

cGMP (21 CFR 111) Regulation and Compliance Overview

Neogen Effective Compliance Seminar

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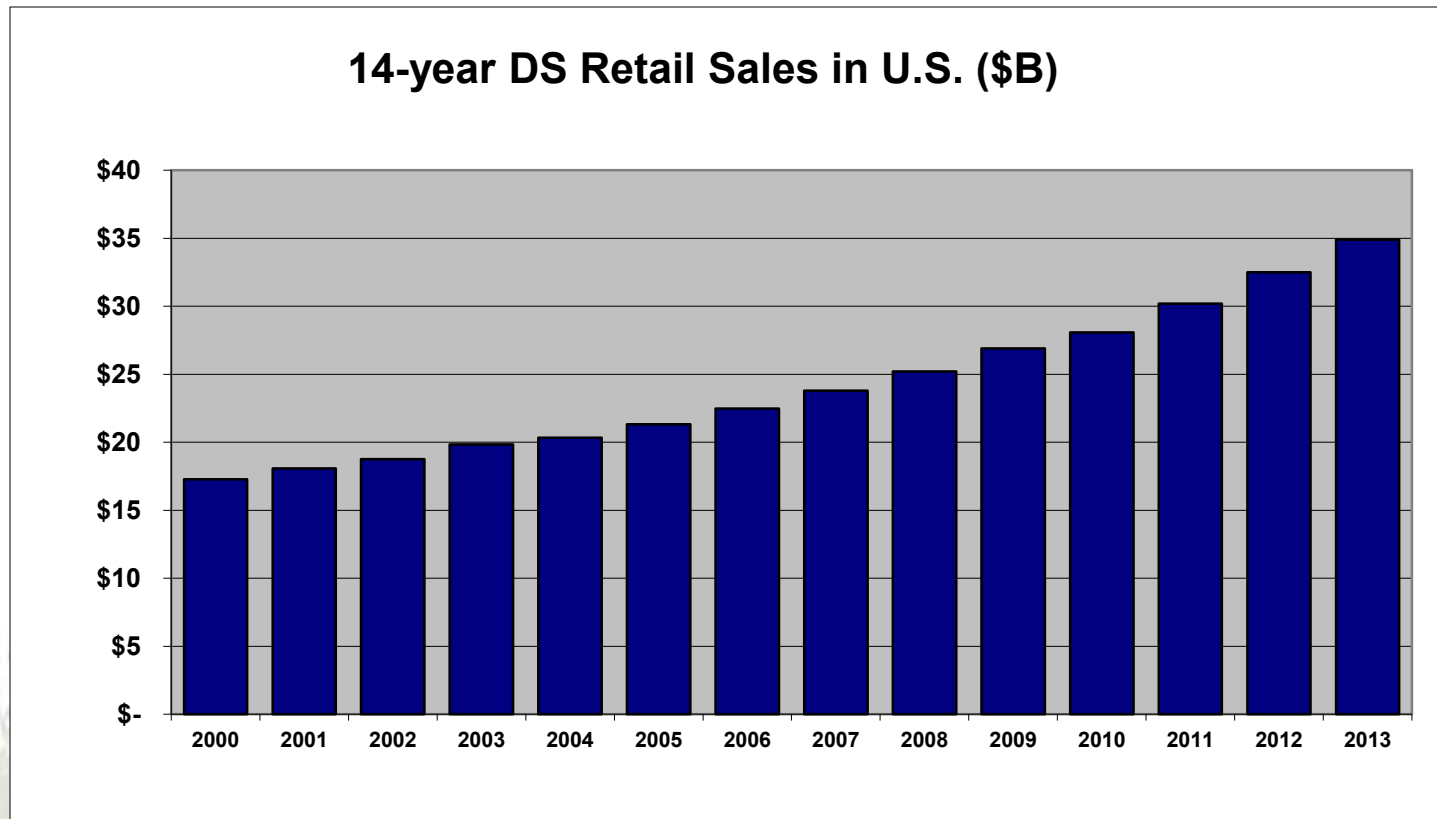
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Regulation of DS in the US

- Ingredients in dietary supplements
- Dietary supplement forms
- New dietary ingredients
- Label / advertising claims
- Good manufacturing practice
- Adverse event reporting

DS Market in the U.S.

From *Nutrition Business Journal*



DS Market in the U.S.

- **Total US population = 314 MM**
- **Adult population = 236 MM**
- **% of population reported to use:**
 - **Any supplement: 53¹ to 62²% (125-145 MM)**
 - **Multi-vitamin: 39¹ to 48²% (92-113 MM)**
 - **Herbal: 11²% (26MM)**

1. NHANES IV (2003-2006)

2. NMI (March 2011)

21 CFR 111

Current Good Manufacturing Practice (cGMP) for Dietary Supplements

Good Manufacturing Practice

21 CFR 111

- Final rule published June 25, 2007
- Effective dates over 3 years
- Based on both food and drug cGMP
- Requires written procedures and written records throughout manufacturing operations
- Key elements: setting and meeting specifications for identity, purity, strength and composition

21 CFR 111: The big ideas




- *The final rule establishes...the minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary supplements to **ensure the quality** of the dietary supplement.*
- *§ 111.55: You must implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplement to **ensure the quality** of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.*
- *The words “ensure the quality” appear 17 times in the final rule.*

21 CFR 111: The big ideas

- ❑ *Ensuring the quality of the dietary supplement means that you consistently and reliably manufacture what you intend and that you establish manufacturing controls to prevent the dietary supplement from being adulterated.*
- ❑ *The essence of good manufacturing practice that is established by this final rule is a production and process control system that is designed to ensure the quality of the dietary supplement.*
- ❑ *[...the final rule's approach] emphasizes that it is important to ensure the quality of the dietary supplement throughout the production and process control system.*
- ❑ *Quality cannot be tested into the product only at the end.*

FDA Inspections

Possible outcomes

-  Establishment Inspection Report (EIR)
-  Form FDA-483 Inspectional Observations
-  Warning Letters

FDA Inspections

- Establishment Inspection Report (EIR):
 - FDA's complete record of an inspection.
 - Includes identifying information about the inspected firm, copies of all FDA forms issued and of records obtained during an inspection, and the inspector's narrative record of the inspection.
 - May form the basis of any recommendations for further regulatory action.

FDA Inspections


- Establishment Inspection Report (EIR):
 - Summary
 - Administrative Data (who, when, where)
 - History (of the company)
 - Interstate Commerce
 - Individual Responsibility/Persons Interviewed
 - Firm's Training Program (citing firm's SOPs)
 - Manufacturing/Design Operations (sometimes with additional detail: facility & equipment; production system; labeling system; etc.)

FDA Inspections

- Establishment Inspection Report (EIR):
 - Manufacturing Codes
 - Complaints and Recall Procedures
 - Objectionable Conditions...
 - Refusals
 - Additional Information
 - Samples Collected
 - Voluntary Corrections
 - Exhibits Collected
 - Photo Exhibits Collected



FDA Inspections

Form FDA-483 Inspectional Observations:

-  To notify the inspected company of “significant objectionable conditions, relating to products and/or processes, or other violations of the [FFDCA] and related Acts which were observed during the inspection.”




FDA Inspections

Form FDA-483 Inspectional Observations:

-  A Form FDA-483 is presented when “in the Investigator’s ‘judgment’ conditions or practices observed, indicate that any food, drug, device, or cosmetic have been adulterated or are being prepared, packed, or held under conditions whereby they may become adulterated or rendered injurious to health.”
-  According to FDA’s IOM, “The issuance of written inspectional observations is mandated by law and ORA policy.”



Focus of Inspections

B – Personnel

-  **111.10:** What requirements apply for preventing microbial contamination from sick or infected personnel and for hygienic practices?
-  **111.12:** What personnel qualification requirements apply?
-  **111.13:** What supervisor requirements apply?


Focus of Inspections

B – Personnel (examples)

-  “Your personnel did not wear outer garments in a manner that protects against contamination of dietary supplement ingredients.” [111.10 (b)(1): “...you must use hygienic practices to the extent necessary ... include[ing] wearing outer garments....”]
-  “Gloves used by the associates were stored loose and unprotected on a table covered with raw material dust.” [111.10 (b)(5): “... Maintaining gloves used in handling components or dietary supplements in an intact, clean, and sanitary condition.”]




Focus of Inspections

B – Personnel (examples)

-  “Individuals responsible for supervising the manufacture, processing, packing, and holding of a drug product lack the education and training to perform their assigned functions ... Specifically, the firm’s President, Vice-president of R&D and Plant manager...” [111.13 (B): “Each supervisor whom you use must be qualified by education, training, or experience to supervise.”]

Focus of Inspections




C – Physical Plant & Grounds

-  **111.15:** What sanitation requirements apply to your physical plant and grounds?
-  **111.20:** What design and construction requirements apply to your physical plant?
-  **111.23:** Under this subpart C, what records must you make and keep?





Focus of Inspections

C – Plant & Grounds (examples)

-  “...no shielding over product line; tape on conveyors ... and on dust collector.” [111.15 (b) “You must maintain your physical plant in repair sufficient to prevent components, dietary supplements, or contact surfaces from becoming contaminated.”]
-  “Your hand washing facility does not dispense water at a suitable temperature....” [111.15 (i): “You must provide hand-washing facilities that are designed to ensure that an employee’s hands are not a source of contamination...”]
-  “...lack of consistency for cleaning documentation.” [111.23 (b): “(b) You must make and keep records of the written procedures for cleaning the physical plant and for pest control.”]





Focus of Inspections

C – Plant & Grounds (examples)

-  “...there were three drums of caustic soda with an accumulation of flakes on the top surface of the drum ... stored next to the scales where dry ingredients are measured.” [111.15 (c)(3) “You must identify and hold cleaning compounds, sanitizing agents, pesticides, pesticide chemicals, and other toxic materials in a manner that protects against contamination of components, dietary supplements, or contact surfaces.”]
-  “...floors and drains ... are pitted and in poor condition” [111.20 (d)(1)(i): “...design and construction must include floors, walls, and ceilings that can be adequately cleaned and kept clean and in good repair.”]



Focus of Inspections

D – Equipment & Utensils

-  **111.25:** What are the requirements under this subpart D for written procedures?
-  **111.27:** What requirements apply to the equipment and utensils that you use?
-  **111.30:** What requirements apply to automated, mechanical, or electronic equipment?
-  **111.35:** Under this subpart D, what records must you make and keep?





Focus of Inspections

D – Equipment & Utensils (examples)

-  “...rough welds were observed on the brackets which hold the earth magnets on the inside of hoppers.” [111.27 (a)(4): “**Equipment and utensils you use must have seams that are smoothly bonded or maintained...**”]
-  “...the quality control department does not review the records of calibrations of the equipment that the pre-weigh and compounding departments use to measure dietary supplement ingredients (scales and water meters).” [111.35 (b)(3): “**You must make and keep the following records: Documentation of any calibration, each time the calibration is performed, for instruments and controls that you use in manufacturing or testing a component or dietary supplement.**”]


Focus of Inspections

E – Production/Process Control System

-  **111.70:** What specifications must you establish?
-  **111.75:** What must you do to determine whether specifications are met?
-  **111.83:** What are the requirements for reserve samples?
-  **111.90:** What requirements apply to treatments, in-process adjustments, and reprocessing when there is a deviation or unanticipated occurrence or when a specification established in accordance with Sec. 111.70 is not met?


Focus of Inspections


E – Production & Process Controls (examples)

-  “You have not established specifications for purity for ingredients used in dietary supplements produced by your contract manufacturer.” [111.70 (a)(2): **“You must establish component specifications that are necessary to ensure that specifications for the purity, strength and composition of dietary supplements manufactured using the components are met.”**]

Focus of Inspections


E – Production & Process Controls (examples)

 “Specifications for dietary ingredient ... requires verification on the supplier's COA that pesticide (tricyclazole) was tested, but COAs ... do not include test results.” [111.75 (a)(2)(ii): “You must ... **determine whether ... component specifications ... are met [by] rely[ing] on a certificate of analysis from the supplier of the component that you receive, provided that ... [the COA] includes a description of the test ... used ... and actual results of the tests or examinations.**”]

 “Reports of analysis ... are accepted in lieu of testing ... without establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.” [111.75 (a)(2)(ii): “...provided that ... you **periodically reconfirm the supplier’s [COA].**”]





Focus of Inspections

E – Production & Process Controls (examples)

-  The inspected facility “inappropriately allows retesting of an [out of specification] product 3 times before a failure investigation is initiated.” [111.77 (a): “**For specifications ... that you do not meet, quality control personnel ... must reject the component, dietary supplement, package or label unless such personnel approve a treatment, an in-process adjustment, or reprocessing that will ensure the quality of the finished dietary supplement....**”]





Focus of Inspections

F – Quality Control

-  **111.103:** What are the requirements under this subpart F for written procedures?
-  **111.105:** What must quality control personnel do?
-  **111.117:** What quality control operations are required for equipment, instruments, and controls?
-  **111.120:** What quality control operations are required for components, packaging, and labels before use in the manufacture of a dietary supplement?



Focus of Inspections

F – Quality Control

-  **111.123:** What quality control operations are required for the master manufacturing record, the batch production record, and manufacturing operations?
-  **111.127:** What quality control operations are required for packaging and labeling operations?
-  **111.135:** What quality control operations are required for product complaints?
-  **111.140:** Under this subpart F, what records must you make and keep?

Focus of Inspections

F – Production & Process Controls (examples)

-  “Batch Production Records ... indicate the product was incorrectly compounded by adding one of the ingredients twice. The investigation never determined which ingredient was added twice, nor ... whether or not any attempt was made to determine which ingredient was added twice.” [111.140 (b)(3)(i): **“You must make and keep ... records [that document] any material review and disposition decision and followup [which] ... must include Identification of the specific deviation or the unanticipated occurrence.”**]
-  “Your SOP ... states that a daily surveillance inspection of the warehouse will be conducted.... However, documentation of the inspections ... could not be provided.” [111.140 (b)(1): **“(b) You must make and keep ... records [of] written procedures for the responsibilities of the quality control operations.”**]

Priority observations

	2007-'08	'09	'10	'11	'12
Sub B:111.10 Personnel / Contamination	✓				
Sub C:111.15 Plant, Grounds / Sanitation	✓	✓	✓	✓	
Sub C:111.20 Plant, Grounds / Design, Construct			✓	✓	
Sub D:111.27 Equipment, Utensils		✓		✓	
Sub E:111.70 P&PC System / Setting Specs	✓		✓	✓	✓
Sub E:111.75 P&PC System / Meeting Specs	✓		✓	✓	✓
Sub F:111.123 P&PC QC / MMR, BR, Ops			✓	✓	✓
Sub F:111.140 P&PC QC / Records		✓			✓
Sub H:111.210 P&PC Master Mfr Records		✓	✓	✓	✓
Sub I:111.260 P&PC Batch Records	✓	✓	✓	✓	✓

Priority observations

	07-08	2009	2010	2011	2012
Subpart B Personnel	■				
Subpart C Plant and Grounds	■ ■	■ ■	■ ■	■	■
Subpart D Equipment and Utensils		■ ■			■
Subpart E Requirement to Establish P&PC System	■ ■ ■	■ ■	■ ■ ■	■ ■ ■	■ ■ ■
Subpart F P&PC Requirements/ QC		■ ■ ■	■ ■ ■	■ ■	■ ■ ■
Subpart H P&PC Requirements/ MMR		■ ■	■	■	■ ■
Subpart I P&PC Requirements for Batch Records	■ ■			■	■ ■
Subpart N Returned DS					■
Subpart O Product Complaints		■			

Key: Most Frequently (■ ■ ■), Frequently (■ ■), Occasionally (■); not to scale

No/Few observations

- **Subpart G** P&PC / Components, Packaging, Labeling
- **Subpart J** P&PC / Laboratory Operations
- **Subpart K** P&PC / Mfr Ops (Design, Sanitation, Rejected DS)
- **Subpart L** P&PC / Packaging and Labeling Ops
- **Subpart M** Holding and Distributing
- **Subpart P** Records and Recordkeeping

Response to FDA Inspections

- FDA advice: Written response to any FDA 483 observations should be made within 15 days
- Responses to FDA 483 observations should be detailed and should provide the proof of response:
 - ...“here is the procedure we developed...”
 - “...here is evidence that the procedure is in effect and being followed...”
- Time to come into compliance should be as fast as can be accomplished

FDA Warning Letters

- Review of these provides excellent “teachings” with respect to cGMP compliance
- Go to Warning Letters on the FDA Home page (www.fda.gov). In the Warning Letters search engine, search “dietary supplement”
- You can also search for particular parts of the cGMP by putting in the regulation number that you are concerned about (e.g., 21 CFR 111.70)

FDA Warning Letters

- FDA to Algaen Corporation 3/8/13 (late July inspection)
 - During the inspection, our investigator collected sample labels [...] and evaluated manufacturing operations [...].
 - In addition, in March 2013, FDA reviewed your website [...], and determined that this website constitutes labeling under section 201(m) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(m)] because the website address appears on the label of your [...] products.

FDA Warning Letters

- ❑ FDA to Algaen Corporation 3/8/13 (late July inspection)
 - ❑ Based on our review of the labeling [...], including your website, [...] we have determined that these products are promoted for conditions that cause the products to be drugs under section 201(g)(1)(B) of the Act [21 U.S.C. § 321(g)(1)].
 - ❑ The therapeutic claims on your website establish that these products are drugs because they are intended for use in the cure, mitigation, treatment or prevention of disease.
 - ❑ The marketing of these products with such claims violates the Act.

FDA Warning Letters

- FDA to Algaen Corporation 3/8/13 (late July inspection)
 - You failed to conduct at least one appropriate test or examination to verify the identity of a component that is a dietary ingredient before using the component, as required by 21 CFR 111.75(a)(1)(i).
 - You failed to prepare and follow a written master manufacturing record for each unique formulation of dietary supplement 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.
 - You failed to prepare a batch production record every time you manufacture a batch of a dietary supplement, as required by 21 CFR 111.255.

FDA Warning Letters

- FDA to Algaen Corporation 3/8/13 (late July inspection)
 - 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 make a disposition decision, and for approving or rejecting any reprocessing, as required by 21 CFR 111.103.
 - The violations cited in this letter are not intended to be an all-inclusive list of violations at your facility. It is your responsibility to ensure that your products are in compliance with the requirements of the Act and applicable FDA regulations.

FDA Warning Letters

- FDA to Algaen Corporation 3/8/13 (late July inspection)
 - In addition, with regards to your dietary supplement manufacturing operations, we note that you have not prepared and kept written procedures for personnel, including written procedures for preventing microbial contamination, hygienic practices, and personnel qualification requirements, as required by with 21 CFR 111.14(b)(1).
 - You should take prompt action to correct the violations cited in this letter and establish and implement procedures that will prevent these and other violations in the future. Failure to promptly correct these violations may result in enforcement action, such as seizure or injunction, without further notice.

FDA Warning Letters

- ❑ FDA to Vita Springs Health 6/24/2014 (late May 2013 inspection)
 - ❑ Vita Springs Health operates a dietary supplement manufacturing facility which manufactures, packages and labels an own-label dietary supplement product.
 - ❑ Investigators found that you have significant violations of the CGMP
 - ❑ These violations cause your dietary supplement products to be adulterated within the meaning of Section 402(g)(1) of the Federal Food, Drug, and Cosmetic Act

FDA Warning Letters

- ❑ FDA to Vita Springs Health 6/24/2014 (late May 2013 inspection)
 - ❑ [Your firm] failed to conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient, as required by 21 CFR 111.75(a)(1)(i).
 - ❑ [Your firm] 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 did not establish specifications for each component that you use in the manufacture of your dietary supplements.

FDA Warning Letters

- ❑ FDA to Vita Springs Health 6/24/2014 (late May 2013 inspection)
 - ❑ [Your firm] failed to ensure that the tests and examinations you use to determine whether specifications are met are appropriate, scientifically valid methods, as required by 21 CFR 111.75(h)(1).
 - ❑ [Your firm] failed to prepare and follow a written master manufacturing record (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).

FDA Warning Letters

- ❑ FDA to Vita Springs Health 6/24/2014 (late May 2013 inspection)
 - ❑ Your quality control personnel failed to ensure that your manufacturing, packaging, labeling, and holding operations ensure the quality of the dietary supplements and that the dietary supplements are packaged and labeled as specified in the master manufacturing record, as required by 21 CFR 111.105.
 - ❑ These letters underscore the importance of procedural and recordkeeping sections of the regulation.
 - ❑ While other sections have varied in frequency of appearance, agency letters frequently discuss these two topics.

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AHPA Chief Information Analyst



THANK YOU!

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American Herbal Products Association

THE VOICE OF THE HERBAL PRODUCTS INDUSTRY