Human Prescription Drug and Biological Products — Labeling for Dosing Based on Weight or Body Surface Area for Ready-to-Use Containers — "Dose Banding"

Guidance for Industry

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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Labeling

Human Prescription Drug and Biological Products — Labeling for Dosing Based on Weight or Body Surface Area for Ready-to-Use Containers — "Dose Banding" Guidance for Industry

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Contains Nonbinding Recommendations

TABLE OF CONTENTS

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Human Prescription Drug and Biological Products — Labeling for Dosing Based on Weight or Body Surface Area for Ready-to-Use Containers — "Dose Banding" Guidance for Industry[1]

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to assist applicants in incorporating information into proposed human prescription drug labeling for injectable drug products[2] when:

- Dosing for the drug product is based on weight or body surface area (BSA),
- The drug product is available in a range of strengths in *ready-to-use containers*, and
- The entire drug content of the ready-to-use container(s) is intended to be administered to a patient.

For the purposes of this guidance, this practice is referred to as *dose banding*.

This guidance applies to proposed labeling in a new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act);[3] a biologics license

[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] For the purposes of this guidance, the term *drug product* or *drug products* refers, unless otherwise specified, to products approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), therapeutic biological products licensed under section 351(a) of the Public Health Service Act (PHS Act), and combination products that have a drug or biological product primary mode of action and for which CDER has primary jurisdiction (see 21 CFR part 3).

[3] There are legal and regulatory considerations that apply to 505(b)(2) applications that rely on information (for example, FDA's finding of safety and/or effectiveness for a listed drug and/or published literature) that the applicant does not own or for which it does not have a right of reference or use to support approval of dose banding information. Applicants of 505(b)(2) applications proposing to rely on such information to support approval of dose banding information should discuss their development programs with the appropriate review division in CDER's Office of New Drugs. For additional information on 505(b)(2) applications, see the draft guidance for industry

application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act);[4] or a supplement to one of these approved applications.

This guidance does not apply to abbreviated new drug applications (ANDAs), which are generally required to have the same labeling as the reference listed drug (RLD).[5] This guidance also does not apply to BLAs submitted under section 351(k) of the PHS Act; the labeling of biosimilar and interchangeable products generally incorporates relevant data and information from the FDA-approved labeling of the reference product, with certain modifications.[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 guidance means that something is suggested or recommended, but not required.

II. BACKGROUND AND SCOPE

Having multiple different strengths of a drug product available in ready-to-use containers from which the entire drug content of the container(s) is administered to the patient may simplify the preparation and administration of a drug compared to preparing and administering an exact weight- or BSA-based dose to the patient.[7] The availability of a drug product in a range of different strengths in ready-to-use containers (for example, pre-mixed infusion bags) that could be administered in their entirety also may reduce significant drug waste from single-dose vials used for exact weight- or BSA-based dosing and would eliminate the need to calculate and extract partial doses from vials. For example, consider a drug product that is available in 1,000 milligram (mg) single-dose vials (100 mg/milliliter (mL)) when the calculated dose for the patient is 1,250 mg. Administering this exact dose would necessitate use of two vials, with the residual 750 mg in the second vial being discarded. The use of a pre-mixed, ready-to-use infusion bag that delivers 1,250 mg of the drug simplifies the preparation and administration steps. Administering the entire drug content of a ready-to-use container, however, may result in

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Applications Covered by Section 505(b)(2) (December 1999). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. To make sure you have 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] A BLA submitted under section 351(a) of the PHS Act is a stand-alone application and must contain all required data and information necessary to demonstrate the safety, purity, and potency of the proposed biological product for each of its proposed conditions of use.

[5] The FD&C Act and FDA's regulations permit labeling differences because of differences approved under a suitability petition or because the generic drug and the RLD are produced or distributed by different manufacturers. See sections 505(j)(2)(A)(v) and (j)(4)(G) of the FD&C Act and 21 CFR 314.94(a)(8)(iv).

[6] See, for example, the draft guidance for industry *Labeling for Biosimilar and Interchangeable Biosimilar Products* (September 2023); when final, this guidance will represent FDA's current thinking on this topic.

[7] Weight refers to either actual or ideal body weight, whichever is appropriate for the drug product.

a patient receiving a dose that *is very close to but not exactly the same as* the dose calculated based on weight or BSA. The labeling must provide clear instructions for health care practitioners on preparation and administration of the drug product,[8] which should include information on how to determine which strength(s) of the ready-to-use containers the patient should receive based on the patient's weight or BSA. In some instances, dosing with ready-to-use containers may entail administration of a single ready-to-use container (for example, one infusion bag). In other situations, a patient may need two (or more) ready-to-use containers (for example, using two infusion bags of different strengths to provide the calculated total dose to be administered) to receive the recommended dose.

The recommendations and examples in this guidance apply when an applicant (1) proposes to develop ready-to-use containers with a range of different strengths and (2) seeks to incorporate dose banding information into the Prescribing Information based on dosing information of a previously approved drug product that is based on weight or BSA and is available in single-dose vials.

III. DATA TO SUPPORT DOSE BANDING

Applicants who seek to include dose banding information in labeling need to provide adequate data to support the safety and efficacy of the proposed ranges.[9] This may include, for example, data or information on dosing based on weight or BSA that the applicant owns or to which it has a right of reference or by relying on published literature to support approval of a 505(b)(2) application.

In general, the application (including a supplemental application) should include data that explain and justify the acceptability of the differences between the proposed to-be-administered dose in the ready-to-use containers (i.e., dose banding) and the exact weight- or BSA-based dose from the approved drug product in single-dose vials. The evidence used to identify acceptable systemic exposure bounds (i.e., acceptable range or differences for dose banding) to support dose banding may depend on the nature of the dose- or exposure-response of the drug, therapeutic index, and pharmacokinetic characteristics of the drug product. The evidence should support the conclusion that the largest potential differences between the administered dose based upon dose-banding and the dose based upon weight or BSA from the approved drug product would not compromise safety or effectiveness of the drug. Model-informed drug development approaches can be used to assist in determining dosing using strengths available in ready-to-use containers (i.e., dose banding).[10] FDA encourages applicants to discuss their proposals to describe dose banding information in the labeling, including any clinical and/or scientific data to justify the

[8] 21 CFR 201.57(c)(3)(iv).

[9] 21 CFR 201.56(a)(3).

[10] For further information regarding model-informed drug development approaches, see the guidances for industry *Population Pharmacokinetics* (February 2022) and *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (May 2003).

proposed dosing and administration recommendations, with the appropriate FDA review division during drug development.[11]

IV. RECOMMENDATIONS FOR LABELING

When included in labeling, dose banding information should be presented in the DOSAGE AND ADMINISTRATION section along with the previously approved recommended dose based on weight or BSA.[12] When applicable, the clinical and/or scientific information supporting the use of dose banding may be included in the CLINICAL PHARMACOLOGY section.

The following list provides recommendations to incorporate dose banding information for ready-to-use containers into the DOSAGE AND ADMINISTRATION section and *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section. However, these recommendations should not be considered comprehensive, and statutory and regulatory requirements for the content and format of human prescription drug labeling apply.[13]

- Information on doses using a range of ready-to-use containers in the DOSAGE AND ADMINISTRATION section should include information about the maximum acceptable differences between the recommended dose of the previously approved drug product based on weight or BSA and the dose based on available strengths of the ready-to-use containers and, if applicable, a cross-reference to the supporting data in the CLINICAL PHARMACOLOGY section.

- The DOSAGE AND ADMINISTRATION section should include information on how to select the appropriate ready-to-use container(s) to achieve the recommended dose for an individual patient based on weight or BSA. For example, if the ready-to-use containers are supplied as infusion bags in a range of strengths, with each bag containing a different total amount of the drug at a specified concentration, this section should explain how to select the correct infusion bag(s) based on the patient's weight or BSA. Presenting drug product selection information for the various strengths of the ready-to-use containers in a tabular format may be useful to health care practitioners.

  - It may sometimes be important to include recommendations for situations when the dose based on weight or BSA falls outside of the dose range for which the ready-to-use containers are supplied. For example, if the calculated dose for a specific weight or BSA is lower than the lowest dose available in the ready-to-use infusion bags, this section should (1) clarify that use of the bags is not

[11] For example, human factors studies may be necessary for the approval of an NDA submitted under section 505(b) of the FD&C Act, a BLA submitted under section 351(a) of the PHS Act, or a supplement to one of these approved applications.

[12] See 21 CFR 201.57(c)(3); see also the draft guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023). When final, this guidance will represent FDA's current thinking on this topic.

[13] See generally, section 502 of the FD&C Act and 21 CFR part 201.

recommended for patients for which the calculated dose cannot be achieved and (2) recommend that use of another drug product containing the same active ingredient be considered.

- When applicable, the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section should include pharmacokinetic information about the maximum difference (for example, as a percentage) between the previously approved drug product's recommended dose calculated based on weight or BSA compared to the proposed product's dose administered using the ready-to-use container(s).

A fictitious labeling example is provided in the appendix.

APPENDIX: Dose Banding Labeling Example

This appendix presents a fictitious example of labeling incorporating dose banding information for using ready-to-use containers into the relevant portions of the DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY sections. The fictitious product is DRUG-X (drugozide injection), available in ready-to-use infusion bags, with dose banding information based on a body surface area (BSA)-based dose of 500 mg/m^2 that was recommended in the labeling for a previously approved drugozide injection drug product available in single-dose vials.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

The recommended dosage of DRUG-X is 500 mg/m^2 administered intravenously over 30 minutes every 4 weeks. Doses administered using DRUG-X infusion bags may vary from the BSA-calculated dose by up to 5% *[see Clinical Pharmacology (12.3)]*. Select the DRUG-X infusion bag(s) based on the patient's BSA as described in Table 1.

DRUG-X is not recommended for use in patients with a BSA less than 1.05 m^2. Dosing for such patients is not possible with DRUG-X infusion bags because the lowest available strength (infusion bag containing 550 mg per 55 mL (10 mg/mL)) exceeds the BSA-calculated dose by more than 5%. Consider the use of another drugozide product for such patients.

Table 1. DRUG-X Infusion Bag Selection Based on BSA

BSA Range	Calculated Dose Range	DRUG-X Infusion Bag(s) (10 mg/mL)
Less than 1.05 m^2	Not recommended	
1.05 to 1.15 m^2	525 mg to 577 mg	550 mg
1.16 to 1.25 m^2	578 mg to 627 mg	600 mg
1.26 to 1.35 m^2	628 mg to 677 mg	650 mg
1.36 to 1.45 m^2	678 mg to 727 mg	700 mg
1.46 to 1.55 m^2	728 mg to 777 mg	750 mg
1.56 to 1.65 m^2	778 mg to 827 mg	800 mg
1.66 to 1.75 m^2	828 mg to 877 mg	850 mg
1.76 to 1.85 m^2	878 mg to 927 mg	900 mg
1.86 to 1.95 m^2	928 mg to 977 mg	950 mg
1.96 to 2.05 m^2	978 mg to 1,027 mg	1,000 mg
2.06 to 2.15 m^2	1,028 mg to 1,077 mg	1,050 mg
2.16 to 2.25 m^2	1,078 mg to 1,127 mg	Use two 550 mg infusion bags (1,100 mg total)

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12 CLINICAL PHARMACOLOGY

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12.3 Pharmacokinetics

There are no clinically significant differences in drugozide pharmacokinetics between the BSA-calculated dose and doses that differ up to 5% from the BSA-calculated dose as described in Table 1 based on drugozide dose proportionality, variability, and exposure-response for safety and efficacy *[see Dosage and Administration (2.1)]*.