Jurisdictional Update: Metered Dose Inhalers, Spacers and Other Accessories

FDA has received inquiries regarding the jurisdiction of metered dose inhalers (MDIs) and accessories to be used with MDIs, such as spacers, actuators, spacers incorporating actuators, dose counters and locking clips. The purpose of this jurisdictional update is to clarify the regulation of these products.

MDIs consist of a pressurized canister containing a drug substance and possibly excipients formulated with a propellant. The formulation is aerosolized through a valve fitted with an actuator (mouthpiece). FDA has concluded that MDIs are drug – device combination products. [1] Based on the agency's determination that the primary mode of action of MDIs is attributable to the drug component, the Center for Drug Evaluation and Research (CDER) has regulated these products under the new drug provisions of the Federal Food, Drug, and Cosmetic Act (the act). This jurisdiction document applies equally to dry powder inhalers.

FDA has received marketing applications covering a variety of accessories intended to be used with MDIs. Many such accessories are "stand-alone" units intended for general use, i.e., they are not provided with or labeled for use in combination with a specific MDI. These products are ordinarily added to CDER-approved MDIs rather used to replace a component of an MDI. When FDA has determined that using the accessory would not alter the safety or efficacy of any MDI regardless of the MDI with which it is used, then the accessory labeling has not limited the use of the accessory to a specific MDI. FDA has ordinarily concluded that such accessories are devices. They have been regulated separately from the MDI by the Center for Devices and Radiological Health (CDRH) under the device provisions of the act. [2] Examples of specific jurisdictional determinations that have been made include the following:

"Stand-alone" Spacers are added to actuators of MDIs. They are essentially hollow tubes through which the aerosol cloud passes to reach the patient, but they are not necessary to deliver aerosolized drug to the patient. They can be "universal" in that they fit many different MDIs and do not replace any components of an approved MDI. These stand-alone spacers ordinarily are not labeled for use with a specific MDI.

Spacers will alter drug delivery characteristics to some extent, but do not specifically modify the approved drug product. CDRH has regulated spacers under the device provisions of the act since the products first became available. Because of this long experience, FDA believes that the safe and effective use of an MDI with a spacer does not ordinarily require that the spacer be labeled for use with a specific MDI. Therefore, CDRH has ordinarily regulated general use spacers under the device provisions of the act.

Locking clips are intended to prevent accidental actuation of the drug while the MDI is in the patient's pocket, purse, etc. Ordinarily, locking clips are removed prior to use of the MDI, although some products permit emergency drug administration while the locking clip is still in place. Locking clips are not ordinarily expected to affect the safety and efficacy of the drug, and locking clip labeling ordinarily does not limit the use of the clip to specific MDIs. In these circumstances, FDA has concluded that these accessories are devices. CDRH has regulated them under the device provisions of the act.

Some accessories are designed to replace a component of a previously approved MDI. In these cases, and in some cases where an accessory is designed to be added to a previously approved MDI, FDA has determined that the accessory must be studied and labeled for use with a particular MDI in order to ensure safe and effective use of the MDI with the accessory. The intended use of these accessories creates a combination product through labeling. 3 In these cases, a lead Center has been assigned based on FDA's determination of the primary mode of action of the combination product. Examples of specific jurisdictional determinations that have been made include the following:

Actuators are an essential part of an MDI; the drug cannot be delivered to the patient without an actuator. Actuators also play a crucial role in the delivery characteristics of MDIs. The concept of a general use actuator is not appropriate because of this link to dosing performance; an actuator significantly affects the safety and efficacy of the drug, and must always be studied with a particular MDI drug. Therefore, replacement actuators have been determined to be device components of combination products. Based on FDA's determination that the primary mode of action of the combination product is attributable to its drug component, actuators have been regulated by CDER under the new drug provisions of the act 4

Spacers incorporating actuators are designed to replace the actuator of an approved MDI. As with replacement actuators without a spacer, the concept of a general use actuator – spacer is not appropriate because an actuator must be studied with a particular drug. Therefore, actuator – spacers have been determined to be device components of combination products. Based on FDA's determination that the primary mode of action of the combination product is attributable to its drug component, spacer - actuators have been regulated by CDER under the new drug provisions of the act.

Dose counters or dose indicators count the number of doses administered by an MDI and display either numerically or by some other means the number of remaining doses, so that the patient will be aware when the drug canister has delivered its labeled contents. The force needed to actuate MDIs may vary from product to product by design, depending on factors such as the valve utilized in the product. For dose counters to provide accurate information, the force needed to actuate the counter must match the force needed to actuate the valve. Otherwise, "count-not-fire" and "fire-not-count" scenarios may occur. The "fire-not-count" scenario is particularly worrisome because the counter may indicate that the drug is available, when in fact the canister is empty.

For this reason, FDA believes that, in most cases, a dose counter must be designed to fit a specific MDI, and labeled for use with a specific MDI. Therefore, dose counters frequently have been determined to be device components of combination products. Based on FDA's determination that the primary mode of action of such a combination product is attributable to its drug component, dose counters have been regulated by CDER under the new drug provisions of the act. If a "universal" dose counter were developed, i.e., one where data demonstrate that the counter would work regardless of the characteristics of the MDI and would not alter drug delivery from the MDI, and so would not need to be labeled for use with a specific MDI, it would likely be considered a device and regulated under the device provisions of the act by CDRH.

For a determination whether a particular accessory to a MDI will be regulated as a device by CDRH or as the device component of a combination product by CDER, contact the Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices, Anesthesiology and Respiratory Devices Branch at 301-796-5580. CDRH will consult with CDER and the Office of Combination Products (OCP) as necessary to make a determination whether the product is a device or the device component of a combination product.

Sponsors who disagree with the placement of a particular product in a particular Center may seek a formal assignment of the product from OCP through the Request for Designation (RFD) process. Further information about the RFD process is available at 21 CFR Part 3 (https://www.ecfr.gov/cgi-bin/text-idx?SID=0fdeb658f6ef1fc1d0344bb72fab9b74&mc=true&node=pt21.1.3&rgn=div5), and in the document "Guidance for Industry and FDA: How to Write a Request for Designation (RFD)," available at the Combination Products (/combination-products) section of the FDA website. It is recommended that sponsors call the Office of Combination Products at 301-796-8930 to discuss their particular situation before submitting an RFD.

For further information about the review and regulation of metered dose inhalers and accessories see:

- Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (/media/70851/download)
- Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators (/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/reviewer-guidance-nebulizers-metered-dose-inhalers-spacers-and-actuators)

Footnotes

1. See 21 CFR § 3.2(e)(1) and (2). See also section VII.A.1(b) of the Intercenter Agreement between CDER and CDRH (/combination-products/classification-and-jurisdictional-information/intercenter-agreement-between-center-drug-evaluation-and-research-and-center-devices-and).

2. See section VII.A.1(a) of the CDER – CDRH Intercenter Agreement.

3. See 21 CFR § 3.2(e)(3).

4. Exception: Actuators that are added to the inspiratory limb of a ventilator circuit, rather than for standard oral inhalation, have been regulated as devices by CDRH under the device provisions of the act.