QC Documentation requirements for demonstrating that methods are scientifically valid and suitable for their purpose: when to validate, when to verify

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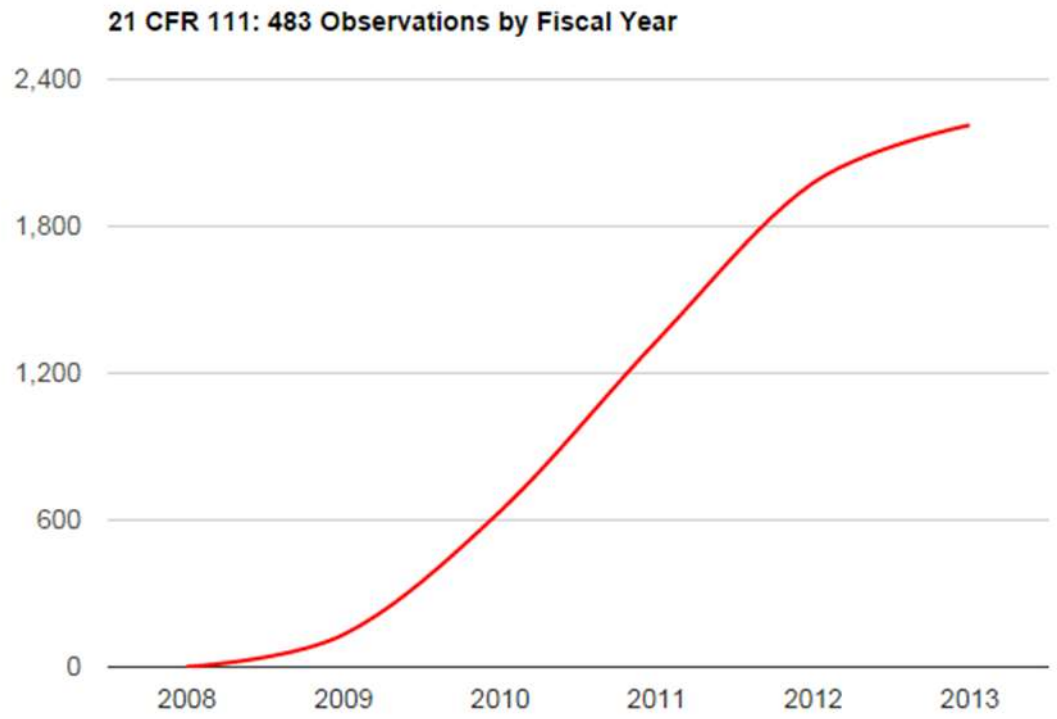
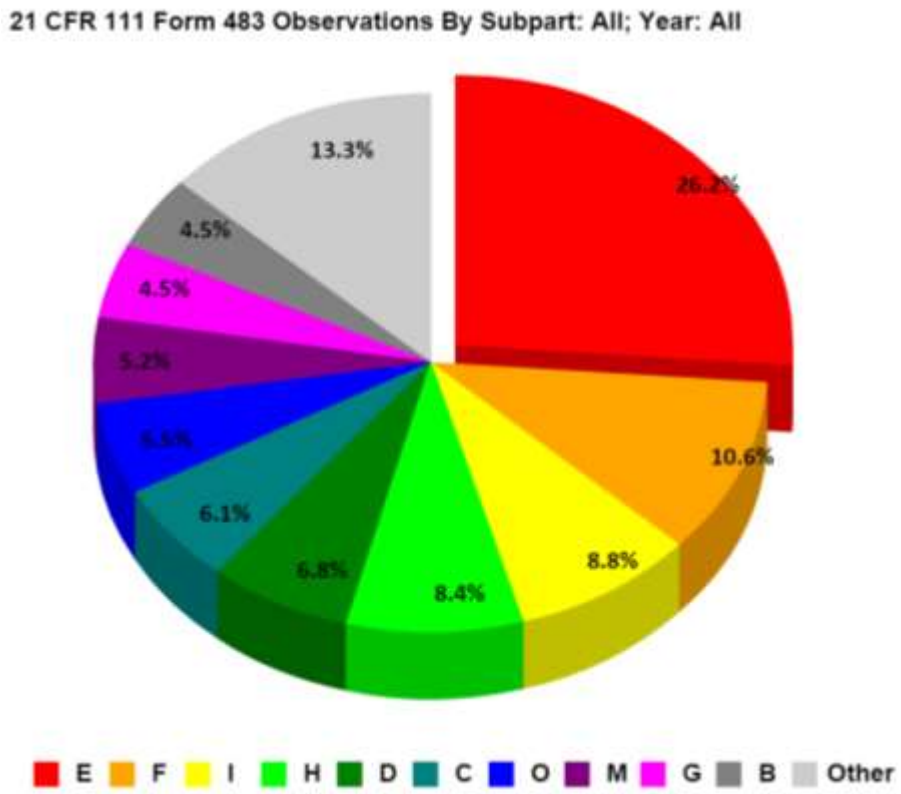
FDA 483's: Observations, 21 CFR 111



From: FDA Inspectional Observation Data Sets

http://www.fda.gov/ICECI/Inspections/ucm250720.htm

DS cGMP 483 Observations: Subparts

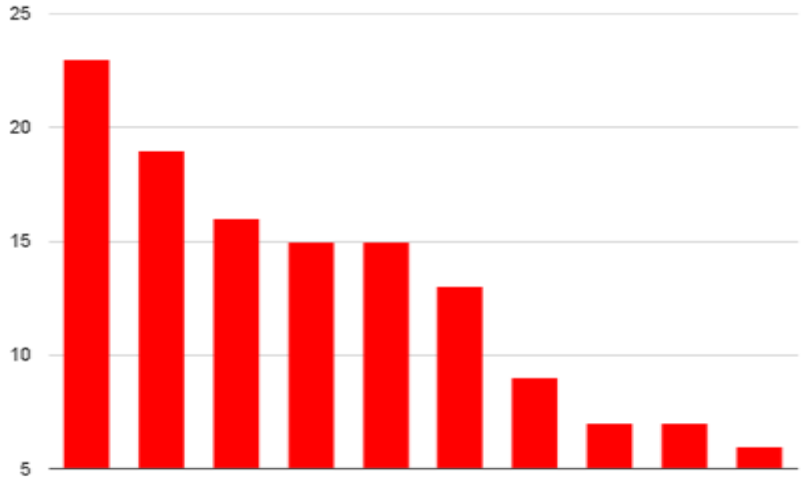


Subpart		# Obs.
E	**Production and Process Control**	**1647**
F	Quality Control	669
I	Batch Record	551
H	Master Manufacturing Record	531
D	Equipment and Utensils	430
C	Physical Plant and Grounds	385
O	Complaints	349
M	Holding and Distribution	324
G	Components Packaging and Label	284
B	Personnel	280
L	Packaging and Label Operations	230
N	Returns	213
J	**Laboratory Operations**	**172**
K	Manufacturing Operations	148
P	Records	52
X	Adverse Events	24

Subpart E: Top 10 Observations

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

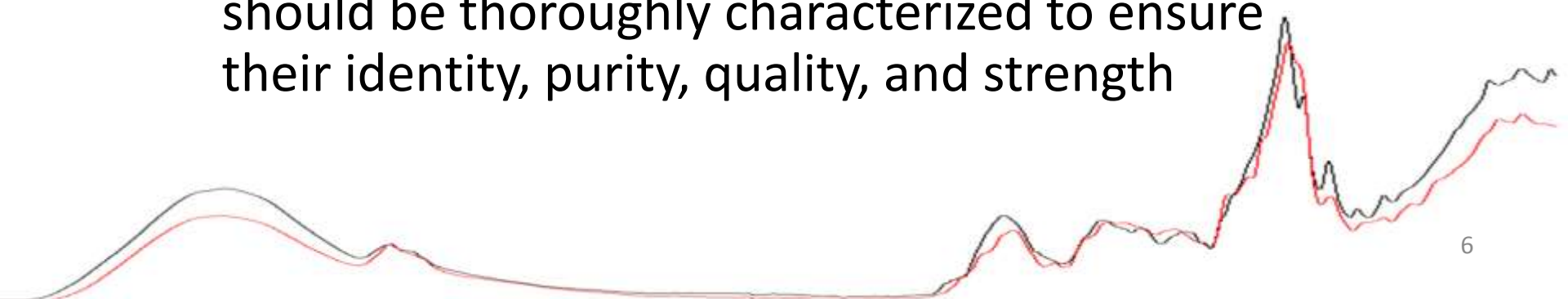
Subpart J: Top 10 Lab Observations



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

High Risk Analytical Behavior

- Misuse/abuse of identity methods (esp. low cost)
  - Organoleptic: when used beyond valid capabilities
  - FTIR/NIR Spectroscopy: selectivity/specificity issues
  - Microscopy: lack of botanical expertise and training/experience; use beyond valid capabilities
- Failure to qualify reference materials
  - 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



Warning Letter: Reference, Authenticate

Pure Encapsulations, Inc.

- Used components as analytical standards in FT-NIR identity testing library
- **Authenticated those standards using organoleptic tests, review of supplier CoA**

FDA Warning Letter 12/23/11

111.75(h)

- Standards must be verified by scientific methods or reference standards, not reliance on supplier's CoA
- **Powdered ingredients cannot be identified through organoleptic testing**

See also: Warning Letter to EnerHealth Botanicals, LLC 8/8/14

Warning Letter: Reference, Specificity

Hillestad Pharmaceuticals USA, Inc.

- Performed identity testing based on initial lot received, without confirming identity.
- Initial lot becomes reference standard for future lots
- **Established a Hit Quality Index of at least [REDACTED] as compared to the reference standard.**
- **When challenged, product was shown to have at least [N] possible matches to the reference standards**

FDA Warning Letter 4/17/13

111.75(h)

- Almost all [materials] show a match at [REDACTED] HQI or higher but you have never re-evaluated your specification limit or determined if a more stringent limit is appropriate
- **Any of these [materials] could have been accepted as the tested material using the method and specifications established**

See also: Warning Letter to Beehive Botanicals, Inc. 2/8/13

Warning Letter: Not demonstrated

Albert Max Inc. dba: Vita Springs Health

- Have not *demonstrated* … that [REDACTED] is an appropriate, scientifically valid method as required to identify dietary ingredients

FDA Warning Letter 6/24/14

111.75(h)

- Specifically, you provided [REDACTED] as the methodology to verify the identity of the dietary ingredients
- **However, your response did not demonstrate that [REDACTED] is an appropriate, scientifically valid test to verify the identity of these dietary ingredients**

Currently Seldom Seen

- Scientifically valid method: Subparts J & E
  - 111.320(a) "*verify that the laboratory examination and testing methodologies are **appropriate for their intended use***"
  - 111.320(b) "*identify and use an **appropriate scientifically valid** method*"
  - 111.75(h) "*ensure that the tests and examinations … are **appropriate, scientifically valid methods***"

111.75(a)(1)(i) "*conduct at least one appropriate test of identity*"

- Quantitative methods
  - e.g. HPLC, GC, ICP-MS/OES etc.
- Specialized or high-investment ID methods
  - e.g. HPTLC, DNA, MS, NMR etc.

Warning Letter: Reference, Verify

Dynamic Pharmaceuticals, Inc.

- Failed to use an appropriate scientifically valid method for each established specification
- **In-process** specification data at the Final Blending step [was] established using spectroscopy data collected from initial batches of the products

FDA Warning Letter 6/23/11

111.320

- Initial batches are not a recognized reference standard and are not part of a scientifically valid method
- **Failed to verify that a test methodology that uses such batches in this way is appropriate for the intended use**

Warning Letter: Modified Method

Capco Custom Packaging Inc.

- Used modified compendial method USP <61>

FDA Warning Letter 2/20/13

111.73

"limits on contamination"

- Laboratory does not follow USP <61> Microbial Limits Method for Total Plate Count and Yeast and Molds as referenced in batch records
  - Total aerobic counts are not performed in duplicate in accordance with the USP
  - Sample volumes for total aerobic count were 1mL and not 10mL as indicated in the USP

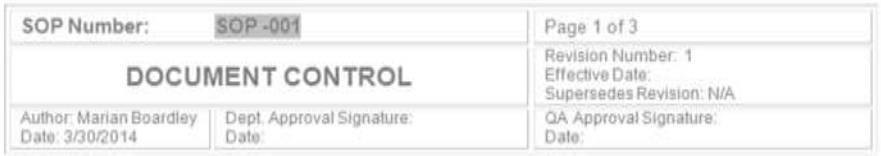
See also: 111.315(d): criteria for reference materials

Verify: Compendial Methods

There are no USP requirements with which you have to comply. The exceptions are only if you claim that a dietary ingredient, component or dietary supplement product meets USP compendial requirements, or that you are using a specific USP analytical protocol, in which case you have to meet the USP compendial requirements or the USP protocol, ***which you have set for yourself***

Documentation Requirements

- QC oversight and documentation of
  - Method's scientific validity
  - Suitability for purpose
  - Modifications to validated methods (verify)
  - Finished product test exemptions, when no scientifically valid method exists *[21 CFR 111.105]*
- Backed by data, with SOP's
  - Qualified reference materials: criteria for selecting
  - Method development with "demonstration of validity"
  - Approval chain for test methods AND references



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Thank You!

More charts?
http://www.marianboardley.com/charts