Overview of Recent FDA Enforcement Activities in Dietary Supplements

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May 2014

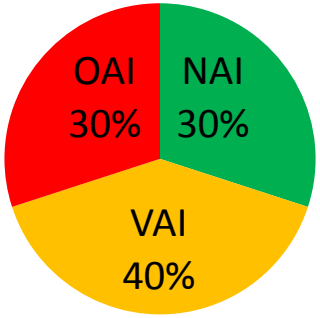
SSW Las Vegas – FDA Session Nov 2013

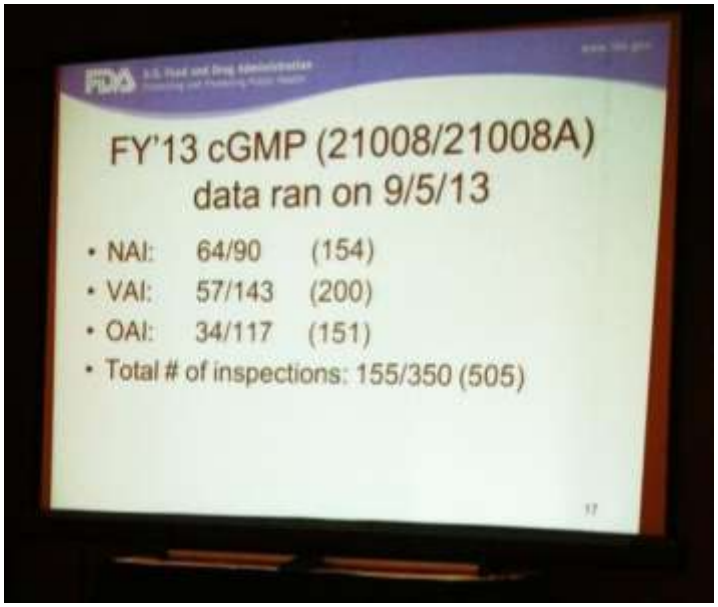
FY'13 (as of 9/5/13)
Inspection Classifications:

- NAI – 154
- VAI – 200
- OAI – 151

2013 DS Inspections: 505

- % NAI: 30%
- % VAI: 40%
- % OAI: 30%



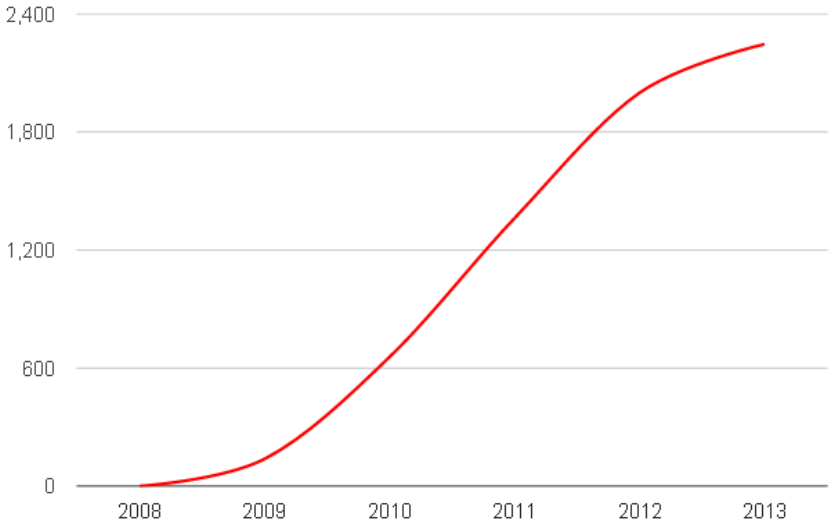


➔ 70% 'failure' rate

Sources of Inspection Data

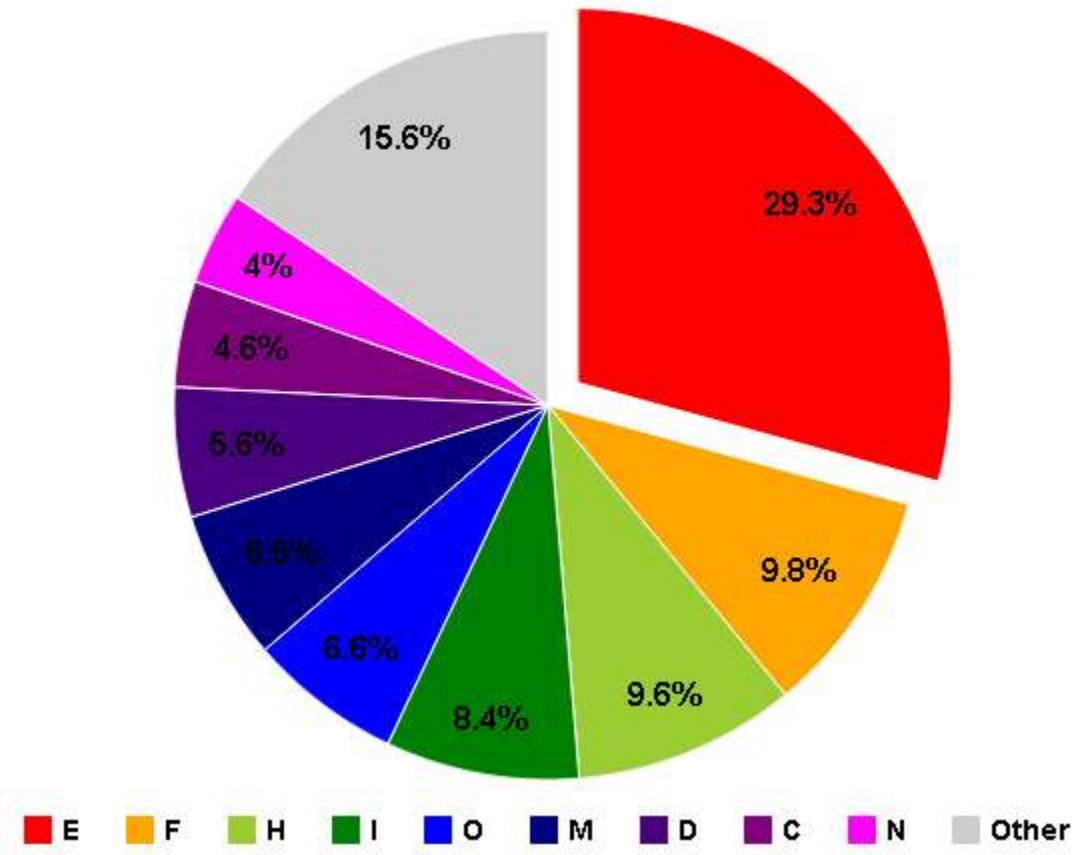
- FDA.gov (*TurboEIR* system)
  - Form 483 Inspection Observations (thru FY 2013)
    - Inspection observations in foods by FDA Fiscal Year and CFR # (also contains pharma, medical devices etc.)
  - Inspection Classifications (thru FY 2013)
    - NAI (No Action Indicated)
    - VAI (Voluntary Action Indicated)
    - OAI (Official Action Indicated) usually => Warning Letter
  - Inspection Citations (currently thru FY 2012 only)
    - By Firm, CFR #, inspection end date etc.
  - Warning Letters
- FOIA Request (specific Form 483, EIR etc.)

FDA 483's: Observations, 21 CFR 111



FDA Fiscal Year	Date Range	# Observations
2008	10/1/2007 - 9/30/2008	1
2009	10/1/2008 - 9/30/2009	139
2010	10/1/2009 - 9/30/2010	657
2011	10/1/2010 - 9/30/2011	1362
2012	10/1/2011 - 9/30/2012	1999
2013	10/1/2012 - 9/30/2013	2246

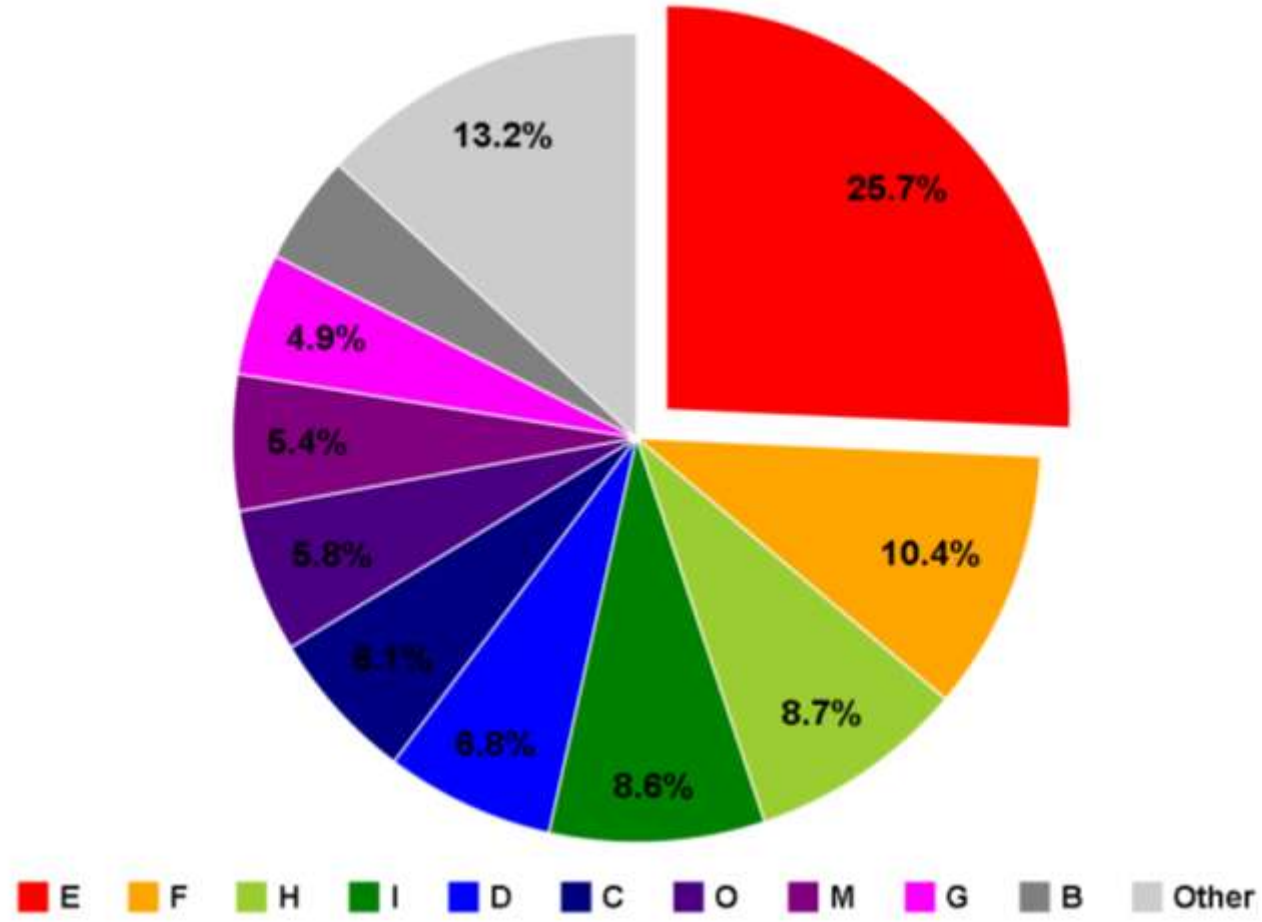
2013 DS cGMP 483 Observations



2013 Observations by Subpart

Subpart	Subpart Description	# Observations
E	Production and Process Control	657
F	Quality Control	220
H	Master Manufacturing Record	216
I	Batch Record	188
O	Complaints	149
M	Holding and Distribution	146
D	Equipment and Utensils	126
C	Physical Plant and Grounds	103
N	Returns	90
L	Packaging and Label Operations	87
G	Components Packaging and Label	81
B	Personnel	80
K	Manufacturing Operations	46
J	Laboratory Operations	37
P	Records	18
X	Adverse Events	2

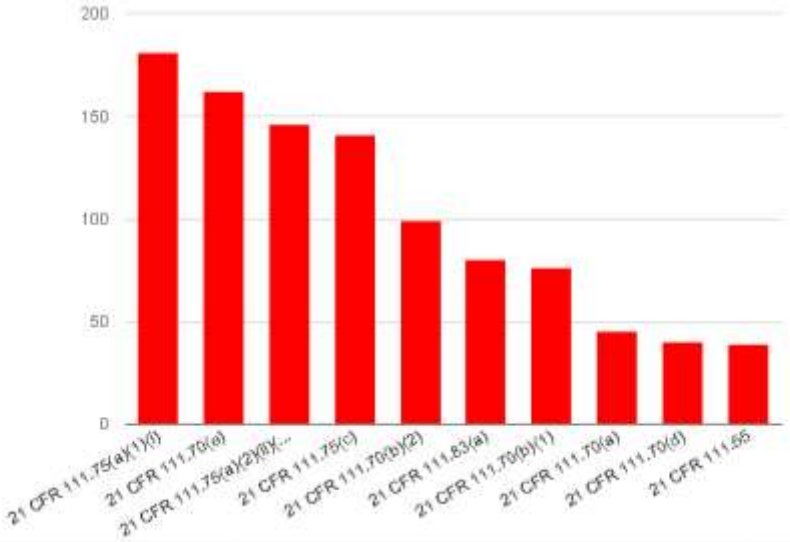
Subpart E: Production & Process Control



483 Observations by Subpart (All)

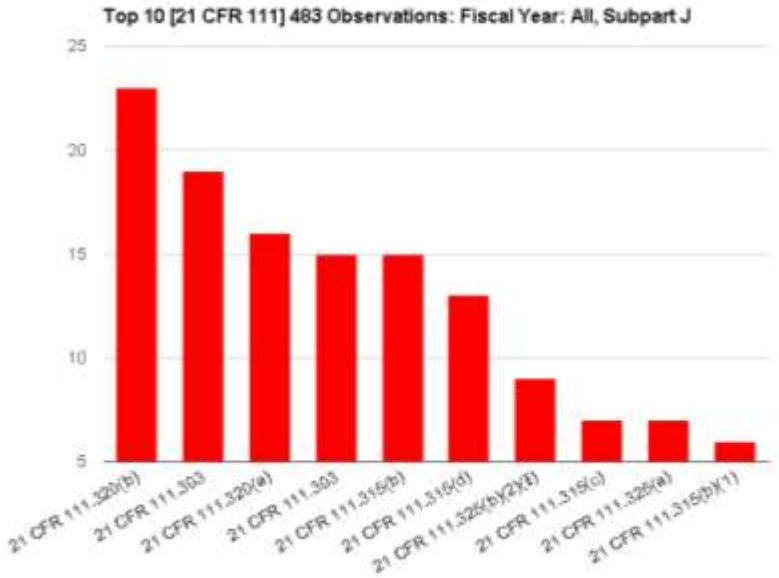
Subpart	Subpart Description	# Observations
E	Production and Process Control	1647
F	Quality Control	669
H	Master Manufacturing Record	558
I	Batch Record	551
D	Equipment and Utensils	433
C	Physical Plant and Grounds	390
O	Complaints	369
M	Holding and Distribution	348
G	Components Packaging and Label	313
B	Personnel	280
L	Packaging and Label Operations	237
N	Returns	213
J	Laboratory Operations	172
K	Manufacturing Operations	148
P	Records	52
X	Adverse Events	24

Subpart E, Top 10 Observations (All)



CFR #	Description	Observations
21 CFR 111.75(a)(1)(i)	Component - verify identity, dietary ingredient	181
21 CFR 111.70(e)	Specifications - identity, purity, strength, composition	162
21 CFR 111.75(a)(2)(ii)(A)	Component - qualify supplier	146
21 CFR 111.75(c)	Specifications met - verify; finished batch	141
21 CFR 111.70(b)(2)	Specifications-component purity, strength, composition	99
21 CFR 111.83(a)	Reserve sample - collect, hold	80
21 CFR 111.70(b)(1)	Specifications - component identity	76
21 CFR 111.70(a)	Specifications - manufacturing process	45
21 CFR 111.70(d)	Specifications - labels, packaging	40
21 CFR 111.55	Production, process controls - implement	39

Top 10 Observations, Lab Ops



CFR #	Description	Observations
21 CFR 111.320(b)	Examination, testing; scientifically valid	23
21 CFR 111.303	Written procedures - tests, examinations; specifications met	19
21 CFR 111.320(a)	Examination, testing; appropriate	16
21 CFR 111.303	Written procedures - laboratory operations	15
21 CFR 111.315(b)	Sampling plans; establish, follow	15
21 CFR 111.315(d)	Standard reference materials; criteria for selecting	13
21 CFR 111.325(b)(2)(ii)	Records - document; results	9
21 CFR 111.315(c)	Examination, testing methods; criteria for selecting	7
21 CFR 111.325(a)	Written procedures, laboratory operations	7
21 CFR 111.315(b)(1)	Sampling plans; components	6

Top 10, Equipment and Utensils

CFR #	Description	# Obs.
21 CFR 111.25(c)	Procedures - equipment - cleaning, sanitizing	51
21 CFR 111.35(b)(2)	Document-equipment date of use, maintain, clean, sanitize	50
21 CFR 111.27(d)	Equipment - maintain, clean, sanitize	38
21 CFR 111.27(b)	Instruments - calibration	36
21 CFR 111.25(a)	Procedures - calibrating instruments	32
21 CFR 111.30(c)	Equipment - automated - calibrate, inspect	22
21 CFR 111.27(a)	Equipment - design - suitable	21
21 CFR 111.25	Equipment - procedures	21
21 CFR 111.30(b)	Equipment - automated - suitability	13
21 CFR 111.35(b)(3)	Documentation - instruments, controls; calibrations	13

Classifications

Distr.	City	Firm	State	Zip	Country	Inspection End Date	Center	Project Area	District Decision
DEN	Draper		UT	84020	US	2009-11-18	CVM	Monitoring of Marketed Animal Drugs, Feed, and Devices	NAI
DEN	Draper		UT	84020	US	2011-07-13	CDRH	Postmarket Assurance: Devices	NAI
DEN	Draper		UT	84020	US	2011-08-08	CVM	Monitoring of Marketed Animal Drugs, Feed, and Devices	NAI
DEN	Draper		UT	84020	US	2012-03-09	CDRH	Project Evaluation: Devices	VAI
DEN	Draper		UT	84020	US	2012-03-29	CFSAN	Foodborne Biological Hazards	NAI
DEN	Draper		UT	84020	US	2012-03-29	CFSAN	Food Composition, Standards, Labeling and Econ	NAI

Inspection Classifications thru FY 2013

- Search at FDA.gov
- Inspection classifications reflect compliance status when the report was generated and may not represent the final Agency determination
- FDA is disclosing the final inspection classification for inspections related to currently marketed FDA-regulated products (i.e. not just DS)
- The disclosure of this information is not intended to interfere with planned enforcement actions, therefore some information may be withheld from posting until such action is taken.

“Anon” Labs

Inspected on 3 occasions, issued 483’s at each inspection, classified OAI

OAI	8/2/2012	Food Composition, Standards, Labeling and Econ…
OAI	6/3/2011	Unapproved and Misbranded Drugs
OAI	6/3/2011	Monitoring of Marketed Animal Drugs, Feed, and Devices
OAI	6/3/2011	Food Composition, Standards, Labeling and Econ…
OAI	12/31/2008	Monitoring of Marketed Animal Drugs, Feed, and Devices
OAI	12/31/2008	Drug Quality Assurance

Warning Letter: 12/5/2011 DS cGMP’s

“Anon” Labs Warning Letter

Failed to establish laboratory control processes reviewed and approved by quality control personnel, including the use of criteria for selecting reference materials used in performing tests and examination, as required by 21 CFR 111.315(d)

- Non-compendia reference standard materials (i.e., spectrum graphs) for the **(b)(4)**transform infrared spectroscopy (**(b)(4)**TIR) are selected from previous component shipments received and analyzed by your **(b)(4)**TIR equipment
- Failed to establish any criteria (i.e., characterization) to establish a reference standard.
- Non-compendia reference standard materials should be of the highest purity by reasonable effort and should be thoroughly characterized to ensure their identity, purity, quality, and strength.

Note: “**(b)(4)”** indicates redacted information, e.g. **(b)(4)**TIR

Another Firm: Warning Letter Issued: 02/17/2012

Distr.	Inspection End Date	Center	Project Area	District Decision
PHI	2010-01-13	CFSAN	Foodborne Biological Hazards	VAI
PHI	2010-01-13	CFSAN	Food Composition, Standards, Labeling and Econ	VAI
PHI	2011-10-06	CFSAN	Foodborne Biological Hazards	OAI
PHI	2011-10-06	CFSAN	Food Composition, Standards, Labeling and Econ	OAI
PHI	2012-08-27	CFSAN	Foodborne Biological Hazards	OAI
PHI	2012-08-27	CFSAN	Food Composition, Standards, Labeling and Econ	OAI
PHI	2013-03-26	CFSAN	Foodborne Biological Hazards	VAI
PHI	2013-03-26	CFSAN	Food Composition, Standards, Labeling and Econ	VAI

Testing into Compliance?

- Finished product specification for *Staphylococcus aureus* (negative) was not met
- Firm conducted multiple microbiological tests when the initial or consecutive microbiological tests failed
- FDA: “you continued to re-test the finished product for the microbial specification until [the] test result indicated that the established specification was met”

Quality Review of Test Results

- …failed to quarantine components until quality control personnel reviewed and approved the results of any tests or examinations conducted on the components, prior to using the components in the manufacture of a dietary supplement, as required by 21 CFR 111.155(c)(2)
- …in-house **(b)(4)** Spectrometry **(b)(4)** results for malic acid…were not reviewed by quality control personnel

Inspection Citations

- Open Government Initiative
- Data from inspections conducted during FDA Fiscal Years 2006 thru 2012 to:
  - Improve the public's understanding of how FDA works to protect the public health
  - Provide rationale for enforcement actions
  - Inform public and industry decision-making, allowing them to make more informed marketplace choices
  - Help to encourage compliance
  - Enhance, improve and expand the information available to those seeking FOIA records

Inspection Citations = 483 Items

2012-08-02	21 CFR 111.113(a)(3)	Your quality control personnel did not conduct a material review and make a disposition decision for an unanticipated occurrence during the manufacturing operations that adulterated or may lead to adulteration of the dietary supplement.
2012-08-02	21 CFR 111.135	Your quality control operations for product complaints did not include reviewing and approving decisions about whether to investigate a product complaint and reviewing and approving the findings and follow-up action of any investigation performed.
2012-08-02	21 CFR 111.260(k)(2)	Your batch production records did not include an actual or representative label, or a cross-reference to the physical location of the actual or representative label specified in the master manufacturing record.
2012-08-02	**21 CFR 111.303**	**You did not establish and follow written procedures for laboratory operations.**
2012-08-02	**21 CFR 111.320(b)**	**You did not identify and use an appropriate scientifically valid method for each established specification for which testing or examination is required to determine whether the specification was met.**
2012-08-02	21 CFR 111.70(b)(2)	You did not establish component specifications for purity, strength, and composition.
2012-08-02	21 CFR 111.70(e)	You did not establish product specifications for the identity, purity, strength, and composition of the finished dietary supplement.
2012-08-02	21 CFR 111.75(a)(2)(ii)(E)	Your quality control personnel did not review and approve the documentation setting forth the basis for qualification and re-qualification of a supplier of a component.
2012-08-02	21 CFR 111.75(c)(2)	You did not conduct appropriate tests or examinations to determine compliance with the specifications established for identity, purity, strength, and composition.
2012-08-02	21 CFR 111.80(a)	You did not collect representative samples of each unique lot of components that you received from a supplier to determine whether the components mee established specifications.
2012-08-02	21 CFR 111.80(c)	You did not collect representative samples of finished batches of dietary supplements that you manufacture before releasing for distribution to verify that the finished batch of dietary supplement meets established product specifications.
2012-08-02	21 CFR 111.90(b)(1)	You reprocessed a dietary supplement for which quality control personnel did not conduct a material review and make a disposition decision to approve the reprocessing.

Citations by CFR e.g. 111.320(b)*

District	City	State	Zip	Country	Inspection End Date
DEN	Boulder	CO	80301	US	2012-02-29
DEN	Spanish Fork	UT	84660	US	2011-04-26
DET	Wabash	IN	46992	US	2011-07-28
FLA	Clearwater	FL	33760	US	2012-08-02
LOS	Chula Vista	CA	91911	US	2012-04-17
LOS	Valencia	CA	91355	US	2012-03-06
LOS	Upland	CA	91786	US	2012-02-21
LOS	Anaheim	CA	92807	US	2012-02-14
NYK	Hauppauge	NY	11788	US	2012-01-10

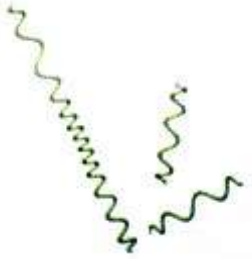
*21 CFR 111.320(b) You did not identify and use an appropriate scientifically valid method for each established specification for which testing or examination is required to determine whether the specification was met.

Other Recent Enforcement Activities

- Identity testing (scientifically valid method)
- Own label marketers/distributors (e.g. outsource responsibilities)
- New Dietary Ingredients (NDI)
- Synthetics vs. naturally occurring
- Misbranded, unapproved new drugs
- Supplements spiked with pharmaceuticals

Identity Method: Fit for Purpose?

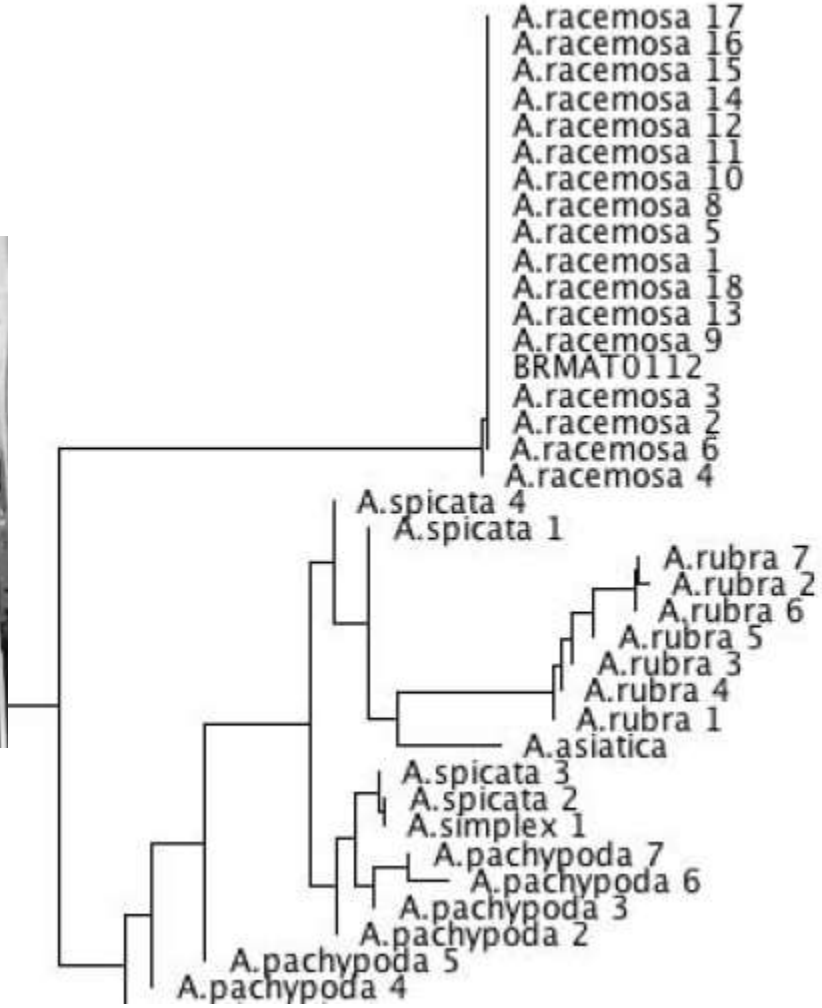
- "Spirulina generally consists of the dried biomass of the cyanobacterium, *Arthrospira platensis*
- … microscopic examination of the Spirulina power is not appropriate in that it does not allow for distinction of one of the three *Arthrospira* cyanobacterium species (*A. platensis, A. maxima,* or *A. fusiformis*) or other similar algae that may possess similar morphology with *Arthrospira*, and therefore, cannot be used to verify the identity of Spirulina powder."



Specificity: Closely Related Species

- “The identity test you perform is based on a specification for fresh root/rhizome that is inadequate
- …in your comparison of A. racemosa [black cohosh] to the possible adulterants A. pachypoda, A. rubra, and A. cimicifuga, you stated that the identity characteristic for the later [sic] species are not described in the literature. Therefore, you do not have a specific characteristic by which to distinguish between the desired rhizome and the adulterants.”

Find Appropriate Methods!



Credit: Dr. Danica Harbaugh Reynaud, AuthenTechnologies Inc. Richmond, CA

Outsourcing

- As a distributor that contracts with other manufacturers to manufacture, package, or label dietary supplements … your firm has an obligation to know what and how these activities are performed so that you can make decisions related to whether the products conform to established specifications and whether to approve and release the products for distribution.

  [72 Fed. Reg. 34752, 34790 (June. 25, 2007)]

Outsourcing: Analytical Labs

- Questionnaires? Are they useful?
- Accreditations e.g. ISO – for what methods?
- On-site visits
  - SOP's: are they followed?
  - COA's: do they comply?
  - OOS investigations or simply testing into compliance?
- Collaborative programs, e.g.
  - NIST Dietary Supplement Laboratory Quality Assurance Program (DSQAP)
  - AOAC
- Method validation – are there data to support method suitability in the sample matrix?
- Send regular "check samples" of known composition

Is it natural? Can you prove it?

- Driven Sports Inc. “CRAZE”
  - Dendrobex™ (Dendrobium Extract) (stem) (concentrated for alkaloid content including Dendrobine, Dendroxine, Dendramine, B-Phenylethylamine, N,N-Dimethyl-B-Phenylethylamine, and N,N-Diethyl-B-Phenylethylamine)
  - No NDI filed
  - Contained synthetics, plus possible meth-like substance? Lab results are disputed by firm (counterfeit product tested?)
  - Withdrawn from market Oct 2013 (USA Today article)
  - Warning Letter April 4, 2014

Is it natural? Can you prove it?

- IP-6 International Inc. “Red Yeast Rice Gold”
  - Warning Letter April 23, 2014
  - enhanced, or added drug ingredient?
  - laboratory analysis conducted by FDA determined that this product contains a significant level of lovastatin, approximately 1 mg per capsule

“The Dog Ate My Homework”

- … failed to conduct at least one appropriate test or examination to verify the identity of a dietary ingredient
- Identity testing in-house is not conducted due to laboratory equipment failure:
  - “Even though you have purchased new equipment, a **(B)(4)**, it is not operational due to issues relating to the **(B)(4)**
  - Furthermore, your firm did not send the raw materials to an outside laboratory for identity testing when your equipment failed
  - The lack of testing affects all **(B)(4)** lots of finished products manufactured in the past year”

Thank You!

Questions?

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Charts URL:
http://www.marianboardley.com/charts

References

- Ion Labs Warning Letter December 5, 2011
  - http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm284400.htm
- Protica, Inc. Warning Letter February 17, 2012
  - http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm296768.htm
- Desert Rose Manufacturing, Inc. Warning Letter March 1, 2013
  - http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm351700.htm
- Algaen Corporation Warning Letter March 8, 2013
  - http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm362383.htm
- Herbalist & Alchemist, Inc. Warning Letter September 19, 2013
  - http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm388701.htm
- Xtra Life Warning Letter April 4, 2014
  - http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm396815.htm
- IP-6 Warning Letter April 23, 2014
  - http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm396822.htm
- FDA Inspection Classifications Search
  - http://www.accessdata.fda.gov/scripts/inspsearch/
  - Inspections Classifications from 10/1/2008 through 9/30/2013 (Report Date: October 2013)(Excel Format) (XLS - 17.9MB)
- FDA Warning Letter Search
  - http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
  - http://www.accessdata.fda.gov/scripts/warningletters/wlAdvancedSearch.cfm
- NIST DSQA Program
  - http://www.nist.gov/mml/csd/dsqaprogram.cfm