Dietary supplements, a global need for regulations and quality control requirements

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Abstract:

There is an increasing number of products imported to our community as foods containing concentrated sources of nutrients to supplement food needs, however, in many countries such products have, up to now, been not regulated by their national institutions of control, So far a few regulations and guidelines were established to facilitate the consumer choices through improved labeling requirements and efficient monitoring of food supplements on the market.

In many cases, the product content is not standardized, therapeutic goals are vague, and evidence of efficacy and safety is absent or ambiguous. Although, from the historical background, a few guidelines and directives in this regard were presented, however, they are still under debate.

A different definitions used worldwide that confusing between drugs and food, resulted in different categories, which have been classified with overlapping properties and goals.

A strong harmonized legislations and rules starting from the manufacturer and ended by the consumers needs are mandatory to be implemented.

In this review, the actual situation of the regulation of these products worldwide is presented, the different important issues of ensuring safety and efficiency are also focused.

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The proposal of taking in considerations, the health claims, labeling, risk assessment as well as the quality control requirements of food supplements in order to improve consumers uses were highlighted.

Abbreviations used in this review

FDCA	The Food, Drug, and Cosmetic Act.
DSHEA	Dietary Supplement Health and Education Act.
OTC	Over the counter drugs
EU	European Union
FDA	Food and Drug Administration
FDCA	conventional food adulteration standard
CCNFSDU	Codex Committee on Nutrition and Foods for Special Dietary Uses.
US	United states
NLEA	Nutrition Labelling and Education Act
RDI	Recommended Daily Intake
DRV	Daily Reference Value

1. Introduction:

Most of our food stuffs have to be complemented with certain additives to support their value and improve health, however, no single food can supply all the nutrients in the amounts needed.

consequently its has to be supplemented by certain additives and constituents to be termed as food or dietary supplements. Supplements are used when the intake of food is insufficient to meet vitamins and minerals requirements or when the consumers considered that their diet required supplementation.

The complementary relation between food and drugs required a lot of information about the main tasks of adding these supplements to our diet. Dietary supplements have shown that they can improve medication safety by identifying and preventing adverse drug events and they could play a similar role in preventing adverse events due to dietary supplement use if they had

sound, evidence-based professional resources (1).

The balance of that foods are functional in that they have some health benefits and drugs that have clearly defined and approved health benefits is essential for implementing harmonized regulation.

1.1 Regulations background:

Traditionally, the addition of certain additives to food came back since long time in different world regions, even though, these were up to the early of the twenties have not been well established under regulatory bodies.

The major trend of legislation addressing the dietary supplements is the Food, Drug, and Cosmetic Act FDCA in the United States of America at 1938 (2), in 1976 addition of section number 411 to the FDCA which termed as the Proxmire Amendment , In June 1992, the health freedom act was renamed as the Dietary Supplement Health and Education Act (DSHEA) (3) which creates the category of functional food, combination of dietary supplement and OTC drugs products. The Dietary Supplement Health and Education Act (DSHEA) provided US companies with the freedom to research, develop and innovate a wide array of nutritional products, many of which have conferred substantial benefits on the population, The Food and Drug Administration (FDA) also has the responsibility for showing that a dietary supplement is unsafe before it can take action to restrict the product's use or can take steps to restrict or stop the sale of potentially harmful dietary supplements within their jurisdictions (4). In Europe, there has been a much more varied legislative climate with regard to food (dietary) supplements, with a small number of countries such as the United kingdom and the Netherlands regarding food supplements as a category of food, while the majority have only been prepared to accept low doses of limited nutrients (including synthetic forms of vitamins and inorganic minerals) as foods. Higher dosage nutrients in the majority of European countries are regarded as medicines. The stated intent of the European Food Supplements Directive 2002/46/EC (5) as an effort to harmonize between the new 25 EU Member States under Article 95 of the European Treaty for the internal EU market (6) of food supplements, health foods, and herbal medicines which has varied from country to country, with some countries taking a liberal approach and others adopting a more restrictive stance, this directive, passed in to European law in 2002 and came into effect in August 2005 and resulted in ban up to 75% of vitamin and mineral forms presently on the UK and Dutch markets.

The European Union is taking steps to harmonize the regulation of nutritional supplements, health foods, and herbal medicines. At present, most legislation affecting these products is at the Member State level. This legislation varies, with some Member States taking a more restrictive approach than others. The new and proposed EU regulations will have a significant impact on the marketing of such products across the European Union.

In the global context, the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) has been attempting to develop international

guidelines for vitamins and minerals since 1991. In November 2004, these guidelines were finalised (7).

In the UK prior to the adoption of this directive there was neither a definition of the term 'food supplements' nor any specific legislation on food supplements.

Internationally and according to WHO objectives of dietary supplement, the guidelines are important to ensure that consumers receive beneficial health effects from vitamins and minerals. The Codex which is an international food standards-setting body established by the UN Food and Agriculture Organization (FAO) and the World Health Organization adopted global guidelines for vitamin and mineral food supplements as one of its first decisions.

1.2 Definitions of a Dietary Supplement:

Traditionally, dietary supplements referred to products made of one or more of the essential nutrients, such as vitamins, minerals, and protein, however, according to the DSHEA, the definition was broaden to include products intended for ingestion as a supplement to the diet. Such as vitamins; minerals; herbs, botanicals, and other plant-derived substances; amino acids concentrates, metabolites and extracts of these substances.

In the European Union, the agreed definition as the Directive 2002/46/EC defines that the term food supplements, contains a list of vitamin and mineral sources that may be used in the manufacture of food supplements, and will be set to be contain the minimum and maximum levels for vitamins and minerals.

1.3 The Dietary Supplement Industry, Economics and Sales

The vast quantity of food supplement production is coming from the European Union, in which the European market for nutritional supplements totalled approximately $14.5 billion in 2001 (8), Germany is the largest market, accounting for more than one third of the European market. France is the second largest market, followed by the United Kingdom and Italy (9). The channels of distribution vary by country, with the majority of sales in the U.K. market occurring in grocery stores and pharmacy chains, while independent pharmacies dominate the markets in France, Germany and Italy ongoing reforms of restrictions on pharmacy ownership in the EU Member States continue to transform (10).

Health sector reform due to tight Member State health budgets has also had an impact on sales in several European countries.

These figures can devoted our concern to the hug production and market flow of these products worldwide and a lot of our attention should be taken to ensure manufacturing of safer and efficient food supplement products.

1.4 Dietary supplements, conventional food, drugs and other new categories:

From different point of view, it will not be easy to differentiate between theses products. Globally, certain drugs are become food supplement due to the implementation of new regulations in certain countries, however certain foods are classified as traditional drugs, so there is a pointer parameter that could marginally circle out the common goal of using these diverse names which I would named it as the **claim**, on other word, for what each product is made? and when we use it? and how much quantity we could take from it? . There are safety and claims provisions relating to dietary supplement, which are not applied to other food categories (11).

Drugs are defined as products used for certain diseases and to cure certain health conditions, these were subjected to restricted regulations and passed with clinical and stability trials. Among other categories are the Functional foods which are essentially conventional foods added to them a functional ingredients for health claims. Currently, sports supplements enjoy enormous popularity within the broader sports nutrition market**.** Some new products claimed to focus on boosting energy [and recovery], increasing muscle mass, or improving muscle restoration (12).

Both dietary supplements and functional foods compose the sports nutrition market.

Nutraceuticals includes dietary supplements and foods with therapeutic value, this is a new term refer to be used for products to maintain health or to treat health related conditions.

1.4.1. Classification of products according to their claims.

1.4.1.1 -Conventional foods with no claims.

This would include bread and frozen food.

1.4.1.2 A food or dietary supplement with a nutrient content claims

A nutrient content claim characterises the amount of a nutrient or dietary ingredient in the product such as low calorie more fibre or high potency extract.

1.4.1.3 A dietary supplement or conventional food with structure \function claims.

These are products with ingredients that have effect on the organs or system of the body without claims about disease (13).

1.4.1.4 A food for special dietary claims.

These are a conventional foods that can be consumed by people with certain diseases, such products are free of certain contents which are aggravate certain illness.

1.4.1.5 Medical foods.

These are foods permitted to make the claim for maintaining the patient with specified conditions such in burns and cancer however, it considered not as a food supplement.

1.4.1.6 Nutraceutical product.

Is a product isolated or purified from foods that is generally sold in medicinal form not usually associated with food. A nutraceutical is demonstrated to have physiological benefit or provide protection against chronic disease (14). Another definition for nutraceutical is "a food, dietary supplement, or medical food that has a medical or health benefit, including the prevention and treatment of disease (15,16).

1.4.1.7 Functional food.

Is a product similar in appearance to be a conventional food, and is demonstrated to have physiological benefits and reduce the risk of chronic disease beyond its nutritional functions (17).

1.4.1.8 food and dietary supplement with health claims.

Dietary supplement and conventional food can carry health claims, such as the connection of fibre and the prevention of the colon cancer or certain vegetables providing protection a against various forms of cancer (18). Health claims are claims that "describe a relationship between a food, food component, or dietary supplement ingredient, and reducing risk of a disease or health-related condition. By law; manufacturers may make three types of claims for their dietary supplement products: health claims, structure/function claims, and nutrient content claims. Some of these claims describe: the link between a food substance and disease (19) or a health-related condition; the intended benefits of using the product; or the amount of a nutrient or dietary substance in a product. Different requirements generally apply to each type of claim **(**20) the requirement of the American Nutrition Labelling and Education Act of 1990 (NLEA) created a health claim approval system for the FDA including the availability of separate procedures for dietary supplement health claims(21). There will be other products rather than the previously mentioned however, these classification can facilitate the set-up of new regulation taking in consideration correct claims that can be officially labelled for secure use of safer products (22).

1.5. Dietary Supplement Labelling:

The regulation requirements of the American Nutrition Labelling and Education Act of 1990 (NLEA) and DSHEA are similar for providing foods, including dietary supplements, to bear nutritional labelling (23). The label of a dietary supplement must list the name of each ingredient and the quantity of such ingredient. Secondly, the label must bear the term "dietary supplement." if the dietary supplement is "covered by the specifications of an official compendium," it must meet these specifications if the dietary supplement represents that it conforms to such specifications. If the dietary supplement is not covered by an official compendium, it must contain the identity and strength that it is represented to have, and it must contain the quality, purity, and composed of the specifications that it is represented, specifically, ingredients present in a dietary supplement in a significant amount and for which there is a recommendation for daily consumption (a recommended daily intake (RDI) or daily reference value (DRV)) must be listed first on the nutrition label (24).

The DSHEA then required all other dietary ingredients present to be listed in the nutrition label even if they had no RDI or DRV. The proposal of EU directive proposed legislation labels on, for example, bottles of vitamin pills will have to include clear instructions for daily dosage, a warning about possible health risk in case of excess use (25) and a statement that the pills should not be used as a substitute for a varied diet. Claims that the product can prevent, treat or cure illness are prohibited. Any language suggesting that a varied diet does not provide the necessary amounts of essential nutrients is equally prohibited. Fraudulent products often can be identified by the types of claims made in their labeling, advertising and promotional literature.

1.6. Dietary Supplement Safety Standards:

There is a strong suggestion that safety has become the ultimate driver of regulation in this sector, yet there has been very little consideration of the costs, economic and otherwise of regulation.

The safety concern is very important and therefore it toke serious measures in implementing safety guidelines that are likely to be adopted either on a voluntary or compulsory basis in many countries around the world. Under the DSHEA , the dietary supplement is deemed adulterated if it "presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.

The dietary supplement is deemed adulterated if it "pose[s] an imminent hazard to public health or safety and the dietary supplement is deemed adulterated if it meets a conventional food adulteration standard in the FDCA

“under the conditions of use recommended or suggested in the labelling of such dietary supplement (26).

The European Commission responded to the need to guarantee a high level of food safety and recognized the importance of nutrition in any food policy, accordingly. The European Union established the European Food Safety Authority (EFSA), which is charged with the responsibility of providing independent scientific advice on all matters with a direct or indirect impact on food safety. The EFSA covers issues ranging from plant health (27), animal health and welfare, scientific issues related to nutrition. The FDA has not passed general regulations concerning such safety standards. Generally, the FDA must gather data on its own (28) through voluntary adverse event reporting from industry and then issue warning letters to manufactures (29).

The FDA has issued many such letters as well as taken other actions since passage of the DSHEA (30).

In an effort to increase harmonization of the internal market and protect consumer health, the EU is in the process of drafting new legislation harmonizing rules for fortification of food. Currently, the addition of nutrients to foods, with the exception of infant formula and certain other foods for particular nutritional uses is regulated at the Member State level.

The new directive will not impact laws already on the books in certain Member States with regard to mandatory fortification of some basic foods. Many of these Member State regulations were founded upon regional characteristics or have cultural considerations that may not be applicable across the EU Member States. The new legislation would affect items such as breakfast cereals, and almost all foods that are fortified with vitamins and minerals. In an effort to provide the consumer with increased information on such foods, the new directive would require substantial nutrition labelling of fortified foods. Additionally, the labelling and marketing of such products must not imply that a balanced and varied diet cannot provide adequate quantities of nutrients. Labelling restrictions on health claims would be subject to the rules included in the recently proposed health claims directive discussed above. Similar to the Food Supplements Directive, the Fortification Directive will include a positive list of allowable vitamins and minerals and allowable sources. Upper limits will also be established, and such limits are expected to be more restrictive than upper limits associated with food supplements. This is because taking a supplement is a conscious decision, while consumers of fortified foods may not be consciously aware or able to calculate their nutrient intake. The directive is also expected to include a list of "prohibited substances" that cannot be added to foods, a list of allowable ingredients that are currently undergoing review by the EFSA due to concerns about public

health, and a "restricted list" which, for example, could establish limits of addition of certain substances to dietary supplements.

1.7. GMP requirements for dietary Supplement production:

Poor manufacturing practices are not unique to dietary supplements, but the growing market for supplements in a less restrictive regulatory environment creates the potential for supplements to be prone to quality-control problems.

The good manufacturing practice GMP are a system, process, and controls used in the manufacture of the consumer products, particularly to ensure the quality of the finished product (31). The applied GMP procedures have been raised a major concern due to the safety requirement with particularly dietary ingredient such as ephedra (32) as well as the consumer fraud issues (e g, Low potency products and contaminants), the variability of raw material sources in herbal products with additional health related claims (33) increasingly being made for the dietary supplement, therefore consumer are relay on the product quality to achieve promised health related benefits.

Such regulations may cover preparation, packaging and handling of dietary supplements and may include expiration date labeling beside the personnel, equipment, production and process controls, holding and distributing, consumer Good Manufacturing Practice (GMP) complaints, and record keeping (34), However, the current good manufacturing practice regulations dietary supplement may not impose standards for which there is no current and generally available analytical methodology.

The expiration date is essential statement of how long a product will maintain its potency over a given period of time at rescannable conditions, for vitamins and minerals the expiration dates can be determined and labelled however, for herbal ingredients, when testing for identity and potency, its is often difficult to pinpoint the biologically significant constituent that indicates the ingredient activity (35). Although FDA has had the authority to establish dietary supplement GMPs for almost a decade, it issued its first proposed rule on the topic in 2003, to establish good manufacturing practices for supplements. The current industry GMP's as well as the proposed food and drug administration GMP's address quality only from a chemical standpoint (36) not a biological standpoint (i.e. absorption, dissolution, bioavailability. Beside there are rules and guidelines that strictly imposed on the dietary supplement industry there are lack of governmental regulations (i.e. no requirement for companies to follow Good Manufacturing Practices) coupled with poor quality control of the manufacturing process leads to a situation in which the amount of active ingredient in the package may be significantly different from the amount specified on the label. A canadian study showed that no North American

product analyzed contained the recommended minimal amount of 0.2% parthenolide believed to be required for its effectiveness (37). Another study of ginseng products found with tremendous variability, with as little as 12% and as much as 32% of the active ingredient in the bottle, compared to the information labeled (38).

A previous study of 54 ginseng products showed that 60% of those analyzed products had very little ginseng, with no ginseng at all in 25% (39).

A screened study in which 500 Asian patent medicines were screened for the presence of heavy metals in which 134 drugs found that 10% were contaminated (40).

Adulteration of imported Chinese dietary supplements sold in Japan is responsible for 622 cases of illness, 148 hospitalizations, and 3 deaths (41).

1.8. Dietary supplements risk assessment:

This issue considering the assessment of risks for individual items, which needs a scientific board and researcher for approved of the reasons of certain dangerous events or adverse effects, and also gathered data from different sources regarding the toxicity or major illness that could resulted from the food supplement use or its interaction with prescribed medications (42).

The restriction of the Daily Minimum and Maximum Amounts was set in EU regulation according to certain circumstances of expecting other risks of exceeding these limits.

The CODEX guidelines attempt to establish upper limits on the dosage of food supplements. while the upper limit on vitamins appears to be established to protect consumers from potential side effects from over-dosage, the very establishment of maximum dosage would likely be misunderstood by the public. Food supplement companies would be required to list the maximum dosage permitted on their labels and would be compelled to limit the actual recommended dosage of vitamins and minerals. Printing upper limits on food supplement labels would likely scare many consumers away from these products. Consumers may falsely believe the maximum level is the toxic level and consume much smaller amounts, fearing serious side effects. But the upper limit would have a built-in safety factor many times below any toxicity. The dietary supplement manufacturers required to perform reliable analytical methods to verify ingredient identity and measure the amounts of declared ingredients" in dietary supplements (43).

1.9. Dietary Supplement Advertising and Marketing Regulation:

As with any consumer product, advertising plays an important role for dietary supplements. Not only do retail outlets engage in advertising for dietary supplements, but so too do dietary supplement manufactures through the use of medical journals, television, radio, magazines, retail trade publications, and public relations campaigns. (44).

Dietary supplement makers must be able to support claims about what their products can do and adequately substantiate those claims implied in advertising, according to guidelines for substantiation as rigorous but flexible. "The amount and type of support needed will depend on consumers' expectations, based on the specific claim being made, how it is presented in the context of the entire ad, and how it is qualified (45).

The guidelines cover the adequacy of an ad's substantiation (what it is claiming), consumer testimonials, expert endorsements, and advertising claims based on historical or traditional use of supplements. The dietary supplement advertising should be truthful and not misleading and have adequate substantiation for all claims (46). The regulations of advertising has to be harmonize to powerful enforcement of advertising claims according to the claims regulated and approved.

The major selling of the food supplement products are carried out through the use of internet sites, therefore companies should take special efforts to protect the privacy of consumers visiting their web sites. The regulatory bodies should further pushed up towards more safer internet shopping of these products.

2.The required steps for importing dietary supplements into the Libyan market:

Due to the huge expansion of the dietary supplement market, the health regulatory authorities in developed country therefore have to imposed firm rules to control the entry of these products in order to decrease the choices of the entrance of low standard products due adulteration.

The importer companies has to provide official documentary and technical files of products which should include approved official certificate of GMPs applying in the raw material, and last product together with analysis certificate for at least the specified ingredients. Its recommended to import theses products from country have strong regulatory authority such as USA, EU and Canada. Using the different sources of communication, the regulated authority can confirmed the official documents presented in the import points before give a release of products, the confirmation can include the labels fact sheet, the health claims and the expiration date when appropriate.

The authority should confirmed the presence of the active ingredient if appropriate and stated in the certificate of analysis of the producer beside the carrying out quality control tests for the freedom from microbial and other source of contamination specially for herbal products.

The national companies wish to manufacturing these products should subjected to strong internal regulations and by apply the recent international requirements of GMPs and which could be inspected for the raw materials sources, packaging and storage.

3. Conclusion:

There are different food supplements ingredient with different categories, the classification of these categories are based on different criteria, this have been led to find different regulation and imposed guidelines in order to control the quality and improve the safety of the food supplements. The classification based on the claim can be taken in concern to build up a frame of regulations including labeling, safety and risk assessment.

The current regulatory framework governing dietary supplements does not provide consumers or health care providers with sufficient information on safety and efficacy to make informed decisions. Furthermore, standards for product quality are currently inadequate. However, the concerns raised by the dietary supplement industry regarding regulating dietary supplements as non-prescription drugs because of the industry's inability to patent product ingredients. To develop a regulatory scheme to ensure that dietary supplements are safe and effective. Although there are new regulation and guidelines, there are a wide gap between these regulations to be harmonized and finalized in international regulation which could be implemented to facilitate the controlling of the dietary supplement products.

Due to the expand of these products marketing its considered as second profited sources after pharmaceuticals, fraud and adulteration of these product can be so high, therefore in the absence of authorities firm grip, low quality and fraud products can be easily brought to the consumer house, specially when using the electronic marketing.

In safety concern, the suggested recommended upper and lower limits of daily dose been set by certain regulation establishments are still under dough, they sometimes lead to false assumption that could emanate from the establishment of upper limits is that food supplements are safe when taken in dosages below the maximum limit. Actually, minerals such as iron, taken in doses under the proposed maximum limits, could pose long-term problems for unsuspecting consumers.

The pharmacists and other health care practitioners should integrate awareness of dietary supplement use into everyday practice and encouraged to increase efforts to prevent interactions between dietary supplements and drugs and support the education of pharmacists and other health care practitioners in the taxonomy, formulation, pharmacology, and pharmacokinetics of dietary supplements and believes that such education should be required in college of pharmacy curricula.

The pharmacists, as medication-use experts and accessible members of the health care team, are uniquely qualified and positioned to counsel patients using or considering the use of dietary supplements.

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