PUBLIC MEETING: RESPONSIBLE INNOVATION IN DIETARY SUPPLEMENTS

COMBINED COMMENTS FROM IPA AND IFAC

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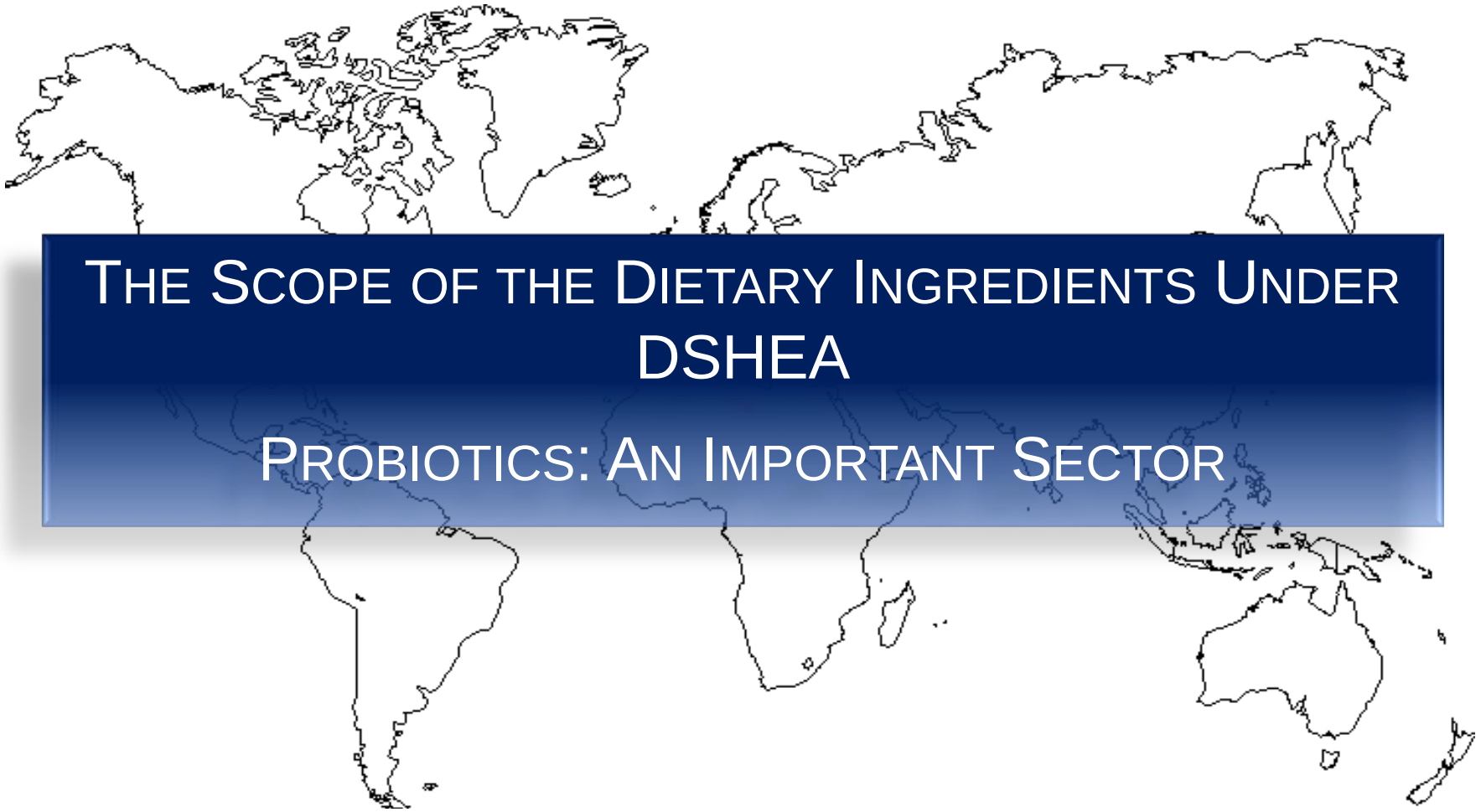
College Park, MD



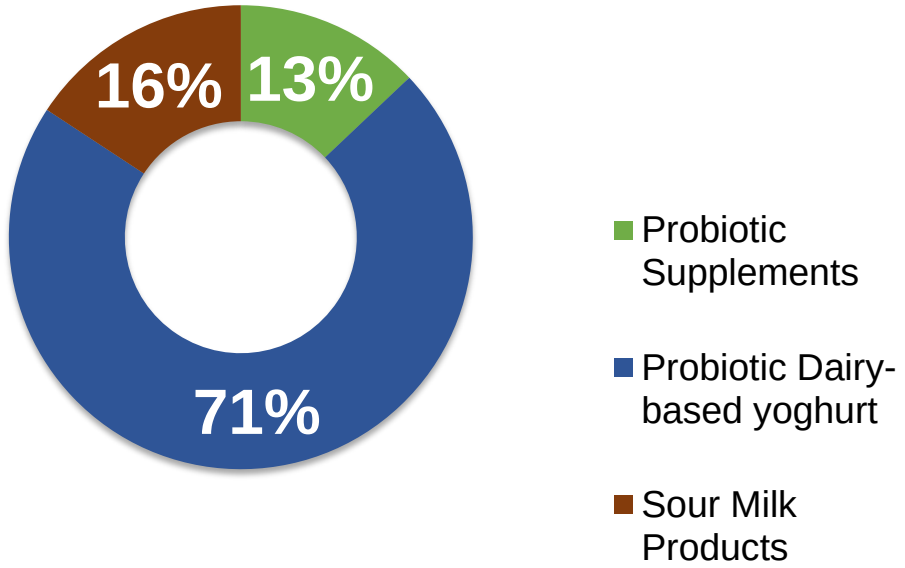
The Scope of the Dietary Ingredients Under DSHEA

Probiotics: An Important Sector

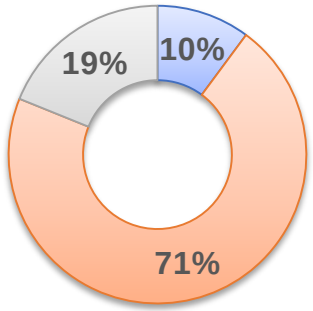
How do we take our probiotics

Consumer Consumption - World

World Retail Value
US$43.8 billion in 2018



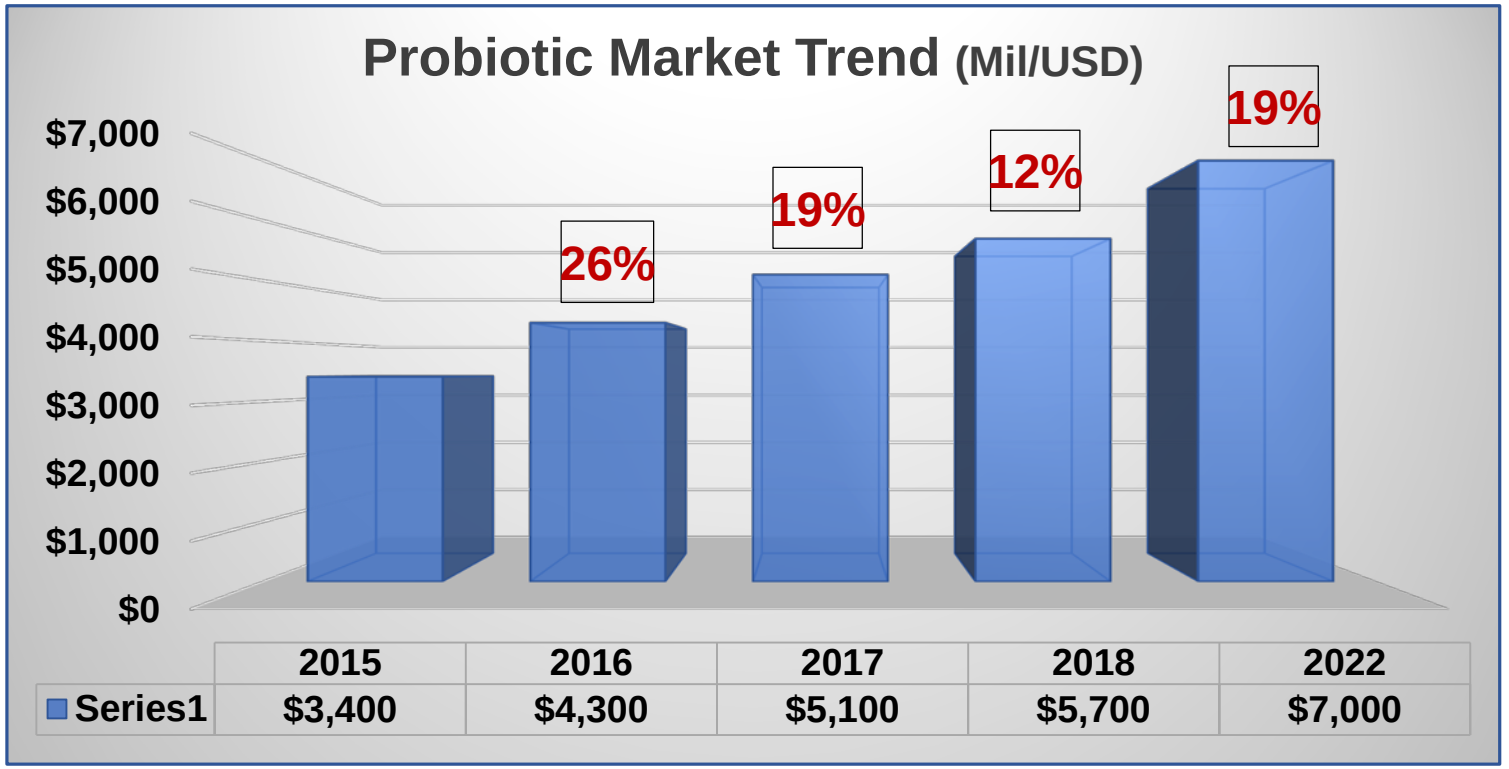
World Retail Value
US$38 billion in 2013



*Euromonitor International

The fastest Growing Supplement Globally

Market Overview

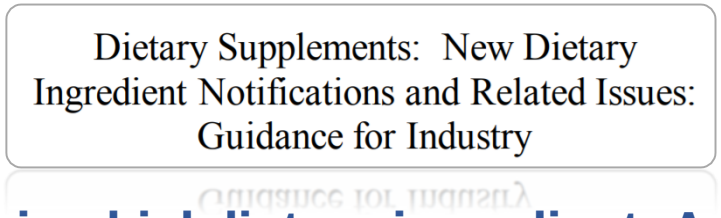


*Euromonitor International

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

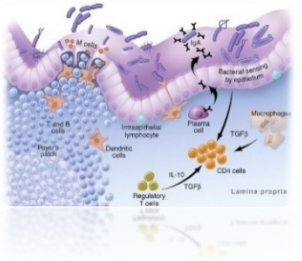
Need to increase intake & supplement the diet

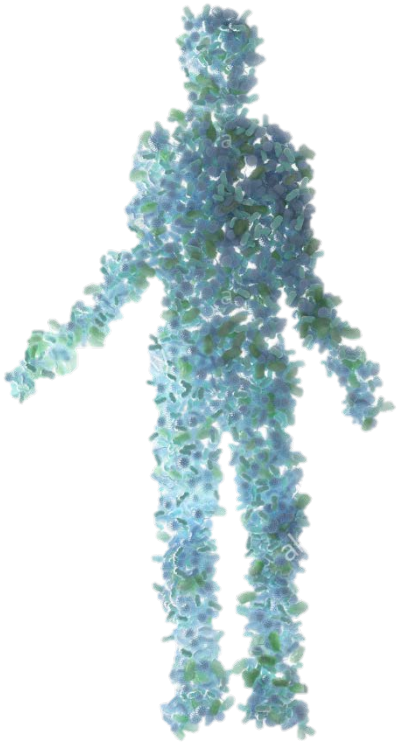
What if we did not ingest probiotic microorganisms?

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

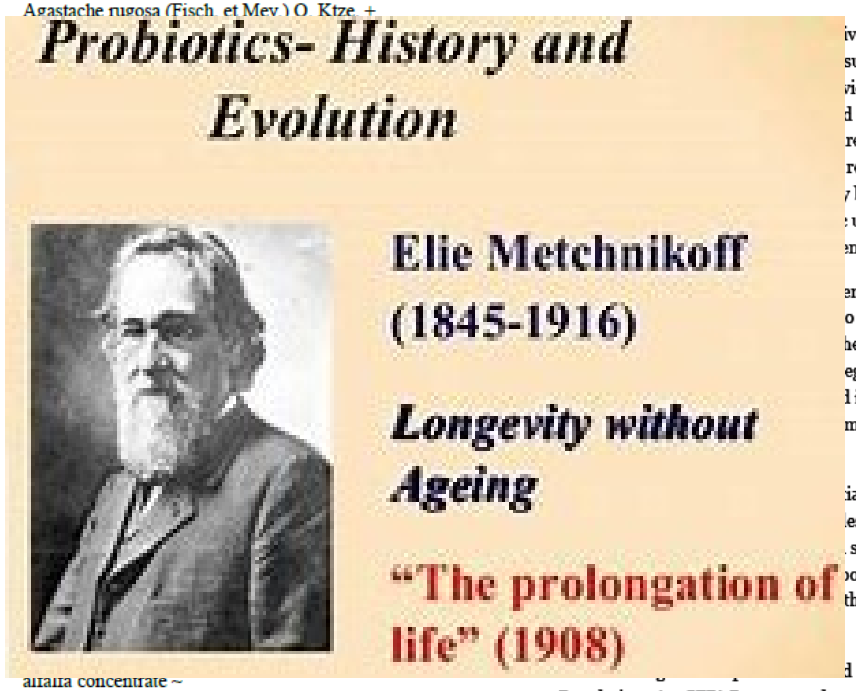
(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

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 hispidium +
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 carmichaelii 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 rugosa (Fisch. et Mey.) O. Ktze. +



alfalfa concentrate ~
Alfalfa leaf powder # ~
Alfalfa seed; juice conc. # ~
alginates ~
alginic acid ~
Alginic acid, alginates #

AHPA +
CRN ~
NNFA #
UNPA *

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 ...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 ...organisms and microbial-derived ingredients may be ...ther information, consult the summary listing of GRAS

...l 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 thermophillus* are also used in the yogurt.

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
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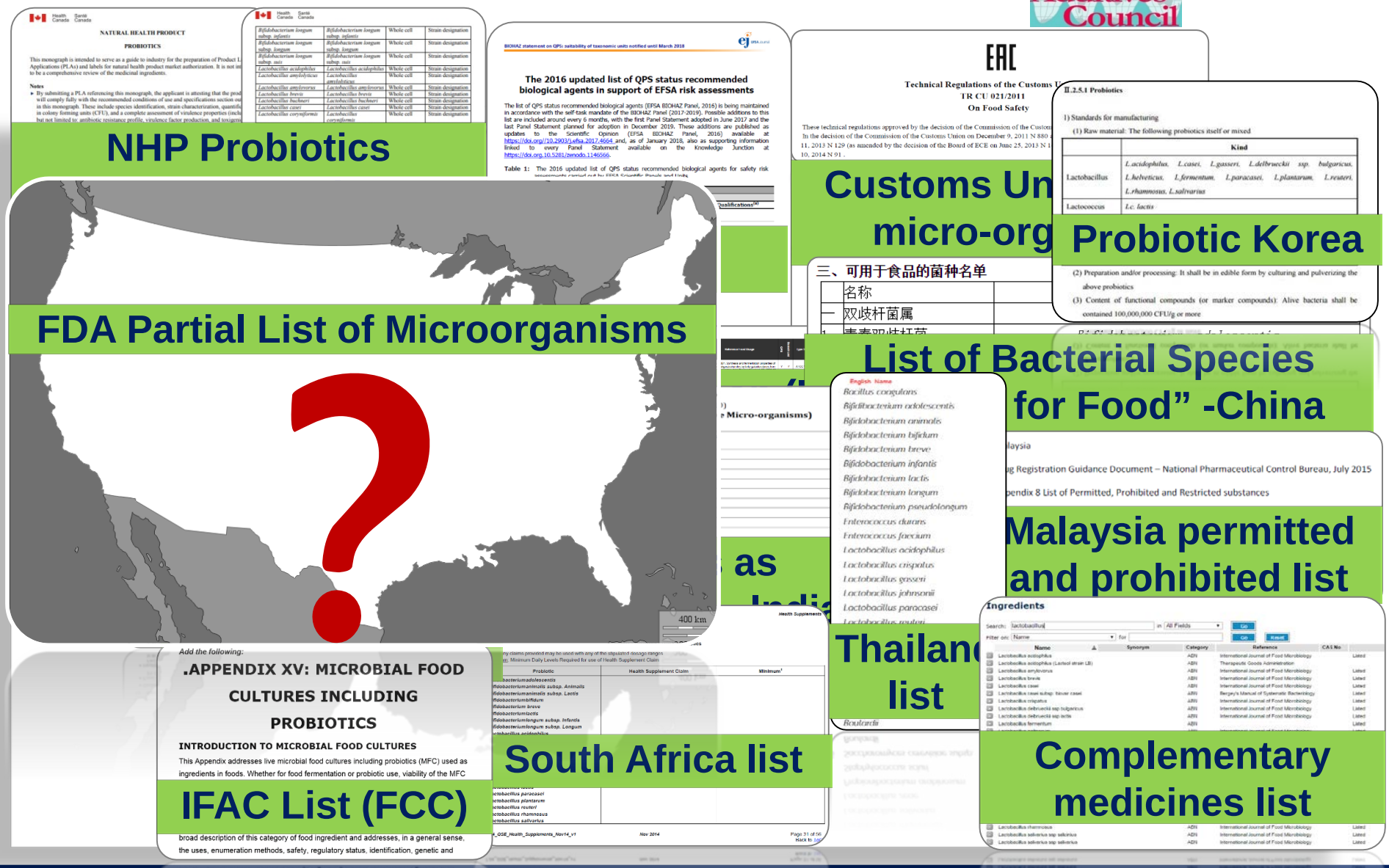
International Probiotics Association



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
    - o 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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