

Association for Official and Analytical Chemists



Southern California Section & Western Compendial Discussion Group

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Administration

Los Angeles District

Vendor qualifications for Dietary Supplements : Challenges in meeting the requirements of 21 CFR 111.75

Good Manufacturing Practice Violations

Under section 402(g)(1) of the Federal Food, Drug and Cosmetic Act (the Act), a dietary supplement is adulterated if it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations.

■ Major deviations from cGMPs include:

Lack of master manufacturing records or significant requirements for master manufacturing records are not met

Lack of finished product release criteria or failure to test (all or subset of finished batches) or meet finished product release criteria critical to product safety and quality

No quality control review procedures or lack of implementation of significant quality control procedures

No batch records

Significant physical plant deficiencies

For significant dietary ingredients, e.g. those that make up the bulk of the product, failure to establish specifications for incoming material or failure to conduct identity testing

In June, 2008, FDA implemented the Dietary Supplements GMPs, 21 CFR PART 111:

CURRENT GOOD MANUFACTURING PRACTICE
IN MANUFACTURING, PACKAGING, LABELING,
OR HOLDING OPERATIONS FOR DIETARY
SUPPLEMENTS

- Under 21 CFR 111.75(a)(1)(i), firms are required to conduct at least one appropriate test or examination to verify the identity of any component that is a **dietary ingredient**.

Dietary Ingredient:

Defined in Section 201(ff) of the Food Drug and Cosmetic Act. Includes, but is not limited to:

Vitamins, minerals, herbs, botanicals, amino Acids.

Difference between an ingredient and a component :

Components are non active entities, such as excipients, fillers, etc. which are not defined as ingredients in Section 201(ff) of the Act

Firms are required to conduct at least one appropriate test or examination to verify the identity of a dietary ingredient

UNLESS

You petition the agency under 21 CFR 75(a)(1)(ii) and the agency exempts you from such testing. The agency will specify the terms under which you must conduct the tests and examinations of the dietary ingredients.

Under 21 CFR 111.75(a)(2)(i), firms are required to confirm the identity of other components and determine whether other [established] and applicable component specifications are met.

This is accomplished by conducting appropriate tests or examinations

OR

Relying on a certificate of analysis from the supplier of the component that you receive **provided that you:**

QUALIFY THE VENDOR

You may rely on a certificate of analysis from a supplier, consistent with the requirements in 21 CFR 111.75(a)(2), to confirm the identity of dietary components that are not dietary ingredients. But, you may not rely on a certificate of analysis from your supplier to confirm the identity of a dietary ingredient [21 CFR 111.75(a)(1)(i)].

Since the implementation of the Dietary Supplement regulations, there have been thirteen instances where Warning Letters issued to firms have referenced inadequacies in meeting 21 CFR 111.75(a)(1), with respect to not properly verifying the identity of dietary ingredients.

There have been two instances where Warning Letters have referenced inadequacies in meeting 21 CFR 111.75(a)(2), with respect to relying on certificates of analysis for dietary components.

In many instances, the firms relied on the suppliers' Certificates of Analysis for either ingredients or components

For ingredients, they failed to conduct at least one appropriate test or examination to verify the identity of a dietary ingredient prior to its use

- For components, they failed to:

- Either conduct appropriate tests or examinations

OR

- Qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations.

With respect to performing identity testing for dietary ingredients, one firm performed microbiological tests, but was still cited for not conducting identity testing

Simply put, FDA wants manufacturers to be vigilant about the quality and identity of dietary ingredients and components

A Challenge to Industry

With respect to dietary ingredients, in many cases there is no compendial method for verifying the identity of the ingredient, and no reference standards exist for many dietary ingredients.

Most of these ingredients are imported

Top Five Ports of Entry

- Los Angeles
- Newark
- San Francisco
- Rio Grande City
- Buffalo-Niagara Falls

Top Dietary Supplement Commodities being imported

- Vitamins
- Minerals
- Proteins
- Herbals and Botanicals

Specifically:

- Vitamin C (Ascorbic Acid)
- Fish Oil (Fats and Lipid substances)
- Vitamin E (Tocopherol)
- Multiple Vitamins
- Zinc

Top ports for Detentions (not necessarily in order)

- Los Angeles
- Newark
- Memphis
- Atlanta

Primary Reasons for Detention

- The article appears to be a drug without an approved new drug application
 - Herbals and Botanicals
 - Vitamins, minerals, proteins, and unconventional dietary specialties for humans and animals

- Required label or labeling appears not to be in English
 - Herbals and Botanicals
 - Vitamins, minerals, proteins, and unconventional dietary specialties for humans and animals

The labeling of the dietary supplement fails to identify the product

What's Missing????

- The primary reasons for detention do not include detentions due to adulteration of dietary supplement components
- In layman's terms, these components may not be what they are represented to be

As defined in the FD&C Act the term adulteration has to do with the content of a product (such as the addition of a substance which makes a product inferior, impure, not genuine, etc.) while misbranding includes statements on labels or labeling that are false or misleading.

WHY?

- Over 20 Million shipments of FDA-regulated products come into our ports yearly
- Port of Los Angeles alone gets over 1,000 shipments daily
- Approximately 1% of our imports are actually sampled and analyzed. However FDA can stop the importation of commodities that have the **appearance** of adulteration or being misbranded

The Food, Drug, and Cosmetic Act authorizes FDA to refuse admission of a regulated product. The test is whether the product “appears to be out of compliance with the Act.”

- Under 801, FDA doesn't have to physically sample the specific product; can base violation on FDA's experience with the same or similar products, or other credible information from foreign or domestic sources.

HOW do we stop products we know are adulterated or misbranded?

- By issuing an Import Alert

- All imported products are required to meet the same standards as domestic goods. Imported foods must be pure, wholesome, safe to eat, and produced under sanitary conditions... and all products must contain informative and truthful labeling in English.

- An Import alert may be implemented for a manufacturer, a product or for a country, or a combination of these

- An Import Alert is a mechanism to detain entries based on evidence other than sampling, e.g., history of unacceptable entries, foreign inspection info. from state/local/foreign health authorities.

- 54-07DWPE03/18/2011 "Germanium Products"

Germanium is a nonessential trace element that has caused nephrotoxicity (kidney injury) and death when used chronically by humans, even at recommended levels of use.

- 54-10DWPE03/18/2011 "Detention Without Physical Examination of Bulk/Finished Dietary Supplements Products Containing Aristolochic Acid"

Aristolochic acid has also been linked to renal failure and other adverse health effects in humans

- 54-08DWPE03/18/2011 "Detention Without Physical Examination of Dried Bulk Plantain Due To The Presence Of Digitalis"
- Effects of digitalis may include nausea, vomiting, dizziness, headache, confusion, hypotension (low blood pressure), vision disturbances, and abnormal heart rate with heart block, a potentially life threatening condition.

- 54-12DWPE03/18/2011 "Detention Without Physical Examination of Foods Labeled As Being Or Containing Siberian Ginseng"
- Eleuthero can worsen some cardiovascular conditions, including hypertension and cardiac arrhythmia.

- 54-11DWPE03/18/2011 "Detention Without Physical Examination of Bulk Dietary Ingredients And Dietary Supplements Containing Androstenedione"

Common precursor of male and female sex hormones

- 54-13DWPE03/18/2011 "Detention Without Physical Examination of Dietary Supplements And Bulk Dietary Ingredients Containing Ephedrine Alkaloids From All Countries"
- Ephedra has been associated with serious health problems, including hypertension, stroke, heart attack, seizure, cardiac arrhythmia, and over 100 deaths

Import alerts are identified by:

- **Import Alert Number**
- **Published Date**
- **Reason for Alert**
- **Guidance: How the product may be offered, i.e.: Product Description**
- **Countries importing the product**
- **Firms importing the product**

- Google “FDA Import Alerts”

Takes you to:

[http://www.fda.gov/forindustry/import
program/importalerts/default.htm](http://www.fda.gov/forindustry/importprogram/importalerts/default.htm)

- Import alerts are generally implemented due to:
 - History of unacceptable entries
 - Domestic or foreign inspection sample results
 - Sample results from point of entry
 - Foreign inspectional findings
 - Foreign firm's refusal to allow an inspection
 - FDA's experience with the same or similar products, or other credible information from foreign or domestic sources such as info. from Federal, State/local/foreign health authorities.

- Import Alerts can be removed in some cases if five consecutive shipments are in compliance within a 6 month period.

PREDICT

- Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting
- Went live in September, 2009 in Los Angeles
- New York March, 2010
- Seattle, San Francisco October, 2010
- Will be implemented nationally, in phases

- PREDICT was designed to assist entry reviewers in targeting higher-risk shipments for examination. It will also expedite the clearance of lower-risk cargo, but only if accurate and complete data are provided by importers and entry filers.
- Will be applied to manufacturers, consignees, importers, and shippers

- Each incoming product is assigned a product code by the broker, reflecting a description of the product
- Product codes are entered into a database that matches risk of the product, manufacturer, country of origin
- Inputs, such as manufacturer complaints, recalls, security risks, importer history, lab analysis of products are also entered into the database
- Collective risk is assessed and graded

- Eliminates manual methods dependent on human familiarity with of past violative history
- Products at highest risk will be inspected more frequently
- Will lead to directed analysis of potentially dangerous products

- Import Alerts: Direct your broker to contact the local FDA Import Office
- PREDICT: Contact Division of Import Operations and Policy (DIOP)

FDA and Industry must both be vigilant in providing safe dietary supplements to the public

