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DRAFT GUIDANCE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
CMC

X:\CDERGUID\2180DFT.WPD
November 13, 1998

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(Due to the length and complexity of this draft guidance, please identify specific comment by line number.)

I. INTRODUCTION

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

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

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

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[1]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.

II. BACKGROUND

A. Metered-Dose Inhalers (MDIs)

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

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

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

1. The container, the valve, the actuator, the formulation, any associated accessories (e.g., spacers), and protective packaging collectively constitute the drug product. Unlike most other drug products, the dosing and performance and, therefore, the clinical efficacy of a MDI may be directly dependent on the design of the container and closure system (CCS).

2. The fraction of the formulation delivered to the patient consists of a mixture of micronized (or solubilized) drug substance in the desired physical form, which may be within a residual matrix of oily excipient material, propellant, and/or solvent.

3. Fixed portions of medication from a multidose container can be directly administered to the patient without contamination or exposure of the remaining material under normal use conditions. Conversely, portions of the immediate container's content cannot be removed from a pressurized container for further modification or manipulation.

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