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August 11, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
http://www.fda.gov/dockets/ecomments

Re: Docket No. 96N-0417; Current Good Manufacturing Practice in Manufacturing, Packaging, or Holding Dietary Supplements

Dear Sir or Madame,

We have spent considerable time reviewing your proposal for the CGMP's for Dietary Supplements and are very impressed in how good a job you have done. There are however several areas of concern that we would like to call to your attention.

1. *One System for All* – In several places you request comment on whether separate systems should be created for different situations. For examples, in Sec 111.5 – (pg 12181) – You invite comment on whether there should be specific CGMP requirements for animal derived materials and in Sec 111.15 (d) (2) – (pg 12185) you request comment on water standards for foreign firms. We believe that the best quality control methods are uniform and simple. If you put too many different systems in place, it will confuse and make for less compliance rather than more. There may be some occasional requirements determined by the unique nature of certain ingredients or products, but for the most part the bulk of the system of CGMP's can and should be accommodated under a single frame work. There should not be separate systems for different situations; be it foreign or domestic, animal or plant, capsule or tablets, etc.
2. The Relationship Between the Manufacturing Department and the Quality Control Department – While the obvious intent of your proposal is to create a very strong Quality Control Department, an admirable objective; we believe that you have not struck the proper balance between the responsibilities of these two Departments. Basic quality control concepts make the Production Department responsible for manufacturing a product of appropriate quality - the concept of "**building in quality**" [see Sec 111.30 (b) – (pg 12193) – in which you make the supervisor responsible] not the Quality Control personnel who can only audit during the manufacturing process and test what Manufacturing has made.

   In a discussion in Section 111.35 (i) (4) – (pg 12199) – you say ..." would require that such a review would be conducted by an individual from the quality

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control unit. This is necessary to ensure that the review is conducted by a person who is qualified by training and experience to conduct such reviews and who understands the production and inprocess control system, understands the significance of a processing deviation, and knows how to respond to a deviation.."

We disagree with this concept. In industry, Manufacturing personnel are generally "engineering types" expert at the use of machinery and people to produce a product and Quality Control personnel are generally "chemist types" expert in testing. Quality Control personnel usually have little expertise in manufacturing and should not be expected to make decisions concerning manufacturing operations; however they should be informed of changes so they can evaluate the results of the change on the finished product, their area of expertise. While Quality Control people that have both capabilities may exist, they are exceedingly rare in the experience of the two authors both of whom have had extensive quality control experience both in the pharmaceutical and nutritional products industry. Most companies will need to use a team of people with different areas of competence to deal with this area of activity. You should change the section to allow the Quality Control Department to take a lead function, but to allow them to use other people in the organization who have expertise as you say in Sec. 111.45 (c) ("The quality control unit can be composed of individuals from various parts of the organization."). You need to make this concept clearer throughout the document.
For example, Section 111.35 (i) (4) – (pg 12199) – should read "You will be able to reprocess a rejected component, dietary ingredient, or dietary supplement if the quality control unit approves ***the results*** of such reprocessing." the ingredients and final dosage form.

3. Excess Record Keeping – We agree with your basic concept that complete records should be kept of Master Formulae and all batches, but we believe that in some cases the records you have requested are of little value. For example in Sec 111.25 (e) (7) – (pg 12192) you invite comment on whether the person performing the maintenance, cleaning, and sanitation described in this section should document these actions. We believe that some actions, like cleaning a compressing machine after completion of a batch, should be recorded as part of the batch records. Other activities covered by this section that are very general, like daily cleaning of the floor, are of little value in a permanent record.
Also in Sec 111.12 – (pg 12183) you invite comment on requiring documentation of consultants used. We disagree with this requirement. Consultants are for the benefit of the company and should not be a matter of record for the FDA. Their recommendations may or may not be used, and a company should not have to explain at a later date why such decisions were made.
The manufacturer should have some flexibility as to what is of significance in assuring product quality and what data should be recorded to assure that adequate information has been captured.

4.Excess Packaging Controls – We agree with your basic concept of good controls on the manufacturing process , but we believe that packaging operations are much less sensitive to quality problems and some of the records you have requested add little to the assurance of quality of the product and will be expensive to maintain.

In Section 111.40 (a) (1) & (2) – (pg 12202) – you treat packaging components in the same manner as ingredients, which will create considerable work for the short run part of our operation. In our experience packaging components (such as bottles, caps, cartons, and partitions) are never a source of quality problems and labels are a very infrequent source of problems. We can establish standards, check each incoming lot, retain samples, and tie incoming batches into large packaging runs. However we should have some flexibility in not tieing in lot numbers of packaging components in the short run part of the operation where we may have dozens of short run lots each day using less than a carton of packaging supplies for each run. We almost always have part boxes left after a run which are put back into stock. If a use-reconciliation were required of packaging supplies, we would have to count part cartons before and after a run which is guaranteed to cause confusion. Because there is little risk of quality problems in this activity, we propose the regulations be changed to allow the use of packaging components that have been approved by the Quality Control unit without tieing in to a specific lot identification number. We can achieve the same level of quality assurance provided by quantitative checks on packaging supplies less expensively by frequent scheduled checks during the packaging operation.

On the other hand, there are some activities that can best be done in the packaging operation. Sec. 111.60 (b) (1) (iii) (pg 12208) – "...would require your laboratory control processes to include the use of sampling plans for obtaining representative samples of : Each batch of packed and labeled dietary ingredients or supplements to ensure that the label specified in the master manufacturing record has been applied." This can better be accomplished at the point of packaging where in-process checking can examine a much larger sample than can a lab remote from the packaging operation. The general principle should be that the more checking that can be done at the point of manufacturing and packaging the better.

5. .Economic Effect of Product Testing– We are a small company in your classification with a staff of less than 100 people, so your estimated total cost for us to institute the proposed CGMP's is $61,000. We believe that you have seriously underestimated the cost; and that we will spend more than that amount for additional controls, equipment, and personnel in the Manufacturing and Quality Control Departments.

Our major additional costs will be due to the required laboratory testing. We are a contract manufacturer who makes products for other companies according to their formulae and also market a line of our own consisting of approximately 150 products. At any given time we have approximately 200 batches of different

products in various stages of our manufacturing operation and process over 2000 batches per year, which is substantially more than your estimate of 554 batches per year on pg 12239. These batches average about 15 active ingredients per formula (weighted average of multi-ingredient and single ingredient formulae), which checks with your estimate of 13 for vitamins-minerals on page 12239. We may be slightly higher than your estimate because we do a number of multiple vitamin-mineral formulations for which Daily Values for 27 nutrients have been established. With so many different formulae with a very wide range of ingredients, we try to keep our raw material inventory low and order when a raw material is needed (a modified "just-in-time" inventory practice). Because of this system, we receive about 2500 shipments per year. Assuming an average cost of $60 per assay (your estimate pg. 12240),

Raw Material Testing
2500 shipments/year x 3 assays/shipment* x $60/assay = $450,000/year
(*Assumes an average of 3 assays per shipment – Identity, potency, and one of the purity tests – your estimate pg. 12239)
This corresponds well with your estimate for the more restrictive CGMP option, but considerably more than your estimate for adjusted total cost for testing for the proposed regulations on pg. 12240. Even if we assume some use of ingredients in multiple batches and some present testing and reduce the total cost by 50%, we still have a number that is far greater than your estimate of $19, 907.

Finished Product Testing
2000 batches/year x 15 assays/batch x $110/asay = $3,300,000

Total Testing Cost $2,250,000

Thus we are faced with **testing costs which almost equal the cost of manufacturing** and would require us to almost double our selling prices.

6. An Alternative To Complete Raw Material Testing –
Section 111.40 (a) (1) & (2) – (pg 12202) – says "..you may not rely on a supplier's certification or guaranty in lieu of such testing.." , but in at least two other places in the proposed CGMP's you accept the concept of vendor certification - Sec 111.5 – (pg 12180) – The paragraph after item 3 says "Manufacturers that rely on supplier certifications to ensure that materials derived from animals are BSE-free would likely need to verify the reliability of supplier certifications by conducting supplier audits at appropriate intervals." and Sec. 111.15 (b) - (pg 12184) allows verification of safety and freedom from contamination by means of suppliers guarantee or certification. Further you acknowledge the concept of increased dependability of vendors in VII Analysis of Impacts, 6 d – (pg 12236) "Because all ingredients and holders would be subject to the same uniform minimum, variation in their practices would decline, so firm monitoring of upstream and down stream vendors could decline."

Considering the huge costs of full ingredient testing of final product and the points in the above paragraph, it seems another system is required to avoid the expense of full testing and yet achieve the same result. If every ingredient vendor were accurate and reliable in their processing and testing, there would be no need for testing of ingredients because every batch would be perfectly correct. What we need is a system to determine how good the ingredient suppliers are and to monitor them according to their dependability

Applying one of the standard quality control concepts would allow sorting of ingredient suppliers according to their dependability, perhaps into three classes

1. A Vendors – These vendors are major companies of extremely high quality levels, who have much more expertise with the product, its quality and its testing than we. For these vendors we would do minor checks (ID or organoleptic), but generally we would accept their CofA's. An example would be Vitamin C from Hoffman-la Roche
2. B Vendors - These are vendors who have good reputations in the industry and/or have been dependable vendors to our company, but are smaller than the A Vendors. Here we would do a statistical sampling of lots, testing with decreasing frequency as we got more assurances of dependable CofA's.
3. C Vendors – These are either new vendors which do not qualify for the A or B class or vendors with which we have had some problems in the past, and here we would do full testing of every batch.

Using a system such as this would substantially reduce the cost of testing, allow us to apply our resources to the areas of greatest concern, and still give a very high level of quality assurance. Of course this ABC system is only one of many other ways to achieve this result. What we need is recognition by the FDA of the costs involved in 100% testing of ingredients and final product, and acceptance of reasonable alternative approaches to achieve the objective of quality nutritional products...

7 . An Alternative To Complete Product Testing –

In a similar logic to #5 above, we need some flexibility to develop alternatives to the testing every active ingredient (those listed on the label). After we have put an enormous effort into checking raw materials and controlling manufacturing operation, we should be allowed some leeway in how we check the final product. Some statistical system of active ingredient testing would give assurance of control, but substantially reduce cost. Another example would be, if we have checked the ingredient and carefully followed the Master Formula in manufacturing then for a 1000 mg Calcium Carbonate Tablet with just a few mg. of excipients, tablet weight should be as good a control as a Calcium assay. Again, we need recognition by the FDA of the costs involved in 100% testing of

the active in finished product and acceptance of reasonable alternative approaches to achieve the objective of quality nutritional products.

8. Quality Control Considerations
   a. Assay Methods - Section 111.35 (g) (1) (pg 12197) – Product Testing
      a. How can Quality Control Demonstrate that a scientifically valid method is not available?
      b. If there are scientifically valid methods available, we must use them. How do we know there are such methods, when we deal with hundreds of items. We can not be expected to have expertise in the assay methodology for so many different ingredients.
      c. 111.35 (h) – What are FDA methods? Are they published anywhere? We are not aware that such things exist. Can we not use methods that we can demonstrate give equivalent results to AOAC or FDA methods? Why are official compendia assays, like the USP, not included in this paragraph.
      d. Sec. 111.60 (b) (iv) (pg 12208) – You say "Noncompendial standards should be of the highest purity that can be obtained by reasonable effort...." and at the end of that paragraph you say "...but if no appropriately characterized inhouse standard exists, you should establish appropriately characterized inhouse materials prepared from representative lots." These two statements seem in conflict. We suggest a change to specify that reference standards be established appropriate to the assay procedure for which they are to be used.
      e. Section 111.35 (k) – (pg 12200) – We need some guidance here. Do we use existing industry standards and the tests now used? For most of the ingredients and components in use, our vendors have much more knowledge as to what tests to run. Can we depend on their advice?
      f. Sec. 1183 (b) (pg 12215) – Requires that for retained samples we use the same container-closure system in which the dietary supplement is marketed and store the samples under the same conditions that you would expect a customer to hold that dietary supplement. Since a substantial amount of our production is shipped in bulk for packaging elsewhere, we often do not know what package is being used and how it is being stored. Insert in the paragraph..."if known and if not in a typical market container-closure system and typical storage condition.
      g. Repeat Assays – We need some guidance as to how many times an ingredient or a product must be tested as it moves down the distribution chain. For example, we do not manufacture softgels in our plant, but buy some from a softgel manufacturer who provides us with a CofA. Very often we package and ship the softgels under the label of one of our customers who then market the product under their own name. Do we have to repeat the assay provided by the softgel manufacturer; does our customer? Is it your intent that the assay should be repeated three times?

9. Other Comments

a. Use of Plain Language - Sec. 111.3 – (pg 12176) - The phrase "***identity, purity, quality, strength, and composition*** " is confusing because it seems the terms are to some degree interchangeable and are used to define each other. For example ***Quality*** is defined as consisting of ***identity, purity*** and ***strength***. Is a case of an under or over potency a problem of ***identity*** (because the product is not consistent with the master manufacturing record and what it is represented to be on the label), or of ***strength*** (because the amount per unit is not correct), or ***composition*** (because it does not contain the intended mix of product)? We do not believe that this phrase meets the intent of the use of Plain Language; no one talks or writes this way in multi-term phrases. We suggest changing this phrase to the term ***Product Quality*** which everyone understands and is comfortable using. Define this term using all the attributes given in this section.

b. Verification - Sec 111.30 (b) – (pg 12194). You seek comment on whether verifications procedures should be included in a final rule. Verification is a not a process familiar to the bulk of this industry, and thus instituting such a procedure would create a major learning effort. With all the steps in this document to be absorbed and instituted, we believe that you should hold off on this until the industry has come into compliance on the other parts of the CGMP's. It may be that a verification program is desirable in the industry, but not now.

c. Documentation – In many places throughout the proposal you request comments on whether written procedures should be required. In or written procedures, but we see the need for flexibility from function to function and company to company. We believe that companies should be required to review the need for written procedures at each crucial step of their operations, make a decision based on the appropriateness in each case, and be prepared to defend those decisions if questioned.

d. Market Package Identification – No where in this proposal do you mention the affixing of a lot number to the container of product marketed to the consumer. All the record keeping proposed in this document is of little value unless we can tie back an individual container, perhaps received from a customer complaint, to a specific batch. We think that this should be a requirement.

Sincerely,

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