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Elemental Impurities Testing Challenges in Dietary Supplements

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FDA Enforcement

- From 2010 - 2015 there have been more than 1200 FDA Observations citing failure to establish specifications per 21 CFR 111.70 and verify those specifications with tests and examinations as dictated in 21 CFR 111.75:
  - Accounts for >50% of observations in past 6 years.

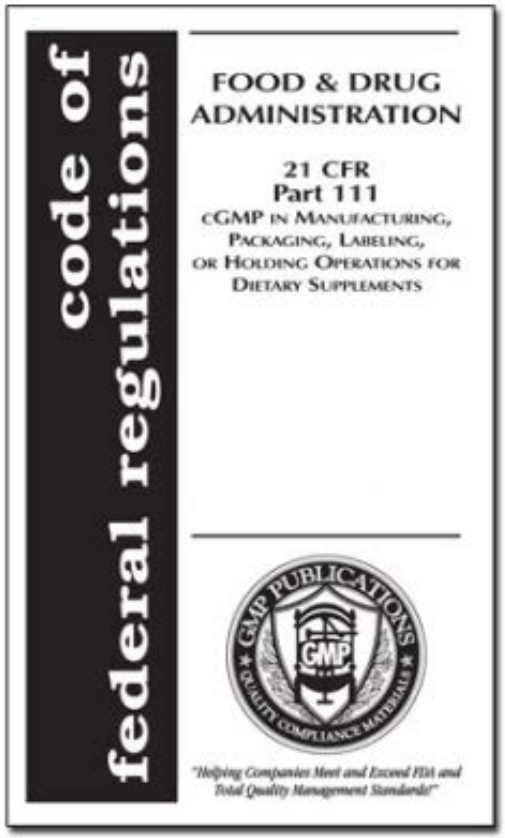
Top FDA Form 483 Observations - Six Year Trend				
Rank	Citation	Description	Number	Percentage
1	21 CFR 111.75	Testing	701	31%
2	21 CFR 111.70	Specifications	548	24%
3	21 CFR 111.255 & 205	MMR & BPR	415	18%
4	21 CFR 111.103	QU Operations	228	10%
5	21 CFR 111.553	Product Complaints	225	10%
6	21 CFR 111.453	Holding & Distribution	159	7%
		TOTAL	2276	

Regulations

- 21 CFR Part 111, *Current Good Manufacturing Practice (cGMP) in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements*.
- Subpart E - Requirement to Establish a Production and Process Control System

  §111.70 – Establishing specifications

  §111.75 – Testing to verify specifications have been met



§111.70 Regulations

- 111.70(b): You must establish **component specifications** for identity; purity, strength and composition as necessary; and limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement.
- 111.70(c): You must establish **in-process specifications** for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplements and, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement.

§111.70 Regulations

- 111.70(d): You must establish specifications for dietary supplement labels (**label specifications**) and for packaging that may come in contact with dietary supplements (**packaging specifications**). Packaging that may come into contact with dietary supplements must be safe and suitable for its intended use and must not be reactive or absorptive or otherwise affect the safety or quality of the dietary supplement.
- 111.70(e): For each dietary supplement that you manufacture you must establish **product specifications** for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

§111.70 Regulations

- 111.70(f): If you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must establish **specifications** to provide sufficient assurance that the **product** you receive is adequately identified and is consistent with your purchase order.
- 111.70(g): You must establish **specifications** for the **packaging and labeling** of the finished packaged and labeled dietary supplements, including specifications that ensure that you used the specified packaging and that you applied the specified label.

Specifications

- Raw Materials
- In-Process Materials
- Finished Products

→ Identity, Purity, Strength, Composition, Limits of Potential Contaminants

- Packaging Components

→ Safe, Suitable for Intended Use, Not Reactive or Absorptive

- Labels - Comply with 21 CFR 101.9, *Nutrition Labeling of Food*

Specifications

- Raw Materials
- In-Process Materials
- Finished Products

Identity
Purity
Strength
Composition
Limits of Potential Contaminants

- Packaging Components

Safe
Suitable for Intended Use
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Suitable for Intended Use
Not Reactive or Absorptive

- Labels - Comply with 21 CFR 101.9, *Nutrition Labeling of Food*

§111.75 Regulations

- 111.75(a): Before you use a **component** you must

  (1) Conduct at least one appropriate test or examination to verify the identity of a dietary ingredient

  (2) Confirm the identity of other components and determine whether other applicable component specifications are met by:

  (i) Conducting appropriate tests or examinations; or

  (ii) Relying on a Certificate of Analysis (COA) from the supplier of the component that you receive, provided that the reliability of the COA has been established through confirmation testing and Qualification of the Supplier.

§111.75 Regulations

- 21 CFR 111.75(c): For a subset of **finished dietary supplement batches** that you identify through a sound statistical sampling plan (or for every finished batch), you must verify that your finished batch of the dietary supplement meets product specifications for identity, purity, strength, composition, and for limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the dietary supplement.

(2) You **must conduct appropriate tests or examinations** to determine compliance with the specifications selected

Contaminants – Heavy Metals

- The type, number, and criteria of contaminant testing performed is dependent on the nature of the raw material.
- Heavy Metals - Ubiquitously found in the environment which results in their presence in dietary supplements from raw materials, particularly minerals and botanical ingredients. They impact human health due to their toxicity and physiological effects even at low exposure levels.
- Raw materials introduce the contaminant but a cumulative affect can result in finished products when multiple raw materials each contribute small amounts of contaminants that sum together.
  - Raw material AND finished product testing may be required.

Prop65

- Heavy metals are regulated in dietary supplements under the State of California Environmental Protection Agency Office of Environmental Health Hazard Assessment Safe Drinking Water and Toxic Enforcement Act of 1986 - Proposition 65 (Prop65)
- Prop65 maximum allowable dose level (MADL)
  - Arsenic: 10 µg/day
  - Cadmium: 4.1 µg/day
  - Lead: 0.5 µg/day
  - Mercury: No MADL
    - Health Canada MADL for Mercury: 0.3 µg/day

Prop65 MADLs

- Prop65 MADL for lead is the lowest in the world
  - Health Canada lead MADL in children 0.3 µg/day
- Obtaining and maintaining this daily lead level is challenging, and in some product formulations, impossible.
  - Single dose, daily gummy:

$$\left(\frac{0.5\,\mu g}{day}\,\text{Lead MADL}\right)\left(\frac{day}{1\,\text{Gummy}}\right)\left(\frac{\text{Gummy}}{4.5\,g}\right) = 0.11\,\mu g/g\ (\text{ppm})$$

  - Multiple dose, daily tablet:

$$\left(\frac{0.5\,\mu g}{day}\,\text{Lead MADL}\right)\left(\frac{day}{3\,\text{Tablets}}\right)\left(\frac{\text{Tablet}}{1.5\,g}\right) = 0.11\,\mu g/g\ (\text{ppm})$$

  - Single dose powder:

$$\left(\frac{0.5\,\mu g}{day}\,\text{Lead MADL}\right)\left(\frac{day}{1\,\text{Scoop}}\right)\left(\frac{\text{Scoop}}{25\,g}\right)\left(\frac{1000ng}{\mu g}\right) = 20\,ng/g\ (\text{ppb})$$

Trace Analysis

- Trace analysis test method is a heat assisted acid digestion, often coupled with organic material oxidation, which requires the use of sophisticated analytical instrumentation to meet these sensitivity levels
  - Susceptible to contamination
  - Dependent on appropriate, representative sampling
  - High level, trained scientific expertise
  - Inductively Coupled Plasma with Mass Spectrometric detection (ICP-MS)
    - Capital expenditure of ~ $250,000

Testing

- Specialty contract laboratory use recommended when scientific expertise not available in house
  - Coordination for sample shipment and results receipt
  - Typical 10-business day turnaround time
  - Costs $75 - $150 per sample, depending on the number of samples submitted

Formulation

- Multiple raw material sources contribute to lead levels and result in a cumulative effect in the finished dietary supplement product.
  - Minerals and botanical
    - Dietary ingredient
    - Excipient
  - Even when raw materials tested and found to have lead concentrations below the ICP-MS test method limit of quantitation (LOQ).

Accommodations

- Warner-Lambert decision of 2011 allows for “naturally occurring lead allowances” from some ingredients when used in multi-vitamins, antacids and calcium supplements.

Calcium	Ferrous fumarate
Magnesium Oxide	Potassium Chloride
Magnesium Carbonate	Zinc Oxide
Magnesium Hydroxide	Zinc Gluconate

- Allows dietary supplement companies to use a Prop65 Warning Label when MADLs cannot be achieved.

WARNING: This product contains chemicals known to the State of California to cause cancer and birth defects or other reproductive harm.

Distribution

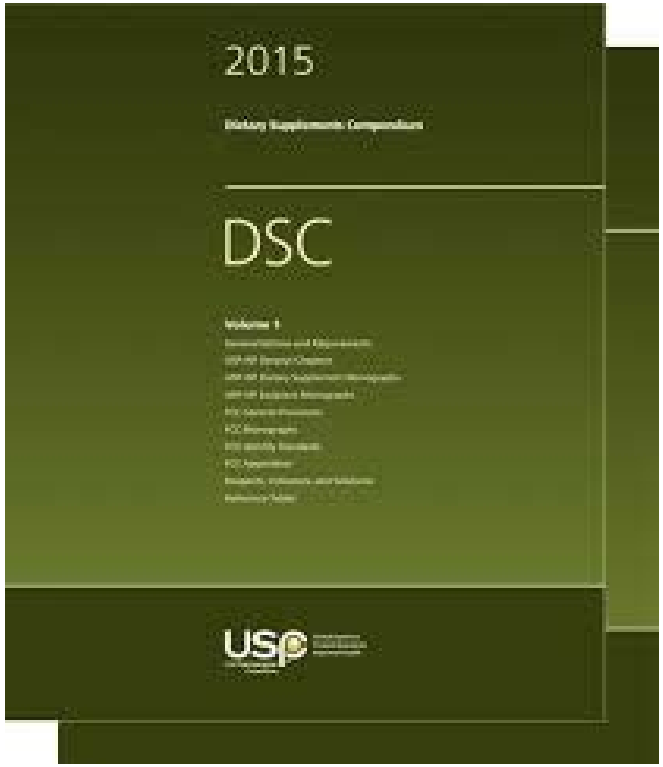
- Prop65 applies only to products distributed in the State of California.
- The Census Bureau estimates that the population of California is 39.5 Million people

$$\left(\frac{39.5\,\text{Million in CA}}{324\,\text{Million in US}}\right)(100) = 12\%\ \text{of US Population in California}$$

- Large segment of the population to ignore for marketing and sales purposes
- Internet sales make it nearly impossible to prevent products from hitting the shelves in California, even when not intentionally marketed there.

USP

- Application of the United States Pharmacopeia (USP) and the Dietary Supplement Compendium (DSC) is voluntary for dietary supplements.
- However, the use of compendial methods, particularly those from the USP, is preferred by the FDA.



USP

- Only scientifically valid test methods are allowed for use of dietary supplement raw materials and products per 21 CFR 111.
  - 111.75(h)(1): Must ensure that tests and exams used to determine whether specs are met are appropriate, **scientifically valid methods**
  - 111.320(b): Must identify and use an appropriate **scientifically valid method** for each established specification for which testing or examination is required to determine whether the specification is met.
- Compendial methods, such as USP, are a good resource for the determination of a potential scientifically valid test method.

USP Heavy Metal Testing

- Heavy metals testing methodologies:
  - USP <211> Arsenic
  - USP <251> Lead
  - USP <261> Mercury
  - USP <231> Heavy Metals
  - USP <233> Elemental Impurities - Procedures
  - USP <2232> Elemental Contaminants in Dietary Supplements

Individual Heavy Metal Chapters

- USP <211> Arsenic
  - Spectrophotometric analysis
  - Chemical interferents are chromium, cobalt, copper, mercury, molybdenum, nickel, palladium, silver, and antimony.
- USP <251> Lead
  - Wet chemical test for presence only
- USP <261> Mercury
  - Method I - Titrimetric test, susceptible to light due to sensitivity of reagent
  - Method IIa and IIb – Atomic Absorption Spectrometer with aeration apparatus

USP <231>

- USP <231> Heavy Metals
  - Wet chemical tests – Method I, II, and III
  - Test conducted with only lead standard
  - Non-specific method with metals recovered including arsenic, cadmium, lead, mercury (depending on method type), bismuth, antimony, tin, silver, copper, and molybdenum.
  - Specification limits provided in individual monographs.

USP <233>

- USP <233> Elemental Impurities
  - Arsenic, Cadmium, Lead, and Mercury.
  - Analytical instrumentation required
    - Procedure 1: ICP with Atomic/Optical Emission Spectrometer detection (ICP-AES)
    - Procedure 2: ICP-MS
  - Limits calculated by division of the Permitted Daily Exposure (PDE) by the maximum daily serving size

USP <2232>

- DSC USP <2232> Elemental Contaminants in Dietary Supplements
  - Arsenic, Cadmium, Lead, and Mercury
  - ICP-AES or ICP-MS Instrumental Analysis
    - Speciation for inorganic arsenic
    - Methylmercury determination

    } as necessary
  - Permitted Daily Exposure (PDE) in finished dietary supplement products
  - Individual Component Option based on maximum daily intake of finished dietary supplement of 10 g.

USP Heavy Metal Specifications

USP Heavy Metal Permitted Daily Exposures (PDEs)		
Element	Finished Product <233>* and <2232>	Individual Component <2232>**
Arsenic (inorganic)	15 µg/day	1.5 µg/g
Cadmium	5 µg/day	0.5 µg/g
Lead	5 µg/day	0.5 µg/g
Mercury (total)	15 µg/day	1.5 µg/g
Methylmercury	2 µg/day	0.2 µg/g
* USP <233> limits calculated by division of the PDE by maximum daily dose.		
** Based on maximum daily intake of 10 g of a dietary supplement.		

USP versus Prop65

- USP Permitted Daily Exposure (PDE) levels dictated in <2232> for heavy metals is irrelevant for dietary supplements marketed and/or distributed into the State of California

USP vs. Prop65 Heavy Metal Limits		
Element	USP <2232> PDE	Prop65 MADL
Arsenic (inorganic)	15 µg/day	10 µg/g
Cadmium	5 µg/day	4.1 µg/g
Lead	5 µg/day	0.5 µg/g
Mercury (total)	15 µg/day	NA
Methylmercury	2 µg/day	NA
PDE = Permitted Daily Exposure		
MADL = Maximum Allowable Daily Level		
NA = Not Available		

Revised USP <2232>

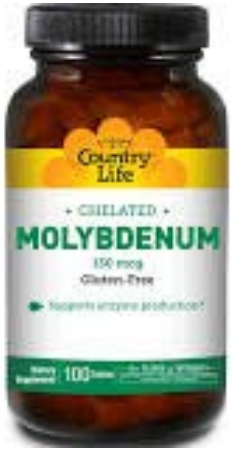
- International Conference of Harmonization, *Guidance for Industry – Q3D Elemental Impurities*, September 2015
- FDA Center for Drug Evaluation and Research (CDER) Draft *Guidance for Industry – Elemental Impurities in Drug Products*, June 2016.
- Significantly expands the list of impurities:
  - Arsenic, Cadmium, Lead, and Mercury $\Rightarrow$

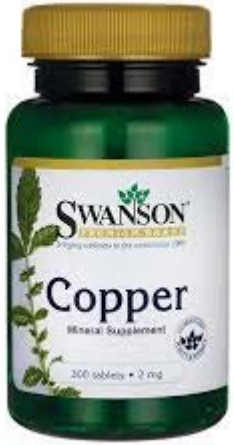
Cadmium	Cobalt	Gold	Rhodium	Platimum	Molybdenum
Lead	Vanadium	Palladium	Ruthenium	Lithium	Copper
Arsenic	Nickel	Iridium	Selenium	Antimony	Tin
Mercury	Thallium	Osmium	Silver	Barium	Chromium

Revised USP <2232>

- A number of these elements are intentionally formulated into dietary supplement products.

Cadmium	Cobalt	Gold	Rhodium	Platimum	Molybdenum
Lead	Vanadium	Palladium	Ruthenium	Lithium	Copper
Arsenic	Nickel	Iridium	Selenium	Antimony	Tin
Mercury	Thallium	Osmium	Silver	Barium	Chromium





Supplement Facts

Serving Size 1 Ampoule (0.07 fl oz)
Servings per Container 30

Each Ampoule Contains		%DV
Zinc (zinc gluconate)	0.067 mg	<1%
Nickel (nickel gluconate)	0.073 mg	*
Cobalt (cobalt gluconate)	0.073 mg	*

* Daily Value (DV) not established

Other ingredients: Purified water, glucose

Supplement Facts

ing Size 1 Tablet

unt Per Serving	% DV
in A 3,500 IU	70%
% as Beta-Carotene)	
	150%
	250%
	150%
	75%
	80%
	76%
	80%
	100%
	50%
	100%
	13%
ng	150%
	21%
	44%

facts

	Amt per Serving	% Daily Value
Iodine (as Potassium Iodide)	150 mcg	100%
Zinc (as Zinc Bisglycinate Chelate) TRAACS®	15 mg	100%
Selenium (as L-Selenomethionine Pentapure™)	400 mcg	571%
Copper (as Copper Bisglycinate Chelate) TRAACS®	2.0 mg	100%
Manganese (as Manganese Bisglycinate Chelate) TRAACS®	2.0 mg	100%
Chromium (as Chromium Nicotinate Glycinate Chelate) TRAACS®	400 mcg	333%
Molydenum (as Molybdenum Glycinate Chelate) TRAACS®	150 mcg	200%
Trace Mineral Blend	5.0 mg	†

† Daily Value and/or Recommended Daily Intake not established.

Other Ingredients: White Rice Flour, Vegetarian Capsule, Magnesium Stearate, and Silicon Dioxide.

Amount Per Serving	% DV
Phosphorus 20 mg	2%
Iodine 150 mcg	100%
Magnesium 100 mg	25%
Zinc 11 mg	73%
Selenium 100 mcg	143%
Copper 0.9 mg	45%
Manganese 2.3 mg	115%
Chromium 35 mcg	29%
Molybdenum 50 mcg	67%
Chloride 72 mg	2%
Potassium 80 mg	2%
Nickel 5 mcg	*
Silicon 2 mg	*
Tin 10 mcg	*
Vanadium 10 mcg	*
Lycopene 600 mcg	*

*Daily Value (DV) not established.

Revised USP <2232>

Permitted Daily Exposures for Elemental Impurities			
Element		Class	Oral PDE (µg/day)
Cadmium	Cd	1	5
Lead	Pb	1	5
Arsenic	As	1	5
Mercury	Hg	1	30
Cobalt	Co	2A	50
Vanadium	V	2A	100
Nickel	Ni	2A	200
Thallium	Tl	2B	8
Gold	Au	2B	100
Palladium	Pd	2B	100
Iridium	Ir	2B	100
Osmium	Os	2B	100
Rhodium	Rh	2B	100
Ruthenium	Ru	2B	100
Selenium	Se	2B	150
Silver	Ag	2B	150
Platimum	Pt	2B	100
Lithium	Li	3	550
Antimony	Sb	3	1200
Barium	Ba	3	1400
Molybdenum	Mo	3	3000
Copper	Cu	3	3000
Tin	Sn	3	6000
Chromium	Cr	3	11000

FDA Daily Values (DV)

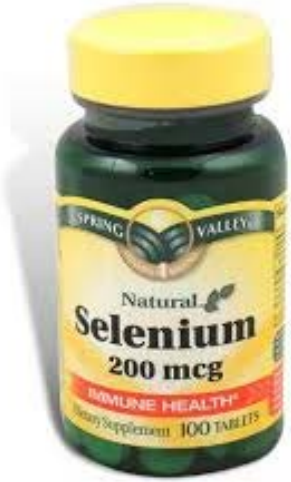
Permitted Daily Exposures for Elemental Impurities			
Element		Class	Oral PDE (µg/day)
Cadmium	Cd	1	5
Lead	Pb	1	5
Arsenic	As	1	5
Mercury	Hg	1	30
Cobalt	Co	2A	50
Vanadium	V	2A	100
Nickel	Ni	2A	200
Thallium	Tl	2B	8
Gold	Au	2B	100
Palladium	Pd	2B	100
Iridium	Ir	2B	100
Osmium	Os	2B	100
Rhodium	Rh	2B	100
Ruthenium	Ru	2B	100
Selenium	Se	2B	150 (FDA DV=70)
Silver	Ag	2B	150
Platimum	Pt	2B	100
Lithium	Li	3	550
Antimony	Sb	3	1200
Barium	Ba	3	1400
Molybdenum	Mo	3	3000 (FDA DV=75)
Copper	Cu	3	3000 (FDA DV=2000)
Tin	Sn	3	6000
Chromium	Cr	3	11000 (FDA DV=120)

* Daily values are the amount of nutrients recommended per day for Americans 4 years of age or older.

Selenium

- Selenium – A study in contrasting guidance
  - USP <2232> PDE = 150 µg/day
  - FDA DV = 70 µg/day
  - Typical dietary supplement strength claim = 200 µg/day

USP Verified Product



Supplement Facts

Serving Size 1 Tablet

Amount Per Serving		%Daily Value
Vitamin A (as Retinyl Acetate and Beta-Carotene)	2,500 IU	50%
Vitamin C (as Ester-C® Calcium Ascorbate)	60 mg	100%
Vitamin D (as D3 Cholecalciferol)	1,000 IU	250%
Vitamin E (as dl-Alpha Tocopheryl Acetate)	30 IU	100%
Thiamin (Vitamin B-1) (as Thiamin Mononitrate)	1.5 mg	100%
Riboflavin (Vitamin B-2)	1.7 mg	100%
Niacin (as Niacinamide)	10 mg	50%
Vitamin B-6 (as Pyridoxine Hydrochloride)	2 mg	100%
Folic Acid	400 mcg	100%
Vitamin B-12 (as Cyanocobalamin)	6 mcg	100%
Biotin (as d-Biotin)	300 mcg	100%
Pantothenic Acid (as d-Calcium Pantothenate)	5 mg	50%
Calcium (as Calcium Carbonate and Ester-C® Calcium Ascorbate)	200 mg	20%
Magnesium (as Magnesium Oxide)	50 mg	13%
Zinc (as Zinc Oxide)	15 mg	100%
Selenium (as Sodium Selenate)	200 mcg	286%
Choline (as Choline Bitartrate)	1 mg	***
Fish Oil and Borage Oil (Containing Omega-3 and Omega-6 Lipids)	5 mg	***
Lactobacillus Acidophilus	5 mg	***
Active Vegetable and Fruit Blend (Broccoli Extract, Cauliflower Extract, Carrot Extract, Kale Extract, Acai (*Euterpe oleracea*) (fruit), Blackberry Concentrate, Blueberry Extract (*Vaccinium spp.*) (fruit), Red Raspberry (*Rubus idaeus*) (leaf), Strawberry (*Fragaria virginiana*) (fruit), Beet Powder)	200 mg	***
Men's Complex Blend (Saw Palmetto Extract (*Serenoa repens*) (fruit), Wheat Germ (*Triticum aestivum*) (seed), Grapeseed Extract (*Vitis vinifera*) (seed), Ginkgo Biloba (*Ginkgo biloba*) (leaf), Pumpkin (*Cucurbita pepo*) (seed), Green Tea Extract (*Camellia sinensis*) (leaf), Lycopene)	60 mg	***

***Daily Value not established.

Other Ingredients: Vegetable Cellulose. **Contains <2% of:** Gelatin, Natural Palm Leaf Glaze, Silica, Vegetable Magnesium Stearate, Vegetable Stearic Acid.

Contains wheat and fish (cod, pollock, haddock, hake, cusk, redfish, sole, flounder, anchovy, sardine) ingredients.

Zinc (as Zinc Oxide)	15 mg	100%
Selenium (as Sodium Selenate)	200 mcg	286%
Choline (as Choline Bitartrate)	1 mg	***

Conclusion

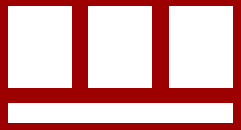
- Application of USP <2232> is not sufficient to meet the lower limit of Prop65 and would therefore be irrelevant for testing of heavy metals: arsenic, cadmium, lead, and mercury.
- Revised USP <2232> includes a number of elements that are intentionally added and therefore defined as Class I Nutrients in dietary supplements.
  - Class I Nutrients must be demonstrated to meet 100% of the label claim in accordance to 21 CFR 101.9, *Nutrition Labeling of Foods.*
- Four of the elements listed in the revised USP <2232> with PDE levels also have FDA Daily Values so are commonly used in dietary supplement products
  - Selenium, Molybdenum, Copper, Chromium

Conclusion

- Regulations and guidelines are contrasting for Selenium
  - USP <2232> PDE = 150 μg/day Se
  - FDA DV = 70 μg/day Se
  - Many products, including USP Verified = 200 μg/day Se

- **The expectation for dietary supplement firms to utilize and comply with revised USP <2232> will require significantly more testing, with all of the associated cost and time losses incurred, with no real benefit to consumer health or safety.**

Thank You



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