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a DuPont affiliated company

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The following commentary is in response to the ANPR for *'GMP in Manufacturing, Packing or Holding Dietary Supplements'* published February 6, 1997 [62 FR 5700]. DCV Biologics, L.P. (DCVB) agrees with the Agency's initiative to insure the quality and safety of the manufacturing of Dietary Supplements. While the majority of companies operating in this industry do so under high ethical and manufacturing standards, some may not, and accordingly regulations might have to be established to assure a consistent standard of quality and manufacturing.

However, the definition of a Dietary Supplement under DSHEA allows for one of the most diverse classes of products. While the 'Industry's Submission' proposes to provide guidelines for the manufacturing & labeling that are for the most part outlined under the Food GMP (part 110), the Agency's queries suggest an intent to impart many Drug GMP (part 211) and other drug-like regulations on the industry. It is our belief that uniformly applying either, or a combination, approach fails to recognize the heterogenous nature of the within this industry. It is our recommendation that the products must first be categorized into one of four categories (possibly additional) in order to identify the proper manner in which to guide their manufacturing. The use of rigid regulations versus published guidelines must also be considered. Some categories are already governed by various regulations within the CFR and should not require additional oversight.

For example, to expect a food or spice with GRAS designations that may also have utility as a Dietary Supplement to be regulated in the same manner as a non-GRAS tropical botanical is inappropriate. Their manufacturing, process control, and packaging are distinct. It would

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seem that before the FDA establishes uniform regulations, one should establish whether it might not be more appropriate to classify these sets of diverse products to be regulated.

Our proposed four categories (others may be appropriate), present standards for establishing safety, and their current regulatory status are as follows:

Category	*Establishment of Safety*	*Manufacturing*	*Quality Control*
Food, Flavorings, Spices or Extracts (GRAS)	1. Listing on GRAS 2. History of use 3. Expert Panel Review	Many under 110 CFR	Many require monitoring and/or inspection by FDA and/or USDA with defined standards and COA's
Botanicals (non-GRAS listed)	1. Self Evaluation based upon History of Use (DSHEA)	Presently None	Presently None
Botanical Extracts (non-GRAS listed)	1. Self Evaluation based upon History of Use (DSHEA)	Presently None	Presently None
Synthetic Compounds (ex. DHEA, Melatonin)	1. Self Evaluation based upon History of Use of natural equivalent	Presently None	Presently None

Therefore depending upon the category, the answers to the Agency's questions may differ with respect to labeling storage and cGMP requirements.

1) Is there a need to develop appropriate defect action levels (DAL's) for dietary ingredients?

The present DAL's are for the most part established with commodity types of products that utilize large numbers on large volumes (batches) to establish a DAL (typically thousands of assays, many batches, etc.). In the agency's example, not only may the intended dose may be significantly different, the dosage form, form of any active ingredients, etc. may also be different. **There is not a practical or rational way to implement DAL's for the supplement industry at this time.** One will have to rely upon adequate Quality Control programs to assure appropriate control of the manufacturing process.

2) *FDA requests comments on appropriate testing requirements to provide positive identification of dietary ingredients, particularly plant materials, used in dietary supplements.*

DCVB products are not botanicals, however, there may be a need to standardize proper taxonomic identification of raw botanical ingredients. Perhaps this should be handled in a similar fashion to any other COA, perhaps a COTI (Certificate of Taxonomic Identification). **The COTI would be issued by an appropriately trained representative of the supplier of the raw ingredient.**

3) *FDA requests comments on standards that should be met in certifying that a dietary ingredient supplement is not contaminated with filth; free of harmful contaminants, pesticide residues or other impurities; that it is microbiologically safe; and it meets specified quality and identity standards.*

Obviously the nature of this question can not be uniformly applied to all dietary supplements. For *Food, Spices or Extracts*: the reference to pesticide residues is applied to these ingredients as food or food additives, further expansion or restrictions would not seem to be required. For botanicals, the diversity of the plant material and its geographic origin poses the problem of what pesticides (or even herbicides, fungicides, etc.) do you test for? In addition, pesticides in the U.S. must undergo a regulatory process that includes possible maximal pesticide residues. Therefore, a differentiation of U.S. approved pesticides (or even herbicides, fungicides, etc.) must be considered. Perhaps a listing of all known pesticides used on any product used as raw material, and the corresponding recommendations and instructions regarding residues should be included with the COA or COTI for the botanical. **The Industry Submission and the part 110 of the 21 CFR seem to already address the most of the issues of filth and microbiological safety**. The potential diversity of pesticides that might be used would seem to present a major hurdle for standardized testing and would require considerable study.

4) *The agency asks for comments on whether there is a need for cGMP to include requirements for manufacturers to establish procedures to document that the procedures prescribed for the manufacture of dietary supplement are followed on a continuing or day-to-day basis.*

While there is no formal requirement for a Quality Control Unit of any Company to implement a Quality Assurance program. it is certainly a procedure that is adapted by most manufactures to insure compliance, not only with the regulations of the CFR but there own SOPs. This same question of monitoring compliance could also be raised regarding the present cGMP for food under the part 110. Unless the FDA has data to substantiate the inference that the Dietary Supplement manufacturers have an unusually high incidence of non-compliance we believe that **the guidelines specified under DSHEA are adequate and do not require additional regulation**.

5) *The agency asks for comments on whether dietary supplement cGMP should require that reports of injuries or illness to a firm be evaluated by competent medical authorities to determine whether follow-up action is necessary to protect the public health.*

Allergens and 'potential pharmacologically active substances' as stipulated within the embodiment of query are ubiquitous and are not limited to Dietary Supplements. Defining what is an 'allergen', under what circumstances (formulation, dose, delivery, frequency, etc.) can atopy be elicited, and the complex genetic factors involved in mounting allergic responses have escaped definition by immunologists for decades and are beyond the scope of any regulations. DCVB is unaware of similar requirements for food or food ingredients in which the total exposure to the consumer is far greater. For workers of manufacturing facilities, there are already OSHA standards to protect the safety and health of workers, reporting of accidents, etc. It should be required that once valid scientific evidence is accumulated regarding the allergenic nature of any product or component of such product that a suitable warning be placed on all labels. Most of the dietary supplement industry already comply with this. Unless the FDA has substantive and statistically valid data (i.e. 'appropriate basis') to support the contention of this query that Dietary Supplements pose an unusual risk, we feel that **there are adequate controls already in place and requires no further regulation**.

6) FDA asks for comments on whether cGMP for dietary supplements should require that manufactures establish procedures to identify, evaluate, and respond to potential safety concerns with dietary ingredients.

We feel that this query is in direct conflict with the mandate of a legislative act, DSHEA, that clearly states that while safety must be assured, it is the responsibility of the FDA to show evidence that any product sold as a dietary supplement is not safe. The basic tenant of DSHEA is based upon a history of prior use. This standard of 'history of use' is similar to the principles of GRAS. Furthermore, many of the substances used in Dietary Supplements have been in use in various forms prior to 1958, and under the CFR might be categorized as GRAS for use in food. This standard of 'history of use' has been used and applied throughout the food industry for decades and has not jeopardized the safety or quality of the food for the consumer. In fact, it has made significant contributions in improving it. Perhaps the GRAS-like standard should be the adopted, with an appreciation that the extensive history of use of many of these products predates the settlement of the Americas! Documentation of unidentified consumer complaints may be appropriate (specifically 'life threatening'), but what are the criteria for identifying a 'true' adverse event, the number of complaints that are required before a complete investigation, the total sales or doses required, and the reporting requirements, etc. needs significant clarification by the agency. Again these are heterogeneous products that are required by DSHEA to be safe before they are marketed. The success or failure in the market are dictated by this standard and the value or benefit to the consumer dictate their continued use. **Guidelines *may be appropriate* for the industry to identify types of acceptable 'history of use' standards from outside the U.S. and what documentation may be appropriate**.

7) The agency asks for comments on whether specific controls are necessary for computer controlled or assisted operations.

The present control measures proposed by the Industry Submission or under part 110 would be adequate.

8) The agency asks for comments on whether certain, or all, of the requirements for manufacturing and handling dietary ingredients and dietary supplements may be more effectively addressed by regulation based on the principles of Hazard Analysis and Critical Control Points (HACCP).

While some of the principles of HACCP may apply to the manufacturing process, the diversity of the potential products to be manufactured in this industry dictate that the principles may not be uniformly applied. Until specific recommendations it is difficult to comment on this proposal.

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9) The agency asks for comments on whether broad cGMP regulations will be adequate, or whether it will be necessary to address the operations of particular segments of the dietary supplement industry.

As per our introduction into these commentary we believe it is absolutely necessary to categorize the various segments of the dietary supplement industry. It is only then that adequate control and safety measures can be identified for Dietary Supplements. Many of the segments within this industry are already thoroughly inspected and regulated, while others less so. The key to successful and workable regulations will be the proper classification and identification of appropriate control measures for each segment of the Dietary Supplement industry. Until specific Agency recommendations regarding HACCP and its applications to the industry are defined it is difficult to respond to this query.

Sincerely,

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