Regulation of Probiotics in the EU

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Safety
Qualified Presumption of Safety

Defined taxonomic group (genus, species)

Four pillars
- Established identity
- Body of knowledge
- Possible pathogenicity
- End use

“Where QPS status is proposed, the Scientific Committee is satisfied that the body of knowledge available is sufficient to provide adequate assurance that any potential to produce adverse effects in humans, livestock or the wider environment is understood and capable of exclusion”
Regulation of QPS Organisms

Meant to be a fast track for species for which there is a sufficient body of information that all strains of the species can be presumed to be safe.

This presumption may be qualified by some restrictions such as the absence of specific characteristics (e.g., transmissible antibiotic resistance, toxin production)
Regulation of QPS Organisms

“... any strain of microorganism the identity of which could be unambiguously established and assigned to a QPS group would be freed from the need for further safety assessment other than satisfying any qualifications specified.”

List of QPS groups (>70 species; most Gram+ non-sporulating) is reassessed and updated annually.
Health Claims
EC Regulation No. 1924/2006

“… health claim means any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health…”

EFSA Definition
Any statement used on labels, in marketing or in advertising that health benefits can result from consuming a given food or from one of its components.
EFSA Review Process: NDA Panel

Panel on Dietetic Products, Nutrition and Allergies (NDA)

Academics rather than government employees.
EFSA Definitions

General function claims (Article 13.1)
“… refer to the role of a nutrient or substance in growth, development and body functions; psychological and behavioral functions; slimming and weight control, satiety or reduction of available energy from the diet.”

Disease risk reduction claims (Article 14)
“… refer to the reduction of disease risk or to children's development or health.”
21 CFR 101.14(a)(1)

Health Claim

“Any claim made in food labeling that expressly or by implication ... characterizes the relationship of any substance to a disease or health-related condition.”
FDA Interpretations

“... characterizes the relationship of any substance to a disease or health-related condition.”

FDA has interpreted this as limited to:

- Reduction in the risk of incurring the disease or condition
- By the currently healthy population
EFSA Two-Step Review

Step 1: The intervention causes the effect
“… a cause and effect relationship is established between the consumption … and the claimed effect for the target group under the proposed conditions of use.”

Step 2: The effect is beneficial to human health
“… the claimed effect is defined and is a beneficial (to human health) physiological effect…”
FDA Review

FDA will approve a health claim “only when it determines, based on the *totality* of *publicly available* scientific evidence..., that there is *significant scientific agreement* among experts ... that the claim is supported by such evidence.”

21 CFR 101.14(c)
EFSA Criterion

*Highest Possible Standard*

Regulation EC No 1924/2006

“Health claims should only be authorized . . . after a scientific assessment of the highest possible standard.”
FDA Criterion

Significant Scientific Agreement

Means there is a sufficient body of evidence that shows consistency across different studies and researchers and permits the key determination of whether a change in the dietary intake of the substance will result in a change in a disease endpoint.

Means that the validity of the relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined.
An Ambiguity

To what does the “highest possible standard” apply?

• Does it require that each cited study be of the highest possible standard?

• Does it require that the totality of the evidence support the conclusion when assessed under the highest possible standard (even though individual studies may be flawed or limited)?

• Does it require only that EFSA’s scientific evaluation itself be of the highest possible standard?
Similar SSA Ambiguity

To what does significant scientific agreement apply?
The putative relationship?
Or the claim?

E.g., “There is life on Mars.”
“There is a non-zero probability that there is life on Mars.”
EFSA Track Record with Health Claims for Probiotics

100% rejection (300+ applications reviewed)

Point finger at EFSA or at EC 1924/2006?

What would be the FDA response to a petition for an unqualified health claim for a probiotic?
Two U.S. Alternatives Lacking in the EU

**Qualified Health Claims**
Provide for claims not meeting the SSA standard for the relationship between the substance and the effect

**Structure/Function Claims**
Provide for claims of a relationship between a substance and an effect without the need to establish that the effect is beneficial to human health
Could the Qualified Health Claim Approach Work in the EU?

I.e., assess whether the claim as written meets the criterion of being of the highest possible standard
EFSA Review Process: Characterization

For microorganisms (e.g. bacteria, yeast), as well as species identification, there should be sufficient characterisation (genetic typing) at strain level by internationally accepted molecular methods and strains should be named according to the International Code of Nomenclature. Although not required for substantiation of a claim, it is in the interests of the applicant that strains are deposited in an internationally recognized culture collection (with access number) for control purposes.

“In the case of a combination of two or more microorganisms, the Panel considers that if one of the microorganisms used in the combination is not sufficiently characterised, the combination proposed is also not sufficiently characterised.”

“There should also be sufficient definition of the strain(s) used in the studies provided for substantiation of the claim.”
EFSA Review Process: Need for Human Studies

“If there are no human studies which are pertinent to the claim (i.e. studies using the food/constituent and with appropriate outcome measures in a group that is representative of the target group for the claim)” a cause and effect relationship is judged not to be established.

FDA Review of Health Claims

“Lacking any data from human studies, animal and in vitro studies alone would not adequately support a health claim.”
EFSA Review Process: Studies in Healthy Populations

“For studies in groups (e.g., subjects with a disease) other than the target group for a claim, the Panel considers on a case-by-case basis the extent to which it is established that extrapolation from the study group to the target group is biologically justified.”

FDA Review of Health Claims
FDA also requires studies to be done on healthy individuals UNLESS it can be shown that the same factors exist in progression of the disease as in etiology.
EFSA Review Process: Amount of Data Required

“There is no pre-established formula as to how many or what type of studies are needed to substantiate a claim... The Panel considers what are the accepted norms in the relevant research fields…”

FTC Review of Claims
“Competent and reliable scientific evidence” based on accepted norms in the relevant fields of research.

FDA Review of Claims
“... tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results.”
Unique Challenges for Human Trials of Probiotics

- Obtaining sufficient statistical power
- Studying appropriate population(s)
- Choosing disease itself as the endpoint
  - Low incidence
  - Long latency
- Choosing an appropriate biological marker
Many (If Not Most) Human Trials of Probiotics Are Underpowered

**Magnitude of effect**
Generally small

**Variability of effect**
Generally large

**Endpoints**
Often have high inter- and intra-individual variance (noise)
Often have confounders (more noise)
Often are poorly measured (reliability, attenuation)
Issues with Study Population(s)

For health claims, must be currently healthy individuals
  – Can be individuals at elevated risk

Must be representative of the target population(s)
  – Less restriction in selection → more noise
  – More restriction in selection → failure to represent the target population(s)
THANK YOU!