What’s new in U.S. regulation of probiotics?

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U.S. Regulatory Challenges for Probiotics: Research and Claims Substantiation

1. How to conduct human research on foods (including medical foods, FSDUs, and dietary supplements)
   - The drug path is clear
   - FDA is asking for human research on foods to be conducted under the Investigational New Drug rubric
     - Exceptions for taste, aroma, nutritive value, approved health claims (or structure/function endpoints for dietary supplements)

2. How to substantiate claims
   - Need human research to do this (see item 1)
   - Must all probiotic strains be validated by strain-specific human studies?
CONDUCTING HUMAN RESEARCH ON PROBIOTICS
Proportion of human studies globally compared to the USA

Probiotic clinical studies in the USA occur at $\frac{2}{3} - \frac{1}{2}$ the rate of clinical studies on any other substance
A total of 8 human trials have been published to date in 2015 on probiotics

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<th>No.</th>
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<td>Croatia</td>
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<td>USA</td>
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Only one in the USA

Why?
- FDA sees probiotics as drugs – “live biotherapeutics”
- Imposed the IND
International Scientific Association for Probiotics and Prebiotics (www.isapp.net)

2015 ISAPP Meeting
May 19-21, 2015
Georgetown University

Chairs: Dan Merenstein MD and Mary Ellen Sanders PhD

Plenary session. Regulatory challenges to moving probiotics forward in the USA

Breakout Discussion Group: What is the future of probiotics in the USA? Regulatory challenges.
What’s new with FDA

- CBER and CFSAN met with ISAPP to discuss regulatory barriers to human research on probiotics

- They realize change is needed with IND process
  - INDs aren’t appropriate for foods
  - If IND is needed, streamline the process

- They are listening and are open to an improved method overseeing probiotic research

- Suggested next steps...
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<tr>
<th>Strength of safety data (history of use or scientific methods)</th>
<th>Subject Vulnerability</th>
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<tr>
<td>Strong safety info, GRAS or NDIN</td>
<td>Low</td>
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<td>CFSAN IRB oversight</td>
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<td>CBER or CFSAN IND discussion</td>
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<td>Unstudied safety</td>
<td>High</td>
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<td>Full CMC not required</td>
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<td>CBER IND Phase 1 safety study</td>
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FDA-Center for Biologics (CBER) Request for Comment


Will facilitate investigator-initiated INDs

Research on commercial products

Does not address unnecessary safety studies

Does not address food (non-IND) research

But still some remaining concerns

- INDs required when not appropriate
  - Foods (including medical foods, FSDUs, and dietary supplements)
The FDA requires INDs for most human studies on foods

- FDA issued a **final** guidance September 2013 that requires essentially all human research conducted on foods to be conducted as an investigational new drug (IND)

- Exception is studies on taste, aroma, nutritive value and approved health claims

FDA re-opened comments through April 7, 2014 – no response yet

Hopefully, this will be repealed
Foods vs Drugs

- **Drug definition:**
  - Cures, treats, prevents or mitigates disease;
  - OR
  - Affects the structure/function of the body

- **Food definition:**
  - Substance used as a food
  - Food functions
    - Nutrition, taste, aroma
    - Impact the structure/function of the human body
    - Reduce the risk of disease

Overlap between drug and food definitions:

FDA seems to interpret drug in the broadest means possible
Sub-Categories of Food

- **Dietary supplements**
  - An ingested product intended to supplement the diet that contains a dietary ingredient

- **Medical Foods**
  - A food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.

- **Foods for Special Dietary Uses**
  - A food that supplies particular dietary needs which exist by reason of a physical, physiological, pathological or other condition, including but not limited to ...diseases
It is the vendor’s intent, and not the endpoints of the research, that dictates the need for an IND

- **Vendor’s intent shown by:**
  - Labeling claims
  - Advertising matter
  - Oral or written statements by vendors or their representatives
  - Other circumstances surrounding the distribution of the article
  - Express or implied claims that a product can be used to diagnose, cure, mitigate, treat, or prevent a disease

- **Not shown by research study endpoints**
SUBSTANTIATING CLAIMS

Must all probiotic strains be validated by strain-specific human studies?
The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic

Colin Hill, Francisco Guarner, Gregor Reid, Glenn R. Gibson, Daniel J. Merenstein, Bruno Pot, Lorenzo Morelli, Roberto Berni Canani, Harry J. Flint, Seppo Salminen, Philip C. Calder and Mary Ellen Sanders
Accumulating evidence

A Meta-Analysis of Probiotic Efficacy for Gastrointestinal Diseases

Marina L. Ritchie*, Tamara N. Romanuk

Department of Biology, Dalhousie University, Halifax, Nova Scotia, Canada

April 2012 | Volume 7 | Issue 4 | e34938

74 studies
84 trials
10,351 patients of different ages
8 GI endpoints
11 probiotic products

“in general, probiotics are beneficial in treatment and prevention of GI diseases”
Shared mechanisms

Rare
Strain-specific effects
- Neurological effects
- Immunological effects
- Endocrinological effects
- Production of specific bioactives

Frequent
Species-level effects
- Vitamin synthesis
- Direct antagonism
- Gut barrier reinforcement
- Bile salt metabolism
- Enzymatic activity
- Neutralization of carcinogens

Widespread
Among studied probiotics
- Colonization resistance
- Acid and SCFA production
- Regulation of intestinal transit
- Normalization of perturbed microbiota
- Increased turnover of enterocytes
- Competitive exclusion of pathogens

Nuanced and not prescriptive
SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to live yoghurt cultures and improved lactose digestion (ID 1143, 2976) pursuant to Article 13(1) of Regulation (EC) No 1924/2006

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

European Food Safety Authority (EFSA), Parma, Italy

This scientific output, published on 12 January 2011, replaces the earlier version published on 19 October 2010.

The food constituent that is the subject of the health claim is “yoghurt cultures (live)”, which contain the starter micro-organisms “Lactobacillus delbrueckii subsp. bulgaricus and Streptococcus thermophilus” as specified by Codex Alimentarius Standard No. 243/2003. The Panel considers that live yoghurt cultures, which are the subject of the health claim, are sufficiently characterised in relation to the claimed effect.

The claimed effect is “lactose digestion”. The target population is individuals with lactose maldigestion. The Panel considers that improved lactose digestion is a beneficial physiological effect for individuals with lactose maldigestion.
Some species include several examples of well-studied strains

“Contains probiotics” is not misleading for well-studied species

Canada and Italy allow for general claims at the species level

Must all probiotic strains be validated by strain-specific human studies?
Is it ever OK to group different strains into a single meta-analysis?

If strains are substantively similar – identity or mechanistically - YES