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Client Alert

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FDA Issues Draft Guidance on Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application

INTRODUCTION

Recently, the Food and Drug Administration issued a Draft Guidance entitled, *Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without An Approved Application*. The Dietary Supplement and Nonprescription Drug Consumer Protection Act (the "Act"), which amended the Federal Food, Drug, and Cosmetic Act ("FDCA"), required the addition of safety reporting requirements for over-the-counter drug products that are marketed without an approved marketing application, such as those sold pursuant to an OTC drug monograph. Before the enactment of the Act, only those OTC drugs marketed with an approved application were subject to mandatory postmarketing safety reporting requirements. A copy of the document can be accessed here.

The Draft Guidance provides specific instruction on the minimum data elements that should be included in the Individual Case Safety Report ("ICSR") for a serious adverse event and the submission of the drug label with the ICSR. Further, the Draft Guidance describes relevant policies and procedures for submitting the ICSR and any follow-up reports to FDA, and includes detailed information on providing paper and electronic submissions.

While not legally binding on FDA or the pharmaceutical industry, the Draft Guidance summarizes the agency's current thinking and recommendations on postmarketing adverse event reporting for OTC drug products without an approved application.

SUBMITTING REPORTS GENERALLY

Section 760 of the FDCA requires responsible persons to submit to FDA any report received of a serious adverse event associated with the use of an OTC drug marketed without an approved application when the product is marketed in the United States. 21 U.S.C. § 379aa. A "serious adverse event" is an adverse event that involves at least one of the following patient outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of an existing inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Id. In addition, a serious adverse event includes situations where medical or surgical intervention is required, based on reasonable medical judgment, to prevent any of the above-referenced patient outcomes.

A "responsible person" is defined as the manufacturer, packer, or distributor whose name appears on the label of the OTC drug. A responsible person is required to submit an ICSR with a copy of the drug label when it receives a report of any serious adverse event involving the use of the drug in the U.S. Generally, the person who first notifies the responsible person about an

adverse event is considered to be the reporter. Reporters can include patients, relatives of patients, consumers, doctors, pharmacists, other health care practitioners, or other individuals. The responsible person completes an ICSR based on information received from the reporter and any other information received or obtained on an adverse event.

The responsible person must submit a follow-up report when new medical information related to a submitted serious adverse drug event report is received by the responsible person within 1 year of the initial report. The FDCA mandates that serious adverse event reports received through the address or telephone number listed on the product label and all follow-up reports be submitted to the FDA within fifteen business days from the receipt of such information, but the agency recommends that serious event reports obtained through other means also be submitted within the same timeframe. Further, the responsible person must maintain and provide FDA with access to records related to any and all adverse event reports received, whether the event was reported or not, for a period of six years.

MINIMUM DATA ELEMENTS FOR AN ICSR AND SUBMISSION OF THE LABEL

To insure the quality of serious adverse event reports and to facilitate the evaluation of the related drug product, FDA recommends that reasonable efforts be made to obtain complete information for the report and any subsequent follow-up reports. FDA encourages the use of trained health care professionals, computer-assisted interview technology, and targeted questionnaires to improve the interview process. In addition, access to an individual's health care practitioner or medical records should be obtained, with the individual's permission, when appropriate.

In the Draft Guidance, FDA has identified four data elements that are critical for case assessment: (1) an identifiable patient, (2) an identifiable reporter, (3) a suspect drug, and (4) a serious adverse event or fatal outcome. Notably, the agency instructs that the initial ICSR should not be submitted until each data element is obtained. For purposes of the aforementioned 15-day requirement, the date the responsible person receives information on all four of the basic elements is considered Day 0 for purposes of reporting. If, despite due diligence, the responsible person is unable to obtain any of the four data elements, FDA intends to defer from taking any enforcement action. In such cases, the responsible person should maintain a record about the adverse event itself and all efforts to obtain the necessary information.

A copy of the labeling on or within the retail package of a drug must accompany each ICSR submitted to FDA. The agency requires the responsible person to submit a copy of the full outer carton/container label and immediate container label (including the Drug Facts panel and the principal display panel) that are the same as the label on the drug products used, or most likely used, by the patient. If the label has changed since the time of the adverse event, the responsible person may also submit a copy of the drug's current label. For ICSRs submitted on paper (i.e., FDA Form 3500A), the responsible person must submit legible paper copies of these labels, no smaller than actual size, as an attachment to the form. However, for ICSRs submitted electronically, labels must be submitted in an appropriate electronic format that FDA can process, review, and archive. Labels do not have to be resubmitted in any follow-up reports, absent any changes to the label.

FDA's guidelines and recommendations on reporting the minimum data elements in the ICSR and the follow-up reports are described below.

1. Identifiable Patient

For the identifiable patient requirement, adequate information should be provided to verify the existence of a specific consumer. If the serious adverse event involves a group of affected consumers, the responsible person must attempt to determine the identity of each individual and submit a separate report on each patient. Care should be taken to distinguish each patient to insure FDA does not mistake the submissions as duplicate reports of a single adverse event. Providing identification by age, age category (e.g., adolescent, adult, elderly), gender, initials, date of birth, assigned codes/names, or patient identification number would automatically qualify a patient as identifiable. As such, names or addresses of the patient should not be provided to FDA. Instead, the responsible person may assign a code to the patient to permit cross-reference to the patient's contact information for the purposes of future follow-up.

2. Identifiable Reporter

The responsible person should have sufficient information to indicate that there is an identifiable person who purports to have knowledge about the patient, adverse event and drug involved. FDA cautions that the responsible person should be careful not to submit reports if there is a lack of information. The reporter is automatically considered identifiable if a personal identifier (e.g., name), professional identifier (e.g., doctor, pharmacist), or contact information is provided. Although a responsible person should try to obtain contact information of the reporter when possible for follow-up, if the reporter does not want FDA to have any contact information, the responsible person can indicate that the reporter requested anonymity in the appropriate field in the ICSR.

3. Suspect Drug

The responsible person must report, at a minimum, sufficient information to determine the active ingredient suspected to be involved in the serious adverse event. Established product attributes such as dosage form, strength, color, SKU, national drug code, or lot number, should be included in the ICSR. If the serious adverse event involves an OTC drug **and** a dietary supplement, which are equally suspect and manufactured, packaged, or distributed by the same responsible person, the same ICSR should be submitted both to the Center for Drug Evaluation and Research and the Center for Food Safety and Applied Nutrition. Although the product should be identified as a drug and a supplement, only one manufacturer report number should be used.

Similarly, if multiple suspect drugs are involved but all the drugs are related to the same responsible person, only one ICSR should be submitted. The responsible person would submit the ICSR either on the drug product considered the most suspect according to the reporter or, if each drug is equally suspect, on the drug product that is first alphabetically. Information on all suspect drug products would be provided with a single manufacturer report number.

If multiple suspect drugs are involved but they relate to more than one responsible person (e.g., manufacturer A and B), manufacturer A, who receives the serious adverse event report, must submit a completed ICSR as usual and copies of the labels for the suspect drug product(s) related to manufacturer A. Such ICSR should include information about the manufacturer B's product, and FDA further recommends that manufacturer A send manufacturer B a copy of the ICSR with manufacturer A's report number. Upon receipt of such report, manufacturer B is required to submit its own ICSR, citing manufacturer A's report number in the narrative section. Manufacturer B would then include copies of the labels for its own suspect drug product(s) with the ICSR.

Although not expressly required, FDA encourages a responsible person who receives a serious adverse event report about a product manufactured, packaged, or distributed by another responsible person to forward such report to the appropriate responsible person. The appropriate responsible person must then submit an ICSR to FDA in the same manner and timeframe as if the serious adverse event report had been received from a reporter.

4. Serious Adverse Event

The Draft Guidance provides that, at a minimum, a serious adverse event should be described in terms of signs, symptoms, or disease diagnosis for purposes of reporting. For instance, a report stating that a patient "experienced unspecified injury" or a patient "suffered irreparable damages" would not be specific enough for reporting purposes. However, a report of death, even without information about events that led to the death, meets the minimum description of a serious adverse event and should be reported to FDA. The agency encourages the attachment of hospital discharge summaries, autopsy reports, laboratory data, and other clinical data, if such information is relevant and appropriate.

An ICSR must be submitted within 15 business days of receipt of the report of the serious adverse event received through the address or phone number on the label.

SUBMISSION OF FOLLOW-UP REPORTS ON NEW MEDICAL INFORMATION

As noted above, the responsible person must make follow-up reports upon the receipt of any new medical information related to the serious adverse event report in the ICSR for a period of one year after the date of the initial report. FDA recommends, but does not require, that follow-up reports be provided after the 1 year period, if appropriate. Follow-up reports should combine relevant information from the initial ICSR, along with any new medical information, to provide a comprehensive description of the responsible person's current understanding of the serious adverse drug event.

Follow-up reports are identified using the exact identification number, without modification, from the initial ICSR to allow for appropriate linkage of the reports in FDA's Adverse Event Reporting System database. In the follow-up report, corrections to the initial report should be noted and inaccurate information should not be repeated. Similarly, the new information or corrections of inaccurate information in the follow-up report should be highlighted in the report, using appropriate methods such as asterisks or underlining. Any attachments that remain unchanged since the initial report should not be resubmitted.

Follow-up reports should be submitted to document any new, serious adverse event associated with the initial serious adverse event. The responsible person must evaluate the clinical relevance of one serious adverse event to another in determining whether a new initial report or a follow-up report is required. For instance, if the new, serious adverse event occurs due to a subsequent administration of the product, a new initial report, which cites to the manufacturer report number for the original serious adverse event, would be more appropriate than a follow-up report.