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An Exhaustive Review on Regulatory Pathway for the Approval of Nutraceuticals as Per India, USA & Japan

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Abstract: ***The global nutraceuticals market, which was valued at $413.0 billion in the year 2020, is expected to see a magnanimous growth of about $650.5 billion by the year 2030, with a compound annual growth rate (CAGR) of about 3.9%. The term nutraceuticals have varied definitions; however, it can simply be put as "food or part of a food that provides medical or health benefits." These can further be used to improve health, prevent chronic diseases, increase life expectancy, or aid functions of the body. In general, the goals of nutraceutical regulation are to pay more emphasis on the product claims and intended use which is accomplished through Good Manufacturing Practices. Howbeit, the regulatory structure for nutraceuticals differs across countries and even regions where, USA primarily categorises nutraceuticals as "dietary supplements" under the Dietary Supplement Health and Education Act (DSHEA), Japan regulates nutraceuticals under Food for Specified Heath Uses (FOSHU) and Indian regulations envelop a wide range of nutraceuticals and novel foods under Food Safety and Standards Authority of India (FSSAI). Bringing nutraceuticals for retail usually follows four basic approaches: a pre - market notification, consumer access, safety, and robust post - market surveillance. Hence, due to the emerging economy of nutraceuticals it is essential to form a food - based regulatory paradigm that focuses on the primary aspects of registration and notification - based system for launching new products in the market.***

Keywords: Nutraceuticals, Functional Foods, Novel Foods, Product Claim

Broadly, nutraceuticals can be defined as products which are derived from both food as well as non - food sources that furnish benefits to support the structure or function of body, prevention or mitigation of diseases and promotion of overall well - being [1]. Nutraceuticals have captivated substantial interest owing to their potential safety, nutritional and therapeutic effects [2]. The term 'nutraceuticals' was first coined by Stephen DeFelice in 1989. He elaborated the concept of 'healthy living' using food derived from natural sources, pharmaceutical conditions or the biochemical compound of food product to keep one healthy and at bay with illness. The scope and extent of the definition for nutraceuticals can vary depending on the country in which it is being approved for marketing. Such products can range from isolated nutrients, dietary supplements, genetically engineered foods, herbal products, and even processed foods such as cereals, soups and beverages [3].

According to the Food Safety and Standards Authority of India (FSSAI), nutraceuticals are categorised as products that provide physiological benefits and help maintain good health. Similarly, the use of dietary supplements and nutraceuticals to reduce the risk of illness and to promote a healthy lifestyle has gained popularity in Japan [3]. However, the terms nutraceuticals and dietary supplements are not very common in countries like Japan, and conversely they are regulated as 'Food with Health Claims' (FHC) [4]. Additionally, health foods in Japan must be marketed in such a way that they do not resemble drugs. 'Health food' is an umbrella term for food products, either food, drink or dietary supplements that carry nutrient function along with an established health claim.

As per the US Dietary Supplement Health and Education Act (DSHEA) of 1994, dietary supplements can be extracts or concentrates which can be present in forms of tablets, capsules, gel caps, liquids or powders. All finished dietary supplement products as well as dietary ingredients are well regulated under the aforesaid Act. It is projected that the US dietary supplement market would reach $56.7 billion by the end of fiscal year 2024 and it is expected to grow by 78.9% in about less than ten years. This is mainly due to increasing consumer awareness to healthy food alternatives and better life quality. This has led to application of stringent regulatory requirements pertaining to health benefit claims and also labelling of the product. Another really important factor in the surge of use of dietary supplements was the outbreak of Covid - 19 which affected the densely concentrated supplement industries in areas of North America, Italy, Spain, France and Germany. These in turn benefitted hugely from the situation due to the high demand of immune - booster products [5].

Laws governing Nutraceuticals

The legislation and regulation for nutraceuticals is very different from that of drugs and is taken care of by discrete regulatory bodies. The regulatory bodies are responsible for the approval or disapproval of certain products under the nutraceuticals category.

The various regulatory bodies for India, USA and Japan are:

1) FSSAI: The Food Safety and Standards Authority of India (FSSAI) was established in the year 2006, under the Food Safety and Standards Act of 2006 and Rules 2011 [6], to amalgamate various Acts and orders that regulate food related issues. FSSAI was formed to lay evidence based scientific standards for food articles and to regulate their

import, manufacturing, sale, distribution and storage. The various central Acts such as, Prevention of food adulteration Act 1954, Fruit Products Order 1955, Meat Food Products Order 1973, Vegetable Oil Products Order 1947, Milk and Milk Products Order were revoked after the implementation of Food Safety and Standards Act.

The latest addition to this Act was published on June 24, 2022 and may be called the Food Safety and Standards (Health supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, and Prebiotic and Probiotic Food) Regulations, 2022 [7] [8]. This regulation will further distinguish between the normal consumable food products from the articles of food formulated for special dietary and nutritional purpose. This would a wide range of products falling into the category of:
Health Supplements (HS)

a) Nutraceuticals (Nutra)
b) Food for Specific Dietary Use (FSDU)
c) Food for Special Medical Purpose (FSMP)
d) Prebiotic and Probiotic Food (Pre - Pro)

The labelling and packing requirements are also mentioned in this regulation for FSDU, FSMP, HS and Pre - Pro categories. These will be mentioned in the later stages of the review.

2) DSHEA: The Dietary Supplement Health Education Act was passed in 1994 in the United States of America by Orrin G. Hatch and this defines dietary supplements and the legal authority to market these products in the USA. According to this Act, dietary supplement may be defined as a product that may contain alone or in combination the following dietary ingredient:

a) Vitamins
b) Mineral
c) Herb or other botanical
d) Amino acid
e) Concentrate, metabolite or extract

In addition to this, DSHEA also states that the dietary supplements must be intended for 'Oral' use only [9].

3) FOSDU: The Ministry of Health, Labour and Welfare (MHLW) in Japan classifies nutraceuticals as 'Food for Special Dietary Uses' also called FOSDU. FOSDU is a broad term for all the food that are approved or permitted to display that the food has special dietary use. There are five categories of FOSDU; they may be classified as:

a) Medical food for the ill
b) Formulas for pregnant or lactating women
c) Infant formulas
d) Food for the adults with difficulty in mastication or swallowing
e) Food for Specified Health Uses (FOSHU)

A standard regulatory approval process is operational for the first four categories of FOSDU, however a separate approval pathway is required for Food for Specific Health Uses (FOSHU) [11].

Approval of nutraceuticals in India:

For any product to be regarded as a nutraceutical in India, it should contain any of the following ingredients specified in the 8 Schedules of the Food Safety Act.
These are:
Schedule I -
Vitamins and Minerals
Schedule II -
Essential Amino acids
Schedule IV -
List of plants and botanical ingredients
Schedule VI -
List of ingredients as nutraceuticals
Schedule VII -
List of strains as pro - biotic
Schedule VIII -
List of pre - biotic compounds.

According to a notice issued by the FSSAI in 2018, there was discontinuance in the use of several nutraceutical ingredients as well as foods. This was due to lack of scientific data to support the use of the product as nutraceutical. This list comprised of 14 such ingredients such as raspberry ketone, silica, tea tree oil, Vit - D3 veg, etc. Hence, increase in the demand arm of the nutraceuticals led to their possible success rate in the mitigation and treatments of disease. And so the role of regulatory authority increased quite noticeably so as to monitor product quality and safety, minimise adverse effects, toxicity, adulteration, misuse and even abuse during consumption [12].

Registration of dietary supplements in India:

The Food Safety and Standards (FSS) Act of 2006 lays down the registration requirements for marketing any nutraceutical in India, however, there is not standard procedure available for the same [13]. This further leads to a lot of inconvenience for the registering parties. In May 2011, FSSAI issued the FSS rules for licensing and registration of food products, food businesses, packaging and labelling methods, standards for food products and approved additives to be used in the food products. According to the FSS regulations, 2011:

a) Registration of manufacturing site/manufacturing licence is a mandatory pre - requisite to market Food product in the country. This must be addressed to the State Licencing Authority/Agency.
b) For the purpose of import of Food material into the country, permission must be taken from Central Licensing Authority.
c) The regulatory process for clearance can be sought for a variety of products. Registration of the facility/site needs to be done on Form 3357. The process for clearance may be summarised as:

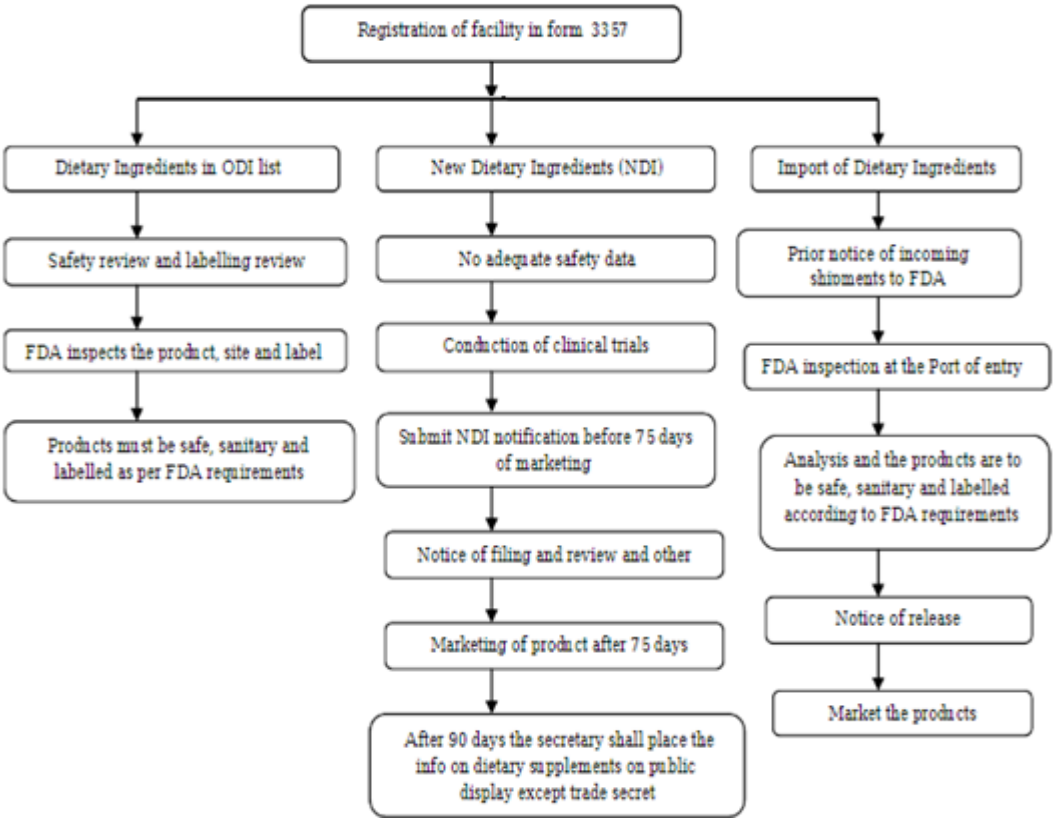

Figure A: Regulatory process for clearance in India

4) Licence for manufacturing/Import licence:

Applicant must apply for site registration to the State Licensing Authority in Form A. a summarised process can be represented in the flowchart given below:

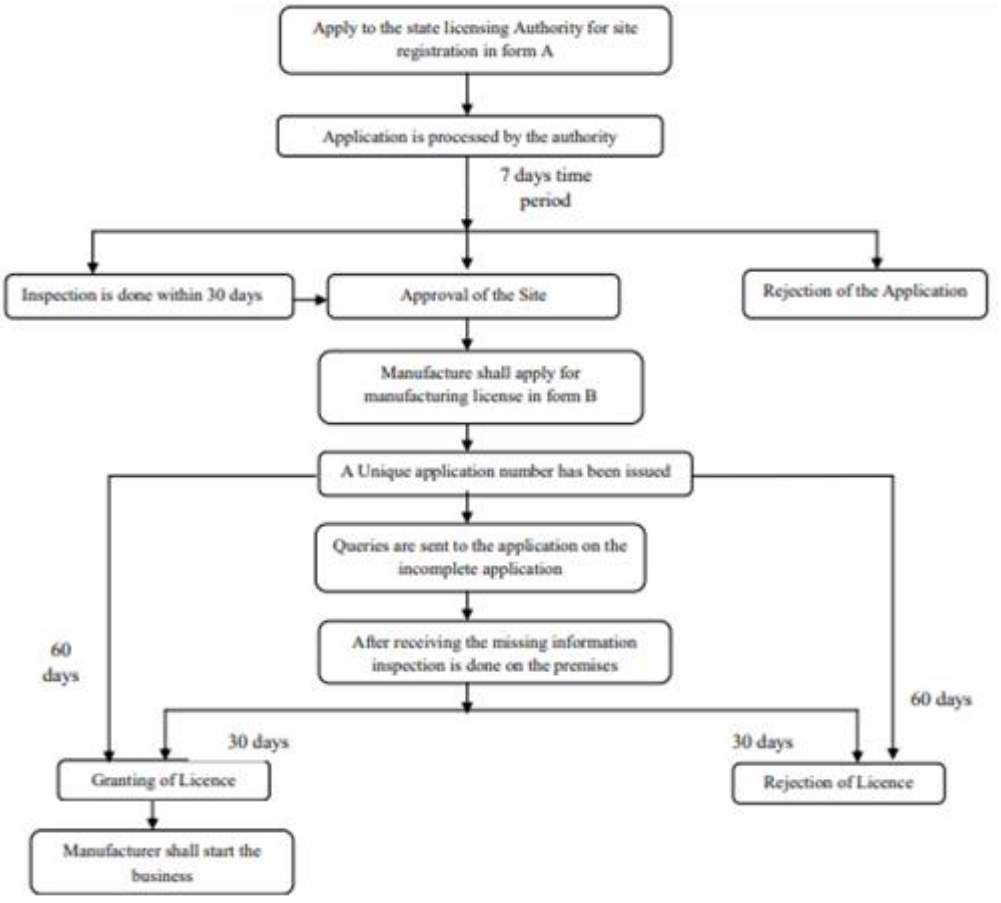

Fig B: Flowchart for approval process of licence for import/ manufacturing.

Documents that need to be enclosed along with the Import licence are:

1) Form A
2) Form B
3) Layout of the manufacturing unit
4) List of Directors
5) Name and model of the machinery being used in the making
6) Photo I. D. and address proof
7) List of food category to be manufactured
8) Authority letter with name of the person responsible
9) Analysis report
10) Proof of possession of premises
11) Partnership details
12) NOC from manufacturer
13) Food safety management system plan
14) Source materials
15) Pesticides residue report of water
16) Recall plan
17) NOCs

Regulatory approval for Health Food in Japan

The Ministry of Health, Labour and Welfare (MHLW) is the regulatory authority for Foods with Health Claims (FHC) in Japan. Furthermore, the Consumer Affairs Agency regulates the advertising and sale of FHC, while manufacturing is the concern of the State authorities. These products can help in either restoring or modulating normal health conditions like blood - sugar level, blood pressure, blood cholesterol level, enhance mineral absorption, improve bone health, lower blood - triglyceride levels, etc. [15]. Based on the functions and purpose, Japan regulates Health Foods as,

1) FOSHU - Foods for Special Health Use
2) FNFC - Foods with Nutrient Function Claim
3) FOSDU - Foods for Special Dietary Use

Foods for Special Health Use (FOSHU) refers to food containing ingredients with functions for health, physiological functions, and biological activity on the body. FOSHU classifies as a special group for food products lying somewhere between regular food and medicines. The history of FOSHU products dates back to 1993 when the first FOSHU products such as hypo - allergenic rice and low phosphorous containing milk were first approved for patients. Based on the application requirements and review process, FOSHU can be classified as:

1) Regular FOSHU

Includes food and food products whose safety and efficacy have been established during elaborate clinical trials, stability and safety tests and have gained approval from the MHLW, for specific health claims.

2) Qualified FOSHU

Qualified FOSHU refers to the food which have some established degree of effectiveness but their scientific data is less concise as compared to other related FOSHU products. Label for FOSHU products must include a statement 'this product includes' (name of the product), which is appropriate with for (Health claim), although the grounds for safety and effectiveness have not been fully established. If the application is approved by the MHLW, the product samples can be qualified into three groups:

a) Council of Pharmaceutical affairs
b) National Institute of Health and Nutrition (NINH)
c) Food safety commission

The Council of Pharmaceutical Affairs evaluates the efficacy of the food product whereas the Food Safety Commission assesses its safety. The NINH establishes analytical procedures for evaluating active ingredient.

3) Standardized FOSHU

Standardized FOSHU includes a range of products whose active ingredients have qualified the standards and also specifications for health claims and quality standard. Foods which have accumulated evidence of scientific specifications qualify under this category after being reviewed by MHLW.

4) Reduction disease risk FOSHU

This category is used to specify and list products that have shown effective results in the treatment, prevention or mitigation of disease/disease condition. FOSHU products are approved on the basis of health claims being claimed for the food

Foods with Nutrient Function Claim (FNFC) refers to the products labelled with the functions of their nutritional ingredients, and include a range of vitamins and minerals such as Vitamin A, C, D, B1, B6, B12, E, Biotin, and five minerals majorly calcium, iron, copper, magnesium, and zinc are currently listed under the FNFC. Since the nutritional requirement is important and peculiar to every individual, FNFC products must mention on their label a standard dosage requirement along with permissible upper and lower limit [16] [17].

Foods for Special Dietary Use (FOSDU) refers to the foods that can use medical and nutritional expressions to indicate that they are appropriate to promote growth or maintain or recover health in infants, children, infirm or pregnant females [14]. Seal for FOSDU approved products must look like:

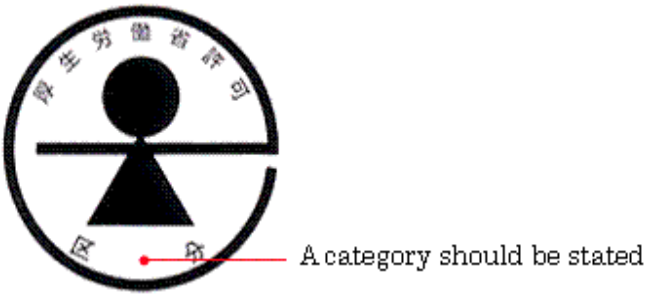

Figure C: FOSDU seal [22]

There are further five categories of FOSDU which have been discussed in the earlier parts of this paper. For foods intended to exhibit special dietary functions, approval must be taken from MHLW, under Article 26 of the Health Promotional Law, Japan. The regulatory approval process for Heath Foods in Japan can be depicted as given:

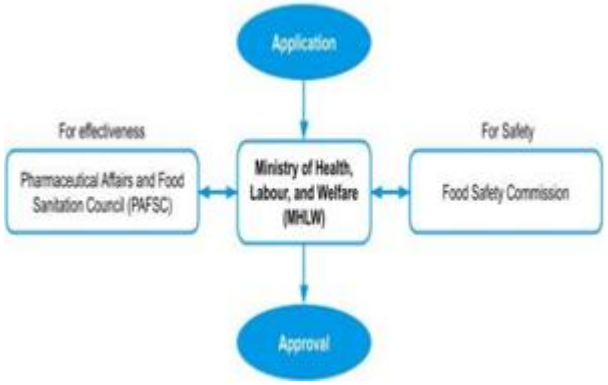

Figure D: Approval process for Health Foods in Japan [22]

The applicant files an application for approval of nutraceuticals directly with the MHLW, on a yearly calendar basis which is divided into four quarters. The received applications are usually accepted within three months of application [18]. The applicant must furnish product samples along with proposed labelling during application process. All the information submitted must be in Japanese language and should be published in Japanese scientific journal [19] [20] [21] [22]. For any person who wishes to qualify his product under FOSDU, he must furnish the following documents with his application:

1) Name of the applicant and his address
2) Name and address of the Head Office and factory
3) Product name
4) Estimated shelf life
5) Content amount
6) How product enhances the consumer's dietary habits
7) List of ingredients along - with composition
8) Precautions and conditions for intake
9) Instructions for preparing pre - mix and storage conditions
10) Product sample
11) Samples of product with label and health claim
12) Clinical and nutritional proof documents
13) Stability testing documents
14) Quality control systems documentation and validation
15) Other relevant information to support the application

Once approved, the applicant can use the FOSHU mark/symbol on his product. The symbol signifies 'Jumping for Health [18]'.

Approval of dietary supplements in the USA

The Dietary Supplement Health and Education Act (DSHEA) of 1994 regulates the approval of both the dietary ingredients and finished dietary products under a different set of regulations than those governing the drug and food products [23]. Under The Federal Food, Drug and Cosmetic Act (FD&C); a dietary ingredient may be defined as a mineral, vitamin, amino acid or other botanical which can be used by humans as supplements to the normal diet. Such supplements can be marketed in the form of tablets, capsules, soft - gels, powders, etc. USA classifies the dietary ingredients as Old Dietary Ingredients (ODI) and New Dietary Ingredients (NDI). Old dietary ingredients were marketed in the U. S. before October 1994 and are also called the "grandfathered" ingredients under pre - DSHEA. The use of ODI is still permissible in the industries, on the grounds of established safety and efficacy data of the ingredient. On the contrary, New Dietary Ingredient (NDI) includes the list of all ingredients approved after the passage of DSHE Act, and was not marketed before October, 1994 [25] [27].

ODI do not need any prior notification to be launched in the US market, however the manufacturer must provide a New Dietary Ingredient Notification (NDIN) before marketing any NDI. This notification must be submitted 75 - days prior sale and distribution. All the received applications are sorted on the basis of NDIN number and can be accessed on the FDA's Docket Management Staff.

Regulation of dietary supplements in the USA

The FD&C Act was amended in 1994 by the DSHE Act, which set out a set of distinct regulations for 'dietary supplements'. Under this Act:

a) FDA does NOT have the authority to regulate or approve dietary supplements. It can also NOT approve the packaging or labelling of the supplements being sold.
b) It is the responsibility of the manufacturer to establish and provide the safety and efficacy data supplements being manufactured at his site.
c) The 'label' of the dietary supplement must contain nutritional particulars in the form of a 'Supplement Form' and should include the serving size, number of servings per container, list and composition of the ingredient list.
d) Statement specifying the use of the supplement, such as 'dietary supplement', 'herbal supplement', 'calcium supplement', etc.

The National Institutes of Health (Office of Dietary Supplements) maintains a data - set of dietary supplements known as Dietary Supplement Fact Sheets [29]. This presents information about the supplements as well as their ingredient. Many of such ingredients are accessible to the common public in dual languages, namely English and Spanish.

Packaging and labelling of dietary supplements

1) India

Under the Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Foods and Novel Foods) Regulation of 2016, the label or package:

a) Must NOT claim that the ingredient or products inside the container help in the diagnosis, treatment, prevention, cure or mitigation of the disease.
b) Every container should contain the following information on its label:
   - The term 'NUTRACEUTICAL'
   - Common name of the product
   - Declaration of the amount and components of each ingredient
   - For nutrients added externally, the quantity must be at - par with the quantity specified by Indian Council of Medical Research (ICMR), in terms of daily - allowance and should specify an advisory statement 'not to exceed the daily recommended dosage'
   - Advisory statement for 'RECOMMENDED USAGE'

- Advisory statement for 'NOT FOR MEDICAL USE'
- Advisory statement for possible danger in case of over - consumption
- Advisory statement of contraindications, product - drug interaction, etc.
- A statement that the product must be stored away from children.

2) Japan

Food products marketed in Japan must have labels written in Japanese. The label must contain details about:

- Name of the product
- Country of origin
- Ingredients and possible allergen
- Name and address of the importer (if any)
- Food additives
- Storage instructions
- Net content
- Nutritional facts
- Best - before date

3) USA

a) Label statements

Five statements are required on the package or label of the dietary supplement:

- Statement of identity (name of the dietary supplement)
- Net quantity of contents (amount of dietary supplement)
- Nutrition labelling
- Ingredient list
- Name and place of business of manufacturer, packer or distributor

b) Placement of label on the container

The label statements must be mentioned on the front label panel or on the information panel which can be easily seen by the consumer (when facing the product). The labelling requirements are mentioned in the 21 CFR 101.

- **21 CFR 101.2** (b) - Quantitative comparison of the nutrient comparison labelled per serving size
- **21 CFR 101.9** - Nutrition labelling of food i. e. information about serve size, calorific value, fat/total fat, trans fat/trans, poly - saturated fat or poly - unsaturated fat, mono - saturated fat or mono - unsaturated fat, cholesterol, sodium, fluoride, dietary fibre, added sugar, total sugar, etc.
- **21 CFR 101.36 (g) -** Contains information about serving size, information of the Reference Daily Intake (RDI) or Daily Reference Value (RDV).

c) Type, size and prominence of the label

It is important to use a print size which is prominent, coherent and readable. The letters must be $1/16^{th}$ inch in height based on the lower case letter 'o'. the height should not be greater than the width by three times.

d) UPC Barcode

For retail purpose in the USA, a UPC barcode must be obtained from the Uniform Code Council. This is a 12 - numeric long code and encodes the company code, country and product code [24].

Conclusion

This review paper has contoured the regulatory requirements for registering nutraceutical products in the top three nutraceutical hubs of the world which are India, Japan and USA. In - spite of the large market prospect there are still some ambiguities in the regulations regarding approval of nutraceuticals specifically in the Indian subcontinent. A majority of regulations are adopted from the DSHEA act for sale and distribution of nutraceuticals in India. However, Japan has a rather elaborate and well - bifurcated category of food and food products as well as product claims.

Sustainable and eco - friendly packaging and ingredients. Adhering to sustainable practices can be costly and complex. Intellectual Property and Counterfeiting: Protecting intellectual property rights and combating counterfeit products remain ongoing challenges, especially for popular cosmetic brands.

In conclusion, while the cosmetics industry in India offers significant growth opportunities, it also faces various challenges, including regulatory complexities, evolving consumer preferences, and the need to adapt to a changing market landscape. Successfully navigating these challenges requires a combination of regulatory reforms, industry innovation, and a deep understanding of consumer dynamics in the Indian market.

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