TOP TEN WAYS TO GET A WARNING LETTER

training from NSF International

NSF®

What are cGMPs?

Current Good Manufacturing Practices

The cGMP final rule establishes the minimum cGMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary supplements to ensure the efficacy, quality, purity and safety of the dietary supplement.

Where are the cGMPs found?

- Code of Federal Regulations (CFR)
  - Dietary Supplements (21 CFR 111)
    - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=111&showFR=1
- On the Web – Guidance documents (www.fda.gov)
- Dietary Supplements Preamble, and
- Comments and Responses. See website link http://www.fda.gov/OHRMS/DOCKETS/98fr/cf0441.pdf

FDA has Legal Authority

- Following cGMPs is **NOT** optional
- All dietary supplements, available for use in the U.S., **must** be produced according to the FDA's cGMP regulations
- cGMPs apply to **all** employees

How does the FDA enforce the cGMPs?

The FDA comes to your facility to perform an inspection

The FDA evaluates **your** conformance to the cGMP requirements – 21 CFR 111

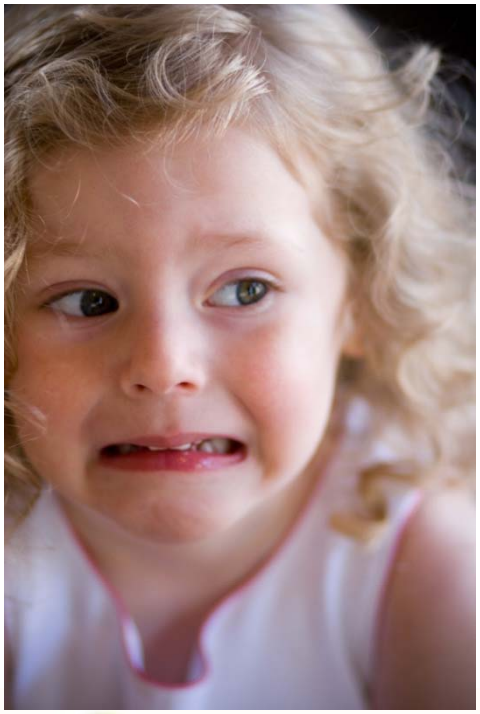

Top Ten Ways to Get a Warning Letter

Actions that FDA may take upon and after an inspection

- 483
- Regulatory meetings
- WARNING LETTER
- Fines
- Consent Decree
- Seizure
- Injunction
- Indictment

WHAT ARE THE TOP TEN WAYS TO GET A WARNING LETTER?

The Top Ten Violations



1. Specifications & identification testing
2. Master batch records
3. Batch records
4. Procedures & documentation
5. Qualification of vendors
6. Quality control
7. Investigations
8. Returned goods
9. Complaints
10. Cleaning

SPECIFICATIONS & IDENTIFICATION

LabTreat™OmniTreat™ Enrichment Tablet 5TCY

DESCRIPTION

LabTreat™OmniTreat™ Enrichment Tablet is a nutritionally complete diet, for non-human primates, rodents, and other omnivorous mammals. Available in several flavors, the OmniTreat™ formula is specifically designed to produce LabTreat™ Tablets ("precision pellets") for enrichment, reward, behavior modification, and general nutrition. (See formula 5TGZ for GLP1 bit version).

Storage conditions are particularly critical to TestDiet® products, due to the absence of antioxidants or preservative agents. To provide maximum protection against possible changes during storage, store in a dry, cool location. Storage under refrigeration (2°-C) is recommended. Maximum shelf life is one year. (If long term studies are involved, storing the diet at -20° C or colder may prolong shelf life.) Be certain to keep in air tight containers.

*Product Forms Available** *Catalog #*

See Second Page

INGREDIENTS

Sucrose, Casein, Microcrystaline Cellulose, Fat Mineral Mix #10 (adds 1.29% fiber), Corn Oil, Silicon Dioxide, RP Vitamin Mix (adds 1 ba% sucrose), Maltodextrin, Milk Product, Magnesium Stearate, Ascorbic Acid, Choline Bitartrate, DL-Methionine, L-Cystine, Taurine, Ferrous Sulfate. Artificial flavors and colors added were applicable.

FEEDING DIRECTIONS

Feed ad libitum. Plenty of fresh, clean water should be available at all times.

CAUTION:
Perishable - store properly upon receipt.
For laboratory animal use only; not for human consumption.

5/30/2012

NUTRITIONAL PROFILE[1]

Protein, %	***18.9***	***Minerals***	
Arginine, %	0.73	***Ash, %***	***6.6***
Histidine, %	0.54	Calcium, %	1.81
Isoleucine, %	1.23	Phosphorus, %	0.70
Leucine, %	1.86	Phosphorus (available), %	0.58
Lysine, %	1.53	Potassium, %	0.46
Methionine, %	0.73	Magnesium, %	0.09
Cystine, %	0.19	Sulfur, %	0.16
Phenylalanine, %	0.99	Sodium, %	0.22
Tyrosine, %	1.01	Chloride, %	0.25
Threonine, %	0.82	Fluorine, ppm	4.9
Tryptophan, %	0.22	Iron, ppm	99
Valine, %	1.47	Zinc, ppm	27
Alanine, %	0.62	Manganese, ppm	65
Aspartic Acid, %	1.35	Copper, ppm	16
Glutamic Acid, %	3.70	Cobalt, ppm	3.20
Glycine, %	0.32	Iodine, ppm	0.57
Proline, %	1.61	Chromium, ppm	2.00
Serine, %	0.93	Selenium, ppm	0.23
Taurine, %	0.10		
Fat (ether extract), %	***5.1***	***Vitamins***	
Fat (acid hydrolysis), %	***5.1***	Carotene, ppm	0.0
Cholesterol, ppm	0	Vitamin A, IU/g	22
Linoleic Acid, %	2.62	Vitamin D-3 (added), IU/g	2.2
Linolenic Acid, %	0.04	Vitamin E, IU/kg	50
Arachidonic Acid, %	0.00	Vitamin K (as menadione), ppm	10.3
Omega-3 Fatty Acids, %	0.04	Thiamin Hydrochloride, ppm	21
Total Saturated Fatty Acids, %	0.83	Riboflavin, ppm	20.2
Total Monounsaturated Fatty Acids, %	1.34	Niacin, ppm	90
Polyunsaturated Fatty Acids, %	2.65	Pantothenic Acid, ppm	56
		Folic Acid, ppm	4.1
		Pyridoxine, ppm	16.42
Fiber (max), %	***7.4***	Biotin, ppm	0.4
Neutral Detergent Fiber[2], %	7.3	Vitamin B-12, mcg/kg	20
Acid Detergent Fiber[3], %	7.2	Choline Chloride, ppm	1,042
Nitrogen-Free Extract (by difference), %	***52.3***	Ascorbic Acid, ppm	4,886.4
Starch, %	1.38		
Glucose, %	20.69		
Fructose, %	20.68		
Sucrose, %	55.81		
Lactose, %	0.21		
Total Digestible Nutrients, %	***71.2***		
Energy (kcal/g)[4]	***3.29***		

From:	kcal	%
Protein	0.744	22.6
Fat (ether extract)	0.456	13.9
Carbohydrates	2.093	63.6

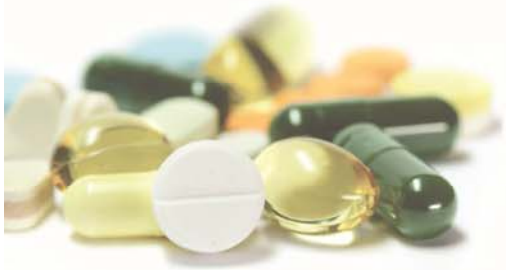
1. Formulation based on calculated values from the latest ingredient analysis information. Since nutrient composition of natural ingredients varies and some nutrient loss will occur due to manufacturing processes, analysis will differ accordingly. Nutrients expressed as percent of ration on an As Fed basis except where otherwise indicated. Moisture content is assumed to be 10.0% for the purpose of calculations.
2. NDF = approximately cellulose, hemicellulose and lignin.
3. ADF = approximately cellulose and lignin.
4. Energy (kcal/gm) = Sum of decimal fractions of protein, fat and carbohydrate x 4,9,4 kcal/gm respectively.

TestDiet
www.testdiet.com

- Identity
- Every component
- in-process specifications
- Limits on contamination
- Labels and packaging material
- Finished product for:
  - Identity
  - Purity
  - Strength
  - Composition
  - Limits on contamination

MASTER MANUFACTURING RECORD

- Specifications for the points, steps, or stages in the manufacturing process must be established
- Controls and procedures must be established to ensure that each batch that you manufacture meets the specifications identified above



BATCH RECORD

A batch production record must:

- Be prepared every time you manufacture a batch of a dietary supplement
- Accurately follow the appropriate master manufacturing record

You must perform each step included in the batch record

PROCEDURES AND RECORDS

What records must be made available to FDA?

- You must have all records, or copies of records, readily available during the retention period for inspection
- You must also allow copying by FDA of all records when requested

VENDOR QUALIFICATION

111.75

You first 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

Quality Control

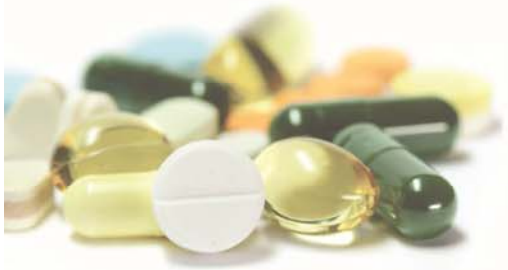
What are the requirements for quality control operations?

You must implement quality control operations in your manufacturing, packaging, labeling, and holding operations for producing 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.

INVESTIGATION

Nonconformance investigations should include:

- Identification of the unexpected event
- Description of your root cause investigation
- Product impact assessment
- Corrective actions, if possible



RETURNED DIETARY SUPPLEMENTS

If reprocessing is approved Quality Control must:

- Determine whether product specifications are met
- Conduct a material review and make a disposition recommendation
- Approve or reject the returned product's release for redistribution

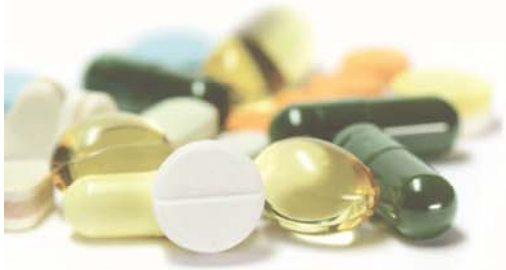
COMPLAINTS

The written record of the product complaint must include the:

- Name and description of the product
- Batch, lot or control number
- Date the complaint was received
- Name, address, or telephone number of the complainant

CLEANING CONTROL

Equipment and utensils must be dismantled for maintenance, cleaning, and sanitizing to their smallest parts.



Conclusion

What <u>YOU</u> must do to comply with CGMPs:

- Have a Master Batch Record for each product
- Carry out all production following the batch record
- Know and follow all procedures and complete all records accurately
- Commit to cleaning and sanitizing regularly
- Perform Identification testing and keep records of it
- Have specifications for everything
- Have an active Quality Operations team within the facility
- Investigate all anomalies
- Have a Return Process in place
- Have a Complaint process
- Report Adverse Events


Top Ten Ways to Get a Warning Letter

NSF Dietary Supplements Training

This slide show is a sneak peak into the training course “Top Ten Ways to Get a Warning Letter”. To view dates and locations please visit our **website** http://www.nsf.org/training-education/all-courses/category/dietary-supplements

call 800.673.6275, ext. 5600

or **email** training@nsf.org

Resources

- U.S. Food and Drug Administration (www.fda.gov)
  - Dietary Supplements (21 CFR 111)
- Dietary Supplements (http://www.fda.gov/OHRMS/DOCKETS/98fr/cf0441.pdf)
- FDA FAQ (http://www.fda.gov/oc/guidance/qsas.html)
- "*Botanical Dietary Supplements: Quality, Safety and Efficacy*" by Gail B. Mahady, Harry Fong, Norman Farnsworth Swets & Zeitlinger
- Pharmacopoeia's- USP, EP, BP, JP
- Methods References: AOAC, etc

Resources

- Draft Voluntary Guideline No. 3: Dietary Supplement Component Supplier Qualification, April 2012, SIDI Work Group

  (http://www.sidiworkgroup.com/resources/Documents/DRAFTComponentSupplierQualificationGuideline_SIDIWorkGroup_April2012.pdf)

- NSF International (www.nsf.org)
  - Dietary Supplements Division, dietarysupplements@nsf.org
    tel +1 (734) 827-6856
  - SOP Resource Book - http://www.nsf.org/training-education/educational-materials-tools/training-materials/gmp-sourcebook/