Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials: Guidance for Industry

Draft Guidance

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For questions regarding this draft document, contact the Food and Drug Administration, Office of Dietary Supplement Programs, 5001 Campus Drive (HFS-810), College Park, MD 20740, Toll Free (855) 543-3784, or 240-402-2375.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

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Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials: Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or we) on this topic.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

The purpose of this guidance is to advise firms that manufacture, market, or distribute dietary supplements of our intent to exercise enforcement discretion with respect to the declaration of live microbial[2] quantity in colony forming units (CFUs), in addition to the quantitative amount by weight declaration required by regulation, within the Supplement Facts label of dietary supplements containing live microbials, provided that certain conditions are met.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

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[1] This guidance has been prepared by the Office of Dietary Supplement Programs in the Center for Food Safety and Applied Nutrition (CFSAN) at the Food and Drug Administration.

[2] A live microbial is a single-celled prokaryotic or eukaryotic microorganism that is intended to be viable at the point of ingestion. Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Draft Guidance for Industry, at 97 (August 2016) (available at https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf). When final, this guidance will represent the FDA's current thinking on this topic. Many dietary supplements that are described as "probiotics" contain live microbial ingredients. "Probiotics" are not defined as a regulatory product category under the Federal Food, Drug, and Cosmetic Act (FD&C Act) or the Public Health Service Act (PHSA), and products that may be considered to be "probiotics" may be foods, drugs, and/or biologics under the FD&C Act and/or PHSA, depending on various factors, such as the intended use of the product. "Probiotics" have been defined in other contexts as live microorganisms which, when consumed in adequate amounts of food, confer a health benefit on the host (see Joint Food and Agriculture Organization and World Health Organization Working Group Report, "Guidelines for the Evaluation of Probiotics in Food" (April 30 and May 1, 2002)). The focus of this document is on live microbial dietary ingredients in dietary supplements.

The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

Under section 403(q)(5)(F) and (s)(2)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 343(q)(5)(F) and (s)(2)(A)(ii)), a dietary supplement[3] is misbranded if the presentation of the nutrition information does not include the quantity of each dietary ingredient (or of a proprietary blend of such ingredients) per serving. Our regulations, at 21 CFR 101.36, establish the requirements for nutrition labeling of dietary supplements, including that dietary ingredients for which a Reference Daily Intake (RDI) or Daily Reference Value (DRV) has not been established must be listed inside the Supplement Facts label along with their quantitative amount by weight per serving in metric units, as described in 21 CFR 101.36(b)(3). Additionally, dietary supplements that contain a proprietary blend of dietary ingredients must, among other requirements, list in the Supplement Facts label the proprietary blend name, the dietary ingredients contained in the blend, and the quantitative amount of the total weight of the proprietary blend per serving, as described in 21 CFR 101.36(c). Further, under 21 CFR 101.36(c)(2), certain dietary ingredients contained in the proprietary blend must be declared in descending order of predominance by weight.

In a final rule published in the *Federal Register* of May 27, 2016, titled "Food Labeling: Revision of the Nutrition and Supplement Facts Label" (81 FR 33742) (Nutrition and Supplement Facts Label Final Rule), we amended the labeling regulations for conventional foods and dietary supplements to provide updated nutrition information on the label. In the Nutrition and Supplement Facts Label Final Rule, in response to a comment, we addressed the issue of whether we should "permit the use of additional units of measure for dietary ingredients to allow for use of more appropriate units of measure when metric weight is not the most accurate way to express the quantity of the dietary ingredient."[4] The comment gave as examples the use of CFUs in the labels of dietary supplements containing live microbials and enzyme assay units for enzymes. Another comment requested that we amend our regulations to state that "these amounts shall be expressed in metric or other appropriate units of measure."[5] We declined to change our regulations in response to these comments, explaining as follows:

> We decline to permit the use of additional units of measure for dietary ingredients. The comment provided the examples of CFUs for probiotics and enzyme assay units for enzymes; however, the broader change suggested in the comment, by including "other appropriate units of measure," would allow for the use of units of measure for dietary ingredients other than just probiotics and enzyme assay units.
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> We recognize that manufacturers are using a number of different units of measure for probiotics, enzymes, and other dietary ingredients. We need to fully evaluate each unit of

[3] Section 201(ff) of the FD&C Act (21 U.S.C. 321(ff)) defines the term "dietary supplement."
[4] 81 FR 33742 at 33933.
[5] Id.

measure for dietary ingredients to determine if it is appropriate for use on the Supplement Facts label, and if there are any implications to allowing for the use of such units of measure on the label. Because of the complexity of these labeling concerns, we plan to issue information related to this subject at a later date. We have, therefore, finalized § 101.36(b)(2)(ii)(A) without change.[6]

Subsequently, FDA received a citizen petition asking us to amend our regulations at 21 CFR 101.36 to "require the quantitative amount of probiotic ingredients in a dietary supplement to be presented in terms of colony forming units (CFUs) instead of by weight."[7] In developing this guidance we have considered, among other things, the evidence submitted to the docket concerning the petition.

III. Discussion

Many dietary supplements, often marketed as "probiotics," include claims that the live microbial ingredient, formulated in adequate amounts, will confer a health benefit on consumers. The weight of microbial dietary ingredient in a product represents the product's total cellular mass, consisting of both live and dead microorganisms, and therefore does not necessarily correlate with the number of viable microorganisms in that product. Additionally, the labeled weight of the microbial ingredient may not accurately reflect the number of live microorganisms throughout the range of times a product is expected to be consumed because live microorganisms are susceptible to cell death throughout the shelf life of a product.[8]

A colony forming unit, or CFU, is a measurement of viable microbial cells that are capable of replicating on agar plates and forming colonies which are then counted.[9] Under existing law, dietary supplements are permitted to bear information about the quantitative amount of live microbial dietary ingredients in CFUs in areas of the dietary supplement label outside of the Supplement Facts label, as long as this information is not false or misleading.[10] However, within the Supplement Facts label itself, these ingredients can be quantified only by weight.[11]

CFU is currently the mostly widely recognized measure of live microbials used by FDA and foreign governmental organizations. In guidance relating to clinical trials for live biotherapeutic products, FDA has stated that potency of live microbial products is generally measured in CFUs.[12] FDA has evaluated and responded to a number of Generally Recognized as Safe

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[6] Id.
[7] Citizen Petition from International Probiotics Association ("IPA Citizen Petition"), November 18, 2016, Docket FDA-2016-P-3968 (available at https://www.regulations.gov/searchResults?rpp=25&po=0&s=FDA-2016-P-3968&fp=true&ns=true).
[8] M. E. Sanders, et al., *Safety assessment of probiotics for human use*, 1 Gut Microbes (2010).
[9] Goldman, E. (Ed.), Green, L. (Ed.). (2015). Practical Handbook of Microbiology, Third Edition. Boca Raton: CRC Press.
[10] 21 CFR 101.13(i)(3).
[11] See 21 CFR 101.36(b)(3).
[12] Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information: Guidance for Industry (June 2016), at page 12, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-bio-gen/documents/document/ucm292704.pdf.

(GRAS) notices, related to uses of live microorganisms in food, where the concentration (or use level) of live microbials was expressed in CFUs.[13,14] FDA also has reviewed and responded to premarket notifications for new dietary ingredients (NDIs) where the subject NDI is a live microbial ingredient, and the proposed conditions of use for such notifications is typically expressed in CFUs for the serving size.[15] A number of other countries have similarly recognized CFUs as the appropriate unit of measurement for live microbial ingredients,[16] and the use of CFU as a quantitative measure of live microbial activity is prevalent in the scientific and other literature.[17]

Because the Supplement Facts label is required for all dietary supplements in a standardized format, allowing firms to declare live microbial quantity in terms of CFUs would permit consumers to more readily identify the amount of viable microorganisms for each product and more easily compare products, without searching through various parts of the product label. Declaring quantity in terms of CFUs also would promote confidence that a particular dietary supplement product contains the labeled amount of live microbial ingredient, providing the specified number of viable microorganisms throughout the shelf life of the product.[18] FDA data suggest that consumers consult supplement labels to, among other things, find out amounts of specific ingredients in a supplement product and compare supplement products.[19]

While we currently believe that CFUs provide a useful description of the quantity of live microbial dietary ingredients, we are aware that researchers are currently evaluating other methods and units of measure for live microbial dietary ingredients and that such alternative methods have the potential to more accurately and more efficiently quantify the number of viable

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[13] Antonia Mattia, Robert Merker; Regulation of Probiotic Substances as Ingredients in Foods: Premarket Approval or "Generally Recognized as Safe" Notification, *Clinical Infectious Diseases*, Volume 46, Issue Supplement_2, 1 February 2008, Pages S115–S118, https://doi.org/10.1086/523329.

[14] FDA GRAS Notice Inventory, available at http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices. (See, e.g., GRN 268, 445, 455, 502, 531, 685).

[15] See, e.g., NDIN 924, available at https://www.regulations.gov/document?D=FDA-2016-S-0023-0068; NDIN 900, available at https://www.regulations.gov/document?D=FDA-2016-S-0023-0014; NDIN 608, available at https://www.regulations.gov/document?D=FDA-2009-S-0608-0141.

[16] See, e.g., Guidance Document – The Use of Probiotic Microorganisms in Food at ¶ 16(d) (April 2009), available at https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/guidance-document-use-probiotic-microorganisms-food-2009.html; Ministerio della Salute, Linee Guida su Probiotici e Prebiotici § 1.3 (March 2018), available at http://www.salute.gov.it/imgs/C_17_pubblicazioni_1016_allegato.pdf.

[17] E.g., Tina Didari, et al., *A systematic review of the safety of probiotics*, 13 Expert Opinion on Drug Safety (2014); F. Guarner, et al., *World Gastroenterology Organisation Global Guidelines: probiotics and prebiotics October 2011*, 46 J Clin Gastroenterol (2012); and M. E. Sanders, et al., *Safety assessment of probiotics for human use*, 1 Gut Microbes (2010).

[18] For further information on our requirements for the minimum quantity of dietary ingredients throughout the shelf life of a dietary supplement, see 21 CFR 101.9(g)(3) and (g)(4), and 101.36(f)(1).

[19] Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration,2014 Health and Diet Survey: Topline Frequency Report (2016), available at https://www.fda.gov/downloads/Food/FoodScienceResearch/ConsumerBehaviorResearch/UCM497251.pdf.

cells in a product at a future time.[20, 21] Therefore, at this time, we intend to continue monitoring the development of new technologies and their potential impact on the use of other units of measure on the Supplement Facts label before deciding whether to engage in rulemaking to revise the Supplement Facts regulations. However, we are mindful that dietary supplement manufacturers are already in the process of preparing new labels to comply with the Nutrition and Supplement Facts Label Final Rule; the compliance date for that rule is January 1, 2020, for manufacturers with $10 million or more in annual food (including dietary supplement) sales, and January 1, 2021, for manufacturers with less than $10 million in annual food sales.[22] In the interim, until we decide whether to engage in rulemaking to amend 21 CFR 101.36, we intend to exercise enforcement discretion for those firms that choose to declare the quantitative amount of live microbial ingredients in the Supplement Facts label by CFUs in addition to weight, provided the following conditions are met:

- The quantity is first listed in terms of weight;
- The declaration of quantity in CFUs is expressed in a manner that is clearly separate and readily distinguishable from the weight, e.g., as a parenthetical or in a subset line;
- The declaration of quantity in CFUs is formatted in clear terms that can easily be understood by a common reader, e.g., 10 billion or 300* (where the unit that "*" is intended to represent, such as million or billion, is a typical measurement of CFUs and is clearly indicated elsewhere in the Supplement Facts label);
- The declaration of quantity in CFUs is accurate and not misleading, and does not render misleading other aspects of the Supplement Facts label, or other aspects of the product label;
- The declaration of quantity in CFUs measures only live microbial ingredients and does not include inactive, dead, or nonviable organisms;
- Live microbial dietary ingredients in a proprietary blend are listed in descending order of predominance by weight; and
- The product label otherwise complies with all applicable laws and regulations.

For the reasons articulated in this document, we have determined that consumers would benefit from permitting the label of dietary supplement products to accurately represent the quantity of live microbial dietary ingredients in the Supplement Facts label in terms of CFUs. Our intended exercise of enforcement discretion is limited to the labeling of dietary supplements containing live microbial ingredients and to the declaration of quantity of such live microbial ingredients on the Supplement Facts label in terms of CFUs. Our exercise of enforcement discretion does not

[20] See, e.g., Hansen SJZ, Morovic W, DeMeules M, Stahl B, Sindelar CW. Absolute Enumeration of Probiotic Strains *Lactobacillus acidophilus* NCFM® and *Bifidobacterium animalis* subsp. *lactis* Bl-04® via Chip-Based Digital PCR. *Frontiers in Microbiology*. 2018:9:704. doi:10.3389/fmicb.2018.00704.
[21] See, e.g., Davis C. Enumeration of probiotic strains: Review of culture-dependent and alternative techniques to quantify viable bacteria. *Journal of Microbiological Methods*. 2014:103:9. doi:10.1016/j.mimet.2014.04.012.
[22] 83 FR 19619 (May 4, 2018).

apply to other foods that contain live or viable microbial ingredients, to dietary supplements that do not contain live microbial dietary ingredients, or to any other FDA-regulated commodities.