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Client Alert

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FDA Publishes Draft Guidance on Medication Guides in Risk Evaluation and Mitigation Strategies

The Food and Drug Administration (FDA) recently published a draft guidance for industry titled *Medication Guides—Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* (Draft Guidance).[1] The document addresses when a medication guide must be distributed with a drug or biological product dispensed to a healthcare professional for administration to a patient instead of being dispensed directly to the patient or to the patient's caregiver. The Draft Guidance also clarifies when a medication guide will be required as part of a REMS.

Background

Medication guides have been required by the FDA since 1998 for certain drugs and biological products that the FDA has determined pose a serious and significant public health concern requiring the distribution of FDA-approved patient medication information necessary to a patient's safe and effective use of the product. Standards for medication guides are set forth in 21 C.F.R. Part 208. 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.

Additionally, medication guides are among the various elements that the FDA has identified for possible inclusion in a REMS submission. The Food and Drug Administration Amendments Act of 2007 (FDAAA) gives the FDA authority to require the establishment of a REMS for certain drugs or biological products when additional elements are required to manage a known or potential serious risk associated with the product. REMS can include any number of strategies designed to ensure that the benefits of the drug or biological product outweigh the risks. Since the enactment of FDAAA, the FDA has considered any new medication guide (or safety related changes to an existing medication guide) to be part of a REMS. However, the FDA has the authority to

1 The FDA notes that the Draft Guidance does not apply to the distribution of medication guides to patients participating in clinical trials conducted under an investigational new drug application. In such cases, the specific information necessary for safe use of the drug is similar to the information in a medication guide and required to be made available to study subjects by federal regulation. A copy of the Draft Guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf.

determine whether a medication guide should be required as part of a REMS when the standards in Part 208 are met. The FDA may decide that a medication guide should be required as labeling, but not part of a REMS, if it concludes that a REMS is not necessary to ensure the benefits of a drug outweigh its risks.

Draft Guidance

Between March 25, 2008, when the REMS provisions of FDAAA took effect, and January 1, 2011, the FDA approved more than 150 medication guides for products approved under new drug applications (NDAs) and biologic license applications (BLAs) as part of a REMS. Of these, 108 REMS were medication guide-only REMS. The Draft Guidance acknowledges that, in some of these cases, medication guides have been approved as part of a 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. As such, questions have arisen concerning the FDA's policy on whether the medication guide must be distributed every time these drugs are dispensed, because Part 208 states that the regulations are intended to apply primarily in the outpatient setting.[2]

Specifically, the Draft Guidance provides that the FDA will exercise its enforcement discretion concerning the distribution of a medication guide to a patient when:

- The product is dispensed to a healthcare professional for administration to the patient in an inpatient setting; or
- In certain outpatient settings, where the healthcare professional administering the product is available to discuss instructions for appropriate use, potential side effects and any follow-up required with the patient.

However, the FDA will continue to require the distribution of a medication guide in the following situations:

- When a medication guide is requested by the patient or his/her agent;
- When the product is dispensed in an outpatient setting (e.g., a retail pharmacy, hospital or ambulatory care pharmacy) and will subsequently be used by the patient without the direct supervision of a healthcare professional;
- The first time the product is dispensed to a healthcare professional for patient administration in an outpatient setting (i.e., clinic or dialysis or infusion center); or
- The first time the product is dispensed in an outpatient setting of any kind after the medication guide is "materially changed" (which is not specifically defined in the Draft Guidance).

2 21 C.F.R. § 208.1(a)

The following table summarizes the FDA's policies:

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 care-giver (e.g., retail pharmacy, hos-pital ambulatory pharmacy)	Must dispense medication guide	Must dispense medication guide	Must dispense medication guide	Must dispense medication guide

The Draft Guidance notes that not every newly-required medication guide will be an element of a REMS and suggests that, in most cases, only REMS with elements to assure safe use will be required to have a medi-cation guide. However, the FDA will make the final determination regarding whether a medication guide should be included as part of a REMS program or merely as part of a product's labeling (i.e., where a REMS is not necessary) and retains the authority to require a REMS in any situation, if a medication guide is necessary to ensure the benefits of the product outweigh the risks.

In addition, the Draft Guidance states that an applicant with a REMS that includes only a medication guide (with a related timetable for assessments) may submit a proposal to eliminate the REMS, through a prior

approval supplement submission, if the applicant believes that the REMS is no longer necessary to ensure the product's benefits outweigh its risks. Applicants with a REMS that includes also a medication guide, communication plan, and timetable for assessments may submit a prior approval supplement submission that proposes a REMS modification to remove the medication guide from the REMS, if they do not believe the medication guide is necessary to ensure that the benefits of the drug outweigh the risks.

The proposal for REMS modification must include a REMS assessment to support the REMS modification that states, if applicable, the REMS has been assessed in the past 18 months or provides an update on the status of any post-approval study or clinical trial required. If the REMS is not eliminated, the applicant must continue to provide any assessments required in the approved REMS. Even if the REMS is eliminated or the medication guide is removed from the REMS, the medication guide will remain part of the approved labeling for the product, unless the FDA approves a supplement providing for its removal from the approved labeling.

Interested parties may submit comments to the Draft Guidance by May 31, 2011, which the FDA will consider before finalizing its policy recommendations.