June 4, 2003

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

Re: Comments to Information Collection pertaining to Docket No. 96N-0417

Dear Sirs:

Overall Assessment

We believe the proposed dietary supplement GMP's as offered by you for comment are well-intended but do not protect the consumer as intended. Rather they unduly complicate certain aspects of good manufacturing practice and completely miss key areas for safeguarding product identity, purity, quality, strength and composition.

Organization of Comments

We are providing these comments as insights on what we at Enzymatic Therapy believe is necessary to make the new proposed dietary supplement GMP's much stronger, more useful to the industry and better accomplish the intended consumer benefits. The organization of our comments is intended to permit you to find our input on any given subject easily as we have the comments organized following the exact flow you provided in the proposed statute. Therefore, we have listed all sections of the proposed statute regardless of whether we had a comment pertinent to a given section or not. If we have offered no comment on a particular section, it is because we cannot offer comments which we feel would make it stronger.

Agreement with Intent

In general, we wholeheartedly agree with the overarching intent of the proposed regulation...to ensure dietary supplement products deliver to the consumer what they are expected in relation to identity, purity, quality, strength and composition. However, the means by which you have proposed to do this which principally has a finished product testing focus at the exclusion of many other important dimensions of product performance is in serious need of many changes. We believe you have a good start on a strong set of regulations guiding this industry but need to revise this proposed regulation in relation to addressing key topics such as expiration dating, in-process controls, written procedures, as well as circumstances where vendor-supplied information can justifiably be used on the basis of their validated qualifications.

Economic Analysis Flawed

We believe your economic analysis, even without considering the incremental cost of important dimensions not included, vastly underestimates the cost of implementation of these proposed regulations. We have provided you much detail which fully quantifies this point. We feel if many revisions and improvements are not made in the proposed regulations they will have a hugely negative effect on our industry, resulting in many companies going out of business. If

enacted as proposed, products will need to become much simpler with less specific content information provided to consumers. Prices will increase as a direct result of cost increases the manufacturer will be forced to bear. Ironically, the intended beneficiary of this, the consumer, will ultimately become the biggest loser.

A Consideration

A question for consideration by you is whether the final regulation will be accompanied by a re-write of the "Description of the Proposed Rule"? We find that our interpretation of the proposed rule doesn't always agree with your "Description" and if some industry comments are incorporated in a new rule, some of the current "Description" sections may not be applicable.

Our Desire: Make the Overall Industry Safer

We offer these comments to you with the hope that you will make considerable revisions to the proposed regulations and will, in turn, provide industry the opportunity to again comment on the revisions. While commenting again may seem cumbersome and possibly slow down the timing for implementation, we feel there are revisions which are critically needed in the proposed regulations. These, if properly dealt with will make the proposed regulations vastly different and better deliver the intended consumer benefits. In our view, industry and FDA will benefit greatly by having another chance to comment following revisions. As you are aware, we operate as a regulated industry at this point in time and the regulations we operate under today, if properly enforced, do have the ability to control this industry. Revising the new set of regulations while FDA and industry continue to work together to get this right will pay dividends in the long run particularly for the consumer.

Sincerely,

Robert C. Doster, Ph.D.
Sr. V.P., Scientific and Regulatory Affairs

PART 111 – CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKING, OR HOLDING DIETARY INGREDIENTS AND DIETARY SUPPLEMENTS

F. Proposal Highlights and Requests for Comments

The following items indicate selections for which FDA has invited comments:

Proposed Recordkeeping Requirements

We wholeheartedly agree that certain critical documents are necessary to assure quality control of dietary supplement products. Your requirements for batch records are one such requirement that is necessary and seems appropriate for the food industry as well where supplementation with vitamins, minerals, and other nutrient claim ingredients are used.

Personnel Records

It is critical that FDA requires written documentation and tracking of employee's training records. For example, FDA should require, in the final rule, that you document and keep records regarding each employee's training. The records should show the content and date of the training. A formal (written) GMP training program will definitely be necessary to track which employees have been trained on the required GMP's. Without formally documenting the training function it is very likely that some employees may not receive any GMP training or insufficient training that allows them to produce a safe, legal, and efficacious dietary supplement. The training program should include an evaluation of the employee's understanding of the training and should specify a frequency for refresher training. This will ensure employees receiving training understand what they have been trained on and will continue to practice GMP's over the long term. ***A training program that does not include documentation will likely lead to adulterated dietary supplements as employees will likely not be appropriately trained on the portions of the final rule that directly apply to them.*** Without written documentation that training has occurred, how does FDA anticipate being able to fully evaluate a firm's compliance to these requirements?

Written Procedures and Control Documentation for Certain Operations

In response to your inquiry whether industry should or should not be required to establish and follow written procedures for certain operations, we believe the industry should. In 21CFR drug cGMPs (parts 210 and 211), there are at least 25 separate citations to written procedures. We believe adhering to written procedures ensures our commitment to providing products that meet all specifications for identity, purity, quality, strength, and composition. ***Written procedures not only contain step-by-step instructions that personnel consult to complete tasks reliably and consistently, but they are necessary as a training tool to new employees to ensure all employees know all steps completely to perform their job.*** Written procedures in the form of SOPs, protocols and manufacturing records are necessary to insure consistency of manufacturing and product testing. Unwritten procedures are likely to be inconsistent and are less likely to be enforced, jeopardizing the safety of dietary supplement products or ingredients. ***Documenting that written procedures are followed and recorded are necessary to ensure compliance to specifications.*** Written procedures are necessary in the final rule to provide an organized means of producing and communicating appropriate information to the employees as well as regulatory authorities during inspections.

Equipment Verification and Electronic Equipment Validation

Expiration Dating and Related Testing

We disagree with the omission of expiration dating as supported by the following comments.

1). Our customers are extremely aware of practices in other industries (most notably the pharmaceutical and food industries) that incorporate expiration, best before, born on, freshness, and other types of dates. As a company that historically did not use best by dates, we took extensive measures to study and assign shelf life dates over a five-year period. These dates are supported by in-house shelf life studies as well as raw material stability information, similar product and packaging configurations, and more. During those years, our number one customer/consumer complaint was the absence of expiration dates on our products. More recently, some larger customers have actually required dates on products they buy from us in order to receive these goods into their computerized inventory systems. ***It would be a disservice to customers and consumers to not include expiration dating.***

2). Not only is it important to assure label compliance at time of manufacture, but it is essential that the consumer receive product that has maintained potency of actives within its label claims until time of use. An excellent example of this was cited on p. 12162 of the section *D. Food Advisory Committee Report, 1. Why Are the CGMP's Needed?* "Folic acid is important in the reduction of neural tube defects." ***The consumer needs the assurance in such critical applications that the levels are maintained throughout the shelf life of the product.***

3). At the end of the Folic acid example cited in *D. Food Advisory Committee Report, 1. Why Are the CGMP's Needed?* it states, "if a label for a folic acid supplement declares that the dietary supplement contains a certain level of folic acid, the folic acid supplement must actually contain the level, or we would consider the folic acid supplement to be adulterated under section 402(g) of the act." This statement directly implies that any time marketplace product is tested, it needs to contain the labeled amount. Karen Strauss, Consumer Safety Officer at CFSAN, also addressed a similar comment during NNFA's *FDA Dietary Supplement GMPs: What you Need To Know* webcast on 3/13/03. ***She stated that if a product did not have an expiration date on the labeling, it would be assumed to meet label claims indefinitely.***

4). In the absence of expiration dates, products cannot simply be assumed to meet label claims indefinitely. Long or possibly indefinite expiration dates may be feasible in limited cases, such as mineral tablet supplements, but this is definitely not the normal situation. You acknowledge on p. 12203 that, "manufacturers intentionally add a specific amount of a dietary ingredient in excess of the declared label amount so that the finished product can meet the label declaration for that dietary ingredient throughout the product's shelf life." ***Without using expiration dates, the manufacturer cannot be sure how long that product will remain in the marketplace, and thus, will not be able to appropriately determine what level of overages for ingredients are necessary to assure label compliance.***

5). By requiring expiration dates, appropriate stability or shelf life testing is needed. This was supported by Karen Strauss, Consumer Safety Officer at CFSAN, at the NNFA's *FDA Dietary Supplement GMPs: What you Need To Know* webcast on 3/13/03. In response to a comment, she stated that if an expiration date was printed on the label, then there should be testing to support such a date. Without this being stated in the proposed regulation, some companies may not comply with this implication. On the other hand, some manufacturers like Enzymatic Therapy have spent a considerable amount of time and money

generating data supporting shelf life assignments used on their products. Not requiring all manufacturers to support their dates will not be fair to companies that have that support in place. ***More importantly it is not fair to the consumers that demand "meaningful" dates be placed on dietary supplement products.***

6). We acknowledge that there is a high cost associated with implementing shelf life studies to determine expiration or best by dates. However, we propose that doing such testing could be used as justification to reduce or supplant the final product testing proposed in 21 CFR 111.35 (g)(1). ***Shelf life studies are more beneficial than final product testing alone, because the rate of decline can be determined in addition to label compliance.***

7). In the section *D. Food Advisory Committee Report, 2. How Will CGMP Regulations Take Into Account Technical Feasibility?* you state that "additional scientific study is necessary before we can propose a dietary supplement CGMP requirement" for such things as expiration dating. On page 12203 you further state, "We are not proposing expiration dating at this time because we have insufficient scientific information to determine the biological activity of certain dietary ingredients used in dietary supplements, and such information would be necessary to determine an expiration date." Although biological activity of the ingredient may be unknown, the compliance to stated label claims must still be assured, as is the case with standardized botanicals. We agree that there are special circumstances that surround many dietary ingredients (e.g., no analytical method for final product testing or significant numbers of ingredients per product), thus the proposal should allow the manufacturer discretion on how they test and/or support their expiration dates. We believe there are valid approaches to shelf life dating other than those found in the drug regulations and guidelines. Other approaches include, but are not limited to, raw material stability data from vendors, accelerated and ambient stability studies, re-testing of reserve samples, testing of only the most vulnerable ingredients per product, extrapolation of data between similar ingredients, products, and/or packaging variations, and other sources of documented information and scientific rationale.

8). On page 12203 you indicated that "we are uncertain whether there are current and generally available methods to determine the expiration dating of other dietary ingredients, especially botanical dietary ingredients." And on page 12204, "...few official methods are available to assess the strength of a dietary ingredient in a dietary supplement." Then on page 12198, when justifying the requirement for extensive finished product testing under proposal 111.35, FDA states that "While there may not be an AOAC or FDA method available, we are not aware of a situation where an appropriate scientifically valid analytical method is not available." These statements directly contradict each other. We would argue that methods do not exist for all dietary ingredients and product matrices available, but where methods do exist, label claims could be confirmed via a shelf life testing program.

SUGGESTED REVISION

The Advanced Notice for Proposed Rulemaking (ANPRM), USP, and NNFA have all proposed expiration dating GMP's. From these we would propose the following revision:

(1) A product with a limited shelf life resulting from its content of unstable dietary ingredients must be labeled with an appropriate expiration date.
(2) Whenever a dietary ingredient or dietary supplement bears an expiration date, such date must be supported by rationale and/or data to reasonably assure that the product meets established specifications at the expiration date.
(3) Appropriate accelerated stability studies or data from related ingredients or product formulations may be used for determination of shelf life. Shelf life may be extended or confirmed on the basis of real time studies on ingredients or products stored under conditions stated on product labels.

If the FDA still decides against mandatory expiration dating, then we would suggest at a minimum that points (2) and (3) above be added to assure that when dates are used there is a basis for their determination, such that the consumer can be believe what they read on the product label.

Requirements for Animal-Derived Dietary Ingredients

Fish Oil Ingredients

You state in Subpart A, 111.5, pg. 12179 that "a manufacturer who produces a dietary supplement that includes fish and fishery products, such as fish oil, would have to comply with HACCP regulations....as well as these CGMP provisions...." However, on pg. 12174 in your discussion of Question 8, you state that HACCP principles will not be required for manufacturers of dietary supplements, but could be implemented voluntarily. As a manufacturer that does not produce fish oil raw materials or fish oil supplements but does distribute finished goods from contract manufacturers that contain fish oil and may use fish oil-containing raw materials in the manufacture of supplements in the future, we would like clarification on whether the HACCP principles would apply to our situation or whether they would just apply to the initial processing of the fish oil (i.e., to the raw material supplier).

Questions

Furthermore, would a domestic dietary supplement manufacturer be required to ensure that foreign fish oil (dietary ingredient) or fish oil capsule (dietary supplement) manufacturers (that they are importing from) comply with HACCP? Would a fish oil dietary supplement imported in finished product form be considered adulterated if the foreign firm was not manufacturing in compliance with HACCP guidelines?

Requirements for Persons Who Handle Raw Agricultural Commodities

Education and Training Assistance for Implementing Regulations

Assurance for Imports Meeting the New Regulations

Pathogen Reduction Approach

You have asked whether or not all contact surfaces should require sanitization. Our response is that each manufacturing operation will need to determine when sanitizing agents are needed after cleaning because of the wide variety of processes in the industry. For example, the *Pharmacopeial Forum 29 (1)* under *<2023> Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements* identifies that non-aqueous or dry dosage forms do not support microbial growth because of low water activity. It also notes that tablet compression causes increases in temperature and pressure that will decrease microbial counts. Manufacturers of extract materials may also use high quantities of ethanol, which acts as a natural sanitizing agent. In comparison, manufacturers who use water extraction processes or manufacture liquid preparations, would need to consider higher levels of microbiological control and most likely sanitization. It must also be noted that widespread use of sanitizing agents is creating more and more resistant microbial strains, so incorporating unnecessary sanitization processes would contribute to this health concern.

SUGGESTED REVISION

Our recommendation is that sanitization procedures should be calibrated to the particular process and by the manufacturer in a declared fashion dependent upon the risk factors of their process and materials. Low risk operations would be able to clean with streamlined sanitization and incorporate raw material and product skip-lot testing to monitor that the environment is not changing. More intense sanitization processes, the determination of a 5-log reduction in disease microorganisms of public health significance, and more vigorous microbial testing would be limited to those processes and industries where the risk level is higher, again in a declared fashion by the manufacturer.

Documentation Regarding Consultants

Requirements for Plant Grounds

Defect Action Levels

GENERAL COMMENTS

The following are general comments and cost analyses.

VII. Analysis of Impacts

7. Costs, c. Major costs by type of activity, iii. Testing

Enzymatic Therapy has adopted a series of quality control processes that ultimately do not require complete testing of each finished product lot yet provide absolute safety and efficacy in our finished product lots due to quality confirmation processes throughout the entire sourcing and manufacturing sequence. These include process validation, cleaning validation, vendor certification, certificate of analysis confirmation testing, raw material and product certification, skip-lot testing, shelf life testing, and more. We feel that the ***100% finished product lot testing is not justified***, and the ***cost of such testing has been far under-estimated*** in the proposed rule. The cost will be crippling to the industry without providing the consumer the intended benefit.

To evaluate the cost impact, we have included a review of our company, testing facility, ingredients, product line, etc. to help the FDA understand the impact of this regulation on Enzymatic Therapy as a typical small dietary supplement manufacturer. This information is tabulated below and specifically includes information for where we feel the FDA's cost estimations were vastly under-estimated or derived from inaccurate industry averages or assumptions.

Category	Explanation
Company size	Small firm of < 250 employees with sales of $50 to 80 million.
Current product profile	We sell approximately 250 products. We manufacture tablets and hardshell capsules and have softgel capsules, powders, and lotions contract manufactured. In-house manufactured products are comprised of over 300 different raw materials including vitamin, mineral, amino acid, standardized botanical extract, herbal extract, herbal powder, animal-derived, other nutrient, excipient ingredients and more. On average, each of our products is comprised of 14.3 ingredients, of which 8.7 are dietary ingredients, and we estimate that 7.6 may be testable in each finished product batch. We also estimate that approximately 200 of the raw materials may be testable in the final product according to the proposed regulation.
Number of raw material and product batches we process annually	In the past 12-month period, we received each of our more than 300 raw materials an average of 6 times. This equates to approximately 1800 raw material releases for our in-house production. We released approximately 1350 product batches.
Current QC / QA operating costs	We currently employee more than 20 QC/Lab/QA employees. The annual operating budget (including wages, benefits, supplies, contract lab fees, repair/calibration of equipment, samples, etc.) of these departments exceeds $1.5 million.
Current testing facility	We operate a lab of approximately 4500 square feet with capabilities in GC, HPLC, FTIR, TOC, microbial analysis, AA, dissolution, conductivity, UV spectrophotometry, and more. The lab start-up costs are estimated to be in excess of $1.5 million.
Current testing profile	In the past 12 months, we have completed approximately 500 product potency assays and approximately 250 raw material potency determinations for release testing. In addition, we have completed approximately 700 product microbial tests and 8,650 raw material

	microbial tests for release. These numbers do not include testing from non-release functions such as shelf life studies, validation studies, vendor certification, etc. and also don't include other test categories such as sensory, physical, and purity analyses. When considering all of these tests, we have logged over 36,000 tests in the past 12 months on over 4400 different samples.
Affect of the new testing regulation on our current QC / QA staffing	Our current staffing is not sufficient to take on the tremendous increase in expected testing. We are also not willing to sacrifice our current GMP processes (e.g., shelf life testing, vendor/raw material/product certification, process/cleaning validation, etc.) by re-directing current staff to the 100% finished product testing proposal. Therefore, all costing and personnel estimates are based on pursuing contract lab analyses. We estimate that handling nearly 10,000 additional contract lab analyses and QA data review would require at least 2 additional full-time QA/QC employees with wages/benefits of approximately $12 - $22 / hour. The contract lab result reporting and investigation of out-of-specifications would require at least one additional QC chemist at an approximate wage/benefit cost of $15 - $24 / hour. These numbers are very low estimates since this example only includes potency testing of 100% of finished products.
Average testing costs	We evaluated four products that ranged in testable ingredient claims from 3 to 35 per product. The products included a single ingredient nutritional product, an herbal and amino acid product, a 15 ingredient multiple and one of our most complex multiples. The average cost per potency test on these products ranged from $99 - $298. Breaking this down differently, we determined the average cost per type of analysis to be as follows: Vitamin = $120, Mineral = $70, Herbal = $290, Other Nutrients = $175. Weighting this average by the profile of ingredient types in our product line, the average cost per potency analysis is $145. The average cost for microbial analysis is $16 per test. For potency testing, we recently had 30 products tested for all applicable USP/NF monograph items. The 287 analyses pursued came at a cost of greater than $30,000 or an average cost of more than $104/test. Since the majority of these analyses represent common vitamin and mineral analyses, it seems appropriate that the average would increase when other nutrients and herbals are included. Cost savings gained by analyzing the same analyte in multiple products are rarely realized for a small company. This is because contract labs rarely offer price discounts for under 10 duplicate analyses, and it is not cost effective to hold inventory waiting for products with similar analytes to be tested concurrently. We have also experienced very few methods in which multiple components are tested simultaneously. For those we are aware of (e.g., minerals by ICP), contract labs still have a specific charge per analyte reported.
Additional testing costs to incur	The number of product release potency tests required by the proposed regulation can be simply calculated as the number of testable ingredients x number of batches annually x avg. testing cost and this equates to **$1,473,374**. This represents an increase of $1.4 million over our current product release potency testing (note that our

	additional potency testing for raw materials, shelf life testing, and material certification is nearly $200,000 annually). Similarly microbial testing of products could escalate to $108,000 or an increase of nearly $97,000 annually. These estimates don't even begin to identify the total cost impact because raw material and in-process tests have not been included nor have other purity, identity, and quality tests.
Method validation costs	In our response to §111.60(b)(1)(v), we identify that the Description of the Proposed Rule makes it unclear as to the level of validation required for products being tested by official or scientifically valid methods. We have received method validation cost estimates of $3,000-$15,000 per analyte and matrix. At a minimum requirement of validating each of our testable analytes (approx. 200) at the lowest cost, the impact would equate to more than $600,000.
Other expected costs	We expect that the necessity of testing 100% of ingredients in finished products will result in the generation of more false negative or failing results due to the complexity of the product matrices being evaluated and due to the large number of tests being run. It is well understood from statistical probability analysis that there is a compounding of error rates as more analyses are run on a single sample, and thus our concern on a product such as the one noted above which contains 35 testable claims seems legitimate. We have partially addressed this above by the addition of a chemist to do out-of-specification investigations, but the potential for unnecessary product re-working is a more difficult number to grasp and potentially much more of a financial burden. To avoid unnecessary re-working due to false negative results, we could also add more ingredient overages to formulas. Again this comes at significant incremental cost in either testing or outright throwaway cost associated with scrapped product.

The magnitude of the cost implications is astounding, but doesn't begin to reflect the other impacts on the industry. One additional example would be the impact on the availability of testing facilities. From our example it appears that there could be more than a 20-fold increase in the number of analyses being pursued by the industry. The fact is that it is doubtful that this large of an increase could be managed by the current contract lab facilities or in-house laboratory facilities, thus requiring costly lab expansions. We also fear that this large increase in workload would affect the turn time at outside labs, and thus further escalate our product costs for holding inventory.

All of these comments point directly to the fact that 100% finished product testing is extremely costly, and not necessary in light of other quality control processes that can be implemented on an industry-wide basis such as process validation, cleaning validation, vendor certification, material and product certification, skip-lot testing, and more. In addition, the proposal states that dissolution testing and expiration dating were not included because further scientific study is needed. If the FDA statement on these procedures is valid, it stands that the FDA should consider this the same reason for not including 100% finished product testing. There are by far more cost effective and scientifically valid means of determining the end product is safe and unadulterated than having to 100% test every batch.

Subpart A – General Provisions

111.1 Who is subject to these regulations?

111.2 What are these regulations intended to accomplish?

In 21CFR 111.2 you state "Our primary purpose in proposing these regulations is to protect consumers from adulterated and misbranded dietary supplements due to improper manufacturing, packaging, or holding practices." ***We wholeheartedly agree with this purpose.*** As a manufacturer of dietary supplements, we have implemented an intensive quality control system to insure that our products contain what they say they contain. Our concern is that this ruling may hamper your efforts rather than enhance them due to the large capital implementation and cost escalation that will be required to comply with them. FDA's narrow focus on finished product testing will not achieve this primary purpose alone. For example, improper manufacturing may or may not be detected through finished product testing. Batch non-uniformity resulting from inadequate mixing could go undetected in the testing of a finished product sample. FDA should broaden its focus by including requirements that control the entire process (i.e., process, supplier and raw material validation) rather than just focusing on testing the end result of the process. This situation is delineated more fully in other parts of these comments.

111.3 What definitions apply to this part?

The meaning of "same cycle of manufacture" in the definition of "batch" needs better clarity surrounding definitions you have made. Did you intend this to mean the same product made with the same lots of raw materials independent of the number of days of production or is it limited to one day's production? If the latter, it seems wasteful to not be able to consider a batch as anything other than a consecutive series of day's production for example during which nothing changed, e.g., no lot changes of raw materials, no process variations, etc. Relatedly, if the quality assurance unit proves that different lots of raw materials are equivalent to each other by meeting all specifications, can consecutive production days with the same formula be considered to be the same batch as relates to the need for finished product testing? There is need to clarify this point. We strongly suggest that it be based on clear logic in relation to whether anything has changed that constitutes a need to assay analytes within a finished product within a production period. If the process and raw materials are consistent, meaning there is equivalency, single point testing of a sample representative of this production period is all that should be required.

Throughout the document, the term adulteration is used to delineate the situation that occurs when a product does not meet the claim specified. However, this term is not defined in 21CFR 111.3. We suggest incorporating into the regulation the definition of adulteration given in Chapter IV – Definitions and Standards for Food – of the Federal Food, Drug and Cosmetic Act. The use of the term adulterated in 21CFR Parts 111 and 112 seems to be in the context of Sec. 402.[342] (b)(1) – Adulterated Food – of this Act, which states "If any valuable constituent has been substituted wholly or in part..." This definition is not inclusive of the tenets of Sec. 402.[342](a), which discusses foreign substance addition to the product, and perhaps to some this is the more generally accepted definition. Since both these circumstances could constitute adulteration, being more specific on what you wish to include in the new regulation would provide clarity in this matter.

On page 12177 FDA provides examples of customer complaints as defined by proposed 21CFR 111.3. Disintegration time and tablet size are given as examples of "product quality related to good manufacturing practices". Although, we agree that disintegration time is an excellent indicator of product quality, we don't see how FDA can list it as a customer complaint example when FDA has not required disintegration testing for dietary supplements. If dietary supplement firms do not have (because it is not

required) product specifications that include disintegration time, how can they be expected to investigate/address a complaint on this subject?

As you know, there are plausible circumstances where a complaint on tablet size does not indicate a problem related to GMP's. A large tablet can meet specifications and be produced according to GMP's, but certain customers may still feel that it is too large based on their personal preference. This does not classify as a customer complaint as FDA has defined it. Size variation would indicate a potential product quality related issue, but tablet size alone would not. More clarity on this issue should be made.

111.5 Do other statutory provisions and regulations apply?

111.6 Exclusions

Subpart B – Personnel

111.10 What microbial contamination and hygiene requirements apply?

On page 12181 and 12182 within the "Description of the Proposed Rule" FDA lists the hygienic practices required, at minimum, to prevent product adulteration. We completely agree with these requirements, as they are all necessary for preventing contamination from microbial sources and non-microbial, such as dirt or hair, thereby ensuring the identity, purity, quality, strength, and composition of a dietary supplement product. FDA's proposal does not include a requirement for documenting these procedures. Procedures that are not written are less likely to be followed on a consistent basis. A written procedure will clearly list the requirements and will require the employees to follow it on a consistent basis. Training employees on the required hygienic practices prior to their first day of handling product is critical to ensuring product safety. Unwritten procedures are likely to be inconsistent and are less likely to be enforced, jeopardizing the safety of dietary supplement products or ingredients. Written procedures which document the required hygienic practices and the associated training provided to employees will provide proof to the FDA that this requirement is being satisfied. Without written documentation, how does FDA anticipate being able to evaluate a firm's compliance to these requirements? We strongly urge the FDA to require written procedures in this area for all companies within the industry.

111.12 What personnel qualification requirements apply?

FDA should require, in the final rule, that manufacturers document and keep records regarding each employee's training. The records should show the content and date of the training. A formal (written) GMP training program will definitely be necessary to track which employees have been trained on the required GMP's. Without formally documenting the training function it is very likely that some employees may not receive any GMP training or insufficient training to permit production of a safe, legal, and efficacious dietary supplement. The training program should include an evaluation of the employee's understanding of the training and should specify a frequency for refresher training. This will ensure employees receiving training understand it and will continue to practice GMP's over the long term. A training program that does not include documentation will likely lead to adulterated dietary supplements as employees will likely not be appropriately trained on the portions of the final rule that directly apply to them. Without written documentation that training has occurred, how does FDA anticipate being able to evaluate a firm's compliance to these requirements? We strongly urge the FDA to require documentation of employee training in all companies within the industry.

111.13 What supervisor requirements apply?

Subpart C – Physical Plant

111.15 What sanitation requirements apply to your physical plant?

111.20 What design and construction requirements apply to your physical plant?

Subpart D – Equipment and Utensils

111.25 What requirements apply to the equipment and utensils you use?

While we feel it is a good step that you have proposed the requirement for cleaning procedures, the regulations should include the requirement for validation of cleaning procedures. We strongly suggest companies within the industry should be required to document their cleaning procedures. Our rationale for this comes from the fact that finished goods testing requirements would not normally dictate the need to look for certain contaminants possible to be present which would normally be validated to be excluded as a result of a properly conducted cleaning validation study. For example, it would not normally be the case that a cleaning compound present on equipment, which was not removed during final rinsing, would even be looked for in a batch of product. These potential contaminants as well as verification of cleaning protocols in relation to microbiological sanitation would be discovered in a properly designed and executed cleaning validation protocol. Enhancing the regulations through inclusion of these written cleaning procedures will ensure prevention of adulteration including how the requirements will ensure the identity, purity, quality, strength and composition of dietary ingredients or supplements.

111.30 What requirements apply to automatic, mechanical, or electronic equipment?

111.50 [Redesignated as 111.72 and Amended]

Transferred to new Subpart E – Production and Process Controls.

mineral enrichment is allowed in foods without confirmation testing of each batch, and also due to the limited claims that dietary supplement products can make.

4). In §111.35(g)(2) you imply that every incoming lot of raw material would require testing of identity, purity, quality, strength, and composition when final batch test methods are not available. The *Description of the Proposed Rule* on p. 12198 goes further to state that "Using a supplier certification, guarantee, or certification in lieu of performing testing on each shipment lot of components, dietary ingredients, or dietary supplements required in accordance with this section is not appropriate." Full testing of every lot of raw material (and/or product) and non-allowance of certificates of analysis go far beyond the acceptable practices in both the food and drug industries. Reduced raw material testing and reliance of certificates of analysis are clearly allowed in the drug industry as cited here:

> 21 CFR 211.84 (d) (2) "Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. **In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component** (emphasis added), provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer **establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals** (emphasis added)."

The allowance of skip-lot testing was also made clear in other GMP proposals. For instance, the USP's General Information section *<2750> Manufacturing Practices for Nutritional Supplements* states for incoming components, in-process control, and finished goods ". . . a skip-lot sampling plan is an alternative to testing every batch" based on acceptable "process validation, in-process controls and statistical confidence." This section goes on to include, "a report of analysis may be accepted from the supplier of a component, provided that at least one identity test is conducted on such component by the manufacturer." During the 5/4/03 FDA-Industry GMP teleForum, Steve Musser also added more confusion to this when he stated that the acceptance of vendor certificates of analysis may be allowed in certain instances where the supplier has confirmed identity, purity, quality, strength, and composition. This doesn't seem to agree with the *Description of the Proposed Rule*, but we agree that his approach is more practical.

5). In the *Description of the Proposed Rule* p.12174, FDA states that "HACCP principles can be applied to a broad range of manufacturing practices and HACCP principles are not solely focused on microbial contamination, but instead, are intended to identify and appropriately control steps in manufacturing where adulteration can occur." The philosophy of controlling these intermediate manufacturing steps through validation and in process controls is one that has worked with great success in the drug (e.g. process and cleaning validation) and food industry. In 1997, FDA published a document entitled *Hazard Analysis and Critical Control Point Principles and Application Guidelines*. The document states: "An effective HACCP system requires little end-product testing, since sufficient validated safeguards are built in early in the process." FDA's narrow focus on the finished product testing of every lot produced is not in line with the philosophy of HACCP, where manufacturing steps are controlled and verified such that the resulting end product is proven safe and effective with minimal effort required in finished product testing. This goes along with the fact that good quality control fundamentals are based on controlling the end by controlling the means. These approaches discourage trying to achieve quality by 100% inspection.

6). It is stated in the *Description of the Proposed Rule* that the final product testing requirement does not restrict a company from testing at the raw material state. However, we feel it would cause much repeated effort for items that are simply more appropriate to test at a raw material stage. It also does not allow the manufacturer the flexibility to determine the most appropriate point in the operation to test for certain specifications. It is more beneficial to identify that the correct material is received and used in the

product beforehand to avoid re-processing or scrapping batches where an untested incorrect material may have been used. It would also be more difficult for us to get reimbursement from a raw material supplier for a non-compliant material unless we tested before manufacturing. Identification of incoming raw materials as required in the original *ANPRM* section (7) (iv) is more in line with customary food and drug industry practices. Repetition of this testing in the final product state is not necessary when good manufacturing controls and documentation, such as those in HACCP, are properly incorporated.

7). In response to question 3 of the *ANPRM*, the FDA states that the use of "a supplier's certification or guarantee would not necessarily ensure that the identity, purity, quality, strength, or composition of a component, dietary ingredient or dietary supplement is met." Since the proposed rule and testing requirements cover the manufacturers of dietary ingredients and dietary supplements this appears to inflict a double inspection process. For example, the manufacturer of the ingredient would be required to do identity, purity, quality, strength, and composition testing before releasing the material and then the rule requires this to be repeated by the dietary supplement manufacturer that uses this ingredient. It appears only logical that both need not test the same criteria, but that the manufacturer determine the reliability of the vendor's certification and eventually accept a material by receipt of the certification document. The Plantain example used in the *Description of the Proposed Rule* assumes that the raw material manufacturer has no burden of compliance, when in fact, under the current proposal, they are required to assure the proper identity, strength, purity, and composition of their material before release.

8). In the absence of a scientifically valid analytical method, the proposed regulation requires a manufacturer to test each shipment lot of components and in-process materials (§111.35(g)(2)(i) – (ii)). It is highly unlikely that an ingredient that can't be tested in the final product will be able to be tested in the in-process matrix. Testing at the raw material stage should suffice for these difficult to test materials. The incoming testing along with proper dispensing, weighing, and cross-check procedures by at least two employees and sign-off by QA authority ensures that the correct material has been added.

9). In the section, *D. Food Advisory Committee Report, 2. How Will CGMP Regulations Take Into Account Technical Feasibility?* you state that "additional scientific study is necessary before we can propose a dietary supplement CGMP requirement" for such things as expiration dating and dissolution testing. We would suggest that this same statement applies to the proposed finished product testing. Although there are recognized industry standard methods for many ingredients such as vitamins and minerals, there are far fewer available methods for botanicals and other nutrients. In addition, the combination of several of these difficult-to-test materials in one product creates a testing nightmare. The variety of product matrices will also make it extremely difficult to establish an officially valid method to encompass all product formulations. To do so, more complex and expensive methods of analysis would be needed such as LC/MS. Testing groups such as the Institute for Nutraceutical Advancement (INA) recognized these issues and began pursuing validation of methods for at least the raw and processed raw material stages in an effort to unify testing and standardization methods.

10). The proposed regulation should also be revised to take into account the lack of scientifically valid identification tests for all components. There are several categories of materials for which unique identification tests are unavailable even at the raw material state. Such ingredients include, but are not limited to, glandular materials (e.g., spleen powder, pancreas gland powder, etc.), non-standardized herbal extracts with non-selective chromatographic fingerprints or unavailable methods, and multiple sources of enzymes (e.g., protease from *Aspergillus oryzae* vs. protease from *Aspergillus melleus*). In these situations, a distinct identification test is not available; therefore the manufacturer of the raw material and the end user of the raw material must rely solely on strict adherence to good manufacturing practices and documentation control. For example, we have been contacted by one of our vendors that supplies glandular materials to the pharmaceutical industry. They have identified to us that their GMP process controls and documentation have been reviewed by FDA drug inspectors and were found to be acceptable

even though unique identification of the material cannot be confirmed by final raw material testing. This approach needs to be specified as being allowed for such materials.

11). We question the practical enforceability of this proposed regulation if a manufacturer chooses to ensure products meet label claims, but achieves that end result without doing 100% inspection of either raw or finished goods for each production batch. An example of this would be for a manufacturer to design products with overage levels adjusted so the product always tests at least 100% of label claim throughout the declared shelf life. In this hypothetical example, the manufacturer has a long history of test data demonstrating consistency in meeting label claims so they chose to do skip-lot testing instead of testing all batches. In an inspection it is discovered that this manufacturer has done skip-lot testing which is not permitted by the proposed regulation, and thus the FDA would deem the product adulterated. Would you cite this manufacturer or take regulatory action against him? Consider the fact that this hypothetical manufacturer has a large database that clearly supports the product is not subpotent and incorporates other GMP procedures. In addition, if the questionable lots were tested they would likely prove compliance with label claims. If this manufacturer were cited by FDA and required to recall the product it would be highly likely that a perfectly good product would be removed from the marketplace and that FDA would unable to prove it was subpotent. If the hypothetical manufacturer challenged the FDA action in court requiring the recall of the product, a subsequent court ruling favoring the manufacturer could well *de facto* invalidate the final rule which disallowed legitimate, scientifically supportable skip lot testing protocols.

12). All of the above arguments are in no way meant to imply that we think raw material and product testing are not important. To the contrary, Enzymatic Therapy has an on-site 20 QC/Lab/QA employees. We have analytical capabilities to run HPLC, GC/MS, FTIR, AA, dissolution, microbial methods, conductivity, TOC, UV/VIS spectrophotometry, and much more. We are concerned that the inclusion of 100% finished product testing strays significantly from the regulations published in the *Advance Notice of Proposed Rulemaking (ANPRM)* in 1997, as well as from related GMP's published by USP and NNFA, and thus has not been the focus of our company's quality program. In fact, we feel that our multi-faceted GMP approach is more rigorous and more likely to determine identity, purity, quality, strength, and composition deficiencies earlier in the process, and thus allow us to strengthen our systems, rather than uncover failing results in the end product.

SUGGESTED REVISION

We suggest integrating skip lot testing, raw material and product certification, process validation, cleaning validation, incoming material control, vendor certification programs, shelf life testing, and other GMP programs as revisions in lieu of 100% finished batch testing. These procedures, constantly implemented and monitored play a vital role in obviating the need to do 100% inspection of each batch now and in the future independent of what historical results show. Not only does your approach appear to be inconsistent with accepted, well proven quality assurance principles, it is also wasteful from both cost and time standpoints. We identify some of these costs in the General Comments section of this submission. We also feel that such a large deviation from the food industry standards in regards to necessary testing seems inappropriate since food is consumed in much larger quantities and by a more widespread consumer base.

Several alternatives to the 100% product testing option are cited throughout the explanations above. These can be found in the *ANPRM*, *USP*, and *NNFA* proposed GMP's.

§111.35(i)

Under §111.35(i) you indicate that manufacturers "must not reprocess any components, dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms or other contaminants, such as heavy metals". We wholeheartedly agree with this proposed requirement. While

you provide good guidance on microbiological limits in another section of this proposal, you have not specified limits on heavy metals anywhere in this proposed regulation. While you may not have comprehensive data on heavy metals in dietary supplements or food products in general, our own data support the fact that heavy metals exist on a widespread basis in the food supply. If you do not address this issue in this proposal this will remain another source of confusion and misinterpretation by the dietary supplement industry. We propose that you assemble an industry consortium of raw material suppliers to learn more about this important health related subject so you are better equipped to specify heavy metal limits building upon existing data you have compiled. You may know that one industry watchdog group ConsumerLab.com has used California Proposition 65 limits on heavy metals which in our opinion is not an appropriate working limit based on existing safety data in the scientific literature. The industry is woefully misguided on this important safety subject. We strongly suggest that you include in the revised regulations a practical working limit on heavy metals in dietary supplements.

In the May 9th FDA satellite broadcast concerning the proposed GMP's FDA indicated that treating a dietary supplement ingredient or component with irradiation as a means to reduce or eliminate the microbial load was acceptable as long as the treatment was part of the process for producing that material. Can FDA confirm that the irradiation of dietary ingredients, supplements or components is allowed per 21CFR179, as they are not listed in the table provided in 179.26(b)? If irradiation of supplements is supported in 21CFR179, FDA should clarify, either in §111.50(f) or in the §111.3 definition for reprocessing, that the manufacturer does **not** have the option of removing a product from manufacturing (due to unacceptable microbial levels) in order to treat/sterilize the product, in-process blends, or raw materials such that microbial levels of all affected materials are reduced/eliminated to acceptable levels. Even once the microbial load is effectively reduced and has been confirmed to be reduced; the manufacture may not reprocess the materials.

§111.35(k)
Similar to the case described in §111.35(i) you describe in 111.35(k) that manufacturers must test for contaminants including but not limited to "filth, insects or other extraneous material; microorganisms; and toxic substances". Again, we agree with this requirement. However, like the case with heavy metals, you specify no limits on toxic substances for example and state you are leaving to industry discretion the decision on "types of tests and when to test" for these types of contamination. Making this requirement a "must" then stating how and when to do the tests is discretionary with no guidance on limits for toxic substances seems to us to be very confusing. We strongly recommend you provide guidance to the industry on allowable limits for these types of contamination. Our judgement is that industry will ignore this section more than you would like without better guidance.

111.37 What requirements apply to quality control?

§111.37(b)(1) through (15)
In the *Description of the Proposed Rule* on page 12200 FDA states that "...all organizational units that are involved in critical formulation and manufacturing steps, such as production, engineering, research, and regulatory affairs, may be included in the quality control functions. Does this mean that employees that are not employed as members of the "Quality Control" department can participate in the functions that would allow a firm to meet the requirements set forth in §111.37(b)(1) through (15)? This interpretation would make the most sense; e.g. the requirements stated in §111.37(b)(6) through (8) concerning equipment calibration are actually better suited for employees that are employed as members of the "Manufacturing" department. Members of our "Manufacturing" department are actually completing the quality control functions outlined in §111.37(b)(6) through (8) currently with great success. Employees of the "Quality Control" department do not need to approve or reject all procedures, as they may not have the qualifications or experience to add any value to the approval process.

Employees of other organizational units may be the most qualified to approve or reject procedures that directly pertain to their function.

Please confirm within §111.37 that employees that are not employed as members of the "Quality Control" department can participate in the functions that would allow a firm to meet the requirements set forth in §111.37(b)(1) through (15).

§111.37(b)(12)
For the first time in the proposed rule, within this section, you propose that manufacturers must keep reserve samples for three (3) years from the date of manufacture. Shouldn't this limit be indexed to the stated or working shelf life set or assumed by the manufacture? For example there are dietary supplements in the marketplace which have a shelf life (and/or expiration date) set one year from manufacture and there are others that have a shelf life three years or longer. It seems to us that you should require reserve samples to be held for a duration exceeding the shelf life by some fixed duration, e.g., one year after the stated or assumed expiration date.

Overall clarification on the requirements for reserve samples is needed. In section 111.37 (b) (11) you list the requirements for the collection of *representative* samples, which includes:

(i) Each shipment lot of components. . .
(ii) In-process materials. . .
(iii) Each batch of dietary ingredient or dietary supplement manufactured. . .
(iv) Each batch of packaged and labeled dietary ingredients or dietary supplements. .

You indicate that these samples are for the purpose of determining whether the component, dietary ingredient, dietary supplement, packaging, or labels meet specifications before releasing for distribution. The proposed rule does not indicate that *these* samples are also collected to serve as *reserve* samples. In 111.37(b)(12) you state: "Keep *the* reserve samples for 3 years from the date of manufacture..." FDA has made no prior reference to reserve samples. Are you implying that a manufacturer of dietary supplements must collect reserve samples from each of the four items listed above? If the answer is yes, then why is it necessary to increase the reserve sample burden on dietary supplement manufacturers in comparison to drug manufacturers? 21CFR 211.170 requires that a sample of each lot in each shipment of each active ingredient is retained and that a sample of each batch of drug product is retained and stored under conditions consistent with product labeling and in the same container-closure system. Section 211 does not require reserve samples for inactive ingredients or excipients, nor does it require reserve samples of in-process materials. Collecting reserve samples of in-process materials and components is not consistent with 21CFR211.170, nor is it necessary to complete investigations. Collection of in-process materials and components as reserve samples is not necessary because the finished dietary supplement product reserve sample will adequately allow the manufacturer to perform testing required for any appropriate investigation. Collecting unnecessary samples is costly and excess samples occupy valuable facility space.

Please review the Drug GMP regulations in this area and clarify the sample collection requirements for reserve samples.

111.45 What requirements apply to establishing a master manufacturing record?

In general, we are in agreement with the requirements for a master manufacturing record. We are, however, opposed to your requirement to include documentation regarding testing procedures performed outside of the manufacturing operation, such as laboratory testing procedures, in the master

manufacturing record. Furthermore, we have suggested an alternative for the identity and verbiage required in the master manufacturing record for dietary ingredients or dietary supplements.

In §111.45(b)(1) you require the name of the dietary ingredient or dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size to be included in the master manufacturing record. We are in agreement with listing the weight or measure for each ingredient, however, we feel including the strength and concentration is unnecessary. We suggest the identity of each dietary ingredient can be controlled instead with the use of a unique item number identifier, along with a brief description of the ingredient.

In §111.45(b)(4) you require the identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement in compliance with section 403(s) of the Federal Food, Drug, and Cosmetic Act to be included in the master manufacturing record. We fully agree with listing all ingredients that will be declared on the dietary supplement labeling in the master manufacturing record. However, we feel it is not necessary for the verbiage to identically match the corresponding label statements. As we previously mentioned in our comments for §111.45(b)(1), we suggest the identity of the ingredients can be controlled within the master manufacturing record with the use of a unique item number identifier, along with a brief description of the ingredient.

In §111.45(b)(8)(ii) you require the sampling and testing procedures for the dietary ingredient or dietary supplement to be included in the master manufacturing record. We feel it is overly burdensome and unnecessary to include the testing procedures that will be performed outside of the manufacturing operation, i.e. laboratory testing, in the master manufacturing record. We suggest the documentation for testing procedures should be maintained separate of the master manufacturing record and be retrievable by appropriate cross-referencing information.

111.50 What requirements apply to establishing a batch production record?

In general, we are in agreement with the proposed requirements for a batch production record. However, similar to our comments for the master manufacturing record in §111.45, we are opposed to your requirement to include documentation regarding procedures performed by functions outside of the manufacturing operation, such as maintenance activities, in the batch production record.

In §111.50(c)(4) you require the date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch to be included in the batch production record. We object to including the date and time of maintenance and suggest this information should be recorded and controlled in an equipment log separate of the batch production record. These equipment logs are established for each individual piece of equipment for which all maintenance performed is recorded. It would be overly burdensome to include this level of detailed documentation within the batch production record and we suggest it should be maintained separate from the batch production record. It is more efficient to recover a full history of equipment maintenance from a central log than from individual batch records and duplicate documentation using both system is not necessary.

§111.50(h)
You previously proposed the requirements for reserve samples in §111.37(b)(12). Why are the requirements reiterated in this section using the same verbiage? If you are implying that the batch production record must indicate that reserve samples should be pulled and documented as such within the batch records, then you should make that clear in this section. The necessity of including this in batch

record rather than a general sampling SOP is also unclear. §111.50(h) as written now is repetitive and adds no additional value to the requirements already stated in §111.37(b)(12).

111.60 What requirements apply to laboratory operations?

§111.60(b)(1)(iii)
You address sample collection in §111.37 and then unnecessarily repeat the requirements in §111.60(b)(1)(iii). Furthermore, the sampling function is not considered to be a laboratory function, but a quality control function. At our facility laboratory personnel would not be involved in the sample collection function, as their qualifications and job descriptions would never include this function. We recommend that you remove §111.60(b)(1)(iii)(A) through (E) as it is completely repetitive to §111.37(b)(11)(i) through (iv).

§111.60(b)(1)(v)
We have some concerns about the interpretation of this section and related statements in 111.35(h) given in the *Description of the Proposed Rule* and presented by Steve Musser during the FDA-Industry GMP teleForum on 5/4/03. The proposed regulation simply states, "Use of appropriate test method validations".

1). In §111.35(h), you state that "an appropriate test is one that is a scientifically valid analytical method." In the *Description of the Proposed Rule* on p. 12198, you state that AOAC or FDA methods ("officially valid") should be used if they are available. If an officially valid method is not available, then you allow the use of a "scientifically valid method" which is defined on p. 12198 as a method "that is based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research." You state that "we are not aware of a situation where an appropriate scientifically valid method is not available." While agreeing with the fact that officially or scientifically valid methods are the best tools to ensure product compliance, we disagree with the fact that there are available, scientifically valid methods for all analytes in all product matrices. The complexity of our product matrices and the industry-accepted standardization of some botanicals by UV spectroscopic methods are just two reasons why valid methods may not be available. In these cases, our data shows incoming component testing is more than adequate to ensure product compliance.

2). On p. 12209 of the *Description of the Proposed Rule,* it states that "If an official valid method does not exist in an official reference, the method you use may be **validated** (emphasis added) by using multiple tests at your laboratory or multiple laboratories performing the same test to document that the intended use of the method is consistently fulfilled." Steve Musser's comments at the FDA-Industry GMP teleForum on 5/4/03, also suggested that matrix-specific in-house or contract lab method validation was necessary for scientifically valid methods. First, considering the statement in §111.60(b)(1)(v), we would not interpret that to mean in-house re-validation is necessary. Second, full validation of a method on each product matrix is not financially feasible. Cost impacts have been noted in the General Comments section of this submission. We feel that a more general requirement similar to that listed in *USP <1225> Validation of Compendial Methods* might be more applicable. In that general chapter it states that when a compendial method is applied, users are not required to validate accuracy and reliability of the methods, "but merely verify their suitability under actual conditions of use." The FDA's choice of the word "validate" implies much bigger requirements for those of us who have our roots in the pharmaceutical industry. The FDA should clarify this definition.

SUGGESTED REVISION

We agree with the statement in §111.35(h) and interpret it to mean that a scientifically valid analytical method must be used. We feel, however, that this statement does not imply that in-house re-validation or matrix-specific validation is necessary as suggested in the *Description of the Proposed Rule* for §111.60(b)(1)(v). The following clarification of §111.60(b)(1)(v) with a reduced "suitability" approach should be addressed in the *Description of the Proposed Rule.*

§111.60(b)(1)(v) Use of appropriate test methods that have been validated or proven to be suitable under actual conditions of use.

111.65 What requirements apply to manufacturing operations?

111.70 What requirements apply to packaging and label operations?

111.74 What requirements apply to rejected components, dietary ingredients, dietary supplements, packaging, and labels?

Subpart F – Holding and Distributing

111.80 What requirements apply to holding components, dietary ingredients, dietary supplements, packaging, and labels?

111.82 What requirements apply to holding in-process material?

111.83 What requirements apply to holding reserve samples of components, dietary ingredients, and dietary supplements?

Please refer to comment on §111.37(b)(12) in relation to reserve sample requirements.

111.85 What requirements apply to returned dietary ingredients or dietary supplements?

The requirement you propose in §111.85(b)(2) that returned products must be retested in the same manner as when initially manufactured will assuredly result in much product being destroyed which is completely in compliance with all specifications including identity, purity, quality, strength and composition. The reason for this is that returned product will commonly be of such small unit volume for many manufacturers that the economics of retesting it will simply be crippling.

Furthermore there could be many instances analogous to that previously described in our §111.35 comments to you where the age of returned product will be such that our stability data clearly shows the product should be acceptable in relation to these specifications. Neither FDA nor we would be able to prove this product does not meet all specifications as a result of confidence in the stability data generated on these products. Retesting would again be superfluous and economically wasteful. We feel you need to revise this section of the proposed regulations to accommodate reasonable scenarios where returned goods could be returned to stock without the need for retesting.

We feel your assumptions in this section imply there could be something wrong with the returned product as opposed to other reasons. There are instances where a customer returns the product for reasons having nothing to do with anything being wrong with the product. Examples of this might be 1)the customer ordered the wrong product 2)customer ordered the wrong quantity, 3)customer didn't pay for the product on time and we asked for stock to be returned, 4)customer went out of business, etc. We are not advising you that no examination of such product is being advocated here, on the contrary. We are simply giving you guidance that you need to revise the regulation to accommodate legitimate instances where it would not be required to retest the product for everything that was required when the product was initially manufactured.

We also wish to point out to you that if testing of returned products is going to remain in the final rule, we find no place in the proposed statute where an economic analysis of the impact of this requirement has been quantified. For your use in generating a better analysis of the impact of this potential throwaway cost, corporate Enzymatic Therapy is on pace to have ***$1.9MM in returns (wholesale value) for the fiscal year***. Under the proposed regulations as written, most if not all of this would need to be scrapped because of the low volume of any given returned sku and the prohibitive cost of retesting it as it trickles in from our thousands of individual customers.

111.90 What requirements apply to distributing dietary ingredients or dietary supplements?

Subpart G – Consumer Complaints

111.95 What requirements apply to consumer complaints?

In response to your inquiry whether we should or should not be required to establish and follow written procedures for receiving, reviewing, and investigating consumer complaints, we believe the industry should be required to do this. In 21CFR drug cGMPs (parts 210 and 211), there are at least 25 separate citations to written procedures including 21CFR §211.198(a) which states "Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed...". We believe adhering to written procedures ensures our commitment to providing products that meet all specifications for identity, purity, quality, strength, and composition. Written procedures not only contain step-by-step instructions that personnel consult to complete tasks reliably and consistently, but they are necessary as a training tool to new employees to ensure *all* employees know *all* steps completely to perform their job.

In the "Description of the Proposed Rule" (page 12217) for 111.95(c) this proposal states if the consumer alleges dizziness, vomiting, or lightheadedness after consuming several dietary supplements, it is an adverse event worthy of investigation. First, "several" needs to be defined and in what terms of use. Does it imply consuming more than the recommended serving size? Does it mean "several" different supplements at one time, or over a period of time; if the latter, how long? Are we to be responsible for those consumers who choose to, or inadvertently, consume more than the recommended dosage amount?

In the "Description of the Proposed Rule" for 111.95(e) FDA suggests we report a consumer complaint and the investigation results to FDA when there is a possibility of a relationship between the consumption of the supplement and a serious adverse event. We recommend you define what your expectations of *serious* and *non-serious* adverse events are. Where do you propose we draw the line between the two, e.g., beyond the obvious seriousness of death, a congenital anomaly, or birth defect?

In proposed 111.95(e) FDA provides a list of what the consumer complaint record must include (but not limited to) which includes, "the nature of the complaint, including how the consumer used the product". Information concerning "how the consumer used the product" may not be offered in every situation, particularly of complaints left as phone messages after-hours by consumers who also do not leave contact information that would enable us to request further information. It would be more suitable to add, "where known" in regards to the requirement for "how the consumer used the product".

On page 12177 of the "Description of the Proposed Rule" FDA has stated that "...for the purpose of this regulation, a communication from a consumer that contains any allegation, written or oral, related to the safety of the use of a product because it contained a particular dietary ingredient...would not be considered a consumer complaint." We disagree with FDA's assessment. The consumer will not have the capacity to determine whether or not an adverse event was caused by a particular dietary ingredient or by a product quality issue related to GMP's. The consumer may claim that the event was caused by the ingredient, but only the manufacturer has the capacity to make this determination. Not classifying the above circumstance as a consumer complaint as defined in 21 CFR 111.3 could cause manufacturers to avoid investigating certain adverse events to determine the appropriate cause and implement the associated corrective action. We urge the FDA to eliminate the potential confusion by classifying all adverse events as consumer complaints, whether or not they may be caused by a particular dietary ingredient.