PERRIGO®

CONFIDENTIAL

August 8, 2003

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

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

Dear Sir/Madam:

The Perrigo Company of South Carolina submits these comments in response to the FDA (Agency) Proposed Rule for Current Good Manufacturing Practices in Manufacturing, Packaging, or Holding Dietary Ingredients and Dietary Supplements which appeared in the Federal Register on March 13, 2003.

Perrigo is a leading Private Label Manufacturer of high quality, Over-the-Counter Drug Products and Dietary Supplements.

The Perrigo Company of South Carolina is a member of the Council for Responsible Nutrition (CRN), Consumer Healthcare Products Association (CHPA) and the American Herbal Products Association (AHPA). These trade associations will be submitting comments to FDA on behalf of their Industry members, and we fully support the comments that these Trade Associations will be making to ensure that the Final Rule, when it is published, will be fair and equitable for all stakeholders in the Dietary Supplement Industry.

For the sake of clarity, we will attempt to organize our comments to follow the same order in which the issues are addressed in the Proposed Rule itself. We will also use headers wherever practical to aid the reader in identifying specific issues related to the Proposed Rule.

Our comments are as follows:

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GENERAL COMMENTS:

The Perrigo Company of South Carolina, in general, supports the need for strong Dietary Supplement Good Manufacturing Practice Regulations. We believe that most of the elements that the Agency has identified in this Proposed Rule are necessary to ensure the identity, purity, quality, safety and composition of Dietary Supplements.

We disagree that Dietary Supplements have unique chemical or microbiological characteristics unlike most Conventional Foods and therefore, require special controls to ensure that a product maintains identity, purity, quality, strength and composition characteristics throughout their shelf life (expressly stated or implied). We believe that the true distinguishing difference between Dietary Supplements and Conventional Food forms is the physical form of delivery to the intended end user.

AMERICAN HERBAL PHARMACOPEIA – AUTHORITATIVE RECOGNITION:

The Agency specifically cites the Association of Official Analytical Chemists (AOAC) and United States Pharmacopeia (USP) as authoritative sources of Standards and Methods for Dietary Supplements. We strongly recognize the value of compendial methods, especially those that are validated using inter-laboratory validation criteria, such as the AOAC – Official Methods of Analysis (OMA). We feel very strongly that the AOAC will meet it's long-term goal by developing Official Methods of Analysis for virtually all types of Dietary Ingredients and Dietary Supplements.

We also agree with the Agency preamble comment that an Official Method of Analysis is the most reliable because it is based on an inter-laboratory collaborative study.

We feel that the current state of the Industry needs additional authoritative sources of technical documentation, especially with reference to Botanical Dietary Ingredients and Botanical Finished Dosage Forms. We recommend that the Agency consider the recognition of the American Herbal Pharmacopeia (AHP) as an authoritative source of methods, quality standards and other technical information for botanical products. We believe that the AHP is the most significant compilation of pure reviewed technical data on botanical products.

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AMERICAN HERBAL PHARMACOPEIA – AUTHORITATIVE RECOGNITION (continued):

We have found that the number of monographs available through the American Herbal Pharmacopeia far surpasses USP and AOAC monograph availability. We also have found that the monographs published by the American Herbal Pharmacopeia provide an incredible amount of specificity and quality of detail for botanical products. Technical information is a critical element to ensure that identity, purity, quality, strength and composition for botanical products are achieved.

In addition, the American Herbal Pharmacopeia monographs have gained International recognition in both Europe and through the World Health Organization. We believe that recognizing the work product of the American Herbal Pharmacopeia would help raise the standard for botanical products in the Dietary Supplement Industry and assist Agency in setting standards for enforcement.

DEFINITIONS:

Any good document starts with clear and concise definition of terms so that there will be minimal chance of misinterpretation of the requirements. Some examples of documents that contain detailed definitions of terms would include, those published by the American National Standards Institute (ANSI) and the International Organization for Standardization (ISO). In fact, these organizations have some standards that are solely dedicated to defining specific words and terms for general use in all their published quality standards.

We feel that the Agency needs to include greater specificity with respect to the definitions of specific words and terms. In addition, we believe that certain words are not defined at all, and need definition to ensure a consistent interpretation amongst all stakeholders, as well as, by the inspectors in the field.

We believe that there are many Manufacturers in this Industry that would benefit significantly from a clarity of terms. In addition, we believe that doing so would make the Proposed Rule easier to read and understand, consistent with the Plain Language Principles under the Presidential Memorandum of June 1, 1998.

Some examples of how the definitions might include more specificity are as follows:

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DEFINITIONS (continued):

Quality, Identity, Purity, Strength and Composition:

We are most concerned about the Agency definition for identity, purity, quality, strength and composition. This is the most critical definition in the regulation, and it is only defined in the Preamble to the Regulation on Page 12176, Federal Register/Volume 68, No. 49/Thursday, March 13, 2003.

In addition to this concern, it is also our opinion that there is significant overlap with respect to the words "identity", "purity", "quality", "strength" and "composition". We believe that the word "quality" is at the highest level, and includes "identity", "purity", "strength" and "composition" elements. Based on this, an appropriate definition of "quality" might be as follows:

> **Quality:** The total characteristics of a product that bear on it's ability to satisfy stated (i.e. labeled) or implied needs of identity, purity, strength and composition.

This takes into account accepted definitions for Quality and also includes some of the elements from the proposed rule.

Definitions for "identity", "purity", "strength" and "composition" should similarly be included in the definition section of the regulations. For example, the definition for "purity" may read as follows:

> **Purity:** Free from objectionable and/or deleterious levels of impurities including, but not limited to, heavy metals, pesticides, mycotoxins, radioactivity, filth, extraneous material, molds, yeasts and bacteria.

Similar definitions could certainly be developed for "strength", "composition" and "identity".

Raw Material, Component, Starting Material:

We believe that Industry-specific language would be more appropriate to define the terms raw material, component and starting material. We believe that using one all-inclusive term such as "raw material", is confusing when there is clearly a difference from a manufacturing perspective.

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DEFINITIONS (continued):

Raw Material, Component, Starting Material (continued):

The term "raw materials" is typically used in this Industry to define the materials that will be used to make the specific dosage form, which includes the dietary ingredients, carriers, processing aids, disintegrants, lubricants, binders, and fillers to provide some examples from the Solid Dosage Industry.

The term "component" is typically used to define the specific items that are used to assemble the finished product for the end-user. These traditionally include the packaging components such as bottles, caps, as well as, all forms of labeling (i.e. primary container label and cartons) and the bulk dietary supplement product.

The term "starting materials" might be more suitable for the dietary ingredient and excipient manufacturers, and specifically refer to the materials that they use to manufacture their end product.

In addition, we believe that the Agency should better define the following terms to ensure consistent interpretation of the GMP Standard at all levels within the Industry:

1. Control Point
2. Scientifically Validated Analytical Method
3. Verification (See ANSI Standard A8402-1994)
4. Validation (See ANSI Standard A8402-1994)
5. Dietary Ingredient (from DSHEA)
6. Ingredient
7. Certificate of Analysis
8. Certificate of Compliance (Conformance)
9. Continuing Product Guarantee (from 21 CFR Part 7.13)

Sanitize:

Under the definition for "sanitize", we believe that the Agency should simply clarify that a sanitizing agent for use on food processing equipment shall be approved in accordance with 21 CFR Part 178-Indirect Food Additives: Adjuvants, Production Aids and Sanitizers.

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DEFINITIONS (continued):

Sanitize (continued):

We believe that the current wording may imply that Dietary Ingredient and Dietary Supplement Manufacturers must perform validation studies to demonstrate that the sanitizers they are using reduce the microbial load on equipment by five log cycles. Although this may be a requirement to truly classify a product as a "sanitizer" under EPA Regulations, we feel that a sanitizer need not be held to such a strict standard for the purpose of reducing microbial loads on food product contact surfaces.

We believe that it is the Agency's intention to ensure that food processing equipment be reasonably free of microorganisms. If this is the case, then wouldn't it be more appropriate to guide the Industry as to what may be suitable levels of microflora on food processing equipment.

We feel that no one in the Industry would argue that the absence of pathogens is an absolute requirement on food processing equipment; however, the total colony forming units on equipment may vary by Industry segment. For example, a Manufacturer of a solid dosage form may not need to "sanitize" their equipment because the processing environment is not suitable for microbial growth due to the low Water Activity (A_w).

A Manufacturer of a liquid dosage form, on the other hand, may require extensive sanitizing procedures to ensure that microbial loads are minimized.

We believe that it would be in the Agency's best interest to cross-reference the following American Public Health Association Guideline as a reference to the Industry in the definition of "sanitize":

- The Compendium of Methods for the Microbiological Examination of Foods, Fourth Edition, Chapter 3, Microbial Monitoring of the Food Processing Environment.

We request that the Agency clarify its expectations to the industry with respect to the documentation necessary to prove sanitizer effectiveness.

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DEFINITIONS (continued):

Temperature Specifications:

We believe that there is no need for the agency to specify storage temperatures for dietary ingredients or dietary supplements. Most of these products are shelf stable based on their low water activity control which limits and slows chemical degradation and microbiological growth.

DIETARY INGREDIENT SUPPLIERS:

We commend the Agency for including Dietary Ingredient suppliers in this Proposed Rule. We believe that Dietary Ingredient suppliers are a critical element of the supply chain and must be held to the same standards as Dietary Supplement Manufacturers.

We believe that including Dietary Ingredient suppliers in this Proposed Rule is necessary to achieve the level of control and ensure the identity, purity, quality, strength and composition of Dietary Ingredients and Dietary Supplements. We feel that the Agency has provided several critical examples of products that were distributed in the public domain and later were found to be a threat to public safety. The most notable of these includes the l-Tryptophan and the digitalis contamination in plantain. The root cause of both these major quality failures can be attributed directed to raw material suppliers.

Although we support the inclusion of Dietary Ingredient Suppliers, we do believe that certain provisions of the GMP's for Dietary Ingredient Suppliers, may be in some cases, unrealistic or too restrictive. We would recommend that the Agency focus the scope of the GMP's for Dietary Ingredient Suppliers exclusively to their end product. For example, we do not believe that the GMP's should apply to the specific starting materials that a Dietary Ingredient Supplier uses to produce its Dietary Ingredients.

We base this on the fact that many of the starting materials used by Dietary Ingredient Suppliers are not food grade, and those ingredients, would not be allowed in food.

This may be due to the nature of the material itself, or due to undesirable impurities. The Dietary Ingredient Manufacturing Process converts these raw materials into a food grade material and in many cases the process itself is designed to remove through purification of undesirable impurities. In this case, impurities may include defects such as, rodent filth, insect frass, mold fragments, bacteria, yeast, heavy metals, pesticides and so on.

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STABILITY REQUIREMENTS:

We believe that the Agency should mandate that stability testing be a requirement in the Final Rule. It is our opinion that stability testing is Critical to Quality (CTQ) and the Agency would be remiss if they do not specify this in the Final Rule.

It is our contention that a Manufacturer/Marketer of a Dietary Supplement must have reasonable assurance that their products meet all specification requirements throughout the anticipated shelf life. This should apply regardless of whether or not an expiration date is expressly stated in labeling or implied (i.e. no expiration date or a stock rotation date). We believe this is necessary to ensure that each end-user is assured that the products that they purchase meet the expected identity, purity, quality, strength and composition characteristics that they are purported to possess.

We do recognize that Dietary Supplement stability characterization presents unique challenges for certain Dietary Ingredients in finished dosage form that consist of multiple molecular entities such as is the case with many botanical-derived ingredients.

In these cases, we believe that most reputable Industry Manufacturers have assessed the stability characteristics of their products through the use of surrogate assays. In the case of a botanical product, the principal moiety (or moieties) is not known; however, the stability characteristics may be assessed by looking at non-marker compound that are indigenous to the specific botanical product. We believe that there are surrogate assays in use in the over-the-counter pharmaceutical industry.

It is our opinion that all reputable Manufacturers are already applying an expiration date to their labeling. This is based on the fact that virtually all retailers require expiration dating to ensure that they are able to manage their inventories on a First In – First Out (FIFO) basis.

We believe that an adequate guidance document could be prepared with input from all stakeholders that would address in a reasonable manner, the key elements of stability characterization for Dietary Ingredients and Dietary Supplements.

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COST IMPACT ANALYSIS:

We believe that the Agency has grossly underestimated the cost impact of the rule as it is currently written and interpreted. We believe that the most significant impact is in the area of raw material testing and/or finished product testing.

Under the Proposed Rule there are significant raw material test requirements as it is stated that reliance of supplier data is not justified (preamble page 12198). There is also a significant impact for finished product testing as the Proposed Rule dictates mandatory end product testing when analytical methods are available.

Using the approach defined by the Proposed Rule, we have calculated that the economic impact to the Perrigo Company of South Carolina would be $681,000 annually. We did not include any onetime expenditures because we feel that these would be insignificant compared to the annual cost.

The breakdown of the cost is included in Table 1 below:

Table 1: Perrigo GMP Cost Impact Analysis

Cost of Quality Attribute	GMP NET COST IMPACT ($)
Prevention Costs	
• Training	25,000
• QC Raw Materials	100,000
Appraisal Costs	
• QC Finished Product Testing	546,000
Internal Failure Costs	0
External Failure Costs	
• Complaint Handling	10,000
Totals	681,000

We believe that the Agency has made some assumptions with respect to the Industry that may be based on such limited data that they are not statistically relevant.

One of the assumptions that we feel is not accurate is the number of batches produced by large Manufacturers on a yearly basis. We believe that the order of difference between Agency's number of yearly batches for the large Manufacturers and Industries value is a factor of ten.

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SUBSTANCES OTHER THAN DIETARY INGREDIENTS:

In Part 111.35 (d), the Proposed Rule clearly identifies that substances that are not Dietary Ingredients within the meaning of the term in Section 201 (ff) must therefore meet the Food Additive Provisions of the Act. These substances must have a legal basis for their use in Dietary Supplements under one of the following approval mechanisms:

1. Authorized for Use as a Food Additive under Section 409 of the Act
2. Authorized by Prior Sanction consistent with 21 CFR 170.3(l)
3. If used as a Color Additive, subject to a listing that, by the terms of that listing, includes the use in a Dietary Supplement.
4. Generally Recognized as Safe (GRAS) for Use in a Dietary Supplement.
5. Must comply with all other Statutory and Regulatory Requirements under the Act.

We certainly do not disagree that there must be a legal basis for a Dietary Supplement Manufacturer to use an ingredient. Our concern is what the Agency's expectations are with respect to substantiating the safety of use of an ingredient in a Dietary Supplement.

We would like the Agency to clarify its expectations with respect to the use of ingredients other than Dietary Ingredients. The following scenario is provided for Agency direction and input:

- A Manufacturer of a substance (other than a Dietary Ingredient) self-affirms their substance as GRAS for Use in a Dietary Supplement up to a certain level. The Finished Dietary Supplement Manufacturer audits this supplier's substantiation for GRAS and finds that the Manufacturer has performed their due diligence with a high level of confidence.

The following questions are posed to the Agency:

1. Does the Finished Dietary Supplement Manufacturer have to perform independent, self-affirmation of GRAS Status?

2. If so, why would this redundant effort be necessary when it has already been done in accordance with the requirements for self-affirmation of GRAS Status of a food ingredient?

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SUBSTANCES OTHER THAN DIETARY INGREDIENTS (continued):

3. If the Agency would not require a redundant effort to perform a second self-affirmation of GRAS, then what would the Agency's expectations be with respect to the documentation available at the site of the Finished Dietary Supplement Manufacturer?

4. Would the Agency require the Finished Dietary Supplement Manufacturer to maintain all the self-affirmed GRAS documentation that the supplier of the ingredient (other than a dietary ingredient) generated during the self-affirmation of GRAS process?

5. Would a summary from the ingredient supplier documenting the specific limitations of use in the Finished Dietary Supplement product be adequate substantiation for the Agency?

We feel that the Agency's expectations should be reasonable and not require redundant efforts by both an ingredient (other than a dietary ingredient) Manufacturer's and a Finished Dietary Supplement Manufacturer.

It is further our opinion that a Dietary Supplement Manufacturer need only verify that a supplier of an ingredient (other than a Dietary Ingredient) has performed their due diligence to establish the safety of that ingredient based on its intended use in the Dietary Supplement. We believe this can be adequately assessed by a review of the substantiation and by obtaining a summary statement from the Supplier that the ingredient is suitable for its intended use at the level proposed in the Finished Dietary Supplement. In other words, there is no need to maintain a full dossier of all the documentation generated by the Supplier in their due diligence effort to affirm the ingredient as GRAS for a specific intended use.

On June 2, 2000 Arnall, Golden & Gregory submitted a citizen petition requesting an amendment to the dietary supplement regulations to allow the phrase "may contain" in labeling ingredients. To date, FDA has not responded to the petition. Perrigo is respectfully requesting FDA's attention and response on this matter.

QUALITY SYSTEM ELEMENTS:

We believe that the Quality System that the Agency has defined in this Proposed Rule to ensure that a product meets appropriate standards of identity, purity, quality, strength and composition are unrealistic. We believe that the Proposed Rule, as written, is too prescriptive and does not provide a Manufacturer (of a Dietary Ingredient or Dietary Supplement) enough flexibility to design a system of value-added quality activities.

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QUALITY SYSTEM ELEMENTS (continued):

We believe that the Final Rule should reflect enough flexibility for a manufacturer to design a system of prevention and appraisal activities that will minimize any potential for failure and still be cost effective.

In our opinion, both the raw material and finished product Manufacturers involved in the plantain incident failed to perform their due diligence and implement a quality system capable of preventing a failure in the field. We believe that if the Manufacturers involved in the plantain incident had a system based on prevention and appraisal activities, the whole situation could have been avoided.

For example, if the Raw Material Manufacturer had performed testing on their Finished Dietary Ingredient (plantain), they would likely have discovered that the product did not meet its identity and purity requirements, and therefore was adulterated. If the Finished Product Manufacturers, upon receipt of the raw material performed identity testing, it is likely they would also have detected the error at this point in the supply chain, and alerted the supplier of the error, thus avoiding a failure in the field.

It is our opinion that identity testing of raw materials should be made a mandatory requirement for the Final Rule. This would certainly ensure that the potential for another digitalis in plantain incident is minimized.

It is common knowledge that well-respected Quality Standards base Quality System Requirements on prevention and appraisal activities with only minimal focus on end product testing. In fact, the whole premise behind Hazard Analysis Critical Control Point Concepts is to balance prevention, appraisal and process verification activities to minimize end product testing.

We strongly believe that reduced testing on the finished dosage forms of Dietary Supplements is justified when the Quality System is well thought out to minimize the potential for end product failure.

We are concerned that the Agency proposal will cause some Manufacturers to eliminate many test requirements from their raw material and finished product specifications. This may be a reaction to control costs as prescribed by the current elements of the Proposed Rule. We believe that this would be detrimental to Quality in the Dietary Supplement Industry because some Manufacturers would choose to characterize their raw materials and in-process materials below minimum Quality Standards.

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QUALITY SYSTEM ELEMENTS (continued):

A Manufacturer could eliminate critical specification requirements from their raw material testing program. For example, a Manufacturer of a botanical product may choose not to test any of their raw materials for impurities such as pesticides and heavy metals. By eliminating these requirements from their raw material specifications, and likewise, eliminating the same requirements from their in-process and finished product specifications, they would eliminate critical elements of their required due diligence.

Based on this, we believe that the Agency should modify its Proposed Rule to show greater flexibility toward the development of a Quality System based on a balance of prevention, appraisal and process verification activities. The following is a brief description of a typical Quality System that is developed on the bases previously described and is a very common practice currently established in the Dietary Supplement Industry.

Raw Material and Component Supplier Qualification:

This is the most important concept in prevention and is consistent with Agency's own recommendation to test raw materials and components prior to use (68 FR Page 12198). It is; however, not a concept that has to be all inclusive to develop a reasonable degree of confidence. This is especially true if supply chain management principals are applied and the supplier understands customer expectations.

We believe that prevention and appraisal testing on raw materials is essential and a basic concept found in any and all Quality System Standards. This includes a reliance on a supplier Certificate of Analysis (CoA). Recognized quality standards including ISO, ANSI and the Malcolm Baldridge National Quality Criteria all accept this type of practice as long as it is defined between the customer and the supplier.

We believe that the basic prevention and appraisal elements applicable to the Dietary Supplement Industry justify reliance on supplier Certificate of Analysis and further justify reduced testing. Some of these elements are as follows:

1. Implementation of a Supplier Qualification Program based on an analysis of the raw material (or component) Supplier's process capability and their finished product testing procedures.

2. Appropriate written specifications for raw materials and packaging components.

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QUALITY SYSTEM ELEMENTS (continued):

Raw Material and Component Supplier Qualification (continued):

3. Identity testing on every raw material (Dietary Ingredient and Ingredient).

4. Raw Material Supplier "Certificate of Analysis" based on actual test analysis using reliable test method. In other words, the Certificate of Analysis must include data based on true test values. The use of historical averages or batch record input data should not be allowed. A Certificate of Compliance or a Continuing Product Guarantee should not be a substitute for a Certificate of Analysis.

5. Verification of raw material Manufacturer's Certificate of Analysis by the Finished Product Manufacturer. This should be verified through actual testing on a representative sample of the raw material using a reliable test method. Discrepancies between the vendor Certificate of Analysis and the verification test data must be investigated by the Quality Control Unit. Reasonable differences, of course, would be allowed to account for the uncertainty of measurement.

6. Verification that the raw material continues to meet pre-established specification requirements for identity, purity, quality, strength and composition on a periodic basis. This might be once every two years for a raw material that is not extremely critical and every year for a raw material that is critical. It could also be based on a supplier performance or product risk system. High risk suppliers or high risk products under this type of system are tested more frequently than low risk suppliers or products,

7. Packaging Component qualification allowed based on Certificate of Compliance or Continuing Product Guarantee. We believe that allowing this specific to Packaging Components is justified, because the Agency provided no examples of any significant issues in the Industry that were traced back to packaging materials as the root cause of failure in the Dietary Supplement Industry. The recall record for the Dietary Supplement Industry also confirms the fact that Packaging Components, defined as bottles and caps, are not a prevalent Quality concern to the Dietary Supplement Industry.

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QUALITY SYSTEM ELEMENTS (continued):

In-Process Controls:

8. Master Manufacturing Records for each product and batch size.

9. Batch Production Records for each product lot that includes verification of confirmation of the quantity, identity, and addition of each ingredient to the batch.

10. Appropriate written specifications for all in-process requirements critical to ensure identity, purity, quality, strength and composition.

11. Calculation and reconciliation of yields against pre-established specification requirements between all critical operations.

12. Documentation demonstrating that equipment is suitable for its intended use. This may be supplied by the Equipment Manufacturer.

Finished Product Controls:

13. Written specifications that contain chemical, physical, organoleptic and microbiological requirements to ensure the product meets appropriate standards of identity, purity, quality, strength and composition.

14. A written Finished Dosage Form Testing Plan based on full testing or reduced testing that establishes with a high degree of assurance that the requirements for identity, purity, quality, strength and composition have been met. The reduced testing logic must be justified based on appropriate data from supplier raw material testing, and Manufacturer in-process testing. The raw material testing requirement may be based on raw material supplier's Certificate of Analysis or on testing conducted by the finished dosage form Manufacturer. The method of establishing the reliability of the raw material supplier's Certificate of Analysis was previously discussed in this section of this document.

This is not intended to be an all-inclusive Quality System outline to justify reduced testing on finished products. Each Dietary Supplement Manufacturer may choose to design their own system that could be equally effective at applying prevention, appraisal and process verification resources to ensure that the standards for identity, purity, quality, strength and composition are consistently met with the application of reduced finished product testing.

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RETURNED GOODS:

Under the provisions of the Proposed Rule, the Agency has mandated that returned goods be inspected and tested to demonstrate that they meet all specifications for identity, purity, quality, strength and composition.

We believe that the inspection and testing requirement for returned goods is not always appropriate. We believe that the minimum requirement is to allow the quality unit to evaluate through a combination of investigation and inspection that the product was not subjected to improper storage conditions or impacted in any negative manner.

Most Dietary Supplement products are shelf-stable and are able to withstand short-term excursions of high heat and high humidity. Most of these products, when they are exposed to detrimental extremes of heat and humidity, become obviously unsaleable. This is due to conspicuous changes in the organoleptic appearance, with discoloration being the most significant and rapid onset defect attributable to high temperature and humidity exposure. This is especially true for solid dosage forms of dietary supplements.

Most reputable Dietary Supplement Manufacturers have procedures in place that deal with returned goods. These include a formal evaluation by the Quality Unit, based on critical factors related to the reason for the return. We believe the Agency needs to consider the rationale for the return and not arbitrarily require a Manufacturer to test the finished product.

We provide the following justification for this opinion:

1. Many returns in the Industry are at the Corporate Customer level. We have found that most of these returns are not Quality related. In fact, most are due to commercial factors, with the most significant reason being "overstock" returns. This is especially true after a large customer holds a promotion that has a specific cut-off date. They will typically return the overstocked material and allow us to reship it to them over time to minimize spatial constraints and financial considerations with respect to holding large quantities of inventory.

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RETURNED GOODS (continued):

2. Most modern-day retailers have a very clear understanding of the storage limitations of the products that they sell. In fact, this is a commercial necessity if they are going to survive amongst their competition. In most cases, the general storage facilities are maintained under temperature and humidity control to protect the integrity of the products that they have accepted. There are some products that in fact, require specialized storage conditions such as chocolate, to prevent "Bloom" defects. Most Dietary Supplements are very stable under typical warehouse storage conditions and are not likely to show any signs of degradation or deterioration. In fact, solid dosage Dietary Supplement products are at such a low water activity (A_w) that microbial growth and chemical degradation are slowed to a minimum.

These factors make corporate customer returns a very low risk issue. We therefore propose that the Agency require the Quality Control Unit to evaluate returned goods and allow for a reduced testing scheme based on the rationale for the return.

If a product is returned for a quality defect, then certainly the Quality Unit should assess the impact of the defect and determine if the product is saleable, can be reworked or if it should be outright rejected. If the product is returned for a reason not related to Quality, such as overstock, then we feel a simple organoleptic evaluation to confirm that the product has not deteriorated is suitable. We feel that testing the product fully against all specification requirements is not necessary in these cases. The bottom line is, the authority must rest in the Quality Control Unit to determine what is suitable for returned goods on a case by case basis.

WRITTEN PROCEDURES:

The Agency has requested input from Industry concerning the need in the Final Rule for written procedures. The Proposed Rule, only requires a written procedure for establishing a calibration program.

In the Industry Draft that was published within the ANPR on February 7, 1997, the Industry had written procedures built into the standard as a key element on the basis that Quality must be built into a process. In order to build Quality into a process, effective communication is essential. SOP's are the basis for effective communication throughout all levels of an organization. They are also a necessary element of any properly designed Change Control System.

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WRITTEN PROCEDURES (continued):

It is our opinion that written procedures are a must requirement in any manufacturing environment. They help ensure the consistency and quality of the process from batch to batch throughout all shifts of operation. They also serve as critical training tools to minimize the chance for failures to occur. Written Procedures are also a critical element to ensure consistent implementation of proper corrective action.

All major well-recognized Quality Systems require the establishment of written procedures to ensure that the process is consistently controlled. This would include ISO, ANSI and the Malcolm Baldridge National Quality Award criteria. It is a known fact among Quality Administrators that written procedures are the best mode of prevention to eliminate quality defects and failures. It is also well known in the same Quality circles that these procedures pay for themselves by reducing the total Cost of Quality with reference to internal and external failures.

It is our opinion that based on the rationale provided, the Agency should require written procedures for the following critical operational elements:

1. The receipt, identification, evaluation, handling, sampling, testing and approval of all raw materials.

2. The receipt, identification, evaluation, handling, sampling, testing and approval of all packaging components. Corrugated shipping containers that are not printed should be an exception to this requirement.

3. The receipt, identification, evaluation, handling, sampling, testing and approval of all labeling.

4. Cleaning and maintenance of equipment and utensils used in the manufacturing process, with special emphasis on product contact surfaces.

5. Procedures to ensure that labeling and packaging materials are correctly issued and utilized.

6. General procedures for establishing requirements for reworking non-conforming product and scrap.

7. Procedure for the investigation, review and approval of all complaints related to product quality.

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WRITTEN PROCEDURES (continued):

8. Procedures to document the reliability and testing requirements associated with analytical methods that are developed in-house. Note that compendial methods would be excluded from this requirement; however, a Manufacturer should establish the suitability of a compendial method.

9. A general procedure to document the minimum investigation, review and approval requirements for failures in manufacturing or packaging operations.

10. A general procedure to document the minimum investigation, review and approval requirements for Laboratory Out of Specification test results.

11. A procedure documenting the responsibilities and authority of the Quality Control Unit needs to be documented

We believe that the cost impact of creating SOP's and maintaining them in an appropriate Change Control System is insignificant compared to the cost that a company would incur for Quality failures due to the absence of SOP's.

CLEANING COMPOUNDS AND SANITIZING AGENTS:

In this section there is a statement that says "you must use cleaning compounds and sanitizing agents that are free from micro-organisms of public health significance and safe and adequate under the conditions of use".

We would like the Agency to clarify its expectations with respect to substantiating that a cleaning compound or sanitizing agent is "free from micro-organisms of public health significance and safe and adequate under the conditions of use".

We believe that is not necessary for a Manufacturer to pro-actively test these types of products and that a Continuing Product Guarantee combined with a statement of intended use from the Manufacturer of the cleaning compound and/or sanitizing agent will suffice to meet the requirements of this section.

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POTABLE WATER:

This section states a Manufacturer must have documentation or otherwise be able to show that water that contacts components, Dietary Ingredients, Dietary Supplements or any product contact surface meets the National Primary Drinking Water Regulations prescribed by the Environmental Protection Agency (EPA) under 40 CFR Part 141 and any state and local government requirements.

We would like the Agency to clarify their expectations concerning what is considered suitable documentation. It is our opinion that if water is sourced through a municipal water system that is monitored by a state, county or city agency in accordance with EPA Primary Drinking Water Standards then no documentation shall be required. We believe this is reasonable because this due diligence is being performed on behalf of the Manufacturer through their tax dollars. There is no added value for the Manufacturer to repeat the protocols of the National Primary Drinking Water Standard when the data is already available to them.

On the other hand the Agency expectations may be significantly different and justifiable so for someone who is using ground water from a private well. It may help if the Agency would clarify expectations for each of these cases.

QUALITY CONTROL UNIT:

Throughout the Proposed Rule the Agency refers to approval activities through the Quality Control Unit. The Agency; however, provides a very general definition of Quality Control Unit to mean "any person or group that you designate to be responsible for quality operations."

We want to be certain that we understand the Agency expectation with respect to Quality Control Unit responsibilities. We believe that a Quality Control Unit must bear the overall responsibility and have final authority for the release of product. We believe, as most quality standards authorize, that operations or production personnel must be responsible and empowered to check and verify that the work that they performed has met the requirements of the pre-established standards applicable to that specific unit operational element. We feel that this is how most quality operations are set up to ensure that quality is "built in" to the operation and not totally based on a post-approval quality activity.

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QUALITY CONTROL UNIT (continued):

For example, in Proposed Rule 111.37(b)(1-15) the Quality Control Unit responsibilities with respect to approvals are stated: however, not clearly defined. In this section it is not clear as to whether the agency expects the formal Quality Control Unit to approve these unit operational activities as soon as they have occurred or if the Quality Control Unit can approve the same operational activities collectively at the end of the process. In-process approvals under a system of empowerment are typically performed by Operations personnel and the Quality Control Unit performs a collective post processing final approval.

To further elaborate, Proposed Rule 111.37 (b)(7) requires that the Quality Control Unit review all records for calibration of instruments, apparatus gauges and recording devices. We believe that this type of verification need not be done by someone in the Quality Control Unit. We believe that this type of verification is better suited to be handled by empowered individuals responsible for the equipment in their particular unit operation. We feel that the Quality Control Unit role should be to audit the calibration process on a periodic basis and to approve all corrective actions when a particular piece of equipment is found to be outside pre-establish calibration limits versus the reference standard material.

Please confirm that it is not an Agency expectation that personnel in a formal departmental Quality Control Unit need not police and approve every unit operational activity as it is performed in the plant.

Please confirm that the Quality Control Unit authority as defined in the Proposed Rule does not require or limit approvals of conformance to pre-establish specification requirements to individuals only in the formal Quality Control Unit.

CORRECTIVE ACTIONS:

In Proposed Rule 111.45(b)(8)(v) the Agency requires written instructions for corrective action when a specification is not met.

We believe that pre-established corrective action requirements can be detrimental to product quality. We believe that this requirement needs to be significantly amended or deleted from the Proposed Rule altogether.

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CORRECTIVE ACTIONS (continued):

We have found that pre-establish corrective actions can be useful for some unit operational activities when the specific corrective action has no impact outside that particular operational activity. For example, in tablet compression operators are trained to make in-process adjustments to ensure that critical tablet parameters including tablet weight, hardness, thickness and friability remain in a state of control between pre-established specification limits. Actually if Statistical Process Control is in use there are typically two sets of limits (alert limits and action limits) established which dictate the type of corrective action that the operator must take.

In other situations the corrective action required may be much more complex and beyond the training and experience level of the particular operator. For example, if product is spilled onto the floor during a blending operation we believe that it is imperative that the Quality Control Unit be notified so that they can make a determination as to the status of the particular batch. In this case, a re-allocation of raw material to compensate for the spillage may be necessary to ensure Dietary Ingredient limits are achieved. This type of correction is best to be assessed by the Quality Control Unit (and typically Research and Development) to ensure that the adjustment is going to achieve 100% of the label claim.

In other words, we believe that there are possible failure scenarios that go beyond simple corrective action and the determination of corrective action must be left to and approved by the Quality Control Unit on a case by case basis.

MASTER MANUFACTURING RECORDS:

Under Proposed Rule 111.45 (b)(7) the agency requires that a description of packaging and a copy of the label be included as part of the Master Manufacturing Record.

We believe that this is contrary to current Industry practices for the Dietary Supplement Solid Dosage Form Industry. Most companies that are manufacturing solid dosage form Dietary Supplement products treat their tablet manufacturing operation and packaging operation as two separate and distinct operational elements.

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MASTER MANUFACTURING RECORDS (continued):

The Master Manufacturing Record only includes the specifics required to manufacture the tablets. The actual description of packaging and label copy requirements are contained in separate documents that are cross-referenced to the Master Manufacturing Record by a product part number. We believe that cross-referencing Master Manufacturing Records to other GMP documents through a part numbering system that includes specific change control elements will satisfy Agency expectations. We would like for the Agency to please clarify its expectations with respect to this element of the Proposed Rule.

BATCH PRODUCTION RECORD:

Under Proposed Rule 111.50 (b)(c)(4) the Agency is expecting Manufacturers to include maintenance and cleaning and sanitizing documentation in the Batch Production Record.

We believe that this is contrary to current industry practices and there is no value to have these records included with a Batch Production Record if they are easily retrievable through equipment cleaning and use logs and maintenance logs.

We believe that the Agency should allow for separate and distinct maintenance and cleaning and sanitation documentation.

REPROCESSING:

Under Proposed Rule111.50(f) the Agency is prohibiting reprocessing, if for example a product becomes contaminated with micro-organisms of public health concern or other contaminants such as heavy metals. We are not clear if this would apply to contaminants that may be indigenous to specific starting materials and by virtue of further processing the product is rendered free of these contaminants.

For example, Calcium Carbonate is manufactured from limestone and to meet industry requirements with respect to heavy metal contaminants, especially lead it is further processed to remove these contaminants. In this case the lead is indigenous to the starting material; however, it is possible under some conditions that the material may have to be subjected to the process several times to reduce the amount of lead to the desired industry level.

A second example might be with respect to indigenous microflora that are found commonly in products of natural origin. A botanical product may be processed specifically to eliminate micro-organisms of public health significance.

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REPROCESSING (continued):

Sometimes this can be accomplished by pasteurizing the material prior to spray drying. In the dry form the product is not susceptible to microbial growth due to its low water activity. Can a Manufacturer reprocess this material if they for example find that it has a higher coliform count than established by its original specification? We believe this would be a reasonable course of action.

We believe that this requirement as proposed is too restrictive and the agency should allow for reprocessing to occur if it is formally approved by the Quality Control Unit. We believe that this is allowed under the food GMP as defined in 21 CFR Part 110.80. We believe that Dietary Supplements should not be treated any differently than the Conventional Food Industry with respect to this requirement.

We would also agree that if the contamination is due to gross mishandling by the Manufacturer and the Manufacturer is not equipped to properly reprocess the material then they should not be allow to reprocess the material. In addition, we would also agree that the mixing of a food containing a specific contaminant above a regulatory specification limit (i.e. defect action levels) may not be mixed or blended with another lot that is not contaminated to attempt to render conforming product.

This restriction may be most limiting to Manufacturers of specific Dietary Ingredients as they may rely on their process design to specifically reduce contaminants to a more desired (and safe) level.

PACKAGING AND LABELING OPERATIONS:

Under Proposed Rule 111.70 (a) a Manufacturer must take necessary actions to ensure that each packaging container for holding Dietary Ingredients or Dietary Supplements meets specifications so that the condition of the packaging container will not contaminate Dietary Ingredients or Dietary Supplements nor cause them to deteriorate.

We would like the Agency to clarify its expectations with respect to substantiating that packaging containers meet specifications and will not contaminate Dietary Ingredients or Dietary Supplements.

We believe that it is not necessary for a Manufacturer to pro-actively test these types of products and that a Continuing Product Guarantee combined with a statement of intended use from the Manufacturer of the packaging material will suffice to meet the requirements of this section.

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PACKAGING AND LABELING OPERATIONS (continued):

We believe that this is consistent with expected practice in other industries that the Agency regulates. We would also like to point out that the preamble of the regulation noted no cases where packaging material failures had caused any type of significant public health concern. In addition, the types of packaging used in this Industry are virtually the same as those used in both the Food and the Over-the-Counter Pharmaceutical Industries.

If the Agency has different expectations then we would like to understand these expectations and the rationale behind why additional controls may be necessary to ensure the identity, strength, quality, purity and composition of Dietary Supplements and Dietary Ingredients.

RECORD KEEPING:

Under Proposed Rule 111.125 (c) the Agency has stated that Manufacturers must have all records required under this part, or copies of such records, readily available during the retention period for authorized inspection and for copying by Agency when requested.

We would like to understand the statutory basis for the Agency to have access to records for Dietary Supplement and Dietary Ingredient Manufacturing facilities.

CONTROL OF REJECTED MATERIALS:

Under Proposed Rule 111.74 the Agency requires that Manufacturers must clearly identify, hold, and control under a quarantine system any component, Dietary Ingredient, Dietary Supplement, packaging and labeling that is rejected and unsuitable for use.

Many companies in the Dietary Supplement Industry like the Pharmaceutical and food industry have electronic Material Resource Planning (MRP) systems to control the status of inventory. We believe that these types of systems provide suitable controls to ensure that only materials that are approved by the Quality Control Unit are used. If this is different from Agency expectations, then we would like to understand the detail behind the Agency expectation so that we can determine if we comply with the expectations.

We have assumed that our current electronic system is acceptable based on the fact that it is a secure system and only Quality Control Unit personnel have the authority to release any material that is on quality hold or quarantine.

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CERTIFICATION PROGRAMS:

In the preamble to the Proposed Rule the Agency stated that the use of certification marks may be misleading if they are not qualified so that the end user clearly understands the basis.

We agree that any certification mark should be qualified so that the end user understands exactly what the certification is all about. Unfortunately due to limited label space it is sometimes difficult to provide the end user with the necessary information to make an informed choice. Would the Agency consider a cross reference on the labeling to information contained in a web site or available through US mail?

The Perrigo Company of South Carolina appreciates the opportunity to comment on the Agency Proposed Rule for Dietary Supplement GMPs. Please feel free to contact me at 864-627-3704 if there are any questions or if additional information is required by the Agency.

Respectfully Submitted

Michael S. Bradley

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PERRIGO

August 11, 2003

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

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

Dear Ms. Butler:

Per our telephone conversation today, August 11, 2003 concerning the Perrigo comments (letter dated August 8, 2003) to the above referenced docket number we request that the agency please disregard the confidential statement appearing throughout this document. We recognize that submissions are fully disclosable to the public and have no objection to the disclosure of our comments to the public domain.

Please call if you have any questions or any additional concerns.

Respectfully submitted,

Michael S. Bradley

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