ABBOTT LABORATORIES

Corporate Regulatory and Quality Science

Richard M. Johnson
Director
Quality Center of Excellence for Drugs
D-03QA, AP6C-1
Telephone: (847) 938-1750

100 Abbott Park Road
Abbott Park, IL 60064-6091
Facsimile: (847) 938-4422
e-mail:
richard.m.johnson@abbott.com

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

Ref: **Docket No 96N-0417 - Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements**

To Whom it May Concern:

Abbott Laboratories is very pleased to have the opportunity to provide comments on the Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements published on March 10, 2003 in the *Federal Register*.

We thank the Food and Drug Administration for your consideration of our comments. Should you have any questions, please contact Kathy Wessberg (tel: 847-938-1264, e-mail: kathy.wessberg@abbott.com).

In addition to the specific comments listed in the attachment, Abbott also agrees with the position from the International Food Additives Council (IFAC) on the GRAS notification process. It should be permissible for a manufacturer to rely on the reasonable GRAS determination of its supplier. We request that the agency reconsider its proposal as it relates to GRAS substances in dietary ingredients and supplements.

Sincerely,

Richard M. Johnson
Encl: Comments

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COMMENTS

Dietary ingredients may be plant derived, animal-derived or chemically synthesized. We agree that each ingredient should be controlled under GMP conditions, however it should be recognized that each material source brings a different set of quality criteria to be evaluated for quality, purity and establishing specifications. In general, we thought the proposed GMPs attempted to create one set of criteria for evaluation. We recommend that when applicable, the proposed GMPs for dietary ingredients be specific to the source. For example, testing for microbial load for botanicals must be tested each time, others can be tested as appropriate.

1) 111.3 - Definitions
Current text reads: "Sanitize means to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying cumulative heat or chemicals on cleaned food contact surfaces that when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer."

The preamble (pages 113-115) discusses the agency's reasoning for choosing this definition as being consistent with other agency definitions. However this definition is from the "Food Code" and not from the food GMP regulations, from which the agency also claimed to have derived these proposed GMPs for dietary supplements. Choosing the "Food Code" definition is therefore inconsistent with the definitions specific to GMPs. We recommend the agency use the same definition for sanitize that was proposed in the APRN and is consistent with the current food GMP definition. Change 111.3 Sanitize to read:

""Sanitize" means to adequately treat equipment, containers or utensils by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer."

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2) 111.15(b)(1)
Current text reads: - "You must use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and safe and adequate under the conditions of use"

The preamble (pages 144-145) discusses how the firm is required to verify the cleaning compounds and sanitizing agents are free from contamination. This requirement is in excess of the drug regulations. The food GMP (21 CFR 110.35) states "free from undesirable microorganisms...". We propose that the GMPs for Dietary Ingredients and Supplements read the same as the food GMPs to minimize confusion and maintain consistency. Change 111.15(b)(1) to read:

"Cleaning compounds and sanitizing agents used in cleaning and sanitizing procedures shall be free from undesirable microorganisms and shall be safe and adequate under the conditions of use. Compliance with this requirement may be verified by any effective means including purchase of these substances under a supplier's guarantee or certification, or examination of these substances for contamination."

3) 111.20(d)(5)
Current text reads: - The physical plant be designed and constructed that includes:
(5) "Equipment that controls temperature and humidity;"

We suggest a qualifier be added to this requirement, such as "as necessary to prevent adulteration of the Dietary Ingredients, ..." etc. or use the text as stated in 211.46(b) "Equipment for adequate control over humidity and temperature shall be provided when appropriate."

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4) 111.35(k)
Current text reads - "You must test or examine components, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or may lead to adulteration. You must use an appropriate scientifically valid method for the test or examination. The types of contamination include, but are not limited to, the following: 1) Filth, insects, or other extraneous material; 2) Microorganisms; and 3) Toxic Substances"

While the preamble gives some latitude in deciding when to test, testing for filth, micro and toxic substances seem to be required regardless of the nature of the material. The open-ended requirement that testing be conducted for "Toxic Substances" is also problematic in that it is limitless. We recommend this section be reworded by replacing the phrase "..include, but are not limited to," to "as appropriate.." . If needed, specific wording to ensure that botanicals are free of pesticide and/or fungicide residues could be added.

5) 111.37(b),(7) and (8)
Current text reads - "Your quality control 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;"

These requirements for the quality control unit are in excess of both the drug regulations (211) and the food regulations (110). The drug regulations (211.22) state the "quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality and purity of the drug product". Based on this wording we recommend that items (7) and (8) be re-worded to require quality control over calibration programs / procedures when there is a negative impact on product (i.e. a calibration failure) and not for routine calibration programs. Change 111.37(b) (7) and (8) to read:

"(7) Review all records when there is a negative impact on product (i.e. a calibration failure) for calibration of instruments, apparatus, gauges, and recording devices;
(8) Review all records when there is a negative impact on product (i.e. a calibration failure) for equipment calibrations, inspections, and checks;"

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6) 111.37(b) (12) and 111.83
Current text reads -
111.37(b)(12) "Your quality control unit must do the following:
(12) "Keep the reserve samples for 3 years from the date of manufacture..."
111.83 "What requirements apply to holding reserve samples of components, dietary ingredients and dietary supplements"

We agree with the collection of samples for the purposes of testing, however to require samples from components or dietary ingredients to be maintained as reserve samples is an excessive requirement, creating a burden for storage of materials and with no value added. If a dictary supplement comes under investigation due to a customer complaint, all components and ingredients can be traced back to their source (i.e. vendor/manufacturer of the material) for a more in-depth investigation if necessary. There is no need to burden the dietary supplement manufacturer to maintain reserve samples of each purchased component and or ingredient. Samples of the packaged and labeled dietary supplements will be maintained which would meet the requirement for retention of samples for the dietary supplement, the package and the label.

We recommend "components" and " dietary ingredients" be excluded from this section Change 111.83 to read:

"111.83 "What requirements apply to holding reserve samples of dietary supplements"

In addition, the requirement to keep reserve samples for 3 years after manufacture will often exceed the expiration dating of most dietary supplements. We recommend adding an alternative statement " Keep the reserve samples for 3 years from the date of manufacture or 1 year after expiration where expiry dating has been established by the manufacturer". Also remove reference to dietary ingredient for the same reason as stated above.

Change 111.37(b)(12) to read:

"Keep the reserve samples for 3 years from the date of manufacture or 1 year after expiration where expiry dating has been established by the manufacturer, for use in appropriate investigations, including but not limited to, consumer complaint investigations to determine, for example whether the dietary supplement associated with the consumer complaint..."

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7) 111.40(c)(1)(ii) requires the signature of the person performing the requirement, whereas other sections such as 111.50(c)(2), 111.50(c)(7) and 111.50(c)(8) only require initials at the time of performance. We recommend the format for the requirement to document the person performing a step be made consistent through the proposed rule.

8) 111.45(b)(5) -
Current text reads - "The master manufacturing record must include the following information:

> (5) A statement that explains any intentional excess amount of a dietary ingredient;"

The preamble (pages 250-251) states "This provision is not intended to allow a manufacturer to add excess dietary ingredients in unspecified amounts that would be in excess of the amount actually needed to meet the label claim". Clarification is needed to understand the intent of this statement. A manufacturer should be able to justify a range for the amount of ingredient (minimum and/or maximum) in the master batch record in order to meet the label claim throughout the product shelf life.

9) 111.50(d)(2)
Current text reads - "The quality control unit must not approve and release for distribution any batch of dietary ingredient or dietary supplement that does not meet all specifications."

Under 111.50(d)(1) there is a requirement for evaluation and disposition if "a batch deviates..". Section 2, however, appears to qualify the limits of any review and does not allow for investigation into the failure. We recommend this section be reworded to be consistent with the drug regulations 211.192. Change 111.50(d)(2) to read:

"Any batch of dietary ingredient or dietary supplement shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated."

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10) 111.70(g) - "The person that performs the requirements of this section must document at the time of performance that the requirements are performed including, but not limited to, documentation in the batch production record of:.."

This section appears to require that all packaging releases be placed in each batch production record. Most packaging material lots are received, dispositioned and then used in multiple batches. A requirement that this information be copied into each production record is unnecessary as long as lot traceability exists and this information is kept in a central files. Change 111.70(g) to read:

"The person that performs the requirements of this section must document at the time of performance that the requirements are performed and maintained in a readily available form including, but not limited to:"