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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Eric Brodsky at (301) 796-0855, or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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)

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Revision 1

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Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants in developing the DOSAGE AND ADMINISTRATION section of labeling as described in 21 CFR 201.57(c)(3), a regulation governing the content and format of this section of human prescription drug and biological product labeling,[2] to ensure that this section contains the dosage- and administration-related information needed for safe and effective use of a drug.[3,4] Applicants should follow the recommendations in this guidance when developing the DOSAGE AND ADMINISTRATION section for a new drug submitted to FDA under a new drug application under section 505(b) of

[1] This guidance has been prepared by the Labeling Policy Team, in collaboration with other staff in the Office of New Drugs; other offices in the Center for Drug Evaluation and Research (including the Office of Clinical Pharmacology, Office of Generic Drugs, Office of Medical Policy, Office of Pharmaceutical Quality, Office of Regulatory Policy, Office of Surveillance and Epidemiology); and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drugs, drug products,* and *drug and biological products* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) that are regulated as drugs.

[3] The standard for licensure of a biological product as *potent* under section 351(a) of the PHS Act has long been interpreted to include effectiveness (see 21 CFR 600.3(s)). In this guidance, we use the terms *safety and effectiveness* and *safety*, *purity*, and *potency* synonymously in the discussions pertaining to biological products. See also the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) and the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] This is one of many guidance documents addressing labeling for human prescription drugs. For additional human prescription drug labeling guidance documents, see the FDA's Labeling Resources for Human Prescription Drugs website (available at https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs).

the FD&C Act or a biologics license application under section 351(a) of the PHS Act, and when revising existing information in the labeling for a currently approved drug in a supplement to such applications.[5] This guidance provides examples (denoted with a sawtooth line in the left margin) of required and recommended information in the DOSAGE AND ADMINISTRATION section.[6]

In general, FDA's guidance documents 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. GENERAL PRINCIPLES

Information in the DOSAGE AND ADMINISTRATION section should be presented in a clear, concise manner, using active voice and command language whenever possible. Because the Prescribing Information is written for health care practitioners, information in this section should be presented in a manner that is pertinent and understandable to health care practitioners, which can help reduce medication errors.[7]

Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.[8] This section must be updated when new information becomes available that causes the labeling to be inaccurate, false, or misleading.[9] Applicants should review this section at least annually[10] to ensure that this section contains accurate, clear, and up-to-date information. Information that would ordinarily be required in this section may be omitted if the information is clearly inapplicable.[11]

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[5] See generally, 21 CFR parts 314 and 601.

[6] In the notice announcing the availability of this draft guidance, FDA also withdrew the guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (March 2010), which formerly provided FDA's thinking relating to certain information in the DOSAGE AND ADMINISTRATION section.

[7] Complicated or detailed patient-use instructions regarding preparation, administration, storage, and/or disposal of prescription drugs that are written for patients or caregivers can typically be found in FDA-approved patient labeling (e.g., Instructions for Use). See the guidance for industry *Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2022).

[8] 21 CFR 201.57(c)(3)(ii) and 21 CFR 201.57(c)(15)(i).

[9] 21 CFR 201.56(a)(2).

[10] See section VII.B. (Changes to the Regulations for Applications Not Covered by the Final Rule) in the guidance for industry *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013).

[11] See 21 CFR 201.56(d)(4).

When developing the DOSAGE AND ADMINISTRATION section, consider if information is more appropriate for other sections or subsections of labeling (e.g., package type information should generally be included in the DOSAGE FORMS AND STRENGTHS and HOW SUPPLIED/STORAGE AND HANDLING sections rather than the DOSAGE AND ADMINISTRATION section).

Cross-references to detailed discussions in other sections of labeling that provide the basis for recommendations in the DOSAGE AND ADMINISTRATION section should be included in this section, as appropriate, such as including a cross-reference to the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section that provides the rationale for when a drug should be administered with food.[12]

When developing the DOSAGE AND ADMINISTRATION section, applicants should use the term *dose* to refer to a specific amount of drug taken at one time, and the term *dosage* to refer to a specific amount of drug administered at a specific frequency (and over a certain duration, if applicable). The appropriate term (dosage versus dose) should be used throughout the labeling depending on the information being discussed.

Except where noted in this guidance, information that is not directly related to dosage, preparation, or administration of the drug or storage of the prepared product should ordinarily not be included in the DOSAGE AND ADMINISTRATION section to avoid distracting from or competing with the required and recommended information in this section. Such information may be appropriate for inclusion in other sections of labeling. For example, FDA generally recommends avoiding including the following information in the DOSAGE AND ADMINISTRATION section:

- Contraindications or statements when use is inadvisable (e.g., avoid use, not recommended) in a specific population or with concomitant use of another drug.[13]

- Efficacy data (e.g., "After 4 weeks of therapy, 40% and 10% of patients treated with DRUG-X and placebo achieved a response, respectively.")[14]

Information that is not specific to the drug and is considered general medical knowledge (e.g., information such as "use the optimal dosage" or statements such as "individual patients will experience a variable time to onset and degree of symptom improvement") should generally not

[12] See section IV.B. (Using Cross-References) in the guidance for industry *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements*.

[13] See sections IV.D.2., E., and F. of this guidance for exceptions to this recommendation.

[14] Information on time to achieve a clinically significant effect (e.g., a time to event endpoint), if appropriate, should generally be included in the CLINICAL STUDIES section instead of the DOSAGE AND ADMINISTRATION section. See also the appendix in the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2006).

be included in this section to avoid distracting from or competing with the required and recommended information in this section.

III. ORGANIZATION AND FORMAT

Information in the DOSAGE AND ADMINISTRATION section should be organized and presented in a manner that promotes comprehension and readability. Because the amount and type of information in this section vary considerably across drugs, a range of different organizational schemes may adequately achieve comprehension and readability.

The sequence of dosage- and administration-related information in this section should be based on its relative clinical importance. The most clinically relevant dosage- and administration-related information should generally appear first (e.g., the recommended dosage for each indication and subpopulation, the route(s) of administration, instructions on how and when to administer an orally administered drug relative to the ingestion of food or food substances).[15] Other types of dosage- and administration-related information (e.g., dosage modifications for drug interactions, instructions on how to reconstitute the supplied lyophilized powder, instructions on how to administer a solid oral dosage form with qualified liquids or soft foods) should generally appear later in the section.

A. Subsections

Distribution of content into subsections or addition of headings within subsections[16] in the DOSAGE AND ADMINISTRATION section may be used to enhance the organization, presentation, and accessibility of information.[17] If subsections are created, FDA recommends the following:

- Using subsection headings that accurately reflect the content.

- Presenting the recommended dosage information in a single subsection if the recommended dosage for a drug is the same across multiple approved indications or subpopulations.

- Placing all information under subsections instead of inserting information between the section heading and first subsection heading (i.e., capture information under numbered subsections instead of between the section 2 heading and subsection 2.1) because floating

[15] See section IV.B. in this guidance.

[16] Headings may also be added under the DOSAGE AND ADMINISTRATION section if there are no subsections.

[17] See 21 CFR 201.56(d)(2). Because subsection headings are required to appear in the Full Prescribing Information: Contents (Table of Contents) (see 21 CFR 201.57(b)), the inclusion of subsections in the DOSAGE AND ADMINISTRATION section may assist health care practitioners with locating specific dosage- and administration-related information.

content will not be associated with a specific subsection heading in Full Prescribing Information: Contents[18] and may therefore be less accessible.[19]

- Creating separate subsections for lengthy or complex information (e.g., **2.x Preparation Instructions** and **2.x Administration Instructions**). However, a single subsection should be considered when such information is straightforward (e.g., **2.x Preparation and Administration Instructions**).

If separate subsections are used for the recommended dosage for distinct indications in the DOSAGE AND ADMINISTRATION section, FDA recommends distinguishing these subsection headings from subsection headings in the INDICATIONS AND USAGE section[20] so health care practitioners can more easily locate information about the approved indications and the recommended dosage. For example, if the INDICATIONS AND USAGE section includes the headings **1.1 Disease-A** and **1.2 Disease-B**, instead of using the same subheadings (i.e., **2.1 Disease-A** and **2.2 Disease-B**), use **2.1 Recommended Dosage for Disease-A** and **2.2 Recommended Dosage for Disease-B** in the DOSAGE AND ADMINISTRATION section.

In uncommon circumstances, if a drug has very complicated dosage- and administration-related information, then this section may include a subsection that provides a summary of these complicated recommendations and/or instructions (e.g., **2.x Dosage and Administration Overview**, **2.x Dosage Overview**). This subsection should generally appear first with a cross-reference to details that appear in the other subsections in this section.

[18] See 21 CFR 201.57(b).

[19] If labeling has floating content between the section 2 heading and subsection 2.1, FDA recommends that applicants move the floating content to the appropriate subsection(s) in the DOSAGE AND ADMINISTRATION section.

[20] Subsection headings are not required under the INDICATIONS AND USAGE section; thus, the indications for Disease-A and Disease-B may be listed directly under the INDICATIONS AND USAGE section heading.

B. Tables and Figures

For complex dosage, preparation and administration instructions, or dosage modifications intended to reduce the risk of adverse reactions,[21,22] FDA recommends using tables,[23] figures, bulleted lists, or algorithms in the DOSAGE AND ADMINISTRATION section. Table and figure titles should reflect the content (e.g., if this section includes two or more tables with dosage- and administration-related information about different subpopulations, each table title should include the subpopulation) and should appear in bolded, title case. The text preceding the table or figure should briefly mention or identify the content in the table or figure (e.g., "See Table 1 for the recommended dosage in pediatric patients aged X years and older.").

IV. CONTENT

Information that must appear in the DOSAGE AND ADMINISTRATION section includes, but is not limited to, the drug's recommended dose[24] and, as appropriate:

- The dosage range[25]
- An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness[26]
- Dosages for each indication and subpopulation[27]

[21] For the purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. See 21 CFR 201.57(c)(7).

[22] See section IV.D.1. of this guidance.

[23] Integrating a human factors engineering process in the development of tables that include a large amount of complex dosing information is recommended to ensure their design supports the user's needs and minimizes medication errors.

[24] 21 CFR 201.57(c)(3)(i). We recommend that the term *usual dose* be avoided in drug labeling subject to the content and format requirements under 21 CFR 201.56(d) and 201.57. The term *usual dose* does not appear in 21 CFR 201.57, which is the subject of this guidance, and could be interpreted to refer to the most prescribed dose, which may be inconsistent with the *recommended dose*.

[25] 21 CFR 201.57(c)(3)(i)(A).

[26] 21 CFR 201.57(c)(3)(i)(B).

[27] 21 CFR 201.57(c)(3)(i)(C).

- The intervals recommended between doses[28]
- The optimal method of titrating dosage[29]
- The usual duration of treatment when treatment duration should be limited[30]
- Dosing recommendations based on clinical pharmacologic data[31]
- Specific direction on administration of the dosage form[32] (e.g., route(s) of administration)[33]

The titles of headings in this section of the guidance are being used to organize information in the guidance and do not necessarily represent FDA recommendations for specific subsection headings to be used in the DOSAGE AND ADMINISTRATION section of labeling.

The DOSAGE AND ADMINISTRATION section generally presents the following categories of information, if applicable to the drug. For many drugs, not all categories described below will be applicable.

A. Critical Information for the Safe and Effective Use of the Drug

When certain dosage- and administration-related information is particularly critical to the safe and effective use of the drug (e.g., lack of knowledge of the information or nonadherence to a recommendation could have serious consequences for patients), this information should appear as the first information presented within the DOSAGE AND ADMINISTRATION section. A cross-reference should be included to other subsection(s) in this section or other sections of labeling that contain additional details (e.g., WARNINGS AND PRECAUTIONS).[34] Examples include but are not limited to the following situations:

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[28] 21 CFR 201.57(c)(3)(i)(D).

[29] 21 CFR 201.57(c)(3)(i)(E).

[30] 21 CFR 201.57(c)(3)(i)(F).

[31] 21 CFR 201.57(c)(3)(i)(G).

[32] 21 CFR 201.57(c)(3)(iv).

[33] See 21 CFR 201.100(d)(1).

[34] Detailed descriptions of the clinically significant adverse reactions or risks, or the steps to take to prevent, mitigate, monitor for, or manage the adverse reactions or risks that are not related to dosage or administration modifications should be described in the WARNINGS AND PRECAUTIONS section instead of the DOSAGE AND ADMINISTRATION section. See section II. (WARNINGS AND PRECAUTIONS SECTION) in the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format* (October 2011).

- Medication errors[35] (e.g., attributable to an inappropriate route of administration) have occurred and resulted in serious adverse reactions.

- The dosage form (e.g., injection) needs to be diluted before administration because administration of undiluted drug may result in toxicity.

- Inappropriate substitution of one drug for another drug (e.g., substituting drugoxide liposome injection for drugoxide injection)[36] may lead to clinically significant adverse reaction(s) or loss of effectiveness.[37]

- Infusion rates that exceed the maximum recommended infusion rate have resulted in clinically significant adverse reactions (e.g., hypotension).

- Contact with the product has serious consequences for the patient or the health care practitioner (e.g., radiation safety for radiopharmaceuticals or safe handling of a container with dry natural rubber or natural rubber latex).[38]

- FDA has determined that a drug must be administered in a specific health care setting (e.g., hospital) or by a specific user (e.g., health care practitioner only).[39]

- Evaluations, procedures, or tests (e.g., pregnancy testing in females of reproductive potential for a drug that has embryo-fetal toxicity) are required[40] or necessary (e.g.,

[35] For the purposes of this guidance, a medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care practitioner or patient (see also National Coordinating Council for Medication Error Reporting and Prevention, About Medication Errors | NCC MERP available at https://www.nccmerp.org/about-medication-errors).

[36] The DOSAGE AND ADMINISTRATION section "should include a statement recommending against substituting the liposome drug product for the nonliposome product or another liposome drug product that contains the same active ingredient unless FDA has determined that the products are therapeutically equivalent." See the guidance for industry *Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation* (April 2018).

[37] See section IV.H.2. of this guidance.

[38] See the guidance for industry and FDA staff *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014).

[39] A labeling provision such as this may be based on a risk evaluation and mitigation strategy that FDA approved with elements to assure safe use (ETASU). In this case, the drug's ETASU may require that (1) the drug be dispensed to patients only in certain health care settings, such as hospitals; (2) health care practitioners who prescribe the drug have particular training or experience, or are specially certified; (3) pharmacies, practitioners, or health care settings that dispense the drug are specially certified; (4) the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results; (5) the patient using the drug be subject to certain monitoring; or (6) each patient using the drug be enrolled in a registry. See Section 505-l(f)(3) of the FD&C Act.

[40] Ibid.

evaluating for active tuberculosis and testing for latent tuberculosis) before drug initiation. For example:

> **2.x Recommended Evaluation and Testing Before Initiating DRUG-X**
> Before initiating DRUG-X, evaluate for active tuberculosis and test for latent tuberculosis *[see Warnings and Precautions (5.1)]*.

B. Fundamental Dosage- and Administration-Related Information

Unless there is critical information for the safe and effective use of the drug (as described in section IV.A. of this guidance), FDA generally recommends that the following information appear first within the DOSAGE AND ADMINISTRATION section, because this information describes the fundamental dosage- and administration-related information:[41]

- Recommended dosage information:
  - This section should express the recommended dosage in terms of the drug's recommended dose and, as appropriate, the recommended intervals between doses (i.e., dosing frequency) and duration, if applicable, for each indication. FDA generally recommends using the term *recommended dosage*, as appropriate, in this section of labeling.[42]
  - If appropriate for the drug, the dosage range must be included in this section[43] and should be included with the other recommended dosage information.
  - If applicable, this section should include the recommended starting or loading dose or dosage; the recommended titration schedule; the maximum recommended dosage; and the maximum recommended duration.[44]
  - For weight-based or body surface area-based dosing based on ideal or adjusted body weight, this section should identify the method for calculating the dose.
  - If applicable, this section should include therapeutic drug monitoring information.[45]

[41] If there is critical information for the safe and effective use of the drug (as described in section IV.A. of this guidance), then the recommended dosage and administration information described in this section of the guidance (section IV.B.) will generally appear immediately after the critical information for the safe and effective use of the drug in the DOSAGE AND ADMINISTRATION section.

[42] FDA recommends that the term *usual dosage* be avoided in drug labeling subject to the content and format requirements under 21 CFR 201.56(d) and 201.57. The term *usual dosage* could be interpreted to refer to the most prescribed dosage, which may be inconsistent with the *recommended dosage*.

[43] 21 CFR 201.57(c)(3)(i)(A).

[44] See sections IV.B.1., IV.B.2., IV.B.3., and IV.B.4. in this guidance, respectively.

[45] See section IV.B.9. in this guidance.

- If applicable, this section should include the formula or formulas for calculating the recommended dosage.

- Administration instructions included with the recommended dosage (e.g., route(s) of administration)[46]

If there are important considerations concerning compliance with the dosage regimen[47] (e.g., patient adherence to the recommended dosage), this information must be included in this section and because of its importance, should appear with the elements cited above, appearing close to the beginning of this section. For example, if adherence to a precise dosage is particularly important for the safe and effective use of the drug (e.g., if doses should be given 8 hours apart instead of three times a day), this section should include such information and cross-reference other sections of the labeling that describe the data supporting these specific recommendations (e.g., CLINICAL PHARMACOLOGY, CLINICAL STUDIES).[48]

1. Recommended Starting or Loading Dose or Dosage

If a dosing regimen includes a recommended starting or loading dose or dosage, this information should be included as part of the recommended dosage in the DOSAGE AND ADMINISTRATION section. For example:

2.x Recommended Dosage and Administration
The recommended dosage of DRUG-X is as follows:

- Day 1: Administer a single 50 mg dose by intravenous infusion over 30 minutes (loading dose)
- Day 2: Administer the first 50 mg subcutaneous dose
- Day 9 and thereafter: Administer 50 mg every week subcutaneously

2. Recommended Titration Schedule

If the dosage of a drug is titrated (e.g., increased incrementally to achieve effectiveness while reducing the risk of adverse reactions), the DOSAGE AND ADMINISTRATION section must include the optimal method to titrate the dosage[49] (i.e., recommended titration schedule) and

[46] See section IV.B.8. in this guidance.

[47] 21 CFR 201.57(c)(3)(i)(I).

[48] For more information about recommendations concerning adherence with the dosage regimen, see sections IV.I. and J. of this guidance.

[49] 21 CFR 201.57(c)(3)(i)(E).

should include specific dosage increments and the frequency and timing of the increments. For example:[50]

> **2.x Recommended Dosage and Administration**
> Administer DRUG-X as a continuous intravenous infusion over 48 hours as follows (dosage is based on ideal body weight):
>
> - Initiate at 50 mcg/kg/hour
> - 0 to 4 hours: 50 mcg/kg/hour
> - 4 to 8 hours: 100 mcg/kg/hour
> - 8 to 12 hours: 150 mcg/kg/hour
> - 12 to 48 hours: 200 mcg/kg/hour

3. Maximum Recommended Dosage

The upper (dosage) limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness (i.e., maximum recommended dosage), must be included in the DOSAGE AND ADMINISTRATION section as appropriate.[51]

4. Maximum Recommended Duration

When treatment duration should be limited, the DOSAGE AND ADMINISTRATION section must include the usual duration of treatment.[52] Examples of when treatment duration should be limited include when there are reasonable concerns about the safety or effectiveness of the drug with longer term use, when the disease or condition being treated is limited in duration, and when only short-term use of the drug is recommended to treat or prevent the disease or condition (e.g., when antibacterial drug is used to treat an uncomplicated urinary tract infection).

However, statements about the lack of longer term data should not be included in this section when all the following items apply:

- The effectiveness of a drug for a chronic condition was evaluated only in short-term clinical trials, but these trials were of sufficient duration to support such an approval, and there are no known or anticipated and reasonable safety or effectiveness concerns with respect to longer term use.

[50] This section must also contain specific direction on administration of the dosage form, if needed (see 21 CFR 201.57(c)(3)(iv)). For drugs administered intravenously, include the rate of administration and the recommended infusion duration, if needed, in the DOSAGE AND ADMINISTRATION section.

[51] 21 CFR 201.57(c)(3)(i)(B).

[52] 21 CFR 201.57(c)(3)(i)(F) and see 21 CFR 201.100(d)(1).

- The drug is indicated for long-term use because of the chronic nature of the disease or condition (e.g., drugs for the treatment of hypertension).

In these circumstances, including statement(s) about the lack of longer term data in the DOSAGE AND ADMINISTRATION section may have the unintended effect of inappropriately encouraging health care practitioners to limit the duration of use of the drug. Information on the duration of use of the drug in the clinical trials should generally be discussed in the CLINICAL STUDIES section instead of this section.[53]

5. Recommended Dosage in Pediatric Patients

The recommended dosage in pediatric patients for all approved pediatric indications must be included in the DOSAGE AND ADMINISTRATION section.[54] If the recommended dosage is different between adults and pediatric patients, or among pediatric subpopulations, this section must identify the recommended dosages for each of the pediatric subpopulations[55] (e.g., by pediatric age group, by weight or body surface area). If a pediatric subpopulation should use only a specific age-appropriate dosage form (e.g., oral solution, tablets for oral suspension), this section should so state.

6. Recommended Dosage in Geriatric Patients

If the recommended dosage is different between geriatric patients and adults younger than 65 years of age, the DOSAGE AND ADMINISTRATION section must include the recommended dosage in geriatric patients.[56] This section must include the recommended dosage in geriatric patients for all approved geriatric-specific indications.[57]

[53] Also see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*.

[54] 21 CFR 201.57(c)(3)(i)(C) and (H) and 21 CFR 201.57(c)(9)(iv)(B), (C), and (D). Also see the guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* (March 2019).

[55] Ibid.

[56] 21 CFR 201.57(c)(3)(i)(C) and (H) and 21 CFR 201.57(c)(9)(v)(B)(3). See also the draft guidance for industry *Geriatric Information in Human Prescription Drug and Biological Product Labeling* (September 2020). When final, this guidance will represent the FDA's current thinking on this topic.

[57] 21 CFR 201.57(c)(9)(v)(A). A geriatric-specific indication is an indication only in geriatric patients (or a subset of the geriatric population) and not in younger adult patients. See the draft guidance for industry *Geriatric Information in Human Prescription Drug and Biological Product Labeling*.

7. Recommended Dosage for Fixed-Combination Drug Products and Co-Packaged Products

For the purposes of this guidance, a fixed-combination drug product (FCDP)[58] is one in which two or more active ingredients are combined at a fixed dosage in a single dosage form. For a FCDP, the DOSAGE AND ADMINISTRATION section should identify the recommended dosage of each drug or biologic component. For example, for the fictitious FCDP, DRUG-X (active-ingredient-a, active-ingredient-b, and active-ingredient-c tablets):

> **2.x Recommended Dosage**
> The recommended dosage of DRUG-X is one tablet (containing 500 mg of active-ingredient-a, 250 mg of active-ingredient-b, and 100 mg of active-ingredient-c) orally once daily.

For co-packaged products,[59] this section should identify the recommended dosage for each drug or biological product that is co-packaged. Although FDA generally recommends avoiding including identifying characteristics of a drug in this section,[60] such characteristics may be included in this section if necessary to facilitate safe use of the co-packaged product. For example, for the fictitious co-packaged product, DRUG-X (active-ingredient-a tablets; active-ingredient-b tablets):[61]

> **2.x Recommended Dosage**
> DRUG-X is a co-packaged product containing active-ingredient-a tablets and active-ingredient-b tablets. The recommended oral dosage of DRUG-X is the following:
>
> - In the morning, take 100 mg of active-ingredient-a (one square blue tablet) and 50 mg of active-ingredient-b (one round yellow tablet)
> - In the evening, take 100 mg of active-ingredient-a (one square blue tablet)

[58] FCDPs include drug-drug combinations, biologic-biologic combinations, and drug-biologic combinations. For the purposes of this guidance, the term *FCDP* does not refer to drug-device or biologic-device combination products.

[59] For the purposes of this guidance, a co-packaged drug product is a product that contains two or more separate drugs (e.g., two drugs, two biologics, one drug and one biologic) in their final dosage forms that are intended to be used together for a common or related therapeutic purpose and that are contained in a single package or unit. For the purposes of this guidance, the term *co-packaged products* does not refer to a separate drug and device or a separate biologic and device contained in a single package or unit.

[60] See section II of this guidance.

[61] Data from human factor studies could be used to inform the development of the dosage- and administration-related information for the co-packaged product.

8. Administration Instructions Included With the Recommended Dosage

Certain administration instructions (e.g., route or routes of administration) should be included with the recommended dosage in the DOSAGE AND ADMINISTRATION section.[62]

For example, for orally administered drugs, this section should include specific instructions on how and when to administer the drug relative to the ingestion of food or food substances[63] next to the recommended dosage. If an orally administered drug should be administered on an empty stomach, this section should provide specific instructions on when to administer the drug relative to the ingestion of food or food substances (e.g., "*[[Include recommended dosage]]* Administer DRUG-X on an empty stomach, at least 2 hours prior to or 2 hours after food"). If an orally administered drug can be administered with or without food, then this section should so state.[64] If there are additional pharmacokinetic details on the effects of food on the absorption of orally administered drugs, this section should include a cross-reference to the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section (e.g., "*[[Include recommended dosage]]*. Administer DRUG-X with or without food *[see Clinical Pharmacology (12.3)]*").

When the DOSAGE AND ADMINISTRATION section provides recommendations regarding the administration of an orally administered drug with food and those recommendations are not based on pharmacokinetic or pharmacodynamic data, this section should refer to appropriate sections of labeling that provide the explanation for the recommendation, if applicable. For example, a recommendation to administer the drug with food to reduce the incidence of drug-associated nausea might be based on clinical data comparing such administration to administration without food. In that case, statements in the DOSAGE AND ADMINISTRATION section conveying this recommendation should refer another section where the information concerning nausea (the adverse reaction) would be further discussed (e.g., WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS).

9. Recommended Monitoring for Effectiveness

Therapeutic drug monitoring is used for some drugs as part of the dosing regimen to achieve or maintain effectiveness or to reduce the risk of adverse reactions. If they are established and clinically significant, efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites must be included in the DOSAGE AND ADMINISTRATION section.[65] This section must also include information on when therapeutic

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[62] For additional administration instructions that are required and recommended in the DOSAGE AND ADMINISTRATION section of labeling, see section IV.L. of this guidance.

[63] See the guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations* (June 2022).

[64] Ibid. Although the DOSAGE AND ADMINISTRATION section should generally not include pertinent negative information, given that health care practitioners are particularly interested in food or food substance effects on the recommended dosage of orally administered drugs (if any), FDA recommends including information on the lack of a food effect (e.g., that the drug can be taken with or without food) in this section, as appropriate.

[65] 21 CFR 201.57(c)(3)(i)(J).

drug concentration monitoring is necessary[66] (including recommended frequency of monitoring) and should include dosage modifications based on levels and a cross-reference to other sections of the labeling that include the data that support these recommendations (e.g., CLINICAL PHARMACOLOGY, CLINICAL STUDIES). For example:

> **2.x Recommended Therapeutic Drug Monitoring**
> Obtain plasma trough concentrations of drugoxide after kidney transplant surgery and maintain drugoxide concentrations *[see Clinical Pharmacology (12.3)]* within the following therapeutic drug concentration windows:
>
> - Post-surgery to Month 1: 15 ng/mL to 20 ng/mL
> - Month 1 to 2: 10 ng/mL to 15 ng/mL
> - Month 2 to 6: 7.5 ng/mL to 10 ng/mL
> - After Month 6: 5 ng/mL to 10 ng/mL

If specific monitoring is recommended during drug therapy to determine the lowest effective dosage (i.e., lowest dosage of DRUG-X needed to achieve or maintain effectiveness), this section should include information on the type of monitoring (e.g., the name of the assay or assays needed to detect drug levels), frequency of monitoring, and how to subsequently modify the dosage.[67]

If there is specific information on when to discontinue a drug because of lack of effectiveness, this section should include this information. For example:

> Discontinue DRUG-X if the patient experiences two or more recurrences of Condition-A while taking the recommended dosage.

C. Other Therapy Used Before, During, or After Drug Treatment or Administration

1. Other Therapy Used Before Drug Administration

If there is important information about administering other drugs before initiating the subject drug,[68] this information should be included in the DOSAGE AND ADMINISTRATION section. For example, if premedication is recommended to minimize potential hypersensitivity reactions, this section should describe the premedication regimen and include a cross-reference to the

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[66] Ibid.

[67] Information on the time to onset of efficacy, if available, should generally be included in the CLINICAL STUDIES section, as appropriate, rather than the DOSAGE AND ADMINISTRATION section. See the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*. Also see section IV.D.1. of this guidance for recommendations on monitoring that are needed during drug therapy to modify the dosage or administration to reduce the risk of adverse reactions.

[68] For the purposes of this guidance, the term *subject drug* refers to the drug for which the labeling is being developed.

detailed discussion of hypersensitivity reactions elsewhere in labeling (e.g., WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS).

2. Other Therapy Used During or After Drug Treatment or Administration

If the drug is indicated for use only in conjunction with concomitant therapy,[69] the DOSAGE AND ADMINISTRATION section should identify the concomitant therapy (e.g., concomitant drug or drug class, surgery, or behavior modification). If a drug must be given at a specific time relative to the concomitant therapy for effectiveness, this section should include this information and cross-reference to other sections of the labeling that summarize the data supporting this recommendation, if applicable (e.g., CLINICAL PHARMACOLOGY). FDA generally recommends including such information with the recommended dosage.

If there are concomitant drugs recommended for use during treatment with the subject drug or other drugs recommended for use after administration of the subject drug or after treatment with the subject drug to reduce the risk of adverse reactions (e.g., antiemetics, antimicrobials, corticosteroids), this section should include this information and, as appropriate, should cross-reference to the detailed discussion of these adverse reactions elsewhere in labeling (e.g., WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS). If the subject drug needs to be given at a specific time relative to the timing of a recommended concomitant drug to prevent or reduce the risk of toxicity of the drug, the DOSAGE AND ADMINISTRATION section should include this information and cross-reference other sections that provide support for this recommendation (e.g., CLINICAL PHARMACOLOGY section).

D. Dosage Modifications

When providing information on dosage modifications in the DOSAGE AND ADMINISTRATION section, to reduce the risk of medication errors, FDA generally recommends providing the precise modified dosage rather than the percentage of the original recommended dosage (e.g., state "Reduce the DRUG-X dosage to 1 mg intravenously once daily" instead of "Reduce the DRUG-X dosage by 50%").

1. Dosage Modifications Intended to Reduce the Risk of Adverse Reactions

If there are recommendations on dosage modifications (e.g., dosage reduction, dosage interruption, or permanent discontinuation) intended to reduce the risks of adverse reactions, this information should be included in the DOSAGE AND ADMINISTRATION section. This section should cross-reference the detailed discussion of the adverse reactions in other sections of labeling, as appropriate (e.g., WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS). Detailed descriptions of the clinically significant adverse reactions (or the steps to take to prevent, mitigate, monitor for, or manage the adverse reactions that are not related to

[69] "If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug)," the INDICATIONS AND USAGE section must include a statement that the drug is indicated as an adjunct to that mode of therapy. See 21 CFR 201.57(c)(2)(i)(A).

dosage or administration modifications) should be described in the WARNINGS AND PRECAUTIONS section rather than in the DOSAGE AND ADMINISTRATION section.[70]

Information on tests, procedures, and/or evaluations that are needed during treatment with the drug to modify the dosage or administration due to adverse reactions should be included in this section.[71] However, if such tests, procedures, and/or evaluations will not result in a modification to the recommended dosage or administration, this information should generally appear elsewhere in labeling (e.g., in the WARNINGS AND PRECAUTIONS section). For information on tests, procedures, and/or evaluations needed before drug initiation, see section IV.A. of this guidance.

2. Dosage Modifications for Drug Interactions

If there are dosage modifications for drug interactions with other drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice),[72] the DOSAGE AND ADMINISTRATION section must include this information, as appropriate,[73] and should cross-reference to a detailed discussion of the drug interactions in other sections of labeling (e.g., DRUG INTERACTIONS, CLINICAL PHARMACOLOGY). More specifically, when there is sufficient information to support specific recommendations to modify the dosage or administration of the subject drug (e.g., dosage reduction, alteration of the timing of a dose relative to dosing of another drug) to reduce the risk of a drug interaction, the specific recommendations should be included in the DOSAGE AND ADMINISTRATION section. When there is not enough information to support a specific dosage or administration modification for the subject drug, the drug interaction should ordinarily not be discussed in this section.

FDA generally recommends that contraindications or statements about when use is inadvisable not appear in this section.[74] However, if dosage modification of the subject drug is recommended when it is used with a subgroup of a specific drug interacting class[75] (e.g., the subgroup of CYP3A inhibitors that are moderate CYP3A inhibitors), then:

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[70] See 21 CFR 201.57(c)(6)(i) and the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format*.

[71] See section IV.B.9. of this guidance for recommendations on specific monitoring during drug therapy to determine the lowest effective dosage or to discontinue the drug due to inadequate effectiveness.

[72] 21 CFR 201.57(c)(8)(i).

[73] 21 CFR 201.57(c)(3)(i)(H).

[74] If a use is contraindicated or inadvisable, this information is included in other sections of labeling. Also see section II of this guidance.

[75] For purposes of this guidance, we use the term *drug interacting class* to mean a group of drugs and/or foods that all share a specific characteristic that is relevant to clinically significant drug interaction(s) (e.g., all members of the class have in common a particular effect on drug metabolism). In the case of drugs, the shared characteristic that identifies the drug interacting class may be unrelated to the drug's therapeutic class.

- This section should generally provide recommendations for use of the subject drug for the remaining subgroups in the drug interacting class (e.g., strong CYP3A inhibitors) for completeness, including subgroups in which concomitant use is contraindicated or inadvisable as well as subgroups in which there are no recommended dosage modifications.

- It is generally unnecessary to include a statement in this section that no dosage modification is needed for a remaining drug interacting class that rarely requires dosage modifications (e.g., weak CYP3A inhibitors).

For example:

> **2.x Dosage Modifications for CYP3A Inhibitors**
> Avoid concomitant use with strong CYP3A inhibitors. Reduce the DRUG-X dosage to 20 mg once daily when used concomitantly with a moderate CYP3A inhibitor *[see Drug Interactions (7.x)]*.

If there are dosage modifications for two or more drugs, classes of drugs, or foods, consider including the dosage modifications in one subsection within this section with appropriate headings (e.g., CYP3A Inducers and P-glycoprotein Inhibitors headings appear under **2.x Dosage Modifications for Drug Interactions**).

The description and mechanism of a drug interaction, study findings, clinical implications, and practical instructions for preventing or managing the drug interaction (except for dosage and administration modifications of the subject drug) should not be included in this section. If there are recommended dosage modifications of the concomitant drug, this information should also not be included in this section; rather, this section should include a cross-reference to this information in the DRUG INTERACTIONS section, as appropriate.

E. Dosage in Patients With Renal Impairment

If the dosage in patients with renal impairment is different from the recommended dosage in patients with normal kidney function, the DOSAGE AND ADMINISTRATION section must include the dosage in the applicable renal impairment subpopulation(s).[76,77]

If there are dosage differences for at least one of the renal impairment subpopulation(s) (e.g., patients with an estimated glomerular filtration rate (GFR) less than 30 mL/minute) compared with patients with normal kidney function, dosage recommendations should generally be provided for all subpopulations within the renal impairment population (i.e., patients with

[76] 21 CFR 201.57(c)(3)(i)(C) and (H).

[77] If a subsection providing dosage information in patients with renal impairment is included in the DOSAGE AND ADMINISTRATION section, FDA recommends using a subsection heading such as *Recommended Dosage in Patients with Renal Impairment* rather than *Renal Impairment* because the latter heading is typically a reserved subsection heading in the USE IN SPECIFIC POPULATIONS section to facilitate coding of structured product labeling.

estimated GFR less than 90 mL/minute) in this section, including renal impairment subpopulations in which the:

- Use of the drug is contraindicated or inadvisable[78]

- Recommended dosage is the same as the recommended dosage in patients with normal kidney function

The example below is for DRUG-X, approved only in adult patients,[79] whose recommended dosage in patients with normal kidney function is 2 grams administered intravenously every 8 hours. The estimated GFR bands are based on the data from the clinical studies, not on a renal impairment classification scheme.[80]

2.x Recommended Dosage in Patients With Renal Impairment

The recommended dosage of DRUG-X in patients with renal impairment with a stable estimated GFR is described in Table 1 *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].* Administer each intravenous infusion over 3 hours.

Table 1. Recommended DRUG-X Dosage in Patients With Renal Impairment

Estimated GFR*	Dose	Frequency
50–89 mL/minute	2 grams	Every 8 hours
25–49 mL/minute	1.5 grams	Every 8 hours
15–24 mL/minute	1.5 grams	Every 12 hours
<15 mL/minute or receiving intermittent hemodialysis**	1 gram	Every 12 hours

* If the estimated GFR (eGFR) for an adult patient is calculated using an equation standardized to a body surface area value of 1.73 m^2 (reported in units of mL/minute/1.73 m^2), then multiply the standardized eGFR value by the patient's body surface area and divide by 1.73 to obtain the eGFR in units of mL/minute. Finally, use the eGFR in units of mL/minute to determine the recommended dose and frequency.

** For adult patients with kidney failure receiving intermittent hemodialysis, administer DRUG-X after dialysis.

[78] If the use of the drug is contraindicated or inadvisable in all renal impairment subpopulations, then this information should be included in other sections of the labeling, as appropriate (e.g., BOXED WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, USE IN SPECIFIC POPULATIONS), rather than the DOSAGE AND ADMINISTRATION section (see section II of this guidance).

[79] If a drug is indicated for use only in adults (not pediatric patients), it is not necessary to include the term *adults* in the DOSAGE AND ADMINISTRATION section.

[80] For additional information on how to assess renal function, see section IV.A., Determination of Renal Function, in the draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing* (September 2020). When final, this guidance will represent the FDA's current thinking on this topic.

The example below is for DRUG-X, whose recommended dosage in pediatric patients with normal kidney function is 40 mg/kg orally once daily. The eGFR bands reflect how the drug was dosed in the clinical studies, not on a renal impairment classification scheme.[81]

2.x Recommended Dosage in Pediatric Patients With Renal Impairment

The recommended dosage of DRUG-X in pediatric patients with renal impairment with a stable estimated GFR is described in Table 2 *[see Use in Specific Populations (8.4, 8.6) and Clinical Pharmacology (12.3)]*.

Table 2. Recommended DRUG-X Dosage in Pediatric Patients With Renal Impairment

Estimated GFR*	Dosage**
60–89 mL/minute/1.73 m^2	30 mg/kg orally once daily
30–59 mL/minute/1.73 m^2	20 mg/kg orally once daily
15–29 mL/minute/1.73 m^2	10 mg/kg orally once daily
<15 mL/minute/1.73 m^2 or receiving peritoneal dialysis or hemodialysis	Use is not recommended

* Estimate GFR using an equation validated for use in the appropriate pediatric age range

** Dosage based on actual body weight.

Furthermore, in this section, FDA recommends the following, as appropriate:

- When providing a recommended dosage in patients with renal impairment receiving dialysis, specify the dialysis modality or modalities (e.g., intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapy) instead of using the nonspecific term *dialysis*.

- When providing recommendations for patients receiving intermittent hemodialysis, specify the timing of drug administration in relation to hemodialysis (e.g., "When administered on a hemodialysis day, administer DRUG-X after hemodialysis").

- Avoid using the terms *end-stage renal disease* or *ESRD* because these terms may not accurately describe the degree of renal impairment given that these terms can include patients with kidney failure as well as those with a kidney transplant with normal kidney function.

[81] When providing dosage recommendations in pediatric patients with renal impairment in the DOSAGE AND ADMINISTRATION section, FDA recommends including the following or similar statement given that widely available eGFR equations for adult patients are generally not appropriate for use in pediatric patients: "Estimate GFR using an equation validated for use in the appropriate pediatric age range." See the draft guidances for industry *Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing* and *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, these guidances will represent the FDA's current thinking on these topics.

F. Dosage in Patients With Hepatic Impairment

If the dosage in patients with hepatic impairment (e.g., mild, moderate, or severe) caused by chronic liver disease is different from the recommended dosage in patients with normal hepatic function, the DOSAGE AND ADMINISTRATION section must include the dosage in the applicable hepatic impairment subpopulations.[82] If the dosage in patients with hepatic impairment is included,[83] this section should identify the method used for classifying hepatic function (e.g., the Child-Pugh Classification).[84]

If there are dosage differences for at least one of the hepatic impairment subpopulations (e.g., Child-Pugh C) compared with patients with normal hepatic function, recommendations for use of the drug should generally be provided for all the hepatic impairment subpopulations (e.g., Child-Pugh A, B, and C) in this section, including hepatic impairment subpopulations in which the:

- Use of the drug is contraindicated or inadvisable[85]
- Recommended dosage is the same as the recommended dosage in patients with normal hepatic function

G. Dosage in Other Specific Populations

If the recommended dosage in other specific patient populations (e.g., males and females, patients defined by certain genetic characteristics[86] (such as patients who are CYP2D6 poor metabolizers), postpartum patients, pregnant patients, racial or ethnic subgroups[87]) is different

[82] 21 CFR 201.57(c)(3)(i)(C) and (H).

[83] If a subsection providing dosage information in patients with hepatic impairment is included in the DOSAGE AND ADMINISTRATION section, FDA recommends using a subsection heading such as *Recommended Dosage in Patients with Hepatic Impairment* rather than *Hepatic Impairment* because the latter heading is typically reserved for a subsection heading in the USE IN SPECIFIC POPULATIONS section to facilitate coding of structured product labeling.

[84] Weissenbaum, K, 2019, Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles, Drugs, 79(Suppl 1):S5–S9; Tsoris, A and C Marlar, 2021, Use of the Child Pugh Score in Liver Disease, StatPearls, epub ahead of print, last updated on March 22, 2021, available at https://www.ncbi.nlm.nih.gov/books/NBK542308/.

[85] If the use of the drug is contraindicated or inadvisable in all hepatic impairment subpopulations, then this information should be included in other sections of the labeling, as appropriate (e.g., BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, USE IN SPECIFIC POPULATIONS), rather than the DOSAGE AND ADMINISTRATION section (see section II of this guidance).

[86] See the guidance for industry *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* (January 2013).

[87] See the guidance for industry and FDA staff *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016).

from the recommended dosage in the general population, the DOSAGE AND ADMINISTRATION section must include the dosage in such specific patient populations.[88,89]

H. Information About Switching[90] and Substitution

1. Switching to the Subject Drug

If there is adequate information to support how to switch to the subject drug from other drugs (e.g., drugoxide tablets to drugoxide extended-release tablets, intravenous heparin to an oral anticoagulant) and this information is important for the safety or effectiveness of the subject drug, the DOSAGE AND ADMINISTRATION section should include this information.

2. Cautionary Statements Relating to Substitution

If applicable to the subject drug, the DOSAGE AND ADMINISTRATION section should advise against substitution of one drug for another drug (e.g., substitution of the subject drug for another drug, substitution of another drug for the subject drug) that would lead to harm or loss of effectiveness.[91] In this situation, FDA recommends the use of phrases such as "do not substitute DRUG-X for [insert drug name] *[see Warnings and Precautions (5.x)]."*

FDA recommends avoiding the term *interchangeable* in this section of labeling because it could create confusion with the same term which is generally used in an interchangeable biosimilarity statement in the Highlights of Prescribing Information of interchangeable biosimilar products.[92,93] For example, this section should not state that "drugoxide liposome injection and drugoxide injection are not interchangeable."

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[88] 21 CFR 201.57(c)(3)(i)(C) and (H).

[89] See section IV.B.5., B.6., E., and F. of this guidance for information about the recommended dosage in pediatric patients, geriatric patients, patients with renal impairment, and patients with hepatic impairment, respectively.

[90] The term *switching* here does not refer to *alternating or switching* as described in section 351(k)(4)(B) of the PHS Act.

[91] When certain dosage- and administration-related information is particularly critical to the safe and effective use of the drug this information should appear as the first information presented within the DOSAGE AND ADMINISTRATION section. See section IV.A. of this guidance.

[92] See answer to Question I.28 in the draft guidance for industry *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (November 2020). When final, this guidance will represent the FDA's current thinking on this topic.

[93] See also sections 351(i)(3) and 351(k)(4) of the PHS Act.

I. Recommendations Regarding Missed Dose(s)

If there is adequate information to support dosage or administration recommendations about what to do in the event of missed dose(s), the DOSAGE AND ADMINISTRATION section should include this information.

J. Recommendations in Event of Vomiting After Oral Drug Administration

If there is adequate information to support dosage or administration recommendations about what to do if vomiting occurs after oral drug administration, the DOSAGE AND ADMINISTRATION section should include this information.

K. Recommendations for Drug Discontinuation or Dosage Reduction When There Are Risks of Withdrawal

If there are risks of withdrawal upon abrupt discontinuation or dosage reduction of a drug (e.g., known withdrawal syndrome),[94] the DOSAGE AND ADMINISTRATION section should include instructions for drug discontinuation or dosage reduction, as applicable, including a specific tapering regimen, if available, and should cross-reference additional information about withdrawal reactions in other sections of labeling (e.g., WARNINGS AND PRECAUTIONS, DRUG ABUSE AND DEPENDENCE). For example:

> **2.x Discontinuation of DRUG-X**
> … When discontinuing DRUG-X, decrease the daily oral dosage by 5 mg once weekly until discontinued *[see Drug Abuse and Dependence (9.3)]*.

A detailed description of the withdrawal syndrome after abrupt discontinuation or dosage reduction of a drug (except for the specific instructions for drug discontinuation or dosage reduction) should not be included in this section.[95]

L. Additional Preparation and Administration Instructions

The DOSAGE AND ADMINISTRATION section:[96]

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[94] See the draft guidance for industry *Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[95] The *Dependence* subsection in the DRUG ABUSE AND DEPENDENCE section must provide details on the effects of abrupt withdrawal. See 201.57(c)(10)(iii). That subsection also should summarize signs and symptoms of withdrawal after abrupt discontinuation or dosage reduction of a drug, and additional sections may discuss the clinical effects of dependence (e.g., WARNINGS AND PRECAUTIONS). See the draft guidance for industry *Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products - Content and Format*.

[96] For other required and recommended administration or preparation instructions, see sections IV.A. and B.8. of this guidance.

- Must contain specific directions for preparation of the drug[97] before administration, if needed (e.g., reconstitution of a lyophilized powder, dilution)

- Should identify the compatible diluents (including the volume of diluent required for reconstitution). FDA recommends the use of the strength and the established name of the diluent in this section. For example, use "0.9% Sodium Chloride Injection" instead of "normal saline" or "saline" and use "5% Dextrose Injection" instead of "dextrose in sterile water"

- Must include the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate.[98] In addition, with respect to diluted solutions, this section should also include the strength of the final dosage form (e.g., oral solution, oral suspension) in terms of milligrams of active ingredient per milliliter of diluted solution (unless another measure of the strength is more appropriate). If a drug requires:

  - Only reconstitution before administration, this section should identify the volume of the reconstituted solution to be withdrawn and administered.

  - Only dilution before administration, this section should identify the volume of the diluted solution to be withdrawn and administered.

  - Both reconstitution and dilution before administration, this section should identify the volume of the reconstituted solution to be withdrawn (for dilution) and also identify the volume of the diluted solution to be withdrawn and administered.

This section must also contain specific directions on (i.e., instructions for) the administration of the dosage form, if needed.[99] For example, for drugs administered as follows:

- Intravenously, include the rate of administration (e.g., infusion rate in milligrams per minute) and recommended infusion duration, if needed.[100] For an intravenous push or bolus administration, include the duration of the injection (e.g., administer over X minutes), if needed.[101]

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[97] 21 CFR 201.57(c)(3)(iv).

[98] 21 CFR 201.57(c)(3)(iv). See also United States Pharmacopeia (USP) General Chapter <7> *Labeling*. Applicable provisions of USP General Chapters numbered below 1000 are requirements for compendial drug products if referenced in an applicable USP/National Formulary (NF) monograph, or if they are made applicable through USP General Notices for products with USP/NF monographs. See, for example, sections 501(b) and 502(g) of the FD&C Act. Otherwise, they are recommendations.

[99] 21 CFR 201.57(c)(3)(iv).

[100] Ibid.

[101] See 21 CFR 201.57(c)(3)(iv).

- Intramuscularly or subcutaneously, state the recommended injection site(s) (e.g., gluteal, deltoid) and the rotation schedule, if needed.

  - If more than one injection is needed to achieve a full dose, provide specific administration instructions (e.g., "Administer the second of the two subcutaneous injections at least two inches from the site of the first subcutaneous injection").

  - If the injection depth is important for administration or the injection duration is lengthy (e.g., two minutes or longer), include the recommended injection depth or the recommended duration of the injection, respectively.

If there are known clinically significant adverse reactions or risks associated with inappropriate administration, this section should briefly state the inappropriate administration that is inadvisable and should generally cross-reference to other sections for additional details (e.g., WARNINGS AND PRECAUTIONS). For example, "Do not administer intrathecally *[see Warnings and Precautions (5.x)]*."[102]

If a pediatric subpopulation should not self-administer a drug,[103] the DOSAGE AND ADMINISTRATION section should include this information.

1. Preparation and Administration Instructions for Parenteral Products

If specific containers (e.g., glass, plastic, non-polyvinyl chloride) or devices (e.g., tubing, needles, syringes) are needed for preparation or administration of a parenteral product,[104] the DOSAGE AND ADMINISTRATION section should include this information. If the container(s) or device(s) will not be approved under the new drug application or the biologics license application, the types of container(s) or device(s) should typically be described in this section in general terms rather than identifying a specific manufacturer's product. If there are data that provide important incompatibility information about the use of the drug with specific containers or devices, this section should include information on which containers or devices are incompatible with the drug.

[102] If such information is particularly critical to the safe and effective use of the drug, this information should appear as the first information presented within the DOSAGE AND ADMINISTRATION section. See section IV.A. of this guidance.

[103] Circumstances when pediatric patients should not self-administer the drug include when human factors testing did not evaluate self-administration in pediatric patients.

[104] For the purposes of this guidance, *parenteral* is a general route of administration that is characterized by injection through the skin or other external boundary tissue or implantation within the body. Specific parenteral routes include intra-arterial, intra-articular, intracisternal, intramuscular, intraocular, intrathecal, intravenous, intraventricular, and subcutaneous. See USP General Chapter <1151> *Pharmaceutical Dosage Forms*.

This section must include essential information on drug incompatibilities if the drug is mixed in vitro with other diluents[105] and should include the explanation of the incompatibility.

For parenteral products, this section must include the following verbatim statement:[106]

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

When appropriate, this section should include a statement on when to discard a parenteral product (e.g., "Discard unused reconstituted solution") (also see section IV.L.3. and L.4. and M. of this guidance).[107]

If a parenteral product needs to be filtered before administration, this section should identify the appropriate filter(s) and filter pore size (e.g., low-protein binding, 0.2 micron, in-line filter).

2. Administration Instructions for Certain Dosage Forms

For certain dosage forms, the DOSAGE AND ADMINISTRATION section should include recommended administration instructions that are important for safe and effective use of the drug. For example:

- For *modified-release* dosage forms (e.g., extended-release tablets, delayed-release tablets), if there are:
  - Data that demonstrate a risk associated with manipulating the modified-release product, this section should include the following (or similar) statement: "Swallow tablets whole. Do not split, crush, or chew the extended-release tablets *[see Clinical Pharmacology (12.3)]*."
  - No data to inform the risk associated with manipulating the modified-release product but there is concern that modification may alter the drug's safety or effectiveness, this section should generally provide a rationale. For example: "Swallow tablets whole. Avoid splitting, crushing, or chewing the extended-release tablets because doing so may compromise the extended-release characteristics, effectiveness, or safety of DRUG-X."

[105] 21 CFR 201.57(c)(3)(iv). See section IV.L.8 of this guidance for recommendations regarding information on drug incompatibilities if the drug is mixed in vitro with other drugs.

[106] Ibid.

[107] Discard statements in labeling should be supported by appropriate data on when to stop using an injectable medical product. See USP General Chapter <7>. Also see the guidance for industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018).

- For *system* dosage forms (a drug-containing delivery system that controls the release rate of the drug from the system by diffusion kinetics, active transport, or other means), this section should provide the rate of release and the total duration of the drug release,[108] and instructions for application, rotation, and removal when applicable.

- For *chewable tablets*, this section should include the following (or similar) statement to inform the health care practitioner that chewable tablets must always be chewed or crushed:[109] "Chew or crush DRUG-X completely before swallowing. Do not swallow the chewable tablets whole."

- For *tablets for oral suspension* or *tablets for oral solution*, this section should include a statement to inform the health care practitioner that these dosage forms should be dispersed in liquid and, if applicable, can also be swallowed whole or chewed.[110]

3. Preparation of a Product Stored in the Refrigerator or Freezer

If applicable, the DOSAGE AND ADMINISTRATION section should discuss the time needed to allow a refrigerated or frozen product (supplied or prepared) to warm to room temperature before use. For example:

> **2.x Preparation Instructions**
> Remove the DRUG-X vial from the refrigerator and allow the vial to sit for 30 to 40 minutes at room temperature 20ºC to 25ºC (68ºF to 77ºF) before use. Do not use an external heat source to heat the product because heat may damage the product.

If a refrigerated reconstituted or diluted product is removed from the refrigerator, this section should include recommendations on the length of time the reconstituted or diluted product can be kept at room temperature before use and appropriate discard instructions. For example:

> **2.x Preparation Instructions**
> After removal of the DRUG-X reconstituted solution from the refrigerator, use the reconstituted solution within 2 hours or discard.

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[108] See Appendix A "Dosage Form Terms for Use in Human Drug Product Labeling" in the draft guidance for industry *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018). See also the draft guidance for industry *Transdermal and Topical Delivery Systems – Product Development and Quality Considerations* (November 2019) for more information about the expression of strength and quality considerations that should be considered when supporting the information that is included in the DOSAGE AND ADMINISTRATION section. When final, these guidances will represent the FDA's current thinking on these topics.

[109] See the guidance for industry *Quality Attribute Considerations for Chewable Tablets* (August 2018).

[110] See USP Nomenclature Guidelines, available at https://www.usp.org/sites/default/files/usp/document/usp-nomenclature-guidelines.pdf.

841 *4. Preparation and Storage of Pharmacy Bulk Packages*
842
843 For products supplied as pharmacy bulk packages (PBPs), the DOSAGE AND
844 ADMINISTRATION section should describe proper techniques for preparation of the product
845 and the time frame during which the PBP may be used after initial entry of the container
846 (provided it is held under labeled storage conditions).[111,112] This section should also state that
847 the PBP is not for direct infusion. For example:
848
849 **2.x Preparation and Storage of the Pharmacy Bulk Package**
850 DRUG-X 1,000 mL is supplied as a pharmacy bulk package (PBP) for admixing only and
851 is not for direct intravenous infusion. Before administration, DRUG-X must be transferred
852 to a separate container, prepared, and used as an admixture.
853
854 • Use only in a suitable work area, such as a laminar flow hood or an equivalent clean
855 air compounding area.
856 • Inspect the DRUG-X PBP for particulate matter.
857 • Penetrate the bulk PBP closure only one time using a suitable sterile transfer device
858 or dispensing set that allows measured dispensing of the contents.
859 • Once the container closure is penetrated, transfer the PBP contents within 4 hours and
860 discard any unused contents.
861
862 *5. Preparation/Administration of Solid Oral Dosage Forms With Qualified Liquids*
863 *or Soft Foods*
864
865 If a liquid or soft food is qualified as a vehicle to be used for the administration of a *solid oral*
866 dosage form (e.g., capsules, granules, tablets), the DOSAGE AND ADMINISTRATION section
867 should include directions for using the recommended liquid or soft food vehicle to administer the
868 drug.[113] For example:
869
870 **2.x Preparation and Administration Instructions**
871 Swallow DRUG-X whole. However, for patients who have difficulty swallowing capsules:
872
873 • Carefully open the capsule and sprinkle the entire contents of the capsule onto room
874 temperature applesauce (between a teaspoonful (5 mL) and a tablespoonful (15 mL)).
875 • Stir the mixture for 10 seconds.

[111] USP General Chapter <7>.

[112] For products supplied as imaging bulk packages (IBPs), the DOSAGE AND ADMINISTRATION section should describe proper techniques for preparation of the product and the time frame during which the IBP may be used after initial entry of the container (provided it is held under labeled storage conditions). See USP General Chapter <659> *Packaging and Storage Requirements* for more information about IBPs.

[113] See the draft guidance for industry *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic.

- Consume the entire mixture within 30 minutes of mixing. Do not save the mixture for later use.

6. Preparation and Administration of Oral Dosage Forms Via Enteral Tubes

If there are adequate data that support the use of an oral dosage form (e.g., capsules, granules, oral suspensions, powders, and tablets) via enteral tube, the DOSAGE AND ADMINISTRATION section should include information on the preparation and administration of the oral dosage form via the enteral tube (e.g., nasogastric, gastrostomy, jejunostomy). This section should include, as applicable, the characteristics of the recommended enteral tube, drug product and enteral tube preparation instructions, recommended administration instructions, and instructions on maintenance of the enteral tube following administration.[114]

If specific data exist to warrant a recommendation to not administer an oral dosage form via enteral tube, then this section should so state and provide a brief rationale, if appropriate.[115]

7. Instructions to Avoid Harm Related to Drug Handling and Administration

If mishandling a drug may have serious consequences for the patient or others who may interact with the product (e.g., flammable products, hazardous drugs,[116] radioactive products, products with latex, transdermal systems), the DOSAGE AND ADMINISTRATION section should include instructions to avoid harm related to drug handling and administration.

For hazardous drugs, this section (as well as the HOW SUPPLIED/STORAGE AND HANDLING section) should include the following statement with a numerical citation to the applicable Occupational Safety and Health Administration (OSHA) reference:[117]

DRUG-X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]

For radioactive products, this section should include instructions for avoiding radiation exposure of the patient and health care practitioners administering the drug (e.g., use effective shielding and waterproof gloves, use only under the direction of health care practitioners who are qualified by specific training and experience in the safe use and handling of radioactive materials).

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[114] See the draft guidance for industry *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations* (June 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[115] Ibid.

[116] See Occupational Safety and Health Administration's website about hazardous drugs at https://www.osha.gov/hazardous-drugs.

[117] In this example, the *x* represents a numerical citation to the reference to "OSHA Hazardous Drugs" that should appear in the REFERENCES section. See http://www.osha.gov/hazardous-drugs.

8. Information on Drug Incompatibilities If the Drug Is Mixed In Vitro With Other Drugs

If the drug is mixed in vitro with other drugs, the DOSAGE AND ADMINISTRATION section must include essential information on drug incompatibilities[118] and should include the explanation of the incompatibility. For example:

> **2.x Drug Incompatibilities**
> Avoid admixture of DRUG-X with calcium gluconate injection because ingredient-a in DRUG-X is unstable in the presence of calcium gluconate.

9. Radiation Dosimetry

For radioactive drugs, the DOSAGE AND ADMINISTRATION section must include radiation dosimetry information (e.g., the estimated radiation absorbed for organs and tissues after drug administration) for health care practitioners administering the drug and the patient receiving the drug.[119] FDA recommends that the radiation dosimetry information be presented at the end of this section under a subsection (i.e., the last subsection) entitled **2.x Radiation Dosimetry** to improve accessibility of this information.

10. Liposome Drug Products

See the guidance for industry *Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation* for recommended dosage- and administration-related information for liposome drug products in the DOSAGE AND ADMINISTRATION section.

M. Storage Instructions for the Reconstituted or Diluted Product

The DOSAGE AND ADMINISTRATION section, as appropriate:[120]

- Must contain storage conditions needed to maintain the stability of the reconstituted product, when important[121] and should contain storage conditions needed to maintain the sterility of the reconstituted product

- Should contain storage conditions needed to maintain the stability and sterility of the diluted product

[118] 21 CFR 201.57(c)(3)(iv).

[119] 21 CFR 201.57(c)(3)(iii).

[120] Typically, storage instructions for the reconstituted or diluted product are included with the preparation instructions in the same subsection in the DOSAGE AND ADMINISTRATION section.

[121] 21 CFR 201.57(c)(3)(iv).

- Should include the duration for which the reconstituted or diluted product can be safely used under these storage conditions,[122] and an appropriate discard statement

For example:[123]

> **2.x Storage Instructions for the Reconstituted Product**
> If the DRUG-X reconstituted solution is not used immediately, store at controlled room temperature at 20°C to 25°C (68°F to 77°F) for up to 6 hours or refrigerate at 2°C to 8°C (36°F to 46°F) for no more than 24 hours. Discard the unused DRUG-X reconstituted solution after 6 hours if stored at controlled room temperature or after 24 hours if refrigerated.

Information on storage conditions of the supplied drug (e.g., unopened package) (e.g., "Keep the supplied vial in the outer carton to protect from light.") should not be included in the DOSAGE AND ADMINISTRATION section.[124]

V. ADDITIONAL RECOMMENDATIONS

A. Abbreviations and Symbols

Applicants should consider whether abbreviations and symbols used in the DOSAGE AND ADMINISTRATION section could create the potential for medication errors, and if so, avoid their use.[125] For example, the abbreviation *QD* should be avoided because it has been misread as *QID*; instead, it is preferable to use a phrase like *once daily*.

However, certain commonly used symbols (e.g., /, >, <, ≥, ≤) may sometimes be preferable in this section when there is minimal risk of medication errors and where the replacement of symbols by lengthier, spelled-out words would make the presented information more difficult to read or understand. For example, applicants should consider stating the following:

- "ALT > 3 times upper limit of normal (ULN) to ≤ 5 times ULN" (instead of "ALT greater than 3 times upper limit of normal (ULN) to less than or equal to ALT 5 times ULN")

[122] USP General Chapter <7>.

[123] If the specific temperature ranges have already been described in the DOSAGE AND ADMINISTRATION section (e.g., for controlled room temperature), it is not necessary to repeat the specific temperature ranges in this subsection.

[124] The HOW SUPPLIED/STORAGE AND HANDLING section of labeling must include, as appropriate, storage conditions of the supplied drug (e.g., unopened package). 21 CFR 201.57(c)(17)(iv).

[125] Refer to the Institute for Safe Medication Practices' list of error-prone abbreviations, symbols, and dose designations at https://www.ismp.org/recommendations/error-prone-abbreviations-list.

- "Estimated glomerular filtration rate of 30 mL/minute to 50 mL/minute" (instead of "estimated glomerular filtration rate of 30 mL per minute to 50 mL per minute")

- "5 mg/kg/day" (instead of "5 mg per kg per day")

Additionally, certain widely understood abbreviations that are not associated with medication errors need not be defined in this section (e.g., mg, kg, mL).

B. Metric System

FDA recommends using the metric system for dosage instead of the British Imperial System (e.g., use *kg* instead of *lbs*, and use *mL* instead of *tsp*). FDA recommends that the DOSAGE AND ADMINISTRATION section not state the dosage in both the metric system and the British Imperial System because presenting both units of measure (e.g., kg and pounds) has contributed to medication errors.[126]

C. USP Descriptor

For drug products regulated under NDAs and ANDAs that are recognized in USP, the descriptor *USP* should not be used next to the established name of the drug product in the DOSAGE AND ADMINISTRATION section to avoid cluttering the required and recommended information in this section.[127]

[126] Ibid.

[127] However, if an applicant wants to use the *USP* descriptor next to the established name of such a drug product in labeling, FDA recommends that it appear as such in the DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and/or HOW SUPPLIED/STORAGE AND HANDLING sections.