Guidance for Industry

Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

DRAFT GUIDANCE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)

April 2007
Labeling

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Guidance for Industry[1]

Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format[2]

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I. INTRODUCTION

This guidance is intended to help applicants and reviewers draft the DOSAGE AND ADMINISTRATION section of labeling required by 21 CFR 201.57(c)(3). The guidance provides recommendations on the following:

- The types of information that should be included in the section
- A format for organizing that information within the section
- When to include information from other labeling sections in the DOSAGE AND ADMINISTRATION section and how to present that information

The goal of this guidance is to help ensure that the DOSAGE AND ADMINISTRATION section contains all the information needed for safe and effective dosing and administration of a drug and that the information is clear and accessible.

[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] This guidance applies to drugs, including biological drug products. For the purposes of this guidance, *drug product* or *drug* will be used to refer to human prescription drug and biological products that are regulated as drugs.

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. DOSAGE AND ADMINISTRATION SECTION — CONTENT

The DOSAGE AND ADMINISTRATION section should include the following categories of information for each of a drug's indications (see section III.D, Drugs With Multiple Indications) to the extent the information is known and relevant to the safe and effective dosing and administration of the drug. In some cases, types of information not described below would also be appropriate for inclusion in the section. The recommendations and other information included in the DOSAGE AND ADMINISTRATION section should be accompanied by cross-references to any more detailed discussions of the basis for the recommendations or other information in other sections of the labeling.

A. Basic Dosing Information

The section must include the following information (§ 201.57(c)(3)(i)):

- Recommended starting dose, if different from the usual recommended dose
- Usual recommended dose, dosage regimen (e.g., single or divided dose, timing of dosing, primary and booster schedule), and dosage range
- Titration regimen, if there is one
- Duration of use, when duration should be limited (e.g., because of lack of data on long-term use, cumulative toxicity, or tolerance)
- Route(s) of administration
- Duration (or rate) of infusion, if applicable (see section II.K)

In describing the dosage range, if it is known that a drug provides no additional benefit above a certain dose or beyond a certain duration of use, that dose or duration must be identified. Similarly, if it is known that above a certain dose or beyond a certain duration of use, toxicity is increased to an extent that the risk exceeds the benefit, that dose or duration must be identified (§ 201.57(c)(3)(i)(B)).

B. Monitoring to Assess Effectiveness

The section should provide information about any monitoring that should be done to assess effectiveness, including, to the extent available, information about the following:

- the type and frequency of monitoring
- the time to expected onset of treatment effect
- how to adjust dose based on results of monitoring
- on what basis to discontinue a drug because of apparent lack of effectiveness

For example, for a lipid-lowering drug, the section might identify which lipids to monitor, when to monitor, and how to adjust the dose based on lipid profile.

C. Monitoring to Assess Safety

The section should provide information about any safety monitoring that should be done before initiating therapy (e.g., tuberculin skin test before initiating tumor necrosis factor alpha inhibitor therapy), or during therapy to determine whether to stop a drug, withhold or decrease the dose of a drug given repeatedly, delay an additional course of a drug given cyclically, or otherwise adjust the dose or regimen. For example, for a chemotherapeutic agent that causes neutropenia, the labeling might state when the neutrophil nadir is anticipated, when and how long to interrupt treatment for neutropenia, the neutrophil counts needed before a subsequent cycle of therapy can be given, and how to adjust the dose of subsequent cycles in patients who experience severe neutropenia. If the dose adjustment scheme is complex (e.g., is dependent on the type and severity of multiple toxic events), the scheme should usually be displayed in a table, flow diagram, or algorithm.

D. Monitoring for Therapeutic Blood Levels

When it is important to maintain specific therapeutic blood levels of a drug or its metabolites, whether for effectiveness or safety reasons, the section must identify desirable levels (§ 201.57(c)(3)(i)(J)). The section should describe the monitoring needed to assess levels and how to adjust dose based on observed levels.

E. Dosage Modifications Because of Drug Interactions

The section must discuss drug interactions that have important implications for a drug's dosing regimen (e.g., dosage reduction, timing of dose relative to dosing of another drug)(§ 201.57(c)(3)(i)(H)). The discussion should also cross-reference any more detailed discussion of the drug interaction in another section of labeling (for example, the DRUG INTERACTIONS or CLINICAL PHARMACOLOGY section). When there is information that a drug interaction occurs or may occur, but no specific recommendation for dosage modification because of the interaction or potential interaction, the drug interaction should usually not be included in the DOSAGE AND ADMINISTRATION section (see section IV).

F. Dosage Modifications in Special Patient Populations

The section must discuss, as appropriate, dosage modifications needed in special patient populations, including children, geriatric age groups, and patients with renal or hepatic disease (§ 201.57(c)(3)(i)(H)). For example, the section could include a table or graph showing how to adjust dose for use in a pediatric population based on weight. For patients with renal disease, the section could describe how to adjust dose based on

creatinine clearance. The DOSAGE AND ADMINISTRATION section should cross-reference any labeling section that provides a more detailed discussion of the information leading to a dosage adjustment recommendation (e.g., USE IN SPECIFIC POPULATIONS section). If there is information about differences, or potential differences, in metabolism or excretion in a particular population, but no specific recommendation about dosage adjustment because of those differences, that information should ordinarily not be included in the DOSAGE AND ADMINISTRATION section (see section IV).

G. Important Considerations Concerning Compliance With a Dosage Regimen

The section must include important considerations concerning compliance with the dosage regimen (§ 201.57(c)(3)(i)(G), (I)). If close adherence to a dosage regimen is particularly important, the section should explain why it is important and the potential consequences of noncompliance. For example, if it is particularly important that doses be given 8 hours apart, as opposed to three times a day at convenient intervals, the section should explain the importance of 8-hour spacing of doses. Similarly, if a drug must be given at a specific time relative to the ingestion of food (e.g., on an empty stomach, with food) or to the dosing of a drug that is often administered concomitantly, the section should explain the importance of the timing of administration. If there is information adequate to support a recommendation about what to do in the event of a missed dose or doses, the recommendation should be included in the section (e.g., if scheduled dose is missed, skip the dose if within 2 hours of next scheduled dose). Recommendations and information about compliance should be based on data specific to the drug (clinical or clinical pharmacology data). Broad recommendations that are applicable to drug therapy generally should ordinarily be excluded.

H. Premedication and Concomitant Medication Information

1. Premedication

The section should describe any important premedication. For example, if a drug has significant potential to cause hypersensitivity reactions and requires premedication to minimize that potential, the section should describe the premedication regimen for hypersensitivity. The section should also describe any hydration regimen needed to correct volume depletion or adjust volume before administering a drug. The section should also discuss premedication options, if any, that could be used for subsequent doses to enable a patient to continue on a drug after the patient has experienced an adverse reaction.

2. Concomitant Medication

The section should identify and describe any recommended concomitant medications intended to minimize toxicity (e.g., antiemetics administered with chemotherapy) or enhance effectiveness (heparin administered with antithrombotics or thrombolytics for

certain indications). If the drug has been demonstrated to be effective only in combination with another therapy (e.g., an add-on epilepsy therapy), the section should identify the therapy and cross-reference the discussion of combination therapy in the INDICATIONS AND USAGE section.

I. Important Administration Instructions

The section should include any specific administration instructions that are important to the safe and effective use of the drug. For example:

- For ***complex dosage forms***, the section should describe any important administration instructions (e.g., for sustained release tablets — do not crush tablets or do not chew tablets).

- The section can include discussion of alternative ways to take ***solid oral dosage forms*** for patients who have difficulty swallowing where there is information adequate to support the recommended alternatives.

- For ***parenteral dosage forms***, the section should indicate whether the drug is light sensitive, needs to be filtered before administration, and must or must not be administered via central line, and should identify appropriate containers, filters and tubing (e.g., glass, plastic, polyvinyl chloride (PVC)).

- For ***drugs administered intramuscularly or subcutaneously***, the section should indicate whether injection site rotation is necessary and, if so, describe the manner of rotation, any special instructions for injection site preparation, and instructions for any specialized devices or other equipment used in the injection process.

- For ***drugs administered intravenously***, the section should identify potential infusion reactions, discuss how to manage them (e.g., premedication), and cross-reference any more detailed discussion in the WARNINGS AND PRECAUTIONS section.

J. Specific Content for Prepared Products

1 Reconstituted Products

For drugs that require reconstitution, the section must contain the following information to the extent it is necessary for dosing and administering the drug (§ 201.57(c)(3)(iv)).

- Directions for dilution, preparation and, if needed, administration of the dosage form
- Strength (concentration) of the final dosage solution in milligrams of active ingredient per milliliter (unless another measure of strength is more appropriate)
- Storage conditions needed to maintain the stability of the drug or the reconstituted product

The section should also specify the duration for which stability and, if applicable, sterility of a reconstituted product can be ensured if stored under appropriate conditions.

2. Other Prepared Products

For drug products that require some type of preparation other than reconstitution before administration (e.g., a product that is drawn up into a syringe and stored for later use, a frozen product that must be warmed to room temperature before use), the section should discuss appropriate handling and administration procedures.

K. Specific Content for Parenteral Products

For parenteral products, the section must contain the following information to the extent necessary for dosing and administering the drug (§ 201.57(c)(3)(iv)).

- Rate of administration (usually in milligrams per minute) or duration of infusion
- Essential information on drug and diluent compatibilities and incompatibilities
- The following verbatim statement:

> "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

If the parenteral product must be reconstituted, the information listed in section II.J.1 is also required (§ 201.57(c)(3)(iv)).

L. Specific Content for Radioactive Products

For radioactive drugs, the section must contain dosimetry information for both the patient receiving the drug and the person administering the drug (§ 201.57(c)(3)(iii)).

M. Limitations on Distribution

The section should briefly summarize any important limitations or conditions on how the drug may be distributed or prescribed. For example, the section should discuss pertinent aspects of a restricted distribution scheme for a drug approved under 21 CFR part 314, subpart H or 21 CFR part 601, subpart E and cross-reference the more detailed discussion in the WARNINGS AND PRECAUTIONS section.

III. DOSAGE AND ADMINISTRATION SECTION — FORMAT

This section of the guidance describes the recommended format and organization of the content of the DOSAGE AND ADMINISTRATION section described in section II above. The amount and type of dosing and administration information varies considerably across drug products; therefore, a range of different organizational schemes could be used to effectively convey the information.

A. Information Essential to Safe Dosing or Administration of a Drug

In unusual circumstances, certain dosing-related information may be so important for practitioners that it should precede the basic dosing information ordinarily placed at the beginning of the DOSAGE AND ADMINISTRATION section. Information should be placed above the basic dosing information only if lack of knowledge of the information or nonadherence to a recommendation would have serious consequences for patients. Examples of the types of critical dosing information or recommendations that could precede the basic dosing information include:

- The need for hospitalization or close monitoring of vital functions during initiation of therapy (e.g., continuous ECG monitoring)
- Important information concerning intravenous administration, such as instructions to dilute the medication prior to administration, to administer by slow infusion, or to avoid PVC containers and administration sets
- Premedication required to avoid or mitigate life-threatening adverse effects
- Special handling of a dosage form where mishandling may have serious consequences for the patient or others who may come in contact with a drug
- Restricted distribution mechanisms

There should be cross-referencing to any section in labeling that contains more detailed discussions of the critical information or recommendations placed at the beginning of the DOSAGE AND ADMINISTRATION section.

B. Basic Dosing Information

Ordinarily, the DOSAGE AND ADMINISTRATION section should first present the basic dosing information. (Section III.A above describes the exception to this sequence.) This information can be presented in text or in a table or other format intended to make the information clear and accessible. Basic dosing information includes the following types of information to the extent the information is relevant to a drug:

- Starting dose
- Usual recommended dose and dosage regimen
- Titration regimen
- Duration

- Dosage range
- Routes of administration
- Duration (or rate) of infusion, if applicable
- Upper dosage level beyond which safety and effectiveness are not established

C. Other Information Relevant to Dosage and Administration of a Drug

The basic dosing information should be followed by any other information described in section II of this guidance that is known and relevant to dosing or administering the drug. The sequence in which different types of information are presented should reflect the relative importance of the information to safe and effective dosing or administration of a drug. Descriptive subheadings should be used, where appropriate, to make this other relevant information more accessible to the reader (e.g., Dosing in Children, Dosing in Hepatic Impairment, Premedication Regimen, Injection Instructions).

D. Drugs with Multiple Indications

For drugs with multiple indications, it is important that the DOSAGE AND ADMINISTRATION section make clear which information applies generally and which information applies only to a particular indication or indications.

Ordinarily, the dosing information specific to an indication should be presented under a numbered subheading for the indication using the same decimal numbering sequence as the INDICATIONS AND USAGE section (i.e., if an indication is described under subheading 1.1 in **1 INDICATIONS AND USAGE**, the dosing information for that indication should be described under subheading 2.1 in **2 DOSAGE AND ADMINISTRATION**). Alternatively, if a drug has several indications, it may be useful to present basic dosing information for all indications in a single table or under one subheading.

The dosing information specific to an indication should be followed by any other relevant dosing and administration information described in section II of this guidance that is generally applicable to all indications. This information should be presented as described in section III.C above. If information is relevant to more than one indication, but not all indications, to save space the information can be discussed once rather than repeated with each indication. The discussion should make clear to which indications the information is applicable.

IV. WHEN TO INCLUDE INFORMATION FROM OTHER LABELING SECTIONS IN THE DOSAGE AND ADMINISTRATION SECTION

Information about a drug that is relevant to more than one labeling section should be discussed in multiple labeling sections in varying levels of detail. For example, information in WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, and other sections could lead to recommendations to alter the usual dosage regimen in particular situations or take extra precautions when administering a drug and thus warrant some discussion in the DOSAGE AND ADMINISTRATION section.

Typically, information is most relevant to one labeling section, and that section should contain the most detailed discussion of the information. Other sections should discuss only the aspects of the information that are pertinent to the purpose of the section. The following general principles and examples are offered to help applicants decide when to include information from other labeling sections in the DOSAGE AND ADMINISTRATION section.

- Ordinarily, information in another section of labeling should be discussed in the DOSAGE AND ADMINISTRATION section only if the information has specific implications for dosing or administering a drug. Information appropriately placed in the DOSAGE AND ADMINISTRATION section could include recommendations
    - — to lower the usual dose in some situations
    - — to avoid another drug that would commonly be prescribed for the patient's condition
    - — to alter the timing of a dose to mitigate a potential interaction
    - — to take unusual precautions when administering a drug (e.g., due to serious consequences of extravasation)

- The discussion in the DOSAGE AND ADMINISTRATION section of information from a another section should be limited to how dosing or administration is affected in light of that information.

- The discussion in the DOSAGE AND ADMINISTRATION section should cross-reference the more detailed discussion in the other labeling section.

For example, if a drug interaction is well characterized and leads to a specific recommendation to modify the dose of the drug when it is co-administered with the interacting drug, the interaction should be mentioned in the DOSAGE AND ADMINISTRATION section. The discussion should ordinarily be limited to the recommended dosage modification, omitting discussion of the mechanism of the interaction, study findings, or other details of the interaction that would be provided in the DRUG INTERACTIONS or CLINICAL PHARMACOLOGY sections. Conversely, if a drug interaction is suspected based on a shared metabolic pathway, but there is not enough information to support a specific dosage adjustment recommendation, the interaction should ordinarily not be discussed in the DOSAGE AND ADMINISTRATION section**.**

In unusual cases, it may be appropriate to discuss the absence of an effect on dosing or administration. For example, it may be important to mention that a drug does not have an effect on dosing or administration that is common to other members of its class.