Guidance for Industry

Integration of Dose-Counting Mechanisms into MDI Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Clinical Medical
March 2003

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Contains Nonbinding Recommendations

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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 for oral inhalation. Although the contents of the guidance should be *considered* by any manufacturer of *any* MDI drug product (including nasal MDI products), this guidance is not specifically intended for manufacturers of already marketed MDI drug products for oral inhalation 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 including dose counters in their products and may find the contents of this guidance useful in their planning.

For the purposes of this guidance, the term *dose counter* includes both mechanisms that use a numeric count to indicated doses remaining, as well as dose-indicating mechanisms that do not enumerate the number of actuations, but rather indicate via color coding or other means when a device is nearing the end of its useful life. Also, the use of the term *integrated* in this document is intended to define dose counters that are an integral part of the MDI canister and/or actuator, and not simply an add-on that can be removed and used multiple times with various products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[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).

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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 or amount of medication. A complicating, but necessary design feature of 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 may in many cases be inconsistent and with continued use beyond the label claim will become negligible. Since the inactive components in the drug formulation may exceed 95 to 99 percent, 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 some in addition may damage the MDI (e.g., the *float-test,* placing the canister in water).

Currently, patients must guess how many doses are left in their MDIs and have two practical options: (1) throw away an MDI that may still contain acceptable metered-doses or (2) use a product when it may be beyond the recommended number of doses and risk not receiving the correct drug dose. The former is wasteful, and the latter is potentially dangerous. The addition of an accurate dose counter to an individual MDI unit would allow the patient to reliably track the numbers of actuations used from that individual inhaler (i.e., to identify when the label claim number of actuations has been reached). This would prevent the patient from discarding an inhaler unnecessarily or using the product beyond the recommendations provided in the labeling for that product.

The recommendations in this guidance address primarily MDI products designed to deliver drugs to the lungs for any indication. This is because the consequences of not receiving an acceptable metered dose are more clinically important for oral inhalation drug products than for the current medications available in 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. However, if a

[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.

nasal MDI were developed where the issue of dosing beyond the recommended label claimed number of doses were associated with a more serious consequence, this guidance would be applicable.

Finally, this guidance is not intended to preclude other accurate means of informing patients as to the remaining number of metered-doses left in an MDI. If manufacturers develop other ways apart from the use of a dose counter, the FDA is willing to consider those innovations and, if satisfactory, to deem them reasonable alternatives.

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. An indication that an MDI is approaching the end of its recommended number of actuations should occur when a sufficient number of actuations are left to give patients 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, enabling 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 the integration 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 undercounting (i.e., the MDI sprays, but the counter does not advance). Undercounting 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. The documentation of dose counter functionality, reliability, and accuracy would ideally be derived from assessments in clinical trials including, where possible, phase-3 trials. However, for dose counters added either late in a development program or postapproval, in-use studies should be designed and conducted to obtain this information. Note that in either case, these studies do not need to establish the clinical benefit of incorporating a dose counter, rather, they should address issues related to ergonomics, ruggedness, and accuracy of the counters in clinical settings. The range of patients in whom this information is developed should include reasonable representation of special populations likely to use the drug (e.g., pediatrics, geriatrics). Finally, if the same dose counter design and mechanism is incorporated into multiple different MDIs, it would not ordinarily be necessary to repeat the in-use studies for each additional MDI product in which a counter of the same design is used, once the in-use data have been satisfactorily developed with the device. However, since dosing characteristics vary between MDIs, in-vitro testing would ordinarily be expected in all such cases.

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 bronchodilator*s, 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.