



August 11, 2003

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

**RE: Docket 96N-0417, Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements**

Reference is made to the Proposed Rulemaking relative to Current Good Manufacturing Practice (cGMP) in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements that was published in the Federal Register on March 13, 2003 [FR 68(49):12158-12263]. Wyeth Consumer Healthcare (Wyeth) has an interest to participate in this rulemaking for dietary supplements, as we are a manufacturer and distributor of various vitamin, mineral and botanical-containing products that would be subject to the final rulemaking. Our dietary supplement product portfolio includes major brands such as Centrum® and Caltrate®. As an example of our commercial presence, our "Adult" Centrum® products enjoy a 35.7% market share\* and our Caltrate® family of products represent a 17% market share\*.

Overall, Wyeth supports the Agency's efforts to establish cGMPs for dietary supplement products. We strongly believe that a separate dietary supplement cGMP regulation is needed in order to incorporate various critical quality, production and process control requirements that are not currently specified in the cGMP for foods. It is our opinion that these additional requirements are necessary to ensure that dietary supplements are produced under conditions that will result in properly labeled products that are not adulterated or misbranded.

In response to the Agency's request for feedback, Wyeth has carefully reviewed and considered the Proposed Rulemaking and we find that many of the provisions are reasonable and appropriate. However, we have identified several significant areas of concern, which require serious reconsideration.

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\* Market share based on dollar sales for food, drug and mass merchandisers, excluding Walmart

In particular, the Proposed Rulemaking:

- is inappropriate in scope with respect to defining non-dietary ingredient suitability. Wyeth recommends that criteria for non-dietary ingredient suitability should be reevaluated outside of the subject cGMP rulemaking.
- applies equally to both dietary supplement and dietary ingredient manufacturers. It is Wyeth's opinion that dietary ingredient manufacturers should be excluded from the subject cGMP rulemaking and regulated in accordance with existing food cGMPs and an FDA Guidance document.
- provides 3 years of unqualified compliance relief to smaller firms (versus a 1 year compliance date for larger firms). Wyeth believes that it would be possible and preferable for the Agency to define a single compliance approach that would be applicable to firms of any size.
- lacks flexibility with respect to facility design requirements. Wyeth proposes that the final rulemaking should provide for alternate approaches.
- is overly prescriptive with respect to sanitization requirements for product contact surfaces. Wyeth suggests that the final rulemaking should allow firms to employ other suitable means of achieving microbiological quality assurance.
- requires validation of all analytical methods. Wyeth recommends that the final rulemaking should clearly allow for method verification and method transfers under appropriate circumstances.
- dictates how firms should comply with the cGMP regulation, but fails to provide firms with organizational and procedural flexibility as should be allowed under a systems-based approach to quality assurance.
- precludes acceptance of a supplier's test result as reported on a Certificate of Analysis. It should be permissible to accept a supplier's test result under a systems-based approach to quality assurance, provided that appropriate procedures are in place to assure the identity of the material.
- specifies full product release testing on a routine basis. Wyeth proposes that firms should have the option to employ reduced/parametric release testing regimens under appropriate circumstances, based on a systems approach to quality assurance.
- does not require products to be expiry dated and/or stability tested. Wyeth suggests it should be mandatory for dietary supplements to bear an expiration date that is supported by appropriate stability data.

Please refer to the attached document for a comprehensive discussion regarding each of above listed concerns. As an overall observation, Wyeth notes that the proposed rulemaking is generally inconsistent with current FDA initiatives to regulate products using risk-based management approaches. It is illogical that the proposed rulemaking for dietary supplement cGMP reflects outdated quality control principles, when the Agency clearly supports innovation in the area of quality assurance, as evidenced by its strong endorsement of scientific advances such as Process Analytical Technologies (PAT). We urge the Agency to remain true to a renewed orientation that recognizes the value of an integrated systems approach in the assurance of product quality.

Wyeth also reminds the Agency that enforcement is a critical component of good manufacturing practices. In our view, the Agency's inspectional efforts in the area of food cGMPs have historically been grossly inadequate, and this situation has enabled many firms to operate in a state of non-compliance. Moving forward, we strongly encourage the Agency to strengthen its compliance program and to devote additional resources to enforcement activities.

Please note that our enclosed comments address how the proposed rulemaking as currently written would have significant financial implications for firms. Wyeth urges the Agency to allow alternate approaches that will ease the economic burden on the industry, while accomplishing the same quality objectives.

Wyeth appreciates the Agency's review and consideration of our comments. We are pleased to have had the opportunity to participate in the rulemaking process that will establish cGMPs for dietary supplements.

Sincerely,

WYETH CONSUMER HEALTHCARE



Susan Beavis  
Director, Regulatory Affairs  
Chemistry, Manufacturing, and Controls

**1. The scope of the Proposed Rulemaking is inappropriate with respect to defining non-dietary ingredient suitability. Wyeth recommends that criteria for non-dietary ingredient suitability should be reevaluated outside of the subject cGMP rulemaking.**

Proposed 111.35(d) indicates that any substance in a dietary supplement other than a “dietary ingredient” should be listed as food additive, listed as a color additive, authorized by a prior sanction, or generally recognized as safe (GRAS). Wyeth finds that it is unnecessary and inappropriate to include proposed section 111.35(d) in the cGMP rulemaking since the stated requirements for non-dietary ingredient suitability are redundant with existing regulations under The Federal Food, Drug and Cosmetic Act (The Act)<sup>1</sup>.

As a separate issue outside of the subject cGMP rulemaking, Wyeth strongly encourages the Agency to work with Congress to revise The Act with respect to the specified criteria for non-dietary ingredient suitability, since we find the current requirements to be overly restrictive. In particular, criteria for defining a non-dietary ingredient as safe and lawful should be expanded to include one or more of the following:

- Substances listed in the USP/NF
- Substances listed in the Food Chemical Codex
- Substances listed in the APhA<sup>2</sup> “Handbook of Pharmaceutical Excipients”
- Substances listed in FDA’s “Inactive Ingredient Guide”

Substances that are included in the above references are generally regarded as safe based on a history of common use. Therefore, it would seem reasonable for the Agency to designate these substances as suitable under the Act for use in dietary supplements. Such action would be consistent with FDA initiatives to apply risk management principles to product quality regulation.

Wyeth would also like to comment on the FDA’s suggestion in the preamble<sup>3</sup> that firms should use “food-grade rather than industrial-grade chemicals” for dietary supplement manufacture. The rulemaking should provide for reasonable exceptions to this general requirement, since certain raw materials (e.g. some trace minerals) that are essential to human health do not have food grade sources.

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<sup>1</sup> Relevant citations would include sections 201(s), 402, and 409 of The Act.

<sup>2</sup> APhA is the American Pharmaceutical Association.

<sup>3</sup> FR 68(49):12162

**2. The Proposed Rulemaking applies equally to both dietary supplement and dietary ingredient manufacturers. It is Wyeth's opinion that dietary ingredient manufacturers should be excluded from the subject cGMP rulemaking and regulated in accordance with existing food cGMPs and an FDA Guidance document.**

The industry-proposed cGMPs for dietary supplements (published by the Agency as an Advance Notice of Proposed Rulemaking on 2/6/97<sup>4</sup>) were principle-based and general in nature. Therefore, the 6/6/97 comments submitted by Wyeth (formerly American Home Products Corporation) in response to the Agency's Advance Notice of Proposed Rulemaking\* reflected our opinion that broad cGMP regulations could be developed to address the diversity of operations conducted by ingredient manufacturers, finished product manufacturers and distributors. In other words, we believed that it would indeed be possible for the various segments of the industry to be guided by a common cGMP to the extent that would be appropriate for each firm's particular processes, *if the regulation was principle-based and general in nature.*

Our former view has changed, however, since the FDA's 3/13/03 Proposed Rulemaking<sup>5</sup> is not principle-based and general in nature, but rather *prescriptive and very detailed in nature.* As such, Wyeth's revised opinion is that the Agency's suggested approach to cGMP cannot be applied equally to both dietary supplement and dietary ingredient manufacturers, since many dietary ingredient processes cannot be adapted to the requirements of the proposed rulemaking as currently written. For example:

- Many dietary ingredients are tested by organoleptic methods that cannot be qualified or validated, as would be required under proposed 111.60(b)(1)(v).
- Many dietary ingredient operations use continuous processes that are not compatible with the use of traditional batch production records, as would be required under proposed 111.50.
- Many ingredient manufacturers use closed systems for processes such as vitamin synthesis or botanical extraction. It would be excessive and unnecessary to require such facilities to have "floors, walls, and ceilings that are of smooth and hard surfaces", as would be required under proposed 111.20(d)(1).

Although Wyeth is suggesting that dietary ingredient manufacturers should be excluded from a final cGMP rulemaking for dietary supplements, *we strongly agree with the Agency that there is a critical need for dietary ingredient manufacturers to adhere to a consistent standard of quality control.* This is particularly true for botanical ingredients, where adulteration may not be detectable after processing. As a starting point, Wyeth would recommend that dietary ingredient manufacturers should comply with existing cGMPs for foods (i.e., 21 CFR 110). Wyeth would further suggest that FDA create a Guidance document to delineate additional controls that would be specifically applicable to the processes of dietary ingredient manufacturers. An FDA Guidance document for dietary ingredient manufacturers could incorporate aspects from various references including, but not limited to:

<sup>4</sup> Advance Notice of Proposed Rulemaking for Current Good Manufacturing Practice (cGMP) in Manufacturing, Packing, or Holding Dietary Supplements, FR 62(25):5700-5709

<sup>5</sup> FR 68(49):12158-12263

- The USP General Information Chapter <1078> entitled Good Manufacturing Practices for Bulk Pharmaceutical Excipients
- The IPEC (International Pharmaceutical Excipients Council) Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients
- The FDA Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, dated August 2001

Please note that Wyeth's suggested approach for regulating dietary ingredient manufacturers has precedence within other cGMP models. For example, the cGMP regulations for finished pharmaceuticals (i.e. 21 CFR 211) apply only to drug products<sup>6</sup>, while active ingredients are subject to the FDA Guidance document cited above. To further enhance our suggested regulatory framework, Wyeth strongly recommends that the Agency specify in the final dietary supplement cGMP rulemaking that it is the finished product manufacturer's responsibility to confirm and require (e.g., through compliance audits, quality agreements, etc.) that their dietary ingredient suppliers have adequate systems in place to assure that materials meet the appropriate standards.

To summarize, Wyeth is proposing that:

- Dietary ingredient manufacturers and dietary supplement manufacturers should both comply with existing cGMPs for foods (i.e., 21 CFR 110).
- Additional controls and requirements for dietary supplement manufacturers should be specified in the subject cGMP rulemaking.
- Additional controls and requirements for dietary ingredient manufacturers should be delineated in an FDA Guidance document.

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<sup>6</sup> Per 21 CFR 211.1(a), the regulations in "Part 211-Current Good Manufacturing Practice for Finished Pharmaceuticals" are applicable to "drug products" only, and a "drug product" is defined in 21 CFR 210.3(b)(4) as "a finished dosage form, for example, a tablet, capsule, solution, etc., that contains an active ingredient generally, but not necessarily in association with inactive ingredients".

- 3. The Proposed Rulemaking provides 3 years of unqualified compliance relief to smaller firms (versus a 1 year compliance date for larger firms). Wyeth believes that it would be possible and preferable for the Agency to define a single compliance approach that would be applicable to firms of any size.**

Wyeth understands that the law<sup>7</sup> requires FDA to consider how to provide relief to small businesses in situations where new regulations have the potential to be overly burdensome. However, Wyeth does not agree that it would be prudent for smaller firms to be given a 3 year period to comply with the final rulemaking prior to any enforcement action, given the FDA's awareness (pursuant to its own survey<sup>8</sup>) that a significant percentage of such firms are currently doing business without regard to any particular GMP model, e.g., without adhering to existing food cGMP requirements. Also, we anticipate that certain aspects of the proposed cGMP may be equally challenging for both larger and smaller companies to accommodate within 1 year of the final rulemaking.

Given these circumstances, Wyeth strongly encourages the Agency to consider it an immediate priority to vigorously enforce existing food cGMPs. At the same time, Wyeth believes that the Agency should assure that firms of all sizes begin to implement the provisions of the final rulemaking as soon as it become available. To accomplish these goals, we propose a single compliance approach that would be suitable for firms of any size. Specifically:

- *Prior to the final rulemaking*, it is proposed that all firms should provide a formal statement to FDA to certify current compliance with existing food cGMPs.
- *After the final rulemaking*, it is proposed that all firms should be expected to achieve full compliance with the dietary supplement cGMPs within 12-18 months,

OR

If full compliance cannot be accomplished within that timeframe, then all firms should be required to submit a master plan to the Agency outlining a strategy to attain full compliance within 3 years. We envision that the master plan would identify and discuss the firm's specific area(s) of non-compliance. The master plan would also include information to justify the firm's need to utilize the extended 3 year compliance period.

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<sup>7</sup> Per the Small Business Regulatory Enforcement Fairness Act of 1996

<sup>8</sup> FR 68(49): 12221 & 12250, Research Triangle Institute, "Survey of Manufacturing Practices in the Dietary Supplement Industry", Contract No. 223-96-2290:Task Order 6, May 2000.

**4. The Proposed Rulemaking lacks flexibility with respect to facility design requirements. Wyeth proposes that the final rulemaking should provide for alternate approaches.**

Proposed 111.20(d) requires that physical plants be designed and constructed in a manner that prevents contamination of components, dietary ingredients, dietary supplements or contact surfaces. Wyeth agrees that this general requirement is appropriate and reasonable. However, Wyeth believes that the specific design and construction requirements in 111.20(d) are inflexible and overly prescriptive. In particular, proposed 111.20(d)(1) states that floors, walls, and ceilings must be smooth and hard surfaces. This requirement could be problematic or unnecessary for certain types of operations. For example:

- Smooth surfaces in milling rooms would make adherence to Occupational Safety and Health Administration (OSHA) workplace noise limits impossible to attain, as some form of baffling is a standard practice.
- Smooth and hard surfaces may not be needed in all parts of a facility. For example, a requirement for such surfaces may be excessive in certain secondary packaging or warehouse areas. Likewise, smooth and hard surfaces may not provide any additional protection to products when processing is conducted in facilities using closed systems.
- Smooth and hard surfaces can be prohibitively expensive. Wyeth estimates that it would cost approximately \$2,000,000 to add smooth and hard surfaces to a 60,000 square foot facility. Please note that this estimate would need to be adjusted accordingly for larger and/or multiple facilities.

Wyeth believes that firms should be empowered to employ alternate approaches under 111.20(d)(1) that would afford products with the same degree of protection from potential contamination. As an example, alternate approaches could include use of equipment shields or dropped ceilings over critical manufacturing or primary packaging operations. For closed systems, such shields would only be required over charging areas. Positive and/or negative air pressurization designs may also be used to help protect product from contamination.

**5. The Proposed Rulemaking is overly prescriptive with respect to sanitization requirements for product contact surfaces. Wyeth suggests that the final rulemaking should allow firms to employ other suitable means of achieving microbiological quality assurance.**

The definition of the term “sanitize” per proposed 21 CFR 111.3 is “to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying cumulative heat or chemicals on cleaned food contact surfaces that when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer”. The preamble<sup>9</sup> to the proposed rulemaking explains that this standard is based on the FDA Food Code that serves as a reference guide for retail outlets (e.g., restaurants, grocery stores) and institutions such as nursing homes.

Wyeth agrees that it is important to have procedures in place to assure proper cleaning of equipment, containers, utensils, and other dietary product contact surfaces. However, it is our opinion that the proposed 5-log reduction requirement is overly prescriptive and we have concerns that it may not always be possible to achieve a 5-log reduction on a surface that has been cleaned prior to sanitizing. We also believe this approach may be inappropriate for certain types of products (e.g., dry products that are not susceptible to microbiological growth, tablets that have a low water activity, etc.). While we have no objection to specifying a 5-log reduction approach as an option that may be suitable for some types of processes, Wyeth would like to suggest that firms should be allowed to utilize alternate approaches to achieve the same degree of microbiological quality assurance. Possible alternate approaches might involve:

- Qualification of standard cleaning procedures against a quality unit’s approved protocol. A typical qualification might be accomplished by evaluating the process of cleaning after dietary supplement manufacture for 3 consecutive cleaning cycles to assure that the process is reliable and reproducible. Acceptance criteria might include limits for residual “worst case” dietary ingredient, residual cleaning agent and/or sanitizing agent, and residual microbiological level. Qualification parameters to be defined might include, for example, the maximum time equipment can remain unclean after use and the maximum time equipment can be held clean prior to use. Also note that qualified cleaning procedures are usually carried out using cleaning check lists that are approved by the quality unit.
- Control of microorganisms through the sanitary design of equipment, containers, utensils, or other product contact surfaces.
- Testing to confirm absence of objectionable organisms and/or testing against alert/action limits for monitoring microbial loads (bioburden) on product contact surfaces. Factors to be considered in establishing microbial specifications for cleaned and sanitized product contact surfaces would include surface counts, surface area, quantity of material processed, and the specified microbial limit for the product itself.

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<sup>9</sup> FR 68(49): 12178

Wyeth also asks that FDA clarify its expectations with respect to evaluating the effects of sanitization on “the product or its safety for the consumer”. Wyeth believes that a product’s ability to meet its established specifications should be adequate to support the lack of adverse impact on the quality of product. Also, if a sanitizer is listed in 21 CFR 178 as an approved Indirect Food Additive (adjuvants, production aids and sanitizers), then there should be no additional burden of proving that it is safe and effective for its intended use.

Wyeth supports that the proposed rulemaking<sup>10</sup> does not specify microbial limits for undesirable organisms in dietary ingredients and/or dietary supplements. We agree with the Agency’s opinion that the industry can and should refer to acceptable and general microbial guidelines, which have been established by non-FDA sources (e.g., USP <2021>, proposed<sup>11</sup> <2022> and proposed<sup>12</sup> <2023>, etc.).

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<sup>10</sup> FR 68(49): 12200

<sup>11</sup> PF 25(5), pages 8761-8769, Microbial Procedures for Absence of Objectionable Microorganisms in Nutritional and Dietary Articles

<sup>12</sup> PF 25(5), pages 8770-8773, Microbiological Attributes of Nonsterile Nutritional and Dietary Articles

**6. The Proposed Rulemaking requires validation of all analytical methods. Wyeth recommends that the final rulemaking should clearly allow for method verification and method transfers under appropriate circumstances.**

The preamble for proposed 111.60(b)(1)(v)<sup>13</sup> reflects that firms “must validate that the official or nonofficial method works under your conditions of use in your setting”. Wyeth would agree that nonofficial (e.g. in-house) test procedures for product identity, purity and strength should be appropriately validated for their intended purpose. We would also concur that a firm may need to validate certain functional test methods (e.g., particle size distribution of raw materials) if such methods are deemed critical to ensure product quality. However, Wyeth does not believe that it should be necessary to revalidate official (e.g., AOAC, USP, etc.) methods. Rather, we would suggest that it is adequate to *verify* (rather than *validate*) official methods. Verification of an official method would confirm that the analytical procedure is suitable for the specific product matrix intended for commercialization by a given firm. In particular, verification of an analytical procedure evaluates the level of agreement between actual results that are obtained by the subject method and theoretical results that are determined by the product’s formula and quality attributes (quantitative composition, etc). A comparison of validation and verification parameters is outlined below:

Method Validation (nonofficial methods)	Method Verification (official methods)
specificity accuracy precision linearity recovery robustness	specificity accuracy precision
\$20,000-30,000/method (cost multiplied for multi-ingredient product)	\$2,000-3,000/method (cost multiplied for multi-ingredient product)

The preamble for proposed 111.60(b)(1)(v)<sup>13</sup> also seems to imply that test methods would need to be validated by each individual laboratory. Wyeth is concerned that such a requirement would preclude method transfers between laboratories. Specifically, it is current and standard practice in the industry for a developing laboratory to validate and then transfer a given method to one or more other receiving laboratories. Although the receiving laboratory must demonstrate the ability to properly perform the method being transferred against pre-approved acceptance criteria, the receiving laboratory should not be expected to revalidate the method being transferred. Methods typically transferred include, but are not limited to, assays, impurities, and dissolution. The method transfer evaluation includes linearity, accuracy and precision, as appropriate. Statistical evaluations and/or historical performance of the procedure are also considered in establishing the acceptability of a method transfer. Note that method transfers are not required for official or compendial procedures. Method transfers are also unnecessary in cases where the laboratory is already qualified in a procedure (e.g., Karl Fischer moisture analysis, pH, heavy metals, etc.).

<sup>13</sup> FR 68(49):12209.

A comparison of method validation and method transfer parameters is outlined below:

Method Validation (nonofficial methods)	Method Verification (official methods)
specificity accuracy precision linearity recovery robustness	accuracy precision linearity
\$20,000-30,000/method (cost multiplied for multi-ingredient product)	\$6,000-7,000/method (cost multiplied for multi-ingredient product)

Wyeth would also like to point out an apparent discrepancy in the preamble to the Proposed Rulemaking. Specifically:

- The preamble for proposed 111.36(h)<sup>14</sup> states that a firm must use a an AOAC or FDA method, if available. This section also suggests that the use of other scientifically valid analytical methods (e.g. proprietary or published methods) would only be considered acceptable in the absence of an AOAC or FDA method.
- In contrast, the preamble for proposed 111.60(b)(1)(v)<sup>15</sup> seems to suggest that it would acceptable to modify an AOAC method or utilize other validated methods (i.e., USP, etc.).

Wyeth believes that the final rulemaking should be clear that firms may utilize any appropriate test method.

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<sup>14</sup> FR 68(49): 12198

<sup>15</sup> FR 68(49):12208-12209

**7. The Proposed Rulemaking dictates how firms should comply with the cGMP regulation. Wyeth notes that the Agency fails to provide firms with organizational and procedural flexibility as should be allowed under a systems-based approach to quality assurance.**

Wyeth believes the cGMP regulation should identify specific requirements without dictating how firms should comply with such requirements. Any non-binding examples of how to comply with stated requirements should be identified as such. We would suggest that any acceptable approaches to complying with the requirements in the regulation be delineated by the Agency in a guidance document.

Wyeth also believes that firms should be empowered to manage and execute quality operations in any scientifically sound manner. As such, it is our opinion that the Proposed Rulemaking should be revised to incorporate additional organizational and procedural flexibility as should be allowed under a systems-based approach to quality assurance. For example:

- Proposed 111.15(j) requires firms to “assign one or more employees to supervise overall sanitation”, the scope of which would cover physical plant facilities, cleaning compounds, sanitizing agents, pesticides, pest control, water supply, plumbing, sewage disposal, bathrooms, hand-washing facilities and trash disposal. Please note that responsibility for sanitation is often shared and coordinated by various functional areas within an organization (e.g., quality assurance, manufacturing, production operations, building management, environmental health and safety, housekeeping, etc.). Wyeth believes that the cGMP regulation should provide organizational flexibility to allow firms to manage sanitation in any appropriate manner.
- Proposed 111.37(b)(7) requires a quality control unit to directly review “all records for calibration of instruments, apparatus, gauges, and recording devices”. Similarly, proposed 111.37(b)(8) requires a quality control unit to directly review “all records for equipment calibrations, inspections, and checks”. Wyeth would agree that the quality unit should assure a comprehensive calibration and maintenance program is in place to manage and monitor the performance of instruments and equipment. While it may be appropriate for a quality control unit to require and periodically audit calibration *procedures and programs*, Wyeth’s experience has shown that the routine approval of calibration *records* can be effectively and competently managed by trained personnel outside of the quality control unit (e.g., equipment management or maintenance groups, etc.). Wyeth believes that the cGMP regulation should provide organizational flexibility to allow firms to manage calibration record review in any suitable way.

- Proposed 111.40(a)(3) requires that the “quality control unit must approve and release the components, dietary ingredients, and dietary supplements from quarantine before you use them”. Wyeth agrees that raw materials (e.g., components and dietary ingredients) should be released prior to use in manufacturing. However, we believe that the cGMP regulation should provide procedural flexibility to package dietary supplements prior to release of the bulk by the quality unit, if there are adequate systems and procedures in place to prevent inadvertent distribution of finished product.
- Proposed 111.45(b)(8)(ii) requires batch production records to include “sampling and testing procedures”. Wyeth agrees that a firm should have defined sampling and testing procedures. However, it is current practice in many firms to describe such procedures in a separate document (e.g., standard operating procedure, etc.). Wyeth believes that the cGMP regulation should provide procedural flexibility to allow firms to document their sampling and testing procedures in any appropriate manner.
- Proposed 111.45(b)(8)(v) requires batch production records to include “corrective action plans for use when a specification is not met”. Wyeth agrees that a firm should have corrective action plans in place. However, it is current practice in many firms to describe such plans in a separate document (e.g., standard operating procedure, etc.). Wyeth believes that the cGMP regulation should provide procedural flexibility to allow firms to document their corrective action plans in any suitable way.
- Proposed 111.50(c)(4) requires batch production records to include the “date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch”. While Wyeth agrees that such records should be maintained, it is current practice in many firms to use logbooks and equipment files for this purpose. Wyeth believes that the cGMP regulation should provide procedural flexibility to allow firms to record maintenance, cleaning, and sanitizing of equipment and processing lines in any appropriate manner.
- Proposed 111.45(b)(8)(iii) requires the master manufacturing record to include “...one person weighing or measuring a component and another person verifying the weight or measure and one person adding the component and another person verifying the addition”. Similarly, proposed 111.50(c)(8) requires the batch production record to reflect the “initials...of the person responsible for verifying the addition of components to the batch”. Wyeth agrees that a second check to verify component weighing and addition is an appropriate and reasonable requirement. However, we disagree that it is necessary for the second check to be performed by a “person”, since electronic computerized verification systems can be successfully used to accomplish the same objective. Please note that electronic computerized verification systems can be validated to show that the computer is capable of reliably performing this second check. Wyeth believes that the cGMP regulation should provide procedural flexibility to allow firms to perform component addition verifications in any suitable way.

- Proposed 111.50(d)(2) states that the “quality control unit must not approve and release for distribution any batch of dietary ingredient or dietary supplement that does not meet all specifications”. For products or components of interest with an established and well-documented safety profile, Wyeth believes that there should be some provision to release products that exceed the upper potency specifications based on an appropriate safety evaluation that would be conducted on a case by case basis. Please note that such releases would be accompanied by an investigation to determine the root cause of the result in question. Wyeth believes that the cGMP regulation should reflect the fact that the quality control unit is expected to objectively evaluate special circumstances related to batch disposition using documented rationale and sound scientific judgment.
- Proposed 111.35(i)(4)(iii) and 111.50(f) prohibit the reprocessing of any product that has been rejected due to contamination that cannot be effectively removed (e.g., microorganisms, heavy metals, etc.). Wyeth agrees that reprocessing should not be employed in such cases. However, Wyeth believes that the proposed rulemaking is too restrictive with respect to reprocessing in cases where contamination can be reliably eliminated (e.g., metal contamination from equipment). Specifically, proposed 111.65(c)(9) indicates that firms should use “effective measures to protect against the inclusion of metal or other foreign material in...dietary supplements”, and compliance per 111.65(c)(9)(iv) would require firms to consider the routine use of “electronic metal detectors”. The preamble<sup>16</sup> for proposed 111.65(c)(9) clarifies FDA’s position that metal detectors should be employed as a preventative measure “to protect against the inclusion of metal”, rather than as a corrective measure “after contamination has or is suspected to have occurred”. The preamble also reflects FDA’s opinion that firms “need to maintain equipment” so that it does not become a source of metal contamination. Our experience has been that maintenance programs, no matter how intensive, cannot completely prevent occasional metal contamination from equipment (e.g., it is common in tableting operations for a compression punch tool to break due to normal wear). Wyeth does not believe that firms should be required to routinely use metal detectors if the only expected source of metal contamination would be from an occasional equipment-related incident. As such, Wyeth believes that the cGMP regulation should provide procedural flexibility to use a metal detector as a corrective measure, for the occasional situation where a batch becomes contaminated with metal arising from equipment. The Agency should note that the routine use of metal detectors could be quite costly. As an example, for a facility that operates thirty 2-sided tablet presses, Wyeth estimates that it would cost approximately \$1,000,000 to install and validate metal detectors for use on each of the compression machines.

As illustrated by the examples provided above, Wyeth finds there is a need for the Agency to incorporate an acceptable degree of organizational and procedural flexibility into various aspects of the Proposed Rulemaking to accommodate current practices in the industry.

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<sup>16</sup> FR 68(49): 12211

**8. The Proposed Rulemaking precludes acceptance of a supplier’s test result as reported on a Certificate of Analysis. Wyeth believes it should be permissible to accept a supplier’s test result under a systems-based approach to quality assurance, provided that appropriate procedures are in place to assure the identity of the material.**

The preamble to the Proposed Rulemaking<sup>17</sup> reflects Agency opinion that a supplier’s certification or guarantee does not necessarily ensure that the identity, purity, quality, strength, or composition of a product is met. Wyeth concedes that there may be situations where a supplier’s Certificate of Analysis (CoA) should not be relied upon. However, Wyeth believes that it should be permissible under appropriate conditions to accept test results (either actual or parametric<sup>18</sup>) as reported on a CoA, pursuant to an adequate qualification program to assess and confirm the supplier's process and testing capabilities, and provided effective procedures are in place to assure the identity of the material (e.g., such as performing an identity test upon receipt). Elements of an adequate supplier qualification program might include:

- In-house testing of multiple supplier lots to confirm comparability of results
- Quality audit of supplier to verify suitability of procedures and capabilities
- Confirmation of change control system
- Independent analysis of supplier test results
- Periodic re-verification of supplier test results at appropriate intervals

A provision to allow acceptance of supplier’s results would be consistent with current cGMP for foods and for drugs:

<i>cGMP</i>	<i>21 CFR</i>	<i>Regulatory Requirement</i>
Food	110.80(a)(2)	“Raw materials...shall either not contain levels of microorganisms...or they shall be pasteurized or otherwise treated...Compliance with this requirement may be verified by any effective means, including purchasing raw materials and other ingredients under a supplier’s guarantee or certification.”
	110.80(a)(3)	“Raw materials...shall comply with...action levels for poisonous or deleterious substances...Compliance with this requirement may be accomplished by purchasing raw materials and other ingredients under a supplier’s guarantee or certification....”
	110.80(a)(4)	“Raw materials...shall comply with...defect action levels for natural and unavoidable defects...Compliance with this requirement may be verified by any effective means, including purchasing the materials under a supplier’s guarantee or certification....”
Drug	211.84(d)(2)	“Each component shall be tested for conformity with all appropriate written specifications for purity, strength and quality. In lieu of testing by the manufacturer, a report of analysis may be accepted from the supplier of component, 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”.

<sup>17</sup> FR 68(49): 12170 and 12198

<sup>18</sup> Parametric results would include in-process test data, composite test data, process capability data, etc.

We also note that the preamble to the subject rulemaking<sup>19</sup> finds it acceptable for a firm "...to perform ...tests yourself or have someone perform ...tests for you". Assuming there is an adequate supplier qualification program in place, Wyeth would consider testing by a *supplier* as reported on a CoA to be equally as valid as testing by a *third party (contract) laboratory*. Third party in this context would be someone other than the supplier of the raw material.

Please note that accepting CoA results should not involve obtaining a complete analytical report (e.g. raw data and chromatograms) from the supplier as a means to confirm that actual testing was performed. Any requirement for appropriately qualified suppliers to provide testing records beyond a CoA would be unnecessary, impractical and inconsistent with current industry practice.

As the Agency may realize, suppliers may report "results" on CoAs that are based on parametric<sup>20</sup> testing, as opposed to actual testing. Wyeth believes that CoAs should be clearly annotated to distinguish an actual test result from a parametric test result. However, Wyeth supports that the final cGMP should allow for the acceptance of parametric results (instead of actual results), when such results can be verified as valid based on process knowledge and controls. As an example, per USP <467>, a supplier should be able to avoid unnecessary testing and report on a CoA that a material meets all requirements for Organic Volatile Impurities, provided that there is no potential (based on process knowledge and controls) for specific toxic solvents to be present and provided that the material would comply with established standards, if tested.

The Agency should be aware that references are available that may serve as industry guides for the preparation and appropriate use of CoAs. For example, IPEC (International Pharmaceutical Excipients Council) has published a "Certificate of Analysis Guide for Bulk Pharmaceutical Excipients". As noted in the September-October issue of the Pharmacopeial Forum<sup>21</sup>, this IPEC guide is being used by USP to develop a new General Information Chapter <1080> entitled "Bulk Pharmaceutical Excipients-Certificate of Analysis".

The Agency should understand that accepting CoA results represents a significant cost saving to firms. As an example, for a single Wyeth facility, total costs would be more than doubled for in-house testing:

<i>Costs</i>	<i>Accepting Supplier CoA</i>	<i>Testing In-house</i>
Personnel (assumes \$65,000/yr.: base salary plus benefits)	\$520,000 (8 analytical chemists)	\$1,430,000 (22 analytical chemists)
Test Supplies (standards, reagents, etc.)	\$72,000-80,000	\$140,000-160,000
Total	\$592,000-600,000	\$1,570,000-1,590,000

<sup>19</sup> FR 68(49): 12198

<sup>20</sup> Parametric results would include in-process test data, composite test data, process capability data, etc.

<sup>21</sup> PF 28(5), pages 1650-1662

In summary, Wyeth believes that it should be the responsibility of the manufacturer to determine on a case-by-case basis whether a certification by a supplier provides adequate assurance that a dietary ingredient is what it purports to be and that it is not adulterated. Reliance on a supplier's certification should be an acceptable alternative to testing raw materials or products, as long as the validity of the supplier's guarantee is appropriately confirmed by the manufacturer and provided effective procedures are in place to assure the identity of the material upon receipt.

**9. The Proposed Rulemaking specifies full product release testing on a routine basis. Wyeth proposes that firms should have the option to employ reduced/parametric release testing regimens under appropriate circumstances, based on a systems approach to quality assurance.**

Firms would be required under proposed 111.35(g)(1) to fully test each finished batch of dietary supplement produced prior to distribution, or in the absence of scientifically valid analytical methods to conduct such testing, firms would need to test incoming and in-process materials under proposed 111.35(g)(2). This proposed requirement appears to embrace an outdated quality control philosophy that focuses on exhaustive end product testing. Wyeth does not agree that such an approach will afford a high degree of product quality assurance. Rather, as recognized in USP's General Notices, "data derived from manufacturing *process validation* studies and from *in-process controls* may provide greater assurance that a batch meets a particular...requirement than analytical data derived from an examination of finished units drawn from that batch". As such, USP's General Chapter <2750> entitled "Manufacturing Practices for Dietary Supplements" provides for reduced/parametric release testing schemes, based on adequate process validation and controls.

We note that in the cGMP regulation of other classes of products (e.g. drugs, medical devices, etc) and in the HACCP regulations for certain potentially hazardous food products, FDA has strongly supported a move away from comprehensive end product testing and has accepted a systems-based approach to assure quality based on validation of raw materials and critical processes. We also note the Agency's leadership role in advancing innovative quality assurance initiatives such Process Analytical Technologies (PAT). Given FDA's current efforts to regulate products using risk-based management principles, Wyeth is perplexed that the Agency has put forth a regulatory scheme for dietary ingredient and dietary supplement products that relies so heavily on end product testing as opposed to quality management and control throughout the process.

Wyeth would encourage the Agency reconsider its overall position on this issue. Since a well-controlled process provides a greater assurance of quality than full end product testing of every batch, it is Wyeth's opinion that the Agency should specify:

- Full end product testing as a "minimum" standard, only in the absence of a process verification program
- Flexibility to use reduced or parametric testing as an alternative approach, provided a firm operates under a quality system that includes an adequate process verification program

The Agency should understand that reduced and/or parametric release testing regimens represent a significant cost saving to firms. As an example, for a single Wyeth facility, comparative costs are estimated as follows:

<i>Costs</i>	<i>Reduced/Parametric Testing</i>	<i>Full End-Product Testing</i>
Personnel (assumes \$65,000/yr.: base salary plus benefits)	\$585,000 (9 analytical chemists)	\$2,015,000 (31 analytical chemists)
Test Supplies (standards, reagents, etc.)	\$120,000	\$240,000
Total	\$705,000	\$2,255,000

General and detailed overviews of the elements that would define an appropriate process verification program are provided in Attachments A and B, respectively. We trust that the Agency will conclude upon review of this information that appropriate process verification and control provide systematic quality assurance that can serve as an alternative for complete end product testing of every batch.

**10. The Proposed Rulemaking does not require products to be expiry dated and/or stability tested. Wyeth suggests it should be mandatory for dietary supplements to bear an expiration date that is supported by appropriate stability data.**

The Agency's Advanced Notice of Proposed Rulemaking<sup>22</sup>(ANPR) specified optional expiration dating and implied conditional stability testing for dietary supplements. In particular, the ANPR<sup>23</sup> stated that "whenever a ...dietary supplement bears an expiration date, such date shall be supported by data and rationale to reasonably assure that the product meets established specifications at the expiration date". The subject Proposed Rulemaking does not require expiration dating and/or stability testing (i.e. the Agency deleted the provision for voluntary expiration dating and the associated stability testing).

Wyeth believes that dietary supplements should be required to bear an expiration date with a corresponding label storage statement<sup>24</sup> that is supported by appropriate stability data. Our opinion is based on the following considerations:

- Per the Dietary Supplement Health and Education Act (DSHEA), dietary supplements are defined as foods. From a regulatory perspective and for compliance purposes, the law currently requires that fortified or fabricated foods including dietary supplements with added ("Class 1") nutrients comply with certain potency requirements through shelf life. Specifically, 21 CFR 101.9 (g)(4)(i) reflects that the content of "Class 1" nutrients should be "at least equal to the value for that nutrient declared on the label". In the absence of expiration dating and/or stability testing, it is unclear how firms would substantiate compliance with the current legal requirement for dietary supplement products to contain at least 100% of the labeled amount of nutrient(s) throughout shelf-life. Also, in the absence of expiry dating on the label, it is unclear what shelf-life would FDA presume for the purposes of verifying compliance with label content claims.
- Many dietary ingredients have a potential to degrade over time (see Attachment C). Therefore, expiration dating is crucial to ensure that a quality product is used by consumers.
- The Agency appears to acknowledge per proposed 111.45(b)(5) that an "intentional excess amount of dietary ingredient" may be needed in a dietary supplement product. However, it is unclear how overages that are added to compensate for degradation over time could be scientifically justified without stability data.
- In accordance with demands from retailers, it is common and standard practice for companies to use expiration dating on dietary supplement products.
- Although some dietary supplement products may not have validated methods to determine potency, expiry dating would still seem warranted as it relates to other types of specifications (e.g. physical appearance, disintegration time, etc.).

<sup>22</sup> FR 68(25): 5704 and 5706

<sup>23</sup> FR 68(25): 5704

<sup>24</sup> Label storage statements should be product-specific based on the stability profile for a given formulation in a given package.

Wyeth also believes that firms should be allowed to execute stability programs for dietary supplements using a variety of scientifically sound approaches. For example, firms should have flexibility to use accelerated stability studies or data from similar product formulations for an initial determination of shelf-life. Matrixing and bracketing schemes should also be considered acceptable.

**Attachment A**  
Alternate to Full Testing of Every Batch:  
General Overview of a Process Verification Program

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A qualified process including the general features summarized below would justify reduced or parametric testing and would assure that a product meets established requirements more effectively than testing every batch. However, in the absence of a qualified process, full end product testing would be considered acceptable as a minimum standard.

Controls for Raw Material and Primary Packaging

- Appropriate written specifications for raw materials and packaging
- Supplier qualification program based on manufacturer's evaluation of the supplier's process and testing procedures
- Procedures to assure identity of every ingredient
- Review of Reports of Analysis and other data as appropriate
- Verification of supplier's test results at appropriate intervals

In Process Controls

- Appropriate written specifications for in-process materials
- Master and batch production records for every product
- Verification of identity and weight of ingredients added
- Calculation of yields
- Data demonstrating that equipment is suitable and that the process consistently delivers expected results
- Specific in-process tests appropriate to specifications for unit operations

Controls for Finished Product

- Appropriate written specifications for finished product
- Representative testing of chemical, physical and microbiological parameters based on an appropriate statistical sampling plan

**Attachment B**  
Alternate to Full Testing of Every Batch:  
Detailed Overview of a Process Verification Program

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A qualified process including the detailed aspects summarized below would justify reduced or parametric testing and would assure that a product meets established requirements more effectively than testing every batch. However, in the absence of a qualified process, full end product testing would be considered acceptable as a minimum standard.

Raw Material Controls/Programs

- Extensive Qualification process
  - Review of Supplier Certificate of Analysis
  - Complete analytical testing of multiple commercial lots
  - Quality Audit of Supplier
  - Evaluation of GMO/BSE/TSE status
  - Stability Data
  - Evaluation of need for accelerated/concurrent finished product stability data
  - Supplier changes monitored through change control program
- Reduced Testing Program
  - Predetermined number of lots evaluated
  - Analytical data required from both the raw material supplier and an independent qualified testing facility
  - Statistical evaluation
  - Yearly requirement for full testing
  - Minimum requirement of chemical identification for each receipt
  - Periodic microbial monitoring of supplier lots
- Packaging Component Controls/Programs (Product Contact)
  - Supplier COA
  - Dimensional Checks as required
  - Microbial Evaluation as required
  - Identification (chemical and/or visual)
- Packaging Component Controls/Programs (Non-Product Contact/ Printed)
  - Supplier COA
  - Proof checked against master component specifications (manual or electronic)
  - Functional Check – Bar Code Legibility where applicable

Manufacturing Controls/Programs

- Detailed Production Batch Record
  - Ingredient Listing
    - Item number
    - Item description
    - Quantity of each ingredient
    - Potency, where applicable
    - Overages
  - Manufacturing Instructions

- Critical Process Control Points
  - Raw Material Weighing
    - Electronic verification of proper quantity dispensed
  - Raw Material Charging
    - Second independent check
  - Granulation Process Parameters
    - Exhaust temperature
    - Airflow
    - Moisture analysis
  - Blend Times
  - Compression/Encapsulation Process Parameters
    - Weights
    - Hardness
    - Thickness
  - Film Coating Process Parameters
    - Air Flow
    - Exhaust Air Temperature
  - Hold Time Restrictions
- Production Yields - Reconciliation
- Master Batch record reviewed/approved by Quality Assurance
- Executed Production Batch record reviewed/approved by Quality Assurance
- Detailed Packaging Batch Record
  - Component Listing
    - Item Number
    - Item Description
    - Quantity
  - Packaging Instructions
  - Critical Process Control Points
- Detection Systems
  - Metal Presence
  - Missing Cap
  - Missing Seal
  - Incorrect label
  - Electronic container counts
- Manual Package Counts
  - Packaging Yields - Reconciliation
  - Master Packaging Record reviewed/approved by Quality Assurance
  - Executed Packaging Record reviewed/approved by Quality Assurance
- QA Shop Floor Raw Material Verification Program
  - QA verification of the physical addition of each raw material ingredient to the blender.
  - Products qualified for this program require potency testing of all dietary ingredients
- Process Validation Program
  - Consecutive batches required
  - Tablet Compression/Encapsulation
    - Distinct time points sampled to represent the batch
    - Marker compounds utilized for multivitamin/multimineral products
    - Potency uniformity assessed

- Tablet Coating
  - Each coating pan evaluated for any active ingredient(s) contained in the film coating
  - Potency uniformity assessed
  - Performance attributes evaluated
    - Disintegration/Dissolution as defined by product specifications
  - Physical evaluation – Tablet appearance/markings legible
- Complete testing of validation batches required. No composite/tracer testing permitted.
  - Cleaning Validation Program
- Active Ingredient – Marker Compound
- Microbial Assessments
- Hold Time Assessments
  - Clean state
  - Unclean state
- Campaign Length
- Cleaning Agent Residue
- Environmental Controls Program
  - HVAC
    - Temperature Control
    - Humidity Control
    - Room Pressurization
    - System Qualification
    - Change Control
    - Manufacturing Equipment Program
  - Formal Qualification Process
  - PMO/Calibration Program
  - Change Control

Analytical Testing Program

- Composite Testing Scheme- As allowed by USP
  - Three batch maximum
  - Process validation required
- Reduced Testing Scheme– As allowed by USP
  - QA Shop Floor raw material verification program required
  - Process validation required
- Tracer Testing Scheme
  - Premixes (Vitamin and/or mineral)
    - Process validation required
    - Equipment/Instrument Qualification
  - PMO/Calibration Program
  - Change Control
    - Test Methods Qualified
  - Stability
  - Control Release
    - Raw Materials
    - Finished Products

Investigation Program

- Manufacturing Investigations
- Process Deviations
- Laboratory Investigations
- OOS Data

Marketed Product Stability Program

- Accelerated Stability Program
  - New Formulations
  - Raw Materials
    - Process change
    - Supplier change
  - Critical manufacturing process change
  - Significant manufacturing deviation
  - Tests
    - Label claim items (no minerals)
    - Disintegration or dissolution depending on product specification
    - Hardness where specified
  - Pre-determined Testing Intervals
- Room Temperature Stability Program/Ambient Humidity
  - Routine batch monitoring
    - Bracketing approach
    - Head space considerations
  - Manufacturing deviations
  - Tests
    - Label claim items (no minerals)
    - Disintegration or dissolution depending on product specification
    - Hardness where specified
  - Pre-determined Testing Intervals

Annual Product Review Program

- Performed Yearly
  - Finished Product disposition
  - Product complaint profile
  - Stability data
  - Change controls

Internal Audit Program

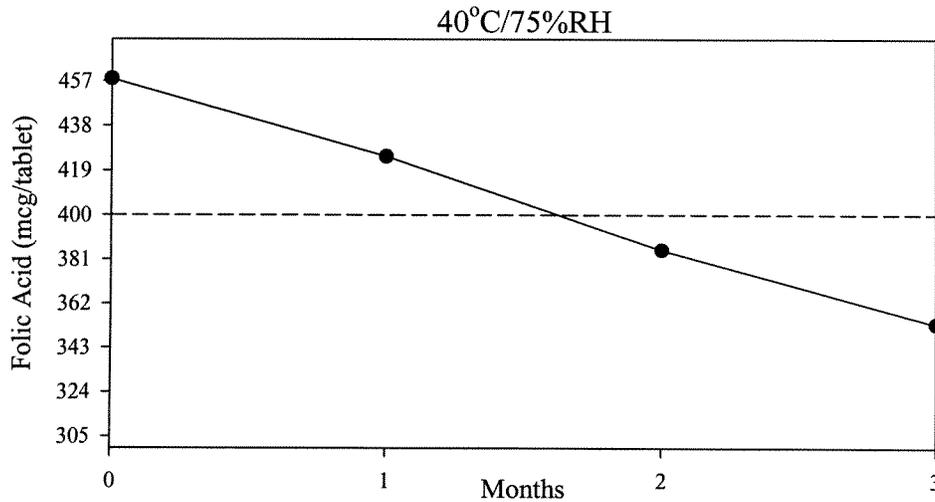
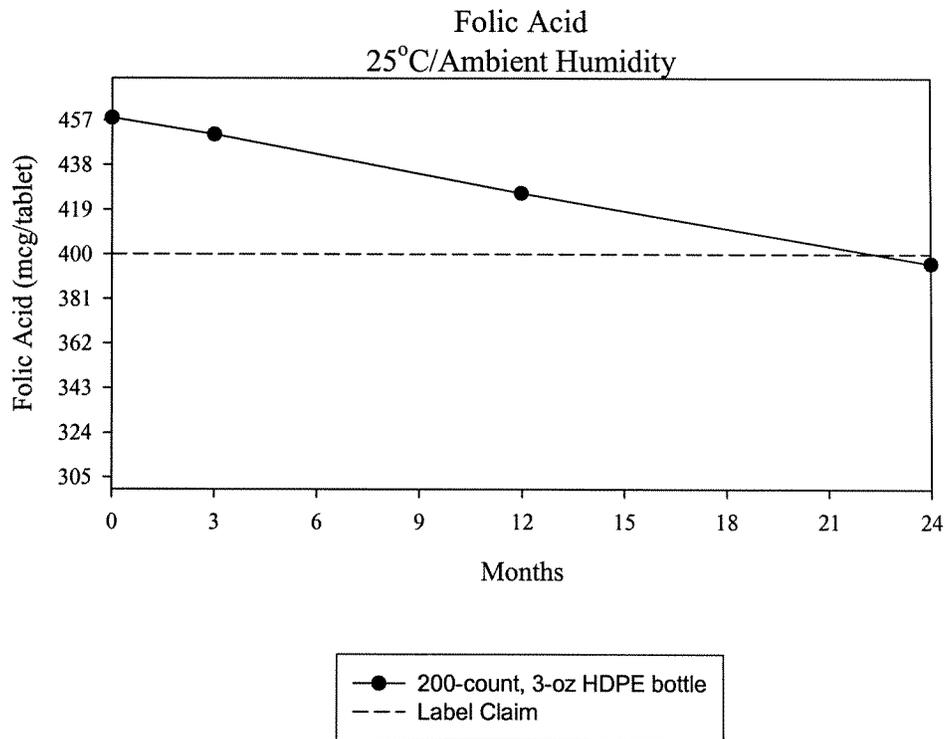
- Yearly Schedule Prepared
- Walkthrough Audits (SOP's, Housekeeping)
- Formal Audits (Systems based)

Training Program

- Curricula established for each employee
  - Position based
- SOP's
- Job Aids/Skill Checks – Tasks
- Policies

**Attachment C**  
Examples of Dietary Ingredient Degradation Over Time

Assay results for a Folic Acid Tablet formulation show degradation of the dietary ingredient to below label claim within 24 months of storage at the “room temperature” condition:



Similarly, assay results for a multi-vitamin/multi-mineral formulation show degradation of the Vitamin C component to below label claim within 24 months of storage at the “room temperature” condition:

