Journal of Advanced Zoology

ISSN: 0253-7214
Volume ***45*** *Issue* ***2*** ***Year 2024*** *Page* ***175:187***

"Regulatory Challenges For The Development Of Probiotics As Foods And Drugs And Cmc (Chemistry Manufacturing And Control) Considerations For Probiotics"

Madhavi Simhadri[1]*, Koushik Yetukuri[2]

*[1]*Department of Regulatory Affairs, Student of Masters of Pharmacy in Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh, simhadrimadhu35@gmail.com*
[2]Department of Regulatory Affairs, Faculty of Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh

***Corresponding Author:** Madhavi Simhadri*
Email: simhadrimadhu35@gmail.com

Article History

Received: 10 Dec 2023
Revised: 25 Dec 2023
Accepted: 20 Jan 2024

Abstract

The purpose of this study is to elucidate the importance of probiotics, regulatory challenges that are faced in developing probiotics as foods and drugs and as well as the Chemistry, Manufacturing and control (CMC)considerations for probiotics. Probiotics are friendly live microorganisms (in most cases, bacteria) that are similar to the beneficial microorganisms found in the human gut and, when consumed, have the potential to improve or maintain the intestinal microbial flora of consumers, thereby benefiting their health. The utilization of probiotics has been in existence for a very long time. Lactobacilli, bifidobacterial, and lactococciare are the examples of probiotics have long been assumed to be safe whereas the most important determinant for probiotics selection is human health safety. Probiotics can be consumed by consumers largely in the form of food and dietary supplements. They are also even available in the form of tablets, capsules and powders and in some other forms as well, yet, their claims of health advantages could put the conventional distinction between food and medicine in jeopardy. The position of the regulatory environment for probiotics within the existing categories has become hazy and quite unclear as a result of the introduction of numerous probiotic products into the global market.

Key words: Probiotics, regulatory challenges, CMC, safety, efficacy.

INTRODUCTION:

Probiotics

Probiotic is a Greek word where "pro" stands for "in favor" and "biotic" stands for "life" [1]. Probioticsare beneficial bacteria that exist in the body and fight out harmful microorganisms to keep the body's bacterial ecosystem in balance [2]. Probiotics are living bacteria that have beneficial qualities for the host, primarily

through the regulation of the gut microbiota. Probiotics can be used therapeutically totreat and prevent disease in both people and animals.

Types of bacteria in probiotics

There are many different types of probiotics including Lactobacillus, Bifidobacterium, and Streptococcus. Each type of bacteria has its own unique benefits and characteristics (Markets and markets https://www.marketsandmarkets.com/Market-Reports/probiotic-market-advanced-technologies-and-global-market-69.html). A number ofbacteria may be present in probiotics. Bacteria from the families Lactobacillus and Bifidobacterium are the most prevalent. As probiotics, other bacteria as well as yeasts such as Saccharomyces boulardi may be employed. Probiotics come in a variety of forms, each with potential impacts (National Centre for Complementary and Integrative Health. Probiotics: What You Need to Know https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know).

Origin and Historical perspectives

From the Greek word "pro-bios," which means "for life," the phrase "probiotic" derives its etymology.Since fermented items were first employed for therapeutic and nutritional purposes in antiquity, they have played a significant role in society. The history of probiotics dates back a century to when scientistHenry Tessler (1899), of the Pasteur Institute of Paris, detected Bifidobacterium in the bowels of breastfed children and found it helpful for their diarrhoea episodes. Parker (1974), who proposed a new definition of probiotics as "microorganisms and compounds responsible for gut microbial balance," provided the following supporting data. After that, a lot of scientists expanded the definition of probiotics to include the host's health advantages. Probiotics are described as "live bacteria that, whenprovided in sufficient proportions, bestow health on the host" by the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO, 2002). Since then, probiotics research has advanced at an exponential rate and been greatly enhanced to comprehendthe function of a wide variety of probiotics in promoting or preventing chronic diseases (Mishra S etal., 2021)

Safety of probiotics

The majority of probiotics are sold as supplements or pharmaceuticals. Determining probiotics' safety is crucial for this reason. A significant amount of experience has proven the safety of the microorganisms that have been historically employed in probiotics. For a very long time, people have consumed foods containing live bacteria, dead bacteria, and metabolites of these microbes. Throughout human history, bacteria including Lactobacillus, Leucon Stoc, and Lactococcus species were also extensively employed in food preparation. Until recently, there hasn't been muchcontroversy over the safety of these bacteria, and there haven't been many reports of them havinga negative impact on the host (Norio Ishibashi etal.,2001).

Laws governing probiotics and their safety

Probiotics as a food ingredient need to be given a legal position on a global scale. To better handle probiotic-related problems such as efficacy, safety, labelling, fraud, and claims, a regulatory framework has to be built. It should be acceptable for probiotic products to mention the specific healthbenefits they have been proven to provide to the host. To document and examine negative reactions toprobiotics in food and track long-term health advantages, surveillance procedures (trace-back, post marketing) should be put in place. It is important to make probiotic products more widely accessible,especially to people at high risk of morbidity and death and those working in humanitarian relief. Foods for specific dietary use, medicinal foods, and dietary supplements are only a few examples of the non-conventional foods that do not fit into the other three food categories that were established bythe US Food and Drug Administration (FDA).

Legally speaking, probiotic-containing foods might fall under several of the four food categories listed by the FDA; nevertheless, probiotic, prebiotic, or culture-added dairy products are not expressly recognizedin the United States as having any health advantages.

How safe are probiotics?

Probiotic foods and supplements are typically regarded as safe because the bacteria used as probioticsalready occur naturally in your body. For the first few days after starting to take them, they may producemoderate stomach distress, diarrhea, or flatulence (passing gas), as well as allergic responses. Some individuals should exercise caution when utilizing probiotic supplements. Certain people run the riskof contracting an infection. These individuals include those with a compromised immune system (thosegoing through chemotherapy, for example).

- A serious illness.
- Have major surgery (Cleveland Clinic. Probiotics. https://my.clevelandclinic.org/health/articles/14598-probiotics).

How effective are probiotics?

Probiotic supplements may be used to treat a variety of illnesses, but researchers are uncertain of their effectiveness. Ongoing research is done in this area. Even though the effects of probiotic supplementshave been the subject of numerous studies, further study is still required. It's also critical to keep in mind that, in contrast to prescription drugs, nutritional supplements are not subject to FDA approval.This implies that producers can simply make "claims" of safety and efficacy when marketing supplements (Cleveland Clinic. Probiotics. https://my.clevelandclinic.org/health/articles/14598-probiotics).

Uses

- Probiotics are typically used to treat gastrointestinal (GI) issues such diarrhea caused by infections, inflammation, or antibiotic overuse.
- They increase the number of beneficial microbes in the gut, reducing the number of pathogenic bacteria that cause diarrhea.
- Probiotics have also been demonstrated to be effective in the prevention and treatment of vaginal yeast infections, urinary tract infections, and allergic diseases like eczema and asthma.
- Their effectiveness in treating and preventing respiratory infections in children, as well as tooth and gum disease prevention and therapy, is being investigated. These products cannot be recommended for the treatment of any disease or condition until more study is conducted.
- Many doctors consider that probiotics can help with a range of ailments, but others disagree. A consultation with a healthcare expert is recommended before taking probiotic supplements to treat or prevent any condition.
- Probiotic supplements are usually thought to be safe for the majority of people and cause little adverse effects. However, little is known about the long-term effects of these supplements, and they may be less safe for persons with weak immune systems (U.S. Pharmacist -The Pharmacist's Resource for Clinical Excellence. (2014). Probiotics. https://www.uspharmacist.com/article/probiotics).

EXAMPLES OF PROBIOTICS

1.Yogurt

2. Kombucha

3. Buttermilk

4. Aged cheese


5. Fermented Veggies


6. Kimchi

Benefits of Probiotics for Gut Health

Bacteria, fungi, viruses, and other microbes of various sorts can be found throughout the digestive system. Although they also defend against germs that cause disease, probiotics can aid in promoting the growth of beneficial bacteria. The gut microbiota, or gut microbiome, refers to the collection of bacteria in the gut and is crucial to maintaining the body's health.

1. **Improve Gut Health by Balancing the Digestive System's Bacteria**

Normal gut function depends on the gut microbiome being in balance; however, some changes to thegut microbes can cause issues. Probiotics can assist in restoring the gut's healthy bacterial balance andhelping the body recover from circumstances that disrupted the microbiome by replenishing it with healthy bacteria. For instance, taking antibiotics causes much of your beneficial gut flora to die. This allows for the overgrowth of harmful bacteria, viruses, and fungus. For long-term health, taking a probiotic before and after antibiotic treatment is essential.

2. **Minimize the Signs and Symptoms of a Few Digestive Diseases**

Changes to the typical bacteria present in the stomach may contribute to the development of digestive issuessuch as irritable bowel syndrome (IBS). According to one study, probiotics may reduce the severity of IBS symptoms such as gas, bloating, diarrhea, and constipation.

3. **Minimize the frequency of diarrhoea**

Developmental disorder Ten specifically chosen bacterial strains are included in Omni-Biotic AB10,which restores the gut microbiota and lessens diarrhea brought on by antibiotics.

4. **Mood enhancement and stress reduction**

The neurotransmitters our body uses as messengers are made by the microorganisms in your stomach. Neurotransmitters assist with sleep, emotions, and the regulation of your heart and bladder. Stress is known to disrupt gut flora, which may impact neurotransmitter production and function.

Probiotic supplements have been demonstrated to enhance mood, sleep, and cognitive performance and can assist in repopulating the gut bacteria during and after stressful times.

5. **Aid for Certain Mental Health Issues**

Depression and anxiety are associated with changes in microbiota composition. This may be the casesince the bacteria in the gut create 95% of the neurotransmitter serotonin, or the "feel-good “hormone.According to one study, healthy subjects who supplemented with the probiotic strains Lactobacillus Helvetius and Bifidobacterium longum for 30 days experienced decreased anxiety and depressive symptoms.

6. **Enhance the immune system to improve the healing process after illness**

While you're sick, your gut flora is frequently out of balance, especially if you have a stomach bug, have had food poisoning, or have had to take antibiotics. Probiotics replenish the beneficial bacteria in your gut and support a healthy immune system.

7. **Prevents the flu and cold**

According to research, specific Lactobacillus and Bifidobacterium strains may lessen the severity andduration of typical cold symptoms.

8. **Defend against antibiotic resistance**

The body may require antibiotics to aid in the fight against infections, but they can disturb the ecosystem in the stomach. The number of beneficial bacteria in the gut is frequently reduced by antibiotics, which might weaken those bacteria's defenses against other disease-causing germs.

Antibiotic-resistant bacteria can occasionally develop, which poses a serious threat to therapy. Infections caused by the methicillin-resistant Staphylococcus aureus (MRSA), which is resistant to a number of standard antibiotics, have been demonstrated to be prevented by some strains of the Lactobacillus bacterium.

Advantages for Women

It's generally safe and advantageous to use probiotic supplements when pregnant. In order to support both mother and new-born health, probiotics are frequently employed. Pregnancy- relateddigestive problems like constipation may be alleviated by probiotics, and they may also lower the likelihood that children will grow up with allergies.

Benefits for Men

Probiotics come in a wide variety of strains, and men may respond better to some beneficial microorganisms than women. Infertile men who take a probiotic and prebiotic supplement are shown to have higher testosterone levels and better sperm quality. Men can also benefit from probiotics by reducing chronic digestive conditions like IBS and gastrointestinal symptoms like diarrhoea (Omni biotic. 21 Health Benefits of Probiotics for Your Gut, Mind, & More.

MATERIALS AND METHODS

The study was organized into 3 steps to achieve the objectives

1. Type of study
2. Sources of data
3. Study process

1. TYPE OF STUDY:

This is study, where effort has been made to study, Regulatory challenges for the development of probiotics as foods and drugs and Chemistry Manufacturing and Control (CMC) considerations.

2. SOURCES OF DATA:

In this comparative study, primary and secondary sources of data have been referred to which include the following:

- ❖ Journal Articles published in peer-reviewed publications
- ❖ Websites of various regulatory agencies and organizations

Developing probiotics integrated functional foods is challenging due to their complex and expensive development procedures.
Probiotic strains are also prone to changes in pH and temperature. Thus, preservation of theseprobiotic microorganisms is challenging.
Probiotic research on humans also seems to receive less funding from industry in the USthan research on other chemicals
Defining a clear path for human research on probiotics for foods, supplements, andmedical foods that do not involve the IND framework.
Streamlining the IND process to enhance investigator-initiated research.
Without enhancing study subject safety, this strategy has slowed down progress and raisedcosts.
The Food and Drug Administration (FDA) mandates that safety studies be carried outbefore efficacy trials as part of the IND procedure.
This is in addition to the challenges of complying with IND requirements if theinvestigated substance is not produced at a pharmaceutical-grade facility.
Rejection of dossiers: The primary reasons for rejecting the various dossiers were that the microorganisms responsible for the effect had not been identified, the claims were poorly definedor not thought to be a health benefit, there were no human clinical trials, or the results were inconclusive.
Its approval is likely to have an important effect on the probiotics industry by limiting claimsthat are not supported by science and allowing those that are. For market participants, this presents significant opportunities as well as obstacles.

RESULTS AND DISCUSSION

Regulatory Challenges for probiotics

The main difficulties were

1) Defining a clear path for human research on probiotics for foods, supplements, and medical foods that does not involve the IND framework;
2) providing a way for human studies that do not automatically enable safety studies if adequatedocumentation of safe use exists for the conditions of use; and

(3) streamlining the IND process to enhance investigator-initiated research. It comprised clinicalexperts, researchers, federal government officials, funding agencies, lawyers and industry experts. published between January and September 2015, according to a PubMed search, were carriedout in the country.

Probiotic research on humans also seems to receive less funding from industry in the US than research on other chemicals. On September 24, 2015, a search of www.clinicaltrials.gov revealedthat 23% of probiotic research was performed in the United States, compared to 59%, 49%, and 46% of industry-funded studies on omega-3 fatty acids, vitamin D, and antioxidants, respectively.Although we are unable to establish what causes these correlations, one possible interpretation is that regulatory restrictions prevent probiotic research on humans in the United States.

This is mostly because probiotics are treated by regulators as pharmaceuticals despite the fact that research endpoints with them can be categorically classified as legal for foods, and asa result,they demand that the study be carried out in accordance with an IND framework. This criterion covers research on probiotic foods, nutritional supplements, and medical foods that aren't meant to be sold as prescription medicines. Without enhancing study subject safety, this strategy has slowed down progress and raised costs. Research is also threatened if research techniques and results are changed in an attempt to get around onerous regulatory constraints.

The Food and Drug Administration (FDA) mandates that safety studies be carried out before efficacy trials as part of the IND procedure. Even when a probiotic is extensively marketed and the subject of a notification that it is generally recognized as safe or has otherwise undergone testing or usage with a great certainty of no damage, safety reviews have been ordered. Despite the fact that this issue has plagued probiotic research for a decade, the FDA's Centre for Biologic Evaluation and Research (CBER), Centre for Drug Evaluation and Research (CDER), and Centre for Food Safety and Applied Nutrition (CFSAN) provided their final instructions forclinical investigators, sponsors, and Institutional Review Boards (IRB). This advice covered allsubjects being studied by human research, going beyond probiotics. "Investigative New Drug Applications (INDs)—Assessing If Human Research Investigations May Be Performed without an IND" was the title of the guidance. This recommendation made it clear that the FDA wantedINDs for the majority of foods and dietary supplements. In accordance with an administrative stay that the FDA issued on October 30, 2015, the agency will prevent some nutrition aspects of itsguideline from being adopted while it continues to investigate the problems.

Because of the health impact of these FDA regulations, many IRBs now demand INDs from researchers who are proposing probiotic research. To bypass the burdensome and irrelevant requirement for an IND, several corporate sponsors that intend to promote foods or dietary supplements (rather than pharmaceuticals) have chosen to conduct their probiotic clinical studies elsewhere or not at all. Companies worry that if research on a new probiotic begins as an investigational new drug, their product may one day be prohibited from being marketed as a foodor dietary supplement.

This is in addition to the challenges of complying with IND requirements if the investigated substance is not produced at a pharmaceutical-grade facility. Given that the FDA Amendment Act of 2007 prevents the distribution of products containing a physiochemical product for which "significant clinical investigations" have been initiated, this is a valid worry for research foods or supplements that are still not being sold. Foods and all of their subcategories are not regarded as being legally acceptable subjects for human study because this requires therapeutic methods that cannot be effective for them. According to the legislation, certain meals can affect how the human body looks or works, lower the chance of getting sick, or help with the medical nutrition therapy of a certain problem (Mary Ellen Sanders etal., 2016).

The whole market for probiotic components in products intended for human consumption, which was projected to be worth $12.9 million (€10.2 million) in 2003, is currently expanding at an estimated pace of 14%. However, according to research consultants Frost & Sullivan, probiotics end-users are particularly worried about impending legislative restrictions because they believe that the proposed health claims regulation, which is currently in written format before the EuropeanParliament and Council, could negatively affect innovation, promotion, and competition. This rulemight be made into legislation as early as 2005. Its approval is likely to have an important effect on the probiotics industry by limiting claims that are not supported by science and allowing thosethat are. For market participants, this presents significant opportunities as well as obstacles.

"The majority of probiotics manufacturers have a wealth of studies demonstrating the potential health advantages of their products. As a result, they are probably at a strategic advantage in a market where all claims with insufficient supporting evidence would be eliminated, "said Frost &Sullivan's Anna Ibbotson, manager of food research. Participants will also be required to get greater scientific evidence of a product's efficacy under the new rules. For the eventual benefit of customers, this is crucial. According to the suppliers, the producers of food and supplements orthe suppliers themselves should be held accountable for this problem.

"It is generally acknowledged that one of the biggest issues facing the probiotics sector is increasing consumer awareness. Despite the fact that this is typically thought to be the job of the producer of the completed product, supplier businesses must be prepared and equipped to support the marketing efforts of their clients by providing comprehensive product and legal information, "Ibbotson disagrees. Suppliers believed that major marketing investments made by businesses like Danone and Yakult had a significant impact on raising customer awareness. Increased consumer choice and media attention on probiotics and digestive health also contributed to higher levels of awareness.

Even so, there are new application fields with market expansion potential. Due to the bacteria's poor stability, probiotics have thus far mostly been used in dairy products. Also, there are new application fields that could help the industry expand. Due to the bacteria's poor stability, probiotics have primarily been used in dairy products up to this point.
Yoghurt and fermented milk beverages are the main probiotic food products for human consumption. While being less developed than its American counterpart, the European dietary supplement market is nevertheless expected to grow, according to the Frost analysis. Moreover, initiatives are being taken to create additional finished goods that include probiotics. Infant formula, fruit drinks, cereal, and extensions of current product lines like fruit yoghurts are just a few of the interesting applications that manufacturers have explored. Applications for probiotics in animal nutrition will also present substantial prospects, particularly in light of the recent prohibition on antibiotic growth boosters. As probiotic bacteria's generally low stability has frequently had a negative impact on consumer views, research organizations, and probiotics (Feed Navigator. Probiotics Market Face EU Challenge. https://www.feednavigator.com/Article/2004/01/08/Probiotics-market-face-EU-challenge).

The term "probiotic" still lacks a specific definition from the FDA. According to the FDA and FTC, who together assess claims made on food and drugs, the preclinical as well as clinical studies carried out to support the "confer a health benefit on the host" statement and the claims based on the results of those studies may categorize the indicated probiotic as either a dietary supplement, food or beverage, or even a drug.

When promoted as a supplement, healthy food or drink, or medicine in the US, probiotics face a number of regulatory obstacles and restrictions. The health of the individual ingesting theprobiotic product is the primary factor that affects how the probiotic is regulated.
A probiotic can be found in three main product categories, each with varying degrees of regulatory compliance:

1) A probiotic is regarded as "food" when it is given to food, with the implication that aprobiotic put to animal feed is regarded as a feed ingredient and so "food";
2) A probiotic may be a component of dietary supplements;
3) If a probiotic is used to treat, prevent, cure, mitigate, or compete with disease-causingorganisms to prevent their proliferation, it will be regarded as a medicine.

In order to maintain a healthy body and mind, dietary supplements are supposed to "supplementthe diet," whereas food is consumed "mainly for flavor, scent, or nutritional value".

"Food with purpose "is a term that the FDA does not recognize, but it implies that some foods have advantages over others in terms of taste, scent, or nutritional content, such as fiber. One food ingredient, probiotics, may be able to provide a wide variety of health advantages that may not fall within the "maintenance" category "or just have nutritional value.

Are probiotics provided in supplement or food form technically "fit" inside the parameters of thedietary supplement definition, to put it another way (Natural Product Insider. Probiotics: Regulatory Challenges of Classification.
https://www.naturalproductsinsider.com/claims/probiotics-regulatory-challenges-classification).

REJECTED PROBIOTICS

1.Yakult

According to the European Food Safety Authority, statements about immune response and digestive health has evidence supporting the A recent European ruling that the health claims made by the probiotics industry, which are worth £200 million annually in the UK, are not supportedby reliable research, has called into question the industry's probiotics sector. An official evaluation of the validity of more than 800 health claims, including the frequently cited claim that probiotic products strengthen the immune system, was published by the European FoodSafety Authority (EFSA). EFSA received the claims from the food sector and member states. The probiotic business has recently focused much of its marketing and advertising on claims that theEFSA's panel of independent scientists has deemed unproven. The panel came to the conclusion that the industry's submissions of evidence were either too general to be considered admissible or could not be demonstrated to have the stated impact on the body's defenses'', immune function, or gut issues.

In a different decision, the tribunal considered a dossier of 12 studies that Yakult had provided for its exclusive strain of probiotic bacteria, Lactobacillus casei, quarterly. All were deemed insufficient to back up the company's assertion that its products preserved immune protection against the common cold. Probiotic drinks are routinely purchased by nearly 60% of UKhouseholds, but the market was created without any impartial examination of its claims, and it has come under fire from consumer advocacy organizations.

The decision to gradually implement new EU regulations was made in 2007 as a consequence ofincreasing pressure from consumer advocacy organizations. They wanted to stop food companies from making health claims about their products unless they could back them up with evidence and unless the products were considered generally healthy enough to support such claims. According to the new regulations, member states were required to send dossiers of scientific evidence, along with health claims from suppliers for evaluation by the EFSA. More than 4,000 claims were submitted to the British Food Standards Agency from the UK sector, and roughly 44,000 claims were reported from all of Europe. The number ofclaims surprised EFSA scientists, who narrowed them down to 4,000 for thorough evaluation.

The most recent in an extensive number of decisions was an assessment that was released today.Although an EFSA statement said EFSA scientists "avoid using the term probiotics" because it has no valid scientific meaning, the EFSA had already published five opinions on claims relating to probiotics, all of which were negative.

When previous negative findings by the scientists regarding the products of other manufacturers were submitted to the EFSA, Danone, the industry leader in probiotic products, submitted its claims that Actemel and Active improved digestive health and immune system function. Since then, the company has stopped making most "immune health" claims in its advertising, and the only technical claim that is still pending EFSA review is that "fermented milk that contains the probiotic Lactobacillus casei reduces the presence of Clostridium difficile contaminants in the gut associated with the development of severe diarrhea."

The EFSA decisions announced today are a serious setback for the food business, which has made significant investments in novel foods known as nutritional foods like probiotics. These typically have high profit margins and help manufacturers stand out from the competition in a highly competitive sector. The EFSA did uphold some health claims, but they pertained to minerals and vitamins whose benefits had long been established, such as iron's capacity to treat anemia.

The manufacturing sector has complained that the EFSA is evaluating the new claims using exceedingly stringent scientific standards. It has requested a number of sessions to go over the requirements.

In a statement, Yakult claimed that the claim it had rejected was only one part of its overall study. Well-planned, double-blind, placebo-controlled human trials were cited as supporting the assertion. The company wants to talk to EFSA about the evaluation procedure and this result in response to the EFSA opinion. The business expects a favorable EFSA opinion in time with the benefit of additional guidance (The Guardian. Probiotic health claims ruled unproven. https://www.theguardian.com/society/2010/oct/19/efsa-rules-probiotic-health-claims-unproven).

1. EFSA rejects 86-study strong Valio probiotic gut health claim

EFSA's health claims panel rejected Valio's gut health dossier, which included 45 human studiesand 41 other than human studies depending on the Lactobacillus rhamnoses GG (LGG) strain (used in products like Valio's Gefilus, the first clinically backed probiotic consumer product on the European market), for not demonstrating the relationship.

According to Finnish dairy and ingredient company Valio, the European Food Safety Authority's (EFSA) denial of its probiotic claim contradicted or disregarded peer-reviewed data in its dossier, which contained 86 studies.

In addition to highlighting the breadth of research on the strain, which includes 600 published studies, 38 doctoral dissertations, and roughly 50 immune-specific studies, Valio DevelopmentManager Dr. Tuula Tuure stated that the company would challenge the opinion in the 30-day window that was available to it.

In its dossier, the Finnish dairy and ingredients company Valio claimed that the strain could aid in "maintaining defense against intestinal pathogens" and included 45 human studies and 41 non-human studies.

The studies, according to the EFSA's Panel on Dietetic Products, Nutrition, and Allergies(NDA), are not adequately reliable to support the claim.

According to the NDA, "In weighing the evidence, the Panel took into account that only one out of five human intervention studies showed an effect of LGG consumption on the development ofGI infections and that two human intervention studies did not show an effect of LGG usage on the development of immune system defenses after bodily (viral) vaccination.

A cause-and-effect connection between the consumption of LGG and the maintenance ofdefense against pathogenic gastrointestinal microorganisms has not been established, the group finds based on the data provided (18. Food stuff South Africa. EFSA rejects 86-study strong Valio probiotic gut health claim. https://www.foodstuffsa.co.za/8972/efsa-rejects-86-stuy-strong-valio-probiotic-gut-health-claim/).

S.NO	REJECTED PROBIOTIC	REASON
1.	**Yakult**	EFSA panel on dietic products nutrition and allergies rejected. The submission, ruling that no cause-and-effect relationship had been established between Yakult consumption and the health outcomes.
2.	**Valio probiotic**	The studies, according to the EFSA's Panel on Dietetic Products, Nutrition, and Allergies(NDA), are not adequately reliable to support the claim. According to the NDA, "In weighing the evidence, the Panel took into account that only one out of five human intervention studies showed an effect of LGG consumption on the development ofGI infections and that two human intervention studies did not show an effect of LGG usage on the development of immune system defenses after bodily (viral) vaccination. A cause-and-effect connection between the consumption of LGG and the maintenance ofdefense against pathogenic gastrointestinal microorganisms has not been established, the group finds based on the data provided.
3.	**Optibac Probiotic**	EFSA needs more details about the particular species and strains being used.
4.	**HEREDITUM LC40**	According to the EFSA, a high Staphylococcus count in breast milk is acknowledged as a risk factor for the emergence of infectious mastitis. The evidence provided indicating a link between probiotic strain usage and a decrease in Staphylococcus in breast milk is insufficient.

CHEMISTRY, MANUFACTURING, AND CONTROL (CMC) INFORMATION

A. Regulatory Considerations

The method disclosed emphasizes that manufacturing controls and the extent to which such controls are required to ensure optimal product quality vary not only between investigational and commercial manufacture, but also across clinical trial phases. During Phase 1 trials, the focus should typically be on factors that ensure subject safety. This should comprise raw material and drug substance identification and control, stability

assurance, and non-clinical safety assessments,if needed. As product development continues, quality control and quality assurance should be enhanced. Although sufficient information is required in each phase of the investigation to ensurethe proper identification, quality, purity, and strength of the investigational drug, the amount of information required will vary depending on the phase of the investigation, proposed duration, dosage form, and other information available (U. S. Food & Drug Administration. (2018). Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. https://www.fda.gov/media/82945/download).

B. Drug Substance

1. Description

The IND must provide a description of the LBP's drug substance, including its physical, chemical, and biological characteristics. The following should be included in a drug substance description:

- Names of biological entities and strains
- Culture/passage history of the strains
- Original source of cells from which the drug component was obtained
- If cells were acquired from a clinical specimen, a description of the donor(s)' clinical health, ifavailable.
- A summary of the product strains' phenotype and genotype, with a focus on biological activity orgenetic loci that may signify activity or potency and
- Documentation and a summary of any changes made to the LBP, such as the intentionalintroduction of other genes or mutations, as well as the genetic construction.

2. Characterization

An LBP's characterization must include a statement of the acceptable limits and analyticaltechniques used to ensure the drug substance's identification, strength, quality, and purity. Insteadof summaries, test reports should include accurate laboratory data in tabular form. Quantitative assay results should be provided as actual data rather than just Pass, Satisfactory, or Within Specification. You should also provide full details of the methods and tests required togenerate and characterize the LBP in your IND (U. S. Food & Drug Administration. (2018). Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. https://www.fda.gov/media/82945/download).

3. Manufacturer

The IND must include the name and address of the drug substance's manufacturer(s), as well as organizational information and a detailed description of all other products manufactured ormodified in the same or adjacent areas as the drug substance. In addition, the floor diagram shouldshow if the manufacture of other products will use the same product contact equipment and, if so,how that equipment will be cleaned between operations for the manufacturing of various products(U. S. Food & Drug Administration. (2018). Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. https://www.fda.gov/media/82945/download).

4. Method of Manufacture

Starting materials, flow charts, the cell bank system, cell growth and harvesting, purification and downstream processing, and in-process testing are all included. Should contain a list of all components (e.g., culture medium, buffers, etc.) used in the synthesis of the drug substance, as well as its tests and parameters, or references to authoritative compendia in the raw materials section. You should offer representative certificates of analysis from the supplier(s) and/ormanufacturer's acceptance criteria for purchased materials. Provide a flow chart for each drug substance's manufacturing process in the flow chart.

A flow chart should illustrate the processes in production, the equipment and materials used, the room or area where the operation is conducted, and a detailed description of in-process controls, including time and temperature limits, product testing performed at each step, and computer- controlled manufacturing procedures. Working Cell Banks (WCBs) are developed from the MCBfor product manufacture (although a WCB may not have been generated prior to Phase 1 study). Should include a detailed description of the cell banking procedures you used, including the banking system, the size of the cell banks, the methods, reagents, and media used for cell bank preparation, the conditions used for cryopreservation and storage, in-process controls, and storage conditions, as well as a description of the procedures used to avoid extraneous microbial contamination and a discussion of precautions (e.g., cell bank storage) to prevent any event that could render

the cell banks unusable (U. S. Food & Drug Administration. (2018). Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. https://www.fda.gov/ media/82945/download).

The media used at each step (including water quality), with details of their preparation and sterilization; the inoculation and growth of initial and sub-cultures, including volumes, time, andtemperature of incubation(s); how transfers, precautions and in-process testing are performed areall described in Cell Growth and Harvesting contamination. The primary culture system including operating conditions and control parameters, antibiotic usage in the medium and rationale, the techniques & criteria for harvesting and determining yields, as well as the criteria for pooling several harvests, if applicable. Provide a description of the procedures and materials used to separate and/or concentrate intermediate forms and the final bulk of entire cellsin Purification and Downstream Processing.

The following analytical tests developed or implemented by the manufacturer to indicate identity, purity, and concentration, as well as the levels of product-related and non-product related impurities, should be included in the description of each stage in downstream processing.Applicants should include a brief explanation of the sampling techniques and test methods used during in-process testing. In-process testing acceptance limits may be required to verify that theproduct can be made consistently. The application should define the criteria for accepting or rejecting an in-process batch for testing performed at critical stages of production (U. S. Food & Drug Administration. (2018). Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. https://www.fda.gov/media/82945/download).

2. Drug Substance Specifications

For each drug substance, provide preliminary specifications and testing. These should include, but not be limited to, assays for identification, purity, microbial bioburden/contamination, potency, and/or biochemical or physicochemical measurements assumed to predict potency, as well as, where appropriate, stability assessments. It is suggested that the applicant provide upper and lower estimates of variability, as well as reasoning for their selection. Specifications are anticipated to become more stringent when manufacturing experience is established and
the product is used in pivotal studies to support licensure.

The identification of each microbial strain contained in the drug substance should be establishedusing a specific and reproducible assay, according to the drug specification. CFUs are a measureof the number of viable cells per unit or dosage of live microbial products. A LBP's purity tests; LBPs may need to be free of extraneous organisms or have a low level of extraneous organisms, depending on the clinical setting and mode of administration in accordance with the US Pharmacopeia Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests.

CLINICAL INFORMATION

A. Previous Human Experience

From prospectively developed, randomized, controlled clinical studies to case reports, previous human experience is diverse. Similarly, different levels of product characterization for theproducts utilized in the research or studies may be reported. Without adequate CMC information, drawing conclusions or making assumptions about the relevance of prior studies may be difficult or impossible.

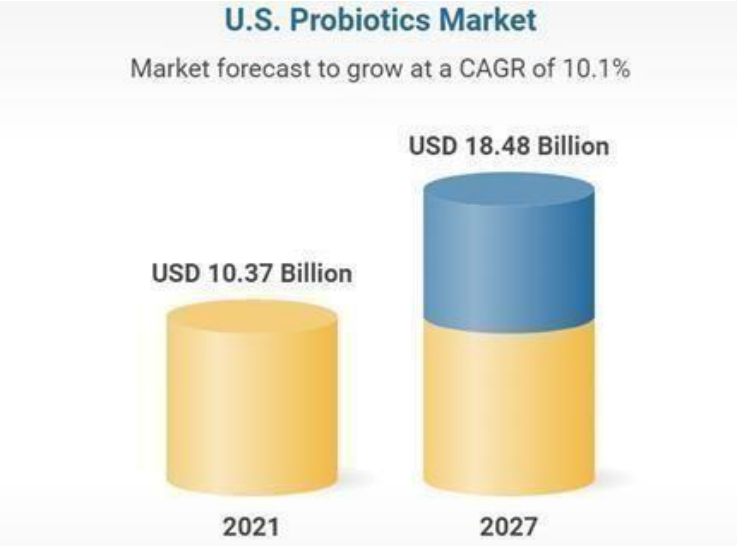
The relevance of previous human experience to support a proposed study is determined by the similarity of the product(s) under study, as well as study design, objectives, and endpoints, the number of individuals exposed, the level and duration of exposure, the type and duration of active and passive surveillance, and the integrity of study conduct, data collection, and subsequent analyses. If the applicant wishes to reference research submitted to the Agency by anyone other than the applicant (the sponsor), the applicant must acquire and provide a signed letter of cross- reference declaring that FDA has authority to access this material in their submission. In order to put the study data into context, an accounting of the final disposition of all randomized or enrolled study subjects is also necessary, because a significant number of dropouts, withdrawals, or protocol breaches makes data analysis and conclusions less compelling.

Multiple statistical analyses without appropriate correction and post hoc analyses, including analyses of population subsets, can be helpful in generating hypotheses for future studies;however, conclusions based

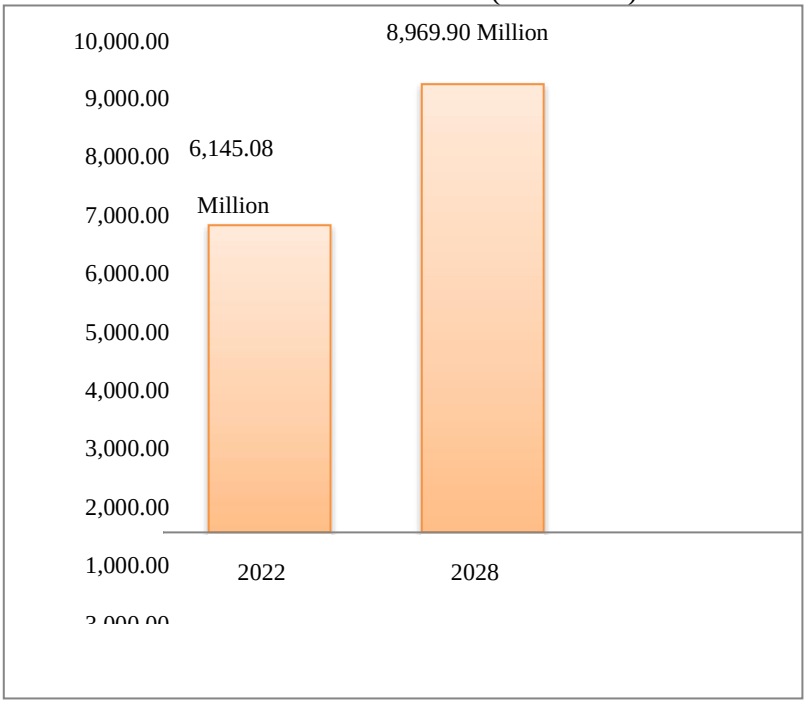
solely on multiple statistical analyses without appropriate correctionmay be misleading. Finally, data based on active adverse event monitoring gives a more relevantsafety profile of a product than data based on passive monitoring and/or reporting of just those instances that an individual investigator deems connected based on his or her own opinion.

Proposed Initial Studies

Before continuing on to trials in more vulnerable populations, such as children or individualswith the disease of interest, safety information received from the administration of an investigational product to healthy volunteers can be useful in detecting common product-related adverse events. Disease definitions and criteria for worsening, improvement, relapse, and other outcomes, as appropriate to the disease and population investigated, should be included inproposed studies evaluating therapy effects for information about clinical investigations in general and clinical research in pediatric andgeriatric populations in particular (U. S. Food & Drug Administration. (2018). Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. https://www.fda.gov/media/82945/download).



United States market share for Probiotics (2020-2027)



European Probiotic Supplements Market Market forecast to grow at a CAGR of 5.6%

Conclusion

Probiotics are live microbes that are consumed or administered to the body to provide beneficial health effects. Consumption of probiotics has increased dramatically during the past few decades. Parallel to this, there was an exponential increase in claims of their beneficial efficacy. The necessity for tougher guidelines in the scientific verification of purported advantages imparted by microorganisms marketed as probiotics has arisen as a result of the probiotics market's expansion. As of 2019, the European Food Safety Authority has denied all requests from commercial producers to make health claims on probiotic products sold in Europe since there is insufficient proof of a cause-and-effect relationship between the claimed benefits, rendering the effectiveness of the product ambiguous.

The Food and Drug Administration (FDA) and Federal Trade Commission (FTC) have issued warning letters and taken action against a number of probiotic product producers in the United States whose labels make a claim about the treatment of an illness or condition. The FTC has taken punitive measures, including a US$21 million fine against a prominent probiotic manufacturer for false advertising and overstated claims of health advantages for yoghurt and probiotic dairy drinks, which were coordinated by 39 different state governments. The main challenge faced is the rejection of dossiers.

The primary reasons for rejecting the various dossiers were that the microorganisms responsible for the effect had not been identified, the claims were poorly defined or not thought to be a health benefit, there were no human clinical trials, or the results were inconclusive. More than ever, companies need to stay up with the changing regulatory landscape by giving members the most recent information on the laws and norms as they work to commercialize probiotic products and turn obstacles into opportunities.

ACKNOWLEDGEMENT:

I am thankful to Chalapathi Institute of Pharmaceutical Sciences for the continuous support and Mr. Koushik Yetukuri who supported and guided for the completion of this article work.

CONFLICT OF INTEREST: None.

REFERENCES

1. Cleveland Clinic. Probiotics. https://my.clevelandclinic.org/health/articles/14598-probiotics.
2. Iris Case. The Regulation of Probiotics, https://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/training/Iris%20Case%202021%20CERSI%20Writing%20Competition.pdf.
3. Markets and markets. Probiotics Market by ingredient, Product type, End user, Distribution, Channel and Region. Global industry Analysis, Size, Share, Growth, Regional Outlook and Forecast. https://www.marketsandmarkets.com/Market-Reports/probiotic-market-
4. Mishra S, Acharya S.(2021). a Brief Overview on Probiotics: The Health friendly Microbes. Biomed Pharmacal J, 14(4). Available from: https://bit.ly/3qlhuKZ
5. Mary Ellen Sanders, Andi L. Shane & Daniel J. Merenstein (2016). Advancing probiotic research in humans in the United States: Challenges and strategies, Gut Microbes, 7:2, 97-100, DOI: 10.1080/19490976.2016.1138198
6. Natural Product Insider. Probiotics: Regulatory Challenges of Classification. https://www.naturalproductsinsider.com/claims/probiotics-regulatory-challenges-classification
7. Norio Ishibashi, Shoji Yamazaki. (2001). Probiotics and safety, The American Journal of Clinical Nutrition, V 73(2), 465s–470s, https://doi.org/10.1093/ajcn/73.2.465s.
8. Omni biotic. 21 Health Benefits of Probiotics for Your Gut, Mind, & More. https://www.omnibioticlife.com/benefits-of-probiotics/
9. Sayyeda Farwa Mazhar,Muhammad Afzal, Ahmad Almatroudi etal., (2020). The Prospects for the Therapeutic Implications of Genetically Engineered Probiotics. Journal of food quality.
10. U.S. Pharmacist -The Pharmacist's Resource for Clinical Excellence. (2014). Probiotics. https://www.uspharmacist.com/article/probiotics
11. U. S. Food & Drug Administration. (2018). Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. https://www.fda.gov/media/82945/download