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THE NEWER DIMENSION OF INHALATION AEROSOLS IN THE PROSPECTIVE OF VALIDATION

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ABSTRACT: Aerosol drug delivery systems are much more importance in present days and have much advantage over other route of administration. Meter dose inhaler was used to deliver asthma medication in easy way and reliable multi dose preparation. The importance of the MDIs device play important role in determining drug delivery to the lungs. The word validation means," Impose of validation or action of proving its effectiveness". The most used inhalation is the metered-dose inhaler(MDI), which operates by delivering from a pressurized container using a liquefied gas propellant. Inhalation is the accessible way to deliver drugs to respiratory track and used in treatment of disease like ASTHMA.A manufacturer can assure that the design of the device, processes, process controls and packaging that all manufactured units will have to meet specifications and have uniform and consequent quality. Validation is defined as the collection and checking of data, from the process design stage throughout commercial production, which provides scientific evidence that a process is capable of consistently delivering quality product.

INTRODUCTION: The inhaled aerosols used for selective treatment of lungs by achieving high drug concentrations in the airway which reduces systemic adverse effects by minimizing systemic drug levels. Advantage is that Inhaled beta2-agonist bronchodilators produce a more rapid onset of action than oral delivery. Some of the drugs are only active with aerosol drug delivery system. Aerosol drug delivery is helpful in painless and convenient administration.[1]

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But there is also disadvantages in aerosol drug therapy. Specific inhalation techniques are necessary for proper use of the available types of inhaler device and less than optimal technique can result in decreased drug delivery. Inhaler devices are less convenient than oral drug administration insofar as the time required for drug administration is greater compared to oral administration and some patients may find the device less portable.

The addition of inhalation devices has resulted in a confusing number of choices for the healthcare provider and confusion for both to physicians and patients trying to use these devices correctly because of existence of huge numbers. Each type of aerosol device has its own merits and demerits. [2]

Rapid and fast MDI is the fastest means of drug delivery used in common clinical practice. By introducing drug into the bloodstream very quickly, it produces a transient peak in arterial drug levels as the drug passes for the first time through the body, before its dilution into the full circulatory volume and distribution into tissues. [3–5] For example, adenosine will restore normal heart rhythm in patients with supraventricular tachycardia only if delivered very rapidly. [6] Similarly, the efficacy of certain anti-migraine agents depends primarily on rate of delivery, not the total dose. [7]

Types of Descriptions of Orally Inhaled and Nasal Drug Products:

a) Metered Dose Inhalers (MDIs) – Propellant-Pressurized Solution or Suspension Metered Aerosols for Oral Inhalation or Nasal Administration

b) Nasal Sprays – Aqueous Metered Solution or Suspension Pump Sprays for Nasal Administration

c) Inhalation Solutions, Suspensions, and Sprays – Aqueous Formulations for Oral Inhalation

d) Dry Powder Inhalers (DPIs) – Solid-Phase Metered Inhalation Aerosols for Oral Inhalation.[8]

TABLE 1: MERITS AND DEMERITS OF INHALATION AEROSOLS [1]

Type	Merits	Demerits
Small volume jet nebulizer	Patient coordination is not necessary. Effective with tidal breathing High dose posses Dose modification posses No release of CFC Used with supplemental oxygen Can deliver combination therapies if compatible	Lack of portability Pressurized gas source are used Treatment time is lengthy Device cleaning required Contamination possible All medicines are not available in solution form Device preparation required Performance variability Expensive when compressor added
Ultrasonic nebulizer	Patient coordination is not necessary High dose posses Dose modification posses No release of CFC Small dead volume removed Faster delivery than jet nebulizer No drug loss during exhalation	It is Expensive Need for electrical power source Contamination possible All medicines are not available in solution form Device preparation required before treatment Does not nebulize suspensions well Possible drug destroy Potential for airway irritation with some drugs
Pressurized metered dose inhaler	Portable and compact Treatment time is short drug preparation is not required No contamination of contents High Dose-dose reproducibility Some can be used with breath-actuated mouthpiece	Coordination of breathing and actuation required Device actuation needed High pharyngeal accumulation Upper limit to unit dose content Remaining doses difficult to find Potential for abuse All medications are not available Many use CFC propellants in USA
Holding chamber or spacer	Reduces need for patient coordination minimises pharyngeal deposition	Inhalation can be more complex for some patients Can reduce dose available if not used properly More expensive than MDI Less portable than MDI
Dry powder inhaler	Breath-actuated Less patient coordination is required Use of Propellant not required Small and portable Short treatment time Dose counters in most newer designs	Requires moderate to high inspiratory flow Some are single dose units This Can result in high pharyngeal deposition All medications are not available.[1]

Validation Protocol:

Development Report: A development report has to be written previous to the process validation protocol by the research and development group this will serve as the basis for items to be included in the validation protocol.

Parameters that should be focused on process limits, formulation compatibility with process equipment, time limitations of production, and any problems arise and their resolution, should be addressed. Aerosol product characteristics includes microbial challenge data, through-life testing of units [13], resuspendability [14, 15], first-shot assays, and typical loss of prime should be well known. The effect by the spray assay methodology on the product produces beneficial information. The product also must be fingerprinted for three-dimensional plume patterns and particle size distribution by two or more methods. Any One of the methods in testing should evaluate the aerodynamic particle size. A development history that describes orderly events during formulation is also useful and frequently will help the specialist preparing the protocol. Reference to the development report(s) may be included in the protocol document.[21]

Preparation and Execution: The qualified manufacturing or validation specialist familiar with aerosols should prepare process validation protocol of a new aerosol product. Others oral dosage forms such as suspensions or solutions would also be helpful for this purpose. These technical specialists may be within the research, validation, or technical support departments, since this work will be done prior to approval of a new product. Approval of the protocol should be done by quality assurance, quality control, production management, and research. Other experts will be involved in aerosols. A packaging specialist will also play an important role, since the function of product of the dosage form depends on the package performance, in which the filled unit may be checked weighed, spray tested, and assembled with the mouthpiece into a boxed unit, further it will need qualification and validation.

In the case of third-party or contract manufacturing, production and quality control management at the manufacturing site should view the validation protocol and report. In special cases, the third party may prepare a protocol; however, the final approval of validation responsibility lies with the new drug application (NDA) or abbreviated new drug application (ANDA) holder and marketer of the aerosol. [9, 18]

Final Process and Product: The process must be validated at the manufacturing site(s) as stated in the regulatory filing (NDA or ANDA). The aerosol product should be prepared with manufacturing equipment and process intended for the routine production. The batch record changes during or after validation batches have begun as a means of improvement. Changes in any manner, such as the order of addition of raw materials, method of weighing, screening of any raw materials, aerosol line functional changes, mixing conditions, or mixing equipment, should be considered as major changes and be documented accordingly. Revalidation would be required to be done for any changes made.

Examples would be adding a dilution step for dissolving or dispersing ingredients or changing homogenization times of wetting a suspension.[10, 19]

Worst-Case Conditions: Meaningful process limits or specifications on conditions will need to be established if it is not done previously during development. Operating beyond the set limits may lead to failure of the process or product specifications. [16] Limits may also be used to demonstrate that process conditions are under consistent control and they are within the specifications. Exam plesare as follows; humidity range (e.g., 30–45%) in the manufacturing room, mixer speed ranges (45 to 55 rpm), mixer position (angle or distances), nitrogen flow to tank (2 to 4 standard cubic feet/hour [scfh-standard cubic feet per hour]), or suspension temperature range (20 30^0F). For example, drug uniformity might be verified by using the condition like lowest mixer speed (45 rpm), lowest temperature (20^0F), and highest nitrogen flow rate (4 scfh). Lack of volatility may be confirmed by testing the highest nitrogen flow (4 scfh) at a high mixing speed (55rpm). The Rates of addition of raw materials (1 to 5 min) may also need to be evaluated. These tests may be conducted during the prevalidation batch in order not to interfere with a supposed production batch.[12, 21]

Timing: Before production batches are started the protocol must be approved and signed. Since aerosol manufacturing involves more critical package components (valves, cans, mouthpieces) than other dosage forms, so receipt and release

testing of these components must be incorporated during planning schedule. Since aerosol products involve lengthier and more finished-product tests compared to other dosage forms, release testing usually requires more analytical laboratory time.[11, 17]

Testing and Specifications: Due to more of extensive testing for aerosol products, the sampling and testing schedule must be carefully reviewed and checked before starting validation. MDI aerosols are suspensions containing volatile propellants that are mixed and filled over long periods that is greater than 6 hr. Many drug samples should demonstrate that there is reproducibility and show that volatility or loss of propellants and drug is under control. Aerosol tests that are frequently done are filled-unit yields, leakage rates, valve-spray reject rates, moisture values, assays, and valve rubber leachables. Alert limits for critical tests are suggested to avoid uncertainty over pass/fail situations and act as a guide when there is a cause of concern. Tentative limits could be used until a history of production batches is obtained.

Examples may be a content uniformity RSD (Relative standard deviation) of 5.0% versus specification of 6.0%. Developmental data on the pilot-scale batches will assist in setting initial alert limits. These alert limits do not substitute for the actual limits but merely serve as a guide for investigation.[10, 20]

Protocol format:

1. The objective: Briefly describes the purpose and need of the validation program. An additional objective is to provide supplemental manufacturing information beyond that recorded in the batch documents.[14, 15]

2. The scope: Section describes what the process validation protocol includes, the number of batches, and what it does not cover. In this part, apart from this packaging validation or mouthpiece testing is included or excluded.

3. Formulation and components: The specified quantitative formulation and components should be listed, and also along with identification or company code numbers. The quantity per can, per batch, and percentages should be listed here. Additional formulation information also may be enumerated; including the following:

a. Amounts per actuation:
b. Amounts per can:
4. Process flowcharts: The flow diagram should include the process flow steps and addition of raw materials. If possible to indicate, major equipment and special environmental conditions may be included in the flowchart. And also In-process tests may also be included.

5. Document checklist: All the documents that should be checked and in proper order previous to the initiation of the validation batches are listed. They should be checked for availability and accuracy. Preparation of batches cannot be commence unless these documents are finalized and signed.

An example is shown below:

a. New drug application (applicable sections, NDA or ANDA)
b. Calibrations:
c. SOP-Standard operating procedures:
d. Product specification sheet (line check-up form, bills of materials).
e. Training documentation.
f. Cleaning procedures (cleaning procedures, cleaning validation report).
g. COA-Certificates of analysis of components (for every validation batch):
h. Master batch record documents or Master formula record:
i. Qualification reports and equipment manuals
j. Development report (research report number).
k. Safety documents MSDS (material safety data sheets).
l. Validation protocol (current document).

6. Process monitoring: This section contains the intended process conditions, specification and factors that will be measured. Items that are not recorded in the batch record but that may be critical should be tabulated here, along with target or expected values. The frequency of the measurement, the method, and where it will be recorded should be recorded and tabulated. Many of these items are based on past experience during development. An example may be the rate of

addition and location of the micronized active ingredient of the aerosol solution or suspension appearance.

7. Sampling and testing: This section provide specifics on the sampling, testing, and acceptance criteria needed during the validation batches. The Methods of sampling concentrate or removing filled cans from the line should be clearly mentioned and checked. Lists of in-process tests, where sampled, number of cans, and responsibility should be tabulated. A separate another table may be needed to describe the test, method, frequency, specifications, and comments

8. Responsibility and timing: This section will provide a guide for specific goals and targets of each group. The target timing requirements (e.g., 6 weeks to place on stability) will show the responsibility of each person(s) from protocol writing to report approval.

9. Appendix: This are formats with blanks may be provided in the protocol to be filled out during each validation batch. These forms used for process monitoring of compounding, line functions, in-process sampling, and so on. They should include such specifics such as types of measuring devices (serial numbers) and include sign-offs for "done by" and "checked by" signatures. A clearer indication of the process requirements results from preparing and reviewing these forms.[12, 20]

Regulatory Requirements of Quality Section of Meter Dose Inhaler as Per Europe: [22]

A. Pharmaceutical developments:

Moisture content: The effect of moisture content on product performance on stability should be recorded.

Delivered dose: This test should be performed to evaluate the uniformity of dose delivered.

Fine particle dose: The particle size distribution of the active substance can be determined by impinge. Priming: priming actuation should be conducted to ensure that the uniformity of content requirements are met in normal use.

Extractable: extractable data should be provided demonstrating the extent of extraction of components into the formulation from the container and valve.

Use of spacer: when spacer is used in some products its use should be validated and relevant information given in the summary product characters.

Breath actuated device: Data should be recorded to demonstrate that all target patient group are capable of triggering the breath actuated device.

In use performance: The performance the product should be observed by normal use of a patient according to the direction.

Cleaning procedure: the cleaning procedure should be clearly written described.

Description of manufacturing process: process validation data demonstrating the validity of the process should be submitted.

Control of excipients: The toxicity and purity data of excipient should be described.[23, 26]

B. Control of drug product:

Moisture content: If it is necessary this test should be performed.

Delivered dose uniformity: This test should be performed to evaluate the uniformity of delivered dose.

Fine particle dose: The particle size distribution of the active substance can be determined by impinge. The particle size distribution of the active substance can be determined by impinge.

Leak rate: To maintain optimal performance characteristics for the drug product, leak rate should meet specific acceptance criteria.

Number of delivers per inhaler: Number of delivers per inhaler should be appropriate so that it meets the given labelled amount.

Particulate matter: where a separate shelf life specification is requested for any parameter, this should be clearly stated and justification provided.

Container Closure System: The specification for each component of the inhaler and its compliance

with the specification for limits of leachable components and extraction studies should be given. If the canisters have an internal coating specification should be given.

Stability: It should include specification test, with the exception of the identity test and leachable moisture and microbial purity.[24, 25]

C. Summary of product characteristics:

Quantitative and qualitative composition: It should be clearly stated in data.

Posology and method of administration: In this the use and direction of the MDI should be stated.

Special precaution for storage: The special precaution which should be taken during storage should be given.

Cleaning: Detailed description of the cleaning procedure should be given.[26, 27]

Cleaning Validation:

Procedure: The CEFIC. APIC Guide to Cleaning Validation recommends three levels of cleaning that may be implemented. This approach is outlined in the following table, however it should be mentioned that additional levels might be necessary depending on the nature of the process and requirements of individual companies. [28]

TABLE 2: LEVELS OF CLEANING

Level	Thoroughness of cleaning	Cleaning validation
2	Carryover of the previous product is critical. Cleaning required until predetermined stringent carry over limits are met.	Essential.
1	Carryover of the previous product is less critical. Cleaning should reduce the potential carry over to a less stringent limit as required for level 2.	Increase from not required to necessary (lower acceptable carry over limits).
0	Only gross cleaning if carryover of the previous product is not critical.	Not required.

A general approach how these levels could be established for typical product change over situations in a multi-purpose API-plant is outlined in **Fig.1.**

API - Process A API - Process B:

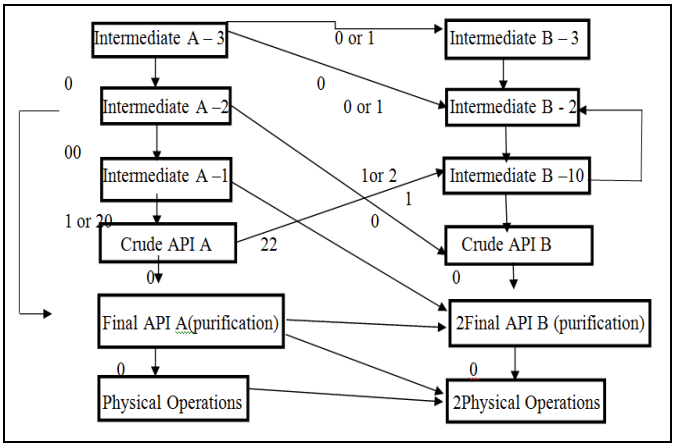

FIG. 1: TYPICAL PRODUCT CHANGEOVER SCENARIOS

The carryover will be reduced and the efficiency of cleaning will be increased by following the above flow chart. The levels established as shown in **Fig.1** are based on the basics that in general the thoroughness of cleaning will increase and the acceptable carryover of the previous product will decrease from early steps in the route of synthesis to the final API due the fact that early steps undergo further processing and/or purification and so the potential carry over will be reduced by further processing.[29]

Principally two different product changeover scenarios exist which have a big impact on the cleaning level required:

1. Previous product and the following product do belong to the same synthetic chain (product changeover within process. A. or within process .B.)
2. Previous product and following product do not belong to the same synthetic chain.[30]

Cleaning between different steps of the same synthetic chain:

There are two different situations possible:

1. The following product is the next step in the synthetic chain: There will be very less risk to effect the quality, safety of the final API, because the previous product is the starting material of the following process so the analytical methods applied for the following product are usually suitable to detect the previous product which is covered and

limited by the impurity profile. For this situation level 0 will be applies

2. The following product is not the next step of the synthetic chain: In general there is a higher potential risk for contamination of the API if the following product in a sequence is close to the final API. So progression of levels from early steps to later steps in the synthetic chain is expected as outlined in **Fig.1**. [28, 30]

Limits for Microbes: It is possible to reasonably predict levels of chemical residues or trace of chemicals in subsequently manufactured products based on the extant of residues present on equipment surfaces. [32, 33] with microorganisms, it is possible to measure levels on equipment surfaces; however, the effect of those residues will depend on what happens to those microorganisms once they come in contact with the subsequently manufactured product. The Areas that has to be evaluated include the species(including the "objectionable" organisms), type of organism (vegetative bacteria versus bacterial spore, for example), the presence of preservatives in that subsequently manufactured product, the water activity of the subsequently manufactured product, as well as any subsequent sterilization process performed on that product. As a there is a general rule, if the water activity is less than 0.6, then it can be expected that microorganisms cannot proliferate (although they may continue to survive without reproducing).[34]

Three methods to set microbial limits will be addressed below.

The first (Case I) involve limits where the Subsequent product does not allow microbial proliferation and there will be no further sterilization process. The second (Case II) involves subsequently manufactured products which are terminally sterilized. The third (Case III) involves subsequently manufactured products that are processed aseptically.

Case I Limits: If the subsequently manufactured product does not allow the microbial proliferation, then the determination of acceptable microbial limits in the cleaned equipment can be calculated using the same principles used for chemical residues with one important exception. This process involves first determining the acceptance limit in the subsequently manufactured product. This limit is typically given in Colony Forming Units (CFU) per gram of product. After this is determined, then the limit per surface area of equipment (assuming uniform contamination) can be calculated based on the batch size of the subsequently manufactured product and the equipment surface area.

A second source of information given in the proposed United States Pharmacopeia (USP) <1111> relating to "Microbial Attributes of Nonsterile Pharmacopeial Articles."[34, 35]

Examples of those limits are given below:

Solid oral: ≤1000 CFU/g
Liquid oral; ≤100 CFU/g
Topicals: ≤100 CFU/g

Once the limit in the subsequently manufactured product allowed from the cleaned equipment surfaces is determined, the second step is to determine the limit per surface area (CFU/cm2). This is calculated exactly as it would be for chemical residues: [35]

$$\text{Limit per surface area} = \frac{\text{LSP x MBS}}{\text{SA}}$$

Where
LSP = Limit in the subsequent product
MBS = Minimum batch size
SA = Product contact surface area

Case II Limits: This involves setting limits for cleaned equipment when the product subsequently manufactured in that equipment is to be sterilized. In this case, the microbial limit in the subsequently manufactured product can be established based on the assumed bio burden of that product at the time of sterilization. In other words, any validated sterilization process depends on the assumed bio burden of the item being sterilized. That assumed bio burden then made the limit in the subsequently manufactured product. [31]

"…it is important to note that control of bio burden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility." [36]

Case III Limits: This third equipment surfaces where the subsequently manufactured product is aseptically produced. This case is slightly different from Case II. In that it is the equipment itself, and not the product, which is subsequently sterilized, hence it is efficient method. This case is relatively straightforward, because the microbial limits on the surfaces of cleaned equipment are established based on the assumed bio burden of the equipment surfaces for sterilization validation of that equipment. There is no information on batch sizes or surface areas is necessary. The assumed bio burden for the sterilization validation can be used directly for limit purposes.[33-35]

Analytical Chromatographic Methods for Aerosol Analysis: Chromatographic Methods for Aerosol Analysis Different high performance liquid chromatography (HPLC) methods were used for analysis of drug quantity versus purity, and for prochlorperazineversus alprazolam. All methods involved reverse phase HPLC with 10 mL injection volume and photodiode array (PDA) detection.[37] Comprehensive information regarding the columns, buffers, and gradients employed in these methods is provided in **Table 3**.

Purity is reported as follows

$$\frac{100\%*\text{Peak area of the drug}}{\text{Peak area of the drug +sum of the areas of all impurity peaks}}$$

For practicality, impurity peaks present at <0.015% of the drug area have been eliminated from purity calculations. In control experiments, both purity methods were shown to be able to detect a broad spectrum of species generated upon forced degradation of drug substance. [38]

TABLE 3: REVERSE PHASE HPLC METHODS FOR DETERMINING DRUG CONCENTRATION AND PURITY. [38]

Drug	Prochlorperazine		Alprazolam	
Method Type	**Quantitation**	**Purity Determination**	**Quantitation**	**Purity Determination**
1.Column	Waters Xterra C8, 4.6*150 mm, 3 mm Particle Size	Waters Xterra C18, 4.6*150 mm, 3 mm Particle Size	Synergi Max-RP, 4.6*50 mm, 4 mm Particle Size	Waters Xterra C18, 4.6*150 mm, 3 mm Particle Size
2.Mobile Phase	A: 51.4 mM KH2PO4, pH 2.5+68 mM NaCl in Water B: Acetonitrile Isocratic (A:B) 60:40	A:Water:Acetonitrile (95:5) B: 5 mMHexanesulfonicAcid+5 mM Ammonium Formate in Water, Adjusted to pH 2.5 With Formic Acid. C: Acetonitrile Gradient (Time-A:B:C) 0–90:10:0 5–90:10:0 15–74:10:16 40–47:10:43 65–0:5:95	A:Water:Acetonitrile (75:25) B: Acetonitrile Gradient (Time-A:B) 0–100:0 6.5–100:0 7.5–7:93 8.5–7:93 9–100:0	A:Water:Acetonitrile (90:10) B: Acetonitrile Gradient (Time-A:B) 0–100:0 1–100:0 26–75:25 36–70:30 56–50:50 76–10:90
3.Flow Rate	1.0 mL/min	1.0 mL/min	3.0 mL/min	1.0 mL/min
4.Detection	254 nm	254 nm, Extracted (200–400 nm PDA)	221 nm	221 nm, Extracted (200–400 nm PDA)
5.Temperature	25^0C	40^0C	25^0C	25^0C

Differential Scanning Calorimetry: Differential scanning calorimetry (DSC) was performed on a TA Instruments Model Q100 (www.tainstruments.com), pre-calibrated with indium and purged with nitrogen, with a 108C/ min temperature rise. Aerosols were captured immediately after their generation by impaction onto an aluminum DSC pan, which was fit into a modified filter housing. The collection efficiency of this approach was ~90%. The pan was then sealed and analysed very shortly after collection. Typical sample masses were ~2 mg. Because of the relatively low sample masses, adequate temperature uniformity was obtained throughout the sample despite the relatively fast temperature gradient employed. [39-42]

X-ray Powder Diffraction: X-ray powder diffraction analysis was performed at SSCI (West Lafayette, IN). An Inel XRG-3000 diffractometer equipped with a curved position sensitive detector collected diffraction data using standard copper K alpha radiation at a resolution of 0.03^0 2 thita. For aerosol collection for X-ray power diffraction analysis, a cascade impactor was modified by taping all of the holes on the top stage shut except for one, under which was placed a small aluminum pan. Aerosols were captured immediately after their generation by impaction onto this pan. The collected aerosol (5–10 mg) was then transferred by tapping out of the pan into a vial for transport to SSCI. [43, 44]

Scanning Electron Microscopy: Scanning electron microscopy was performed at Accurel Systems (Santa Clara, CA). Aerosols were captured shortly after their generation by gravitational sedimentation onto a silicon wafer. The samples were then coated with a thin (~5–10 nm) layer of gold/palladium, and the resulting metal coated particles imaged using a Phillips XL30 FEG field emission instrument with an accelerating voltage of 2.5 kV. Similar particle shapes are by impaction; however, sedimentation allows for more facile collection of individual aerosol particles, which is beneficial for imaging. [45]

CONCLUSION: Inhalation products are gaining much more importance in the pulmonary drug delivery. Meter Dose Inhaler are mostly used in lung diseases such as Asthma and COPD and its regulation is necessary as it delivers the drug to the lungs. Reports on general uses and importance of inhalation aerosol for health are highly captured in literatures, but the validation aspects of inhalation aerosol from point of quality assurance is still under developmental stage in our country. Hence this review will enable the reader to understand the changing face and newer validation aspects of inhalation aerosol so as to enhance its potential as medication for future.

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CONFLICT OF INTEREST: It is to specifically state that "No Competing interests are at stake and there is No Conflict of Interest" with other people or organizations that could inappropriately influence or bias the content of the paper.

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