Current good manufacturing practices for dietary supplements: Recent FDA inspection trends and compliance with 21 CFR 111.

Merle Zimmermann, Ph.D. (mzimmermann@ahpa.org)

American Herbal Products Association

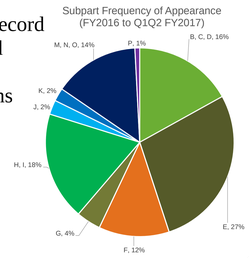
AHPA AMERICAN HERBAL PRODUCTS ASSOCIATION (1982-2017 35 YEARS)

Introduction

FDA regularly inspects dietary supplement facilities for compliance with 21 CFR 111 ("Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements "). This poster offers a overview of the American Herbal Products' Association's repository of inspection data, including examples of establishment inspection reports (EIRs) and 483 observation forms from across the United States.

21 CFR 111 contains 16 subparts covering the following:

A. General Provisions & Definitions
B. Personnel
C. Physical Plant and Grounds
D. Equipment and Utensils
E. Production and Process Control System (PPCS)
F. PPCS: Requirements for Quality Control
G. PPCS: Components, Packaging, and Labels for Product that you receive for packaging or labeling as a dietary supplement
H. PPCS: Master Manufacturing Record
I. PPCS: Batch Production Record
J. PPCS: Laboratory Operations
K. PPCS: Manufacturing Operations
L. PPCS: Packaging and Labeling
M. Holding and Distributing
N. Returned Dietary Supplements
O. Product Complaints
P. Records and Recordkeeping



Data Sources

Data was collected with a combination of both Freedom of Information Act requests for specific releasable FDA Form 483s and EIRs as well as statistics on dietary supplement inspections released directly by the agency.

Approximately 1600 individual documents have been received from FDA regarding releasable inspections and reinspections covering facility visits from 2007 through 9/30/2017, and 1161 non-releasable facility inspections from a variety of sources including FDA's Inspections Classifications database.

Observation types

Observation types catalogued appear in Figure #1. Key areas include establishing specifications, determining that the established specifications have been met, and tracking the manufacturing process through creating and keeping Master Manufacturing and Batch Production Records.

After these mostly record keeping-related subjects, the next most commonly mentioned topics discuss aspects of operating a safe and hygienic facility with qualified staff.

The most recent records follow a similar pattern as the overall recorded observations as seen in Figure #2, with only minor variation.

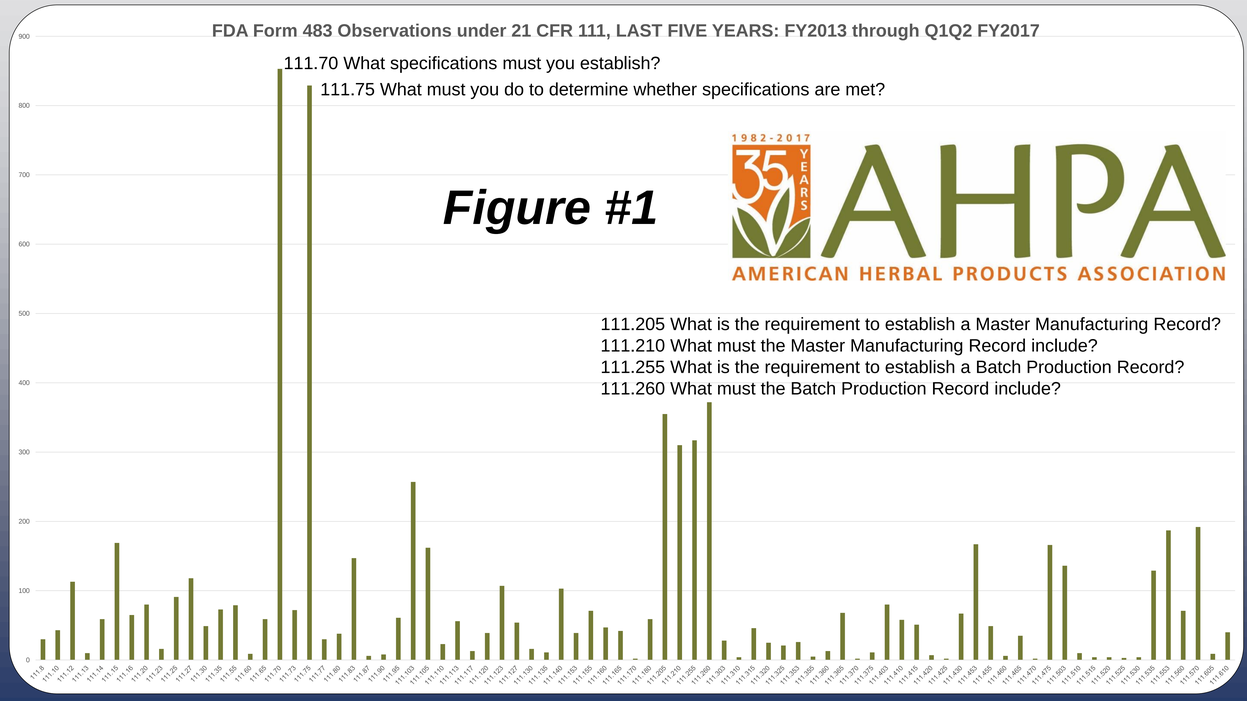


Figure #1

Examples

All of the sections in 21 CFR 111 remain important. Agency attention throughout FY2016 and FY2017 appeared focused on the following subjects:

- Component specifications and testing (111.70, 111.75)
- Master and batch production (111.205-210, 111.255-260)
- Clear recordkeeping (across the board)
- Facility and equipment sanitation and safety (in 111.15-111.35)

Observation: You did not conduct at least one appropriate test or examination to verify the identity of a dietary ingredient, prior to its use. Specifically, the firm only relies on Certificates of Analysis from suppliers of each dietary supplement ingredient or component received. The firm does not conduct any tests to verify the identity of ingredients or components. [21 CFR 111.75(a)(1)(i)]

Observation: You did not establish a specification for a point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Specifically, you have no specifications for the dietary supplement [name omitted] that you package, label, and distribute. [21 CFR 111.70(a)]

Discussion Item: Your batch production record did not include complete information relating to the production and control of each batch. Specifically, your batch record does not include the following: [21 CFR 111.255(b)] **a.** the unique identifier that you assigned to each component including that [specific components], and containers used for packaging; [21 CFR 111.260(d)] **b.** the identity and weight or measure of each component used; [21 CFR 111.260(e)] **c.** a statement of yield at appropriate phases of processing; [21 CFR 111.260(f)] **d.** the results of any testing or examination performed during the batch production; [21 CFR 111.260(h)] **e.** documentation that the finished dietary supplement meets specifications; [21 CFR 111.260(i)] **f.** documentation of the person responsible for verifying the weight or measure of each component used in the batch; [21 CFR 111.260(j)(2)(i)] **g.** documentation, at the time of performance of packaging and labeling, to include the unique identifier that you assigned to packaging and labels used, the quantity of the packaging and labels used, an actual or representative label. [21 CFR 111.260(f)]

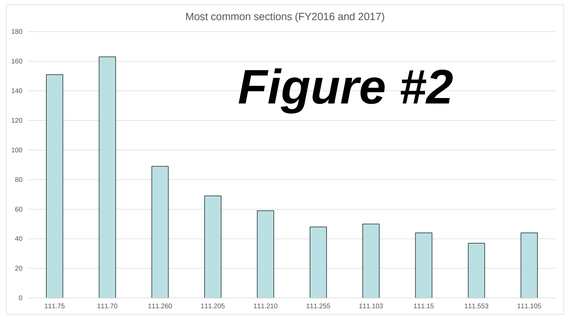


Figure #2

Outcomes

Data from FY2015 showed 42% of inspections of dietary supplement facilities conducted that year resulted in no action being indicated by FDA. This is about 10% more frequent compliance than agency inspections of food manufacturing facilities (28-34%) and close to that of drug facilities (45-48%).

From January 2010 through September 2017, 1953 unique domestic facilities were inspected a total of 2753 times. 1015 (52%) of the most recent inspections resulted in no action being indicated by FDA.

Since the passage of FSMA, FDA has been directed to inspect all operating facilities by October 2017, then visit "high risk" facilities at least once every 3 years and others at least every 5 years, to make sure facility inspections focus on areas where the agency is concerned safety problems may occur. The current times between inspections appear in Figure #3.

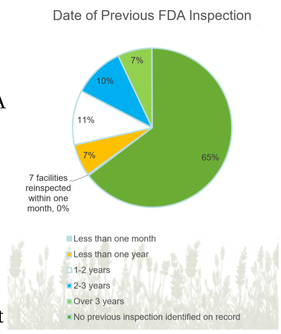


Figure #3

The establishment inspection data continues to show that immediate investigation and intervention can sometimes improve an observation into a discussion item. Conditions were addressed during an inspection and shown to the inspector prior to closeout appear in the reports received from the agency.

If it is impossible to correct a condition observed by an FDA inspector immediately and directly, preparing and scheduling the implementation of new procedures (to also include documenting any staff training which takes place) to remedy the circumstances has also been seen in facility inspections with relatively better outcomes.

Other AHPA Resources

Good Herbal Compounding and Dispensing Processes
ahpa.org/Resources/GoodHerbalCompoundingandDispensingPractices.aspx

Botanical Identity References Compendium
ahpa.org/Resources/BotanicalIDReferencesCompendium.aspx

AHPA Code of Ethics, Business Practices, Trade Requirements and Guidance
ahpa.org/AboutUs/AHPAsPolicies.aspx

Good Agricultural Collection Practices (GACP) and Good Manufacturing Practices (GMP) for Botanical Materials
ahpa.org/Resources/GoodAgriculturalandCollectionPractices(GACP).aspx

Field Guide to Herbal Dietary Supplements
ahpa.org/Portals/0/Documents/fieldguide.pdf

Guidance for Organic Dietary Supplements
ahpa.org/News/LatestNews/tabid/96/ArtMID/1179/ArticleID/903/Default.aspx

Guidance on Foreign Matter Limits in Herbal Ingredients
ahpa.org/News/LatestNews/tabid/96/ArtMID/1179/ArticleID/874/Default.aspx

Guidance on CA Prop 65 for Herbal Products
ahpa.org/Resources/Regulations/State.aspx

AHPA Member Directory
ahpa.org/AboutUs/MemberDirectory.aspx