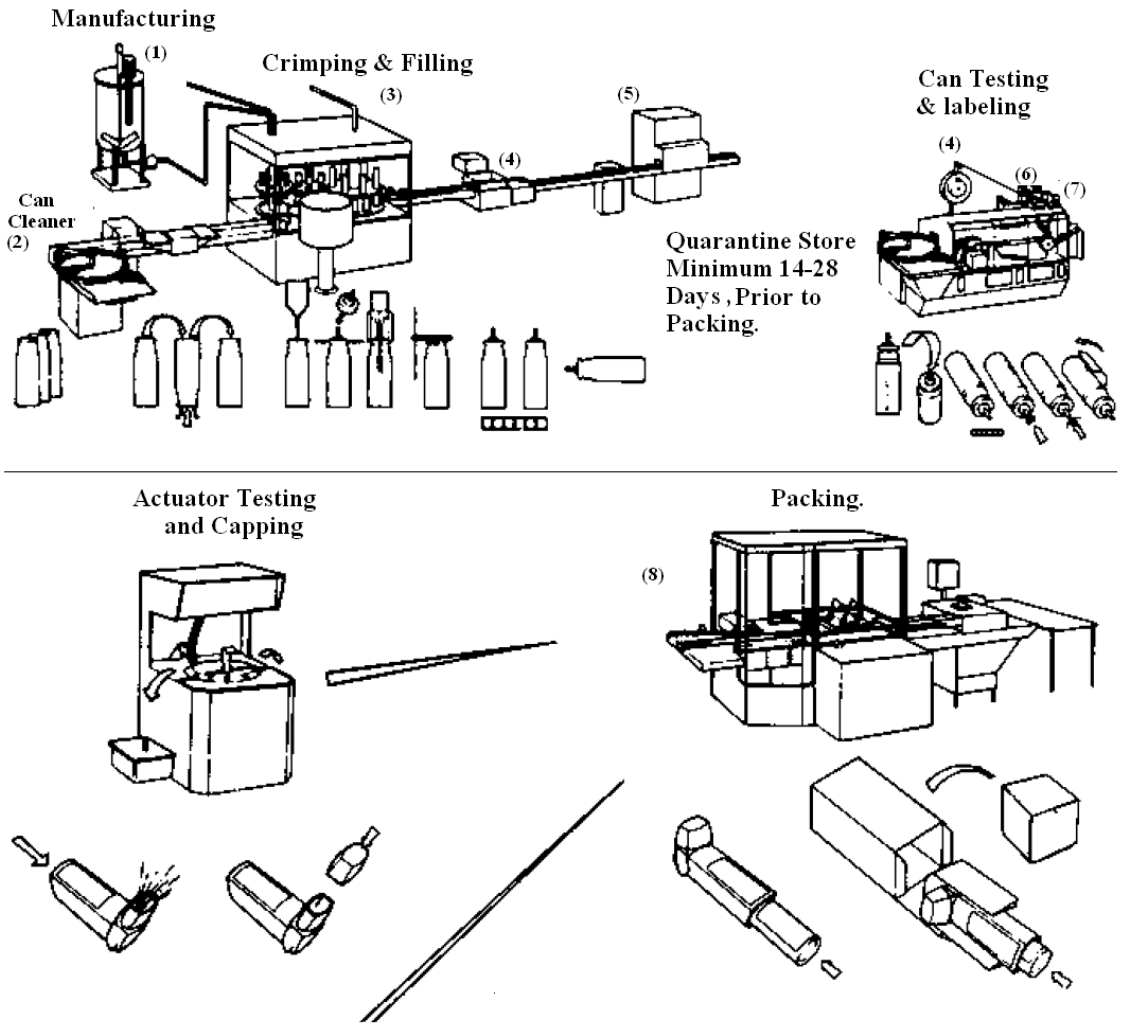

Fig. 03 Schematic production sequence for the manufacture of Metered-dose inhalers by pressure filling: (1) suspension mixing vessel; (2) can cleaner; (3)can crimper and filler; (4) check weigher; (5)can coder & heat tester; (6) priming & spray testing; (7) labeler; (8) feeds for tested cans & actuators.

CONCLUSION

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. Validation has been proven assurance for the process efficiency and sturdiness and it is the full-fledged quality attributing tool for the pharmaceutical industries. Apart from all the consistency and reliability of a validated process to produce a quality product is the very important for an industry. Finally it can be concluded that process validation is a key element in the quality assurance of pharmaceutical product as the end product testing is not sufficient to assure the quality of finished product.[18]

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.

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