

Bringing Probiotic Products from Bench to Market in the U.S.: Regulatory Implications

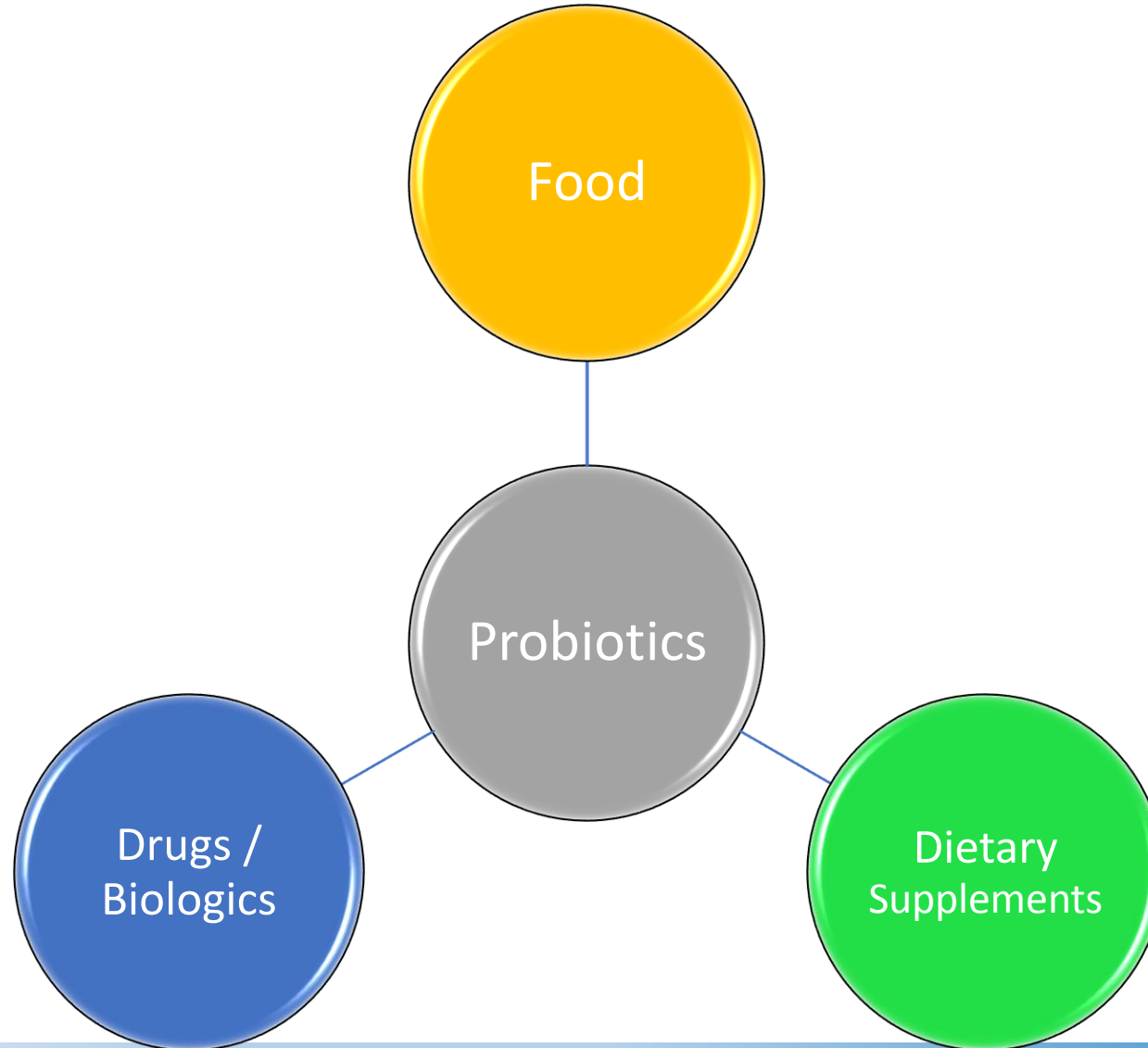
Translational Microbiome Conference

April 17, 2019

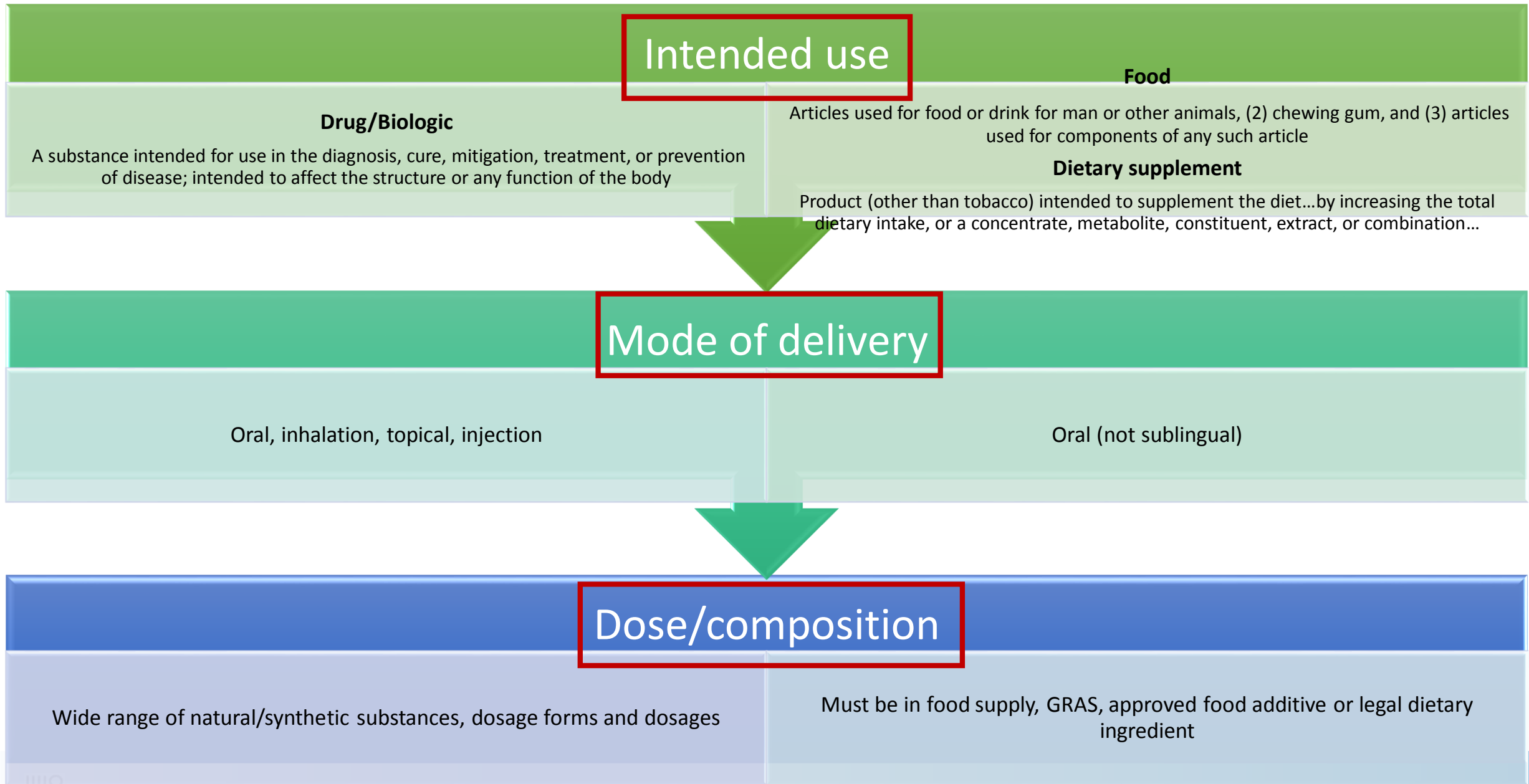
Andrew Shao, PhD



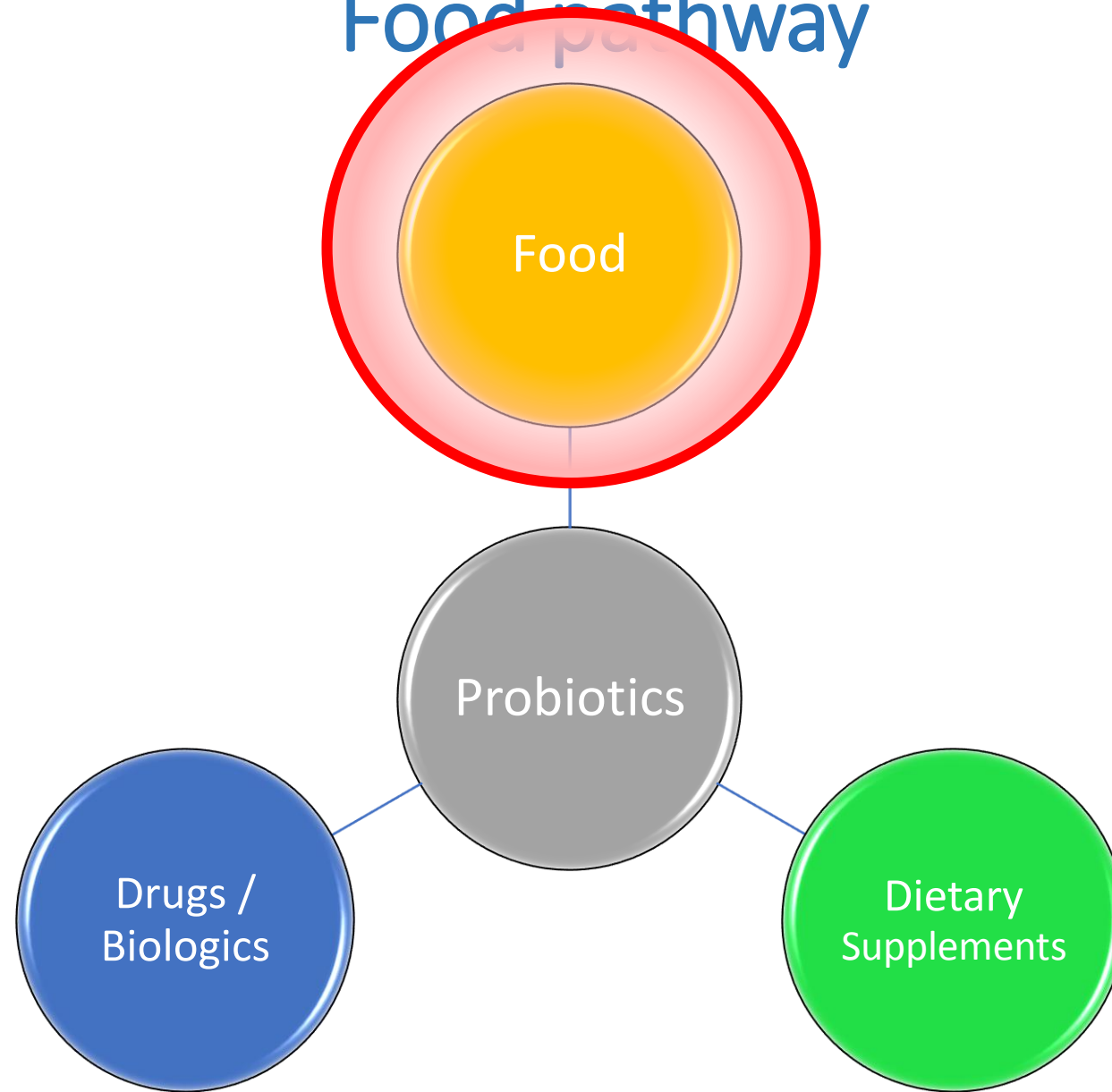
Potential market pathways for probiotics



Which regulatory pathway?

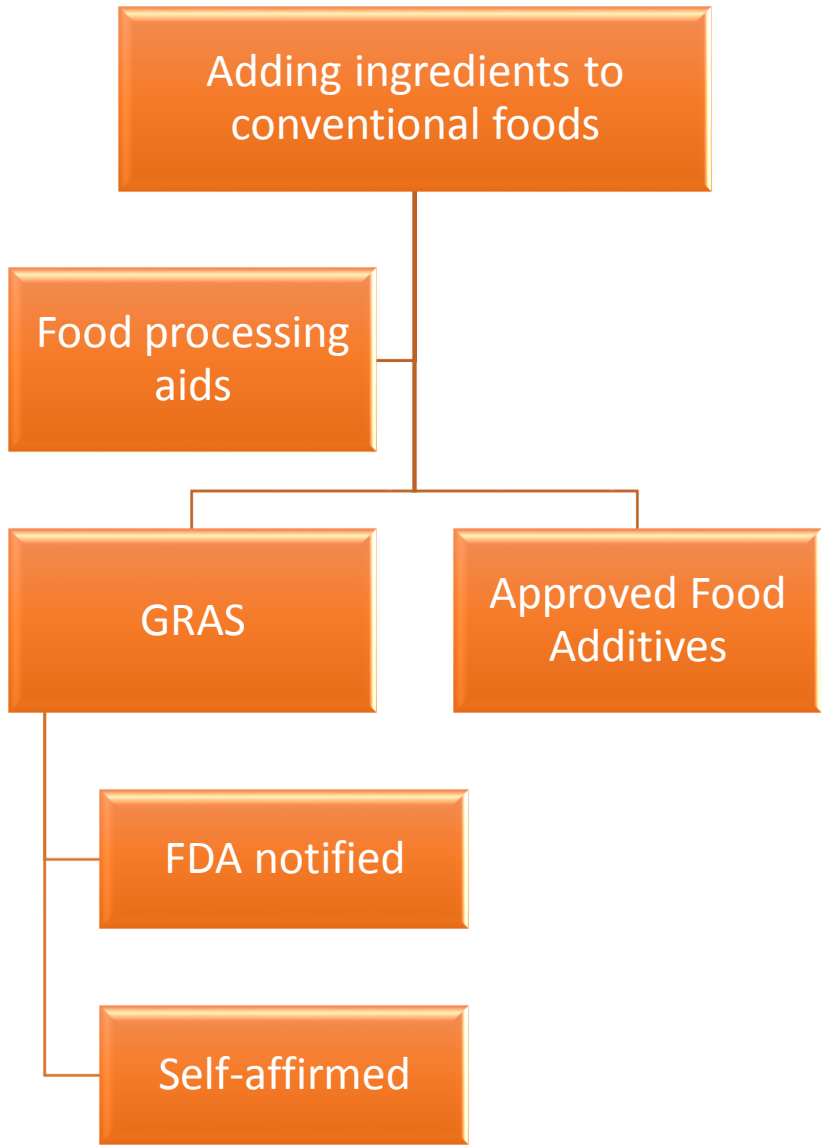


Food pathway



Any substance intentionally added to food is a food additive, unless:

- It is Generally Recognized as Safe (GRAS) under the conditions of its intended use, or
- Its use is otherwise exempted from the definition of a food additive.



Sections 201(s) and 409 of the FD&C Act

Analyses of probiotic GRAS notices

- 600 GRAS Notices (GRN) analyzed
- 21 GRN for probiotics
- 243 Average number of days for FDA review
- 43 Percentage of GRN closed in less than 180 days (9/21)
- 52 Percentage of GRN closed between 200 and 350 days (11/21)
- 1 One GRN withdrawn

Food Chem Toxicol. 2017 105:140-150



<https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices>

[A to Z Index](#) | [Follow FDA](#) | [En Español](#)

[Home](#) | [Food](#) | [Drugs](#) | [Medical Devices](#) | [Radiation-Emitting Products](#) | [Vaccines, Blood & Biologics](#) | [Animal & Veterinary](#) | [Cosmetics](#) | [Tobacco Products](#)

GRAS Notices

[FDA Home](#) | [Generally Recognized as Safe](#) | [Food Ingredient & Packaging Inventories](#) | [GRAS Notices](#)


The inventory of GRAS notices provides information about GRAS notices filed since 1998, when FDA received its first GRAS notice. As of October 17, 2016, the GRAS final rule (81 FR 54960; August 17, 2016) requires a specific format for a GRAS notice. Prior to that date, FDA processed GRAS notices under the framework of the GRAS proposed rule (62 FR 18938; April 17, 1997). Notices received prior to the effective date of the GRAS final rule provide examples for potential notifiers for the types of information that may support a GRAS conclusion. In the inventory, notices follow the requirements for the format and content of a GRAS notice as of the effective date of the GRAS final rule.

We will update this information approximately monthly. More information about this inventory is available on the [GRAS Notice Inventory Introduction page](#).

Search and display hints:

- Select the specific GRN number below to view additional details about any GRAS Notice.
- To sort by a specific field, click on the column header for that field.
- To browse the records, use the Show All, First/Previous/Next/Last, and Jump To options at the bottom of the data table.
- To search for a specific substance/term, enter the term in the Search box and select Show Items to display only those records that contain the selected term. (The search results also includes terms not shown on this page, but included in the full record on the detail page.)
- The search results will return hits of records containing words that include the search term. For example, a search for the color **red** will return results that include terms such as **reduce**, **ingredient**, and **cultured**. To limit results to only the searched term, place a space before and after the word in the basic search or in the advanced search "this exact phrase" field.

[Basic Search](#) | [Advanced Search](#) | [Field Search](#)

 Search:

 Records Found: 827 [Show All](#) Page 1 of 17

GRN No. (sorted Z-A)	Substance	Date of closure	FDA's Letter
827	Preparation containing three bacterial phages specific to several <i>Escherichia coli</i> serotypes		Pending
826	Dihydroquercetin		Pending
825	Beta-galactosidase from <i>Kluyveromyces lactis</i>		Pending
824	Salmocin		Pending
823	Rebaudioside E		Pending

GRAS safety standard

- “...common knowledge, throughout the expert scientific community knowledgeable about the safety of substances directly or indirectly added to food”
- “...a **reasonable certainty** that the substance **is not harmful** under the conditions of its intended use”



21 CFR Parts 20, 25, 170, 184, 186, and 570
[Docket No. FDA-1997-N-0020 (formerly 97N-0103)] RIN 0910-AH15
Substances Generally Recognized as Safe
Federal Register/Vol. 81, No. 159/Wednesday, August 17, 2016



Example of recent letter of no objection



Emily Gregoire
Chr. Hansen, Inc.
9015 West Maple St.
Milwaukee, WI 53214

“Based on the information that Hansen provided, as well as other information available to FDA, we have no questions at this time regarding Hansen’s conclusion that L. curvatus DSM 18775 is GRAS under its intended conditions of use”

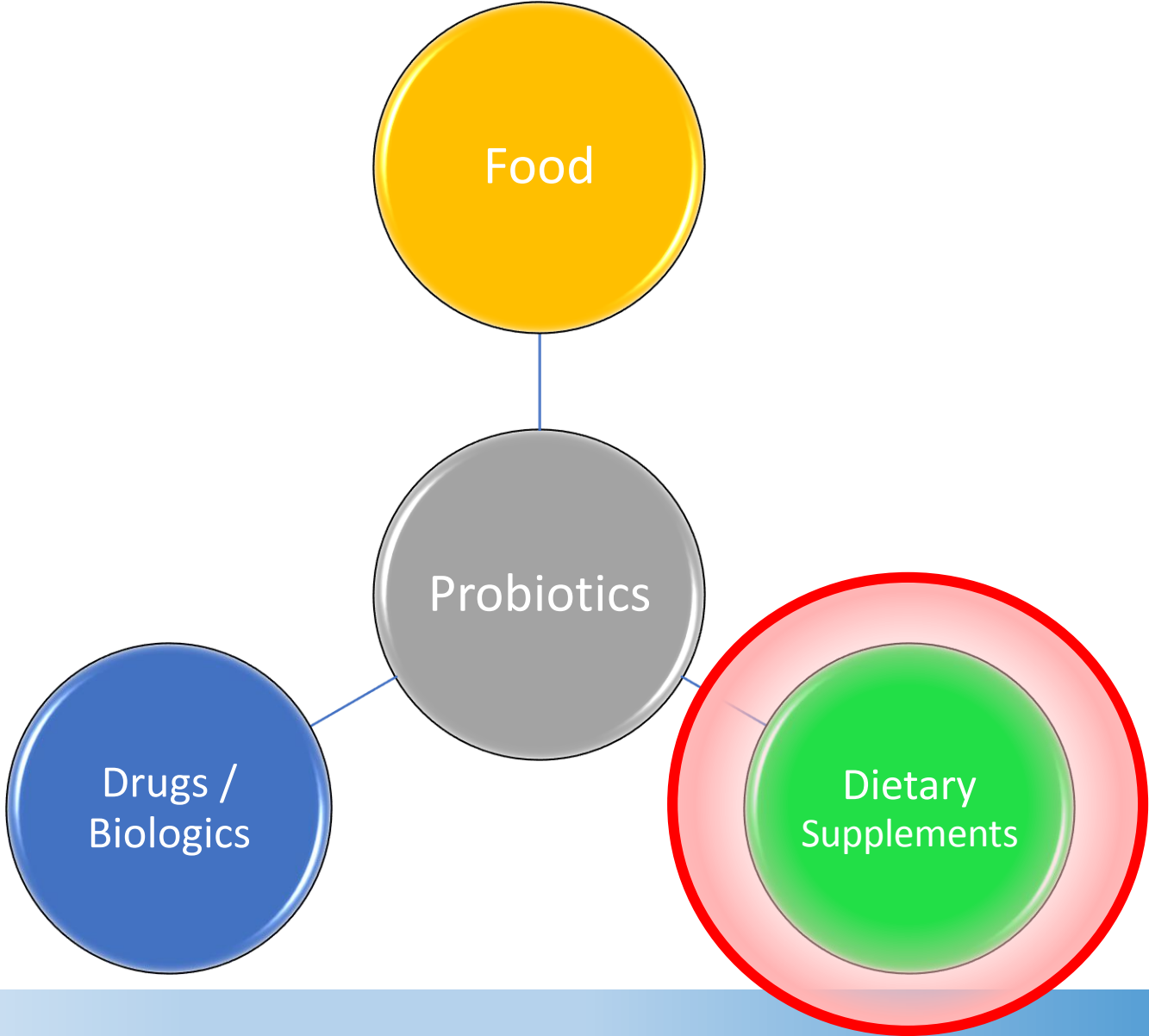
Re: GRAS Notice No. GRN 000760

Dear Ms. Gregoire:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000760. We received Chr. Hansen, Inc.’s (Hansen) notice on February 8, 2018, and filed it on April 13, 2018. Hansen submitted amendments to the notice on December 3 and December 5, 2018, that provided additional detail regarding the manufacturing process and additional information regarding dietary exposure, respectively.



Dietary supplement pathway



Dietary ingredients – where do probiotics fit in?

- Vitamin
- Mineral
- Herb or other botanical
- Amino acid
- Dietary substance for use by man to supplement the diet by increasing the total dietary intake
- Concentrate, metabolite, constituent, extract, or combination of the above



Section 201(ff)(1) of the FD&C Act



New Dietary Ingredients (NDIs)

- A NDI is a dietary ingredient that was not marketed in the U.S. before October 15, 1994.
- A 75-day premarket NDI notification must be submitted to FDA.
 - Exception: The NDI has been present in the food supply as an article used for food in a form in which the food has not been chemically altered

ODI: Dietary ingredient that was marketed in or as a dietary supplement, or for use in a dietary supplement — in the U.S. before October 15, 1994



NDI safety standard

- “...a *reasonable expectation of safety* under the proposed conditions of use”

*Contains Nonbinding Recommendations
Draft-Not for Implementation*

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

Draft Guidance

This guidance is being distributed for comment purposes only.





Home

Food

Drugs

Medical Devices

Radiation-Emitting Products

Vaccines, Blood & Biologics

Animal & Veterinary

Cosmetics

Tobacco Products

Food

[Home](#) > [Food](#) > [Dietary Supplements](#) > [New Dietary Ingredients Notification Process](#)

New Dietary Ingredients Notification Process

[New Dietary Ingredients in Dietary Supplements - Background for Industry](#)

[How to Submit Notifications for a New Dietary Ingredient](#)

▶ [Submitted 75-Day Premarket Notifications for New Dietary Ingredients](#)

Submitted 75-Day Premarket Notifications for New Dietary Ingredients

[f SHARE](#)

[t TWEET](#)

[in LINKEDIN](#)

[p PIN IT](#)

[e EMAIL](#)

[p PRINT](#)

The spreadsheet available for download from this page contains a list of publicly displayable New Dietary Ingredient Notifications (NDINs) that we have reviewed to date. For each NDIN, there is a link to information at <http://www.regulations.gov> relevant to that notification. The notifications are organized by the NDIN number and are sortable and searchable by:

- NDIN number; <https://www.fda.gov/Food/DietarySupplements/NewDietaryIngredientsNotificationProcess/ucm534510.htm>
- ingredient name;
- name of the party that submitted the notification;
- date of submission;
- and date of FDA's response.

The information for each NDIN that is available using this website is the same information that is available through [FDA's Division of Dockets Management](#) (Dockets) and at <http://www.regulations.gov>. However, some of these notifications contain copyrighted material that can only be obtained through a Freedom of Information (FOI) request or viewed in person at the Dockets Public Reading Room. Please see FDA's FOI website for more information on how to view materials in person or to submit a [FOI request](#).



Probiotics as dietary ingredients: FDA's thoughts

- “(N)ot all bacterial microorganisms are dietary ingredients, and a microorganism that is not a dietary ingredient cannot be an NDI.”
- “Bacteria that have never been consumed as food are unlikely to be dietary ingredients.”

May be the most significant barrier to bringing novel probiotics to market as dietary supplements

“FDA has determined that your ingredient (“Probiotic Y”) isolated from mouse feces is not a “dietary ingredient” within the meaning of 21 U.S.C. § 321(ff)(1) (section 201(ff)(1)) that may be lawfully used in dietary supplements”

2015 FDA response letter to NDIN filed for probiotic

New Dietary Ingredient Notifications and Related Issues: Guidance for Industry, August 2016

<https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf>





Other FDA objections

- *“FDA...has significant concerns about the evidence on which you rely to support your conclusion that your dietary supplement containing “Probiotic X” will reasonably be expected to be safe under the conditions of use described in your notification.”*

Areas of opportunity for improved probiotic NDIN:

- Proper characterization and identification method(s) (strain specific)
- Demonstration of proper manufacturing controls and consistent process
- Stability test methods for shelf-life support
- Evidence of safety under proposed conditions of use
- Status as a dietary ingredient



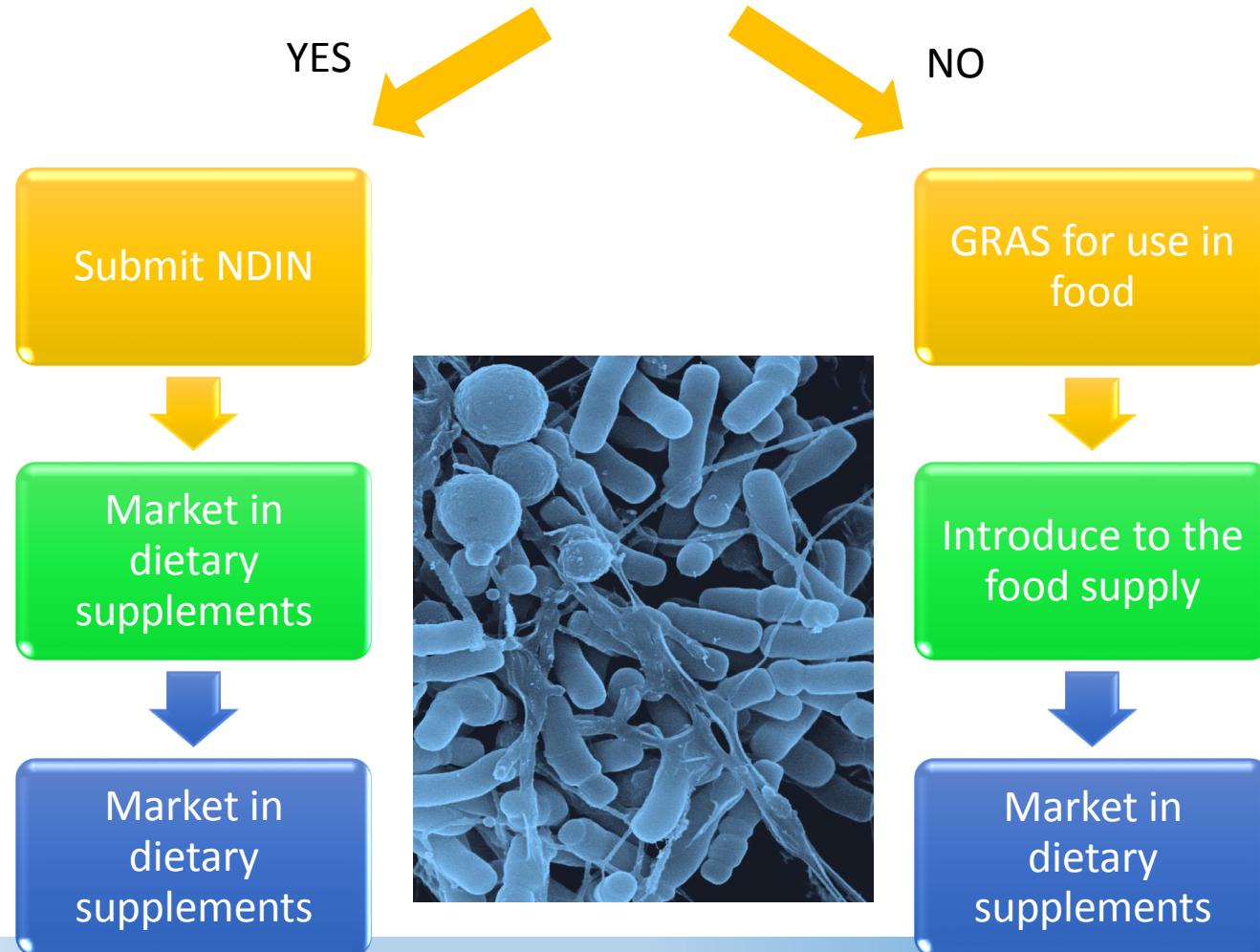
NDIN for probiotics

- What information should I submit to demonstrate the safety of a microbial NDI (live or killed)?
 - Identify/document any **human pathogens, toxins or classes of toxins** that are phylogenetically related at the species or genus level
 - Document **resistance to clinically relevant antibiotics**; if applicable, the genetic nature of the resistance
 - For history of use, assessment of the **relative level of historical exposure** compared to the proposed conditions of use of the NDI
 - If history of use data are inadequate to support safety, **human or animal safety studies** should be included.



Route to supplement market for new ingredients

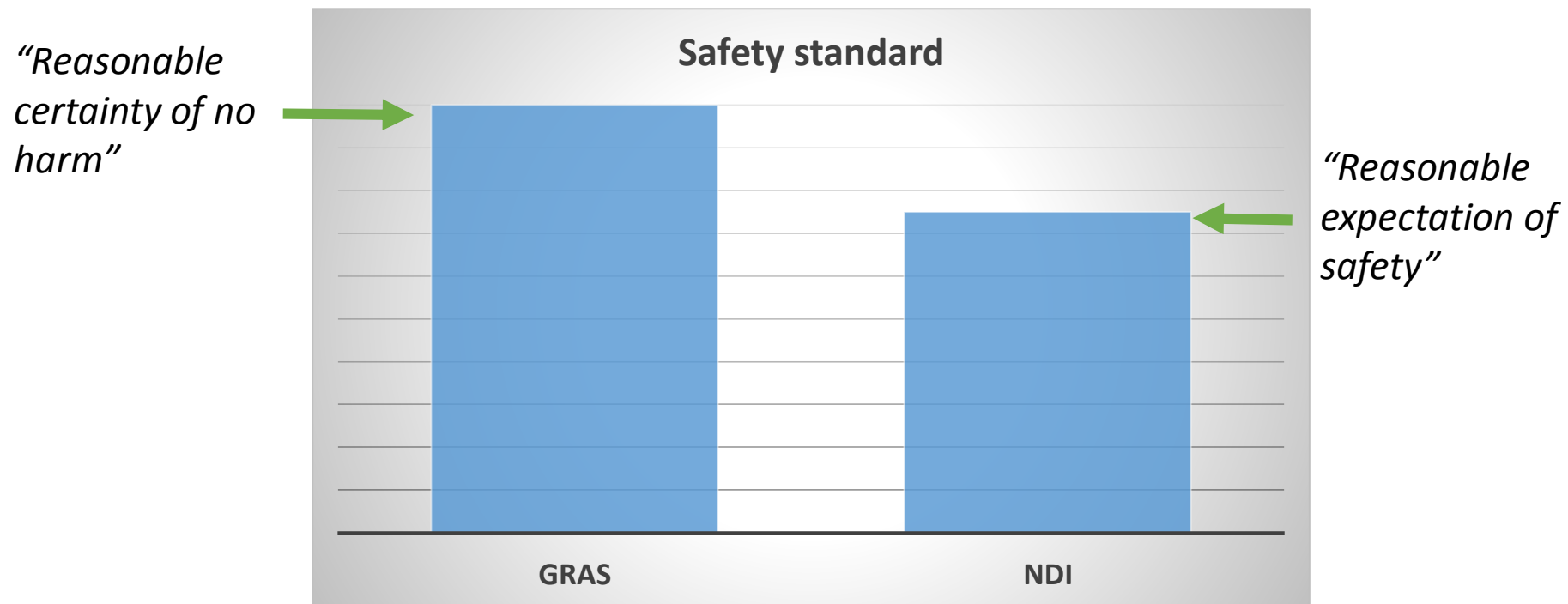
Does it meet the definition of a dietary ingredient?



A source of confusion: Different safety standards

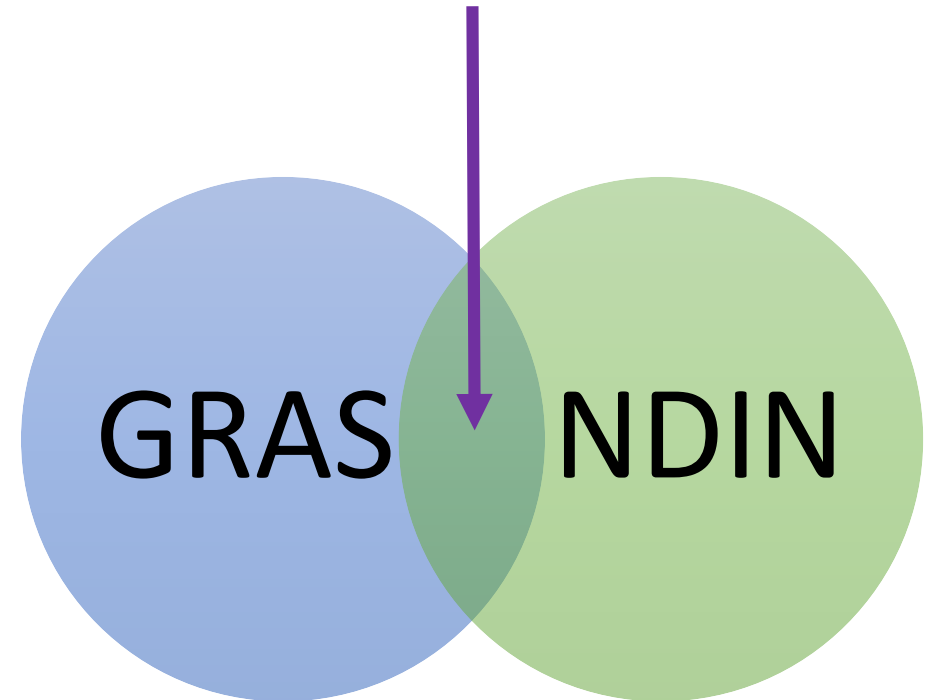
GRAS vs. NDIN

- Why different standards?
 - Conventional food: potential for more widespread use
 - Dietary supplements: more controlled use



GRAS vs. NDIN: Common themes

- Demonstration of safety under intended conditions of use
 - Dose, composition, frequency, duration of use
 - Characteristics of target population
- Ingredient characterization
- Manufacturing process (quality and consistency)



GRAS vs. NDIN: Key difference

- FDA appears to be *less* flexible in determining what qualifies as a dietary ingredient
 - FDA example of probiotic that would qualify as a legal DI: bacteria used to produce fermented foods that are consumed without a cooking/pasteurization step (e.g., lactic acid bacteria used to produce cheese or yogurt)
 - **What about innovative strains not from traditional food sources?**
- FDA appears to be *more* flexible in determining what qualifies as a GRAS substance
 - GRN 722 for *Lactobacillus plantarum* – strain (Lp-115) isolated from plant silage; there is history of use for *L. plantarum* and other *Lactobacillus* species in food but not specific uses of Lp-115 in food
 - Notifier did provide tox studies conducted specifically on Lp-115 to support safety

<https://www.fda.gov/downloads/food/ingredientspackaginglabeling/gras/noticeinventory/ucm593675.pdf>





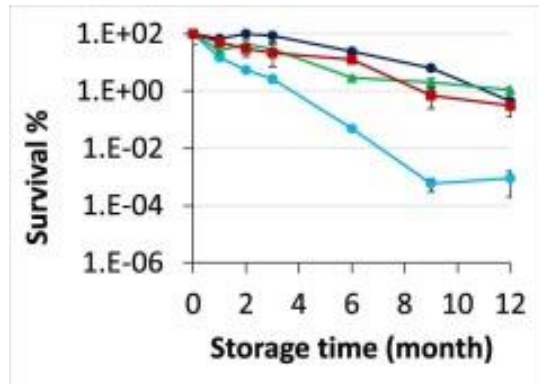
Council for Responsible Nutrition

The Science Behind the Supplements

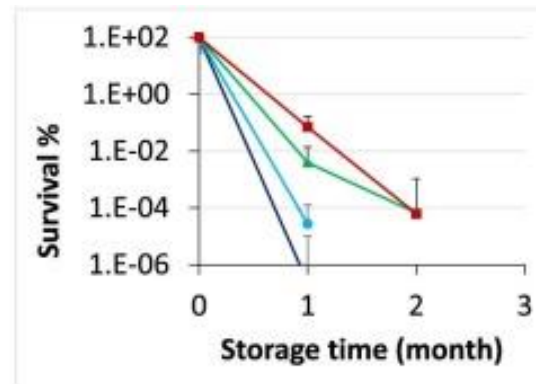


Best Practices Guidelines for Probiotics

- Guidelines for
 - ✓ Labeling
 - ✓ Stability testing
 - ✓ Storage



A



B



<http://crnusa.org/sites/default/files/pdfs/CRN-IPA-Best-Practices-Guidelines-for-Probiotics.pdf>



Labeling confusion

- FDA intends to exercise enforcement discretion for products declaring live microbial ingredient quantity in CFUs within the Supplement Facts label
- ?Quantity must be first listed in terms of weight?

“...it is the CFU, and not weight, that is the scientifically accepted unit of measure for declaring quantitative amounts of live microbial ingredients...live microorganisms are the beneficial and relevant portion of the ingredient. As such, only live microorganism quantity should be declared on a Supplement Facts label.”

-Council for Responsible Nutrition comments to the Docket

*Contains Nonbinding Recommendations
Draft - Not for Implementation*

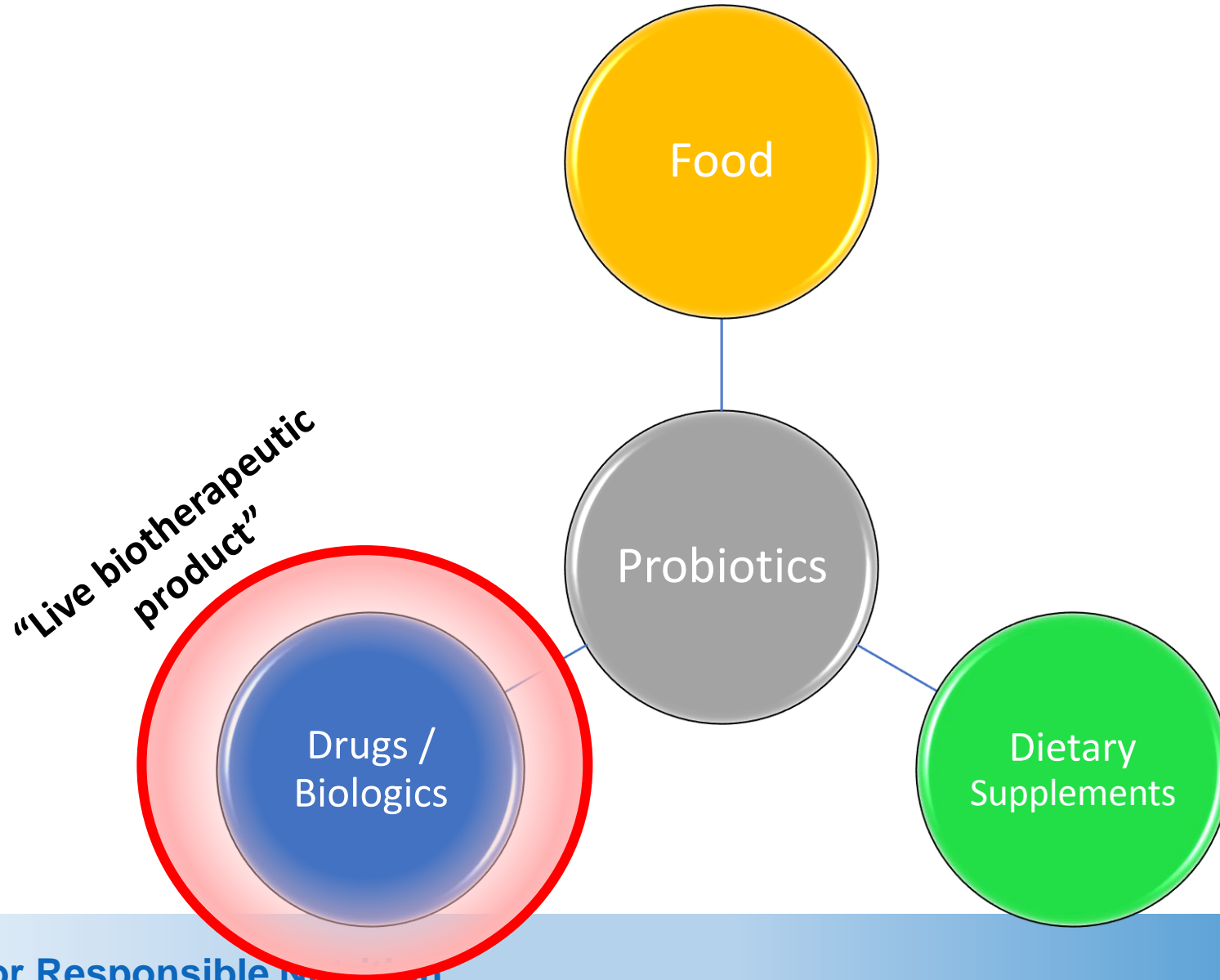
Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials: Guidance for Industry

Draft Guidance

This guidance is being distributed for comment purposes only.



Drug/biologic pathway



Drug or biologic?

Saccharomyces boulardii

2004:

- FDA announced that *S. boulardii* was eligible for consideration to be included in the monograph for OTC antidiarrheal drug products
- Requested data and information on safety and effectiveness

2009:

- FDA withdrew the notice of eligibility, indicating that *S. boulardii* is more appropriately regulated as a biological product
- *S. boulardii* is not eligible for consideration to be included in an OTC drug monograph

Today:

- *S. boulardii*-containing dietary supplements widely available*



U.S. Regulatory Considerations for Development of Live Biotherapeutic Products as Drugs

SHEILA M. DREHER-LESNICK, SCOTT STIBITZ, and PAUL E. CARLSON, JR.
Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review,
Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993

- *“An important aspect of regulatory review of proposals for the use of live LBPs...in clinical trials is the vulnerability of the study target’s population.”*

Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information

Guidance for Industry

- Live biotherapeutic product (LBP): “...a biological product that:1) contains live organisms, such as bacteria; 2) is applicable to the *prevention, treatment, or cure of a disease or condition of human beings*; and 3) is not a vaccine”

HOME > PHARMA & HUMAN HEALTH > FDA Clears 4D Pharma's IND Application for Blautix

FDA Clears 4D Pharma's IND Application for Blautix

ENROLMENT IN THE PHASE 2 STUDY IS EXPECTED TO COMMENCE IN THE SECOND HALF OF 2018

© May 9, 2018 Staff Editor Pharma & Human Health 0

Control Information. Guidance for Industry, February



Claims quandary

- Supplements/food products cannot bear claims of diagnosing, treating, curing or mitigating disease
- Majority of human studies on probiotics involve disease patients and/or endpoints (IBD, diarrhea, eczema, constipation, dementia, etc...)
- Care should be taken to appropriately match substantiation, study population, design etc...to the desired and permissible claim(s)



Does not consider
“supports
intestinal health”
to be a beneficial
physiological
effect

Summary – Key Takeaways

- Several regulatory pathways exist in the US to bring probiotic products to market
- Significant challenges exist within each pathway, in part due to the complexity of and safety concerns with probiotics
- Conflicting approaches among the pathways has created confusion in the marketplace
- For dietary supplements, FDA's interpretation of a legal dietary ingredient could be the most significant barrier for bringing novel probiotics to market



Acknowledgements

- Andrea Wong, PhD – CRN
- Duffy MacKay, ND – CV Sciences



Thank you!

Andrew Shao, Ph.D.

ashao@crnusa.org

www.crnusa.org

202-204-7656

