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Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
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Re: Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements (Docket No. 96N-0417)

These comments are submitted by Roche Vitamins Inc. to the Food and Drug Administration pursuant to Federal Register publication of February 6,1997 relating to the above mentioned proposed rule (21 Federal Register 1997).

Roche Vitamins Inc. is a leading bulk manufacturer and distributor of vitamins, nutrients and other ingredients to the food, cosmetics and dietary supplement industries. Roche does not produce any dosage/finished form dietary product in the U.S. We have the following comments:

- As a general introductory comments, the Dietary Supplement Health and Education Act of 1994 (DSHEA) contains several provisions relating to GMP's. According to DSHEA, a dietary supplement is adulterated under Section 402 of the FD&C Act if it has been prepared, packed or held under conditions that do not meet current good manufacturing practice regulations. Further, FDA is specifically authorized to prescribe good manufacturing practices for dietary supplements. DSHEA requires that such regulations be modeled after current good manufacturing practice regulations for food. DSHEA provides that, if GMP's are established, they must be established through formal notice and comment rulemaking.

As a final general comment, we note there is no specific mention that these proposed GMP's are to apply to all dietary supplements and dietary ingredients consumed by the public within the United States. These standards ensure protectionof the health and safety of the U.S. consumer. Clearly, they must be implemented by manufacturers within the U.S. and it's territories. However, there is no mention nor mechanism described, by which FDA can assure that these standards are applied to all dietary supplements and ingredients which will be imported into the U.S. This unbalance in application and enforcement does not protect the U. S. consumer and provides an unfair financial advantage to manufacturers outside of the U.S. who do not follow the GMP's, due to the high cost of implementing, and manufacturing under these high quality and safety standards.

-On page 5700, Under "B. The Industry Draft -Statement of Purpose", in the second sentence of the second paragraph of this section, we recommend this sentence be

modified to "Dietary ingredients may include vitamins; minerals; herbs or other botanicals; amino acids; **formulations thereof which may contain non-active ingredients**; other dietary substances used to supplement the diet; and concentrates, metabolites, constituents, extracts, or combinations of these. " to clarify the scope of the definition.

-On page 5701, under "Definitions (b) a batch or lot is defined as " a specific quantity of a finished product or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. We object to the use of only the term "and" when referring to "is produced according to a single manufacturing order during the same cycle of manufacture". This is because the statement is too restrictive to allow for continuous processes, for which the last section of this provision is not appropriate. We recommend the addition of the term "**and/or** is produced according ....".

- On page 5702, under "Sanitation of Buildings and Facilities", (b)(1) concerning cleaning compounds and sanitizing agents and their verification of being free from undesirable microorganisms. This provision states that compliance may be verified by any effective means including purchase under a supplier's guarantee or certification or examination for contamination. We believe this provision is too restrictive and it should be the responsibility of the manufacturer to comply with the regulation. Additionally, these agents are usually dictated by compliance with local kosher requirements. We recommend that this section should have the following revisions, to increase the clarity of the definition:

> "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, **to the extent necessary to protect against adulteration or contamination of such materials.** ~~Compliance with this requirement may be verified by any effective means including purchase of these substances under a suppliers guarantee or certification, or examination of these substances for contamination."~~

- On page 5703, under "Sanitation of Buildings and Facilities" (d) concerning water supply. We believe the term "potable water " may in some instances be inappropriate (i.e. distilled water). We recommend the use of the phrase "**potable water as a minimum quality water**" would be more appropriate and encourage the use of higher standards.

-On page 5704, under "Equipment and Utensils" (11), concerning written records in individual logs for major equipment cleaning and use. We agree that cleaning records should be maintained. However, a cleaning log is not the only answer. This information is often recorded on the batch record directly or could be in a computer software system as a recorded activity, etc. The requirement to maintain a cleaning log, as stated, is overly

restrictive. We recommend the term "written record in individual logs" be changed to "**cleaning records**".

-On page 5704 under "Quality Control and Laboratory Operations" (a)(1), concerning the Quality Control unit. We recommend the addition of the term "independent" to the phrase "There shall be an **independent** quality control unit..." to further define the scope of the unit's function. Additionally, under subpart (l), the unit's responsibility and authority are stated to "approve or reject all procedures, specifications, controls, tests and examinations, or deviations from them that impact the purity, quality, safety and composition of a dietary ingredient or dietary supplement". We feel this statement is overly restrictive . The QA unit should make sure that this is done, but the actual components of some of these actions could be performed by other designated areas.

-On page 5704 under "Quality Control and Laboratory Operations"(c)and (c)(1) concerning expiration dating. We feel that the term expiration dating is inappropriate for dietary supplement ingredients, as most dietary ingredient manufacturers have retest dates based on the stability of the ingredient and use the term "shelf life or re-evaluation date". This would allow a re-evaluation of the dietary ingredient to take place at the end of the shelf-life. Re-evaluation would allow for the retesting of a dietary ingredient at the end of it's labeled shelf life and comparison of these results to the original release specifications. If the retested dietary ingredient continues to meet the original release specifications, this would result in an extension of the ingredient usability. We therefore recommend the following additions:

"A expiration date **or shelf life/re-evaluation date** for a dietary supplement **or ingredient.."**

-On page 5704 under "Production and Process Controls" (a)(1), concerning the review of the Master production and control records review and approval by the quality control unit. We feel this requirement is overly restrictive because this function can be performed by other units in the organization, and need only be audited or periodically verified by the quality unit. We recommend that the subsection be changed to "The quality control unit shall assure that a master production and control record shall be prepared for the manufacture of each dietary ingredient and dietary supplement", rather than state that it directly reviews and approves them.

-On page 5704 under "Production and Process Controls"(a)(2)concerning the components of the Master Production and control records. We recommend items i-viii should be reordered and more carefully defined because some items apply only to dietary supplements themselves, while others apply to both. Items (i), (vi), (vii) and (viii) apply to both and should be listed first. Those that apply to dietary supplements alone and not dietary ingredients are (ii), (iii), (iv)and (v) and should be designated as such. Item (ii)

cannot apply to formulations or vitamin premixes, particularly if no carriers are used in the premix.

-On page 5704 under "Production and Process Controls" (b)(2). We recommend that the word "reproduction" be replaced by "representation" in the phrase "These records shall be an accurate representation of the appropriate...", as the word reproduction may imply that a photocopy or exact likeness is required.

-On page 5706 under "Production and Process Controls"(d)(13). We recommend that the phrase "to the extent necessary to protect against adulteration or contamination of such materials." be added to the end of the last sentence of this item. This will provide more flexibility to allow for continuous manufacturing operations.

-On page 5706 under "Production and Process Controls"(d)(16)(ii), the phrase "or caustic " should be added after "Controlling the amount of acid" to allow for the other alternative in controlling pH.

-On page 5706 under "Warehousing, Distribution and Post-Distribution Procedures" (a)(2), concerning storage of distribution records. We recommend the addition of the phrase "restest date or expiration date " to the sentence "... at least 1 year beyond the expected shelf-life**/re-evaluation date or expiration date**, whereby..." to provide more flexibility.

-On page 5706 under "Warehousing, Distribution and Post-Distribution Procedures" (b) and (c) concerning reserve samples and records retention. We recommend that all references to expiration date within these subsections have the phrase "**or shelf-life/re-evaluation date**" added, to provide more flexibility.

-On page 5707 under Economic Issues, FDA asks how close current practices are to this proposal and how costly it would be to conform to the proposals. We believe it would not be a cost added activity if the industry proposal is adopted, providing the above changes are made. We also feel that a standard less than this would not meet the needs of our customers, as expressed to us during their frequent audits of our sites. Our reply to the Agency's further questions in this section, is that we feel that new cGMP's are needed for Dietary Supplements, they should be mandatory and they should be required immeditately.

Additionally , economic concern should be give to the 9 additional issues FDA asks for commentary on in pages 5707 to 5708. The safety evaluation/reporting proposed in questions 5 and 6 would be costly programs to implement for many synthetic products that have well characterized safety profiles and a relatively low potential for safety issues. The HACCP proposal in question 8 would provide minimal incremental value yet incur

significant additional costs to manufacturers for implementation and is still a voluntary program for most of the food industry.

Finally, we note that there is no specific mention that these GMP's are to apply to all dietary supplements and dietary ingredients consumed by the public within the United States. These standards ensure the protection of the health and safety of the U.S. consumer. Clearly, they must be implemented by manufacturers within the U.S. and it's territories. However, there is no mention nor mechanism described, by which FDA can assure that these standards are applied to all dietary supplements and ingredients which will be imported into the U.S. This unbalance in application and enforcement does not protect the U.S. consumer and provides an unfair financial advantage to manufacturers outside of the U.S. who do not follow the GMP's, due to the high cost of implementing, and manufacturing under these high quality and safety standards.

-On pages 5707 to 5708 under "Summary and Request for Comments", the Agency asks for comments on 9 issues. As general commentary on these issues, we are concerned that some of the Agency's questions suggest that the FDA has an inappropriately broad view of the scope of issues that should be covered by GMP's. We note that the requirement of DSHEA that dietary supplement GMP's be modeled after food GMP's is quite specific and must be honored. We will strongly oppose any effort to circumvent the intent of DSHEA by imposing a requirement for mandatory proof of safety or a system of post-marketing surveillance for dietary supplement ingredients. Our specific comments are as follows:

1. We believe that DAL's would be inappropriate for synthetic dietary ingredients, which are often compendial items, as they are not subject to contamination that could be controlled by DAL's. Additionally, if DAL's are deemed needed for natural products, this rule making should be undertaken outside the scope of these cGMP's due to the large undertaking it would require due to the diversity of the products.

2. We have no comment on this issue as most of our products have recognized and established identity tests as part of their compendial status. However, the selection of the test should depend on the physical form of the ingredient and should be left to the judgment of the manufacturer.

3. We believe that establishing specific test procedures and requirements to assure the absence of filth, freedom from harmful contaminants, pesticides and other residues will become enormous in scope and cost prohibitive to manufacturers. Certification from a supplier is sufficient, provided the reliability of the supplier has been confirmed.

4. We agree that written procedures should be established for dietary supplements to assure product consistency on a day to day basis. We believe conformance to these procedures should be assured by periodic independent internal audits.

5. We strongly disagree with this proposal to establish GMP regulations for reports of injuries or illnesses for dietary supplements. Dietary Supplements are by definition foods, for which this is not a requirement. This proposal is similar to post marketing surveillance reporting for drugs and DSHEA does not authorize FDA to establish drug like requirements. A costly and burdensome safety surveillance system is not warranted for these type of products. Also, safety reporting and evaluation is not appropriate in GMP regulations which govern manufacturing.

6. We reiterate our position in the above item 5: Dietary Supplements are foods, not drugs. Many synthetic dietary supplement ingredients have also been qualified as GRAS. In general, these products are well established, compendial items and should be exempted from any future requirements for summaries of scientific information.

7. Roche currently uses computer controls in their manufacturing operations. However, we feel it is inappropriate to use the stringent drug standard of "validation" of these operations, and recommend the substitution of the term "evaluate". We develop appropriate assurances to meet the ranges within the processes and also control these processes through in-process monitoring.

8. A HACCP program is inappropriate for compendial dietary supplement ingredients because they are generally chemically based, long shelf-life products. Their manufacturing process is well controlled throughout the process. HACCP programs, as they are currently employed, are geared towards perishable items and are still voluntary for most of the food industry. Additionally, the HACCP federal register notice referred to in this Proposed Rule states "an alternative to HACCP is end product testing and GMP regulations". The proposed dietary supplement cGMP regulations in this federal register notice, with the modifications we have supplied herewith, are an adequate basis to assure the safe manufacture of a dietary supplement. If a HACCP program is required, it would provide minimal incremental value at significant additional costs for implementation. broad based enough to be appropriate for all areas of the dietary supplement industry. Development of specific GMP's for dietary ingredients alone would not offer any additional value. We have attempted in this letter to comment on all areas wherewe believed there should be further clarification between requirements for dietary ingredients and dietary supplement final products, or made recommendations to change a provision to make it broad enough to cover both ingredients and supplements. There may be some areas where we were not aware where the Agency wanted to differentiate between ingredient and supplement and request that these areas be clearly defined.

Should Roche be able to assist the Agency in any way with this proposed rule please feel free to contact the undersigned at (201) 909 -6747.

Respectfully submitted,

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