Guidance for Industry

Integration of Dose-Counting Mechanisms into MDI Drug Products

DRAFT GUIDANCE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)
Clinical
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Guidance for Industry[1]

Integration of Dose-Counting Mechanisms into MDI Drug Products

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I. INTRODUCTION

This guidance is intended to assist manufacturers who are developing or plan to develop drug products for oral inhalation using metered dose inhalers (MDIs). The guidance reflects the Agency's current recommendations regarding the integration of dose-counting mechanisms into MDI drug products. Although the contents of the guidance should be considered by any manufacturer of any MDI drug product, this guidance is not intended for manufacturers of already marketed MDI drug products, nor for manufacturers developing MDIs for other routes of administration (e.g., nasal MDIs). It is also not intended for manufacturers developing multidose dry powder inhalers (MDPIs), which already incorporate dose-counters as an integral part of the delivery system. (Manufacturers developing new MDPIs are encouraged to continue that practice and may find the contents of this guidance useful in their planning.)

II. BACKGROUND

Metered-dose inhalers have been available for nearly 50 years and have come to be regarded as the preferred method of delivery for many important drugs intended to treat obstructive airway diseases, such as asthma, emphysema, and chronic bronchitis.[2] MDIs represent a reliable, convenient dosing device for delivery of medications to the lungs. However, they have one major disadvantage over other dosage forms. Currently, available MDIs offer no practical way for patients to track the remaining numbers of doses. A complicating, but necessary design feature of

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[1] This guidance has been prepared by the Division of Pulmonary and Allergy Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] *Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 2*, National Asthma Education and Prevention Program of the National Institutes of Health, NIH publication #97-4051, April 1997.

MDIs is that they contain more formulation than strictly required to expel the labeled number of actuations. This additional amount of formulation (propellant, drug substance, and any excipients) is necessary to ensure the dosing consistency of each spray through the labeled number. For instance, an MDI labeled to deliver 120 metered-actuations may expel 20 to 30 additional actuations (depending on the specific fill target for that product). However, the amount of drug per spray in those additional 20 to 30 actuations will be inconsistent and will eventually become negligible. An MDI used beyond the recommended dose may appear to be delivering a therapeutic spray when it isn't. Other than carefully and consistently tracking each actuation in writing and subtracting this total from the labeled number of actuations, there is no method by which a patient can determine how many effective doses are left in an MDI. Various means of *testing* the inhalers (e.g., shaking the canister) are unreliable and can damage the MDI (e.g., the *float-test,* placing the canister in water).

Currently, patients have two practical options: (1) throw away an MDI that still contains acceptable metered-doses or (2) use the product beyond the recommended number of doses and risk not receiving the correct drug dose. The former is wasteful, and the latter is potentially dangerous. Although dose-counting mechanisms have been integrated into multidose dry-powder inhalers (MDPIs), to date, no marketed MDI drug product in the United States has incorporated a dose-counter.

Dose-counters are mechanisms integral to the device and are designed to accurately track the number of actuations used by a patient over the life span of the individual MDI unit. The dose-counter provides the patient with continuing, accurate data on the amount of medication left in the MDI during its full period of use. Technological advances have made it possible for manufacturers to incorporate into their devices economical, reliable, integrated dose-counters to reflect how many actuations remain in a canister.

This guidance is intended primarily for MDI products designed to deliver drugs to the lungs. This is because the consequences of not receiving an acceptable metered dose are more clinically important for oral inhalation drug products than for nasal MDIs. Medications delivered to the lungs often play a vital role in the treatment of airway diseases and are potentially life-saving. Nasally delivered drugs are more typically intended to treat bothersome, but non-life-threatening, conditions.

III. INTEGRATION OF DOSE-COUNTING MECHANISMS INTO MDI PRODUCTS UNDER DEVELOPMENT

A. General Recommendations

The Agency recommends that manufacturers with metered-dose inhalers under development for oral inhalation integrate a dose-counting device into the development of their MDI drug product. Dose-counters should provide, either through a direct numeric count or color coding, a clear indication of when an MDI is approaching the end of its recommended number of actuations as well as when it has reached or exceeded that number. The indication that the MDI is approaching the end of its recommended number of actuations should be designed in such a way as to occur

with sufficient numbers of actuations left so that patients can have enough time to obtain a new MDI. If a numeric count is chosen, we recommend that the counter be designed so that it counts downward from the recommended number of actuations to zero, rather than counting upwards. This should enable patients to know when a device is approaching the end of its life (i.e., the number of actuations is approaching zero).

As previously mentioned, this guidance specifically refers to orally inhaled MDI drug products currently under development or which are being planned for development. Although the integration of dose-counters into currently approved MDIs is also encouraged, it is recognized that the economics of doing so may be burdensome, particularly for MDIs using chlorofluorocarbons as propellants (since these products will eventually be universally phased-out under the provisions of the Montreal Protocol on Protection of the Ozone Layer). Manufacturers with MDI drug products in the latter stages of development are encouraged to integrate a dose-counter into their product as soon as feasible, although this may not be possible prior to submission of a new drug application. In such cases, manufacturers are encouraged to commit to developing an integrated dose-counter in the postmarketing period.

B. Reliability Issues

Dose-counters should be engineered to reliably track actuations and should be designed to be as close to 100 percent reliable as possible. However, if some low frequency of error is unavoidable, the device should be designed to specifically avoid under-counting (i.e., the MDI sprays, but the counter does not advance). Under-counting could result in patients assuming they have medication left in their MDI when they do not, a circumstance that is potentially dangerous. The reliability of dose-counters should be established during development under in-vitro testing (simulating use and potential abuse), as well as in clinical use studies that are designed and conducted to obtain information on the technical function and the perceived utility for patients of the counters in actual use.

C. Other Considerations

A lock-out mechanism to prevent doses beyond the labeled number of actuations would be an optional feature of dose-counters. However, a lock-out feature would not be recommended for bronchodilator medications used to treat acute bronchospasm. For these *rescue bronchodilators*, the ability of the MDI to actuate beyond the labeled number of actuations and to provide even a partially therapeutic dose of drug could be life saving.