VENABLE

Current Good Manufacturing Practices (cGMPs) and Their Impact on the Natural Products Industry

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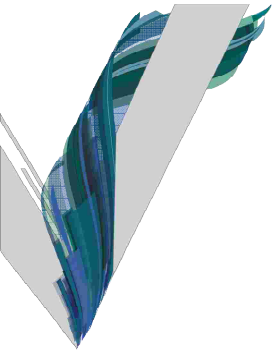


Why Are cGMPs Important?

Federal Food, Drug, and Cosmetic Act
(402(g)(1))

- A food shall be **adulterated**:
  - If it is a dietary supplement and it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations

Federal Food, Drug, and Cosmetic Act

(301(a) and (b))

The following acts and the causing thereof are prohibited:

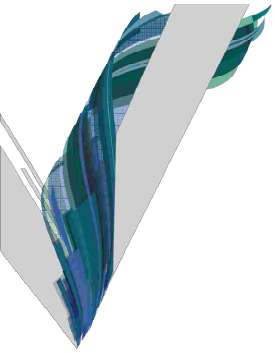
(a) The introduction or delivery for introduction into interstate commerce of any **food***, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

(b) The adulteration or misbranding of any **food***, drug, device, tobacco product, or cosmetic in interstate commerce.

*Includes dietary supplement

Penalties

- Criminal
- Civil
- Injunction
- Seizure



cGMPs Are Important—
Even If You Do Not Manufacture

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Cincinnati District Office
6751 Steger Dr.
Cincinnati, OH 45237

VIA United Parcel Service

April 26, 2013

Charles J. Kubicki, Owner
Pristine Bay, L.L.C. d.b.a. Vianda
7175 E. Kemper Rd.
Cincinnati, OH 45249

WARNING LETTER CIN-DO 13-361158-19

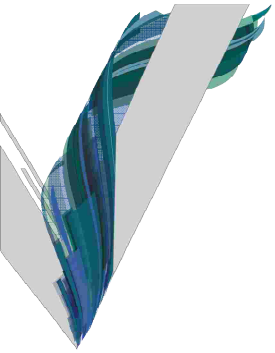
Dear Mr. Kubicki:

The U.S. Food and Drug Administration (FDA) conducted inspections at your facilities, located at 1661 Waycross Rd., Cincinnati, OH, on August 28 – September 17, 2012, and 7165 E. Kemper Rd., Cincinnati, OH, on August 28, 2012. The inspections revealed that you have significant violations of the Current Good Manufacturing Practice (CGMP) regulations for dietary supplements, Title 21, Code of Federal Regulations, Part 111 (21 CFR 111). These violations cause your "Enzyte", "Ogoplex", and "Avlimil Complete" dietary supplements to be adulterated within the meaning of Section 402(g)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 342(g)(1)] in that they have been prepared, packed, or held under conditions that do not meet the CGMP requirements for dietary supplements. You may find the Act and FDA regulations through links in FDA's home page at www.fda.gov.

Warning Letter to Pristine Bay (Private Label Distributor)

As a distributor that contracts with other manufacturers to manufacture, package, or label dietary supplements that your firm releases for distribution under your firm's name, your firm has an obligation to know what and how manufacturing activities are performed so that you can make decisions related to whether your dietary supplement products conform to established specifications and whether to approve and release the products for distribution [72 Fed. Reg. 34752, 34790 (Jun. 25, 2007)]. Your firm introduces or delivers, or causes the introduction or delivery, of dietary supplement products into interstate commerce in their final form for distribution to consumers. As such, your firm has an overarching and ultimate responsibility to ensure that all phases of the production of that product are in compliance with dietary supplement CGMP requirements.

Although, your firm may contract out certain dietary supplement manufacturing operations, it cannot by the same token, contract out its ultimate responsibility to ensure that the dietary supplements it places into commerce (or causes to be placed into commerce) are not adulterated for failure to comply with dietary supplement CGMP



What Are cGMPs?

Quality System

Ensures quality of a dietary supplement product through the manufacturing, packaging, labeling, or holding processes

21 C.F.R. Part 111:

- Personnel
- Physical Plant and Grounds
- Equipment and Utensils
- Quality Control
- Holding and Distribution
- Product Complaints
- Records

Implementation

Standard Operating Procedures (SOPs):
If it was not documented, it did not happen . . .

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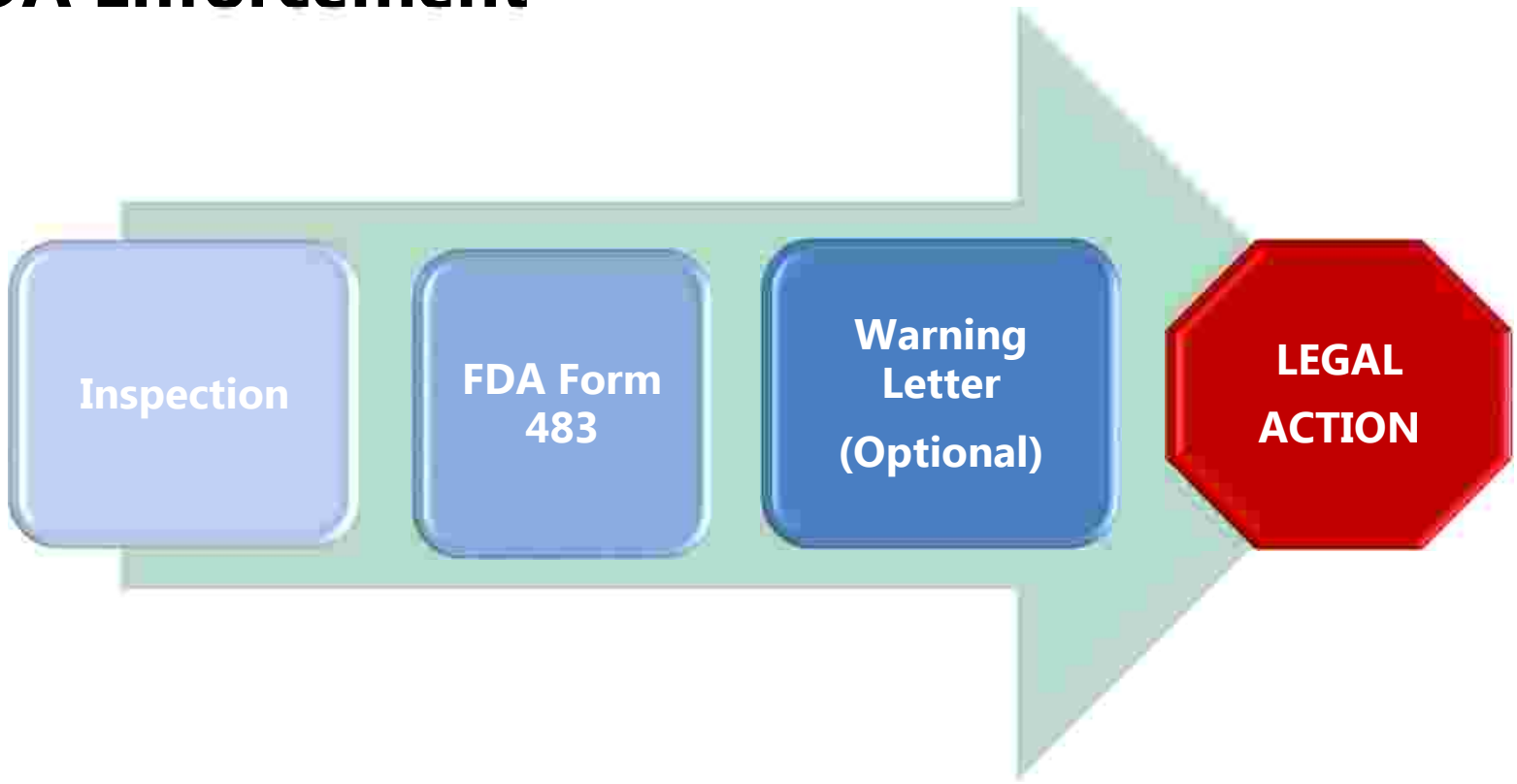
FDA Enforcement



FY2017: Observation Statistics

Inspections Receiving Form 483: 379

Total number of observations: 1,949

Average number of observations per Form 483: 5.14
(calculated using inspections issued a Form 483)

Source: Natural Products Insider

Top Part 111 Observations:

- Establish product specifications for identity, purity, strength, and composition of finished supplement (89)
- Establish or follow procedures for quality control operations (70)
- Establish or follow procedures for review and investigation of product complaint (63)

cGMP Warning Letters

Approximately 10 Warning Letters issued in 2017 for violations of 21 C.F.R. Part 111

– Example: DSE Healthcare Solutions (March 2017)

The inspection revealed the following significant violations of the CGMP requirements for dietary supplements:

1. You failed to establish specifications for each dietary supplement for the identity, purity, strength, and composition of the finished batch of the dietary supplements, and for limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the dietary supplement to ensure the quality of each dietary supplement, as required by 21 CFR 111.70(e). During the inspection, your management

2. You failed to satisfy the requirements for the review and investigation of product complaints, as required by 21 CFR 111.560(a). Your complaint log reveals that you received thirty complaints in calendar year 2015 and fifteen complaints from January to August 2016. However, your management stated that your firm only investigates complaints involving **(b)(4)**. Limiting the review of investigations of product complains in this manner is insufficient, as 21 CFR 111.560(a)(1) requires review of all product complaints to determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of 21 CFR Part 111, including those specifications and other requirements that, if not met, may result in a risk of illness or injury.

cGMP Warning Letters

– Example: Herbal Sciences Int'l (March 2017)

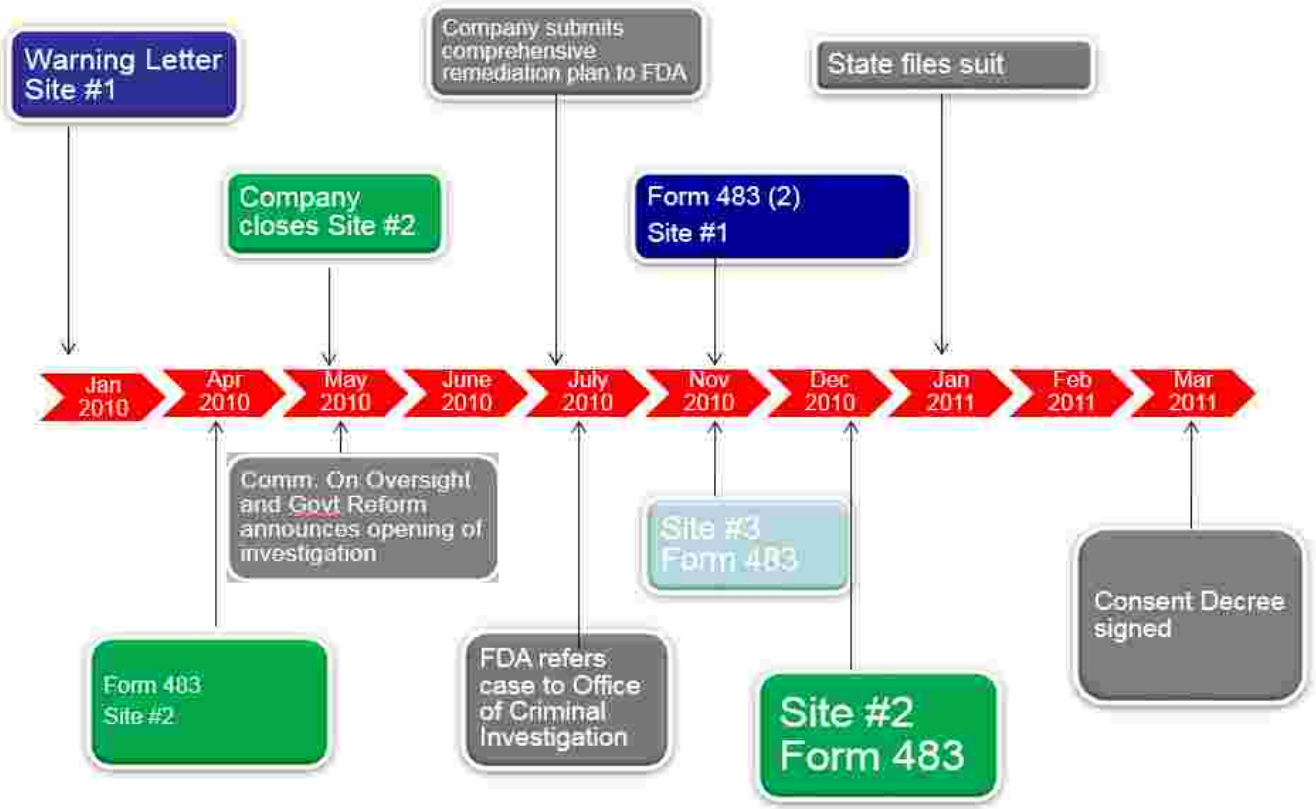
1. You failed to establish specifications for each component that you use in the manufacture of a dietary supplement, as required by 21 CFR 111.70(b). Specifically, you have not established identity, purity, strength, and composition specifications for each of the components you use to manufacture your finished dietary supplement products.

3. You failed to establish and follow written procedures for the responsibilities of the quality control operations, including written procedures for conducting a material review and making a disposition decision, as required by 21 CFR 111.103. Specifically, you did not have any written procedures for quality control operations for the dietary supplements you distribute.

4. You failed to prepare and follow a written MMR for each unique formulation of dietary supplement that you manufacture, and for each batch size, to ensure uniformity in the finished batch from batch to batch, as required by 21 CFR 111.205(a). Specifically, you did not prepare and follow MMRs for the following batches of finished dietary supplements manufactured by your firm:

5. You failed to prepare batch production records (BPRs) that include complete information relating to the production and control of each batch and failed to include all information required in a BPR, as required by 21 CFR 111.255(b) and 111.260.

Enforcement Case Study



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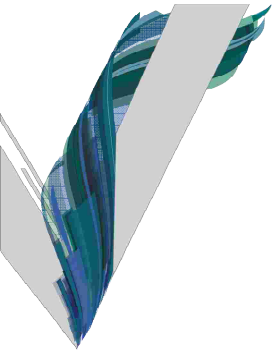

What Should I Do?

Be Prepared!

Standard Operating Procedure/Policy:

- ❑Understand scope of FDA inspector's authority
- ❑Protect against charge of refusal/delay of inspection
- ❑Employee training** = Critical

Section 704 – Inspection

- **Refusals**
  - The refusal to permit access to or copying of any record (FDCA Section 301(e))
  - The refusal to permit entry or inspection as authorized by section 704 (FDCA Section 301(f))

FDA GUIDANCE: Circumstances that Constitute Delaying, Denying, Limiting or Refusing a Drug Inspection http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf

Inspection

- Present credentials (Form 482)
  - Warrant not required
  - Consent not required

- Limitations:
  - Financial data
  - Sales data (other than shipment data)
  - Pricing data
  - Personnel data (other than qualifications to perform function)
  - Certain research data
  - Internal audits

Section 704 – Inspection

- Issues:
  1. Photographs
  2. Affidavits
  3. Employee Interviews