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Dietary Supplement Usage: Better Science Equals Better Outcomes

Richard J. Bloomer, PhD[1*], Charles R. Yates, PharmD, PhD[2]

[1]*University of Memphis, Center for Nutraceutical and Dietary Supplement Research, Memphis, TN, USA*

[2]*University of Tennessee Health Science Center, College of Pharmacy, Memphis, TN, USA*

**Corresponding author: Richard J. Bloomer, School of Health Studies, 106 Roane Fieldhouse, The University of Memphis, Memphis, TN 38152, Tel: 901-678-5638; Fax: 901-678-3591; Email: rbloomer@memphis.edu*

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Abstract

The use of dietary supplements is widespread in most industrialized countries. While current Good Manufacturing Practices (cGMPs) are now adhered to by most companies, this does not guarantee that all products being sold are both safe and effective. Many finished products and ingredients have little to no human clinical safety or efficacy data to support their use. Moreover, some products that do have science to support individual ingredient inclusion often contain said ingredients at a very low dosage—decreasing the likelihood that the product will deliver results as claimed. Companies have the responsibility to produce products that can match label claims for both ingredients used and claimed health benefits. Consumers have the responsibility to ask the right questions when considering product purchase and use. This article discusses the role of science as pertaining to dietary supplement formulation and use by consumers.

Keywords: Nutraceuticals; Dietary Supplements; Research; Regulation; cGMP

Introduction

Dietary supplements are big business in the United States and China, with other markets such as Japan, India, and the EU accounting for market share [1]. According to a 2015 report from the *Nutrition Business Journal*, consumer sales of dietary supplements are estimated at approximately $37 billion annually. While this number is up from past years, expectations for continued and rapid growth are not consistently positive [2-4], partly due to the States' and Federal Attorneys General crack down on rogue dietary supplement companies who refuse to comply with manufacturing, ingredient use, labeling, and marketing guidelines. A primary concern is the fact that many companies formulate products using ingredients which are largely uncharacterized, have not been evaluated for safety or efficacy in human subjects, and often have little to no scientific basis for use.

A large number of adults in the United States, Asia, and the EU report using dietary supplements, with variance across genders and region [5-10]. Savvy consumers and health care providers seeking to determine the validity of supplement manufacturers' label claims are increasingly relying upon freely accessible online medical literature provided by a plethora of consumer groups representing the dietary supplement, health, and nutrition industries. Alarmingly, consumers' online research often uncovers negative reports describing adulterated and misbranded products found in highly reputable retail establishments, most of which have not been evaluated by the Food and Drug Administration (FDA). Consequently, bewildered consumers and healthcare providers are left with uncertainty related to what they should expect from supplement manufacturers and retailers.

So, what are some reasonable consumer expectations regarding dietary supplements? First, the ingredients chosen for use in product formulation and the associated health-related claims, e.g., intended benefits of using the product, should be substantiated with the appropriate level of scientific evidence including, as appropriate, outcome data from human clinical trials. Second, the chosen ingredients should be included at a dosage that will provide a meaningful physiological effect. Third, the finished product should be manufactured under strict conditions adhering to so-called current Good Manufac-

turing Practices (cGMPs). Fourth, and related to the cGMPs, the nutrient content claims found on the label should be analytically validated. Lastly, labels should contain contact information for consumers who elect to provide suspected supplement-related adverse events (such as the Safety Reporting Portal in the US). The obvious question is, "How do we ensure that these 'Great Expectations' are met considering there are literally thousands of dietary supplement companies?"

Regulatory Oversight

Numerous agencies exist world-wide to protect consumers from unfair, deceptive, and fraudulent business practices. Examples of regulatory bodies include the US FDA, the Federal Trade Commission's Bureau of Consumer Protection, the China FDA, the Food Safety and Standards Authority of India, and the European Food Safety Authority. Each of these agencies is actively involved in the oversight of dietary supplements as a consequence of escalating consumer interest in these products, as well as the expanding field of dietary supplement companies.

The Dietary Supplement Health and Education Act (DSHEA) of 1994 delineates certain regulations regarding the manufacture and sale of dietary supplements [11]. Moreover, the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006 [12] specifically requires the reporting of adverse events as a means for the FDA to inform consumers of incidents related to a supplement's usage.

Under the aforementioned and in adherence with cGMPs, dietary supplement manufacturers are tasked with meeting requirements for strict ingredient testing (both upon facility entry and following finished product production), validation of label claims, and ensuring that the ingredients used in product formulation are approved for use and are safe for human consumption. In many cases, the companies should be commissioning clinical studies designed to determine the efficacy of the products tested, in an attempt to support the claims that are being made.

Increased consumer education and demand surrounding the use of validated and efficacious ingredients will continue to drive growth in this area, with more companies looking to perform pre-clinical and clinical studies to support their products. While Contract Research Organizations have historically been the outlet of choice for such work [13], more companies are now choosing to work with scientists in university-sponsored research facilities specifically designed to study nutraceuticals and dietary supplements. See www.memphis.edu/nutraceutical for one example of such a facility. These scientists not only have the specific expertise to work with the ingredients or products of sale, but also have the mission of publishing the research in an attempt to enhance the scientific literature in the field of dietary ingredients and supplements.

Current Problems

While many high quality dietary supplements are being manufactured and used by consumers, others are of poor quality, with little to no scientific basis for formulation and/or claims. Moreover, some products are potentially unsafe for human consumption and/or may contain substances banned by the World Anti-Doping Agency (WADA). Having collectively spent close to 40 years in research, formulation, and consultation in the field of dietary supplements, we see many potential problems that need to be addressed. Those of greatest importance in our opinion are as follows:

1. Many companies use ingredients/nutrients in marketed products that lack evidence to support their safe, let alone effective, use by human subjects. Review of medical literature databases, e.g., PubMed, often reveals that there is little to no evidence, either *in vitro* or *in vivo* (human or animal), to support ingredient efficacy claims. Yet, bold claims are often made touting the purported benefits of use. Companies making these unsubstantiated claims are essentially doing little more than guessing as to a product's salutary effects.

2. Even when ingredients have been evaluated using the appropriate scientific rigor and do appear to have evidence supporting their efficacy, they are very often used at such low dosages that there is no reason to suspect that they would elicit the intended pharmacologic effect. Case in point: many studies involving coenzyme Q10 involve daily dosages of 200-300mg, yet some products currently sold on the market contain only 50 mg, or less, of this agent. The question that companies and consumers should ask is, "What potential benefit can be expected from such sub-therapeutic dosing?"

3. Many products are being manufactured without strictly following cGMPs and this can lead to finished products that in no way match the product label. Moreover, because some products have been claimed to contain counterfeit ingredients, there may be some cases when consumers really have little idea what they are consuming and whether the product would prove ineffective and/or potentially dangerous.

Company Checklist

To address some of the most basic concerns, companies that develop and sell dietary supplements should aim to do the following, which can serve as a simple checklist in formulating, developing, and marketing products that are scientifically sound.

1. Make certain that the primary ingredients used in product formulations have been investigated in animals and/or humans. This will provide evidence as to how the ingredient is absorbed and tolerated, what dose and dosage form is appropriate for use, what benefits can be expected, and what if any

adverse effects are noted. While animal data can sometimes prove useful, the ideal situation would involve the ingredient(s) of interest being evaluated in human subjects using an oral delivery route.

2. If the ingredients to use have been decided upon, attempts should be made to match the dosage used in the published literature. Formulation cost is often a concern at this stage of product development, as many novel ingredients can be expensive and companies may not be able to afford the inclusion of the optimal dose of each ingredient within the finished product. In addition, capsule or tablet size becomes a problem when it comes to the use of gram quantities of ingredients. Practical decisions need to be made concerning what can be included and how this might change the marketing and promotion of the finished product.

3. Beyond individual ingredient testing, testing of the actual finished product of sale would be helpful, as this would provide information as to how individuals may respond to use of the product.

4. Once the exact formulation is decided on, making certain that the contract manufacturer is in full compliance with cGMPs should be of utmost importance. This will ensure that the products produced will meet all requirements for identity, purity, quality, and composition to support nutrient label claims.

5. Once the product is developed, further considerations can be made, such as applying for verification through the United States Pharmacopeia (USP) or Informed-Choice. The latter is of particular importance for companies who market products to competitive athletes, as the service of Informed-Choice involves a manufacturing audit, including the evaluation of products for a variety of WADA banned substances.

Consumer Checklist

Unless a consumer is a dietary supplement researcher by profession, selecting high quality products off the store shelf or an internet website can be challenging. The following list of questions might help to navigate through this area and make the best, educated decision. Some follow-up questions addressed to a qualified healthcare provider and/or answered through independent online searching may be needed.

1. Was the ingredient shown to be effective and safe when used by human subjects?

2. What is the included dosage of each ingredient in the product and how does it compare to the dosage used in the clinical studies?

3. How was the ingredient administered in the studies (e.g., oral, intravenous, etc.) and is the recommended route of administration the same as for the product of sale?

4. If individual ingredients have been shown to be effective, have any studies been performed to test the finished product's efficacy?

5. Have the results been published in a peer-reviewed journal or is the company simply relying on aggressive marketing campaigns and testimonials?

6. Are there any known or possible side effects or potential interactions with prescription medications associated with use of this product? If the user is a competitive athlete, will the product put them at risk for testing positive for banned substances?

Conclusions

With the growth of scientifically formulated products and a renewed consumer trust in the industry, there is reason to believe that dietary supplement usage will escalate, with sales potentially approaching $40 billion annually in the coming years [14]. Many ingredients and finished products have demonstrated efficacy, with human clinical data often available to support the claims being made. However, many others have little to no evidence to support their consumption, nor would they be expected to have such evidence based on the relevant biochemistry associated with their use. Consumer demand, as well as government regulation, for scientifically validated products is growing. Dietary supplement companies need to recognize this and be at the forefront of both product development and product testing within a controlled research environment. Doing so should help not only with increased sales and growth of the company, but most importantly the continued marketing and use of safe and effective dietary supplements for consumer use.

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Conflict of Interest

Both authors have received research funding from and acted as a consultant to nutraceutical/dietary supplement companies. Both authors read and approved the final manuscript.

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