Part 1

SCIENTIFIC BASIS FOR LABELING, CLAIMS & REGULATIONS FOR PROBIOTICS: A GUIDANCE DOCUMENT

By
Knowledge Center
on
Functional Foods,
Immunity and Gut Health
(K-FFIG)

International Life Sciences Institute India

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Preface

The Science of Gut Microbiome and Probiotics has evolved into an evidence based knowledge. Based on this knowledge, research and development has led to the formulation of several food products as well as supplements and even drugs. This Guidance Document by ILSI India is intended to compile the science and the evolution of this science into products. Due to its novelty probiotics are still viewed with scepticism largely due to the unrealistic and extremely broad based claims made by some manufacturers. This document is an attempt to put together all the evidences related to the functionality of the gut microbiome and the regulatory requirements to develop products that contain these live beneficial bacteria.

Regulations do vary between regulatory environments with countries like Japan and South Korea being extremely promotive and Europe being fairly restrictive. Nevertheless, all of them base their approvals based on scientific data that has emerged over the years through basic as well as clinical studies in their respective regions. India followed soon after the WHO-FAO guidance and formed its own guidelines which were incorporated into the Food Safety and Standards Authority of India (FSSAI) regulations. Label claims are also addressed in these regulations and form a section of this Guidance Document.

This is a dynamic document and will be updated from time to time to reflect changes. This has been prepared by Ms. Rekha Sinha, Executive Director, ILSI India and Ms. Swati Dogra, Dy. Director, ILSI India with inputs from several experts.

We sincerely hope that this will be a ready reckoner for all stakeholders and students.

(Dr B Sesikeran)
Chairman, K-FFIG

Scope

The purpose of this document is to provide guidance for making claims on probiotics. It will be useful for industry involved in the production and manufacturing of food products with added probiotic ingredients or food products with added prebiotic ingredients or it can be both. This document will be of help to organisations/personnel in addressing claims related issues.

The Guidance Document is in two parts. **Part I** is divided into five main sections. The **first section** gives an overview about the "microbiome and its role in promoting health". It explains how microbiome gets adversely affected due to environmental factors, lifestyle, diet and briefly outlines the role of nutrition and functional food in general and prebiotics and probiotics in particular in correcting it.

The second section primarily explains the role of probiotics and prebiotics in promoting healthy gut and the current research undertaken in India in this area.

The third section of this document briefly explains the Indian regulatory mechanism for ensuring safety of probiotics and prebiotics.

The fourth section describes the role of labelling and claims in establishing consumers communication. This section explains about claims and its different types relevant for probiotics and prebiotics; process involved in introducing products with claims in India- covering both aspects where approval is not required and where approval is required; how to substantiate claims for prebiotics and probiotics and why there is need for evidence generation for probiotics and prebiotics in India. This section is quite important as it identifies various issues critical for making claims related to probiotics under India scenario.

The fifth section provides an overview of global guidance regulatory framework for probiotics/ prebiotics and CODEX guidelines.

Part II includes all the Appendices.

SECTION -1

Introduction

Microbiome and its Role in Promoting Health

The term ***Microbiome*** describes the genome which is present in all microorganisms, symbiotic and pathogenic, that live on and in all vertebrate (Veena Taneja, 2017). According to Julian R. Marchesi and Jacques Ravel, 2015 microbiome consists of an entire habitat which includes microorganisms, their genetic materials and the environmental conditions. It is entirely based on the biome which is a biotic and abiotic factor of the given environment.

Thus, *Microbiome* can be defined as "the human micro flora which refers to the communities of bacteria, viruses and fungi that reside in the human body and interact with the host to perform a variety of functions and interactions both in health and disease".

As per the Human Microbial Project Consortium, 2012 the human microbiome has an estimated 100 trillion microbes. These microbial community are in bulk and they live in the gastro-intestinal tract of humans. Each microbial community is unique to an individual as a fingerprint and thus the microbiome is unique in providing immense health benefits. Bifidobacterium, Lactobacillus, Bacteroides, Clostridium, Escherichia, Streptococcus and Ruminococcus are the most commonly recognized genera of gut bacteria in adults. Previous studies have shown that approximately 60% of the bacteria in human gut belong to the Bacteroidetes or Firmicutes phyla (Backhed F et al, 2005).

The microbiome is essential for human development, immunity and nutrition. The bacteria which are living in human gut are beneficial colonizers and are involved in maintaining the balance. When the normal individual balance of microbes is disturbed it results in numerous diseases conditions. Understanding the role of the human microbiome in health and disease is among the most rapidly expanding areas of scientific research today and gives opportunities to use this knowledge to improve human health. It has been pointed out that the microbiome plays an important role in maintaining intestinal health, ensuring optimal nutrient absorption, educating the host immune system or limiting colonization with potential pathogens. Recent studies have revealed that dysregulation of the microbiome predisposes the host to pathologies ranging from chronic inflammation and obesity to metabolic syndrome, Irritable Bowel Syndrome (IBS) and even cancer.

1.1- Factors Influencing the Microbiome and Impact on Health

- **Microbial Products:** A vast range of products known as microbial metabolites are produced by gut microbes which depend on factors such as nutrient availability, luminal environment and particular pH (Duncan, S.H. et al, 2009). These microbial metabolites such as short-chain fatty acids (SCFAs) are responsible for mediating the beneficial systemic effects of microbiota. **Examples of short-chain fatty acids (SCFAs): are acetate, propionate and butyrate and the gases-hydrogen sulfide, ammonia, hydrogen, methane, carbon monoxide and carbon dioxide** (Oleskin and Shenderov, 2016). These microbial metabolites are produced in large intestine by the fermentation of dietary fibres under anaerobic conditions (Cummings and Macfarlane, 1991; Topping and Clifton, 2001; Donohoe et al, 2011; Flint et al, 2012) and have multiple effects on host such as acting as an energy source, promoting glucose and energy homeostasis, regulating anorectic hormone, tumor suppression and regulating central and peripheral nervous systems (Cox and Blaser, 2013; Bienenstock et al, 2015).

- **Life Stage:** The human gut is colonised by microbes during or shortly after birth. Research has shown that the composition of the microbe undergoes most dramatic changes during period of infancy and early childhood (Palmer et al, 2007). **It has also been found that during period of infancy the intestinal microbiome is affected by the following factors: gestational age (full term or premature), mode of delivery (vaginal birth or caesarean section), type of feed (breast milk**

or formula feeds), maternal nutritional status (overweight or undernourished) and use of antibiotics (Huurre et al, 2008; Kelly et al, 2007; Harmsen et al, 2000; Coopa et al, 2006; Arslanoglu et al, 2008; Meropol and Edwards, 2015). Moreover, the infant microbiota shows complexity and plasticity during early life development which plays a very crucial role in maintaining the homeostasis within the host's immune system and has an impact on health in the later years of life (Charbonneau et al, 2016). Further, the gut microbiota stabilises by three years of age which is similar to that of adults and it is supposed to be unique and specific to an individual like a fingerprint (Aeri B T and Lamba J, 2019).

- **Lifestyle:** Studies have been shown that **smoking and lack of exercise** influences the large bowl (influences the microbiota) which may leads to increase in risk factor for colorectal cancer (CRC) and Crohn's Disease (CD) (Huxley et al, 2009; Benjamin et al, 2012).

  Another lifestyle factor is **stress** which has an effect on colonic motor activity through gut-brain axis which may lead to changes in the gut microbiota profile and hence results in decrease in the numbers of potentially beneficial bacteria such as Lactobacillus which may increase the chances for developing IBS (most common functional bowel disorders) among individuals (Lutgendorf et al, 2008). Since the gut brain axis involves bi-directional pathway which includes both hormones and neurons (Grenham et al, 2011) therefore changes in the gut microbiome may have an impact on the brain activity which may significantly contribute to the risk factor for the development of neurological disorder like Autism which occurres due to significant shifts in gut microbiota populations (Clarke et al, 2013; Finegold et al, 2010; Parrcho et al, 2005; Wang et al, 2011).

  Obesity is another lifestyle disordorer which results from excess energy intake along with no or in adequate exercise. Exercise could be an important factor which may influence the shifts in microbial populations that may be associated with obesity. This is highlighted in a new research which shows that the bacteria which is the member of the genus ***Veillonella*** is found in the microbiomes of elite athletes and not in the gut of the sedentary people. This ***Veillonella*** metabolizes lactic acid which is produced by exercise and converts it into propionate (short chain fatty acid) which is utilized by human body to improve exercise capacity among athletes (Aleksandar D. Kostic, 2019). Another study shows that exercise and associated diet may leads to increase in the diversity of intestinal microbial populations in professional athletes (Clarke et al, 2014). Previous studies have shown that in human and animal models with obesity, changes in the gut microbial populations occur with increase in the Firmicutes and decrease in the Bacteroidetes which may contribute to adiposity through greater energy harvest (Ley et al, 2005; Ley et al, 2006; Turnbaugh et al, 2006). However, some of the statistics suggests that the **high fat obesogenic diets** are responsible for shifts in the intestinal microbial populations (Delzenne and Cani, 2011; Lin et al, 2012). Further, dietary saturated fats are associated with increased numbers of proinflammatory intestinal microbes which stimulate the formation of taurine conjugated bile acids that promote the growth of Staphylococcus, E coli, Enterobacteriaceae which are linked to poor health outcomes (Collado et al, 2008; Kalliomaki et al, 2008; Devkota et al, 2012).

- **Geographical regions** may also contribute to significant changes in the composition of gut microbiome populations. This has been highlighted in a study which indicates that there is increase in the diversity of fecal microbes among children from rural Africa as compared with that of children of developed communities in the EU. The study identifies the microbes that are present in the fecal (De Filippo et al, 2010). Another Study shows that **the type of fecal bacteria and their functional genes differ between individuals** in the USA and in the rural areas of Venezuela and Malawi (Yatsuneenko et al, 2012).

- **Environment:** One of the environmental factors is **air pollutants** which contribute to alterations in gut microbiome. A recent study shows that the exposure to air pollutants via inhalation or ingestion may leads to shift in the intestinal microbial populations, decreased gut barrier integrity and increased inflammation in the murine GI tract. Moreover, researchers have found that the association between exposure to air pollutants and obesity and type 2 diabetes may be partially mediated by exposure-induced changes to the gut microbiota (Tanya L. Alderete, 2020).

Previous studies have also shown that **air born toxic particles may be associated with increased incidence of inflammatory Bowel Disease** (IBD) cases as they reach the large bowel by clearance from lungs (Beamish et al, 2011). Another environmental factor includes **travelling particularly to overseas destinations** which may increase the risk of spreading and contracting infectious diseases which may include diarrhoea. It may result due to poor sanitary conditions and poor personal hygiene which may facilitate the spread of infectious agents. Circadian disorganization occur because of travel, shift work which also has an effect on gut health and cause changes in the gut microbiome populations (Voigt et al, 2014).

Most people are chronically exposed to both natural and human-made environmental contaminants which leads to alterations in the gut microbiome and associated health challenge. Further, study data suggest that during various stages of life the exposure to the environmental chemicals can change the intestinal microbial population in ways that influence health which includes immune dysfunction, altered carbohydrate and lipid metabolism and neurological and behavioural impairments (Karen Chiu, et al, 2020).

- **Diet and Dietary Changes:** Diet is another component which influences the gut health. Studies have shown that the genera Bacteroides, Bifidobacterium and Eubacterium account for more than 60% of culturable microbes present in human stool. Moreover, Clostridium, Enterobacteriaceae and Streptococcus are also important but they are less numerous. Researchers have also mentioned that approximately 90% of microbes in the human intestine or gut are mapped into two phyla, bacterioidetes and Firmicutes and their proportions. People have most similar proportions of Bacterioidetes and Firmicutes (Jeffery et al, 2012). Another study which shows that **high-fat, low-carbohydrate diet is associated with unfavourable changes in gut microbiota, fecal microbial metabolites, and plasma proinflammatory factors in healthy young adults** (Yi Wan et al, 2019). Long-term, habitual diet and short-term dietary variation influence gut microbiota composition.

The effects of Western style diet and vegetarian / vegan diet on Gut Microbiome are given below.

The Effects of Western-Style Diet on Gut Microbiota: Western style diets are energy dense, high in animal protein, total and saturated fats and simple sugars but low in fruits, vegetables and other plant-based foods. This means they are typically low in dietary fibre (DF), non starch polysaccharides (NSP) like cellulose and refined sugars (RS). Researchers have shown that **western diet is associated with increased risk of chronic diseases such as cardiovascular disease, CRC and type 2 diabetes which impose high socio-economic burden** (Cordain et al, 2005; Michael and Anthony, 2015). Cross sectional studies have shown that western style diet is rich in gut microbial population- Bacteroides enterotype whereas diet rich in plant-based food is rich in Prevotella enterotype (Wu et al, 2011). Study on analysis of fecal microbiota of USA children has provided supporting evidence that gut microbiota is dominated by Bacteroides (Lina et al, 2013; Yatsunenko et al, 2012).

A large-scale population-based study shows that certain gut microbial features are associated with the consumption of certain food items. It also links Western diet pattern to an altered microbiota composition. Study results indicate that food items which are significantly and positively associated with **α-diversity** are raw fruit and fish whereas food items such as fried products, sodas, sugary drinks, fatty sweet products, processed meats, ready to cook meals and desserts **(Western-Style Diet)** are negatively associated with α-diversity. Also, the change within the microbiota composition has been seen for certain foods (fruits, fried products, ready to cooked meals and cheese) towards **β-diversity** (Valentin Partula et al, 2019).

The Effects of Vegetarian and Vegan Diets on Gut Microbiota: Plant based diet has been proven to be beneficial for promoting human health by the development of more diverse and stable microbiome systems. Latest research has shown that both vegans and vegetarians have significantly higher counts of certain Bacteroidetes-related operational taxonomic units compared to omnivores. Fibres (that is, non-digestible carbohydrates, found exclusively in plants) most consistently increase ***lactic acid bacteria (LAB)***, such as ***Ruminococcus, E. rectale,*** and ***Roseburia***, and reduce ***Clostridium*** and ***Enterococcus species*** and polyphenols (abundant in plant foods) increase

Bifidobacterium and ***Lactobacillus***, which provide anti-pathogenic and anti-inflammatory effects and cardiovascular protection. High fibre intake also encourages the growth of species that ferment fibre into metabolites such as short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. **The positive health effects of SCFAs are myriad, including improved immunity against pathogens, blood-brain barrier integrity, provision of energy substrates, and regulation of critical functions of the intestine and thus a vegetarian/vegan diet is effective in promoting a diverse ecosystem of beneficial bacteria to support both human gut microbiome and overall health** (Aleksandra Tomova et al, 2019). Result of a randomized clinical trial study shows that after feeding plant-based diet for 16 weeks, there was a significant reduction in the body weight among the vegan group (treatment effect average -5.8 kg), particularly due to a reduction in fat mass (average -3.9 kg) and in visceral fat. Insulin sensitivity also increased significantly in the vegan group (Hana Kahleova, Andrea Tura and Neal Barnard, 2019).

Inter-Individual Variation in Gut Microbiota: Each individual possesses a unique combination of gut microbiota species**. Inter-individual differences in the population may also influence the gut microbiome as the capacity to utilize dietary components are different and there are difference in levels of disease risk. One recent study shows that the interaction of bacteria in the gut with the food differs markedly between individuals.** The highly personalized nature of the gut microbiome requires dietary interventions to optimize the microbiome. Scientists have also found that foods with similar nutrition levels can have vastly different effects on the microbiome and in order to promote or suppress a particular bacterial species through a food-based intervention, the diet may need to be individually tailored according to a person's specific microbiome (Abigail J. Johnson et al, 2019).

1.2- Probiotics and Prebiotics as Nutritional Strategies to Improve Health

A Nutritional strategy which promotes good health involves the usage of probiotics and prebiotics which are responsible for supporting good health of the host by improving the composition of the gut microbiome. Prebiotics and probiotics both increase the numbers of selected bacteria which includes Bifidobacterium and Lactobacillus (Michael A. Conlon and Anthony R. Bird, 2015). Recently many studies have reviewed in depth the role of prebiotics and probiotics in promoting good metabolic health, gastrointestinal transits, gut microbiota and reducing risk of colorectal cancer and other systemic disease (Mattea Muller et al, 2020; Clark, et al 2012; Roberfroid et al, 2010; Brownawell et al, 2012; Saad et al, 2013). The next section provides an overview about role of prebiotics and probiotics in promoting health and the current research associated with that.

SECTION- 2

Role Of Probiotics And Prebiotics In Promoting Healthy Gut

2.1- What are: Probiotics/ Prebiotics/ Synbiotics?

Probiotics

Probiotics are "live microorganisms which when administered in adequate amount confer a health benefit on the host" (FAO and WHO, 2002; B Srilakshmi, 2019).

Commonly used bacterial probiotics include various species of Lactobacillus, Bifidobacterium and Streptococcus , Bacillus coagulans as well as Lactococcus lactis and some Enterococcus species. According to Morrow, Gogineni and Rastegar, Saccharomyces boulardii is the only non- pathogenic probiotic yeast which is currently used.

Prebiotics

Prebiotics are non-digestible dietary ingredients that beneficially affect the host by selectively stimulating the growth or activity of a limited number of bacteria in the colon.

The term "Prebiotics" was coined by Gibson and Roberfroid in 1995 and it is defined as "a nondigestible food ingredient that is known to selectively stimulate the growth and the activity of one or more beneficial bacteria in the colon and which in turn improves the host's health status. To perform as prebiotics, the components of functional foods and supplements must be able to withstand the digestive processes, before they reach the colon and preferably persist throughout the large intestine (Gibson et al, 2011; 2017).

Oligosaccharides, which are relatively short chain carbohydrates, have now been acknowledged to have prebiotics properties. According to Longvah et al, 2017, various types of oligosaccharides are found in natural foods available abundantly in the Indian diets like fruits (watermelon, pomegranate, dates, figs), vegetables (onion, beetroot, green peas, sweet corn, garlic), legumes (chickpea, lentils, red kidney beans, soyabeans), cereals (barley, wheat bran), nuts (cashew, pistachio), milk and honey.

Synbiotics

The term synbiotics is used for a product which is a combination of prebiotics and probiotics which have a synergistic effect by inhibiting the growth of pathogenic bacteria and enhancing the growth of beneficial organisms (De Vrese and Schrezenmeir, 2008).

According to Cencic and Chingwaru 2010, a synbiotics product positively affects the host in improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract by selectively stimulating the growth and/or activating the metabolism of one or a limited number of health-promoting bacteria. The word "synbiotics" alludes to synergism which should be reserved for products in which the prebiotic compound(s) selectively favor the probiotic organism(s).

In synbiotics formulations the following major probiotic strains are used, for example, Lacbobacilli, Bifidobacteria spp, S. boulardii, B. coagulans etc., while the major prebiotics used should comprise of oligosaccharides like fructooligosaccharide (FOS), galactooligosaccharide (GOS) and xyloseoligosaccharide (XOS), inulin, prebiotics from natural sources like chicory and yacon roots (Pandey et al, 2015). The health benefits of synbiotics consumption are as follows:

1) Increases the levels of lactobacilli and bifidobacteria and balanced gut microbiota.
2) Improves liver function in cirrhotic patients.

3) Promotes immunomodulating ability.
4) Helps in the prevention of bacterial translocation and reduces incidences of nosocomial infections in surgical patients (Zhang et al. 2010).

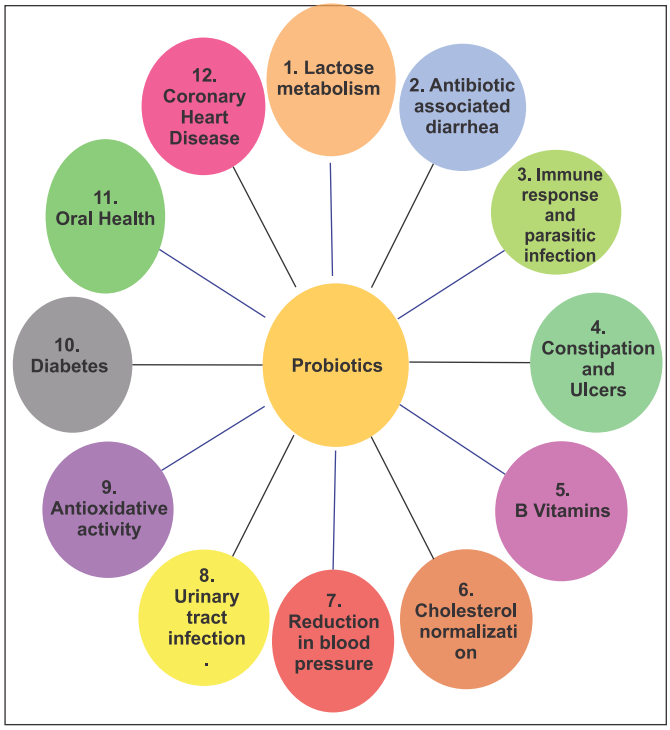
2.2- How Probiotics and Prebiotics Help

Probiotics and Prebiotics help in building health by influencing the Gut Microbiome in a positive way. The major health impacts are given below.

2.2.1- Role of Probiotics in Health

Probiotics play an important role as a nutritional strategy which is beneficial for the health. Consumption of a probiotic therapeutically involves intake of beneficial microorganism cultures of the healthy human microflora. It holds great promise for the prevention and treatment of various clinical conditions associated with impaired gut mucosal barrier functions and sustained inflammatory responses (Ouwehand, Salminen & Isolauri, 2002). Probiotics have the following health benefits as described in Fig 3:

Figure 3: Health Attributes of Probiotics



Source: Nagpal et al, 2012

a. Probiotics and Gut Health: The imbalance or dysbiosis of gut microbiome plays a crucial role in the pathogenesis of both intestinal and extra-intestinal disorders such as Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS), allergies, asthma, type 1 diabetes, cardiovascular disease, metabolic syndrome, and obesity (Carding et al, 2015). Researchers have been investigating the effectiveness of probiotic therapy in correcting various gastrointestinal and other disorders.

The most common digestive disorder is Lactose Intolerance which is commonly seen among Asian populations and it has following symptoms like loose stools, abdominal bloating, pain, flatulence and nausea. In lactose intolerance the patient is unable to digest the lactose present in the milk, however they are able to tolerate the lactose present in the curd as very little amount of lactose is present in curd and most curds contain live bacteria that can help break down lactose. In previous studies the investigators have studied the effects of probiotics on constipation and the improvement in the intestinal mobility.

Researchers have also evaluated various ranges of **probiotic strains for anti-diarrhoeal capabilities**. In acute infantile, the therapeutic treatment with Lactobacillus rhamnosus GG has shown reduction in the duration of diarrhoea by around 50% which generally occur due to the rotavirus (Tuohy et al, 2003). In children and adults, the administration of probiotics has been shown to reduce the incidence and duration of antibiotic-associated diarrhoea (Goldenberg, 2015). Administration of probiotics strain L. rhamnosus GG has been found effective in reducing the incidence of diarrhoea, nausea and taste disturbance in patients who received antibiotics like rabeprazole, clarithromycin and tinidazole for eradication of H. pylori (Armuzzi et al, 2001). Moreover, the following probiotics including Lactobacillus acidophilus, Lactobacillus johnsonii, Bifidobacteria and Streptococcus boulardii show similar result.

b. Maintaining Integrity of the Intestinal Barrier: Many researchers have studied the massive potential of probiotics bacteria in maintaining the integrity of intestinal barrier function (Bron et al, 2017).

Intestinal barrier provides multiple line of defence against microbial invasion including commensal bacteria which competitively inhibit the colonization of pathogenic bacteria and produce metabolically protective compounds such as butyrate (Koning et al, 2016). Also, Lactobacillus plantarum (well known as a commensal bacteria species) regulates intestinal integrity by stimulation of toll like receptor 2 (TLR2) in the gastrointestinal or gut epithelium (Karczewski, 2012).

c. **Probiotics and Immunity:** There is substantial evidence which shows that probiotics promote health benefits by modulating immune function (Ibnou-Zekri, 2003). In animal model scientists have observed that probiotic supplementation offers protection from spontaneous and chemically induced colitis by down regulating inflammatory cytokines or by induced regulatory mechanisms in a strain-specific manner (Liu et al, 2007). Probiotics play a very important role in epithelial cell proliferation and differentiation and also promote the development and the homeostasis of the immune system (Cammarota et al, 2009).

d. **Probiotics and Cancer:** Probiotics promote beneficial effects by supporting the beneficial anaerobic microbiota during chemotherapy. Researchers have found that commensal gut bacteria play an important role in amelioration of inflammation and bacteremia - a condition characterized by abnormal presence of bacteria in blood which occur due to the chemotherapy-induced mucositis (Van Vliet, 2010). Further, in the rat model of chemotherapy-induced mucositis a study has shown that there was a decrease in the number as well as diversity of the fecal microbiota including anaerobes and Streptococci, although the number of Bacteroides was relatively increased (Fijlstra, 2015).

e. **Probiotics and Eczema, Asthma and other Disorders:** Researchers have reported various intervention with probiotics which show effectiveness in the treatment of eczema, atopic dermatitis and other disorders. This could be highlighted in the studies which show that there was an improvement in the atopic dermatitis scores along with decrease in IFN- γ, eosinophil, and Interleukin-4 counts (Han et al, 2012). A randomized, double-blind placebo-controlled study explored the usage of ***L. paracasei (LP), L. fermentum (LF), and LP+LF*** together in children, and found that the SCORAD scores were lower in the group that received probiotics as compared to placebo group (Wang and Wang, 2015). Another study also demonstrated the effectiveness of ***L. sakei*** supplementation among children.There was substantial clinical improvement along with decrease in chemokine levels (Woo et al., 2010). A most recent meta-analysis concluded that probiotics significantly improved the Severity Scoring of Atopic Dermatitis (SCORD) Index in patients aged 1 year or older with AD [mean difference, -4.51; 95% CI, -6.78 to -2.24] (Kim et al., 2014). A longitudinal study among children. These was shows that daily intake of ***Lactobacillus rhamnosus HN001*** when given for the first 2 years of life only and extended to at least 4 years of age resulted in the reduction of the incidence and severity of eczema as well as rhino conjunctivitis (Wickens et al, 2008, 2012).

f. **Probiotics and Mental Health:** There is a growing body of evidence showing the role of probiotics on mood, cognition, brain function and mental health. A study on rats has shown that besides keeping the gut healthy, consuming a diet rich in probiotics may help protect against depression (Abildgaard et al, 2017). Another study shows that probiotic-based diet supplementation is the potential treatment for Autism Spectrum Disorders (ASDs) because of the existing gut microbiota profile-mental health (Aurelie Razafindralambo and Hary Razafindralambo, 2019). A systematic review on the usage of pre and probiotics as treatment strategy for depression and /or anxiety disorders shows a significant improvement in one or more of the outcomes which measured the effect of taking pre/probiotics compared with no treatment/placebo, or when compared to baseline measurements (Sanjay Noonan et al, 2020).

g. **Probiotics and Cardio-Metabolic Health:** There are clusters of metabolic disorders which are associated with lifestyle. These are diabetes, obesity and cardiovascular diseases .They are recognized as a crucial risk factor for human health and life. Genetic and sedentary lifestyle are the major contributors to the development of these metabolic malfunctioning which are further accompanied by stress and bad eating habits. They have drastic effect on quality and human life span.

A recent study shows the effect of dietary intervention with L. mesenteroides SD23 improves **metabolic dysfunction related to obesity** in (high fat diet) HFD-fed mice (Diana et al, 2020). Another

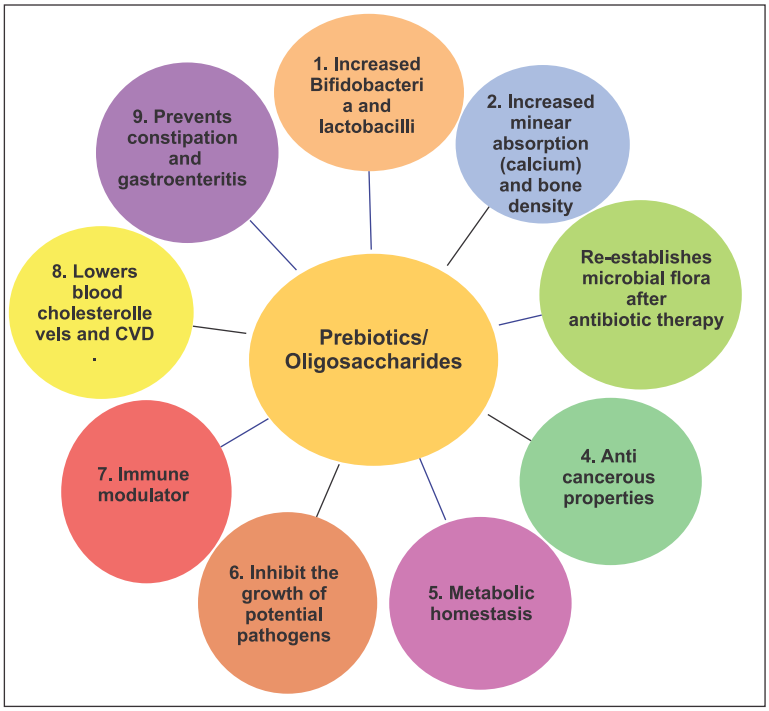
recent study review suggests that **the probiotics and/or prebiotics** may **reduce the serum cholesterol level** more significantly and can be used as a remedy for hyper cholesterolemic problems without any side effect to the consumers (Anandharaj, Sivasankari and Rani, 2020).

Probiotics also play a significant role in reducing hypertension which is well supported by the meta-analysis of the human studies, however the mechanism of this antihypertensive effect of probiotics and its protective effect on endothelial function has not been clear and it requires further investigation (Robles-Vera et al, 2017).

2.2.2- Role of Prebiotics in Health

Prebiotics consumption has been linked to several beneficial effects in the body like maintain gastro intestinal health, immune stimulation, cholesterol reduction and mineral absorption (ILSI India, 2018). Beneficial effects of prebiotics on health is briefly described through a schematic representation in Fig. 4.

Figure 4: Schematic Representation of Beneficial Effects of Prebiotics on Health and Nutrition Absorption



Source: ILSI India Monograph on Prebiotics in Foods and their Beneficial Effects

a. **Maintaining Gastrointestinal Health:** Studies have shown that there has been a strong correlation between intestinal microbiota and development of various metabolic syndrome in humans (Clemente et al, 2012). Hence, the role of prebiotic in intestinal health has received attention. Researchers have found that prebiotic play a very crucial role in promoting good bacteria in the intestine which prevents the colonization of pathogens by resisting them and get involved in the interaction with the host by modulating innate and adaptive immune responses by producing metabolites which may affect the body (Clemente et al, 2012). Diet composition and intake of drugs (antibiotics) play a major decisive role as an environmental factor, along with the host's genetic factors to determine the microbiota pattern of intestine. A study has shown that oligosaccharides as a prebiotic alter both the composition and the activity of the gut microbiota which impacts the health status of the host directly (Rochfort et al, 2007). Another study shows that Oligosaccharides play a promising role in

combating acute gastroenteritis, E.coli gastroenteritis, Salmonella and Helicobacter pylori–associated gastroenteritis and irritable and inflammatory bowel conditions and inflammatory bowel disorders (Macfarlane et al, 2006). Moreover, there are many clinical trial studies which have shown the role of prebiotics on human health specifically in Irritable Bowel Syndrome (IBS), gastrointestinal disorders, elimination of Helicobacter, inflammatory bowel disease (IBD), diarrhea (Bruzzese et al, 2006; Costalos et al, 2007; Scholtens et al, 2008; Welters et al, 2002; Lindsay et al, 2006).

b. **Prebiotics and Obesity:** Studies have been conducted on role of prebiotic and its effects on obesity. A clinical trial has shown that intake of oligofructose supplementation (OFS) among healthy adults with a body mass index (Kg/ m^2) >25 for almost 12 weeks reduced body weight i.e. 1.03 ± 0.43 kg. Glucose and insulin concentration were decreased among OFS group as compared to control group. Also, OFS supplementation did not affect plasma active glucagon-like peptide 1 secretion. Further, oligofructose was well tolerated by the subjects according to visual analogue scale designed to assess side effects (Parnell and Reimer, 2009). Scientists have mentioned that the bacterial population present in the gut of the obese and lean people is entirely different and if obese people lose weight then their microbiota could resemble that of lean people (Kavita, Suresh, and Babu, 2015). Another study has shown that diets which contain high fibers have a low density of fat and energy content which is quite helpful in reducing the risk of obesity among people by promoting good level of satiety and weight loss (Ley et al, 2006). It is well supported by another study which verifies that in mice both lean and obese, the gastrointestinal microflora will affect the energy balance by influencing the efficiency of calorie driven form of diet as well as utilization and storage of harvested energy (Stienstra et al, 2012). Further, a recent study has shown the effects of wheat dextrin on overweight adults. It demonstrated a progressive and significant increase in satiety and decrease in hunger feeling (Erejuwa et al, 2014).

c. **Prebiotics and Type 2 Diabetes:** Clinical studies have supported the role of prebiotics in type 2 diabetes (T2D). A study has shown that intake of a supplement of 15 g/day of Arabinoxylan- rich fiber (AX) for 5 weeks can significantly improve glycemic control in people with type 2 diabetes (Lu Z. X. et al, 2004). According to Garcia, Otto and Reich, (2007) AX intake by patients with impaired glucose intolerance improved fasting serum glucose and triglycerides.

d. **Effects of Prebiotics on Cholesterol Reduction and Cardiovascular Disease Risk:** Studies have shown the potential of normalizing lipid profiles in obese individuals, who were administered enhancement prebiotics along with Lactobacilli and this was also characterized by a decline in LDL, and an enhancement of HDL cholesterol levels (Naruszewicz et al., 2002; Pereira et al., 2003) and enhancement in bile acid production, which in turn degrades the excess cholesterol by bacterial activity. Another study showed that feeding of 5-15g of oligosaccharides for a period of two-three months lowered the blood lipid profiles and glucose levels along with an inhibition of lipogenic enzymes and also enhanced production of short-chain fatty acids. Many human studies have shown reduction in blood triglyceride levels in hypercholesterolemic men who consumed 20 g inulin/day, for a period of three months (Mahendra and Sheth, 2013).

In a study researchers have found that the daily intake of 50g of rice based ready to eat cereal containing 18 % inulin significantly reduced plasma total cholesterol and triacylglycerols by 7.9% (±5.4) and 21.2% (±7.8), respectively, compared to control group (Brighenti et al, 1999). An administration of 10 g/ 100g of resistant starch to male guinea pigs for 4 weeks showed significant reduction in plasma cholesterol by 27.4% and LDL cholesterol by 28% compared to control group (Fernandez et al, 2000). A randomized, double-blind, and crossover study has shown that daily intake of 20 g of inulin will significantly reduce serum triglycerides (Causey et al, 2000). A study in mice shows that intake of 10% long chain fructan for 16 weeks significantly reduced blood cholesterol by 29.7%, LDL-cholesterol concentration by 25.9%, IDL-cholesterol level by 39.4%, and VLDL-cholesterol concentration by 37.3% as compared to the control group (Mortensen et al, 2002). Another study in rats showed that daily consumption of 25 g / Kg of β-cyclodextrin significantly reduced plasma cholesterol and triacylglycerols by 25.9% and 35.0%, respectively (Favier et al, 1999).

e. **Cancer:** Large bowel cancer is a major inducer of mortality in the western world. According to Cummings et al, 1979 cooking of meat result in the production of cyclo-hexanes which is mutagenic in nature and the presence of prebiotics with essential bacteria, prevents such mutagenic induction. Another study shows that intake of inulin leads to in growth inhibition and induction of apoptosis in human colorectal carcinoma (Munjal et al, 2009).

f. **Effect on Mineral Metabolism:** Consumption of oligosaccharides has a direct impact on calcium absorption which promotes bone and teeth mineral density. According to Gibson and Roberfroid, 1995 an administration of chicory root extract increases gut absorption of calcium which enhances the bone mineral density and hence delays osteoporosis in aged individuals. Studies have shown that intake of prebiotic mainly fructans will result in the enhancement of absorption. A study in adolescent shows that ingesting 8 g/ day short and long chain inulin Fructans significantly increases calcium absorption and improves greater bone mineral density (Abrams et al. 2005).

Animal studies reveal that consumption of inulin enhances calcium and magnesium absorption in rats (Delzenne et al, 1995). It is further supported by the study in which ovariectomized rats were fed with inulin and FOS (Web, 2011). The increase in calcium absorption is due to increase in availability because of its transfer from the small intestine to the large bowel and the osmotic effect of inulin and oligofructose, which increases the solubility of calcium by advancing the bacterial phytase activity and which in-turn decreases the pH of ileum, resulting in increased concentration of ionized minerals leading to an enhanced passive absorption (Lopez et al, 2000).

2.3- Overview of Current Research in India

A number of research institutes from public sector and private sector are involved in research on probiotics and prebiotics including: Indian Council of Agricultural Research (ICAR) –National Dairy Research Institute (NDRI), Indian Council of Medical Research (ICMR), National Institute of Nutrition (NIN), Translational Health Sciences and Technology Institute (THSTI), Tata Chemicals Ltd. (TCL), Institute of Microbial Technology (IMTECH), Central Food Technology Research Institute (CFTRI) and National Centre for Cell Science (NCCS).

Research "Man as a Superorganism: The Human Microbiome (HUM)" from 2012-2017 was the first National Programs on Human Microbiome in the country conducted by IMTECH. This project contributed to a large number of scientific publications in the field related to immunology, microbiology, genomics, and evolutionary aspects of human microbiome of Indian origin. The details are mentioned in **Appendix 1**.

2.4- Mode of Action of Probiotics and Prebiotics

While antimicrobial activity was the primary focus for probiotic usage for some time, many of the mechanisms of action of probiotic usage today are associated with immune responses triggered from the intestine. The probiotic mechanism of action includes the following actions: enhancement of the epithelial barrier, increased adhesion to intestinal mucosa, and concomitant inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, production of anti-microorganism substances and modulation of the immune system.

SECTION- 3

Ensuring Safety Of Probiotics And Prebiotics

3.1- Regulatory Authority

In India **Food Safety and Standards Authority of India** (FSSAI) is the governing body which plays a very crucial role in regulating all Acts and Orders related to foods and beverages. FSSAI was established as an independent statutory Authority under Food Safety and Standards Act, 2006 which consolidated various food related Acts and Orders. It lays down science-based standards for articles of food and to regulates their manufacture, storage, distribution, sale and imports to ensure availability of safe and wholesome food for human consumption. Food Safety and Standards Authority of India (FSSAI) and the State Food Safety Authorities enforce various provisions of the Act. **Ministry of Health & Family Welfare**, Government of India is the **Administrative Ministry for FSSAI**. The head office of FSSAI is located in Delhi.

FSSAI has been Mandated by the FSS Act, 2006 for Performing the following functions:

- **Framing of Regulations to lay down the Standards and guidelines in relation to articles of food and specifying appropriate system of enforcing various standards thus notified.**
- Laying down mechanisms and guidelines for accreditation of certification bodies engaged in certification of food safety management system for food businesses.
- **Laying down procedure and guidelines for accreditation of laboratories and notification of the accredited laboratories.**
- To provide scientific advice and technical support to Central Government and State Governments on the matters of framing the policy and rules in areas which have a direct or indirect bearing of food safety and nutrition.
- **Collect and collate data regarding food consumption, incidence and prevalence of biological risk, contaminants in food, residues of various, contaminants in foods products, identification of emerging risks and introduction of rapid alert system.**
- Creating an information network across the country so that the public, consumers, Panchayats etc. receive rapid, reliable and objective information about food safety and issues of concern.
- **Conduct training programs for persons who are involved or intend to get involved in food businesses.**
- Contribute to the development of international technical standards for food, sanitary and phyto-sanitary standards.
- **Promote general awareness about food safety and food standards.**

3.2- Regulations for Probiotics / Prebiotics/ Synbiotics

Three major regulations introduced by FSSAI which are important for probiotics, prebiotics and synbiotics are:

A. Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2016

https://www.fssai.gov.in/upload/uploadfiles/files/Nutraceuticals_Regulations.pdf

These regulations are proposed to be amended through FSSAI Draft Notification dated October 29, 2020. These can be downloaded from : https://www.fssai.gov.in/upload/uploadfiles/files/Draft_Notification_Health_Supplements_06_11_2020.pdf

B. Food Safety and Standards (Advertisement and Claims) Regulations 2018

https://www.fssai.gov.in/upload/uploadfiles/files/Gazette_Notification_Advertising_Claims_27_11_2018.pdf

and

C. Food Safety and Standards (Labelling and Display) Regulations, 2020

https://www.fssai.gov.in/upload/notifications/2020/12/5fd87c6a0f6adGazette_Notification_Labelling_Display_14_12_2020.pdf

It may be noted that the Nutraceutical regulations do not define Synbiotics. However, as explained by FSSAI in second para of FAQ No. 9 of these regulations there is no restriction in combining ingredients . It will be the responsibility of the FBO to keep in mind the potential synergistic or antagonistic interaction amongst a combination of ingredients leading to impact on stability, bioavailability, safety and efficacy. The FBOs are , however, required to provide data on scientific rationale for formulating such combinations based on scientific literature in peer reviewed publications or data generated by FBOs/innovators or suppliers of such ingredients to the Authority as and when demanded.

This section briefly describes regulations related to added probiotics and prebiotics in foods.

3.2-A- Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2016

The FSSAI introduced the Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for special Medical Purpose, Functional Food and Novel Food) Regulations, 2016 in the Gazette of India on 23rd December 2016. These are called Nutraceutical Regulations henceforth in this document.

The regulations cover the following eight categories of foods:

- **Health Supplements**
- **Nutraceuticals**
- **Food for Special Dietary Use**
- **Food for Special Medical Purpose**
- **Speciality Food containing Plant or Botanicals**
- **Foods containing Probiotics**
- **Foods containing Prebiotics and**
- **Novel Foods**

A-1: General Provisions of the Regulation

Applicable to all 8 categories of food

- These regulations specify essential composition, claims and labelling etc. for 8 categories of foods mentioned above.
- The regulations do not allow the use of hormones or steroids or psychotropic ingredients in any of the articles of food.
- The regulations specify that formulation of articles of food shall be based on the principles of sound medicine or nutrition and supported by validated scientific data, wherever required.
- The regulations include various Schedules with detailed provisions relating to ingredients (vitamins, minerals, and amino acids, botanical ingredients, nutraceuticals ingredients), food additives, probiotics and prebiotics.
- One of the Schedule list (Schedule- IV as per FSSAI) has 400 ingredients of plant or botanical origin (proposed to be raised to 439 ingredients)[a] which can be used as ingredients in the foods covered under these regulations.
- The regulations specify that all labels on articles of food shall specify the purpose, the target consumer group and the physiological or disease conditions which they address, recommended duration of use, and the specific labelling requirements as mentioned against each type of article of food.
- It is also laid down that the label, accompanying leaflet or other labelling and advertisement of each type of article of food, referred to in these regulations shall provide sufficient information on the nature and purpose of the article of food and detailed instructions and precautions for its use, and the format of information given shall be appropriate for the intended consumer.
- Under these regulations the Food Authority may, at any time, direct a food business operator manufacturing and selling such special type of article of food, to furnish details regarding the history of use of the novel or modified ingredients

added and their safety evaluation.The regulations have clarified that labelling on the article of food shall be in accordance with the Food Safety and Standards (Packaging and Labelling) Regulations, 2011, and the specific labelling requirements provided in these regulations .

- The articles of food are required to conform to the Food Safety and Standards (Contaminants, Toxins and Residues) Regulations, 2011.
- No person is allowed to manufacture, pack, sell, offer for sale, market or otherwise distribute or import any food products referred to in these regulations unless they comply with the requirements laid down in these regulations.
- It has been specified that the tolerance limit for variation in case of articles of food covered in these regulations during analysis of samples of finished products, shall not be more from the declared value of the nutrients or nutritional ingredients on the label .
- The tablets, capsules and syrups are required to fulfil the general quality requirements and standards as specified in Indian Pharmacopoeia, British Pharmacopoeia or United States Pharmacopoeia.

The Draft Amendments of October 29, 2020 propose the following:

- Products covered under these regulations for children below the age of 5 years shall be given only under medical advice by physician/ certified dietician/nutritionist.
- For combining ingredients there shall be a rationale based on available scientific and technical evidence which shall be made available to the Food Authority as and when called for.
- Any products which are to be sold as Health Supplement/Nutraceutical/Specialty food containing plant or botanical ingredients with safe history of usage/food with added probiotic ingredients/ food with added prebiotic ingredients for the age above 6 months till 24 months is not permitted without prior approval of the Food Authority.

Note: As per Draft Regulation dated October 29, 2020 to further to amend the Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Foods and Novel Foods) Regulations, 2016

A-2: Ingredients, Additives , Probiotic Strains and Prebiotic Compounds Permitted under the Regulations

The eight important schedules under these regulations specify the ingredients, additives, probiotic strains and prebiotic compounds that can be used. These are:

- **Schedule – I:** List of vitamins and minerals and their components;
- **Schedule – II:** List of amino acids and other nutrients;
- **Schedule – III:** Values for vitamins, minerals and trace elements allowed to be used in food for special dietary use and food for special medical purpose (other than those intended for use in infant formula);
- **Schedule – IV:** List of plant or botanical ingredients,
- **Schedule – VA:** List of food additives for health supplements, nutraceuticals and food with added probiotics and prebiotics;
- **Schedule – VB:** List of food additives for foods for special dietary use and food with added probiotics and prebiotics;
- **Schedule – VC:** List of food additives for foods for special medical purpose (other than those products intended for foods for infants) and food with added probiotics and prebiotics;
- **Schedule – VD:** List of food additives for foods for special medical purpose (other than those intended for infant foods); formula for slimming purpose and weight reduction and food with added probiotics and prebiotics;
- **Schedule – VE:** List of food additives to used (at GMP levels) for- Nutraceuticals, Foods for special dietary use other than foods for infants, Foods for special medical purpose, Foods with added probiotic ingredients and prebiotic ingredients, Specialty foods containing plant or botanical ingredients, and Health supplements;
- **Schedule VF:** List of food additives to be used in formats such as Tablets, Capsules and Syrups- Nutraceuticals, Foods for special dietary uses other

than foods for infants, Foods for special medical purpose, Foods with added probiotic ingredients and prebiotic ingredients, Speciality foods containing plant or botanical ingredients, and Health supplements;

- **Schedule –VI:** List of ingredients as nutraceuticals;
- **Schedule –VII:** List of strains as probiotics (live micro-organisms) and
- **Schedule – VIII:** List of prebiotic compounds.

Out of these schedules the most relevant are: Schedule VII, Schedule VA to Schedule VF and Schedule VIII. In Part 2 of this document these schedules have been put together under different Appendices as follows:

- **Schedules VII** in Appendix II
- **Schedule VA to Schedule VF** in Appendix III
- **Schedule VIII** Appendix IV

FSSAI FAQ No. 6 further explains that in addition to the above these products may also be used as ingredients other than additives which are either standardized or permitted for use in the preparation of other standardized foods as specified in FSS (Food Product Standards and Food Additives) Regulations 2011.

A-3: Food with Added Probiotic Ingredients

Section 10 of Nutraceuticals Regulations lay down the provisions related to "Food with Added Probiotic Ingredients". It has been laid down that only those probiotic ingredients - probiotic culture of the microorganisms – can be used in food which are specified in Schedule VIII (Appendix II) or those probiotic microorganisms approved by the Food Authority from time to time. Probiotic preparations may contain added prebiotics permitted under these regulations.

Further, the viable number of organisms in food with added probiotic ingredients shall be $\geqslant 10^8$ CFU/g (Provided that a lower viable number may be specified with proven studies on health benefits with those numbers subject to the prior approval of the Food Authority). However, the Draft Amendments dated October 29 proposes removal of the lower viable counts while specifying that the "viable number of organisms in food with added probiotic ingredients shall be $\geqslant 10$ CFU in the recommended serving size per day".

It has been explained that the Food Authority may, from time to time, specify the probiotic microorganisms approved by it after proper scientific evaluation, provided that the presence of the commonly used starter cultures of lactic acid producing bacteria such as Lactococcus spp., earlier known as Streptococcus spp., Lactobacillus spp. and other such microorganisms used in the preparation of fermented milk (dahi) and related products shall not be considered as probiotics, if the probiotic properties have not been substantiated.[8]

Note: - The guidelines issued by the Indian Council of Medical Research and Department of Biotechnology with respect to probiotics provide additional information on their use.

Section 10.3 of the regulations prohibit use of additives in probiotic preparations except those specified in Appendix III.

A-4: Foods with Added Prebiotic Ingredients

Section 11 of Nutraceuticals Regulations lay down the provisions related to "Food with Added Prebiotic Ingredients". No food business operator is allowed to use prebiotics in manufacturing food containing prebiotics except those specified in Appendix IV or those prebiotics approved by the Food Authority from time to time.

It is explained that the ***prebiotic component***, not an organism, for which the claim is being made, shall be characterized for a given product by providing the source, origin, purity, chemical composition and structure, vehicle, concentration and amount in which it is to be delivered to the host.

The 29 October 2020 amendments propose that "Maximum limit for prebiotic per day shall not exceed 40g/2000 kcal for adults".

Section 11.3 of the regulations prohibit use of additives in probiotic preparations except those specified in **Appendix III.**

Section 10 and Section 11 of the Regulations have specific provisions for foods with added probiotics and foods with added prebiotics and allow use of food additives as per the given Schedules (Appendices in Part 2 of the document).

SECTION- 4

Consumer Communication - Role Of Labelling And Claims

Labelling is an important vehicle for "consumer communication". It enables the manufacturers / packers to explain the nature of the product, ingredients used, date of manufacture, shelf life, best before date, storage conditions as also benefits associated with consumption of the product – both for general or specific segments of the population – through "claims". FSSAI has laid down regulations for "labelling" as well as "claims" for food products.

This section is divided into two parts. Section-4. 1 explains the labelling regulations and Section-4. 2 explains the regulations on claims. There may be some duplication in these two sections. This has been done to clarify the provisions.

4.1- Labelling Provisions for Foods with Added Probiotics / Prebiotics

The labelling of food products were governed by the Food Safety Standards (Packaging and Labelling) Regulations 2011. Section 3 (22) of the Nutraceuticals Regulations specifies that the labelling of articles of food shall be according to these regulations and specific labelling requirement provided in the Nutraceutical Regulations. It may be noted that in FSSAI has divided the 2011 Packaging and Labelling Regulations into two parts:

A. The Food Safety Standards (Packaging) Regulations, 2018; and

B. The Food Safety and Standard (Labelling and Display) Regulations 2020

The Labelling Regulations issued in November 2020 surpasses the FSS (Packaging and Labelling) Regulation of 2011. Hence, labelling of foods with added probiotic and prebiotics are governed by two regulations:

A) The Food Safety and Standard (Labelling and Display) Regulations 2020 ; and

B) Specific provisions of Nutraceutical Regulations, 2016

Both the regulations have to be referred to for labeling purposes.

4.1-(A): The Food Safety and Standard (Labelling and Display) Regulations 2020

The Labelling Regulations specify the terminologies such as: best before date, date of manufacture, date of packing, lot number/code number/batch number, pre-packaged food, and principal display panel, use by/expiry date, RDAs, vegetarian/non-vegetarian food, infants, package/container etc. These regulations will come into effect after one year from the date of their publication in official Gazette except chapter 3 of these regulations which have to be complied by 1st January 2022 which relate to food service operators.

The Labelling and Display Regulations include following chapters :

Chapter 1-General –This includes title and definition

Chapter 2-It specifies labelling requirement of pre-packaged food. It exempts food products falling under FSS (Health Supplicate, Nutraceuticals Regulations) 2016 from mandatory nutrition labelling (Section 5 (3C-XIII). However nutritional information has to be given if nutrition or health claim is made on the lable.

Chapter 3- This specifies display of information in food service establishments.

Chapter 4- This specifies labelling requirement for non-retail containers.

Chapter 5-This is about labelling of food additives when sold as such.

For further information visit: https://www.fssai.gov.in/notifications.php?notification=gazette-notification

4.1-(B): Nutraceuticals Regulations - Provisions for Labelling of Probiotics & Prebiotics

Rules 10.2 and 11.2 have some common provisions for labeling of foods with added probiotics and prebiotics. These are :

- The labelling, presentation and advertisement shall not claim that the probiotic food has the property of preventing, treating or curing a human disease, or refer to such properties.
- The label on articles of food shall specify the purpose, the target consumer group and the physiological or disease conditions which they address, recommended duration of use, and the specific labelling requirements as mentioned against each type of article of food.
- The label, accompanying leaflet or other labelling and advertisement of each type of article of food, referred to in these regulations shall provide sufficient information on the nature and purpose of the article of food and detailed instructions and precautions for its use, and the format of information given shall be appropriate for the intended consumer.
- The statement by the food business operator relating to structure or function or the general well-being of the body may be allowed by the Food Authority, if the statement is supported by the generally accepted scientific data.
- **Labelling of Probiotic Food – Additional Provisions**

  Every package of probiotic food is required to carry the following information on the label, namely:

  - ❖ The words "PROBIOTIC FOOD";
  - ❖ Genus and species including strain designation or culture collection number, where applicable, in brackets where probiotics are mentioned in the list of ingredients;
  - ❖ Viable numbers at the end of the shelf-life of probiotic strain corresponding to the level at which the efficacy is claimed;
  - ❖ The recommended serving size which shall deliver the effective viable dose of probiotics related to health claims and recommended duration of use, proper storage temperature conditions, and time limit for 'Best Use' after opening the container;
  - ❖ An advisory warning 'NOT FOR MEDICINAL USE' prominently written; and
  - ❖ A warning or any other precaution to be taken while consuming, known side effects, if any, contraindications, and product-drug interactions, as applicable.
- **Labelling of Prebiotic Foods- Additional Provisions**

  Every package of food containing prebiotics are required to carry the following information on the label, namely:

  i) The words "PREBIOTIC FOOD";

  ii) Name of prebiotic;

  iii) The suggested or recommended serving size which shall deliver the effective dose of prebiotic related to the health claim;

  iv) An advisory warning 'NOT FOR MEDICINAL USE' prominently written; and

  v) A warning or any other precautions to be taken while consuming, known side effects, if any, contraindications, and product-drug interactions, as applicable

4.2- Claim Regulations in India

Claims for food products with added Probiotics / Prebiotics are governed by the following regulations:

1. Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2016 and
2. Food Safety and Standards (Claims and Advertising) Regulations , 2018

For making any Claim both the Regulations have to be referred to. These are explained in Section-4.2.1 and Section 4.2.2.

4.2.1- Provisions for Claims under Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2016

Rule 4 of these Regulations incorporate provisions for making "Claims". The Rule allows for making nutritional or health claims in respect of an article of food.

A. Nutrition Claims

A nutritional claim shall consist of the 'Ingredients (nutrient or nutritional) content' of an article of food which shall be subject to the nutritional supplement requirements specified in Schedule I, Schedule II, Schedule III, Schedule IV, and Schedule VI of the regulations. These schedules refer to : vitamins and minerals, amino acids, values of vitamins and minerals and trace elements, plants or botanical ingredients and nutraceuticals. These schedules are not included in this document.

B. Health Claims

Health claim means any representation in respect of an article of food that states, suggests or implies that a relationship exists between the 1) constituent of that nutrient or nutritional, health, and 2) specific disease conditions. The health claim in respect of an article of food consists of the following two essential components, namely:

(I) Nutrient or nutritional ingredients; and

(ii) Health related benefits.

The regulations further specify that health claim in respect of an article of food may include the following types, but not limited to:

(i) Ingredients (nutrient or nutritional) function claims;

(ii) Enhanced function claims;

(iii) Disease risk reduction claims;

(iv) Health maintenance claims;

(v) Immunity claims – increased resistance (excluding vaccines); and

(vi) Anti-ageing claims.

The regulations allow other claims in an article of food that are not drug claims subject to prior approval of the Food Authority.

It is important that "health claims" in respect of an article of food shall be commensurate with the adequate level of documentation and valid proof made available for review by the Food Authority when called for.

- ***Health Claims : Claim for Ingredients, Nutrient or Nutritional in Food Products***

To claim ingredients, nutrient or nutritional, in respect of an article of food for enhanced function and disease risk reduction, regard shall be had to:

(i) Claims that led to ingredients (nutrient or nutritional);

(ii) Available scientific literature including official traditional texts and post market data or consumer studies or cohort or retroactive studies based on eating pattern and health benefits, epidemiological international and national data, and other well documented data;

(iii) Consensual, congruent and concurrent validity studies;

(iv) Health promotive and disease risk reduction based on proof from literature and human data of efficacy and safety of the nutrient;

(v) Not only controlled clinical trials for efficacy and safety data; but also nutraepidemiological data;
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(vi) Qualified structure function claims for specific organ or function which are comprehensible to consumer;

(vii) Prohibition of implied claims for curing disease or claims of drug like efficacy such as 'Prevents bone fragility in post menopausal women';

(viii) Prohibition of implied cure for disease claims by the name of the product such as cancer cure or through a pictures, vignettes or symbols, namely, electrocardiogram tracing, lipid profile; and

(ix) For structure-function claims, a case-to-case basis consumer information for specific age or gender or vulnerable population.

- ***Health Claims: Product Led Claims***

Regulations lay down that for the product led claims in respect of an article of food based on human studies with evidence based data, regard shall be had to:

(a) Valid data and suitable statistical design proving the benefit for disease risk reduction, that is, human intervention studies;

(b) Ingredient, that is, nutrient or nutritional;

(c) The product compatibility for the proposed claim benefit and suitable qualifiers such as heart healthy claim on polyunsaturated fatty acids;

(d) The use of word "shown" as depicted in the example below when a single human intervention study shows significant benefit:

"Product *<Name of the Product> is 'shown' to be helping in <keeping your heart healthy> or <heart healthy>:*

(e) The use of word "Proven" as depicted in the example below when more than one human intervention studies or epidemiological evidence on Indian population have been provided with concurrent validity:

"Product <Name of the Product> is 'proven' <to make you lose weight>:

- **Prior Approval**

For health claims where scientific support does not exist, or if a novel ingredient is to be introduced, prior approval of the Authority has to be taken. Approval will be given based on provision of adequate scientific evidence.

- **Prior Notice**

If the health claims are product led, the food business operators are required to notify to the Food Authority before putting the same in the market, by submitting relevant documents along with a copy of the label.

- **General Principles for Query or Challenge**

As per the regulations food business operator shall:

(I) Prepare and make available the comprehensive product information, safety and claims support data and shall periodically get it reviewed and scrutinised by a scientist or expert with relevant qualifications and experience;

(ii) Attach the scientific view of the reviewer on claims and its veracity along with the qualification and experience of the reviewer as an essential part of the document;

(iii) Clarify, in case of a technical query from the Food Authority or on a public complaint lodged with the Food Authority, and assist the Food Authority to examine or authorise an appropriate expert group to review the case; and

(iv) Alter or modify or stop claim when directed by the Food Authority which shall be based on the opinion of an expert group.

- **Specific Provisions for Claims for Food with Added Probiotics**

Rule 10 particularly relate to Food with added Probiotic ingredient. They specify that :

1. The labelling, presentation and advertisement shall not claim that the probiotic food has the property of preventing, treating or curing a human disease, or refer to such properties.

2. The statement by the food business operator relating to structure or function or the general well-being of the body may be allowed by the Food Authority, if the statement is supported by the generally accepted scientific data..

3. An advisory warning 'NOT FOR MEDICINAL USE' prominently written; and

4. A warning or any other precaution to be taken while consuming, known side effects, if any, contraindications, and product-drug interactions, as applicable.

- **Specific Provisions for Claims for Food with Added Prebiotics**

Rule 11 relating to Food with added Prebiotic Ingredient specifies that :

1. The labelling, presentation and advertising shall not claim that the prebiotic has the property of preventing, treating or curing a human disease, or refer to such properties.

2. The statement by the food business operator relating to structure or function or the general well-being of the body may be allowed by the Food Authority, if the statement is supported by the generally accepted scientific data.

3. The labels have to include warning or any other precautions to be taken while consuming, known side effects, if any, contraindications, and product-drug interactions, as applicable.

The Nutraceutical Regulations further specify that:

- The Food Authority may suspend or restrict sale of such articles of food as have been placed in the market that are not clearly distinguishable from articles of food for normal consumption and are not suitable for their claimed nutritional purpose, or may endanger human health, in accordance with the provisions of the Act.
- The Food Authority may, at any time, direct a food business operator manufacturing and selling such special type of article of food, to furnish details regarding the history of use of the novel or modified ingredients added and their safety evaluation.

4.2.2- Food Safety and Standards (Claims and Advertising Regulations , 2018

- **Claims Definition**

The Nutraceuticals Regulations have provided for "Nutrition and Health Claims" to be made by FBOs (Rule 4) and Sub-Rules 1-9 explain the definitions of different types of Nutrition and Health Claims; basis of claims and data and document requirement for scientific validation of claims. Rule 5 specifies the general principles of queries and challenges. These have been explained in Section-4.2.1. "Claims" as such have not been defined under these regulations.

The Food Safety and Standards Authority of India brought out a specific regulation named Food Safety and Standards (Advertising and Claims) Regulations, 2018 (C&A regulation). Under this Claims have been defined as: "Any representation which is printed, oral, audio or visual and states, suggests, or implies that a food has particular qualities relating to its origin, nutritional properties, nature, processing and composition".

Claims relating to probiotics, prebiotics or synbiotics have to conform to the Claims and Advertising Regulations in addition to the Nutraceutical Regulations as mentioned in Section 3 of C&A Regulations.

❖ **General Principles of Claims**

In General, all Claims related to any Food, Food Products, probiotic or prebiotic have to follow the General Principles of Claims defined under Section 4 of C&A Regulation. The Principles are as follows:

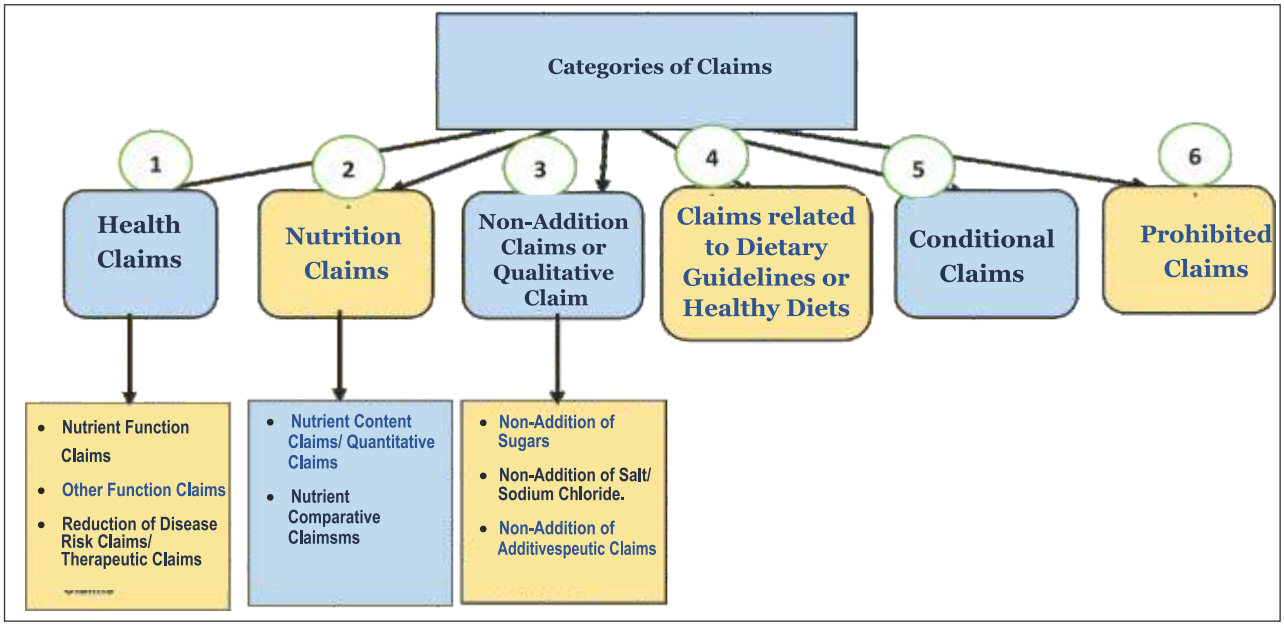
- It must be truthful, unambiguous, meaningful, not misleading and help consumers to comprehend the information provided.
- Not encourage or condone excess consumption of a particular food.
- It shall not state, suggest or imply that a balanced and varied diet cannot provide appropriate quantities of nutrients as required by the body.
- The claim benefit is related to or dependent on the method of preparation of the food, the same shall be provided on the label.
- It should specify the number of servings of the food per day for the claimed benefit.
- Claim regarding the food which has certain nutritional or health attributes shall be scientifically substantiated by validated methods of characterising or quantifying the ingredient or substance that is the basis for the claim.
- To avoid misleading consumer a disclaimer in not less than 3mm size shall be given at appropriate place on the label stating that - "This is only a brand name or trade mark and does not represent its true nature". This is applicable in the case where the meaning of a trade mark, brand name or fancy name containing adjectives such as "natural", "fresh", "pure", "original", "traditional", "authentic", "genuine", "real", etc., appear in the labelling, presentation or advertising of a food that could leads to false interpretation by consumer about the nature of the food.

- All disclaimers related to a claim shall be conspicuous and legible.
- No Claim or promotion of sale, supply, use and consumption of articles of foods shall be made using Food Safety and Standards Authority of India logo and license number.
- Claims in advertisements shall be consistent with information on the label of the food or beverage.

Categories of Claims

There are 6 different types of Claims as per FSSAI which are schematically presented in Fig 5.

Figure 5: Schematic Representation of Categories of Claims



Source: FSSAI, Claims and Advertisements Regulation, 2018

Overview of Categories of Claims

Table 1: Categorizing of Claims with Definition

Types of Claims	Definition	Categories, if Any
Health Claims	Any representation that states, suggests or implies that a relationship exists between a food or a constituent of that food and health.	**Nutrient Function Claims** It describes the physiological role of the nutrient in growth, development and normal functions of the body. For Example: Nutrient 'A' - naming a physiological role of nutrient 'A' in the body in maintenance of health and promotion of normal growth and development. (Food X is a rich source of or high in nutrient "A") **Other Function Claims** It describes the specific beneficial effects of the consumption of foods or their constituents, in the context of the total diet or normal functions or biological activities of the body, which relate to a positive contribution to health or to the improvement of a function or to modifying or preserving health. For Example: Substance A naming the effect of substance A on improving or modifying physiological function or biological activity, associated with health (Food Y contains X grams of substance 'A'). **Reduction of Disease Risk Claims** As per FSSAI, it refers to claims that state, suggest or imply that consumption of such foods or food constituents, in the context of total diet, reduce the risk of developing a disease or health related condition. According to CODEX (Guidelines for Use of Nutrition and Health Claims) the risk reduction means significantly altering a major risk factors for a disease or health-related condition. The presentation or description of risk reduction claims must ensure, for example, by use of appropriate language and reference to other risk factors, so that consumers do not interpret them as prevention claims. Example: (a) A healthful diet low in nutrient or substance 'A' may reduce the risk of disease D. Food X is low in nutrient or substance 'A'. (b) A healthful diet rich in nutrient or substance 'A' may reduce the risk of disease D. Food X is rich in nutrient or substance 'A'.
Nutrition Claims	It refers to any representation which states, suggests or implies that a food has particular nutritional properties including but not limited to the energy value and to the content of protein, fat and carbohydrates, as well as the content of vitamins, minerals and other permitted listed nutrients.	**There are two types of Nutrition Claims:** **Nutrient Content Claims/ Quantitative Claims** This type of nutrition claim directly or indirectly describes the level of a nutrient contained in a food. Examples: contains or source of; high in; rich in; low in, etc **Nutrient Comparative Claims** It compares the nutrient levels or energy value of two or more foods. Examples: reduced; less than; fewer; increased; more than, etc.

Non-Addition Claims	It refers to any claim that an ingredient or additive has not been added to a food, either directly or indirectly and the ingredient or additive is one whose presence or addition is permitted in the food and which consumers would normally expect to find in the food.	There are three types of Non- Addition Claims • Non- addition of Sugars • Non-Addition of Salt (Sodium Cholride) • Non-Addition of Additives
Claims related to Dietary Guidelines or Healthy Diets	Not Defined.	
Conditional Claims	Not Defined.	-
Prohibited Claims	Not Defined.	-

Source: FSSAI, Claims and Advertisements Regulation, 2018

4.3- How to Introduce Products with Claims in India

The **Food Safety and Standard Authority of India (FSSAI)** plays a very crucial role in operationalizing, implementing and monitoring of various aspects of food safety through various regulations which are developed in accordance to the need of the consumer safety.

As per the FSSAI C&A regulation many claims listed in this regulation with criteria permit or allow their use by food business operators without required prior approval from the food regulator. However, other types of claims which are not standardised under the C&A regulation may require approval from the Food Authority if be supported with sound scientific basis. Claims which require prior approval and which do not require approval based on the defined criteria in the regulation (Claims and Advertisements) are mentioned below (Table 2):

Table 2: Categorizing Claims which do not require Approval and which require Approval based on defined Criteria in the Regulation- FSSAI

Name of the Claim	Criteria for Making Claims that Do Not Require Approval
Health Claims *Section 7*	**1. Health claims are structured on the following criteria:** a. Health claims are always to be stated as part of a balanced diet. b. To obtain the claimed benefit two conditions are to be complied with (i) A specified amount of the nutrient/ingredient per serving of the food for example 1 g 'X' nutrient) (ii) A statement that in order to obtain the claimed benefits, the daily intake of the nutrient/ingredient (for example 3g of 'X' nutrient) should be taken either from the same food or any other food that provides the beneficial nutrient/ingredient.

Name of the Claim	Criteria for Making Claims that Do Not Require Approval
	c. The health claims regarding vitamins and minerals – a statement regarding the RDA for the specific vitamin and mineral shall be given. Where no RDA is established by ICMR, the RDA provided in Codex/WHO guidelines shall be applicable. d. The claim statements provided in **Appendix VII** may be used on labels and/or advertisements. Provided further that Food Business Operators may choose to use same or similar terms in the claim statements as provide in the **Appendix VII** under the regulation of Advertisement and Claim while ensuring that the intent and meaning of the claim is not changed. **2. The following conditions and declarations shall comply with health claims**: a. The health claim must consist of two parts: I. Information on the physiological role of the nutrient or substance or an accepted diet- health relationship. ii. Information on the composition of the product relevant to the physiological role of the nutrient or substance or the accepted diet-health relationship unless the relationship is based on a whole food or foods whereby the research does not link to specific constituents of the food. b. If the claimed benefit is attributed to a constituent in the food, for which a recommended dietary allowance value is established the food in question shall be- i. In case increased consumption is recommended- A source of or high in constituent in accordance with conditions mentioned in **Appendix V**. ii. In case reduced consumption is recommended- Low in, reduced in or free of the constituent in accordance with conditions specified in **Appendix V**. c. A statement of the quantity of a nutrient or a substance that is the subject of the claim, per 100g or 100ml or per pack (single consumption pack) of the food. d. Where applicable, target group shall be mentioned or where a certain contraindication exists, advice to vulnerable groups on consumption or avoidance of the food shall be made available. e. Directions for use of the food to obtain the claimed benefit in the context of the diet and other lifestyle factors where appropriate. f. Maximum safe intake of the food or the constituent, if necessary **3. Nutrient Function Claims and Other Function Claims:** i. They are made based on current relevant scientific substantiation and to provide sufficient evidence on the type of claimed effect and the relationship to health as recognised by generally accepted scientific review of the data. ii. The scientific. substantiation shall be reviewed by food business operator and when the new knowledge becomes available the claims updated accordingly. **4. No reduction of disease risk claims shall be made that is not in accordance with the conditions specified** in **Appendix VII.** **5. Food articles that are fortified** as per Food Safety and Standards (Fortification of Foods) Regulations, 2018 may make health claims as provided in **Appendix VIII** and flexibility in the wordings of the claim statement is acceptable, if the meaning of the claim is not altered. **6. Where a claimed health benefit is attributed directly to the product,** it shall be based on statistically significant results from well-designed human intervention studies, conducted by or under guidance of established research institutions, in line with the principles of GCP (Good Clinical Practices) and peer reviewed or published in a peer reviewed reputed scientific journal.
Nutrition Claims ***Section 5***	**1. Nutrition claims** may be.- (a) nutrient content claim; or (b) nutrient comparative claim 1. ***The following do not constitute nutrition claims:*** a. The mention of substances in the list of ingredients b. The mention of nutrients as a mandatory part of nutrition labelling c. Quantitative or qualitative declaration of certain nutrients or ingredients on the label if required by Food Safety and Standards Act, 2006 (34 of 2006) and the rules and regulations made thereunder. 2. Nutrient content or nutrient comparative claim or any synonymous claim shall be made in accordance with the conditions specified in **Appendix V**. The flexibility in the wording of a nutrition claim is as per **Appendix VI**, or the use of any other word should be such that it does not alter the meaning of the claim.

Name of the Claim	Criteria for Making Claims that Do Not Require Approval
	3. Where a **nutrient comparative claim** is made, the foods shall be different versions of the same food or similar foods being compared and shall be easily identifiable and the relative difference of the claimed parameter between the compared foods is: a. At least twenty-five per cent. in the energy value or nutrient content and a minimum absolute difference equivalent to the figure defined as "low" or as a "source" in **Appendix V**, for claims about energy or macronutrients and sodium respectively. b. At least ten per cent. of recommended dietary allowances, for claims about micronutrients other than sodium. 4. In addition, where a **comparative claim** is made, the identity of the foods being compared and the amount of difference expressed as a percentage, fraction or an absolute amount shall be given in close proximity to the claim. 5. The **equivalence claims in form of phrases** such as "contains the same amount of [nutrient] as a [food]" and "as much [nutrient] as a [food]" may be used on the label or in the labeling of foods, provided that the amount of the nutrient in the reference food is enough to qualify that food as a "source" of that nutrient, and the labeled food, on per 100g or 100ml, is an equivalent, source of that nutrient. Example "as much fiber as an apple," and "contains the same amount of vitamin C as___glass of orange juice etc
Non-Addition Claims *Section 6*	**1. Non-Addition of Sugars** a. Claims regarding the non-addition of sugars to a food may be made if the following conditions are met: iii. No sugars of any type have been added to the food (Examples: sucrose, glucose, honey, molasses, corn syrup, etc.). iv. The food contains no ingredients that contain sugars as an ingredient (Examples: jams, jellies, sweetened chocolate, sweetened fruit pieces, etc.). v. The food contains no ingredients containing sugars that substitute for added sugars (Examples: non-reconstituted concentrated fruit juice, dried fruit paste, etc.) and vi. The sugars content of the food itself has not been increased above the amount contributed by the ingredients by some other means (Example: the use of enzymes to hydrolyse starches to release sugars). b. **Claims regarding the non-addition of sugars to a food may also be made, where sugars are naturally present in the food**, and in such case the following indication shall also appear on the label **"CONTAINS NATURALLY OCCURRING SUGARS".** **2. Non-Addition of Salt (Sodium chloride):** Claims regarding the non-addition of salt (sodium chloride) to a food, including "no added salt", may be made if the following conditions are met: a. The food contains no added salt (sodium chloride). b. The food contains no ingredients that contain added salt (sodium chloride) including but not limited to sauces, pickles, pepperoni, soya sauce, salted fish, fish sauce. **3. Non-Addition of Additives:** Claims regarding the non-addition of additives including functional classes of additives as specified in Food Safety and Standards (Food Product Standards and Food Additives) Regulations, 2011 to a food may be made, **if the additive for which claim is made:** a. Has not been added to the food b. Is not contained in any ingredient of the food c. Is one which is allowed to be added in particular products as specified in Food Safety and Standards (Food Product Standards and Food Additives) Regulations, 2011. d. Has not been substituted by another additive giving the food equivalent characteristics. **4. Additional Conditions for Non-Addition Claims:** The additional conditions or disclaimer statements may be used with non-addition claims to assist consumer understanding of the claims provided that the disclaimer statements shall be conspicuous and legible.
Claims related to Dietary Guidelines or Healthy Diets *Section 8*	***Section 8* of Claims and Advertisements Regulation provides the following:** 1 Claims may be made related to a "healthy diet" or any synonymous term referring to the pattern of eating as per current Indian Council of Medical Research Dietary Guidelines for Indians and the label shall carry a statement relating the food to the pattern of eating described thereof. 2 Foods, which are described as part of a healthy diet, balanced diet shall not be based on selective consideration of one or more aspects of the food and shall also satisfy the criteria for other major nutrients related to the current Indian Council of Medical Research Nutrient Requirements and Recommended Dietary Allowances for Indians and Indian Council of Medical Research Dietary Guidelines for Indians, based on scientific evidence.

Name of the Claim	Criteria for Making Claims that Do Not Require Approval
	3 Foods shall not be described as "healthy" or be represented in a manner that implies that a food in and of itself will impart health. 4 Flexibility in the wordings is acceptable, if the claims remain faithful to the pattern of eating outlined in the current Indian Council of Medical Research Nutrient Requirements and Recommended Dietary Allowances for Indians and Indian Council of Medical Research Dietary Guidelines for Indians.
Conditional Claims *Section 9*	1. A claim may be made where a food is by its nature high or low or free of a specific nutrient provided the name of the nutrient or substance is preceded by the words 'natural or naturally' in the claim statement. Example: "a naturally low food" or "a naturally free food". 2. Claims containing adjectives such as "natural", "fresh", "pure", "original", "traditional", "Authentic", "Genuine", "Real", etc. , when used, shall be in accordance with conditions laid down in **Appendix IX** and the claims containing words or phrases like "home-made", "home cooked", etc., which may give an erroneous impression to the consumer shall not be used.
Prohibited Claims *Section 10*	1. No claims shall be made which refer to the suitability of the food for use in the prevention, alleviation, treatment or cure of a disease, disorder or particular physiological condition unless specifically permitted under any other regulations made under Food Safety and Standards Act, 2006 (34 of 2006). 2. There shall not appear in the label of any package, containing food for sale the words "recommended by the medical or nutrition or health professionals" or any words which imply or suggest that the food is recommended, prescribed, or approved by medical practitioners or approved for medical purpose. 3. No product shall claim the term "added nutrients", if such nutrients have been added merely to compensate the nutrients lost or removed during processing of the food. 4. Foods for special dietary uses or foods for special medical purposes shall not carry a claim unless specifically permitted under any other regulations made under Food Safety and Standards Act, 2006 (34 of 2006). 5. Claims which do give rise to doubt or suspicion about the safety of similar food or which may arouse fear shall not be made. 6. No health claims shall be made for foods that contain nutrients or constituents in quantity that increase the risk of disease or an adverse health-related condition. 7. No advertisements or claims for articles of foods shall be made by any food business operator that undermines the products of any other manufacturer for the purpose of promoting their products or influencing consumer behavior.
	Criteria for making Claims which Require Approval
Health Claims *Section 7*	1. In case if food business operators wish to make **Disease risk reduction (DRR) claims or Therapeutic Claims which is not specified in Appendix VII** then he/she will require **prior approval** from FSSAI. **DRR is only for reduction of risk factor for disease.** Note: The approval procedures are mentioned separately in this section.

Source: FSSAI, Claims and Advertisements Regulation, 2018

4.3.1- Procedure for Approval of Claims in India

The procedure for getting approval for Claims are clearly laid down under regulations. Any food business operator who wishes to apply for "claims approval" will have to submit an application along with applicable fees as prescribed by Food Safety and Standards Authority of India. The applicant has to provide the following information:

- Claim to be made.
- Name of ingredient.
- Nutrient or substance on the basis of which the claim is to be made.
- Validated Method of analysis of ingredient or substance for which the claim is to be made.
- Scientific information or materials substantiating the claim.
- Well-designed human intervention studies in case of health claims conducted by or under guidance of established research institutions.
- Any other useful information.
- The claim should be clear and meaningful and help consumers to comprehend the information provided.

Application Form along with general information is given in Appendix XI.

It may be noted that adequate published scientific literature/ studies should form part of Claim Support Dossiers (CSD) to be submitted by the applicants. Further:

a. Such dossiers should provide a succinate summary of published scientific data comprising *in-vitro, in-vivo* and human studies data.

b. Hard copies of important publications be also appended to the summary data in the CSD with a commitment to provide copies of any other publications listed in the summary statement, If demanded by the Authority.

c. Such succinct summary shall be provided separately in respect of each claim statement for which application has been made.

d. Unpublished or under communication studies, if any, either undertaken by the applicant or reported by other organisations may also be provided where available in full form.

The regulations mention that information provided in the CSD shall not be guarantee for approval of claims.

The application is to be made manually and submitted along with the fees. The important documents that need to be submitted along with the Application Form are:

a. Copy of Central/ State License.

b. If the Ingredient/Product fall under Non- Specified Category then a copy of Approval Letter from FSSAI.

c. Scientific Substantiation Supporting Documents/ Materials.

4.3.2- Claims relevant for Probiotics and Prebiotics in India

The following table categorizes Claims where prior approval is required and Claims where prior approval is not required based on FSSAI, C&A Regulation, 2018.

Table 3: Categorizing Claims for both Probiotics and Prebiotics- Where Approval is required and Approval is not required

	Probiotics	Prebiotics
Prior Approval Not Required	• Nutrition Claims: Nutrient Content Claims/ Qualitative Claim • Health Claims: Other Function Claims	• Nutrition Claims: Nutrient Content Claims/ Qualitative Claims • Health Claims: Nutrient Function Claim and Other Function Claims
Prior Approval is Required	• Health Claims: Disease Risk Reduction Claims or Therapeutic Claims Note: In case when FBO want to make Disease risk reduction (DRR) claim which is not specified in Appendix VII.	• Health Claims: Disease Risk Reduction Claims or Therapeutic Claims Note: In case when FBO want to make Disease risk reduction (DRR) claim which is not specified in Appendix VII

Source: FSSAI, Claims and Advertisements Regulation, 2018

4.3.3- How to Substantiate Claims for Probiotics and Prebiotics in India

The Claims and Advertisements Regulation lay down the procedures for substantiating claims. The Claim Support Dossiers (CSD) has to be submitted along with application form (the details are on Page no. 28). Further, a summary of published scientific data comprising *in-vitro*, *in-vivo* and human studies have to be submitted under CSD which are notified by FSSAI on https://www.fssai.gov.in/upload/advisories/2020/05/5eb29516d7dc2Notice_Fees_Claims_Fomat_06_05_2020.pdf and are explained below:

1. Summary of *In-Vitro* Data

Material tested (1)	Microbes/Cell lines/ Organ culture/ other test system (2)	Concentrations tested negative and positive controls used (3)	Variables. Biomarkers, performance indicators evaluated measured (4)	Result obtained (5)	Reference of publication (6)

1. Describe the material tested, purity, in case of botanicals or biological material provide information on their standardization / marker compounds tested/ activity tested.
2. Provide information on bacteria, yeast or any other microbes against which testing was done including their NTCC/ Acc. Number/ details of cell line/ details of organ culture or tissue culture or any other system.
3. Provide information on Concentrations tested, negative and positive controls used in the experiments.
4. Provide information on what aspects were measured as outcome of the test. For example, IC 50, cytotoxicity, dye uptake or reduction in dye uptake, preventing rate of growth.
5. Give a brief summary of the results obtained, comparison with controls and any dose response relations reported.
6. Provide complete reference of the publications. If the data is not published in a peer review journal, but forms a study report give details of report covering where the study was undertaken, name of the institute or laboratory and its accreditation status and provide authenticated copy of the same. Provide full length paper copy of the most important study only and give a commitment to provide a copy of other publications listed in the table when requested.

2. Summary of Human Study Data

Nature of study (1)	Material tested and their levels (2)	Nature of volunteers/ subjects/ populations/ patients (3)	Design of study and n=? (4)	Inclusion exclusion criteria (5)	Duration of study (6)	Variables measured (7)	Results obtained (8)	Reference of publication (9)

1. Describe briefly the nature of study namely: open label, intervention study, randomization, blinding or population study or diet and outcome surveys or epidemiological data collection and analyses.
2. Provide information on Concentrations tested, negative and positive controls used in the experiments.
3. Give brief information on nature of subjects/ volunteers/ patients involved in the study. For example, normal healthy volunteers, pre-diabetics, mild to moderate hypertensive patients, volunteers with specified BMI etc.
4. Give brief summary of the design of the study like matched panels, groups involved, cross over design, superiority study, addition study. State the number of volunteers or subjects or population or patients in each group giving details of number screened, number enrolled, number whose data is available, number drop outs. Also state the statistical analyses of the data reported and test of significance. Also

provide approval status of the study by DRB/ EC, adoption of informed consent.

5. List the inclusion and exclusion criteria.
6. State duration of the study – study period, duration of intervention, wash out period if any and period of observation post stoppage of intervention.
7. Provide information on what aspects and variables were measured as outcome of the study. For example, pharmacological activity measures, biochemical markers, physiological parameters measured using instrumental technics like EEG, TMT, echo, bone density, image analyzers etc. Provide information on ADRs and safety aspects evaluated including quality of life measurements and reported in the study. Specifically, state if the study does not report the safety or ADRs or no mention is made of this aspect. If any of the study provided in the summary table covers a Cochrane review or a meta-analyses review provide summary of the same.
8. Give brief summary of the results obtained, comparison with controls, and any dose response relations reported. Provide information on ADRs and safety aspects evaluated including quality of life measurements and reported in the study. Specifically, state if the study does not report the safety or ADRs or no mention is made of this aspect.
9. Provide complete reference of the publications. If the data is not published in a peer review journals, but forms a study report give details of report covering where the study was undertaken, name of the institute or laboratory and its accreditation status and provide authenticated copy of the same. Provide full length paper copy of the most important study only and give a commitment to provide a copy of other publications listed in the table when requested.

The food regulations in India as created and implemented by a young regulatory authority – FSSAI- is dynamic and has been keeping pace with international developments and technological advancements, Gut microbiome is an emerging field and it has been shown that it plays an important role in promoting health. Functional foods including Probiotics /Prebiotics / Synbiotics are also outputs of scientific research and have shown to improve the gut microbiome. The Indian regulations on Labelling and Claims while on the one hand provide guidance to industry on the other hand provide safeguards and key information to consumers to enable him/her make a choice about most suitable products for him/her.

DISCUSSION

Need For Evidence Generation For Probiotics & Prebiotics In India

In India many studies have been conducted by various institutes which show that probiotics influence the human health by modulating metabolic activities, immunity and microbial homeostasis (see Appendix I). **Although a lot of researches has been done in last decade on the impact of different diet and functional foods including prebiotics and probiotics on Gut Microbiome, The Science is still evolving.** Work is going on **"New Generation of Probiotics for their Health Effects".** The data that has been provided so far are good in certain areas however, there is a need for further research as well as meta-analysis of already done researches to substantiate the claims. It will be necessary also to harmonize the methodologies used for research not only in India but across the world. There is need for evidence generation in the area for further strengthening the process for or substantiating the claims:

1. **Identification and validation of relevant biomarkers** that can detect early signs of homeostatic disturbance and/ or predict potential benefits relating to maintenance or improvement of a function and those associated with reduced risk of disease.

2. **The strength and limitations of different source of evidence** (e.g. randomized controlled trials/ human intervention studies, epidemiological prospective cohort studies, *in vitro* and animal studies, history of use).

3. **Methodologies** for assessment of the totality of the available data and **development of the scientific framework** for weighing the strength, consistency and biological plausibility of the evidence.

4. **Consumer understanding of research to link the totality of available data** and **weight of the evidence** to claims that they are truthful and meaningful to the consumers.

5. **Use of probiotics for public health problems is still an emerging area. Hence more studies need to be conducted to explore the benefits of probiotics for different health problems** such as:
   - Neonatal sepsis.
   - Immune modulation and long-term effects.
   - Clinical conditions like metabolic syndrome.
   - Geriatric health needs.

6. India has a diverse food culture and population with diverse microbiome which changes from one region to another. **The area of regional food and their prebiotic potentia**l is still untouched and **need to be explored**.

SECTION- 5

Overview Of Global Regulatory Framework For Probiotics/ Prebiotics And Codex Guidelines

Background

In the past decades there has been increase in the supporting evidence related to the health benefits of gut microflora which lead to an upsurge in research, demands and introduction of new probiotic products across the globe. In 2018 probiotics ranked as the fastest growing sector among food (s) and /or supplement(s) products with a total global product market valued at about 47.1 Billion USD and is projected to grow at a CAGR of 6.8% from 2019 to 2026. Indian probiotic market has very bright future, with expected CAGR of 19.80% during 2014-19 (TechSci Research "India Probiotic Market Forecast and Opportunities, 2019). (https://www.techsciresearch.com).

A rapid growth has been seen in the consumer demands for probiotics product which has been underpinned by a mounting scientific data from researchers and the increase in health awareness, as well as the positive health outcomes from the consumer side. Research is yielding new developments, advances and discoveries in the field of probiotics. Thus, it becomes important to adopt regulations which are science based, safeguard consumer interest and enables industry to offer the best products and choices to consumers.

Worldwide probiotics are regulated broadly under 4 categories:

- **Food**
- **Supplements**
- **Drugs, and**
- **Medical Foods**

These regulatory differences are based on definitions and/or categories, allowable label claims and approved list of strains of probiotics. In addition, the definitions and/or categories for probiotics are usually country specific. This leads to the major challenge for probiotic industry which has to navigate through heterogeneous regulatory landscape.

According to WHO probiotics is classified as dietary supplements whereas the European Food Safety Authority (EFSA) evaluates probiotic products, under 'Food & Food Supplements and does not allow the use of the term "Probiotic" in its guidelines. As per EFSA, probiotics are microbes which are claimed to promote health and well-being. Specific terms, such as 'live' or 'active' can be used to describe bacteria which also imply a "probiotic function" and are considered to be health claims. Under the EFSA regulations (and since no health claims have been approved for 'probiotic'), any term that imply a probiotic function is therefore, not permitted. Currently, efforts are underway to get "probiotic" term approved as a "generic descriptor" without making health specific claims. However, both Italy (a member of European Union) and Switzerland have guidelines in place to allow probiotics claims.

5.1- Case Studies: Country Specific Regulations on Probiotics

There is a need for effective regulatory framework to ensure safety, stability and efficacy of the probiotic organisms during the production and storage of the product. It has been explained earlier that at present probiotics are regulated under 4 main categories globally i.e. Food, Dietary Supplements, Drugs and Medicinal Foods. Table 4 shows probiotic sub-categories in different countries. It is evident that each country uses different sub-categories for probiotics. Although in some countries the probiotic product is considered as food with specific nutritional, functional or therapeutic characteristics or dietary supplement, others classify them as medicine. This situation poses challenges for the regulators along with industry and

Table 4: Probiotic Sub- Categories in Different Countries

S. No.	Country	Category
1.	Denmark/ Sweden/ Finland	Food Supplements
2.	Canada	Natural Health Products
3.	Italy	Dietary Food
4.	European Countries/ Belgium/ Germany	Biotherapeutic Agent
5.	Japan/ India/ China/ Malaysia	Functional Foods
6.	USA	Dietary Supplements/ Drugs/ Live Biotherapeutic Agents/ Medical Food

Source: Venugopalan, Shriner and Wong-Beringer (2010)

international trade. It creates an ambiguity and adversely affects international trade as single product will be regulated differently in different countries (Arora, Sharma & Baldi 2013). Another possible reason for lack of regulation is lack of both standard enumeration technique and a reliable selective medium (Temmerman et al. 2003). Therefore, there is an urgent need for globally accepted uniform regulatory guidelines for probiotic food.

Canada

- Probiotics can be used in food and natural health products
- Health Canada has monograph on Probiotics.
- Probiotic products make function claims, which involve support of bodily functions associated with good health or performance.
- Whereas function claims cannot claim to cure disease or reduce risk of disease such as heart disease and cancer.
- Claims must be strain-specific if the product contains at least 10^9 CFU of eligible microorganisms from the Bifidobacterium or Lactobacillus genus.
- Probiotics can also be sold in pharmaceutical dosage forms (e.g. tablets, capsules) as Natural Health Products (NHPs).
- The manufacture, packaging, labelling and importation for sale of NHPs is regulated under the Natural Health Products Regulations.

Japan

- In Japan, probiotics can be used in Foods, which can make claims under Foods for Specific Health Uses (FOSHU) certification when scientific evidence proves:
- Effectiveness on the human body.
- The absence of safety issues.
- The use of nutritionally appropriate ingredients
- Compatibility with product specifications by the time of consumption.
- Established quality control methods, such as specifications of products and ingredients, processes, and methods of analysis.
- Japan is a key player in probiotic based functional foods accounting for more than half of global probiotic foods market. Only nation which has legally defined functional/health foods and introduced the FOSHU system to regulate Food for Specific Health Use.

Australia & New Zealand

Food Standards Australia & New Zealand regulate probiotics not only as complementary medicine ingredient but also as food. There are additional regulations for advertisement that prohibit:

- Endorsement from government agencies, healthcare facilities, or healthcare professionals, or incentives for non-healthcare professionals to recommend or supply therapeutic goods.

- Testimonials that are inauthentic, not genuine, misleading, or a typical.
- Messaging that leads to self-diagnoses or causes fear or distress through consumer ignorance or belief that there are harmful consequences if the product is not used.
- Encouragement of excessive use.
- Promises or guarantees, claims that the product is magical, a miracle, or infallible.
- Claims that the product is completely safe or has no side-effects.
- Targeting of minors.
- Offerings of samples.

USA

- In USA, probiotics are regulated by Dietary Supplement Health and Education Act (DSHEA) and Food and Drug administration (FDA).
- Probiotics are sub-categorized into Dietary Supplements/Drugs/ Live Biotherapeutic agents and Medical food (FDA, 2009).
- FDA has described only the manufacturing guidelines; however, these seem to be insufficient for the safe use of probiotics and hence must be harmonized with respect to each and every aspect (Arora, Sharma & Baldi 2013).

Asia Pacific Region

- Most APAC countries generally classify probiotics as health functional foods or dietary supplements (Japan, Korea, Taiwan, Singapore, Malaysia, Philippines); except for Australia and New Zealand, which classify probiotics under "complementary medicine". In these countries, any claim on probiotics requires scientific substantiation from human intervention or observational studies.
- Strains from either the Lactobacillus or Bifidobacterium genus are generally approved for safety and intestinal health claims in countries such as Japan, Korea, Malaysia and Philippines.
- The regulations clearly specify that claims must be strain specific and not be overly generalized to cause misinterpretation by consumers.

Indian Council of Medical Research (ICMR)

- ICMR has prepared guidelines for regulation of probiotic products in the India. These guidelines define a set of parameters required for a product/strain to be termed as 'probiotic'. These include identification of the strain, *in vitro* screening for probiotic characteristics, animal studies to establish safety and *in vivo* animal and human studies to establish efficacy.
- The guidelines also include requirements for labeling of the probiotic products with strain specification, viable numbers at the end of shelf life, storage conditions, etc., which would be helpful to the consumers to safeguard their own interest (ICMR-DBT, 2011).

World Gastroenterology Organization (WGO)

- WGO has prepared global guidelines for probiotics and prebiotics.
- These guidelines focus on the genus, species, and strain for each probiotic in a product, along with the number of viable cells of each probiotics strain that will remain viable till the end of shelf-life (Guarner et al. 2012).

International Life Science Institute India

- ILSI India has prepared guidelines for evaluation of safety of probiotics for human's consumption and has given essential requirements of infant food formula.
- Under efficacy evaluation, demonstration of dose or cfu ingested per day, period of use and scientific substantiation of health claims have been included in these guidelines (ILSI India, 2009).

5.2- Regulations on Dosage

Generally, there is no consensuses regarding the recommended levels of probiotic organism in foods. The suggested levels of organism are based on the results of the *in-vitro* and *in-vivo* studies and the requirement that organism must be present throughout the manufacturing and storage conditions.

Different countries have different regulations on dosage of probiotics. Also, different studies recommend

different specified dosage of probiotic bacteria to be present in food under different conditions. For example :

- According to FAO/ WHO (2002), A probiotic food is a processed product containing viable probiotic microorganisms in amounts of about 10^6-10^7 cfu/ g.
- The recommended minimum probiotic count should be at least 10^6 cfu/ ml in claimed probiotic foods by US FDA.
- In Japan, the Fermented Milk and Lactic Beverages Association has specified that there should be at least 10^7 cfu /ml of viable bifidobacteria cells in fermented milk drinks, to be considered as probiotic in nature.
- Different studies recommend or suggest the following: According to Shah (2000) a minimum LAB count of not less than 10^6 cfu/g is recommended in fermented dairy product. According to Vasiljevic & Shah 2008 they have suggested the levels of organism ranging from 10^6 cfu/ml to over 10^7 and 10^8 cfu/ ml. Karimi, Mortazavian & Cruz (2011) has stated that probiotic products should be consumed regularly with an approximate amount of 100 g/ day in order to deliver about 10^9 viable cells into the intestine. Another study suggests that a minimum count of viable probiotic bacteria i.e., at least 10^8 cfu/ ml to achieve desired effects in probiotic yoghurt (Lourens-Hattingh & Viljoen 2001). However different standards for different organism were also established keeping minimum levels of 10^7 cfc/ml for Lactobacillus acidophilus and 106 of Bifidobacteria in fermented milk products at the time of sale (Talwalkar & Kallasapathy 2003).

The need to formulate the guidelines for evaluation of probiotics in food was emphasized by FAO/ WHO almost two decades back in 2001 and it lead to work on substantiation of health claims. In 2002, a working group was set up by FAO/ WHO to prepare guidelines, recommend criteria and methodology for the evaluation of probiotics. The group worked on standardizing the ways to identify and define data required to accurately substantiate health claims. Thus, guidelines were prepared to meet this objective.

5.3- Regulations on Health Claims

This report recommended that the probiotic effect of a particular food is strain specific. Whereas a combination of *in-vitro* and *in-vivo* tests provide the efficacy of a probiotic in a food. In vitro tests are useful to gain knowledge of strains and the mechanism of the probiotic effect. However, the current available tests are not fully adequate to predict functionality of probiotic microorganisms in the human body. Further, in case of in-vitro studies the data available for particular strains is not adequate for counting them as probiotic.

Probiotics for human use will require combinations of human trials along with in vitro studies. Appropriate target-specific in vitro tests that correlate with *in vivo* results have been recommended. The following tests are required for the studying probiotic strains:

- Resistance to gastric acidity
- Bile acid resistance
- Antimicrobial activity against potentially pathogenic bacteria
- Ability to reduce pathogen adhesion to surfaces
- Bile salt hydrolase activity

The Working Group also recommended labelling requirement of a probiotic food/supplement. The label of any probiotic food should have the following information:

- Genus, species and strain designation. Strain designation should not mislead consumers about the functionality of the strain.
- Minimum viable numbers of each probiotic stain at the end of the shelf-life.
- The suggested serving size which must deliver the effective dose of probiotics related to the health claim.
- Health claim(s).
- Proper storage conditions.
- Corporate contact details for consumer

5.4- Overview of Guidelines / Practices on Process of Assessment of Scientific Support for Claims

CODEX

Process for the Substantiation of Health Claims are based on the CODEX recommendations on the scientific basis of health claims (2009). These includes following steps:

1. Identify the standard of evidence for substantiation and other national policies for health claims.
2. Identify the proposed relationship between the food or food constituent and the health endpoint for a health claim.
3. Identify appropriate measurements for the food or food constituent and the health endpoint.
4. Identify and categorize all the relevant studies.
5. Assess and interpret each relevant study.
6. Evaluate the totality of the evidence across studies and determine if and under what circumstances a claimed relationship is substantiated.

The details about the scientific substantiation required by international agencies are given in Table 5.

Table 5: International Agencies Requirements for Scientific Substantiation

Codex scientific substantiation of claims require:	WHO recommend that trials carried out in human:
• **Human intervention studies**, and support with human observational studies, animal studies and *in vitro* studies. • Identification of **all evidence** that supports, contradicts, or is inconclusive towards claim • Evidence of **consistent association** between the food and health effect, with **little or no contrary evidence**	• Be **randomized**, **double blind**, **placebo-controlled** (DBPC). • Include phases for standard clinical trials- first **safety** then **efficacy** • Be repeated through more than one centre.

Source: Ms. Isha Singh

FDA

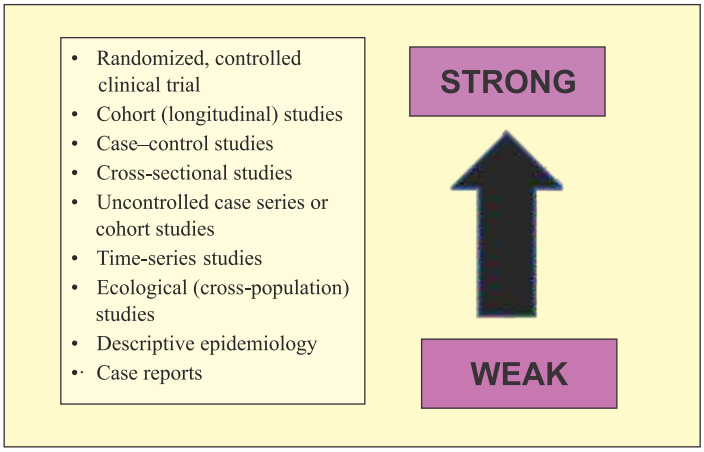
A system of evaluating qualified health claims as guidance for the food industry has been developed by the FDA (FDA/CFSAN (2003a); Rowlands and Hoadley, 2006; Schneeman B, 2007 and Turner, Degnan and Archer, 2005) which has described the rating system for evaluating the level of evidence supporting claims; the type of studies supporting claims; and the strength of the total body of scientific evidence (Table 6).

Table 6: Level of Evidence, Types of Studies and Strength of the Total Body of Scientific Evidence for Supporting Claims- FDA

The Level of Evidence Supporting Claims (FDA/CFSAN, 2003a) will be evaluated based on the following rating:	The Types of Studies Supporting Claims (FDA/CFSAN, 2003a) will be evaluated based on the following rating:	The Strength of the Total Body of Scientific Evidence (FDA/CFSAN, 2003b) will be evaluated based on the following rating:
• A: Significant scientific agreement exists—no qualifications are necessary.	• Type 1: Randomized Controlled Intervention Trial.	• Quantity: the number of studies and number of individuals tested, weighted by study type and quality.
• B: The evidence is not conclusive.	• Type 2: Prospective Observational Cohort Study.	• Consistency: similarity of results from high quality studies of design types 1 and 2.
• C: The evidence is limited and not conclusive.	• Type 3: Non-Randomized Intervention Trial with Concurrent or Historical Control.	• Relevance: magnitude of effect (observed in high quality studies of design types 1 and 2), and consideration of whether the effect is physiologically meaningful and achievable.
• D: There is little scientific evidence supporting the claim.	• Type 4: Cross-Sectional Study, Case Study.	-

Ranking of the Type of Research Supporting Efficacy by FDA, 2005 (in descending order of persuasiveness) is represented in Fig 6. For details see Appendix X.

Figure 6: Ranking of Scientific Studies (Weak to Strong)



Source: FDA/CFSAN (2005)

5.5- Need for Global Harmonization of Regulations on Probiotics

Harmonisation of the regulations is the key to strike a balance between the scientists, industry, regulators and the consumers. From evidence perspective, scientists want to generate high quality science, whilst industry wants to make high quality and profitable products with scientifically validated and consumer-friendly claims. Regulators do play vital roles in protecting consumers from misinformation. Consumers also want to obtain reliable information to make informed choices to achieve the desired health benefits from the products they consume. However, it can be seen that science has moved too quickly and regulations are unable to cope up with amount of information generated by the evolving science. Hence, it is of utmost importance that scientists, industry and regulators join hands to educate and guide one another to create best practices and harmonized regulations in order to meet the common goal through robust scientific evidence and compliance to help in the communication of complex scientific information to the consumers in the most practical way.

Glossary

- **Alpha Diversity:** According to Metagenomics alpha diversity means variation of microbes in a single sample.
- **Beta Diversity:** According to Metagenomics Beta diversity means variation of microbial communities between samples.
- **Wash out Period:** According to the U.S. National Library of Medicine, a washout period is defined as "a period of time during a clinical study when a participant is taken off a study drug or other medication in order to eliminate the effects of the treatment".
- **Food Business Operators (FBOs):** As per Food safety act 2006 it is defined as any undertaking, whether private or public, for profit or not, carrying out any of the activities related to any stage of manufacture, processing, packaging, storage, transportation, distribution of food, imports and including food services, sale of food, or food ingredients.
- **Balanced Diet:** A diet containing all essential (macro and micro) nutrients in optimum quantities and in appropriate proportions that meet the requirements is called Balanced Diet.
- **Food with Added Probiotic Ingredients:** means food with live micro-organisms beneficial to human health, which when ingested in adequate numbers as a single strain or as a combination of cultures, confer one or more specified or demonstrated health benefits in human beings.
- **Food with Added Prebiotic Ingredients:** means food that contains added prebiotic ingredients which are nonviable food components that confer health benefits to the consumer by modulation of gut microbiota.
- **RDA:** Recommended Dietary Allowances (RDA) means the average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97 to 98 per cent.) healthy individuals in a particular life stage and gender group.

About ILSI India

ILSI-India is an entity of the International Life Sciences Institute (ILSI), headquartered in Washington DC., USA. ILSI India provides scientific inputs and secretariat assistance to the South Asian Region, which includes Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka. It has headquarters in New Delhi.

ILSI India designs programs to foster multi-sector collaboration for conducting, summarizing, and disseminating science related to most pressing health issues in the region. ILSI strategy encourages global action on identifying and then resolving outstanding scientific questions in the four thematic areas that capture the core of ILSI / ILSI India's work: Food Safety, Risk Science and Toxicology, Nutrition and Health , Sustainable Agriculture and Nutrition Security. They also help elucidate new opportunities for driving scientific progress.

ILSI-India carries out its mission through sponsoring workshops, symposia, conferences, seminars, training programs, research projects, and publications. ILSI India works on tripartite basis with scientists from Government, Industry and Academia. It receives funds from public sector as well as private sector. ILSI India's work is guided by its Code of Ethics, Scientific Integrity and Organizational Standards of Conduct.

Gut Microbiome is an exciting new field of research. Most of the bacteria in the gut are found in the large intestine (colon) and, over the past 30 years or more, interest in the gut microbial population – the microbiota – and its environment has intensified. Environmental factors like Diet, Antibiotic usage and Lifestyle behaviors influence the diversity and composition of microbiota (healthy microbiota profile). Many national and international organizations from public sector and private sector have devoted attention to microbiome and health and strategies required for healthy microbiome. ILSI India also devoted considerable attention since 2009 to this area and carried out number of scientific activities to understand and explore this new emerging area in the arena of great relevance to public health.

About K-FFIG

The ILSI India center of excellence entitled "Knowledge Center on Functional Foods, Gut Health and Immunity" (K-FFIG) was launched in October 2019. It has a separate Governing Council. It is a Think Tank, involving stakeholders from Government, Academia as well as Industry and work towards sharing relevant research and technological developments in the emerging area of human microbiome and functional foods. *This unique Center* is focusing on dissemination of information generated by research organizations worldwide and acts as a bridge between research and practical applications.

A number of activities have been undertaken by K-FFIG. These include preparation of Status Paper on Role of Probiotics in Promoting Healthy Microbiome for Health and Immunity, Survey on Probiotics & Consumer Perception, **Resource Centre** on latest research on Microbiome and Gut Health, Functional Foods including Probiotics and Prebiotics. Recent Studies on Probiotics and Prebiotics, Immunity and Probiotics, Probiotics and Health Benefits , Recent Studies on Gut Microbiome and Health Effects and Recent Studies on Antimicrobial Resistance.

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Abbreviations

ADBRC	-	A Deep Binary Reconstruction
ADRs	-	Adverse Drug Reactions
AMR	-	Antimicrobial Resistance
ASDs	-	Autism Spectrum Disorders
AX	-	Arabinoxylan-rich Fibre
BMI	-	Body Mass Index
BV	-	Bacterial Vaginitis
CFTRI	-	Central Food Technology Research Institute
CSD	-	Claim Support Dossiers
CD	-	Crohn's Disease
CODEX	-	Codex Alimentarius Commission
CRC	-	Colorectal Cancer
DF	-	Dietary Fibre
DSHEA	-	Dietary Supplement Health & Education Act
DRR	-	Disease Risk Reduction
FAO	-	Food and Agriculture Organization
FBOs	-	Food Business Operators
FDA	-	Food and Drug Administration
FOSHU	-	Food for Special health Uses
FSSAI	-	Food Safety and Standard Authority of India
FOS	-	Fructooligosaccharide
GRAS	-	Generally Recognized As Safe
HDL	-	High Density Lipoprotein
HUM	-	Human Microbiome
ICAR	-	Indian Council of Agricultural Research
ICMR	-	Indian Council of Medical Research
IBD	-	Inflammatory Bowel Disease
IBS	-	Irritable Bowel Syndrome
IMTECH	-	Institute of Microbial Technology
IPR	-	Intellectual Property Rights
LAB	-	Lactic Acid Bacteria
LDL	-	Low Density Lipoprotein
MAM	-	Moderate Acute Malnourished
MLST	-	Multi Locus Sequence Typing
NDR	-	National Dairy Research Institute
NIN	-	National Institute of Nutrition
NE	-	Necrotizing Enterocolitis
NSP	-	Non-Starch Polysaccharides
OFS	-	Oligofructose Supplementation
RS	-	Refined Sugar
SAM	-	Severe Acute Malnourished
SCFAs	-	Short-Chain Fatty Acids
TCL	-	Tata Chemical Limited
THSTI	-	Translational Health Sciences and Technology Institute
T2D	-	Type 2 Diabetes
VLDL	-	Very Low-Density Lipoprotein
WGO	-	World Gastroenterology Organization
WHO	-	World Health Organization

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