Guidance for Industry

Medication Guides — Adding a Toll-Free Number for Reporting Adverse Events

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

June 2009
Procedural

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance is intended to assist manufacturers of prescription drugs approved under section 505 of the Federal Food, Drug, and Cosmetics Act (the Act) (21 U.S.C. 355) that are required to have an FDA-approved Medication Guide. On July 1, 2009, FDA expects affected entities to be in compliance with 21 CFR 208.20(b)(7)(iii), which requires that Medication Guides contain a verbatim statement that includes: (1) FDA's toll-free MedWatch phone number and (2) a statement that the number is to be used for reporting purposes only, not to receive medical advice (the side effects statement). Manufacturers must also notify the Agency that the side effects statement has been added to their Medication Guides.

This guidance explains:

- the content and format of the side effects statement,
- where in the Medication Guide to add the side effects statement, and
- how to report to the Agency that the side effects statement has been added to a Medication Guide.

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.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

II. BACKGROUND

The requirement to add a side effects statement to Medication Guides is the result of a series of statutory and regulatory actions. These actions are outlined briefly here.

- In 2001, the Best Pharmaceuticals for Children Act (the BPCA) (Public Law 107-109) directed FDA to issue a final rule requiring the labeling of each human drug product for which an application is approved under section 505 of the Act (21 U.S.C. 355) to include: (1) a toll-free number maintained by FDA for the purpose of receiving reports of adverse events regarding drugs and (2) a statement that the number is to be used for reporting purposes only, not to receive medical advice.
- On April 22, 2004 (69 FR 21778), FDA published a proposed rule entitled *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products*.
- On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). Section 502(f) of FDAAA stated that "the proposed rule *** 'Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products'***shall take effect on January 1, 2008," unless FDA issues a final rule before that date.
- FDA did not issue a final rule prior to January 1, 2008, so by operation of law, the proposed rule took effect on January 1, 2008.
- On January 3, 2008 (73 FR 402), FDA issued an interim final rule, which established a compliance date of January 1, 2009, for including the side effects statement in the labeling for human drug products subject to the rule. The interim final rule stated that FDA anticipated that affected entities would need time to update labeling and systems to comply with the new requirements and that FDA intended to exercise its enforcement discretion and not take action to enforce the requirements in the toll-free number interim final rule until January 1, 2009. The interim final rule codified the modifications made by FDAAA to the proposed rule, including changes to certain requirements for over-the-counter drug products. The rule also stated that FDA planned to complete research begun on the proposed labeling statements and issue a final rule taking into account the results of that research.
- On October 28, 2008 (73 FR 63886), FDA issued a final rule with an effective date of November 28, 2008 and a compliance date of July 1, 2009. FDA delayed the compliance date until July 1, 2009 because of the short time interval between the publication date of the final rule and the original compliance date of January 1, 2009. All affected entities are required to be in compliance by July 1, 2009.

III. HOW TO COMPLY WITH THE REGULATIONS

A. Format and Placement of Required Side Effects Statement

Under section 208.20(b)(7)(iii) (21 CFR 208.20(b)(7)(iii)), the following verbatim statement must be added to FDA-approved Medication Guides for prescription drug products approved under section 505 of the Act:

> **Call your doctor for medical advice about side effects.**
> **You may report side effects to FDA at 1-800-FDA-1088.**

All other provisions of section 208.20(a) (21 CFR 208.20(a)) regarding the content and format of a Medication Guide apply to this labeling statement (e.g., the letter height or type size of the statement should be no smaller than 10 points (1 point = 0.0138 inches) as required by 208.20(a)(4)). No changes or additions may be made to the verbatim statement.[2]

FDA's regulations require affected manufacturers of prescription drug products approved under section 505 of the Act to place the required side effects statement under the following heading in their FDA-approved Medication Guides (see 21 CFR 208.20(b)(7)):

> "What are the possible or reasonably likely side effects of (name of drug)?"

As required by the regulations, this heading must be followed by:

(1) A statement of the adverse reactions reasonably likely to be caused by the drug product that are serious or occur frequently (21 CFR 208.20(b)(7)(i)),

(2) A statement of the risk, if there is one, of patients' developing dependence on the drug product (21 CFR 208.20(b)(7)(ii)), and

(3) For drug products approved under section 505 of the Act, the following verbatim statement: Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 (21 CFR 208.20(b)(7)(iii)).

[2] In some circumstances a manufacturer may wish to include its own phone number for reporting side effects in this section of a Medication Guide. Under section 208.20(b)(7)(iii), a manufacturer may not change FDA's verbatim statement. In accordance with FDA's regulations (see 21 CFR 208.20(b)(8)), the manufacturer's, packer's, or distributor's contact information is included in a general information section of the Medication Guide. To reduce redundancy, we encourage manufacturers to list their contact information in this general information section only. However, if a manufacturer elects to include a phone number for reporting side effects in the section entitled "What are the possible or reasonably likely side effects of... ?" , it can do so after the verbatim statement. The additional language should be separated from FDA's required verbatim statement. Also, the additional language should not modify the intent or meaning of FDA's verbatim statement. We suggest the following language: "You may also report side effects to (manufacturer) at (manufacturer's phone number)". If a manufacturer elects to add this language, it should notify us of this change in an annual report. *See* Section III.B of this document.

B. Submission of Change

For new drug applications (NDAs) and abbreviated new drug applications (ANDAs), regulations at 21 CFR 314.70(b)(2)(v)(B) generally require that any change to a Medication Guide under part 208 be submitted and approved prior to distribution of the product (i.e., in a prior approval supplement). Notwithstanding this general requirement, 21 CFR 314.70(a)(3) requires an applicant to make such a change in accordance with a regulation or guidance that provides for a less burdensome notification of the change.

Pursuant to 21 CFR 314.70(a)(3), notification of inclusion of the side effects statement in a Medication Guide should be provided in an annual report. FDA regards the addition of the side effects statement to a Medication Guide to be a minor change in labeling under 314.70(d)(21 CFR 314.70(d)), particularly since the format and content of the statement are specified by the statute and regulations. A supplemental application should not be submitted to the Agency for preapproval.