

NUTRACEUTICALS: USES, RISKS AND REGULATORY SCENARIO**MEERA CHANDRADATT SINGH^{1*}, KISHORE N. GUJAR²**¹Pacific Academy of Higher Education & Research Society's Pacific University, Udaipur, Rajasthan, ²S.T.ES's Sinhgad College of Pharmacy, Pune, Maharashtra, India.*Received: 19 Apr 2013, Revised and Accepted: 22 May 2013***ABSTRACT**

Food and Nutrition is the basis of growth and health of human beings. The concept of use of specific food/food ingredient for a particular beneficial health effect, lead to the concept of food can be used as medicine. This old concept is reintroduced in today's era, backed up by scientific research and clinical evidence. With increasing percentage of chronic and lifestyle diseases utility of nutraceutical/dietary supplements/functional food is proving beneficial. In twenty-first century very less new drug molecules are invented. The focus of Pharmaceutical industry is thus diverted to allied areas like formulation and development, herbal actives and nutraceutical/dietary products. Regulatory aspects of such products were in a state of confusion in 20th century. Till date the regulations are not harmonized for the globe and change from country to country. But now it is clearly understood that the regulations for clinical evidence and safety of such products can't be less stringent than rules for modern medicines and thus the science of nutraceuticals is progressing. This article is a review about regulatory scene of such products in few selected countries.

INTRODUCTION

The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ. According to DeFelice, nutraceutical can be defined as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease [1]." However, the term nutraceutical as commonly used in marketing has no regulatory definition [2].

Nutraceuticals, dietary supplements, functional food are sometimes overlapping terms. Over the years the rules and regulations in this area of products have provided distinct definitions and regulations for such products, keeping safety aspects in mind. These standards have evolved more as numbers of products introduced in the market are increasing. Research in the area of food science is providing basis for development of such products. Such products have special health benefit claims or many a times claims for cure for certain diseases or disorders. Regulations in the area of such products vary from country to country and many products launched in market sometimes take benefit of existence of no clear rules and thus can pose health risks. Some products may not have risk of adverse effect but may not serve the claim made. There are many reports of adverse reactions and non functionality of such products at times. Such cases mostly happen because the regulations are not clear and the products escape in market finding loopholes from such regulations. Admixtures of herbal drugs under the title of dietary supplement are a common scene existing even in a developed country like USA. At the same time as the science of nutrition and food is progressing, the use of specific food, isolated ingredients of food or specially formulated mixtures have proved their use in treatment, prevention or as an adjuvant in main treatment of many diseases and disorders. The numerous papers published claiming use of such products and ingredients reflect the potential of such products. Any type of nutraceutical formulation needs thorough study guarded by regulations for the safety of such products whether the product is from pure pharmaceutical origin, herbal or food origin. In this article, authors have overviewed existing regulations for such products in India, USA, Europe and Japan.

A clear understanding of nutraceuticals in a regulatory system will reduce the confusion in establishing the policy for nutraceuticals. For an effective regulatory framework, nutraceuticals need to move from a blurred idea with many and sometimes conflicting definitions to a sharply defined and quantifiable concept. However in current scenario the regulatory position of nutraceuticals would be different depending on the country's regulatory framework [3].

Regulations about such products in India

The Food Safety and Standards Authority of India (FSSAI) has been established under Food Safety and Standards Act, 2006 in India which consolidates various acts & orders that were in existence to handle food related issues in various Ministries and Departments. FSSAI has been created for laying down science based standards for articles of food and to regulate their manufacture, storage, distribution, sale and import to ensure availability of safe and wholesome food for human consumption. Thus it applies to products like dietary supplements and nutraceuticals too. Various central Acts like Prevention of Food Adulteration Act, 1954, Fruit Products Order, 1955, Meat Food Products Order, 1973, Vegetable Oil Products (Control) Order, 1947, Edible Oils Packaging (Regulation) Order 1988, Solvent Extracted Oil, De- Oiled Meal and Edible Flour (Control) Order, 1967, Milk and Milk Products Order, 1992 etc. have been repealed after commencement of FSS Act, 2006 [4].

Highlights of the Food Safety and Standard Act, 2006

This act defines food as "Food" means any substance, whether processed, partially processed or unprocessed, which is intended for human consumption and includes primary food, to the extent defined in clause (ZK) genetically modified or engineered food or food containing such ingredients, infant food, packaged drinking water, alcoholic drink, chewing gum, and any substance, including water used into the food during its manufacture, preparation or treatment but does not include any animal feed, live animals unless they are prepared or processed for placing on the market for human consumption, plants prior to harvesting, drugs and medicinal products, cosmetics, narcotic or psychotropic substances: Provided that the Central Government may declare, by notification in the Official Gazette, any other article as food for the purposes of this Act having regards to its use, nature, substance or quality [4].

Establishment of Food Safety and Standard Act, 2006 makes a provision for constitution of scientific panels. It states The Food Authority shall establish scientific panels, which shall consist of independent scientific experts.

(1)The Scientific Panel shall invite the relevant industry and consumer representatives in its deliberations.

(2) Without prejudice to the provisions of sub-section (1), the Food Authority may establish as many Scientific Panels as it considers necessary in addition to the Panels on:

(a) Food additives, flavourings, processing aids and materials in contact with food

(b) Pesticides and antibiotic residues;

- (c) Genetically modified organisms and foods;
- (d) Functional foods, nutraceuticals, dietetic products and other similar products;
- (e) Biological hazards;
- (f) Contaminants in the food chain;
- (g) Labelling
- (h) Method of sampling and analysis.

(3) The Food Authority may from time to time re-constitute the Scientific Panels by adding new members or by omitting the existing members or by changing the name of the panel as the case may be [4].

As per provisions made under this Act no person shall manufacture, distribute, sell or import any novel food, genetically modified articles of food, irradiated food, organic foods, foods for special dietary uses, functional foods, nutraceuticals, health supplements, proprietary foods and such other articles of food which the Central Government may notify in this behalf.

For the purposes of this section, "Foods for special dietary uses or functional foods or nutraceuticals or health supplements" means:

(a) foods which are specially processed or formulated to satisfy particular dietary requirements which exist because of a particular physical or physiological condition or specific diseases and disorders and which are presented as such wherein the composition of these foodstuffs must differ significantly from the composition of ordinary foods of comparable nature, if such ordinary foods exist and may contain one or more of the following ingredients, namely:

- (i) Plants or botanicals or their parts in the form of powder, concentrate or extract in water, Ethyl alcohol or hydro alcoholic extract, single or in combination;
- (ii) Minerals or vitamins or proteins or metals or their compounds or amino acids (in amounts not exceeding the Recommended Daily Allowance for Indians) or enzymes (within permissible limits)
- (iii) Substances from animal origin;
- (iv) A dietary substance for use by human beings to supplement the diet by increasing the total dietary intake;

(b) (i) a product that is labelled as a "Food for special dietary uses or functional foods or nutraceuticals or health supplements or similar such foods" which is not represented for use as a conventional food and whereby such products may be formulated in the form of powders, granules, tablets, capsules, liquids, jelly and other dosage forms but not parenterals, and are meant for oral administration;

(ii) such product does not include a drug as defined in clause (b) and Ayurvedic, Sidha and Unani drugs as defined in clauses (a) and (h) of section 3 of the Drugs and Cosmetics Act, 1940 and rules made there under [4].

Nutraceuticals and Dietary supplement scene in USA

Mounting evidence in USA suggests that increasing numbers of Americans are falling seriously ill after taking dietary supplements that promise everything from extra energy to sounder sleep. The victims include men and women of all ages as well as children whose parents are feeding them snacks, drinks and nostrums made with herbal supplements that are neither regulated by the federal government nor tested for their effects on the young [5].

Such kind of reports makes one take a review of regulations of such products in USA

The Regulation of Dietary Supplements in USA

The U.S. Food and Drug Administration (FDA) is responsible for regulating dietary supplements through its centre for Food Safety and Applied Nutrition. The Food Drug and Cosmetic Act (FDCA) as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA) is the law that regulates dietary supplements. Under

FDCA, the United States Pharmacopeia and National Formulary (USP-NF) are specifically recognized as providing specifications for dietary supplements. Adherence to these standards, however, is voluntary. Dietary supplement manufacturers are not legally required to meet these specifications. The FDCA regulates dietary supplements as foods. Under the law, supplement regulations are the same as those that cover conventional foods.

- Before producing or selling their products. Dietary supplement manufacturers do not need to register with FDA, or obtain FDA approval,
- Prior to marketing a product, manufacturers are responsible for ensuring that a dietary supplement (or a new ingredient) is safe before it is marketed. FDA has the authority to take action against unsafe dietary supplement products.
- Manufacturers must ensure that their product label information is truthful and not misleading.

Monitoring of Dietary supplement safety in USA

Dietary supplement manufacturers are not legally required to report "adverse events" to the FDA, including injuries or illnesses that may be related to the use of their products. The FDA monitors supplement safety through such avenues as voluntary adverse event reporting, labelling claims, product literature, and occasional laboratory testing.

Regulation of dietary supplement advertising in USA

The Federal Trade Commission (FTC) regulates dietary supplement advertising for false and misleading health claims [6].

USDA regulates both finished dietary supplement products and dietary ingredients under a different set of regulations than those covering "conventional" foods and drug products (prescription and Over-the-Counter). Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the dietary supplement or dietary ingredient manufacturer is responsible for ensuring that a dietary supplement or ingredient is safe before it is marketed. FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market. Generally, manufacturers do not need to register their products with FDA nor get FDA approval before producing or selling dietary supplements. (Domestic and foreign facilities that manufacture/process, pack, or hold food for human or animal consumption in the United States are required to register their facility with the FDA.)

Manufacturers must make sure that product label information is truthful and not misleading. Under the FDA Final Rule 21 CFR 111, all domestic and foreign companies that manufacture, package, label or hold dietary supplement, including those involved with testing, quality control, and dietary supplement distribution in the U.S., must comply with the Dietary Supplement Current Good Manufacturing Practices (cGMP) for quality control. In addition, the manufacturer, packer, or distributor whose name appears on the label of a dietary supplement marketed in the United States is required to submit to FDA all serious adverse event reports associated with use of the dietary supplements in the United States.

FDA's other responsibilities include product information, such as labelling, claims, package inserts, and accompanying literature. The Federal Trade Commission regulates dietary supplement advertising [6].

Regulations in Europe

In Europe till 1999 due to a much more restrictive regulatory climate and a lack of harmonization, the functional food sector remained a tedious development opportunity, with many products not becoming commercially successful. But the explosive growth of the US and Japanese markets has created similar expectations for the European market. Thus, food supplements and particularly plant extracts have developed considerably in 1999.

In Europe, the functional food market is dominated by prebiotics/probiotics due to a large dairy products market (five times the size of the comparable market in both the US and Japan).

The European Commission 2000 White Paper on Food Safety announced 80 proposals for new and improved legislation in this field. Among others, it foresaw the establishment of a General Food Law Regulation, laying down the principles of food law and the creation of an independent Food Authority endowed with the task of giving scientific advice on issues based upon scientific risk assessment with clearly separated responsibilities for risk assessment, risk management and risk communication. Since then, more than 90% of the White Paper proposals have been implemented. However, there is not, as such, a regulatory framework for 'functional foods' or 'nutraceuticals' in EU Food Law. The rules to be applied are numerous and depend on the nature of the foodstuff. The rules of the general food law regulations are applicable to all foods. In addition, legislation on dietetic foods, on food supplements or on novel foods may also be applicable to functional foods depending on the nature of the product and on their use. Finally, the two proposals on nutrition and health claims and on the addition of vitamins and minerals and other substances to foods, which are currently in the legislative process, will also be an important factor in the future marketing of 'nutraceuticals' in Europe. The basis of EU legislation on food products, including functional foods and nutraceuticals is 'safety'. Decisions on the safety-basis of legislation are based on risk analysis, in which scientific risk assessment is performed by the European Food Safety Authority and risk management is performed by the European Commission, the Member States, and in case of legislation, together with the European Parliament. In the risk management phase, both the precautionary principle and other legitimate factors may be considered in choosing the best way of dealing with an issue. Due to the numerous pieces of legislation applying and to the different procedures to be followed, the process of having 'functional foods' ready for the market is certainly a costly and time-consuming task. However, it may also be clearly worth it in terms of market success and improved consumer health [7].

EU Framework

In December 2006, EU decision makers adopted a Regulation on the use of nutrition and health claims for foods which lays down harmonized EU-wide rules for the use of health or nutritional claims on foodstuffs based on nutrient profiles. Nutrient profiles are nutritional requirements that foods must meet in order to bear nutrition and health claims. One of the key objectives of this Regulation is to ensure that any claim made on a food label in the EU is clear and substantiated by scientific evidence.

Independent scientific advice on food and feed safety in EU countries

The European Food Safety Authority (EFSA) was set up in January 2002, following a series of food crises in the late 1990s, as an independent source of scientific advice and communication on risks associated with the food chain. EFSA was created as part of a comprehensive programme to improve EU food safety, ensure a high level of consumer protection and restore and maintain confidence in the EU food supply.

EFSA's work includes providing scientific advice on:

- . General function health claims under Article 13.1 of the EU Regulation
- . New function health claims under Article 13.5 of the EU Regulation
- . Claims regarding disease risk reduction and child development or health under Article 14 of the EU Regulation
- . Criteria for setting nutrient profiles

EFSA is responsible for verifying the scientific substantiation of the submitted claims, some of which are currently in use, some of which are proposed by applicants (companies who want to submit claims for authorization in the EU). This information serves as a basis for the European Commission and Member States, which will then decide whether to authorize the claims [8].

In Europe "nutraceuticals" are subject to existing EU food laws which are implemented on a national basis. This can make it

particularly challenging for a company to determine the best route to market. Companies also have to consider whether the food or ingredient could be classed as "novel" and therefore require authorization under the EU procedures for novel foods (regulation (EC) No 258/97).

To avoid any confusion, it is important that companies consult professionals, such as Global Regulatory Services, who are familiar with the regulations of governmental bodies such as the MHRA (UK Health Authority) or the Food Standards Agency (FSA) [9].

Japan: Health conscious society

The primary role of diet is to provide sufficient nutrients to meet the nutritional requirements of an individual. There is now increasing scientific evidence to support the hypothesis that some foods and food components have beneficial physiological and psychological effects over and above the provision of the basic nutrients. Today, nutrition science has moved on from the classical concepts of avoiding nutrient deficiencies and basic nutritional adequacy to the concept of "positive" or "optimal" nutrition. The research focus has shifted more to the identification of biologically active components in foods that have the potential to optimise physical and mental well being and which may also reduce the risk of disease. Many traditional food products including fruits, vegetables, soya, whole grains and milk have been found to contain components with potential health benefits. In addition to these foods, new foods are being developed to enhance or incorporate these beneficial components for their health benefits or desirable physiological effects.

Many academic, scientific and regulatory organisations in Japan are actively working on ways to establish the scientific basis to support claims for functional components or the foods containing them. Any regulatory framework will need to protect consumers from false and misleading claims and to satisfy the needs of industry for innovation in product development, marketing and promotion. For functional foods to deliver their potential public health benefits, consumers must have a clear understanding of, and a strong confidence level in, the scientific criteria that are used to document health effects and claims.

Japan has led the world in this area. In 1991, the concept of Foods for Specified Health Use (FOSHU) was established. Foods identified as FOSHU must be approved by the Minister of Health and Welfare after the submission of comprehensive science-based evidence to support the claim for the foods when they are consumed as part of an ordinary diet.

With a large elderly population and with strong domestic phytotherapy tradition and expertise in bio products, Japan was the first country to recognize and regulate functional food. It is named Food for Specific Health Use (FOSHU) and it was founded in the early 1980s. Japan is the most advanced market with a flexible regulatory environment. Today it is worth more than \$12 billions for nutraceuticals [10].

The awareness of Japanese people and scientific fraternity is involved in the progress of the field of nutraceuticals, currently Japan has announced The 13th International Conference on Functional and Medical Foods with Bioactive Compounds: Science and Practical Applications and will be located in Kyoto, Japan. On May 2013 .Conference topics include: Functional and Medical Food Ingredients: Sources and Potential Benefits in Public Health Functional, Medical, Bioactive Foods, and Chronic diseases, carotenoids as a source of functional and medical food, flavonoids as a source of functional and medical food Prebiotics and Probiotics as a source of functional and medical food, functional and medical foods in the management of chronic diseases: Cancer, Obesity, Diabetes, CVD. The agenda of such conferences shows that nutraceuticals and functional foods is a growing research area and well planned scientific research [11].

Nutraceutical industry is a dynamic and evolving industry that offers exciting opportunities to merge scientific discovery with growing consumer interest in health-enhancing foods and it will continue to have great appeal because they are more convenient for today's life style. Although, field of Nutraceuticals offers a good opportunity for

phytochemicals research but still, several hurdles have to be crossed in research for beneficiary effects in human health. There is need to set up an *in vivo* system to test the biological potency of a given diet with a specific biological property and the gap between the scientific community with updated knowledge on nutraceuticals and health care professional has to be filled. Future research in the science of nutrition may be directed towards evaluating the potency of phytochemicals in foods [12].

Nutraceutical Market

The preference for the discovery and production of nutraceuticals over pharmaceuticals are well seen in pharmaceutical and biotech companies. Some of the pharmaceutical and biotech companies, which commit major resources to the discovery of nutraceuticals include Monsanto, American Home Products, DuPont, BioCorrex, Abbott Laboratories, Warner-Lambert, Johnson & Johnson, Novartis, Metabolex, Scio-tech, Genzyme Transgenic, PPL Therapeutics, Unigen, and Interneuron29,30. The nutraceutical industry in the US is about \$86 billion. This figure is slightly higher in Europe and, in Japan, represents approximately a quarter of the \$6 billion total annual food sales. 47% of the Japanese population consumes nutraceuticals even without specific financial figures, business reports continually suggest that the nutraceutical market is consistently growing. The approach to regulating and marketing nutraceuticals is notably heterogeneous on the global level. This is largely due to the challenges in classifying these products, absence of a suitable regulatory category for these hybrid products.

GIA (Global Industry Analysts) announces the release of a comprehensive global report on Nutraceuticals market. The global nutraceuticals market is projected to exceed US\$243 billion by 2015, owing to consumer desire for leading a healthy life and increasing scientific evidence supporting health foods [13].

CONCLUSION

Twenty first century is seeing very less new drugs. Most Pharmaceutical industries who invested in development of new drugs have come with no much new discoveries. The quest for new remedies is now focusing in various allied areas which include nutraceuticals and herb based products. The field of nutraceuticals and functional foods is offering research products claiming various health benefits and cure for various ailments. This field is showing signs of more and more research and have yielded modern approaches in the prevention and management of chronic diseases using innovations of herbal remedies, food additives and non-traditional plants as functional foods. The most highlighted areas include research in the area of antioxidants, carotenoids, dairy-based ingredients dosage forms, fibres and carbohydrates, minerals, nutritional lipids and oils, phytochemical, plant extracts, probiotics and prebiotics, proteins, peptides, amino acids, soy-

based ingredients, vitamins & premixes cosmeceuticals and non-traditional herbs as health remedies. All the ingredients under such research are not blindly believed to be safe and thorough research and safety data is expected by various regulatory authorities in order to introduce such products in market. This review has tried to compile regulatory status of such products in most significant countries, which suggests that the scene may vary a little from country to country. But it is evident that the regulations for such products are getting stringent and thus the marketed products are believed to be efficacious, safe and confirming to the claims.

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