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

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Chris Wheeler, 301-796-0151, or (CBER) Office of Communication, Outreach and Development, 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)

July 2022
Labeling

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 provides recommendations to assist applicants in incorporating information into proposed human prescription drug labeling when:

- Dosing for the drug product[2] is based on weight or body surface area (BSA).
- The drug product is available in a range of strengths in *ready-to-use containers*.
- The entire drug content of the ready-to-use container(s) is intended to be administered to a patient.

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 to drug products approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act and therapeutic biological products licensed under section 351(a) of the Public Health Service Act, including drug-led and biologic-led combination products, unless otherwise specified.

[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 *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

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.[5] This guidance also does not apply to 351(k) BLAs; the labeling of biosimilar and interchangeable products generally incorporates relevant data and information from the reference product labeling with certain modifications.[6]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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. 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 1000 milligram (mg) single-dose vials (100 mg/milliliter (mL)) when the calculated dose for the patient is 1250 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 1250 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 a patient receiving a dose that *is very close to but not exactly the same as* the dose calculated

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. A 351(a) BLA may not rely on FDA's finding of safety, purity, and potency for another product. See section 351(a)(2)(C)(i)(I) of the PHS Act and 21 CFR 601.2(a); compare section 351(k) of the PHS Act.

[5] See section 505(j)(2)(A)(v) and (j)(4)(G) of the FD&C Act.

[6] See the guidance for industry *Labeling for Biosimilar Products* (July 2018). Additionally, for considerations regarding labeling for interchangeable biosimilar biological products, see 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 FDA's current thinking on this topic.

based on weight or BSA. Therefore, labeling must provide clear instructions for health care practitioners on preparation and administration of the drug product, 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.[7] 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 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 of the proposed drug product based on dosing information of a previously approved drug product that is based on weight or BSA.

III. DATA TO SUPPORT DOSE BANDING

As a scientific matter, applicants who seek to include dose banding information in labeling need to support this information with adequate evidence of safety and substantial evidence of effectiveness.[8] This may be accomplished, for example, with 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 the Agency's finding of safety and effectiveness for a previously approved drug product or on published literature to support approval of a 505(b)(2) application.

In general, the application (or 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. The evidence used to identify acceptable systemic exposure bounds to support dose banding may depend on the nature of the dose/exposure-response of the drug, therapeutic index, pharmacokinetic characteristics, and the availability of strengths of the ready-to-use containers to span the range of the administered doses for the proposed drug product. Model-informed drug development approaches can be used to assist in the comparison of the dose based on weight or BSA and dosing using strengths available in ready-to-use containers (i.e., dose banding). 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 proposed dosing and administration recommendations, with the appropriate FDA review division during drug development.[9]

[7] 21 CFR 201.57(c)(3)(iv)

[8] 21 CFR 201.56(a)(3)

[9] 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.

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.[10] 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 other statutory and regulatory requirements for the content and format of human prescription drug labeling remain applicable.[11]

- 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 (i.e., dose banding) 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). 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 recommended for patients of this weight or BSA because the calculated dose cannot be achieved and (2) recommend that use of another drug product containing the same active ingredient be considered.

- When applicable, information on dosing when using the ready-to-use containers in 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

[10] See 21 CFR 201.57(c)(3) and the guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (March 2010).

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

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: 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 for the fictitious DRUG-X (drugozide in sodium chloride injection) with a body surface area (BSA)-based dose of 500 mg/m^2 that was recommended in the labeling for a previously approved drugozide in sodium chloride injection drug product.

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 1027 mg	1000 mg
2.06 to 2.15 m^2	1028 mg to 1077 mg	1050 mg
2.16 to 2.25 m^2	1078 mg to 1127 mg	1100 mg (550 mg and 550 mg)

…

12 CLINICAL PHARMACOLOGY

…

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 and variability.