Guidance for Industry

Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)

DRAFT GUIDANCE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)
Center for Biologics Evaluation and Research (CBER)

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Drug Safety

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION[2]

This guidance is intended to address two topics pertaining to Medication Guides for drug and biological products:[3]

- When FDA intends to exercise enforcement discretion regarding when a Medication Guide must be distributed with a drug or biological product dispensed to a healthcare professional for administration to a patient[4] instead of being dispensed directly to the patient for self-administration or to the patient's caregiver for administration to the patient.
- When a Medication Guide will be required as part of a risk evaluation and mitigation strategy (REMS).

[1] This guidance has been prepared by the Offices of Regulatory Policy, Medical Policy, Surveillance and Epidemiology, New Drugs, Compliance, and Generic Drugs in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] This guidance does not apply to the distribution of Medication Guides to patients participating in clinical trials conducted under an investigational new drug application (IND) because the specific information necessary for safe use of the drug, which is comparable to that contained in a Medication Guide, is required to be made available to study subjects in the informed consent forms and the investigators' brochure. See 21 CFR 50.20 and 50.25; 21 CFR 312.23(a)(5) and 312.55.

[3] When used in this guidance, the term *drug* includes biological drug products.

[4] For purposes of this guidance, the terms *administration* or *administer to a patient* include both (1) when a healthcare professional administers the drug to the patient (e.g., by injection or intravenously) and (2) when the healthcare professional provides the drug to the patient to self-administer while under the healthcare professional's direct supervision (e.g., the healthcare professional hands the patient or the patient's caregiver the drug for the patient to take before leaving the healthcare professional's office).

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

II. BACKGROUND

A. The Medication Guide Regulations

In 1998, FDA issued final regulations establishing requirements for the distribution of patient labeling for certain prescription drug and biological products used primarily on an outpatient basis without direct supervision by a health professional (63 FR 66378, December 1, 1998). These regulations, codified in 21 CFR part 208, apply to certain drug and biological products that FDA determines pose a serious and significant public health concern requiring the distribution of FDA-approved patient medication information that is necessary to patients' safe and effective use of the drug products (a Medication Guide). All Medication Guides are subject to the standard in § 208.1 and the requirements of part 208.

Section 208.1(a) states that Medication Guides apply primarily to human prescription drug products used on an outpatient basis without direct supervision by a health professional and are applicable to both new and refill prescriptions.

Section 208.1(c) authorizes FDA to require a Medication Guide if FDA determines one or more of the following circumstances exist:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Part 208 specifies the content and format of Medication Guides and manufacturer requirements to provide Medication Guides for distribution. Manufacturers of drug products for which a Medication Guide is required must:

- obtain FDA approval of the Medication Guide before the Medication Guide is distributed, and
- ensure that Medication Guides are provided in sufficient numbers, or provide the means to produce Medication Guides in sufficient numbers, to distributors, packers,

and authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the drug product.[5]

Part 208 also specifies the requirements for distribution of Medication Guides:

- Distributors and packers who receive the Medication Guides, or the means to produce Medication Guides, must provide the Medication Guides or the means to provide them to authorized dispensers.[6]
- Each authorized dispenser of a prescription drug product for which a Medication Guide is required must provide the Medication Guide directly to each patient or each patient's agent when the product is dispensed, unless an exemption applies.[7]

Section 208.3(a) and (b) contain the following definitions:

Authorized dispenser is "an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to provide drug products on prescription in the course of professional practice."

Dispense to patients means the "act of delivering a prescription drug to a patient or an agent of the patient either:

(1) By a licensed practitioner or an agent of a licensed practitioner, either directly or indirectly, for self-administration by the patient, or the patient's agent, or outside the licensed practitioner's direct supervision; or

(2) By an authorized dispenser or an agent of an authorized dispenser under a lawful prescription of a licensed practitioner."

B. FDAAA Requirements for Medication Guides as Part of REMS

The Food and Drug Administration Amendments Act of 2007 (FDAAA)[8] created new section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1), which authorizes FDA to require a risk evaluation and mitigation strategy (REMS) when necessary to ensure that the benefits of a drug outweigh the risks. Under section 505-1(e), FDA may require that a REMS for a drug include one or more of the elements described in the subsection,

[5] 21 CFR 208.24(a) and (b).

[6] 21 CFR 208.24(c).

[7] 21 CFR 208.24(e).

[8] Public Law 110-85, September 27, 2007.

including when the criteria in 21 CFR part 208 are met, the requirement for an applicant[9] to develop a Medication Guide for distribution to each patient when the drug is dispensed.

Under part 208, Medication Guides may be safety-related, addressing serious risk(s) (relative to benefits) of which patients should be made aware, and/or efficacy-related, when patient adherence to directions for use is crucial to the drug's effectiveness.[10] Since the enactment of FDAAA, FDA has considered any new Medication Guide (or safety-related changes to an existing Medication Guide) to be part of a REMS. However, the Agency has the authority to determine, based on the risks of a drug and public health concern, whether a Medication Guide should be required as part of a REMS when the standard in part 208 is met, and may decide the Medication Guide should be required as labeling but not part of a REMS if FDA determines that a REMS is not necessary to ensure the benefits of the drug outweigh its risks.

Between March 25, 2008, when the REMS provisions of FDAAA took effect and January 1, 2011, FDA has approved over 150 Medication Guides for products approved under new drug applications (NDAs) and biologic license applications (BLAs) as part of a REMS. One hundred and eight of these REMS were Medication Guide-only REMS. In some cases, Medication Guides have been approved as part of REMS for drugs that are often distributed in inpatient settings or in outpatient settings where the drug is dispensed to a healthcare professional who then administers the drug to the patient. Questions have arisen concerning FDA's policy on whether the Medication Guide must be distributed every time the drug is dispensed because part 208 states that the regulations are intended to apply primarily in the outpatient setting.[11]

FDA can require the development of — or safety-related changes to — a Medication Guide and require these changes to be implemented quickly, whether or not a Medication Guide is part of a REMS. Medication Guides are part of labeling (21 CFR 201.57(c)) and are subject to the safety labeling change provisions of section 505(o)(4) of the FD&C Act, added by FDAAA. Under these provisions, FDA can require the development of a Medication Guide (or safety-related changes to an existing Medication Guide) based on new safety information of which FDA becomes aware after approval of the product. Section 505(o)(4) includes tight timeframes for applicant submission of a supplement containing the labeling changes or a statement detailing the reasons why such a change is not warranted, as well as authority for FDA to order the labeling changes if agreement is not reached within the statutorily specified timeframes.

[9] The Medication Guide regulations refer to *manufacturers*. For purposes of this guidance discussing Medication Guides in the context of the FD&C Act as amended by the FDAAA, we use the term *applicant* to include "holder of an approved covered application" in section 505-1 of the FD&C Act and "responsible person" in section 505(o)(4) of the FD&C Act (21 U.S.C. 355(o)(4)).

[10] 21 CFR 208.1(b) and (c).

[11] 21 CFR 208.1(a)

III. DISCUSSION AND POLICY

A. Distribution of Medication Guides in Certain Settings

1. Discussion

Questions have arisen concerning the requirements for distribution of a Medication Guide when a drug is not dispensed directly to a patient for self-administration or to the patient's caregiver, as anticipated in § 208.1(a), but rather is dispensed or distributed to a healthcare professional who then administers the drug to the patient. For example, in an inpatient setting such as a hospital or nursing home, drugs are dispensed by the hospital pharmacy and then administered by hospital staff to patients. Similarly, in an outpatient setting such as a clinic or infusion center, drugs are dispensed or distributed to a healthcare professional who then administers the drug to the patient, sometimes without the involvement of a dispensing pharmacy or pharmacist. In some cases, these drugs are administered to a patient several times a day or several times a week.

One goal of this guidance is to articulate the circumstances under which FDA intends to exercise enforcement discretion regarding the requirement to dispense Medication Guides in certain settings, such as when it is dispensed to a healthcare professional for administration to a patient in an inpatient setting. We believe that this exercise of enforcement discretion will give patients important information about the drugs they will be taking without burdening the healthcare system to provide repetitive information when no material changes have been made.

2. Distribution Requirements Under Part 208

Medication Guides must be dispensed according to the requirements in 21 CFR part 208. See section II.A.

a. Circumstances under which FDA intends to exercise enforcement discretion regarding Medication Guide distribution

A Medication Guide need not be distributed (i.e., FDA intends to exercise enforcement discretion concerning distribution of a Medication Guide to a patient) when a drug is dispensed under the following circumstances:

- When the drug is dispensed to a healthcare professional for administration to a patient in an inpatient setting, except as provided in b. below.
- When the drug is dispensed to a healthcare professional for administration to a patient in an outpatient setting, such as in a clinic or dialysis or infusion center, except as provided in b. below.

In these settings, the drug will be dispensed to a patient by a healthcare professional who should provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or followup that may be required as appropriate, and answer any questions the patient may have.

b. Circumstances under which FDA will not exercise enforcement discretion and a Medication Guide must be dispensed to a patient in inpatient and outpatient settings

A Medication Guide must be distributed (i.e., FDA does not intend to exercise enforcement discretion) in the following situations:

- When the patient or the patient's agent requests a Medication Guide.
- When a drug is dispensed in an outpatient setting (e.g., retail pharmacy, hospital ambulatory care pharmacy) and the product will then be used by the patient without direct supervision by a healthcare professional.
- The **first** time a drug is dispensed to a healthcare professional for administration to a patient in an outpatient setting, such as in a clinic or dialysis or infusion center.
- The **first** time a drug is dispensed in an outpatient setting of any kind, after a Medication Guide is materially changed. FDA plans to specify in the letter approving a revised Medication Guide when a change is considered to be a material change and applicants will be directed to notify healthcare professionals that a material change was made.

We believe the Medication Guide should be dispensed in outpatient settings, even when the drug is dispensed to a healthcare professional for administration to the patient, the first time the drug is dispensed, and if the Medication Guide is materially changed. In these instances, we would expect the Medication Guide to assist the healthcare professional in communicating important information about the drug to the patient.

FDA intends to exercise enforcement discretion with regard to Medication Guide distribution in certain circumstances as described above. The following table reflects those circumstances, in accordance with the above-described policy.

Table 1: Medication Guide Enforcement Discretion Policy

Setting	Patient or Patient's Agent Requests Medication Guide	Medication Guide Distributed Each Time Drug Dispensed	Medication Guide Distributed At Time of First Dispensing	Medication Guide Distributed When Medication Guide Materially Changed
Inpatient	Must dispense Medication Guide	FDA intends to exercise enforcement discretion; Medication Guide need not be dispensed	FDA intends to exercise enforcement discretion; Medication Guide need not be dispensed	FDA intends to exercise enforcement discretion; Medication Guide need not be dispensed
Outpatient when dispensed to healthcare professional for administration to patient (e.g., clinic, infusion center)	Must dispense Medication Guide	FDA intends to exercise enforcement discretion; Medication Guide need not be dispensed	Must dispense Medication Guide	Must dispense Medication Guide
Outpatient when dispensed directly to patient or caregiver (e.g., retail pharmacy, hospital ambulatory pharmacy)	Must dispense Medication Guide	Must dispense Medication Guide	Must dispense Medication Guide	Must dispense Medication Guide

Please note that when a drug is subject to a REMS that includes specific requirements for the review of a Medication Guide (possibly in conjunction with distribution), FDA does not intend to exercise enforcement discretion regarding those specific requirements set forth in the REMS (e.g., when healthcare providers are required to review the Medication Guide with patients before patients are enrolled in a REMS program as an element to assure safe use).

B. Medication Guides as Part of REMS

1. Policy

While all Medication Guides must meet the standard and requirements in part 208, not every newly required Medication Guide will be an element of a REMS. A REMS is a strategy for managing the risks associated with a drug and a Medication Guide can be one part of that strategy. As the risks associated with the use of a drug increase, the tools needed to ensure safe use of a drug also increase. Depending on the risks involved, FDA may approve a Medication Guide under part 208 without requiring a REMS when that is adequate to address the serious and significant public health concern and meets the standard in § 208.1. In other cases, FDA may determine that a Medication Guide and other elements of a REMS are necessary to ensure that the benefits of a drug outweigh the risks, such as elements to assure safe use. In most cases, FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. However, FDA will include a Medication Guide in a REMS that does not include elements to ensure safe use if we determine that having the Medication Guide without a REMS will not be sufficient to ensure that the benefits of the drug outweigh the risks.

Medication Guides that are required as part of REMS under section 505-1 are subject to the assessment and modification provisions of section 505-1(g) and (h) of the FD&C Act.

2. Procedure for Requesting Removal of Medication Guides from REMS

Applicants who currently have a REMS that includes only a Medication Guide and a timetable for submission of assessments may submit a prior approval supplement that proposes a REMS modification to eliminate the REMS if they do not believe that the REMS is necessary to ensure that the benefits of the drug outweigh the risks. Applicants with a REMS that includes a Medication Guide, a communication plan, and a timetable for assessment also may submit a prior approval supplement that proposes a REMS modification to remove the Medication Guide from the REMS, if they do not believe that a Medication Guide that is a part of the REMS is necessary to ensure that the benefits of the drug outweigh the risks. FDA will review any such supplements and determine whether the Medication Guide is necessary to ensure that the benefits of the drug outweigh the risks of the drug, as a tool of a REMS under section 505-1.

The proposed REMS modification must be accompanied by a REMS assessment.

- If the REMS has been assessed in the past 18 months, the assessment may consist of a statement to that effect.
- If the REMS has not been assessed in the past 18 months, the assessment may consist of an update on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken by the responsible person to investigate a safety issue, including the information required under section 505-1(g)(3)(B) and (C). If the REMS is not eliminated (e.g., the Medication Guide is removed from the REMS but the approved modified REMS still includes a communication plan and timetable for submission of assessments), this assessment to support the REMS modification will not replace any assessments required by the timetable for submission of assessments in the approved REMS.

Even if the Medication Guide is removed from the REMS or the REMS is eliminated, the Medication Guide will continue to be part of the approved labeling in accordance with part 208, unless the FDA approves a supplement removing the Medication Guide from the approved labeling.