

Docket No. 96N-0417

BEFORE

THE UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

TRADITIONAL MEDICINALS, INC.

COMMENTS ON
THE PROPOSED RULE FOR
CURRENT GOOD MANUFACTURING PRACTICE
IN MANUFACTURING, PACKING, OR HOLDING
DIETARY INGREDIENTS AND DIETARY SUPPLEMENTS

Traditional Medicinals, Inc.
4515 Ross Road
Sebastopol, California 95472
707.823.8911
jbrinckmann@tradmed.com

96N-0417

C168

23 July 2003

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

Traditional Medicinals, Inc., a manufacturer and marketer of herbal dietary supplement products for the US market and natural health products for the Canadian market submits in duplicate the following comments in response to the FDA's proposed rule for current good manufacturing practice in manufacturing, packing, or holding dietary ingredients and dietary supplements.

Subpart A—General Provisions, §111.6 Exclusions

The regulations in this part do not apply to a person engaged solely in activities related to the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary ingredient or dietary supplement by other persons.

We recommend that the farm exclusion be somewhat expanded in order to include a few other typical farm preliminary processes as follows:

The regulations in this part do not apply to a person engaged solely in activities related to the harvesting, cleaning and drying, cutting and sifting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary ingredient or dietary supplement by other persons.

Subpart B—Personnel, §111.12(b)

*Each person engaged in manufacturing, packing, or holding must have the training **and** experience to perform the person's duties.*

It is our opinion that the phrase "*training and experience*" should be replaced with the phrase "*education, training, and experience, or any combination thereof*" because the finished pharmaceuticals GMPs (Part 211, Subpart B, §211.25(b))¹, in this regard, appear to be more flexible than the proposed dietary supplement GMPs:

Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in

¹ Food and Drug Administration. Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals. §211.25 Personnel qualifications. In: *Code of Federal Regulations, Title 21*. Washington, DC: The Office of the Federal Register National Archives and Records Administration. 2003.

such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

Subpart E—Production and Process Controls, §111.35(e)(1)

Specifications must be established for:

The identity, purity, quality, strength, and composition of components, dietary ingredients, or dietary supplements that you receive;

We agree that specifications must be established for components and dietary ingredients as well as for the finished consumer product. However, we request that FDA clarify whether it is proposing that every specification sheet must include separate, specific qualitative or quantitative standards and tests to be established for each of the five main points (identity, purity, quality, strength, and composition) or whether a specification sheet that is modeled after a compendial monograph (e.g. Peppermint NF or Senna USP) would in fact meet the proposed requirement. If so, for example in the case of Peppermint NF, how would FDA define the proposed specification requirement for ensuring “strength” and/or “composition”? The *United States National Formulary* monograph for peppermint leaf includes macroscopic, microscopic, and organoleptic descriptions plus an upper limit for stems and other foreign organic matter, and organic volatile impurities². The monograph, however, does not include a requirement for a minimum level of essential oil nor are there any other quantitative standards in the monograph. Therefore, it is not clear to us whether a specification sheet for peppermint leaf based entirely on the official Peppermint NF monograph would comply with FDA’s proposed specification requirement for ensuring the “strength” and “composition” of the ingredient. We recommend that the terms “strength” and “composition” should be struck from the requirement unless FDA clarifies that the five stated specification requirements (identity, purity, quality, strength, and composition) can be ensured collectively, rather than individually, by virtue of an ingredient’s conformance with monograph, even if the referenced monograph includes no quantitative standards directly related to ensuring strength or composition, as is the case with the Peppermint NF and Senna USP monographs, respectively, among many others.

Also, how does FDA define the requirement that a specification must ensure “quality”? Would a botanical raw material that is tested to be in conformance with pharmacopoeial standards (e.g. Peppermint NF) also meet FDA’s proposed requirement for ensuring “quality”? Please clarify in the rule.

It is our opinion that the proposed requirement for specifications that ensure the identity, purity, quality, strength, and composition of a dietary ingredient, particularly of a botanical raw material or extract, could be satisfied by an FDA

² United States Pharmacopoeial Convention, Inc. Peppermint. In: *U.S. Pharmacopoeia & National Formulary (USP 26–NF21)*. Rockville, MD: United States Pharmacopoeial Convention, Inc. 2003.

guideline that ingredient specification sheets should be modeled after an official pharmacopoeial monograph (e.g. JP, Ph.Eur. USP-NF) or after a non-official, but nonetheless authoritative pharmacopoeial monograph (e.g. AHP, BHP, IHP).

Our company routinely buys over 120 different botanical raw materials and/or extracts and for almost all of them we have been able to obtain a suitable pharmacopoeial monograph from which to base our internal specification requirements. For those ingredients with no monograph available, we have been able to write a suitable specification that is based on the general monograph "*Herbal Drugs*" of the European Pharmacopoeia ³.

In our opinion, any of the following official or non-official authoritative sources for English-language monographs could be recommended by FDA for the purpose of writing specification sheets that would help dietary supplement ingredient distributors as well as finished product manufacturers conform with the proposed requirement to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements:

- American Herbal Pharmacopoeia (AHP) (1997-2003)
- Ayurvedic Pharmacopoeia of India (API), Volume 1 (1989), Volume 2 (1999), Volume 3 (2003)
- British Herbal Pharmacopoeia (BHP), 2nd edition (1983), 3rd edition (1990), 4th edition (1996)
- European Pharmacopoeia (Ph.Eur.), 4th edition (2003)
- Herbal Drugs and Phytopharmaceuticals, English 4th edition (2003)
- Indian Herbal Pharmacopoeia (IHP), Revised New Edition (2002)
- International Organization for Standardization (ISO): specifications, standards, and tests for various herbs and spices
- Japanese Herbal Medicine Codex (JHMC) (English translations available in The Japanese Standards for Herbal Medicines, 1993).
- Japanese Pharmacopoeia (JP XIV), 14th edition, Crude Drugs Monographs (English Edition 2001)
- Pharmacopoeia of the People's Republic of China (PPRC English Edition 2000)
- Standardisation of Single Drugs of Unani Medicine, Central Council for Research in Unani Medicine (CCRUM), Part I (1987), Part II (1992), Part III (1997)
- Unani Pharmacopoeia of India (UPI), Part I
- United States National Formulary (USNF), 21st edition (2003)
- United States Pharmacopoeia (USP), 26th revision (2003)
- World Health Organization (WHO) Monographs on Selected Medicinal Plants, Volume 1 (1999), Volume 2 (2002), Volume 3 (2003)

³ European Pharmacopoeia Commission. Herbal Drugs—Plantae medicinales. In: *European Pharmacopoeia*, 4th edition. Strasbourg, France: Council of Europe. 2003;510.

In addition, for companies with multi-lingual personnel in their quality control units and/or research and development departments, there are, of course, many other non-English pharmacopoeial monographs available for a wide range of botanical raw materials & extracts and other natural ingredients from which a suitable specification sheet could be modeled (e.g. Deutscher Arzneimittel-Codex (DAC), Deutsches Arzneibuch (DAB), Pharmacopée Française (Ph.Fr.), Schweizerischen Pharmakopöe (Ph. Helv.), and many others).

Subpart E—Production and Process Controls, §111.35(g)

*You must ensure, through testing or examination, that **each specification** that you established under paragraph (e) of this section is met.*

First of all, we believe that with adequate process controls, periodic or skip lot testing is sufficient. Skip lot testing is acceptable under the regulatory frameworks for herbal products in other countries, including EU countries and Canada. Once a certain number of batches are consistently shown to meet their specifications, subsequent batches can be audited.

Secondly, referring to page 12198 of the preamble, second paragraph, it states that using a supplier's certificate of analysis (C of A) document in lieu of performing testing on **each shipment** lot of ingredients is not appropriate because it is possible that a supplier's certification or guarantee may not ensure the identity, purity, quality, strength, or composition of an ingredient.

The dietary supplement CGMPs, which are to be modeled after food GMPs, clearly should not have a higher standard imposed over what is permitted in the corresponding drug CGMP section §211.84(d), wherein it states:

(d) Samples shall be examined and tested as follows:

- (1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.
- (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**, 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.⁴

⁴ Food and Drug Administration. Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals. § 211.84 Testing and approval or rejection of components, drug product containers, and closures. In: *Code of Federal Regulations, Title 21*. Washington, DC: The Office of the Federal Register National Archives and Records Administration. 2003.

We believe that the dietary supplement CGMPs must make an allowance for the acceptance of certain data from C of A documents that are generated by qualified and audited GMP ingredient suppliers. The proposed CGMPs apply to the wholesale suppliers of dietary ingredients as well as to the manufacturers of consumer products. Therefore, the identity, purity, quality, strength, and composition of every component and ingredient will be required to be ensured by the supplier before the product manufacturer receives the ingredient, which is subsequently released from quarantine by the QC unit for use in a batch.

More importantly, however, because the purpose of CGMPs includes consistent manufacturing, conformance with specifications, and batch-to-batch uniformity, the GMPs should encourage the development and use of as detailed of specifications as possible. The proposed CGMPs in their present form will do just the opposite. Ingredient suppliers and product manufacturers may need to minimize or weaken their written specifications and test procedures if each specification established under paragraph (e) must be tested and confirmed by both the supplier and the product manufacturer. For example, companies who do not own an HPLC may decide to remove any quantitative standards from their specifications that require HPLC testing, even though their supplier can conduct the test, unless they can afford to have each lot number tested at an independent laboratory, which may be cost prohibitive. Although our company models its specification sheets according to pharmacopoeial monographs, our QC unit has most, but not all, of the apparatus in-house necessary to conduct every test in every botanical monograph. While we have the in-house capabilities to conduct macroscopic, organoleptic, and HPTLC identity tests as well as determination of volatile oil content, water-soluble extractive, total ash, AIA, water content, foreign matter, and microbial limits, among others, we do not have a GC, which would be necessary for confirming certain quantitative standards in the Chamomile NF monograph, nor do we have an HPLC which would be necessary for confirming certain quantitative standards in the Echinacea purpurea root NF monograph. We do not want to remove these important quantitative specification requirements from our specification sheets just because we do not have a GC and/or HPLC in our QC laboratory.

Once we have qualified and audited a quality ingredient supplier, we do not believe that we should also have to pay the expense to have samples from every raw material lot number sent out to an independent lab for certain tests that we are unable to conduct in-house (e.g. those requiring HPLC or GC). The analytical testing program of a GMP ingredient supplier is an important value-added service that consumer product manufacturers, particularly small and very small companies, should be able to rely upon. We believe that there should be a mechanism in the CGMPs for the qualification of GMP ingredient suppliers that releases the product manufacturer from having to test **each** specification for **each** lot of ingredients. Otherwise, some companies may end up removing certain important specifications from their specification sheets if they, in fact, cannot afford the technology necessary for confirming the

specification. One likely result of less stringently defined ingredient specifications is greater variability or less uniformity from batch-to-batch in the finished products, which we believe would be an unfortunate and unintended result of these rules if finalized in their present form. It is therefore in FDA's interest to encourage companies to develop detailed specifications, for example based on pharmacopoeial standards, but at the same time allow the QC unit to accept certain data from a qualified supplier's C of A document for those tests that are outside of the company's in-house testing capabilities.

Furthermore, the new Canadian regulations for Natural Health Products (NHPs) a product category that is closely comparable (in many cases identical) to dietary supplement products in the US, also include new GMPs that are necessary and relevant to consider particularly for companies presently doing business with the same products in both countries. Our products are dietary supplements in the US and NHPs in Canada, and therefore we must model our internal GMPs according to both regulatory frameworks. NHPs fall under OTC drug regulation and therefore each lot or batch of raw material must be tested against specifications that are based on a monograph from a recognized pharmacopoeia listed in Schedule B of the *Food and Drugs Act*⁵. Schedule B lists the most recent editions of the *European Pharmacopoeia* (Ph.Eur.), *Pharmacopée Française* (Ph.Fr.), *Pharmacopoeia Internationalis* (Ph.I.), *The British Pharmacopoeia* (BP), *The Canadian Formulary* (CF), *The National Formulary* (NF), *The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals*, and the *United States Pharmacopoeia* (USP).⁶ However, the testing may be performed on each lot of raw material or the product manufacturer can undertake periodic complete confirmatory testing if the manufacturer has satisfactory evidence demonstrating that the raw materials sold to him/her by the ingredient supplier are consistently manufactured in accordance with and consistently comply with the specifications of the raw materials, and if the raw material has not been transported or stored in any manner that may affect its compliance with the specifications for that raw material⁷. We believe that the aforementioned allowance for the periodic testing of ingredients used in OTC drug / NHPs in Canada would also be acceptable for comparable food / dietary supplement products in the US. Specifically, in the new NHP GMPs, it states that *"Every natural health product shall be manufactured, packaged and labelled using only material that, prior to its use in the activity, has been approved for that use by the quality*

⁵ Health Canada Health Products and Food Branch Inspectorate. Raw Material Testing. Regulation C.02.009. In: *Good Manufacturing Practices Guidelines 2002 Edition*. Ottawa, ON: Health Products and Food Branch Inspectorate. 2002;28.

⁶ Health Canada. Schedule B. In: *Food and Drugs Act and Regulations*. Ottawa, ON: Her Majesty the Queen in Right of Canada. 2003;11.

⁷ Health Canada Health Products and Food Branch Inspectorate. Raw Material Testing. Regulation C.02.009. In: *Good Manufacturing Practices Guidelines 2002 Edition*. Ottawa, ON: Health Products and Food Branch Inspectorate. 2002;28.

assurance person.”⁸ The NHP GMPs include only the specification requirements for finished consumer products but no specific requirements are outlined for the specifications or testing requirements of ingredients used in NHPs. Because NHPs are OTC drugs, ingredient specifications that conform with a Schedule B monograph are acceptable, and periodic testing rather than each lot testing are acceptable under certain conditions.

Subpart E—Production and Process Controls, §111.35(k)

You must test or examine components, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or lead to adulteration. You must use an appropriate scientifically valid method for the test or examination. The types of contamination include, but are not limited to, the following:

- (1) Filth, insects, or other extraneous material;*
- (2) Microorganisms, and*
- (3) Toxic substances.*

Based on language used in the preamble on page 12162, we are concerned about the requirement to test for toxic substances (and presumably ensure that the product does not contain toxic substances). On page 12162, fourth paragraph, it states:

“For example, aflatoxin and mycotoxin (toxic compounds produced by certain molds) are known to contaminate certain herbal and botanical dietary supplements. Under this proposed rule, a manufacturer would have to establish specifications for botanicals that may contain toxic compounds and conduct testing to ensure that there are not toxic compounds present that may adulterate the dietary ingredient or dietary supplement.”

Based on the above language from the preamble, we are concerned about the intended meaning of the proposed regulation under section §111.35(k). The statement **“ensure that there are not toxic compounds present that may adulterate”** is a wide reaching statement. Whether a toxic compound detected to be present at any level would be considered to be of public health significance could be open to debate and interpretation of the rule unless FDA provides further clarification. Knowing that certain levels of mycotoxins are, in fact, present in the US food supply, FDA should clarify this to mean **“ensure that the levels of toxic compounds present occur below reasonable maximum allowable limits.”** For example, ochratoxin A, a mycotoxin produced by several fungi (*Penicillium* and *Aspergillus* species) has been detected as a natural contaminant in many food products including cereal products, corn, peanuts, storage grains, as well as spices, coffee (green and roasted) beans, cocoa beans, soybeans, fatty oil-containing seeds, raisins and other dried

⁸ Health Canada Natural Health Products Directorate. Good Manufacturing Practices. In: Food and Drugs Act: Natural Health Product Regulations. *Canada Gazette Part II*. 2003;137(13):1550-1555.

fruits, grape juice, wine, and beer.⁹ According to the European Community Scientific Committee for Food, investigations of the frequency and levels of occurrence of ochratoxin A in food and human blood samples indicate that foodstuffs are frequently contaminated.¹⁰ The Canadian Food Inspection Agency has estimated that about 25% of the world's food production is contaminated with mycotoxins.¹¹

We believe that FDA should clarify that certain toxic compounds, such as the aforementioned mycotoxins, are known to be present throughout the food supply and therefore dietary supplement ingredients and products should not contain levels that are higher than reasonable or recognized maximum allowable limits as opposed to the currently implied zero tolerance for toxic compounds. For example, the European Commission Regulation No 472/2002 has set maximum levels for mycotoxins naturally occurring in coffee and cocoa products as well as in certain spices such as cayenne and paprika, white and black pepper, nutmeg, ginger, and turmeric, which could be used as one reasonable guideline in this regard.¹² In an article posted by FDA CFSAN entitled "*Emerging International Contaminant Issues: Development of Codex Alimentarius standards to address the issues*" it states "Codex Committee on Food Additives and Contaminants (CCFAC) also adopted a draft Maximum Level (ML) at Step 3 of 5 ppb for ochratoxin A. It is not clear why this level is more appropriate than others, for example, 2 ppb, 10 ppb or 20 ppb. Therefore, it is important for the Joint Expert Committee on Food Additives (JECFA) to address the risk assessment, because a level of 5 ppb may cause major disruptions in international trade and we need to understand what the public health benefits are compared to the feasibility of attaining these various levels."¹³ This example illustrates that FDA is willing to balance the need for establishing reasonable MLs for certain toxic compounds (e.g. mycotoxins) against international trade issues, among other issues.

Equally important, it is also critical to view the content of naturally occurring toxic compounds in botanical dietary supplement ingredients in the context of acceptable daily intakes (ADIs), tolerable daily intakes (TDIs) and/or tolerable

⁹ European Community. Commission Regulation (EC) No 472/2002 of 12 March 2002 amending Regulation (EC) No 466/2001 setting maximum levels for certain contaminants in foodstuffs. *Official Journal of the European Commission*. 16.3.2002;L75/18-L75/20.

¹⁰ European Community. Commission Regulation (EC) No 472/2002 of 12 March 2002 amending Regulation (EC) No 466/2001 setting maximum levels for certain contaminants in foodstuffs. *Official Journal of the European Commission*. 16.3.2002;L75/18-L75/20.

¹¹ Charmley LL, Trenholm HL. Mycotoxins: Canadian Food Inspection Agency Animal Products - Animal Health and Production Fact Sheet. Nepean, Ontario: Canadian Food Inspection Agency. November 2000.

¹² European Community. Commission Regulation (EC) No 472/2002 of 12 March 2002 amending Regulation (EC) No 466/2001 setting maximum levels for certain contaminants in foodstuffs. *Official Journal of the European Commission*. 16.3.2002;L75/18-L75/20.

¹³ Troxell TC. *Emerging International Contaminant Issues: Development of Codex Alimentarius standards to address the issues*. *Food Safety Magazine* February-March 2000. Available at FDA website: <http://www.cfsan.fda.gov/~cjm/codexfa2.html#authors>

weekly intakes (TWIs).¹⁴ American consumers are likely to consume much larger daily and weekly quantities of mycotoxin-containing coffee, chocolate, beer, wine and cereals than the amounts detected in the occasional cup of ginger herbal tea or capsule containing a typical 0.5-1.0 g of ginger rhizome.

Additionally, in the preamble on page 12199, third column, it states:

“Contamination also can create conditions that promote further contamination by other organisms. For example, contamination resulting from possible fungal growth on a botanical component can provide the environment for mycotoxin production, especially aflatoxin. Therefore, if a toxic substance is a type of contamination that may adulterate or lead to adulteration of the dietary ingredient or dietary supplement, you must perform an appropriate test to detect the toxic substance.”

Our concern about this proposed requirement is whether non-dietary supplement food product manufacturers who use certain botanical ingredients that are known to routinely contain measurable levels of mycotoxins, for example coffee bean, ginger rhizome or licorice root, would not have the same requirement to test for mycotoxins as dietary supplement product manufacturers who also use ginger and licorice raw materials. In other words, will the licorice candy manufacturer in the confectionery industry not have to test for mycotoxins but the licorice herbal tea manufacturer in the dietary supplement industry will have to test for mycotoxins? Will there be consistency in the regulations?

Concerning the same section §111.35(k), and referring to related language in the preamble on page 12200, first column, it states:

“Although the proposal does not specify microbial limits for undesirable microorganisms, other non-FDA sources have established acceptable, general limits of microbial levels for dietary ingredients and dietary supplements.”

The non-FDA source referenced here is the USP, whose microbial limits for dietary supplement ingredients are still controversial and out of step with guidelines from other authoritative bodies such as the European Pharmacopoeia Commission¹⁵, the World Health Organization¹⁶, and the American Herbal Products Association among others. Current USP total-plate-count upper limits of 10,000 cfu's/g may be appropriate for finished products but they are not appropriate levels for botanical raw materials, especially ingredients that are

¹⁴ Joint FAO/WHO Expert Committee on Food Additives (JECFA). Sixty-first meeting, Rome. Summary and Conclusions. Geneva, Switzerland: JECFA. 10-19 June 2003.

¹⁵ European Pharmacopoeia Commission. Microbiological Quality of Pharmaceutical Preparations. Category 4. In: *European Pharmacopoeia*, 4th edition. Strasbourg, France: Council of Europe. 2003.

¹⁶ World Health Organization. Determination of microorganisms. In: *Quality Control Methods for Medicinal Plant Materials*. Geneva, Switzerland: World Health Organization 1998;64-74.

going to be subjected to boiling solvents in the manufacture of extracts or herbal teas. The Ph.Eur. Guidelines *Microbiological Quality of Pharmaceutical Preparations*, General Text Section 5.1.4, are more appropriate than the current USP limits:

Microbiological Quality of Pharmaceutical Preparations
(Ph.Eur. General Texts, Section 5.1.4.)

Category 4: Herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered)

Category 4A: Herbal medicinal products to which boiling water is added before use

- Total viable aerobic count (2.6.12). Not more than 10^7 bacteria and not more than 10^5 fungi per gram or per milliliter.
- Not more than 10^2 *Escherichia coli* per gram or per milliliter (2.6.13, using suitable dilutions).

Category 4B: Herbal medicinal products to which boiling water is not added before use

- Total viable aerobic count (2.6.12). Not more than 10^5 bacteria and not more than 10^4 fungi per gram or per milliliter.
- Not more than 10^3 enterobacteria and certain other gram-negative bacteria per gram or per milliliter (2.6.13).
- Absence of *Escherichia coli* (1 g or 1 ml) (2.6.13).
- Absence of *Salmonella* (10 g or 10 ml) (2.6.13).

Subpart E— Production and Process Controls, §111.45

FDA has invited comment on whether any final dietary ingredient and dietary supplement CGMP rule should contain provisions regarding expiration dating and the feasibility of conducting tests needed to support such dates. FDA also invited comments on whether to require expiration dating on certain dietary ingredients and not others, for example, require expiration dating of vitamin, mineral, and amino acid, but not of botanical dietary ingredients.

We must already include an expiry date on the labels of our products in Canada as required under the Canadian NHP regulations. According to the NHP GMPs¹⁷:

Part 3 Stability

52. Every manufacturer and every importer shall determine the period of time that, after being packaged for sale, the natural health product will continue to comply with its specifications when

- (a) it is stored under the recommended storage conditions; or
- (b) if it does not have recommended storage conditions, it is stored at room temperature.

¹⁷ Health Canada Natural Health Products Directorate. Good Manufacturing Practices. In: Food and Drugs Act: Natural Health Product Regulations. *Canada Gazette Part II*. 2003;137(13):1550-1555.

Many US dietary supplement manufacturers who sell their same products in other markets such as Australia, Canada, or the EU will already have to comply with expiration date and stability requirements. Therefore, we have no objection to a requirement for expiration dates on herbal dietary supplement products in the US. Additionally, there are shelf-life, storage and stability data available for a wide range of herbal ingredients and herbal products published in the following authoritative European references, among others:

- ABDA–Bundesvereinigung Deutscher Apothekerverbände. Haltbarkeit von Zubereitungen. In: *Neues Rezeptur-Formularium (NRF)*. Band I. Stuttgart, Germany: Deutscher Apotheker Verlag. 1997-2003
- Braun R, Surmann P, Wendt R, Wichtl M, Ziegenmeyer J (eds.). Haltbarkeit von pflanzlichen Arzneimitteln. In: *Standardzulassungen für Fertigarzneimittel. Text und Kommentar*, mit 14. Ergänzungslieferung. Stuttgart, Germany: Deutscher Apotheker Verlag. 2002.
- *Deutsches Arzneibuch–Deutsche Demokratische Republik 7*. Ausgabe mit 9. Lieferung (DAB 7 - DDR). Berlin, Germany: Akademie Verlag. 1972.
- Meyer-Buchtela E. Haltbarkeit. In: *Tee-Rezepturen–Ein Handbuch für Apotheker und Ärzte*. Stuttgart, Germany: Deutscher Apotheker Verlag. 2001.

Subpart E– Production and Process Controls, §111.60(b)(3)(d)

You must identify and use the appropriate validated testing method for each established specification for which testing is required to determine whether the specification is met.

We recommend that “validated testing method” should be replaced with a “scientifically valid method.”

Subpart F–Holding and Distributing §111.80

FDA has invited comment on whether it should require, in a final rule, that you establish and follow written procedures for holding components, dietary ingredients, dietary supplements, packaging, and labels.

In response to this, we cannot understand how a company could be considered to be a GMP operation without having written Standard Operating Procedures (SOPs) for every product manufacturing activity including holding and distributing. It is self evident, that without written SOPs for control of storage locations, manner of storage, container and storage location identification codes, etc... mix-ups and adulterations will be more likely to occur.

Subpart F—Holding and Distributing §111.85(b)(2)

(b) You must not salvage returned dietary ingredients and dietary supplements, unless:

- (1) Evidence from their packaging (or, if possible, an inspection of the premises where the dietary ingredients and dietary supplements were held) indicates that the dietary ingredients and dietary supplements were not subjected to improper storage conditions; and*
- (2) Tests demonstrate that the dietary ingredients or dietary supplements meet all specifications for identity, purity, quality, strength, and composition.*

We believe that proposed section §111.85(b)(2) should be struck for the following reason. If there is evidence that the returned product was held and stored properly in its original unopened container, the proposed requirement to test the returned item again is unnecessary, costly and burdensome. It is not unusual for a wholesale distribution company to return only one or two undamaged, properly stored product units for any number of reasons. A requirement for the product manufacturer to again test for all of the specifications for a single case of returned product, one that has evidence of proper storage and handling, would introduce labor and lab expenses that would clearly outweigh the value of the product. Therefore, this proposed rule would guarantee the unnecessary destruction of inventories that could otherwise be determined to be safely re-sold without the proposed testing requirement.

VII. Analysis of Economic Impacts

We disagree with FDA's of impacts. We are a small company that produces approximately 750 finished product batches annually, which incorporate 560 annual ingredient batches, 500 annual packaging component batches and 750 blend batches. We anticipate that the proposed CGMPs if finalized in their present form would create significant additional testing expenses.