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Dockets Management Branch (HPA-305)
Food and Drug Administration
5830 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Public comment on Docket Number 96N-0417. Proposed Current Good Manufacturing Practice in Manufacturing, Packaging or Holding Dietary Ingredients and Dietary Supplements

Comments compiled by
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Overview

We welcome the move towards introducing regulations that will ensure the good quality of dietary supplements, in particular, botanical products. While we are in agreement with many of the regulations proposed, there are a number of areas that we feel should be re-evaluated or clarified. These are listed in the following sections.

Detailed Comments

Subpart A: General Provisions

Section 111.3 Definitions

The definition for "Sanitize" needs further clarification. We agree that the manufacturer should validate their sanitization methods at least once a year, and whenever their method changes, or if there is doubt regarding its efficacy. However, the definition as it is written may imply that the manufacturer would have to demonstrate a 5 log reduction in microbial count EVERY time a food contact surface is sanitized.

Section 111.6 Exclusions

The businesses involved in producing or distributing raw agricultural commodities (growers, harvesters, dryers) should bear some of the burden of these regulations. We believe that there is a potential for safety issues to arise from this early stage of manufacturing. The use of improper handling (through improper training) has a significant risk of adulteration. These include microbial contamination, confusion of identity, inclusion of foreign particles etc. If these are introduced at the evolution of the product/ingredient, they will remain with the product/ingredient throughout. The

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advantage at the grower's end is that they have access to the whole, fresh plant material, where unambiguous genus/species identification can be made. This is not always possible with dried plant parts (the usual item of commerce), in particular where it has been cut into smaller pieces or even powdered. We recommend that the growers bear initial responsibility for identification of the plant material and ensuring that the material supplied is free of foreign matter (organic or inorganic). This can be done without the use of sophisticated analytical equipment.

The Guidance document (ref. 53) is helpful but its recommendations should be mandatory rather than a mere guideline. If these procedures are adopted, there will only be a small burden to the processor and there would be less of a need for some of the heavy testing requirements as mentioned in section Subpart E. What is the point of testing for adulteration once it is there? These preventative measures at the onset would decrease the proportion of raw material samples failing manufacturer's tests and improve quality at the beginning of the process. We believe that the (EMEA) European Agency for the Evaluation of Medicinal Products (EMEA/HMPWP/31/99/Rev.3) Good Agricultural Practice is a good example of requirements that should apply to herbal raw material processors.

Section 111.12, 111.13 and 111.15(j) Personnel and Supervisor Requirements
The requirement that personnel should be qualified by TRAINING AND EXPERIENCE needs to be clarified. We agree that experience is important and that training within the company should be required. It would not be reasonable to require all employees to have relevant training from outside the company since there is very little formal training available, external to the company, that is relevant to the industry. Most of the production personnel draw their knowledge from direct vocational training.

This section should clearly state that all personnel (except Quality Control and Sanitation Supervisors – see below*) should be qualified by experience and on-site training only. Companies should develop written procedures for the minimum GMP training common to all departments. Additionally each department must have its own set of Standard Operating Procedures that they are to follow. The training should be documented and should be given for all new personnel and also it should be repeated on a regular basis (we propose annually). Our position is that training is very important, especially since production personnel can be transient at times. Without adequate training, it is very likely that a product may be adulterated unknowingly.

It would be helpful if the FDA provided training material for this purpose such as texts, videos, Internet training, seminars etc. Topics could include sanitation, maintenance of records, analytical methods applicable to quality assurance of dietary supplements, microbiological testing, botany (macroscopic and microscopic features) etc.

* The only department that should have BOTH training and experience should be the Quality Control Department and the Sanitation Supervisor.

Here it would be useful to have some indication of what the FDA would regard as adequate qualifications for these roles.

Subpart C: Physical Plant

Section 111.15 Sanitation Requirements

The necessity that water used for cleaning contact surfaces meets EPA regulations is an unnecessary burden for companies that do not have access to municipal water. We believe that if the water is potable this is sufficient. Since the finished goods have to be tested for adulteration then it is a duplication to require further testing of the water source. The main problem with this section is that the frequency of testing has not been defined. If companies are required to meet EPA regulations (as the section is currently written) it would cost $1500 per annum. It would be more effective to invest this money in finished product testing where it would be more relevant.

Section 111.20 Physical Plant Requirements

Subsection (d) 5

The necessity for equipment that controls humidity and heat should be changed to clearly state that this should only be required if there is a concern that the environment may damage and/or adulterate materials, components, packaging, in-process materials or finished goods. This was the verbal answer given on the May 9th satellite meeting, but it is not clear in the written GMP's.

Section 111.30 Equipment Requirements

Subsections (a) and (b)

This entire subsection should specify that it only applies to critical process equipment.

Section 111.35 Production and process Controls

Subsection (e)

This section identifies the 5 attributes that must be written into specifications (identity, purity, quality, strength and composition). This language needs to be more specific because the terms are very subjective. There is nothing to stop a company from adopting very indeterminate specifications in order to meet the GMP's yet their specifications may be meaningless.

We believe that there should be an industry standard for purity as everyone has a different idea on what an impurity is. Quality is a vague term, which in fact encompasses identity, purity and composition, and should be removed as a separate term. Strength is meaningless (or requires better definition) for non-standardized traditional herbal products because there is no current industry standard. This should be clarified in the regulations that it applies to ingredients with a label claim only. (i.e.: standardized

ingredients) . Alternatively, if "strength" refers to having the correct amount of a stated ingredient eg Feverfew leaf powder, then this should be made clear.

Subsection (g) and (h)
We believe that the manufacturer should have the choice of whether to test the finished good OR the raw material. Here are the arguments:

- Providing that the manufacturing steps are monitored by the Quality Control unit there is no reason to test every component in the finished good.
- Many companies produce finished goods in very limited numbers (small lots) and it would be superfluous to test every component within each lot of finished product. It is very costly and the proposed regulations underestimate this cost to the manufacturer. It is far more efficient to test the materials that may be used in several batches.
- There is a lack of analytical methodology for many ingredients, especially in the finished good form. In our case, we buy many herbs in whole form (un-milled) so that we can identify them organoleptically and by use of microscopy and Thin Layer Chromatography. This would may be feasible for the finished good. It would also be difficult to analyse individual components in a product containing a mixture of ingredients. We should not have to research and document this for every product. It should be a matter of choice to the manufacturer.

Section **h** cites that the method used must be a scientifically valid method. This is applicable to quantitative methods only. The regulations do not give guidelines for validating a qualitative method. For example, Thin Layer Chromatography, Microscopy.

Therefore we propose that the sentence is changed to "scientifically validated method if pertaining to quantitative methods"

We believe that there should be an option to allow the manufacturer to adopt a "skip-lot" testing program and a valid Certificate of Analysis (C of A) from the supplier once the manufacturer has established confidence in their supplier product in correlation to their C of A. This is particularly significant when receiving the same batch number from the supplier, but it is received as a distinct manufacturer lot number. Being a smaller company we buy our materials in smaller quantities (for example, 25 kilos from a supplier batch of 1000 kilos. If we were to receive this item on 5 distinct occasions, we would have to duplicate all the tests five-fold). This would effectively be the same as receiving a larger quantity from the supplier, testing it once and keeping it in our warehouse. The system of testing only one batch for agreement with the C of A and then using this information for further purchases would work well if the suppliers were required by law to provide reliable and valid C of A documents.

Subsection (i) 3 (also applies to section 111.50 f)
This would be better-defined to list that only materials contaminated with microorganisms that are health-hazards (e.g. *E.coli, salmonella*) should not be re-

processed. The preamble mentions health-hazardous microorganisms but the language in this section states only "microorganisms". It is also important to clarify that the batch be rejected only if the levels of the microorganisms or heavy metals were such that they posed a risk to human health, rather than their presence *per se*.

Subsection (k)
The requirement here is weakly stated. The appropriateness of the 4 techniques listed depends on the material being tested. Gross organoleptic analysis would only be relevant to whole material and not powdered material, but with the weakness of the regulations the option of which of the 4 methods to choose is left open to the manufacturer. The method selected may be inappropriate and would achieve nothing. A choice of any 2 methods may be more appropriate.

Additionally, this section appears to contradict subsection (g) in that there is no option to test the raw material in lieu of the finished good. Here too, we believe that the option should be given to the manufacturer providing that they monitor their facility and equipment for filth, insects, microorganisms and toxic substances.

The preamble makes reference that herbs are always likely to be contaminated with microorganisms and filth. We believe that other dietary supplements are just as likely to be adulterated as herbs.

It would be helpful if the FDA provides some data of the types of adulterants and if there is an association with certain herbs so that we can target our tests and specifications to eliminate these hazards.

Section 111.37 Quality Control Requirements
Subsection (b) 12
Many manufacturers assign an expiration of greater than 3 years and therefore the regulations need to stipulate that the samples and documentation be kept for "3 years OR the shelf-life of the product, whichever is longer". This also applies to the documentation in section 111.125 section a.

Section 111.45 Master Manufacturing Record Requirements
Subsection (a)
It is an undue burden to enforce the manufacturer to prepare Masters for each DISTINCT BATCH SIZE produced. This creates document-control issues and is not necessary. In lieu of this we recommend that the master is written per dose unit and that when a batch record is created there is a QC check to ensure accuracy. This can be done at any point in the manufacturing process. To ensure that there are no errors there should be a written procedure for generating batch records.

Section 111.50, Subsection (f) - See comments under **Subsection (i) 3**

Section 111.65 Manufacturing Operations
Subsection (c) 9
The statement that refers to the necessity of effective measures to prevent against heavy metal inclusion in product needs to be clarified. We propose that it is sufficient to impose the responsibility to all facets of production that they inspect their equipment before and after use so that there is assurance of exclusion. If any piece is missing, the entire batch must be disposed. There should be written procedures for this. This type of contamination is most likely to occur at the early stages of production for herbal manufacturers especially with harvesting equipment and so we reiterate the need for Raw material Processors to follow regulations.

The alternative is a costly metal detection device which is not 100% effective.

Section 111.85 Returns
Subsection (b 1 and 2)
The section b allows salvage of returned material if the requirements of both 1 and 2 are satisfied. We propose that it should be either section 1 OR 2. Inspection of the facility can achieve assurance that the product has not been adulterated or retained at the incorrect temperature.

Section 111.125 Documentation
Subsection (a)
Many manufacturers assign an expiration of greater than 3 years and therefore the regulations need to stipulate that the samples and documentation be kept for "3 years OR the shelf-life of the product, whichever is longer". This also applies to the reserve samples in section 111.37 (b) 12.

General Comments

Written procedures and documentation
The FDA has requested comments on the need to require written procedures and to document processes for many areas such as sanitation, manufacturing methods, complaints, training etc. In all cases we agree that this would be of benefit to ensure that processes are carried out correctly and to be able to check that this was the case should there be any question at a later date. The only limitation on this is that for use of manufacturing equipment, this should only apply to critical processes. We also agree that records of distribution of products should be required to be maintained, to facilitate recalls should they be necessary.

Training materials from FDA
Booklets, videos, seminars etc. on the following topics would be of use:

Sanitation, development and maintenance of records, analytical methods applicable to quality assurance of dietary supplements, microbiological testing, botany (macroscopic and microscopic features)

Animal based products
We do not make any products containing animal derived products. However we understand that there are special risks associated with these (such as the presence of pathogenic viruses), and we would therefore support a special set of regulations being developed to cover these. The methods stated in the proposal (organoleptic, microscopy, chemical) for establishment of identity and purity would also not be applicable to animal products and a separate list of test methods should be identified for those materials.

Regulation of imported materials
For imported raw materials, we propose that the suppliers should be required to provide a C of A for all materials (at least confirming botanical identity). Ideally, they should also provide to the buyer an authenticated voucher specimen for each botanical material, against which future batches can be compared.

For imported finished products, we suggest that the FDA requires the manufacturers to submit documentation on their procedures which would allow the FDA to evaluate their GMP compliance. Products not meeting the standards should not be permitted. The proposed rules should apply equally to imported dietary supplements and those manufactured in the USA. Otherwise, the market will be flooded with products made overseas, perhaps on behalf of local manufacturers. It may also be necessary for the FDA to provide inspectors to visit overseas manufacturing sites and accredit them before they are allowed to export products to the USA.

Expiration dates
We agree that there is currently very little data supporting specific expiration periods for most of the dietary supplements available. However, it is not reasonable for products to have endless, unspecified shelf-lives. We propose that a general maximum shelf-life to be applied to dietary supplements is included in the regulations. However, it is important to include the provisions that as scientific data becomes available, the shelf-life for individual products may be shortened or lengthened above the norm. From our experience, we would suggest 4 years for dried herbs or powders and 5 years for liquid extracts containing alcohol (as they would be resistant to microbial contamination).

Regulation of vitamins and minerals
On Page 12221 of the proposed GMP's (Section VII analysis of impacts, regulatory options), option b suggests fewer requirements for vitamins and minerals. We would be strongly against such a policy. This scenario makes no sense and jeopardizes many people. The majority of the population takes a multivitamin/mineral preparation as their primary and sole dietary supplement and therefore the scope for adverse events arising from adulteration, misidentification or misformulation of products is much higher.