STUDY OF QUALITY REQUIREMENTS OF METER DOSE INHALER REGULATION IN US AND EUROPE

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ABSTRACT
Aerosol drug delivery systems are gaining much more importance in present and have a great advantage over other route of administration. Meter dose inhaler was introduced to deliver asthma medication in a convenient and reliable multi dose preparation. The key components of the MDIs device play important role in determining drug delivery to the lungs, hence the regulation of the MDIs device is necessary. Centre for drug evaluation and research (CDER) under FDA and Committee for proprietary medicinal products (CPMP) under EMA is responsible for regulation of MDI in US and Europe respectively. The registration of MDIs in US as well as Europe is done through Common Technical Document (CTD) format. This article gives information of regulatory requirements of quality section of MDIs in US and Europe. The regulatory requirements of quality section are varying from each other so it is challenging for globalized pharmaceutical companies to develop MDIs which comply with regulatory requirements of both countries.

KEYWORDS: Meter dose inhaler, FDA, EMA, Common technical Document, Quality Requirements.

INTRODUCTION
A metered-dose inhaler (MDI) is a handheld aerosol device use to delivers a specific quantity of drugs to the respiratory tract, by producing a metered dose of aerosolized drug
that is self-administered by patient. It is the ordinarily used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. Metered-dose inhalers are recognized as those devices that contain pressurized formulation that is aerosolized through an atomization nozzle.\(^1\)

**MDI is composed of mainly essential components\(^2\)**

![Diagram of MDI components](image)

**Fig. 1: Components of MDI**

**The container** or canister is produced in aluminium or stainless steel by means of deep drawing where the formulation resides.

**The metering valve** it is required to retain and protect the contents of the canister at the same time as delivering a fixed volume of the formulation in a reproducible manner and has a volume ranging from 25 µl to 100 µl.

**An actuator (or mouthpiece)** allows the patient to operate the device and directs the aerosol into the patient's lungs. The design of the actuator will influence the size and velocity of the drug particles, and propellant droplets emitted from the mouthpiece. The actuator contains the mating discharge nozzle and generally includes a dust cap to prevent contamination.

**Propellants:** One of the most crucial components of a MDI is its propellant, the propellants serve as a source of energy for atomization of the liquid formulation as it exists the nozzle. They also function as liquid phase for the dispersion of drug and excipient that are present in suspension.
**Mechanism of Meter Dose Inhaler**[3]

The MDIs are operated by pressing own top of the canister, Actuation produces a fine atomized spray that deliver dose which contains the drug either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of those droplets, ends up in the generation of an aerosol consisting of micro meter-sized medication particles that are then inhaled.

**Regulatory requirements for meter dose inhaler for abbreviated new drug application**

An Abbreviated New Drug Application (ANDA) is use for Generic drug. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.

An Abbreviated New Drug Application (ANDA) is that contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. [4] Meter dose inhaler is regulated by U.S. department of health and human service food and drug administration. Center for drug evaluation and research (CDER) is regulatory authority which monitors meter dose inhaler regulation.

An Abbreviated New Drug Application (ANDA) in Europe it is filling through Decentralize procedure. Meter dose inhaler is regulated by European medicinal agency (EMA) and it is monitored by Committee for proprietary medicinal products (CPMP).

Regulatory requirements for meter dose inhaler require the data should be submitted in to the common technical document (CTD).[5] CTD has five modules which are described below:
Fig. 2 Overview of CTD

The Requirements of Module 1 and Module 2 for Meter dose inhaler are same for both US and EUROPE which is described below.

**MODULE 1: AS PER REGIONAL INDUSTRY CRITERIA**
Table of Contents of the Submission Including Module 1
Documents Specific to Each Region (for example, application forms, prescribing information)

**MODULE 2: QUALITY OVERALL SUMMARY AND CLINICAL OVERVIEW**
In general, the Quality Overall Summary (QOS) is an outline of data presented in Module3. Summary of drug Substance, Summary of drug Product should be given. And in clinical overview data of Bioavailability and bioequivalence should be given.

**Regulatory requirements of quality section of meter dose inhaler as per us** [6]

**Module 3: Quality section**
The quality section contains chemistry, manufacturing, control test (CMC) data that are described below.
**Drug product:** MDIs is the complex units, the quality and reproducibility of which can be better ensured by appropriate controls of all components (active ingredients, excipients, device components, protective packaging) used in the drug product, controls during manufacture of the drug product, and controls for the drug product.

**Components of product:** A list of all components (i.e., ingredients) used in the manufacture of the drug product formulation, should be given and each component should be identified by established name by its complete chemical name, using structural formulas when necessary for specific identification.

**Compositions of product:** The composition of an MDI formulation is crucial, particularly in defining the physical stability and the performance characteristics of a suspension MDI. In a MDI, the propellant(s) and co solvent(s) constitute the majority of the formulation composition, and the type and amount of these components determine the internal pressure of an inhalation aerosol, a critical parameter related to the MDI performance.

1. **Specifications for the Formulation Components**

**Active pharmaceutical ingredient:** The comprehensive characterization of the physical and chemical properties of the drug substance to be used in meter dose inhaler should be given. Important properties of the drug substance may include. Appropriate acceptance criteria and tests should be given. The purity of the drug substance and its impurity profile should be characterized and controlled with appropriate specifications is given.

**Excipients:** For most MDIs, excipients (when used) comprise a significant portion of the formulation content by weight and their quality has a substantial effect on the safety, quality, stability, performance, and effectiveness of such drug products. The source of each excipient should be identified and the material supplied should meet appropriate acceptance criteria. A full description of the acceptance criteria and the test methods should be given.

**Manufacturers:** The name, street address, building number, and Central File Number (CFN), if available, of each facility involved in the manufacturing of the drug substance and excipients should be given.

**Method of Manufacture and Packaging:** A detailed description of the manufacturing, processing, and packaging procedures for the drug product should be included. A schematic
diagram of the proposed production process, a list of in-process controls, and a master batch production and controls record should be submitted.

2. **Specifications for the Drug Product:** The following test parameters are recommended for MDI drug products.

- **Appearance and Color:** The appearance of the content of the container and the appearance of the container and closure system should be appropriate. If any Color is associated with the formulation then a quantitative test with appropriate acceptance criteria should be established for the drug product.

- **Identification:** Specific identification tests are recommended to verify the identity of the drug substance in the drug product.

- **Microbial Limits:** Appropriate testing should be done to show that the drug product does not support the growth of microorganisms and that microbial quality is maintained throughout the expiration period.

- **Water or Moisture Content:** Testing for the presence of water or moisture in the container should be performed, and should be strictly limited to prevent changes in particle size distribution, morphic form, and other changes such as crystal growth or aggregation.

- **Dehydrated Alcohol Content:** If alcohol is used as a cosolvent in the formulation, there should be a specific assay with acceptance criteria for this excipient.

- **Net Content (Fill) Weight:** The total net weight of all formulation components in the container should be determined.

- **Drug Content (Assay):** The concentration of drug substance in the entire container should be determined analytically with a stability indicating method.

- **Impurities and Degradation Products:** The levels of degradation products and impurities should be determined by means of stability indicating methods. Acceptance criteria should be set for individual and total degradation products and impurities.
**Dose Content Uniformity**: Discharged dose per actuation should remain same. The number of actuations per determination should not exceed the number of actuations in the minimum dose approved in the labelling.

**Dose Content Uniformity through Container Life**: The purpose of this test is to assess whether the product delivers the labelled number of full medication doses throughout the life of the MDI unit, and ensure that there is dose content uniformity for discharges within the same container.

**Particle Size Distribution**: The most important parameter for MDIs is usually the aerodynamic particle size distribution of the outgoing aerosol. This parameter is dependent on the formulation, the valve, and the mouthpiece. The optimum aerodynamic particle size distribution for MDIs has generally been recognized as being in the range of 1–5 microns.

**Microscopic Evaluation**: microscopic examination of the formulation was used to determine drug substance particle size.

**Spray Pattern and Plume Geometry**: Characterization of spray pattern and plume geometry is important for evaluating the performances of the valve and the actuator. Spray pattern testing should be performed on a routine basis as a quality control for the drug product.

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

**Pressure Testing**: This test is recommended for MDI products that are formulated using a cosolvent and/or more than one propellant. The test verifies the internal pressure of the container and ensures the use of proper propellants or propellant mixture ratio.

**Valve Delivery**: This test is directly related to the metering ability of the valve, and it evaluates valve-to-valve reproducibility of the drug product.

**Leachable**: The drug product should be evaluated for compounds that leach from elastomeric plastic components or coatings of the container and closure system.

3. **Drug product characterization studies**

**Determination of Appropriate Storage Conditions**: This test recommended to determine the appropriate stability test storage conditions for the drug product intended for marketing.
Temperature Cycling: A stress temperature cyclic study should evaluate the effects of temperature and associated humidity changes on the quality and performance of the drug product, under extremes of high and low temperatures that may be encountered during shipping and handling.

Effect of Resting Time: This test is recommended to determine the effect of increasing resting time on the first actuation of unprimed MDI units followed immediately by the second and the third actuations.

Priming/Repriming: This test should be performed to characterize the drug product in terms of initial priming and repriming requirements after various periods of non-use.

Effect of Storage on the Particle Size Distribution: During primary stability studies for suspension aerosols, the effect of storage on particle size distribution from the initial actuation to the labelled number of actuations should be evaluated to determine any trends.

Drug Deposition on Mouthpiece: The amount of drug deposited per actuation mouth piece should be documented.

Cleaning Instructions: The frequency of cleaning and related instruction should be included in the labelling.

Profiling of Actuations Near Canister Exhaustion: This test helps to determine proposed overfill of the containers is justified or not and also gives a profile of the dose delivery after the labelled number of actuations.

Plume Geometry: This test should be performed to characterize the plume geometry to help evaluate the performances of the valve and the actuator.

Microbial Challenge: This test should be performed to determine the viability of microorganisms in drug product formulation that has been inoculated intentionally.

In Vitro Dose Proportionality: This test should include characterization of the in vitro dose proportionality in terms of the emitted dose content uniformity and the particle size distribution.
Effect of Varying Flow Rates: This study assesses the sensitivity of the drug product to widely varying flow rates that will be generated by patients of different age and gender and with different severity of disease.

CONTAINER AND CLOSURE SYSTEM
The container closure system consists of the container, the actuator, the valve and its components and spacer (if required) as well as protective packaging if applicable. For MDIs use of a dose counting mechanism should be consider.

STABILITY: stability studies provides a means for checking the acceptable performance of the meter dose inhaler as well as physical and chemical stability of the drug product and compatibility of the formulation with the component of the device.

Regulatry requirements of quality section of meter dose inhaler as per europe [7]
Module 3: Quality section
The quality section contains chemistry, manufacturing, control test (CMC) data that are described below:

1. Pharmaceutical developments

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

Delivered dose: 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.

Priming: priming actuation should be addressed 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 use in some products its use should be validated and relevant information given in the summary product characteristic.

Breath actuated device: Data should be provided 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 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 given.

2. Control of drug product

Moisture content: If necessary this test should be performed.

Delivered dose uniformity: This test should be performed to evaluate the uniformity of delivered dose. 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.
3. Summary of product characteristics

Quantitative and qualitative composition: It should be clearly stated.

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.

MODULE 4: NON CLINICAL SECTION

It is not recommended for both US and EUROPE.

MODULE 5: CLINICAL SECTION

Bioavailability and bioequivalence: Following steps are essential to prove bioequivalence of MDIs.

![Diagram of Step wise approach for bioequivalence](image)

Fig. 3: Step wise approach for bioequivalence

CONCLUSION

Inhalation products are now a days gaining much more importance in the pulmonary drug delivery. Meter Dose Inhaler is widely used in lung diseases such as Asthma and COPD so its regulation is necessary as it delivers the drug to the lungs. From the above study it is concluded that registration of Meter Dose Inhaler in US is more stringent because number of test required as compare to Europe. As discuss above the quality requirements of Meter Dose
Inhaler will be useful from regulatory point of view to the industries which will help them to frame a better strategies for marketing product in US and Europe.

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