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RE: Docket Number FDA-2011-D-0376 for "Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials; Draft Guidance for Industry; Availability" 83 *Federal Register* 45454. (Publication Date: September 7, 2018).

Dear FDA Desk Officer,

The Natural Products Association (NPA) appreciates the opportunity to respond to the U.S. Food and Drug Administration's (FDA's) notification of request for public comment on a new draft guidance titled "Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials; Draft Guidance for Industry". NPA is submitting this document as a formal comment to the Center for Safety and Applied Nutrition's (CFSAN's) request for information seeking input from stakeholders on the FDA's new enforcement discretion policy regarding quantitative labeling of dietary supplements containing live microbial ingredients. NPA has identified this issue in its previous regulatory reform comments as an example of how current labeling regulations should be modified because they are either obsolete, unnecessary, ineffective, or burdensome to achieve meaningful burden reduction while allowing FDA to continue its public health mission. NPA has a concern over current supplement labeling regulations in 21 CFR 101.36 on quantity declaration as they apply to probiotics. The labeling regulation in this case, as applied to probiotics, is obsolete and ineffective for probiotics because there are better ways to convey quantity per serving to consumers than milligrams of a live microbial ingredient. The current state of science in probiotics has necessitated the need to modify this regulation for live microbial ingredients; however, the vast majority of companies label probiotics with CFUs to convey that critical information to

consumers already. Since industry has already made the adjustment, the industry would like FDA to follow through with the modification of the regulation in retrospective. Why would FDA CFSAN not modify this food labeling regulation for probiotic live microbial dietary ingredients in order to create a stronger, safer food supply and provide greater clarity and nutrition information to consumers? Members of the NPA applaud the present Executive Administration's request for stakeholder input as part of the implementation of Executive Order 13771 ("Reducing Regulation and Controlling Regulatory Costs") and Executive Order 13777 ("Enforcing the Regulatory Reform Agenda"). NPA applauds FDA's efforts to target regulations for regulatory reform as per the President's agenda. NPA would like to see this regulation targeted for regulatory modification and reform on the next Unified Agenda by the Agency.

Background

NPA was founded in 1936 to promote and protect the unique values and shared interests of retailers and suppliers of natural nutritional foods, dietary supplement, and other natural consumer products. NPA is a non-profit 501(c)(6) association whose mission is to advocate for the rights of consumers to have access to products that will maintain and improve their health, and for the rights of retailers and suppliers to sell these natural products. We are the oldest, largest, and trade association in the natural products industry representing over 1,100 members accounting for almost 10,000 retail, manufacturing, wholesale, and distribution locations of natural products, including conventional foods, dietary supplements, medical foods, health/beauty aids, and probiotics. Therefore, the NPA and its member companies, have a significant interest in FDA's new draft guidance on the "Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials" available for stakeholder comment.

On September 7, 2018, FDA released guidance to advise firms that manufacture, market, or distribute dietary supplements of its intent to exercise enforcement discretion with respect to the declaration of live microbial 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 states that "manufacturers are using a number of different units of measure for probiotics" and that they "need to fully evaluate each unit of 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." FDA further writes in its draft guidance that "[b]ecause of the complexity of these labeling concerns, we plan to issue information related to this subject at a later date. We have, therefore, finalized [the supplement labeling regulations for probiotics] without change."

A colony forming unit, or CFU, is a measurement of viable microbial cells that are capable of replicating on agar plates and forming colonies when they are counted. Under existing law, live microbial dietary ingredients can only be quantified by weight (in metric units) within the Supplement Facts label itself. While FDA has decided to reject any changes to the federal regulations to require probiotic supplements to list only CFUs, FDA has decided 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 n a manner that is clearly separate and readily distinguishable from the weight; the declaration of quantity in CFUs is formatted in clear terms that can easily be understood by a common reader; 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.

NPA Identifies 21 CFR 101.36 as Ideal for Regulatory Reform

In 2017, NPA identified multiple areas in final rules, codified federal regulations of Title 21, and guidance documents which fall under Executive Order 13771, "Reducing Regulation and Controlling Regulatory Costs",[1] and Executive Order 13777, "Enforcing the Regulatory Reform Agenda".[2] The purpose of Executive Order 13771 is to be prudent and financially responsible in the expenditure of funds, from both public and private sources, and that it is essential to manage the costs associated with complying with Federal regulations. Order 1377 directs each Agency to establish a Regulatory Reform

[1] Executive Order 13771 (January 30, 2017); available at *https://www.federalregister.gov/documents/2017/02/03/2017-02451/reducing-regulation-and-controlling-regulatory-costs.*
[2] Executive Order 13777 (February 24, 2017); available at *https://www.federalregister.gov/documents/2017/03/01/2017-04107/enforcing-the-regulatory-reform-agenda.*

Task Force (RRTF) to evaluate existing regulations and identify those that may merit repeal, replacement, or modification. Section 3(d) of Executive Order 1377 provides that, at a minimum, each RRTF must attempt to identify regulations that … "[a]re outdated, unnecessary, or ineffective;" [i]mpose costs that exceed benefits; [c]reate a serious inconsistency or otherwise interfere with regulatory reform initiatives and policies;" and "[a]re inconsistent with the requirements of the Information Quality Act, OR the guidance issued pursuant to that Act, in particular those regulations that rely in whole or in part on data, information, or methods that are not publicly available or that are insufficiently transparent to meet the standard for reproducibility". In particular, NPA identified regulation 21 CFR 101.36 for change to account for the fact that probiotic dietary ingredients are unique compared to most other dietary ingredients.

Name of Regulation	**Nutrition Labeling of Dietary Supplements**
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 101.36(b)(3)(ii) and 21 C.F.R. § 101.36(c)(3)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0813
Brief Description of Concern	Firms selling probiotic dietary supplements must list the total quantity by weight per serving of their live microbial ingredients in metric units. This requires firms to list the amount in micrograms quantities. While this makes sense for dietary ingredients that do not convey activity, it does not make regulatory sense for dietary ingredients in which activity is an essential parameter to convey to consumers (ie. probiotics, enzymes). Two firms could sell the same quantity of live microbial dietary ingredient in metric units, but one firm may have activity data (ie. Colony Forming Units or CFUs) essential to consumers. Metric units for probiotics does not convey the necessary serving level information of activity. The same can be said for enzymes and other dietary ingredients with activity.
Available Data on Cost or Economic Impact	The only economic impact is for firms to conduct activity and stability assessments for the shelf life of their dietary ingredients. The majority of probiotics are sold with "CFUs" to indicate activity. They have gone above and beyond the current labeling requirement to inform consumers as to how much of their probiotic is a 'live microbial ingredient' as opposed to a probiotic product with no activity. Firms should already possess stability data on their probiotic dietary ingredients, so the economic impact to firms is minimal.

Proposed Solution	Probiotic and other dietary ingredients where conveying 'activity' to consumers is important should be listed with units of activity rather than metric units. For example, probiotics should be listed with colony forming units in the Supplement Fact panel and not metric milligram quantities.

NPA requests FDA to reconsider its decision not to change 21 CFR 101.36(b)(3)(ii) and 21 CFR 101.36(c)(3) at this time.

Title 21 CFR 101.36(b)(3)(ii) can be amended with the addition of the following language

> "For probiotic dietary ingredients, or live microbials, the quantitative amount by weight per serving shall be represented in the Supplement Facts panel in terms of colony forming units (CFUs) per serving at the end of the product's shelf life and not at the time of manufacture."

Title 21 CFR 101.36(c)(3) can be amended with the following language to require all probiotic proprietary blends in a supplement to be labeled with CFUs.

"The quantitative amount by weight for most dietary ingredients or by colony forming units for proprietary blends of live microbial dietary ingredients as described in paragraph (b)(3)(ii) of this section, specified for the proprietary blend shall be the total weight in metric units or colony forming units of all other dietary ingredients contained in the proprietary blend."

FDA's Draft Guidance to Allow for CFUs Does Not Go Far Enough

NPA is seeking regulatory reform to address the unique concerns of live microbial dietary ingredients in probiotic dietary supplements. A guidance document does not adequately address consumer concerns about probiotic supplements in the marketplace displaying only quantity and not CFUs. A guidance document only represents the Agency's thinking about a topic and is NOT legally binding in anyway on the FDA or public. Addressing this issue through guidance provides no regulatory enforcement teeth necessary to level the playing field when it comes to current labeling practices for probiotics. Probiotics should be labeled with quantity per serving information that is truthful and not misleading to consumers. Consumers should have access to consumer products with clear labels that convey useful information about the product to guide their decision making. Live microbial probiotics with serving size declarations in weight do not supply useful information to the consumer. Products with

no probiotic activity (dead cells) are permitted to be sold in the U.S. under current regulations. Current federal labeling laws which address quantity per serving with weight declarations in milligrams rather than activity in CFUs is problematic. FDA's current labeling laws therefore allow for unscrupulous companies to "fly under the radar" and sell probiotics with no viable microbial ingredients in the product.

Under current U.S. regulations, dietary supplements are allowed to bear truthful and not misleading information about the quantitative amount of live microbial dietary ingredients in CFUs in other areas of the dietary supplement label outside of the Supplement Facts panel. Most companies are already providing this information as a way to best communicate quantity information to consumers. This guidance does not change anything as manufacturers can already communicate CFUs to consumers in product labeling. A regulatory change is needed to require only CFU declarations in the Supplement Facts panel. This regulatory change would level the playing field and force all manufacturers to adhere to one standard that is based upon the latest state-of-the-art science by ensuring that probiotic quantity per serving declaration is based upon viable microbial ingredients rather than total live and dead microbial content in the product. Reasonable consumers expect that the quantity declared on the label of probiotics is based upon live, active cultures.

The "Reasonable Consumer" Has an Expectation that Microbial Ingredients in Probiotic Products Are Alive

Requiring probiotic live microbial dietary ingredients to be declared only with CFUs to convey activity corrects the regulatory loophole. Regulatory reform of 21 CFR 101.36 to require CFUs on probiotic supplements will help consumers to compare products and make informed decisions. CFU declarations are necessary to prevent false and misleading statements that are conveyed through weight declarations. When a consumer purchases a probiotic dietary supplement, the expectation is that the microbial ingredients contained therein are alive and not dead, unless otherwise stated on the label. It is reasonable for consumers to believe that probiotics confer a health benefit through their actions as live microbials.

The weight of a 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. Furthermore, 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.

CFUs are Consistent with International Accepted Definitions of Probiotics as Live Microorganisms

CFU is currently the most 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 microbials is generally measured in CFUs.[3] CFUs is consistent with the internationally accepted definition of probiotics as live microorganisms such that when administered in adequate amounts, they confer a health benefit on the host (FOA/WHO). CFUs emphasize and address the unique nature of probiotics compared to other dietary ingredients such as vitamins and minerals. FDA has evaluated and responded to a number of Generally Recognized as Safe (GRAS) notices, related to uses of live microorganisms in food, where the concentration (or use level) of live microbials was expressed in CFUs.[4,5] FDA has also 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 in lieu of weight per serving.[6] A number of other countries have similarly recognized CFUs as the appropriate unit of measurement for live microbial ingredients,[7] and the use of CFU as a quantitative measure of live microbial activity is

[3] 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/fdagovpublic/@fdagov-bio-gen/documents/document/ucm292704.pdf.
[4] 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.
[5] 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).
[6] 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.
[7] 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/guidancedocuments/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.

prevalent in the scientific and other literature.[8] Furthermore, clinical studies investigating the effect and dose-response of probiotics, apply CFUs as a dose measure. Declaring the probiotic content in CFUs will therefore support consumers and health care professionals in making informed choices when choosing the product with the desired properties.

Because the Supplement Facts label is required for all dietary supplements, allowing firms to declare live microbial quantity (or weight) per serving in terms of CFUs would permit consumers to more readily identify the quantitative number 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 probiotic product contains the labeled amount of live microbial ingredient, providing the specified number of viable microorganisms throughout the shelf life of the product. FDA's own empirical research based upon consumer studies suggest that consumers consult supplement labels to, among other things, find out amounts of specific ingredients in a supplement product to compare supplement products.[9]

Manufacturing Potency Specs for a Probiotic Live Microbial Dietary Ingredients Can Vary Batch to Batch

The current labeling regulations in 21 CFR 101.36(b)(3)(ii) requires the total quantity by weight per serving for '(b)(3)' dietary ingredients to be listed in metric units, which includes a 'milligram' or 'gram' designation. Probiotics should be listed in a way so as to convey their activity to consumers. For example, a gram of *Lactobacillus paracasei* may not be the same for company A as it is for company B. If the two companies are required to list their 'activity' units per serving, this would be more useful to informing the consumer. Company A could theoretically manufacture 10 grams of probiotic ingredient that is 100 percent dead and inactive at the time of packaging while company B manufactures the same ingredient with 95% as live microbials in 1 gram of the dietary ingredient. The two dietary ingredients

[8] 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).

[9] 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.

are not the same and how they are processed and handled during manufacture dictates whether they are alive with activity or dead cultures.

Manufacturing, handling, packaging and storage can all have an effect on the potency of the live microbials contained in a probiotic supplement. Small variations in the potency batch to batch require finished probiotic manufacturers to provide overages, which are allowed within part 111 dietary supplement cGMPs. Since the purpose of manufacturing probiotics in the finished product is to normalize potency to a particular CFU for the shelf life of the product, it does not make sense to convey units of milligrams, which can vary depending on the overages applied in manufacturing, to consumers.

Testing Probiotics for Meeting Label Claim Would Involve Counting Colonies to Determine CFU

There is no practical way of determining whether a probiotic product meets label claim with a milligram weight declaration on the product label. This task becomes impossible if there is more than one live microbial dietary ingredient in the product. One scientifically acceptable way one could verify that there is more than one live microbial dietary ingredient in the product is to count colonies on agar plates and determine the CFUs for each live microbial. Therefore, it only follows by common sense that one would require only CFUs per serving on probiotic product labels rather than weight.

Conclusion

NPA believes the FDA's guidance is a start toward change but falls short as a remedy to the problem. Current labeling laws requiring the quantity of probiotics to be declared in terms of milligram weight allows for false and misleading products to be on the market. One could state the quantity of dead bacteria on the product label through weight in milligrams and be in complete compliance with FDA's labeling laws. The reasonable consumer, on the other hand, is expecting to receive live microbial dietary ingredients. Regulatory reform in labeling of dietary supplement probiotics for quantity of live microbial ingredients with CFUs would be an effective measure to ensure microbial ingredients manufactured in finished products are alive. It forces manufacturers to use an ingredient supplier's data or their own shelf life stability data through testing to communicate to consumers the quantity in CFUs of each live microbial dietary ingredient or probiotic blend in the finished product. Declaring quantity, in terms of CFUs, promotes confidence that a probiotic product contains the labeled amount of viable

microbial ingredient throughout the shelf life of the product. The viability of probiotic microorganisms is highly impacted by production factors, formulation and packaging. Ensuring viable and active cells throughout the product lifetime is an important indicator of quality and provides essential information to the consumer.

CFU is the scientifically accepted unit of measure for probiotics. Labeling quantity in CFUs provides meaningful information to consumers about the quantity of viable microorganisms present in the product throughout shelf life. The quantitative amount(s) of probiotics in a product should be expressed in CFUs because the labeled quantity of probiotics should reflect the quantity of live microorganisms at the end of the stated shelf life, not at the time of manufacture.

Thank you for the opportunity to comment on this complex labeling topic for probiotic products. We hope that the Agency will consider our suggestions for regulatory reform of 21 CFR 101.36. The NPA thanks FDA and looks forward to future participation with the Agency in developing a workable solution that communicates meaningful information to consumers.

Sincerely,

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CEO/President