

13 August 1999

TO: Dockets Management Branch (HFA – 305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

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RE: **[Docket No. 99N-1174]**  
(Comments: CFSAN Strategy for Dietary Supplement Regulation)

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I submit these comments as both a clinician and an educator with expertise in both nutrition and drug therapy. I also submit these comments as an individual without a vested interest in the marketability of dietary supplements, but find myself a significant stakeholder in the regulation of dietary supplements (DS) nonetheless.

#### General Comments

As a strong patient/consumer advocate responsible for training healthcare professionals in clinical nutrition and pharmacy practice, I feel it necessary to express a number of general comments regarding regulation of DS. Regulations should be in place in order to protect patients/consumers, and not to simplify access to the marketplace for the DS industry. Trying to defend the current regulatory environment, given FDA's limited authority under DSHEA, and the subsequent impact on the marketplace is tantamount to choosing profits over people – how this benefits my patients is unclear to me. The patient/consumer is bombarded by fierce marketing full of hyperbole not matched by the data, and products whose quality is not required to meet any minimum standard based in science – all this with the manufacturers staying within the lax framework designed under DSHEA. Patients/consumers assume a level of truth in advertising and a level of safety and quality in marketed products, and for this reason alone consumer safety should be paramount in defining strategies for DS regulation. Access to safe DS with truthful, non-misleading labeling should be the ultimate goal. This means that the identity, safety, quality and purity of DS should be established before products appear on the shelves, allowing compliant manufacturers to state this in their labeling. This would provide both consumer and healthcare provider the confidence desperately needed. The claim by industry proponents that DS are basically safe is a cavalier supposition that needs to be borne out by facts.

Subsequent comments address the 7 questions posed by the FDA (FR 64(92):25889-25890, 13 May 1999 )

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Question 1.

In addition to ensuring consumer access to safe DS that are truthfully and not misleadingly labeled, are there other objectives that an overall DS strategy should include?

Other objectives would merely support the ultimate goal already stated in the question. Ensure the safety, quality, and purity of dietary supplements and the materials used to manufacture them. Product safety and quality relate both to acute issues such as adverse events/reactions and chronic issues such as good manufacturing practices (GMPs). Make it easier for pharmacists and consumers to report adverse events. A credible system for reporting, evaluating, and disseminating data on adverse events with DS is needed. Endorse the use of standards for DS as available in the 24<sup>th</sup> revision of the USP/NF. I would be much more confident in my recommendations for, and evaluation of, the therapy my patients receive if the products are held to some higher and independent standard.

Question 2.

Are the criteria for prioritizing the tasks within the supplement strategy appropriate? Which specific tasks should FDA undertake first?

Enhancing consumer safety comes first. Safety and quality is more important than substantiation of claims for now. Consumers use labeled claims for self-selecting products, but assume safety and quality. Pharmacists and consumers should be able to make appropriate evidence-based, informed decisions when they recommend or choose to use dietary supplements. The safety and quality, as well as the efficacy, of DS are in question, and consumers look to pharmacists for some validation. Pharmacists in turn still do not have enough data. Confidence of the consumer and pharmacist is critical, and may wane as they discover how relaxed the regulations are.

Consider contracting to have consumer surveys taken by an independent group (e.g. Good Housekeeping Institute) to learn which specific products/classes consumers feel are safe, why they take specific products/classes, what their dosing behaviors are, and what their source of information on DS is. Can the consumer even differentiate between structure/function and health claims, and are we wasting our time on the semantics of definitions instead of identifying poor quality or unsafe products. Answers can provide direction in task prioritization.

### Question 3.

What factors should FDA consider in determining how best to implement a task (i.e. use of regulations, guidance, etc.)?

Base implementation of tasks on the likelihood that manufacturers will participate in protecting patients/consumers. Creation of an advisory committee with working groups or formal panels should be strongly considered. The advisory committee (e.g. DS Advisory Committee) should be different from the Food Advisory Committee, and include adequate representation of practitioners and academicians with expertise in nutrition science, nutritional epidemiology, pharmacotherapy, pharmacognosy and pharmaceuticals. The committee or panels could also contain a member representing industry trade organizations, keeping in mind that the committee purpose should not be to please the industry, but to protect the consumer. This advisory committee may need to evaluate products by class (e.g. recognized nutrients, botanicals, and other substances). Panels could review GMPs, adverse events associated with DS, and even review claims using grading of evidence. USP panels are already in place to review some of this information. Independent organizations (e.g. International Life Sciences Institute) or NIH could facilitate performance of safety, or even efficacy, studies.

### Question 4.

What tasks should be included under the various DS program elements in the CFSAN 1999 Program Priorities document?

Use DS Advisory Committee panels to address boundary issues, claims, GMPs, and adverse event reporting.

Boundary Issues – Consider what will happen when traditional over-the-counter medicines become hybrid products with DS, how will those be regulated? We already see traditional food products that include DS and making structure/function claims, which should remain regulated as foods. The boundaries are blurring, and need to be laid down forcefully, with guidance if not regulations. Boundaries between groups of DS also need to be laid down. DS containing ingredients (recognized nutrients) found in the typical diet could make up one class, botanicals could make up another, and the remaining substances with a smaller evidence-based foundation could be a third class. Those products containing multiple ingredients would fall under the latter. At the very least, differentiate recognized nutrients from botanical medicines. Given the history of compendium standards and uses in managing disorders, botanicals need to be considered as over-the-counter medicine for distribution where a healthcare professional is available. Furthermore, despite the statutory and regulatory framework, nutrients exhibit behavior similar to other substances delivered in a pharmaceutical dosage form (i.e. drugs).

Claims – Evaluate labeling to prevent the misleading use of terms (e.g. standardized, quality-tested, etc.) that the consumer associates with regulated quality products. When examining the claims (esp. health claims), some DS need to meet more than just the significant scientific agreement standard. Some require consensus (although not unanimous agreement) by an independent panel, similar to the over-the-counter review panels, and preliminary evidence (subject to change) should not be used because of the likely consumer confusion. Provide specific criteria as to the meaning of significant scientific agreement, so that consumers, clinicians, government agencies, and industry are on the same page. For data supporting efficacy claims, a mechanism to give exclusivity to manufacturers willing to sponsor such research should be established.

GMPs – Ideally, appropriate GMPs, set by the FDA and not the industry, should be based on those of other pharmaceutical dosage forms not those for food or food additives. Even if they are modeled after food GMPs, the burden of safety should be placed on the industry. I have as much concern with contamination and ingredient purity, as with sanitary and wholesome conditions. Even contamination of a product within one facility from a previous product, which used the same equipment on the production line, has the potential to cause adverse effects. All raw materials should be tested prior to reaching the production line, and all completed batches should be tested for purity, and pharmaceutical quality. Differentiate ingredients by status as generally recognized as safe (GRAS) versus new entities. Require USP standards to be met, including those for microbial contamination. The incentive for manufacturers that meet USP standards is that they will lead the marketplace.

Adverse Events – There is no adverse event rate for classes of DS because of underreporting and no denominator figures. Perhaps industry could be responsible for providing denominator data, as well as adverse event reporting. The industry can be helpful through postmarketing surveillance requiring them to report adverse events associated with any of their DS products. Right now there is no formal evaluation of existing reports (e.g. CFSAN-AEMS data) by an independent committee. Adverse events monitoring could include periodic panel review of reports, and their strength of association/causation. Besides the AEMS, and MedWatch data, the NIH IBIDS database can be used. Public disclosure in summary format of the adverse event reports considered possible/probable should take place (e.g. via CDC). While maintaining confidentiality of the consumer affected, other information including the event, product, manufacturer, lot number, etc. should be made available. Keep in mind that the inherent active ingredient(s) may not always be the culprit, but that the product quality of a manufacturer may be to blame. The manufacturer should be notified of all such reports. Reputable firms would prefer to be rid of the outliers in their midst. There is a need to look at models for the safety of DS dosing (e.g. risk assessment models as used by the Institute of Medicine-Food and Nutrition Board in developing upper tolerable limits, the levels unlikely to pose adverse effects).

Question 5.

Are there current safety, labeling, or other marketplace issues that FDA should address quickly through enforcement actions to ensure, for example, that consumers have confidence that the products on the market are safe, truthful, and not misleadingly labeled?

Work with the FTC to review misleading claims in advertising. Clear, comprehensive, evidence-based labeling is needed with periodic product testing for quality. There is currently no external accountability for safety and quality provided for in the regulations.

New dietary supplement ingredient 75-day notices should include proof of safety, rather than an expectation of safety if used within labeling parameters, as part of the notification. While allowing manufacturers to make claims skirting the edge of drug claims or even fraudulent claims may be problematic for the FDA, my concern is with proof of safety – and that burden should be borne by the manufacturers. While now exempted by congress, a new chemical entity by any other name is still a new drug. Remove any products known to have caused harm from the market. Also remove those ingredients/products not classified as either recognized nutrients or botanicals or otherwise GRAS, which lack evidence of safety, off the market. An example of a drug entity marketed in the guise of a supplement to the diet has been GBL. If called upon to prove safety, the product could not remain on the market.

Contraindications to the use of a product should be clearly stated on the product label as they are with over-the-counter products. Data is scarce on interactions between DS and foods, drugs, and other supplements? For nutrient ingredients, use the most current nutrient standards (e.g. dietary reference intakes - DRIs) in the labeling, which take into account no/lowest observed adverse effect level (N/LOAEL) when available. Use these DRIs for determining %DV, and use µg (not mcg) or mg rather than the now outdated IUs on the Supplement Facts labels.

Question 6.

Toward what type or area of research on DS should FDA allocate its research resources?

The industry is making significant profits, perhaps they could proportionally be assessed a user fee to fund independent research possibly through ILSI or NIH. Research is needed especially for ingredients for which little peer-reviewed data is available. This would include ingredients not GRAS, or not recognized as nutrients or botanicals. Time does not need to be spent on developing standards for nutrients or botanicals, as many are becoming available (e.g. 24<sup>th</sup> revision of the USP/NF).

Question 7.

Given FDA's limited resources, what mechanisms are available, or should be developed, to leverage FDA's resources to meet effectively the objective of the strategy?

Consider working with USP to publish monographs in the CFR for DS, particularly those not classified as recognized nutrients. These ingredients would likely be the focus of much of the limited resources available, but this would be best spent in protecting the consumer from products with a less known track record in terms of safety and product quality.

Poor quality products and disreputable firms will eventually fall out of the marketplace, but will patients/consumers be harmed in the meantime? Hopefully, the FDA's goal of ensuring consumer access to safe dietary supplements that are truthfully and not misleadingly labeled will be realized. I thank the agency for the opportunity provided to all stakeholders to comment on this issue.

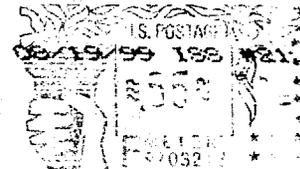
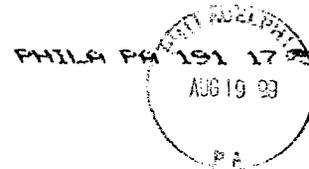


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