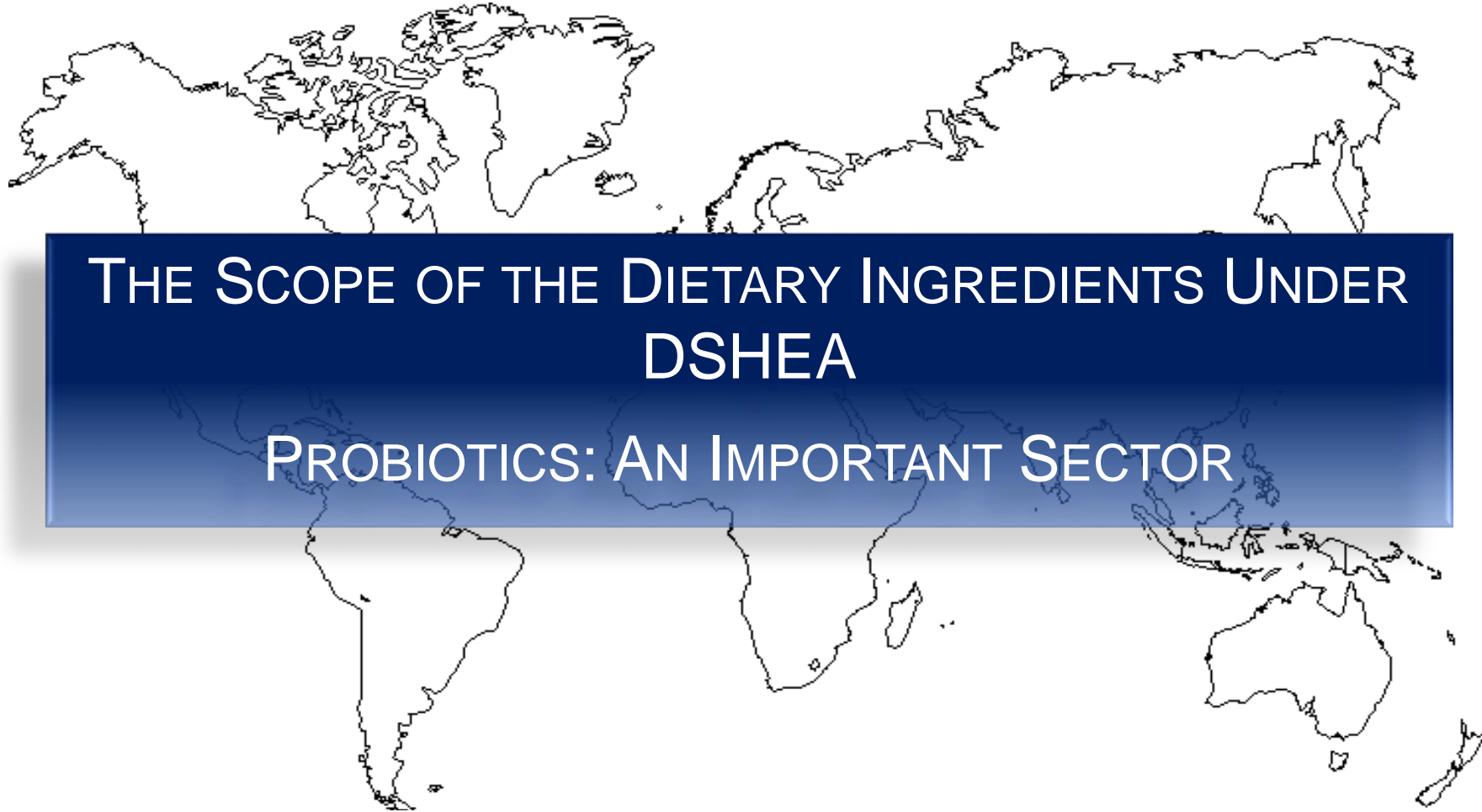




PUBLIC MEETING: RESPONSIBLE INNOVATION IN DIETARY SUPPLEMENTS

COMBINED COMMENTS FROM IPA AND IFAC

George Paraskevakos, MBA
Executive Director IPA
May 16, 2019
College Park, MD



THE SCOPE OF THE DIETARY INGREDIENTS UNDER
DSHEA

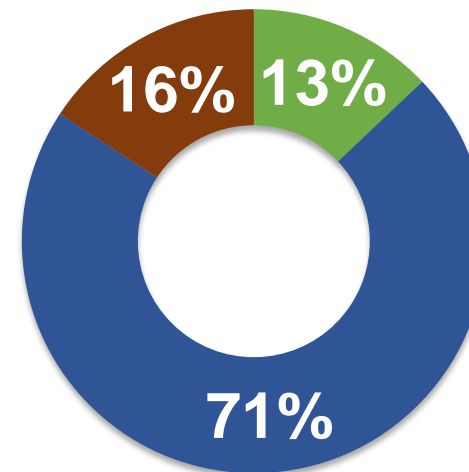
PROBIOTICS: AN IMPORTANT SECTOR

How do we take our probiotics



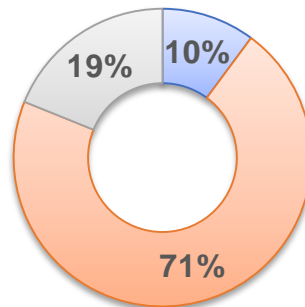
Consumer Consumption - World

World Retail Value
US\$43.8 billion in 2018



- Probiotic Supplements
- Probiotic Dairy-based yoghurt
- Sour Milk Products

World Retail Value
US\$38 billion in 2013

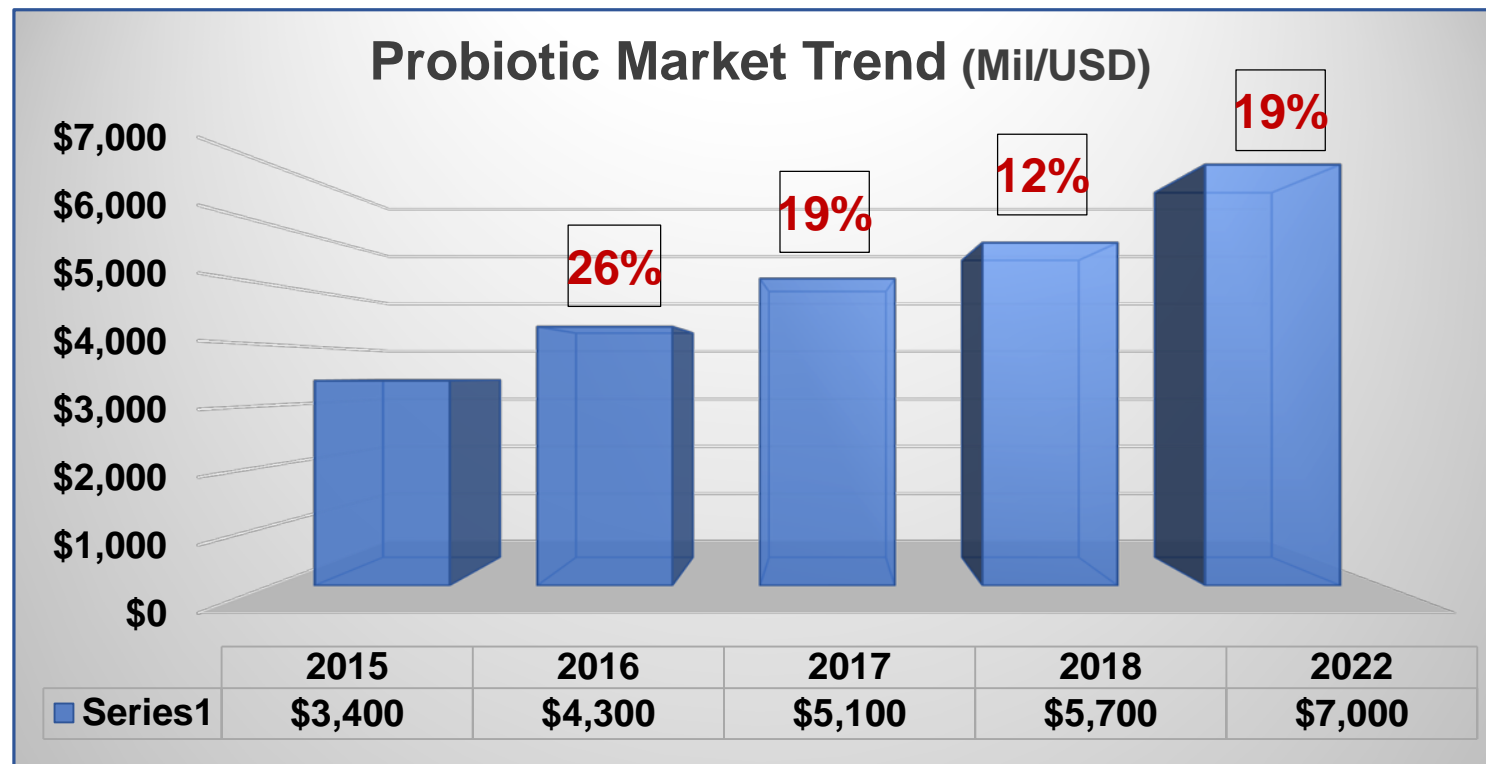


*Euromonitor International

The fastest Growing **Supplement** Globally



Market Overview



*Euromonitor International

Definitions



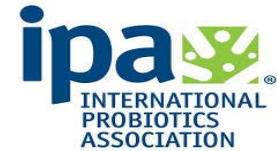
“Live microorganisms which when administered in adequate amounts confer a health benefit on the host”

FDA – ODSP (NDI guidance, 2016):

Dietary Supplements: New Dietary
Ingredient Notifications and Related Issues:
Guidance for Industry

**“Live microbial dietary ingredient: A single
celled prokaryotic or eukaryotic microorganism that is intended to be viable
at the point of ingestion”**

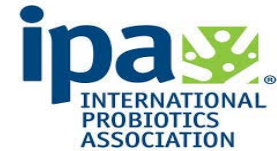
DSHEA: what is a dietary ingredient



- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

So where do probiotics fall ?

Probiotics fit under 201 (ff) E



(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake

This statement implies:

- 1) Need to increase the intake and to supplement the diet with that particular substance to help the maintenance of health & normal body functions
- 2) Is a dietary substance

Need to increase intake & supplement the diet

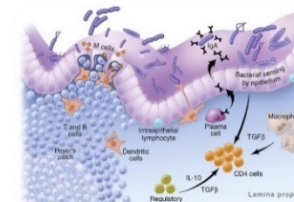


What if we did not ingest probiotic microorganisms?

Benefits and role:

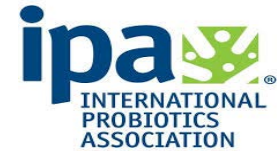
"The panel further considered two common general benefits often associated with probiotics: supporting a healthy digestive tract and a healthy immune system" Hill C. et al. 2004

- Humans are made of bacteria
- Beneficial to gut
- Allow better digestion of nutrients
- Bacteria in gut have multi functional roles
- Aging process decline the bacteria in the gut possibly shifting the function of the body
- Immune supporting role
- Skin, Gut-Brain axis and more



Necessary like vitamins & minerals!

So why did DSHEA not include...



- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;

(&) a probiotic or live microbial

- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

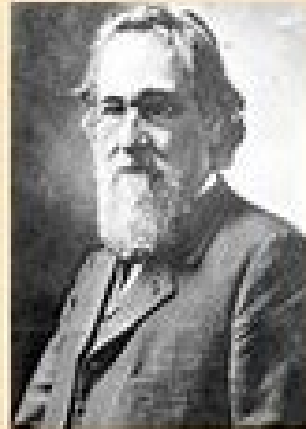
They were prevalent prior to 1994!

OLD DIETARY INGREDIENT LIST

#0 Red Opaque Conisnap capsule #
 200 Bloom GM1 gelatin #
 Abelmoschus esculentus +
 Abelmoschus moschatus (Medik.) +
 Abies webbiana +
 Abrus precatorius +
 Abutilon indicum +
 acacia (arabic gum) ~
 Acacia (arabic gum) (arabia gum) #
 Acacia arabica, Linn. +
 Acacia catechu Willd. +
 Acacia concinna D.C. +
 Acacia farnesiana Willd. +
 Acacia leucophlaea Willd. +
 acacia powder, NF ~
 Acacia senegal +
 Acacia seyal +
 Acacia vera +
 Acalypha indica +
 Acanthopanax gracilistylus +
 Acanthopanax sessiliflorus +
 Acanthospermum hispidum +
 Acanthus virilis +
 Ac-di-sol # ~
 Acer spicatum +
 acerola ~
 acerola concentrate ~
 acerola extract ~
 acerola pulp powder ~
 Acetaminophen #
 Achillea millefolium L. +
 Achyranthes bidentata Bl. +
 Achyranthus aspera Linn. +
 Aconitum camichaelii Debx. +
 Aconitum columbianum +
 Aconitum ferox Wall. +
 Aconitum heterophyllum Wall. +
 Aconitum nepellus L. +
 Aconitum plamatum +
 Acorus calamus L. +
 Acorus gramineus Soland. +
 Adenophora tetraphylla (Thunb.) Fisch. +
 Adenophorus stricta Miq. +
 Adhatoda vasica +
 Adiantum capillus - veneris L. +

Adiantum lunulatum +
 Adiantum pedatum L. +
 adipic acid ~
 Adonis vernalis +
 Adrenal # ~
 Adzuki sprouts # ~
 Aesculus hippocastanum L. +
 Aframomum melegueta (Roscoe) K. Schumann +
 agar agar ~
 Agastache rupeosa (Fisch. et Mey.) O. Ktze. +

Probiotics- History and Evolution



**Elie Metchnikoff
(1845-1916)**

Longevity without Ageing

“The prolongation of life” (1908)

algaia concentrate ~
 Alfalfa leaf powder # ~
 Alfalfa seed; juice conc. # ~
 alginates ~
 alginic acid ~
 Alginate acid, alginates #

AHPA +
 CRN ~
 NNFA #
 UNPA *

© Utah Natural Products Alliance, 1999

1



Microorganisms & Microbial-Derived Ingredients Used in Food (Partial List)

ives" that are approved by FDA for specific uses or substances. A substance may be GRAS only if its general views of experts qualified to evaluate the safety of the d either on a history of safe use in food prior to 1958 or re the same quantity and quality of evidence as would regulation. Because GRAS status may be either affirmed y by qualified experts, FDA's regulations do not include : uses described in the GRAS regulations may not be ents.

ents that are not listed in 21 CFR but have been the o individuals who asked whether FDA would object to he basis of an independent GRAS determination. egular basis, questions about the regulatory status of l ingredients that are not on this list may be directed to markt@fda.hhs.gov)Premarkt@fda.hhs.gov

ially from FDA's regulations in Title 21 of the Code of es approved food additives, substances whose GRAS . substances that FDA listed as GRAS based on a history oorganisms and microbial-derived ingredients may be ther information, consult the summary listing of GRAS

d additives listed in Title 21 of the Code of Federal Regulations (21 CFR) Part 172 and 173, which are derived from microorganisms. This list

Prior sanctions were granted for the use of harmless lactic acid producing bacteria, such as *Lactobacillus acidophilus*, as optional ingredients in specified standardized foods. These bacteria are permitted for use in cultured milk (which includes buttermilk) (§ 131.112), sour cream (§ 131.160), cottage cheese (§ 133.128), and yogurt (§ 131.200), provided that the mandatory cultures of *Lactobacillus bulgaricus* and *Streptococcus thermophilus* are also used in the yogurt.

mesa m me logo

Probiotics fit under 201 (ff) E



(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake

This statement implies:

- 1) Need to increase the intake and to supplement the diet with that particular substance to help the maintenance of health & normal body functions
- 2) Is a dietary substance**

International Probiotics Association



NATURAL HEALTH PRODUCT

PROBIOTICS

This monograph is intended to serve as a guide to industry for the preparation of Product L Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredients.

Note:
By submitting a PLA referencing this monograph, the applicant is attesting that the product will comply fully with the recommended conditions of use and specifications section of this monograph. These include species identification, strain characterization, quantity in colony forming units (CFU), and a complete assessment of viability properties (which but not limited to: antibiotic resistance profile, virulence factor production, and virulence).

Health Canada	Dominion of Health Canada	Whole cell	Strain designation
<i>Bifidobacterium longum subsp. infantis</i>	<i>Bifidobacterium longum subsp. infantis</i>	Whole cell	Strain designation
<i>Bifidobacterium longum subsp. infantis</i>	<i>Bifidobacterium longum subsp. infantis</i>	Whole cell	Strain designation
<i>Lactobacillus acidophilus</i>	<i>Lactobacillus acidophilus</i>	Whole cell	Strain designation
<i>Lactobacillus casei</i>	<i>Lactobacillus casei</i>	Whole cell	Strain designation
<i>Lactobacillus rhamnosus</i>	<i>Lactobacillus rhamnosus</i>	Whole cell	Strain designation
<i>Lactobacillus reuteri</i>	<i>Lactobacillus reuteri</i>	Whole cell	Strain designation
<i>Lactobacillus salivarius</i>	<i>Lactobacillus salivarius</i>	Whole cell	Strain designation
<i>Lactobacillus casei</i>	<i>Lactobacillus casei</i>	Whole cell	Strain designation
<i>Lactobacillus acidophilus</i>	<i>Lactobacillus acidophilus</i>	Whole cell	Strain designation
<i>Lactobacillus casei</i>	<i>Lactobacillus casei</i>	Whole cell	Strain designation
<i>Lactobacillus reuteri</i>	<i>Lactobacillus reuteri</i>	Whole cell	Strain designation
<i>Lactobacillus salivarius</i>	<i>Lactobacillus salivarius</i>	Whole cell	Strain designation
<i>Lactobacillus casei</i>	<i>Lactobacillus casei</i>	Whole cell	Strain designation
<i>Lactobacillus acidophilus</i>	<i>Lactobacillus acidophilus</i>	Whole cell	Strain designation
<i>Lactobacillus casei</i>	<i>Lactobacillus casei</i>	Whole cell	Strain designation

NHP Probiotics

FDA Partial List of Microorganisms

South Africa list

Add the following:

APPENDIX XV: MICROBIAL FOOD CULTURES INCLUDING PROBIOTICS

INTRODUCTION TO MICROBIAL FOOD CULTURES

This Appendix addresses live microbial food cultures including probiotics (MFC) used as ingredients in foods. Whether for food fermentation or probiotic use, viability of the MFC

IFAC List (FCC)

broad description of this category of food ingredient and addresses, in a general sense, the uses, enumeration methods, safety, regulatory status, identification, genetic and

2016 updated list of QPS status recommended biological agents in support of EFSA risk assessments

The list of QPS status recommended biological agents (EFSA BIOHAZ Panel, 2016) is being maintained in accordance with the self-task mandate of the BIOHAZ Panel (2017-2019). Possible additions to this list are included around every 6 months, with the first Panel Statement adopted in June 2017 and the last Panel Statement planned for adoption in December 2019. These additions are published as updates to the Scientific Opinion (EFSA BIOHAZ Panel, 2016) available at <https://doi.org/10.1059/efsa-2017-5064> and, as of January 2018, also as supporting information linked to every Panel Statement available on the Knowledge Junction at <https://doi.org/10.5933/kjnews11-65656>

Table 1: The 2016 updated list of QPS status recommended biological agents for safety risk assessments. (EFSA Panel on Biological Hazards, 2016)

Customs Union micro-organism

三、可用于食品的菌种名单

名称	
双歧杆菌属	
乳杆菌属	

List of Bacterial Species for Food - China

English Name
Bacillus coagulans
Bifidobacterium adolescentis
Bifidobacterium animalis
Bifidobacterium bifidum
Bifidobacterium breve
Bifidobacterium infantis
Bifidobacterium lactis
Bifidobacterium longum
Bifidobacterium pseudolongum
Enterococcus faecium
Enterococcus faecalis
Lactobacillus acidophilus
Lactobacillus crispatus
Lactobacillus gasseri
Lactobacillus johnsonii
Lactobacillus paracasei
Lactobacillus ruminantium

Thailand list

EAC Technical Regulations of the Customs Union TR CU 021/2011 On Food Safety

11.2.5.1 Probiotics

(1) Standards for manufacturing

(1) Raw material: The following probiotics itself or mixed

Kind	
Lactobacillus	<i>L. acidophilus</i> , <i>L. casei</i> , <i>L. gasseri</i> , <i>L. delbrueckii ssp. bulgaricus</i> , <i>L. helveticus</i> , <i>L. fermentum</i> , <i>L. paracasei</i> , <i>L. plantarum</i> , <i>L. reuteri</i> , <i>L. rhamnosus</i> , <i>L. salivarius</i>
Lactococcus	<i>L. lactis</i>

(2) Preparation and/or processing: It shall be in an edible form by culturing and pulverizing the above probiotics

(3) Content of functional compounds (or marker compounds): Alive bacteria shall be contained 100,000,000 CFU/g or more

Malaysia permitted and prohibited list

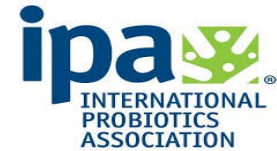
Registration Guidance Document – National Pharmaceutical Control Bureau, July 2015
Appendix 8 List of Permitted, Prohibited and Restricted substances

Ingredients

Search: *Lactobacillus* in All Fields

Name	Synonyms	Category	Reference	CAI No.	Listed
<i>Lactobacillus acidophilus</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus acidophilus (Lactulose ester LR)</i>		ADI	Therapeutic Goods Administration		Listed
<i>Lactobacillus arborofaciens</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus brevis</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus casei</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus casei (Syn: Shiro, Shiro casei)</i>		ADI	Bergey's Manual of Systematic Bacteriology		Listed
<i>Lactobacillus crispatus</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus delbrueckii ssp. bulgaricus</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus delbrueckii ssp. lactis</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus fermentum</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus reuteri</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus salivarius</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus salivarius ssp. salivarius</i>		ADI	International Journal of Food Microbiology		Listed
<i>Lactobacillus salivarius ssp. salivarius</i>		ADI	International Journal of Food Microbiology		Listed

Probiotics fit under 201 (ff) E because



(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake;

- Probiotics have been in the food supply for thousands of years as dietary substances
- Like vitamins and minerals, there is health benefit to “increase the total dietary intake” of probiotics above and beyond what can be easily consumed in food alone
- Probiotics were prevalent in “dietary supplements” in the USA prior to 1994 but not taken into account in a clearer manner does not make them fall outside of the definition
- Advancements in science should not prohibit new strains from being included in this definition as they are still in the general category of “dietary substances” (i.e. changes in vitamins and minerals could trigger NDI issues, it does not take them out of the definition of “dietary ingredient”)

How to be Practical –

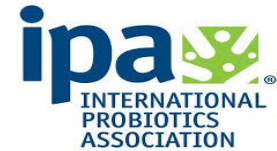


1. Proposed grandfathered / exempted list

- A list of species with a safe history of use
- Manufacturers of strains within these species, intended to be used as dietary ingredients, have the onus to establish safety based on an abbreviated criteria of safety and identity
- Similar to the requirements of global regulatory agencies which allow strains within each listed species to be anticipated as safe
- Safety assessments would not be foregone in the grandfathering process
 - Strains within the species list would not require a NDIN
 - Minimum safety assessments should be conducted

How to be Practical –

2. Master Files



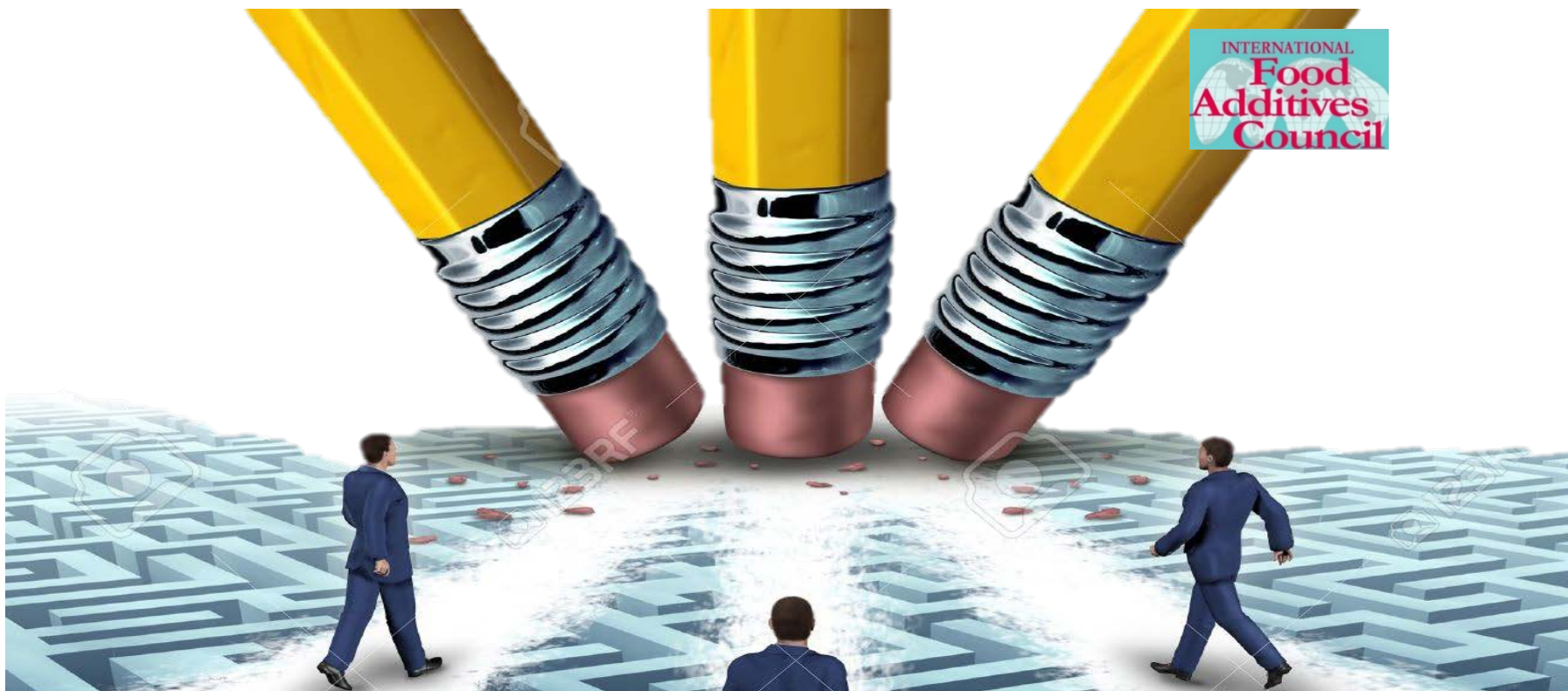
- Make information accessible to the FDA while avoiding unnecessary notifications
- To include but not limited to:
 - ✓ Whole Genome Sequencing for Identification
 - align with well-characterized strain and explain differences in the genome
 - ✓ Genome Mining **the lack of** genetic regions responsible for the production of virulence factors characteristic of the Genus
 - ✓ Genome Mining to demonstrate **the lack of** genetic regions responsible for the production of toxins characteristic of the Genus
 - ✓ Appropriate toxicological studies when necessary – novel bacteria
 - ✓ Genomic Analysis for the presence of biogenic amine genetic regions
 - ✓ Antibiotic Resistance profile targeting clinically relevant antibiotics
 - ✓ Genomic Analysis for evidence **of lack of** antibiotic resistance transfer potential

- Hence MF + grandfathered / exempted list is the logical way forward
- But as...
- Science evolves
- Innovation continues
- New strains on the horizon:
 - ✓ NDI to be filed



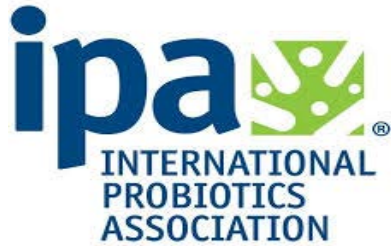


IPA and IFAC are here to help



We want to be part of the WG





REFERENCES & CONTACT DETAILS

The **International Probiotics Association (IPA)** is a global non-profit organization bringing together through its membership, the probiotic sector's stakeholders including but not limited to academia, scientists, health care professionals, consumers, industry and regulators. The IPA's mission is promote the safe and efficacious use of probiotics throughout the world. Holding NGO status before *Codex Alimentarius*, the IPA is also recognized as the unified **Global Voice of Probiotics®** around the world.

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The **International Food Additives Council (IFAC)** is a global association representing manufacturers of food ingredients, including food additives and GRAS substances.

IFAC strives to promote science-based regulations, standards and specifications for food ingredients worldwide.

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The research from Euromonitor International is part of a global strategic intelligence that offers a complete picture of the commercial environment including but not limited to; market analysis, markets share, distribution channels, forecasting and much more.

