GUIDELINES AND CRITERIA FOR

EVALUATION OF EFFICACY, SAFETY AND HEALTH CLAIM OF

PROBIOTIC IN FOOD PRODUCTS IN INDIA

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1. Background

With the growing interest in health care and the quest for optimum health at all ages the functional food market is fast expanding. Among the functional foods one area that is rapidly expanding is the Probiotic category. India is also witnessing the entry of a variety of probiotic dairy products in the market.

The use of dairy products as delivery vehicle for human probiotics has been practiced for many centuries particularly in Europe, Asia and the Middle East. While the optimism associated with use of these foods is undeniable it is often counterbalanced by the fact that this area has been largely unregulated from the scientific point of view. It is imperative that these products be standardized based on evidence that they produce the desired effects. It is thus important to establish a set of guidelines that would ensure product safety, quality and reliability and a level playing field for all organizations / companies introducing and producing probiotic products.

The guidelines should constitute a set of parameters required for a strain/ product to be classified as a probiotic. Keeping in mind the above stated facts, a Task Force was constituted by International Life Sciences Institute-India (ILSI-India), comprising of experts from varied fields to draft guidelines for evaluation of probiotics in India with Dr B Sesikeran, Director, National Institute of Nutrition (NIN) as the Chair.

2. Scope

The scope of this document is to formulate guidelines for Probiotics in food to evaluate the safety and efficacy of the probiotic strain for infants, young children and adults. Health claims, if any, will be substantiated with adequate scientific validation. This document does not cover biotherapeutic agents, beneficial organisms not used in food, or genetically modified organisms.

Note: FSSA (Food Safety and Standards Authority) should set up a control mechanism for conducting clinical trials in the country. The objective of this committee should be to guide the food industry:

- On the requirement of clinical trials if any in view of the existing scientific data in India and abroad.
- To review project proposals, and
- To monitor the safety and conduct of clinical trials.

3. Definitions

Probiotic – "Live microorganisms which when administered/ingested in adequate amounts confer a health benefit on the host." - **FAO/ WHO**

Biomarker includes characteristics measured objectively, which have been evaluated as a marker of normal biological processes, pathogenic processes, or pharmacological responses to the intake of probiotic.

Health claim means a demonstration of benefits of a food, food ingredient, or nutrient which is related to health, either directly or indirectly.

4. Guidelines on Evaluation of Probiotic

In making a health claim that a specific food contains probiotic as an ingredient, it is necessary to conduct an evaluation of quality, safety and effectiveness of probiotic. Criteria for evaluation of probiotics for use in food are presented in Annex 1.

4.1 Evaluation of Identity and Safety of Probiotic Microorganisms

4.1.1 Examination of identity of genus/species/strain

There is enough evidence to show that probiotic benefits are strain specific. Strain identity is important to link a strain to a specific health benefit. Speciation of the bacteria must be established using the most current valid methodology. A combination of phenotypic and genotypic tests should be used. As regards the nomenclature of microorganisms, it must conform to current names which are scientifically recognized as per:

- Approved Lists of Bacterial Names (Int. J. Syst. Bacteriol, 1980, 30:225-420) or www.bacterio.cict.fr/
- Validation Lists, published in the International Journal of Systematic and Evolutionary Microbiology (or International Journal of Systematic Bacteriology, prior to 2002).
- The latest Bergy' Manual

Phenotypic Tests:

- Patterns generated from the fermentation of a range of sugars and final fermentation products obtained from sugar utilization.
- Colony characterization on defined media such as MRS medium, Rogosa media etc.

Genotypic Tests:

- DNA- DNA Hybridization.
- Pulsed Field Gel Electrophoresis (PFGE).
- Randomly Amplified Polymorphic DNA (RAPD)

Note: The strain should be tested periodically for its originality to ascertain that it has not mutated.

4.1.2 ***Test method used to screen whether a microorganism possesses probiotic properties.***

When a microorganism has duly passed through an examination and its strain is definitely identified, the next stage is to screen such microorganism as to whether it has probiotic properties. Both in vitro and in vivo tests should be carried out to study the mechanism of the probiotic properties

Target specific in vitro tests that should correlate with in vivo tests and may include:

- Resistance to gastric juice or bile or a protective delivery system which ensure resistance.
- Adherence to mucus and/or human epithelial cells and cell line.
- Antimicrobial activity against potentially pathogenic bacteria.
- Assessment of certain metabolic activities (e.g. D-lactate production etc).
- Bile salt hydrolase activity. (Additional test method might be required if appropriate).

4.1.3 ***In vivo tests to correlate with in vitro tests***

Results obtained with in vitro models are insufficient and require in vivo testing to substantiate the in vitro effect. Animal models are often used for in vivo testing and they are recommended prior to human trials. In many cases tests with animal models substantiate the in vitro effects and determination of probiotic mechanism. Requirement of clinical trials should be evaluated as per the claim that is being proposed. For general claims, the primary concern should be safety of the probiotic use especially if it is for long term use. However, specific health claims, should be supported by results of clinical trials. Ideally, randomized clinical trials are currently considered having a high level of evidence. However, in case randomized trials are not possible, substantial clinical evidence should be produced to justify the claims. Clinical trials conducted outside the country should be submitted to the evaluation committee. The committee should evaluate the evidence on the safety and efficacy as per the proposed health claim. In case the committee is not satisfied with the evidence provided to support the health claim, they may recommend appropriate in vivo assessments to substantiate the claim.

4.2 Evaluation of Safety of Probiotic to Humans

Lactobacilli, or Bifidobacteria and Yeast have a long history of having been used in foods, and, moreover. The information obtained from epidemiological studies shows that there are no side effects in humans (Adams & Marteau, 1995). Hence, experts have concluded that both groups of microorganisms are safe and do possess probiotic properties.

Some of the tests that are recommended for a probiotic strain to be characterized as safe are as follows-

1. Determination of antibiotic resistance patterns.
2. Evaluation of metabolic activity.
3. Evaluation of side effects during studies in humans.
4. If the strain under evaluation belongs to a species that is a known mammalian toxin producer or of hemolytic potential it must be tested for toxin production and hemolytic activity respectively

4.2.1 ***Scientific Committee Report on Food: Report on the Revision on essential requirements of Infant Formulas and Follow-on Formulas -*** http://ec.europa.eu/food/fs/sc/scf/out199_en.pdf

Only bacterial strains with identity and genetic stability demonstrated by cultural and molecular methods should be used. Such strains can be considered as generally safe when added to the individual food and shown to survive the gastrointestinal passage. The identity of probiotic strains should be described by molecular methods in a dossier and be available to the food control authorities. The number of viable bacteria in the final package and by the end of shelf life should be of the same number as that shown to be effective in clinical studies.

4.3 Evaluation of Efficacy of Probiotic to Health

Upon a microorganism having passed an evaluation that it possesses probiotic properties and also having passed safety evaluation, the evaluation of efficacy of probiotic in the product needs to be supported by scientific substantiation in well designed human intervention study. Further, it must have at least two results of studies from two institutes anywhere in the world, whereby the results of studies must at least have the related parameter as follows:

- CFU ingested per day;
- Period of use required to yield intended results; and
- Scientific substantiation (For the criteria on evaluation of scientific substantiation supporting health claim, please see Annex 2).

5. Health Claim and Labeling

Currently in most countries, only general health claims are allowed on foods containing probiotics. The Task Force recommends that specific health claims on foods be allowed relating to the use of probiotics, where sufficient scientific evidence is available as per the guidelines set forth in this report. Such health claims should be permitted on the label and promotional material. (Please see Annex 3 and Annex 4).

Appropriate labeling and health claims are a pre-requisite for the consumer to make an informed choice. Hence, the following information must be displayed on the label:

1. Genus species and strain – To clarify the identity of a probiotic present in food the microbial species must be stated on the label. If the selection process has been undertaken, the identity of the strain should also be included since all probiotic effects are strain specific. Strain designation should not mislead consumers about the functionality of the strain.

2. Minimum viable numbers of each probiotic strain at the end of shelf life – The number of probiotic bacteria in food products should be clearly enumerated in order to include them on the label. The label should state the viable concentration of each probiotic present at the end of shelf life. (The minimum efficacy level for each probiotic strain should be maintained till the end of shelf life of product-scientifically proven).

3. The suggested serving size must deliver the effective dose of probiotics related to the health claim.

4. Substantiated health claims with the required scientific evidence.

5. Proper storage conditions including the temperature at which the product should be stored (For the criteria on evaluation of scientific substantiation supporting health claim, please see Annex 2).

6. Corporate contact details for consumer information.

References:

1. Report of Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria; 1-4 October; Cordoba; Argentina; 2001.

2. Report of a Joint FAO/WHO Working Group on drafting guidelines for the evaluation of probiotics in food; April 30 and May 1; London Ontario; Canada; 2002.

3. Richardson David P, Binns Nino M and Viner Penelope, Guidelines for an evidence-based review system for the scientific justification of diet and health relations under Article 13 of the new European legislation on nutrition and health claims. Food Science and Technology Bulletin, 2007; Vol.3:pp. 81-95.

4. Richardson David P. The scientific substantiation of health claims with particular reference to the grading of evidence and consumer understanding; Food Science and Technology Bulletin: Functional Foods; Vol.2: 2006: Article 4

5. Aggett P.J. et al, PASSCLAIM Process for the Assessment of Scientific Support for Claims on foods, Eur J. Nutr. 2005; 44(1):1-30.

6. Foods Act B.E. 2522 (1979).

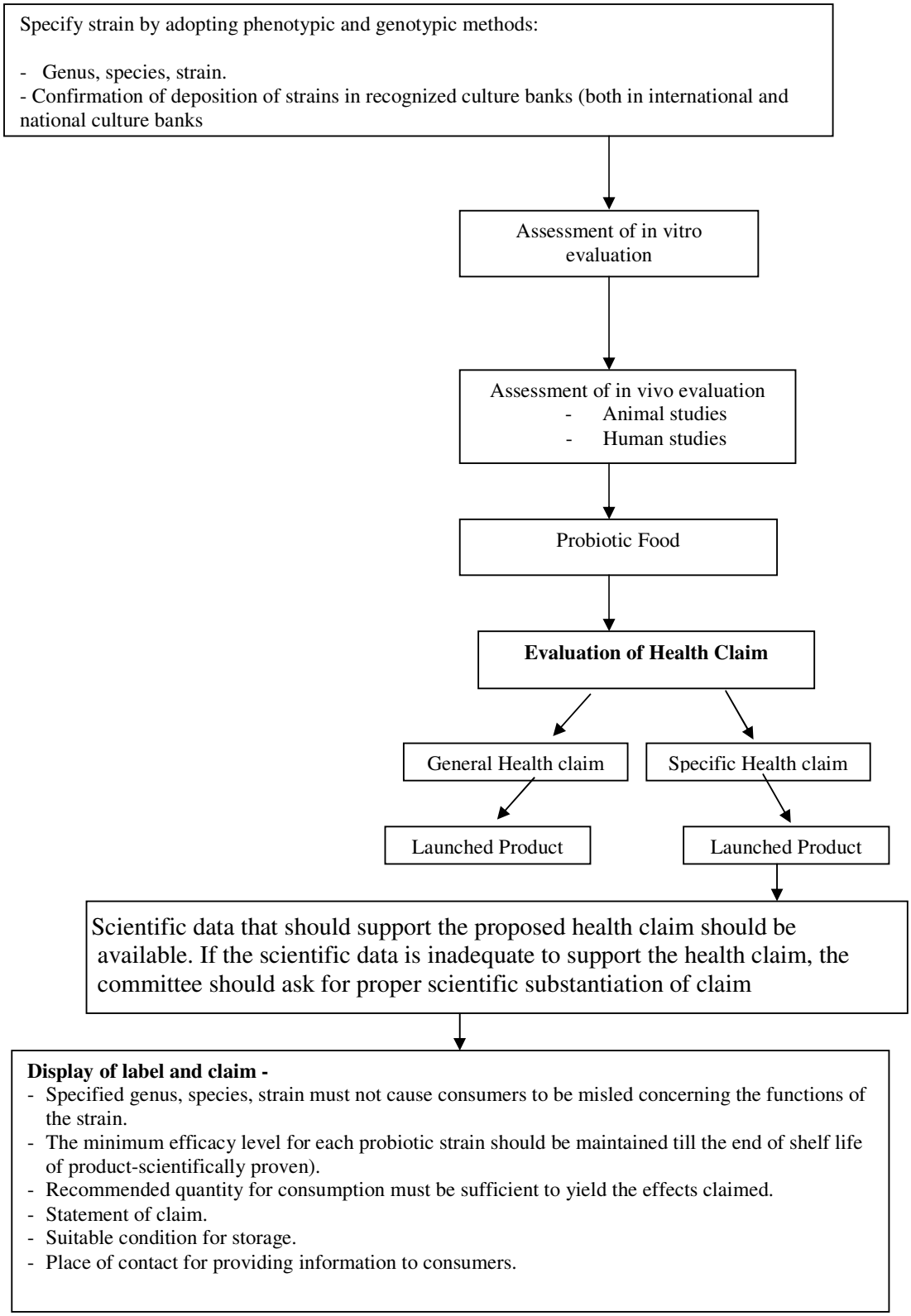
7. MoPH. No. 194 Re. Labelling

8. MoPH. No. 182 Re. Nutrition Labelling

9. MoPH. No. 289 Re. Fermented Milk

Annex-1

Criteria on Evaluation of Probiotic for Use in Food[2]



Annex-2

Criteria on Evaluation of Scientific Substantiation Supporting Health Claim

An evaluation of scientific substantiation of health claim shall be based on the following respective criteria:

Criteria 1

The food or ingredient of the food for which the claim is made must be of specific characteristics which can be clearly classified.

Criteria 2

Proof of claims should be based on in-vivo studies, the following designs of which should be considered:

1. Safety of the probiotic should be documented with the proposed or higher dose of the probiotic strain.
2. Efficacy of the probiotic to substantiate the specific health claim. The trials should demonstrate the effect of the probiotic as per the proposed claim. The trials should have a documented statistical methodology to validate the results.
3. The quantity of food and ingredient of the food that is in conformity with the intended form of consumption.
4. Influence of category of food and context of food towards the effects on functions of food ingredient.
5. Inspection of compliance on consumption of food or food ingredient used in the test.

Criteria 3

In case the endpoint of the effects of the claim cannot be measured directly, suitable markers may be used instead. However, the use of these markers should be justified with scientific evidence and should be justified with the necessary reasons of which are as follows:

- Effects on health or main benefits that take a long time to show the results.

Criteria 4

The markers used must:

- be biologically correct, whereby the relations to the final results and the variations within the target population are widely known.

- be a validated marker based on analysis of the characteristics of such markers.

Criteria 5

The target variables should be changed in a direction that is of statistical significance, and such a change should be biologically meaningful for the target group that is in line with the claim.

Criteria 6

A claim must be scientifically proven, by considering all of the existing information as well as the weight of the following evidence:

- The results obtained are in line with the results from other evidences or methods.
- It must be correct according to food technological method.
- Sampling must be of a random method.
- There must be an association between the response of the food or ingredient in the food and the health effects concerned.

Source: Aggett, P.J. et al.Criteria for the Scientific Substantiation of Claims. Eur.J.Nutr.2005 ; 44 (1): 1-30.

Annex-3

Categories of Health Claim and Markers

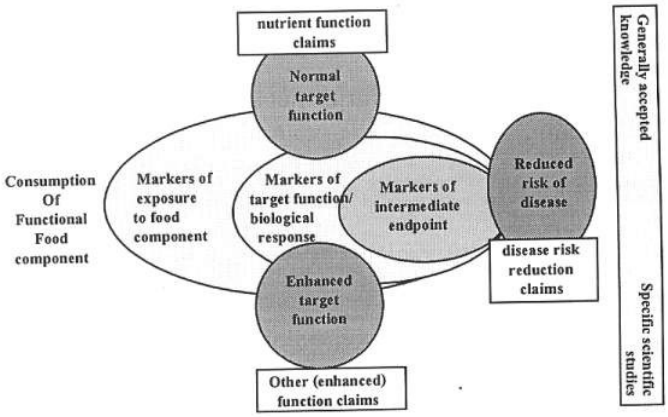
Health claim means a showing of efficacy, benefits of a food or ingredient of a food or nutrient as related to health, both directly and indirectly or implied, as follows:

(1) Nutrient function claim means a showing of efficacy, benefits relating to the role of nutrient which has physiological effects on the body, such as growth, development, or normal functions of the body, and which has been academically proven and accepted. For example, calcium strengthens bones and teeth.

(2) Other function claim means a showing of other efficacy, benefits than (1) of a food or ingredient of the food which has specific beneficial effects, or which improves a function. For example, a claim on functions of ingredient of a food that stimulates an absorption of calcium.

(3) Reduction of disease risk claim means a showing of efficacy, benefits of a food or ingredient of the food which renders an effect on reduction of risks of diseases, symptoms, or any health-related conditions, whereby it is a change of major risk factor for such diseases significantly. For example, a claim that a food or ingredient of the food helps reduce a risk for osteoporosis.

Health Markers Used for Health Claim of Various Categories Shall be Shown as Per the Following Illustration:



Source: Aggett, P.J. et al.Criteria for the Scientific Substantiation of Claims. Eur.J.Nutr.2005 ; 44 (1): 1-30.

Annex-4

Criteria on Health Claim of Food on Label and Food Accompanying Document

(1) The food that a claim is to be made shall be as follows:

(1.1) Must be safe.

(1.2) Health claim must come from food or ingredients of such food, without relying on the benefits received from consumption jointly with other foods, though it is a normal practice or with an intention that it be consumed together. For example, cereal breakfast that is consumed with milk.

(1.3) Must display nutritional label and must be in compliance with regulatory requirements of the country

(2) Health claim must be a claim about a nutrient or an ingredient of a food without making a claim on the product itself specifically, except where there is a reliable specific scientific substantiation as a result of studies of the product and which is sufficient to support the said statement of health claim.

(3) Statement of health claim of food, ingredient of food, or nutrient must be as follows:

(3.1) Must be in English language, the characters of which must be of similar size, and must be clearly legible.

(3.2) Must not cause the consumers to understand that consumption of the food, ingredient or nutrient of such food, can treat, relieve, cure or prevent a disease.