Guidance for Industry and FDA Staff

Dear Health Care Provider Letters: Improving Communication of Important Safety Information

DRAFT GUIDANCE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)

November 2010
Procedural

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TABLE OF CONTENTS

Guidance for Industry and FDA Staff[1]

Dear Health Care Provider Letters: Improving Communication of Important Information

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

This guidance provides recommendations to industry and FDA staff on the content and format of Dear Health Care Provider (DHCP) Letters.[2] DHCP letters are correspondence — usually in the form of a mass mailing from the manufacturer or distributor of a human drug or biologic, or from FDA — intended to alert physicians and other health care providers responsible for patient care about important new information regarding a human drug or biologic (hereafter "drug" also refers to biologic and small molecule drug products). These recommendations are also intended to apply to DHCP letters distributed by electronic means (e.g., email) to the extent practical for the type of electronic communication used. This guidance provides recommendations on when to use a DHCP letter, the types of information to include in a DHCP letter, how to organize that information so that it is communicated effectively to health care practitioners, and formatting techniques to make the information more accessible.

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

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] Although not specifically intended for this purpose, the guidance may be used, in appropriate circumstances, to help develop correspondence to meet certain of the communication plan requirements for Risk Evaluation and Mitigation Strategies (REMS) under section 501-1(a)(3) of the Federal Food, Drug, and Cosmetic Act.

New information about prescription drug products emerges throughout a product's lifecycle. For marketed products, there are occasions when it is important to communicate new information promptly to health care practitioners involved in prescribing or dispensing a drug, or in caring for patients who receive a drug. The DHCP letter is one of the mechanisms used to communicate important new information about a marketed product. FDA regulations describe the process for mailing important new information about drug products (21 CFR 200.5), but do not provide criteria for the format and content of the actual letter.

Formal and informal evaluations of DHCP letters have shown that the communication quality of DHCP letters — the extent to which the information is accessible and can be understood — varies widely. A 2005 study (the Mazor study) evaluated the quality of a group of DHCP letters sent during 2000 and 2001 that were intended to communicate important new drug safety information.[3] The Mazor study found a correlation between the quality or perceived quality of a DHCP letter and the extent to which physicians perceive the new information as important. Letters that were evaluated as clearer, more concise, better organized and formatted, and focused on the most important aspects of the new safety information were also considered to be more effective in communicating the new information.

Therefore, FDA believes guidance on the format and content of the DHCP letter would help improve the effectiveness of DHCP letters in communicating drug information. Based on some of the findings and recommendations from the Mazor study, FDA's own experience in evaluating DHCP letters, and the Agency's risk communication experience generally, this guidance provides recommendations to help improve the quality of DHCP letters and their ability to effectively communicate important drug information.

III. FDA CONSULTATION ON DEVELOPMENT OF HDCP LETTERS

FDA believes that effective communication of important new information in DHCP letters can best be accomplished if FDA and the manufacturer work together to determine:

- Whether a DHCP letter should be used to convey new information
- How to present the new information in the letter
- The target audience for the information in the letter

Therefore, FDA encourages manufacturers to consult with the appropriate review division in the development of a DHCP letter to ensure that the letter clearly and accurately reflects both the manufacturer's and FDA's understanding of the issue and the action required to address the issue. In addition to providing a broader range of input into the content of the letter, such consultation could potentially avoid the need to send a corrective letter in the event that FDA determines, after a DHCP letter has been sent, that the content of the letter was somehow false or misleading.

[3] Mazor K, Andrade S, Auger J, et al., "Communicating Safety Information to Physicians: An Examination of Dear Doctor Letters," *Pharmacoepidemiol Drug Safety* 2005;14:869-875.

IV. WHEN TO USE A DHCP LETTER/WHICH TYPES OF DHCP LETTER TO USE

When is a DHCP Letter Needed?

In general, a DHCP letter is used to inform health care practitioners about important new information about a drug. In most cases, the new information is about an important new safety concern that could affect the decision to use a drug or require some change in behavior by health care practitioners, patients, or caregivers to reduce the potential for harm from a drug. In some cases, the new information is about how to improve the effectiveness of a drug. A DHCP letter may also be needed to correct misinformation in advertising or other types of prescription drug promotion. There are three types of DHCP letters described in FDA regulations (21 CFR 200.5):

A. Important Drug Warning Letter

Important Drug Warning DHCP letters should be used to convey important new safety information that "concerns a significant hazard to health" (21 CFR 200.5) and, therefore, could affect the decision to use a drug or require a change in behavior concerning use of the drug (e.g., a specific type of monitoring). This type of DHCP letter should be used for information that is to be incorporated into one or more of the following labeling sections: BOXED WARNINGS, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS. Examples of the types of safety concerns that should be communicated in Important Drug Warning DHCP letters include, but are not limited to:

- Previously unknown serious or life-threatening adverse reactions
- Clinically important new information about a known adverse reaction
- Identification of a subpopulation at greater risk in whom the drug should be used with added caution (e.g., patients with renal or hepatic failure, HIV+ patients)
- Identification of a subpopulation in whom the drug is contraindicated
- Drug interaction or medication error that may result in a serious or life-threatening adverse reaction

B. Important Prescribing Information Letter

Important Prescribing Information DHCP letters should be used to convey important changes to the prescribing information other than those changes that should be described in an Important Drug Warning letter (section IV.A). An Important Prescribing Information DHCP letter should ordinarily be used to convey substantive changes to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections. The types of information that should be communicated in Important Prescribing Information DHCP letters include the following:

- A change in the INDICATIONS section intended to minimize risk or improve effectiveness
- A change to the dose or dosage regimen intended to minimize risk or improve effectiveness

If the new information results in the addition of warning information to the BOXED WARNINGS, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS section and a change to the INDICATIONS or DOSAGE AND ADMINISTRATION section, the letter should be an Important Drug Warning letter. A DHCP letter should not be used merely to announce a new indication.

C. Important Correction of Drug Information Letter

Important Correction of Drug Information DHCP letters are intended to correct false or misleading information or other misinformation in prescription drug promotional labeling and advertising that is the subject of a Warning Letter or other Agency action. Although the circumstances in which FDA would seek to have a manufacturer disseminate corrective information using a DHCP letter are outside the scope of this guidance, this guidance provides recommendations for the format and content of such letters (see, in particular, section V.A.4.b of this document).

V. CONTENT AND FORMAT OF DHCP LETTERS

A. Content Recommendations

In general, to most effectively communicate new information, FDA believes a DHCP letter should clearly state the following at or near the beginning of the letter:

- The purpose of the letter (e.g., to inform prescribers about a specific new drug safety issue)
- The new information
- Existing information that has changed, if any (e.g., information that is no longer valid in light of the new information)
- The action, if any, a health care provider should take in response to the new information

The letter should be clear, concise, and contain sufficient detail to meaningfully inform the target audience. We recommend the letter not exceed two pages. It should also avoid discussion of non-critical information that could obscure the more important information. The letter should contain the appropriate contact information. For example, if the letter concerns an adverse reaction, it should provide manufacturer and FDA contact information for reporting new cases of the reaction. Ordinarily, it will not be sufficient to merely state that the labeling for Drug X has changed and what the new labeling language says. The new information should be summarized, highlighted, and presented as described below, using language from the new labeling, as appropriate.

The content recommendations below are also intended to apply to DHCP letters distributed electronically to the extent practical for the type of communication used. Those intending to distribute a DHCP letter electronically should also consult FDA guidance on using electronic

means to distribute certain product information for additional recommendations specific to electronic distribution.[4]

1. Letter Heading

Depending on the nature of the information contained in the DHCP letter, one of the following statements (corresponding to the three types of DHCP letters) should appear on the envelope (21 CFR 200.5, see section IV). The electronic distribution guidance referenced above contains recommendations on how to make electronically distributed DHCP letters similarly distinctive.

- IMPORTANT DRUG WARNING

- IMPORTANT PRESCRIBING INFORMATION

- IMPORTANT CORRECTION OF DRUG INFORMATION

The letter heading should repeat whichever statement appears on the envelope in the same format (a smaller font may be used, as needed). For a DHCP letter distributed electronically, the letter heading should be the statement that would have appeared on the envelope if paper distribution had been used. Manufacturers whose letters have been reviewed by FDA may also include a statement in the heading indicating that FDA has reviewed the letter and agrees with its contents. Alternatively, FDA's concurrence can be mentioned in the text of the letter.

2. Addressees (Target Audience)

A DHCP letter should be directed to all health care providers who are likely to prescribe, dispense, or administer the drug and others who would have a need to know the information being disseminated. Ordinarily, potential prescribers — the gatekeepers to access to the drug — would be the most important audience for a DHCP letter. Therefore, a manufacturer should make certain to direct the letter to the full range of health care providers who would have occasion to prescribe the drug, including nurse practitioners and physician assistants who have prescribing authority. A DHCP letter should also be directed to other health care providers who may not have occasion to prescribe the drug, but for whom it would otherwise be important to know the information in the letter. For example, the letter should be directed to emergency department or primary care physicians who might not have occasion to prescribe the drug that is the subject of a DHCP letter, but could be providing care for patients with a drug-induced adverse reaction described in the letter. Similarly, a DHCP letter that announces the introduction of a new Medication Guide should be directed to pharmacists who would be required to distribute the Medication Guide to patients.

[4] Guidance for industry on *Using Electronic Means to Distribute Certain Product Information* http://www.fda.gov/RegulatoryInformation/Guidances/ucm125164.htm.

3. Subject Line

Immediately following the heading, a DHCP letter should have a subject line that includes the drug name (proprietary and generic) and a concise description of the issue (e.g., drug safety concern) that is addressed in the body of the letter. The subject line may also include characterization of the relative seriousness of the problem (e.g., serious, life-threatening, or fatal adverse reactions) and the population at risk. Numerical estimates of incidence rate and imprecise terms intended to characterize the incidence of a reaction (e.g., rare, infrequent) should be avoided in the subject line. However, a well-defined increase in the magnitude of risk or rate of a reaction (e.g., rate of reaction X is doubled) might be appropriate. It may also be useful to place the subject line within a border or box, or in bold type, to further draw attention to the information. See the following examples:

Subject: Severe, Life-Threatening, and Fatal Cases of Hepatoxicity Reported with DRUG NAME

Subject: Limitations on Use of DRUG NAME in Patients with Decreased Renal Function Because of Risk of Worsening Renal Function and Increased Mortality

Subject: Threefold Increase in Risk of Macular Edema in Elderly Taking DRUG NAME

4. The Body of the Letter

The beginning of the body of the DHCP letter should briefly summarize only the information essential to a practitioner's understanding of the nature of the problem and how to manage it. This guidance describes a two-paragraph format, but in some cases a single paragraph will be adequate to convey the most important information.

(a) Important Drug Warning or Important Prescribing Information Letters

For letters intended to convey an important drug warning or important new prescribing information, the beginning of the body of the letter should generally be limited to the following types of information to the extent known and relevant to the issue that is subject of the letter:

First Paragraph – Concise Description of the Issue

- The name of the affected product(s) and brief description of what it is used for (more detail about indications can be included in subsequent paragraphs if warranted)

- A brief description of the issue that is cause for the new warning or other change in the prescribing information, including the nature and severity of the issue (e.g., adverse reaction or other potential harm)

- The population or populations at risk, if narrower than the population for whom the drug is indicated

- The degree of risk, if known. If there are reliable rate data from a controlled trial, observational study, or other source, the rate can be included. If the new information is based on spontaneous reports, the number of reports over a specified time period may be included if that number is an important factor in explaining why the Agency is taking regulatory action (even though spontaneous report numbers quickly become outdated).

- Whether the issue is associated with use of the drug for an unlabeled use or population

- Rationale for change in indication or dose

- Why a Medication Guide is needed

Second Paragraph – How Practitioners Should Address the Issue

- Recommended action. Examples include, but are not limited to:

    - Discontinue use
    - Monitor patient for specific clinical findings or laboratory results
    - Perform additional testing before prescribing
    - Reduce dose
    - Limit use to patients with certain characteristics or clinical features (e.g., treatment failures on another drug, patients who do not have a concomitant condition)

- What to tell patients who may be at risk. Examples include, but are not limited to:

    - Patients should be advised to contact their doctor if they experience a specific clinical sign or symptom
    - Patients should be advised to stop the drug immediately if they experience a specific clinical sign or symptom
    - Patients who experience a specific clinical sign or symptom should be advised to consult with their doctor before discontinuing the drug

(b) Correction of Drug Information Letters

For letters intended to correct information in prescription drug advertising or promotional labeling, the first paragraph should specify the following:

- That the purpose of the letter is to correct false or misleading claims or other misinformation
- The information that is false or misleading and why it is incorrect
- The correct information
- Where and in what format the incorrect information was conveyed to health care practitioners
- That the incorrect information was the subject of a Warning Letter or other regulatory action by FDA, if applicable

The remainder of the correction of information letter should be modeled on the general organization and content described in this section.

5. The Interior Paragraphs

Interior paragraphs should be used to provide additional detail that would be helpful in understanding the issue, such as:

- Attributes of affected patient populations or subsets
- Summary of the data or other information that is the basis for a new safety warning (e.g., summary information about a controlled clinical trial, epidemiologic study, or spontaneous adverse event reporting)
- The limitations of that data and information (e.g., what is known and what is not known)
- The mechanism of the adverse reaction
- Whether the event is common to a drug class
- Discussion of additional research being done to better understand an adverse reaction
- Why a promotional claim was false or misleading
- Broader discussion of a drug's indication(s)

6. The Final Paragraph

The final paragraph should include the following information, to the extent relevant:

- Information on how to report new cases of the adverse reaction described in the letter including (1) FDA contact information for reporting events, and (2) company contact information for reporting events and obtaining additional information (this should be a health care provider who can respond directly to inquiries)

- Reference to the full prescribing information (which must be enclosed in the letter) and a Medication Guide or other approved Patient Information, if any

7. Types of Information That Should Generally Not Be in a DHCP Letter

Additional detail that could obscure more important information should generally be omitted from a DHCP letter or placed in a location that would not cause it to divert attention from more important information. Examples of such information include, but are not limited to:

- Information about the worldwide market for the drug or device, including numbers of prescriptions, patient exposures, approvals, and pending approvals
- Extensive details about the design of a clinical study
- Information about a safety review panel convened to assess a safety issue

- A sponsor's plans to further investigate the problem
- Promotional language or claims

B. Format Recommendations

The letter should be formatted in a way that will help make the information in the letter easily accessible to the reader. We recommend use of typographic and formatting techniques to maximize readability, including:

- Informative paragraph headings
- Vertical lists with bullets or numbering, where appropriate
- Text emphasis techniques to draw attention to major points (e.g., bold font, larger font, italics)
- Minimum 12 point font size
- Easily readable font
- Upper and lowercase letters (e.g., avoid all caps)
- Adequate kerning and leading (i.e., letters should not touch within lines, lines of text should not touch one another)
- Use of white space to delineate paragraphs and organize text[5]

These format recommendations are also intended to apply to DHCP letters distributed electronically to the extent practical for the type of communication used (see footnote #4).

VI. ASSESSSMENT OF THE DHCP LETTER IMPACT

To determine whether a DHCP letter has had its intended effect, we recommend that manufacturers conduct an evaluation of the extent to which the target audience received the DHCP letter and is aware of the information that was communicated in the letter. For letters that are intended to modify behavior in the target audience, ideally there would also be an evaluation of the extent to which the DHCP letter changed behavior in the manner described in the letter.

[5] See, for example, Chapparro, B, Baker, JR, Shaikh, AD, Hull, S, and Brady, L, "Reading Online Text: A Comparison of Four White Space Layouts," *Usability News*, 2004. 6(2). Available at http://psychology.wichita.edu/surl/usabilitynews/62/whitespace.htm.