

December 31 2004

To: Vickey Lutwak
Office of Nutritional Products, Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition
Food and Drug Administration

Commentary on:

“Guidance for Industry: Substantiation for Dietary Supplement Claims made under Section 403 R (6) of the Federal Food, Drug and Cosmetic Act – Draft Guidance”

I applaud the FDA's recent efforts to bring forth a clear cut understanding regarding many issues that the nutrition industry and the public face when communicating about dietary supplements. The FDA has been doing a splendid job in soliciting comments regarding New Dietary Ingredient definitions (see Nov. 15, 2004 meeting) and with respect to “Substantiation”.

In terms of a workable framework for dietary supplements, one must first acknowledge that the Dietary Supplement Health Education Act of 1994 makes a clear distinction between dietary supplements and prescription or Over-the-Counter monographed medications.

It is my contention that a system can be formatted to increase Federal and consumer confidence regarding the safety of dietary supplements. Further, the groundwork for this was initiated in 1994 (DSHEA 1994). Among the issues facing the industry is the defining and determination of what constitutes substantiation for safety and efficacy claims.

The dietary supplement industry does not maintain some of the privileges that the pharmaceutical industry has as related to patent protections and tax credits along with governmental assistance for research and development. It is certainly true that dietary supplement companies can apply for patents (methods of use, utility) but the “fingerprint” for exclusiveness is not on the same level as the pharmaceutical industry.

It is also true that companies can apply for certain types of grants (small business, department of education, SBIR, etc.) and these grant/developmental programs may offset some of the research and development costs associated with conducting preclinical and clinical studies. However, it appears that successful funding is only achieved by less than 25% of applicants. We also have to acknowledge that without the proper Internal Revenue Service (IRS) tax breaks or credits, the costs of R&D may be too cumbersome for small start-ups or many nutrition companies (further exploration of IRS Code 174 is warranted). There is no excuse not to have any safety data, but if R&D tax credit is

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applied to the nutrition industry and the FDA and the IRS would work together to educate on the opportunities for the industry, a spark of greater research may occur.

With the above said, what follows is a non-comprehensive framework that may be used to develop a reasonable program for the nutrition industry with the sole purpose of increasing confidence and support for a cooperative relationship between the FDA and industry.

Safety

Before one can discuss what the proper studies or data sets are for determination of safety, a definition of what constitutes safety is in order. The term safety may be interpreted by some as "doing no harm". In other words, the product causes no ill effects in the acute exposure or in longer-term exposures.

Safety may be defined as the lack of any observed adverse events/effects (in animal and human studies) or it also may be defined as the lack of any noticeable changes in liver function, renal function, glucose, electrolytes, hemoglobin, hematocrit, platelets and the white blood cell differential (coupled with clinical notation of changes in blood pressure, heart rate, electrocardiograms and other related itemized testing). Further, we may combine the data from animal safety (mutagenicity/carcinogenicity) and toxicology studies with that of a properly powered human trial to denote that a product is safe for the intended audience.

The FDA may want to consider the following in recommendations to the Industry for guidelines on obtaining safety data:

1) Prior published "third-party" literature whereas human or animal exposure and documentation of observed adverse effects/events is noted (or lack thereof). This data may be used to build a case that a single ingredient or multi-ingredient formulas are safe when used as intended and in the type of population being studied. This dataset may be considered one form of safety documentation. In-house animal studies (often contracted out with a university or a private contract lab) may also offer safety data sets much like that used in "GRAS" applications or in New Dietary Ingredient (NDI) applications.

One issue that arises when considering third-party literature, is that of products that are currently on the market versus those that have not made into a finished product on the market as of yet. The exact of definition of what constitutes a need for a NDI is not clear and outside the scope of this communication. Obviously if a NDI is approved by the FDA, the ingredient should be viewed as safe. The pre-defined denotation of safety of products currently on the market that is legally being sold (DSHEA 1994) may be outside the scope of this communication.

2) Animal studies – the proper type to determine mutagenicity, carcinogenicity, upper and lower limits of "no observed adverse effects/events levels" (NOAEL's) as well as the

effects on metabolism for acute and longer-term exposure (24 hour and 90 day) are surely appropriate.

The following FDA Guidance documents may be helpful in determining safety and what safe doses for human exposure to a dietary supplement is

- a) Guidance for Industry & Reviewers: Estimating the Safe Starting Dose in Clinical Trials for Therapeutics and Adult Healthy Volunteers (Draft Guidance, Dec. 2002)
- b) Guidance for Industry – Developing Medical Imaging Drug & Biological Products: Part 1 – Conducting Safety Assessments (June 2004)

It is estimated that about two or three animal studies can be undertaken in order to obtain the data needed to generate a human safe (expected) dose for a dietary supplement. However, the fact that many dietary supplements are multi-ingredient products may compound the issue regarding the number of animal studies needed for determining various exposure risks and levels of safety.

Once the animal data is evaluated, one can use the December 2002 FDA Draft Guidance report on estimating safe dosage to determine the dosage for a human safety study. Thus, animal studies plus at least one human study may be suggested for this framework to denote substantiation of safety. The difference of safe use for the intended population versus not unsafe for human consumption (at predetermined dosage levels) is outside the scope of this communication.

3) Human Studies – In terms of substantiation the claim of safety, a properly designed study that is adequately powered to find a difference in clinical and meaningful markers of safety (given that the right assessment system is used for determining relationship of both objective and subjective adverse events) may be sufficient when coupled with prior data (animal and/or prior published literature) to denote safety of use in the intended population. Some bearing of responsibility for “safe-use” also needs to be placed on the consumer. If a consumer does not follow label directions, uses a product when there is a clear contraindication or otherwise, a dietary supplement should not be held responsible for any adverse events that may occur to that individual (given that the label is written properly as related to instructions for use and who should not use the product).

A dietary supplement company may want to do a proper open-label safety study of proper design (specific to the intended use and population for that dietary supplement) to either complement any prior animal or third party literature that they may have or as a preceding data set to a randomized double blind placebo controlled clinical trial (RDBCT). If conducting a RDBCT, it would need to be adequately powered and designed appropriately for the intended use of that dietary supplement and the results demonstrate that those receiving product had markers of safety (the proper blood tests, vitals, etc.) that were no different than those receiving placebo, the determination should be -- within the confines tested and parameters measured that the product is not unsafe. The interpretation of “safe” may be made on the human studies (pilot study, RDBCT

– meaning that if 2 studies do not support the intended claim and one study does, than the claim does not have support (if all studies were of equal quality and design). Therefore a definition is needed of how many positive studies in comparison to negative or equivocal studies would be needed to support a claim if there is prior science on the ingredient, combination of ingredients or finished supplement product to support a claim (“what constitutes a preponderance of the evidence“?).

Some may argue that determination of safety is more important than determination of efficacy. If a product is safe for the intended population and with its intended use, than perhaps the lack of any efficacy is not that important (as long as misleading claims are not being made).

In closing, the system of defining and determining just what constitutes substantiation is not a simple one. Smaller issues such as protection of intellectual property (patents, inventions, etc.) along with the appropriate tax credits may be worthwhile to explore in order to properly stimulate the nutrition industry to undertake the studies that will be required for safety and efficacy.

I would be happy to work with the FDA on any advisory committee in developing the final guidelines for determining what level of science is needed for substantiation.

Respectfully Submitted by,

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