August 11, 2003

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

RE: Docket No. 96N-0417, Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Ingredients and Dietary Supplements

Banner Pharmacaps, Inc. is a leader in the development and manufacture of prescription, over the counter pharmaceuticals and nutritional supplements sold in softgel and Soflet gelcaps. Our customers range from major pharmaceutical and nutritional companies to small start-up firms.

Our company has extensive experience in the development and implementation of drug GMPs and has monitored the progress of the Agency relative to DSHEA.

The Proposed GMPs for Dietary Ingredients (DI) and Dietary Supplements (DS) was part of your overall strategy for regulating DI and DS in a manner that promotes and protects the public health.

Although we understand that when Congress enacted DSHEA it authorized the FDA to adopt GMPs that were "modeled after" food GMP regulations, we recognized that the industry suggested proposed GMPS that went beyond the food regulations and we support that approach.

In order to provide nutritional products that promote and protect the public health *appropriate* controls need to be in place throughout the entire process beginning with the DI used in formulations to the distribution of the DS to the consumer.

Analytical Procedures

Of paramount importance is the availability of validated analytical methodologies to properly characterize DI as well as assuring DS formulations contain the labeled claim active ingredient levels. Additionally the existence of such methods provide the technical support for assuring processes are in control as well as data to support expiration dating for DS.

It has been our experience that the greatest challenge facing the industry relates to a lack of uniformly accepted methodology for testing DI and finding analytical procedures

that work within the matrix of the various DS formulations. While there has been some progress made through the efforts of the USP and the CRN's Working Groups Voluntary Monograph for Fish Oils, there is much work to be done.

It is interesting to note that in Section II, General Issues, Subpart A. Legal Authority of the Proposed GMPs you state:

> "...section 402 (g) (2) of the act states that any such (GMP) regulation shall be modeled after current good manufacturing practice regulations for food *and may not impose standards for which there is no current and generally available analytical methodology".*

This is a important point to keep in mind as we move forward in developing the GMPs for DI and DS. While you do not *require* DS to be tested (as long as the firm has documented that a scientifically validated analytical is not available) you also state

> "..while there may not be an AOAC or FDA method available we are not aware of a situation where appropriate scientifically valid analytical method is not available".

We believe you have overestimated the availability of methodology.

Before implementation of these proposed GMPS it is therefore critical that you have a clear understanding of the challenges facing the industry relative to lack of uniformly accepted testing methods for DI and the significant effort needed to develop methods for many very complex matrices in DS formulations.

Written Procedures

You have stated that you are not proposing written procedures in many sections of the proposed GMPs "in order to limit the burden on manufacturers". We do not agree with that position and support the Industry Drafted GMPs submitted in 1995 that placed a heavy emphasis on the need for written procedures. Written procedures are essential to any company's ability to maintain control over all aspects of their operations.

We do support the inclusion of written procedures in all sections where a request was made for such input.

Expiration Dating

We do support the need for appearance of an expiration date on the labeling of DS. However, we do not recommend that this be a requirement for all products. We would recommend, that if a firm decides to place an expiration date on the package that they have the data to support the stated shelf-life. Our concern is based on the lack of available validated stability indicating methodologies for all formulations and the significant effort needed to develop such methods.

Animal Derived Ingredients

FDA has requested comment on whether they should include in the final rule specific requirements for manufacturing, packaging and holding animal-derived ingredients. The

agency is considering whether to require specific requirements under proposed 111.35 that are designed to prevent the use of materials derived from certain animals from BSE countries as defined by the USDA 9 CFR 94.18. Such requirements would likely include manufacturer procedures and records and supplier certifications to ensure that a component, DI or DS is free of the agent of BSE.

FDA further states that " we are not aware of DS manufacturers current procurement and handling practices of such DI..." We believe that the industry members who handle such ingredients have already implemented many of the controls referenced by the Agency. These controls have originated either from the USDA or the DI suppliers in response to demands by various governments or consumers. We feel such matters should remain with the USDA to avoid duplication of effort.

Validation

FDA commented that they have no basis to conclude that validation of instruments and controls is a standard applicable to drugs and not to foods.

We support the qualification of equipment to assure that it was installed properly and is operating as designed.

We do not support process validation because of its reliance on validated analytical methodology (see above) that may not be available.

Economic Impact on Small Entities

FDA rightly emphasizes a number of small business concerns. It should be recognized that being small or even "very small" does not relieve a company of its obligation to be competent in its operation in order to protect the public health. We do not believe inadequately controlled operations of any size should be allowed to continue for three years after the new GMPs are finalized before enforcement would occur.

SPECIFIC COMMENTS

Subpart D, Equipment & Utensils Section 111.25 (a) (2) states:

> "equipment will not result in contamination of your components, dietary ingredients, or dietary supplements with lubricants, fuel...."

The agency needs to recognize that lubricants are an integral part of the encapsulation of gelatin enrobed products as well as other dosage forms. The required lubricants are not considered potential contaminants for our products and are processing aids to assist in the movement of the gelatin ribbon through the encapsulating machines. It is therefore recommended that this section be amended to reference "lubricants not intended for product contact." to clarify the intent of this requirement.

Subpart E Production & Process Controls, 111.35 (g) (2) (i) and (ii)

> "...if your QC unit documents that a scientifically valid analytical method for testing each batch of dietary supplement is not available or any one of those specifications then you would be required to test incoming shipment lots of dietary ingredients for any such specification.."

This section goes on to say

> "..using a supplier certificate in lieu of performing testing on each shipment lot of dietary ingredient in accordance with this section is not appropriate because it is possible that a suppliers certification may not ensure identity, purity, quality, strength or composition..."

We disagree with the position that a supplier's certificate cannot be used to accept dietary ingredients even though no finished product testing is being performed. It is our position that if historical C of A results from a vendor have been shown to be the same as those generated by the firm, the supplier is considered to be "validated" and such materials may be accepted on a C of A provided an identity test is performed and periodic full testing is performed. This approach would not be applicable to microbiological testing if required.

Subpart E. Production & Process Controls 111.35 (m)

> "..if a test or examination performed on a production batch , you must record the test or examination result in the batch production record in accordance with 111.50 (c) (10) *(actual test results for any testing performed during batch production in accordance with 111.35 (m))*

We do not believe it is necessary to record all *(actual)* test results in the batch production record because a Certificate of Analysis is included in all batch records and documents the conformance to specification requirements. We believe this is sufficient information and it would be a duplication of effort to reproduce such data.

Additionally a requirement to include all test results in a batch record is overly burdomesome because master batch records would have to be revised each time a specification is changed.

Subpart E. Production & Process Controls 111.37 (b) (7) (8) & (11)

> "..would require that your QC unit must do the following:
>
> (7) review all records for calibration of instruments, apparatus, gauges and recording devices
>
> (8) review all records for equipment calibrations, inspections, and checks;

We disagree that the QC unit has to review these checks and recommend these sections be revised to allow this review to be performed by "adequately trained

personnel". ..to not allow this change would be inconsistent with Section 111.13 (b) that supervisors be made responsible for compliance.

We agree that the QC unit should perform audits of these checks and be informed if any unit fails to meet its calibration requirements.

(11) "..collect representative samples.."

We believe representative sample can be taken by individuals who are properly trained to perform this task.

Section E Production and Process Controls 111.50 (c) (10)

"...certain information must be included in the batch production record, including but not limited to, the following information;

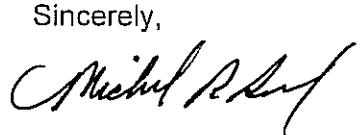
- the date and time of the maintenance, cleaning and sanitizing of equipment and processing lines used in producing the batch.."

We believe such information is better maintained in readily available logbooks. This approach allows an equipment "history of use" information which would not be available if contained in individual batch production records.

Thank you for the opportunity to submit initial comments on the issues related to the proposed cGMPs for Dietary Ingredients and Dietary Supplements.

Banner Pharmacaps, Inc. looks forward to working with FDA to facilitate timely implementation and will avail themselves of every opportunity for interaction and comment as this process moves forward. Banner Pharmacaps will be pleased to respond to any specific questions FDA may have regarding these comments.

Sincerely,



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