

# Safety Assessment of Nutraceuticals

Koppal Suryanarayana Rao

## INTRODUCTION

Nutraceuticals are products isolated from foods that are generally sold in medicinal forms. They are defined as any food (or part thereof) which provides health benefits – including prevention and treatment of disease – in addition to the basic nutritional value found in foodstuff. Nutraceuticals are of particular interest as a way to reduce the expensive, high-tech disease treatment approaches currently employed in developed countries.

The nutraceutical industry represents a dynamic, evolving entity that offers novel opportunities to merge scientific discovery with growing consumer interest in health-enhancing foods. It tracks and monitors consumer trends, thus the products of this industry can represent a direct response to their demands. The nutraceutical industry encompasses three main segments which include functional foods, dietary supplements, and herbal/natural products.

### Global Demand for Nutraceuticals

The global nutraceutical market has experienced maximum growth in the last decade. Although nutraceuticals as an industry emerged in the early 1990s, the world has witnessed its explosive growth in the first decade of this century. From 1999 to 2002 the industry grew at an annual average growth rate of 7.3 percent, while in this century the rate doubled to 14.7 percent.

Today, global nutraceutical market is estimated at 117 billion USD. Personalization and customization are current trends in the development of nutraceuticals, especially in developed markets of the world. Investment in research and development to find innovative approaches, verifying health claims of the products and market research represent key strategies for the industry.

A primary impetus for such growth is consumer demand; consumers are looking to follow healthy lifestyles and obtain optimum nutrition to keep diseases such as diabetes, high blood pressure and obesity at bay. Although the US, European Union and India are currently the world's largest nutraceuticals markets, China is likely to surpass them all by 2030.

### Industry in Different Countries

The US nutraceutical market still represents the largest nutraceutical market in the world. Companies are looking to diversify their products and move towards natural nutraceutical ingredients in their product

offering. The latter is a consequence of the push from US consumers, who are extremely health conscious and demand specific ingredients in the products they consume.

The market for nutraceuticals in Europe is witnessing heavy consolidation, with a focus on innovation and new product development. A result is a considerable increase in research and development – from 0.24% at the beginning of the century to 1 percent in 2010. Germany, Netherlands and Sweden have emerged as the key nutraceutical innovation hubs of Europe, whereas Spain and Great Britain act as decisive test markets for new products.

According to a recent report, total market for nutraceuticals in India is growing at 21 percent per year. It is currently a nascent market trying to incorporate traditional herbal ingredients (most often ayurvedic) into the nutraceutical portfolio. Still, its growth has surpassed global rates in recent years, mostly driven by functional food and beverages categories.

### Science of Nutraceuticals

Nutraceuticals is a broad umbrella term that is used to describe any product derived from food sources with extra health benefits in addition to the basic nutritional value found in foods. They can be considered non-specific biological therapies used to promote general well-being, control symptoms and prevent malignant processes.

The term “nutraceutical” combines two words – “nutrient” (a nourishing food component) and “pharmaceutical” (a medical drug). The name was coined in 1989 by Stephen DeFelice, founder and chairman of the Foundation for Innovation in Medicine, an American organization located in Cranford, New Jersey.

The philosophy behind nutraceuticals is to focus on prevention, according to the saying by a Greek physician Hippocrates (known as the father of medicine) who said “let food be your medicine”. Their role in human nutrition is one of the most important areas of investigation, with wide-ranging implications for consumers, health-care providers, regulators, food producers and distributors.

### Categories of Nutraceuticals

The definition of nutraceuticals and related products generally depends on the source. They can be classified on the basis of their natural sources, pharmaco-

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DOI : 10.5530/bems.3.2.9

#### Article Available online

<http://www.bemsreports.org>

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Cite this article : Rao KS. Safety Assessment of Nutraceuticals. BEMS Reports, 2017;3(2):70-2

logical conditions, as well as chemical constitution of the products. Most often they are grouped in the following categories: dietary supplements, functional food, medicinal food, pharmaceuticals.

A dietary supplement represents a product that contains nutrients derived from food products, and is often concentrated in liquid, capsule, powder or pill form. Although dietary supplements are regulated by the FDA as foods, their regulation differs from drugs and other foods.

According to their generally accepted definition, functional food is a category which includes whole foods and fortified, enriched or enhanced dietary components that may reduce the risk of chronic disease and provide a health-benefit beyond the traditional nutrients it contains.

Medical food is formulated to be consumed or administered internally, under the supervision of a qualified physician. Its intended use is a specific dietary management of a disease or condition for which distinctive nutritional requirements are established by the medical evaluation (on the basis of recognized scientific principle).

Pharmaceuticals are medically valuable components produced from modified agricultural crops or animals. The term is a combining of the words “farm” and “pharmaceuticals”. Proponents of this concept are convinced that using crops (and possibly even animals) as pharmaceutical factories is much more cost effective than conventional methods, with higher revenue for agricultural producers.

### Potential Health Benefits

Over the years nutraceuticals have attracted considerable interest due to their potential nutritional, safety and therapeutic effects. They could have a role in a plethora of biological processes, including antioxidant defences, cell proliferation, gene expression, and safeguarding of mitochondrial integrity.

Therefore nutraceuticals may be used to improve health, prevent chronic diseases, postpone the aging process (and in turn increase life expectancy), or just support functions and integrity of the body. They are considered to be healthy sources for prevention of life threatening diseases such as diabetes, renal and gastrointestinal disorders, as well as different infections.

A wide range of nutraceuticals have been shown to impose crucial roles in immune status and susceptibility to certain disease states. They also exhibit diseases modifying indications related to oxidative stress including allergy, Alzheimer’s disease, cardiovascular diseases, cancer, eye conditions, Parkinson’s diseases and obesity.

### Regulation of Nutraceuticals

Nutraceuticals are natural, bioactive chemical compounds that have health-promoting, disease-preventing or general medicinal properties. This category encompasses vitamins, minerals, herbal supplements, and certain animal products. In addition, nutraceuticals also include “functional foods” – i.e. foods that tout a specific health benefit based on their ingredients.

Regulation presents noteworthy challenge to the globalization of nutraceuticals, with murky and somewhat dissimilar definition of these products in different countries. For example, in Japan, functional foods are defined according to their use of natural ingredients. On the other hand, functional foods in the US can contain ingredients that are products of biotechnology.

In general, the goals of nutraceutical regulation have been focused on safety and labeling with a lesser emphasis (as compared to pharmaceuticals) on product claims and intended use. This is accomplished through Good Manufacturing Practice (GMP) regulations and a recent increase in enforcement.

Consumers are largely responsible for determining the usefulness and value offered by nutraceuticals. Still, increased regulation related to quality and safety of these products will benefit the industry on the whole and help mitigate the risk of regulatory backlash.

### Regulatory Rules in Different Countries

#### USA:

In the USA, the FDA regulates dietary supplements under a different set of regulations than those covering “conventional” foods and drug products (prescription and over the counter). As per the Dietary Supplement Health and Education Act of 1994 (DSHEA), the dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed.

The United States represents a somewhat unique situation where no product

notification is required unless the product contains an New Dietary Ingredient (NDI).

The FDA is empowered to take action against any unsafe dietary supplement product after it reaches the market. Generally, manufacturers do not need to register their products with the FDA nor get FDA approval before producing or selling dietary supplements. Manufacturers must make sure that product label information is truthful and not misleading. FDA is authorized to take action against any unsafe product after it reaches the market. Manufacturers have to make sure that the information on the product label is truthful and not misleading, but they are not obliged to register their products with the FDA nor get FDA approval before producing or selling nutraceuticals.

The EU is an example of a region that utilizes the notification approach. In the European Union, food legislation is largely under the umbrella of European Food and Safety Authority (EFSA). This legislation focuses on “food supplements”, which are defined as concentrated sources of nutrients (e.g. proteins, minerals and vitamins) and other substances with a beneficial nutritional effect. The main EU legislation related to food supplements is Directive 2002/46/EC.

New products from Europe are presumed to have passed stringent European development and quality requirements. As a result, European nutraceutical companies, which are generally considered leaders in innovation, enjoy a perception of producing the highest quality products. In Canada and Australia, nutraceuticals are regulated more closely as a drug than food category.

#### Regulatory Requirements in India

Food Safety and Standard Authority of India (FSSAI) was passed by the parliament in 2006. This Act consists of 12 chapters and chapter IV article 22 of the Act addresses nutraceutical, functional food, dietary supplements and need to regulate these products such that anyone can manufacture, sell or

distribute or import these products. These products include novel foods, genetically modified article of food, irradiated food, organic food, and food for special dietary uses, functional food, Nutraceuticals and health supplements.

The Food Safety and Standard Rules, 2011 have been issued, effective from 5th May, 2011. The Food Safety and Standard Authority has also issued regulations. there is no clarity as to the permitted structure function claims for nutraceuticals and dietary supplements. Under the new rule each state will have a food safety commissioner who would be the implementing agency.

Product evaluation: In order to perform product assessment as per Indian regulatory definition, it is of utmost importance to examine each

active ingredient and additive in the context of permissibility, standards and dosage of vitamins / minerals allowed as per the Therapeutic, Prophylactic or Recommended Daily Allowance for Indians.

**Licenses:** To get a product registered in India, number of licenses (almost 4 - 5) might be required, depending on the actual product status.

**Health & label claims:** Developing health and label claims, specific to Indian regulatory guidelines, is a major element to be considered while entering the Indian market.

**Health Claims:** "Health claims" means any representation that states, suggests or implies that a relationship exists between a food or a constituent of that food and health and include the:

**Nutrition claims** which describes the physiological role of the nutrient in growth, development and normal functions of the body. Ex: Food A is rich in calcium and calcium is good for bone health. Other functional claims concerning specific beneficial effect of the consumption of food or its constituents, in the context of the total diet on normal function or biological activities of the body and such claims relate to a positive contribution to health or to the improvement of function or to modifying or preserving health, or disease. Ex: Food A is low GI food. Low GI food helps in sugar management. Health claims can further be grouped into nutrient function claims, other function claims and reduction of disease risk claims.

**What toxicology Tests are Required for Regulatory Approval**

There is no single thumb rule. However, testing needs depends upon how novel the product and the ingredient(s) are. Based on various considerations of the product content, one has to decide on the extent of testing. However, as a general rule, typically, a 4-week to 13-week study

along with mutagenicity (Ames and CHO) should be sufficient. If the product is intended for women of child bearing age and for extended long term use, a teratology and reproduction studies may be required.

Advinus is a pioneer in nutraceutical testing. We have conducted a number nutraceutical testing for global clients who have submitted our data/reports to US FDA who have accepted them without any reservation. In addition, Advinus is the only lab in India which has been successfully inspected by US FDA for GLP.

## Global Market Entry Requirements

For the majority of countries, nutraceuticals are regulated as a category of food. In some regions or countries, there is an explicit set of regulations for supplements (e.g. United States, European Union, and Association of South East Asian Nations) and nutraceuticals (India), which stem from a food-based regulatory paradigm. Therefore some form of a registration or notification-based system is needed to bring new products to market.

In Latin America, the market entry requirements for nutraceuticals vary, with registration-based approaches employed in Colombia, Brazil, and Argentina, and notification-based approaches in Mexico and Chile. In countries such as Brazil, China and Taiwan, the regulators require animal and/or human clinical studies as a requirement of the product registration requirement.

Bringing nutraceutical products to market usually follows three basic approaches. The notification-based approach ideally balances pre-market resources, consumer access, and consumer safety. Nevertheless, a key aspect to guarantee product safety and quality in the marketplace (regardless of the pre-market requirements) is robust post-market surveillance.

**Cite this article :** Rao KS. Safety Assessment of Nutraceuticals. BEMS Reports, 2017;3(2):70-2