Clinical Research and Regulatory Affairs

ISSN: 1060-1333 (Print) 1532-2521 (Online) Journal homepage: informahealthcare.com/journals/icrr20

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**To cite this article:** John W. Finley (2016) The nutraceutical revolution: Emerging vision or broken dream? Understanding scientific and regulatory concerns, Clinical Research and Regulatory Affairs, 33:1, 1-3, DOI: 10.3109/10601333.2016.1117096

**To link to this article:** https://doi.org/10.3109/10601333.2016.1117096

CLINICAL RESEARCH AND REGULATORY AFFAIRS, 2016
VOL. 33, NO. 1, 1–3
http://dx.doi.org/10.3109/10601333.2016.1117096

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EDITORIAL

# The nutraceutical revolution: Emerging vision or broken dream? Understanding scientific and regulatory concerns

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**ABSTRACT**

'Nutraceuticals' are a category of substances without a legal definition, often sold as dietary supplements or components of conventional foods. Nutraceuticals are considered to impart health benefits beyond ordinary nutrition; many nutraceuticals do improve health, but for others evidence is often equivocal or based on animal and/or *in vitro* data. Moreover, evidence that a component of a substance in a food has a beneficial effect often does not translate into benefits of a substance that has been isolated and consumed in greater quantities. Increasing regulatory requirements from multiple government agencies complicate the design, testing, and marketing of these substances. Dietary advice also is contradictory to much of the marketing of nutraceuticals as it emphasizes using whole foods and ensuring that the overall diet is adequate, rather than focusing on individual components. How the nutraceutical industry responds to these changing conditions will determine the health and growth of the industry over the coming decade(s).

**ARTICLE HISTORY**
Received 3 September 2015
Revised 6 October 2015
Accepted 3 November 2015
Published online
28 December 2015

**KEYWORDS**
Nutraceutical; food industry; regulations; nutrition; dietary supplement; health

Nutraceuticals, defined as 'substances with health benefits beyond ordinary nutrition' (1), gained much attention in the early 1990s, spurred in part by the landmark 1994 Dietary Supplement Health and Education Act (DSHEA) (the regulatory framework for foods, nutraceuticals, and supplements has been reviewed, see (2)), which seemed to promise less restrictive access to many natural substances with purported health benefits. This interest also pushed nutraceuticals into the mainstream food supply, and a 1995 article in Trends in Food Science and Technology stated the 'nutraceutical revolution is in full swing and will dramatically change the nature of the food industry by the year 2000' (1). However, now, more than 20 years later, while the industry is still here, it continues to fight for a share in the mainstream and is facing challenges that threaten growth and long-term viability. Continued survival and growth may well depend on how the industry responds to a lack of definition, an increasing and confusing web of regulations, questions of product efficacy, and changes in dietary guidance.

From within, the nutraceutical industry may see itself as reasonably well-defined, however from outside it is vague. The definition of 'nutraceutical' is self-made with no corresponding legal definition. Moreover, the term is used in different contexts with different nuances, often synonymously or in conjunction with 'bioactive', 'functional foods', or 'dietary supplements' (the only legally-defined term). For example, a vitamin manufacturer states that vitamin/mineral fortified breakfast cereals are nutraceuticals (3), an ingredient supplier promotes as nutraceuticals natural substances isolated from plants such as polyphenols and beta glucan (4), whereas the Academy of Nutrition and Dietetics (AND) makes no mention of nutraceuticals, but does comment on functional foods stating 'all foods are functional . . . because there's no legal definition . . . American consumers are left to evaluate a food's health claims on their own' (5). Myriad health messages and claims around nutraceuticals, from maintaining mental sharpness, to promoting bone health, to implying reduction of cancer risk, serve to further compound the confusion regarding the identity and purpose of nutraceuticals.

A growing web of regulations builds barriers and fosters confusion to the manufacturer and consumer alike. A primary confusion is the FDA food/drug distinction, which states that no drug may enter the food market. By definition, 'food' means 'used for food or drink . . . (or) components of any such article', whereas 'drugs' 'diagnosis, cure, mitigate, treat, or prevent disease' (2). This creates a fine line for developing products and marketing claims for substances intended to impact health. Potential confusion is exemplified in FDA guidance regarding whether an Investigational

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New Drug application (IND) is needed for a substance used in a clinical trial (6). Although being reviewed, the guidance implies the need for an IND before conducting a clinical trial with an isolated compound where the outcome could be linked to a disease state. For example it states that a study of the effect of guarana on maximal oxygen uptake does not need an IND, whereas studies of the effect of a dietary supplement on osteoporosis, docosahexaenoic acid in formula on visual acuity of infants, and the ability of a food to block carbohydrate absorption in the gut all would require an IND.

There also is confusion regarding the regulation of advertising by the FDA and the Federal Trade Commission (FTC). Since 1954, the agencies have utilized a Memorandum of Understanding to divide regulatory responsibility, with the FDA regulating labeling and the FTC regulating other forms of advertising. The FTC has stated that it 'has traditionally accorded great weight to FDA's scientific determinations in matters of nutrition and health' and that is unlikely they will pursue legal action 'regarding nutrient content and health claims if they comply with FDA's regulations' (7). Although FTC does give substantial weight to FDA rulings, this division of enforcement also greatly increases regulatory oversight, and products not addressed by FDA have been harshly dealt with by the FTC. For example, FTC has the ability to seize assets and use avalanche clauses to impose even hundreds of millions in fines if injunctions are not adhered to. FTC also has shown the willingness and ability to impose its own guidelines, such as a ruling against POM-Wonderful™ that required claims be supported by two clinical trials (7). FTC is sensitive to drug claims and goes beyond the wording on the label and looks at other factors, even art on the package, to determine whether a drug claim is implied. It is instructive to read case studies of FTC actions to determine its thinking behind enforcement actions.

Evidence needed to support claims of efficacy is debated within the nutraceutical community and many structure/function claims are based on *in vitro* and animal studies. However, Ioannidis (8) has eloquently argued that it is impossible to predict the efficacy of a treatment in humans from studies done in animals, even when many studies show the same result. He gives the example of 525 published animal studies that described 16 efficacious interventions for stroke, but, in human trials, only one of those 16 was effective. He further gives statistical analyses that show that, among underpowered, loosely controlled RCTs, only 17% have outcomes that hold up to further testing (9). Even well conducted, well powered RCTs can yield spurious results; consider the example of selenium and prostate cancer where numerous animal studies and small human studies, and one well powered RCT ($n > 3500$) showed up to a 70% decrease in prostate cancer with selenium supplementation. However, a much larger study of over 35 000 subjects found no benefit of supplementation, but did find potential harm (for a summary see Finley et al. (2)). Many nutraceutical substances show benefits in animal and cell culture models and limited human studies. The pharmaceutical industry has a well-defined pathway for taking substances that show initial signs of efficacy all the way to demonstrated benefits in well designed and powered clinical trials. While the pharmaceutical model may not be practical for food-based substances, the nutraceutical industry does need to develop its own guidelines so that substances with a demonstrated ability to improve health readily stand out from those with only initial indications of efficacy.

An associated issue is whether isolated nutraceuticals have the same efficacy as a compound naturally present in a whole food. Clinical trials with beta-carotene/lung cancer are illustrative—because fruits and vegetables high in beta carotene appeared to be protective against cancer, it was theorized that beta carotene was the active ingredient and doses of isolated beta carotene would be efficacious against lung cancer in smokers. However, beta carotene administered to over 50 000 smokers resulted in an increased risk of lung cancer (10). These studies not only question the extrapolation of evidence from compounds in whole plants to isolated compounds, but also show the potential danger of recommending a substance without knowing its effects in specific populations (e.g. in smokers). The above comments are also apropos and the industry should be able to delineate compounds that show robust benefits as consumed from those that have been demonstrated to benefit only select groups under select conditions, or from compounds where efficacy has been suggested within a food matrix, but not as an isolated compound.

Finally, the nutraceutical industry faces the challenge of the changing guidance from the nutrition community regarding nutrients, foods, and diets. In recent years the nutrition community has moved away from recommendations for individual nutrients and components and placed more emphasis on whole diets. The AND position on dietary supplements is 'Most people don't need supplements. Eating a wide variety of nutrient-rich foods is the best way for most people to obtain the nutrients they need to be healthy and reduce their risk of chronic disease' (11). The Dietary Guidelines for Americans states:

> A basic premise . . . is that nutrient needs should be met primarily through consuming foods. In certain cases, fortified foods and dietary supplements may be useful in

providing one or more nutrients that otherwise might be consumed in less than recommended amounts (12).

Thus, the guidance of both influential groups restricts the use of supplemental ingredients/substances to isolated cases where specific nutrient needs are inadequate. There are only a very few nutrients in the American diet that meet such criteria, and there are no established nutritional requirements for other specific phytochemicals. It will be up to the nutraceutical industry to develop strong arguments for why particular substances need to be added to foods or consumed as supplements. The worldwide epidemic of obesity and diabetes may provide the argument for this.

In conclusion, 20 years ago many thought we were on the verge of a food and health revolution, but in many ways, the predicted health benefits and 'dramatic change to the food industry' have failed to materialize. Although many nutraceutical compounds do truly benefit health, the message for those substances often is lost in the background of other problems facing the industry. The lack of precise definitions regarding what nutraceuticals are and their functions has left many consumers confused and even fearful regarding the purpose of the industry. Too often claims around the newest nutraceutical have implied major health benefits, only to have further evidence diminish claims or even suggest harm (13); each instance erodes public confidence in 'expert' opinion and advice. Regulatory pressure is unlikely to decrease, and negative rulings by the FDA or FTC often make the popular press and are generalized as faults of the industry as a whole. Further, even when the benefits of food-derived substances are supported by sound science, the benefit of the same isolated ingredient often is equivocal, and current dietary advice urges whole foods over isolated substances. So where will the nutraceutical industry be in another 20 years? Will it be relegated to another food fad that had a brief flash but then died? Or will it have found a niche based on proven benefits of trusted products? Success will likely require introspection, hard choices and much more rigorous self-regulation by the industry.

## Declaration of interest

J. Finley is an employee of the US Department of Agriculture. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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