Best Practices for Probiotics

INTRODUCTION

The Council for Responsible Nutrition (CRN)[1] and the International Probiotics Association (IPA)[2] support and encourage responsible production and marketing of dietary supplements and functional foods that contain probiotics. Therefore, CRN and IPA have developed scientifically-based voluntary guidelines that address labeling, stability testing, and storage recommendations for probiotic-containing dietary supplements and functional foods. These guidelines are intended to facilitate transparency and consistency.

Labeling guidelines were developed to provide information about the identity and quantity of the probiotics in a product that will help consumers make informed choices. Stability testing guidelines were established to ensure that the stated shelf life of a given probiotic product is scientifically supported. Storage recommendations were provided to facilitate the communication of storage and handling instructions to customers.

The guidelines take into account the current United States (U.S.) laws and regulatory requirements. While the guidelines do not specifically address regulatory requirements outside of the U.S., the scientific principles underlying the guidelines may apply to international regulatory paradigms. The guidelines reflect the most up-to-date science and industry thinking, and will be updated as best practices evolve.

The precise definition of probiotics is the subject of ongoing discussions. For the purposes of the guidelines, probiotics are defined in accordance with the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization

[1] The Council for Responsible Nutrition (CRN) is the leading trade association representing dietary supplement and functional food manufacturers and ingredient suppliers. CRN represents more than 150 companies that manufacture dietary ingredients and/or dietary supplements, or supply services to those suppliers and manufacturers.

[2] The International Probiotics Association (IPA) is an international organization bringing together through its membership the probiotic sectors stakeholders, from academics, scientists, health care professionals, consumers, industry, and regulators. IPA's mission is to be the unique platform where all these stakeholders interact and collaborate to increase probiotic awareness among all users and help enable the probiotic industry's sustainable growth.

(WHO) definition: "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[3]

GUIDELINES

In addition to compliance with applicable labeling laws and regulations, CRN and IPA recommend that their members adhere to the following guidelines:

I. Labeling Recommendations

A. The quantitative amount(s) of probiotics in a product should be expressed in Colony Forming Units (CFUs).[4]

B. 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.

C. The label should identify the genus, species, and strain for each microorganism in the product.

D. Quantities should be declared as specified below.

i. Product containing only one strain: Declare the quantity of the strain in CFUs.

ii. Product containing multiple strains: Declare the total count of the blend in CFUs.[5]

E. Proprietary blends are permitted by the law for dietary supplements. Individual dietary ingredients within a proprietary blend should be

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[3] Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria. (2001). Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Available at: ftp://ftp.fao.org/docrep/fao/009/a0512e/a0512e00.pdf.

[4] 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. However, FDA regulations require that the quantity of probiotic dietary ingredients be declared by weight in metric units (21 CFR 101.36(b)(3)(ii) and 101.36(b)(3)(ii)(A)). FDA issued draft guidance in September 2018 contemplating a policy of enforcement discretion for those firms that declare the quantitative amount of live microbial ingredients in the Supplement Facts label in CFUs in addition to the required metric weight (See draft guidance at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-policy-regarding-quantitative-labeling-dietary-supplements-containing-live). Additionally, the draft guidance states that live microbial dietary ingredients in a proprietary blend should be listed in descending order of predominance by weight. CRN and IPA disagree with the draft guidance because listing quantitative amount in CFUs and by metric weight is not feasible since CFUs do not directly correlate directly with weight (See CRN's comments, IPA's comments, and IPA's citizen petition to FDA on labeling in CFUs).

[5] When technically feasible, also declare the quantity of each genus or species in the blend.

listed in descending order by CFUs.[4,6] If a claim pertaining to individual strains or a blend of strains contained in the product is made, the manufacturer should maintain evidence that the amount(s) provided in the product is consistent with the scientific evidence in support of the claim.

II. Stability Testing Recommendations

A. Stability testing should be conducted under the same temperature conditions as the recommended storage conditions on the finished product label. The storage temperature should be well defined in the stability testing protocol. When defining storage temperatures, firms may consider the following storage conditions from the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Stability Testing of New Drug Substances and Products Q1A(R)2[7] or the United States Pharmacopoeia (USP) General Chapter <659> Packaging and Storage Requirements[8].

ICH guideline for Stability Testing Q1A(R2) storage conditions for long term stability studies	
Storage	*Storage condition*
Products intended for storage in a freezer	- 20°C ± 5°C
Products intended for storage in a refrigerator	5°C ± 3°C
General case*	25°C ± 2°C/60% Relative Humidity (RH) ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH

* The general case applies if the product is not specifically covered by other conditions listed in the guideline.

USP General Chapter <659> storage condition definitions	
Storage	*Storage condition*
Refrigerated	2°C to 8°C
Cold	Not exceeding 8°C
Cool	8°C to 15°C
Controlled room temperature	20°C to 25°C

[6] 21 CFR 101.36(c)(2) requires that dietary ingredients in a proprietary blend be declared in descending order of predominance by weight.
[7]ICH. (2003). Harmonised Tripartite Guideline. Stability testing of new drug substances and products Q1A (R2) (Section 2.2.7). Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2__Guideline.pdf.
[8] United States Pharmacopeial Convention. (2016). General Chapter <659> Packaging and Storage Requirements. *United States Pharmacopeia and The National Formulary (USP 39-NF 34)* (pp. 479-486). Rockville, MD.

B. Stability testing should be conducted under real-time conditions to support the stated shelf life of the product. Use of accelerated or other testing in a program to support product release should be scientifically justified and documented.

C. The product and packaging conditions used in stability testing should be supported by scientifically sound evidence. Similar to the recommendation in the ICH guideline[9], stability testing should be conducted under conditions that are representative of the finished product in the final packaging proposed for marketing.

D. Products should contain 100% of the quantity of probiotics declared on the product label at end of shelf life, except for any variability that is attributable to methods.

E. All stability testing methods, including proprietary testing methods, should be scientifically sound, repeatable, and reproducible. The specific testing method used should be documented.

III. Storage Recommendations

Probiotic organisms are generally sensitive to changes in temperature and humidity. The degree that an individual product is impacted by temperature and humidity is dependent on the probiotic strains in the product, formulation matrix and dosage form, and product packaging.

Manufacturers should provide storage and handling instructions to customers, taking into account individual formulations and packaging. Instructions should be based upon data and experience with each product, and should take into account all of the environments in which the product will be reasonably expected to be held throughout its lifecycle (e.g., warehouse, shipping, retail and consumer shelves).

IMPLEMENTATION

Within twelve months of the effective date, CRN and IPA recommend that companies comply with these guidelines for products manufactured for sale.

Effective Date: January 9, 2017
Updated: November 12, 2020

[9]ICH. (2003). Harmonised Tripartite Guideline. Stability testing of new drug substances and products Q1A (R2) (Section 2.2.4). Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2__Guideline.pdf.