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# Guidance for Industry

## Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products

**Chemistry, Manufacturing, and Controls  
Documentation**

### ***DRAFT GUIDANCE***

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
October 1998  
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### Chemistry, Manufacturing, and Controls Documentation

Additional copies are available from:

Drug Information Branch (HFD-210)  
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## **GUIDANCE FOR INDUSTRY<sup>1</sup>**

### **MDI and DPI Drug Products Chemistry, Manufacturing, and Controls Documentation**

*(Due to the length and complexity of this draft guidance,  
please identify specific comment by line number.)*

#### **1 I. INTRODUCTION**

2 This document provides guidance for industry on the chemistry, manufacturing, and controls  
3 (CMC) documentation to be submitted in new drug applications (NDAs) and abbreviated new  
4 drug applications (ANDAs) for metered dose inhalation aerosols and metered dose nasal aerosols  
5 (also known as oral and nasal metered dose inhalers respectively or MDIs) and inhalation powders  
6 (also known as dry powder inhalers or DPIs). This guidance also covers CMC information  
7 recommended for inclusion in the application regarding the components, manufacturing process,  
8 and controls associated with each of these areas. The recommendations in this guidance should  
9 also be considered for investigational drug applications (INDs). The guidance does not address  
10 inhalation solutions and aqueous nasal sprays.

11 The guidance sets forth information that should be provided to ensure continuing drug product  
12 quality and performance characteristics for MDIs and DPIs. The guidance does not impose  
13 mandatory requirements but does put forth acceptable approaches for submitting CMC-related  
14 regulatory information. Alternative approaches may be used. Applicants are encouraged to  
15 discuss significant departures from the approaches outlined in this guidance with the appropriate  
16 Agency division before implementation to avoid expending resources on development avenues  
17 that may later be deemed unacceptable.

18 Reference to information in Drug Master Files (DMFs) for the CMC section of the application is  
19 acceptable if the DMF holder provides written authorization that includes specific reference (e.g.,  
20 submission date, page number, item name and number) to the pertinent and up-to-date  
21 information (21 CFR 314.420(d)). Refer to FDA's *Guideline for Drug Master Files* (September  
22 1989) for more information about DMFs.

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<sup>1</sup>This guidance has been prepared by the Inhalation Drug Products Working Group of the Chemistry, Manufacturing and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on inhalation drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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23 **II. BACKGROUND**

24 **A. Metered-Dose Inhalers (MDIs)**

25 Metered-dose inhalers have grown in popularity since their introduction in the late 1950s,  
26 and they are currently used by over 25 million Americans for a variety of diseases, such as  
27 asthma, chronic obstructive pulmonary disease (COPD), and other lung diseases  
28 characterized by obstruction of airflow and shortness of breath.

29 Metered-dose inhaler products contain therapeutically active ingredients dissolved or  
30 suspended in a propellant, a mixture of propellants, or a mixture of solvents, propellants,  
31 and/or other excipients in compact pressurized aerosol dispensers. An MDI product may  
32 discharge up to several hundred metered doses of one or more drug substances.  
33 Depending on the product, each actuation may contain from a few micrograms (mcg) up  
34 to milligrams (mg) of the active ingredients delivered in a volume typically between 25 and  
35 100 microliters.

36 Although similar in many features to other drug products, MDIs have unique differences  
37 with respect to formulation, container, closure, manufacturing, in-process and final  
38 controls, and stability. These differences need to be considered during the development  
39 program because they can affect the ability of the product to deliver reproducible doses to  
40 patients over the life of the product as well as the product's efficacy. Some of the unique  
41 features of MDIs are listed below:

- 42 1. The container, the valve, the actuator, the formulation, any associated accessories  
43 (e.g., spacers), and protective packaging collectively constitute the drug product.  
44 Unlike most other drug products, the dosing and performance and, therefore, the  
45 clinical efficacy of a MDI may be directly dependent on the design of the container  
46 and closure system (CCS).
- 47 2. The fraction of the formulation delivered to the patient consists of a mixture of  
48 micronized (or solubilized) drug substance in the desired physical form, which may  
49 be within a residual matrix of oily excipient material, propellant, and/or solvent.
- 50 3. Fixed portions of medication from a multidose container can be directly  
51 administered to the patient without contamination or exposure of the remaining  
52 material under normal use conditions. Conversely, portions of the immediate  
53 container's content cannot be removed from a pressurized container for further  
54 modification or manipulation.

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