Quality Concerns With Dietary Supplements

Dietary Supplement Quality

Why it Matters in Your Practice

Why Should You Care About Quality?

- Patient outcomes
- Patient safety
- Patient cost and ROI
- Your practice reputation
- Minimize legal risk
- Provide ethical care

Clinical Impact of Dietary Supplement Quality

First and foremost, your duty is to patient care.

If recommending dietary supplements is part of the care provided, it's imperative that you ensure what you recommend is high quality in order to ensure clinical outcomes.

If your patient doesn't improve, you should consider the following:

- Do I have the correct diagnosis?
- Did I build an evidence-informed treatment plan?
- Do the products have in them what I think they do?

Clinical research outcomes may also be affected by poor quality product!!

Ethical Considerations of Quality

- Patients trust you to recommend a care plan that will help and not harm
  - There is a documented risk of harm in the retail dietary supplement marketplace, particularly if “price shopping”
- Referral to a store to self-shop leaves patients in the hands of the salesclerk
- As healthcare practitioners, we too have a responsibility
  - Demand evidence-based quality
  - Demand transparent quality practices
  - Use quality as a differentiator in product selection

Legal Considerations of Quality

- Could you be held liable for recommending a poor-quality product if it causes harm?
- If you are selling your own branded supplement line (private label), do you understand the legal implications associated with that?

Top Quality Issues
and the Root Cause

Types of Quality Issues

Manufacturing Errors

- Potency (i.e., vitamin D)
- Degradation of ingredient
- Microbial contamination
- Allergen contamination

Intentional & Economic Adulteration

- Undeclared drug ingredients (sildenafil, sibutramine)
- Cut actives with cheaper ingredients (bilberry v. blueberry)
- Boost nutrient content in testing (melamine in pet food)
- Cheaper plant part used but less potent

Ingredient and Supply Chain Verification

- Ingredient quality can decline
- The biggest area of true risk today

Claims, Claims, Claims!

- Marketing copy can change the classification of a dietary supplement to a drug
- This is by far the greatest FDA action in the marketplace today

Manufacturing Errors

Manufacturing Errors

- Potency (i.e., vitamin D)
- Degradation of ingredient
- Microbial contamination
- Allergen contamination

Potency Errors: Vitamin D

Manufacturing challenges, ingredient qualities, can lead to dosage variability, such as with vitamin D.

LeBlanc ES, Perrin N, Johnson JD, Ballatore A, Hillier T. Over-the-Counter and Compounded Vitamin D: Is Potency What We Expect? *JAMA Intern Med.* 2013;173(7):585–586. doi:10.1001/jamainternmed.2013.3812

Over-the-Counter and Compounded Vitamin D: Is Potency What We Expect?

Because vitamin D insufficiency can be harmful to health,[1-3] supplementation is often prescribed. However, the Food and Drug Administration (FDA) does not regulate vitamin D supplements, so potency may not be well evaluated. In a recent trial examining vitamin D ir
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tion. To standardize variability and compare across doses, we calculated the coefficient of variation (CV)—the ratio of the standard deviation to the mean.

Results. *Analysis of 5 Pills From the Same Bottle.* The OTC pills contained 52% to 135% of expected dose (**Table**). When averaged over 5 pills, two-thirds of bottles met USP Convention standards for OTC cholecalciferol solution,[5] which state that contents should be within 90% to 120% of the stated dose. In approximately one-fourth of bottles, all 5 pills met USP Convention standards. Two-thirds of bottles had less than 10% variability (CV). The one manufacturer that was USP verified (No. 4) was highly accurate (101.7%), and all

Table: Vitamin D_3 (Cholecalciferol) Potency of 5 Pills From 1 Bottle

Manufacturer No.	Dosage of Pills, IU	Potency Pill (% of Expected)		Potency of 5 Pills, Mean (SD), %	Coefficient of Variation, %
		Highest	Lowest		
1	10 000	130	123	126.4 (2.7)	2.1
2	10 000	114	85	97.6 (12.7)	13.0
3	5000	121	113	118.0 (3.2)	2.7
4[a]	5000	106	99	101.7 (2.5)	2.4
5	5000	132	129	130.8 (1.1)	0.8
2	1000	97	75	90.5 (8.8)	9.8
3	1000	131	102	115.2(10.7)	9.3
5	1000	124	56	99.6 (25.7)	25.7
6	1000	108	104	105.8 (1.6)	1.5
7	1000	103	95	99.9 (3.9)	3.9
8	1000	122	63	82.2 (23.2)	28.2
9	1000	108	87	97.7 (10.1)	10.4
10	1000	88	52	65.9 (14.0)	21.3
11	1000	110	107	108.6 (1.1)	1.0
12	1000	135	122	128.6 (5.0)	3.9

[a] US Pharmacopeial Convention–verified dietary supplement.

Contamination

- Heavy Metals
- Microbial contaminants

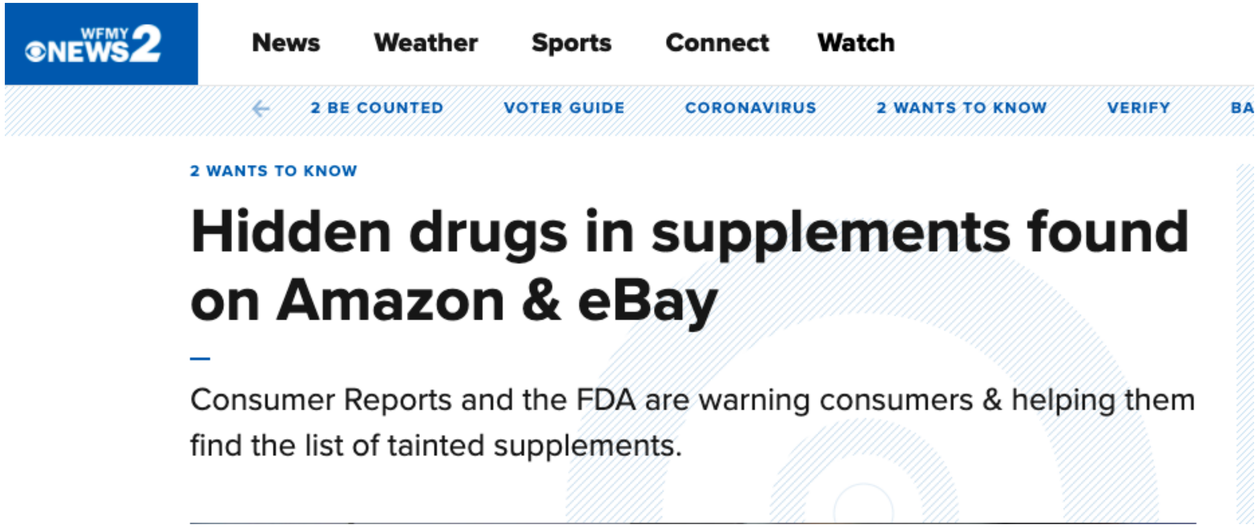
https://www.pbs.org/newshour/health/analysis-some-natural-supplements-can-be-dangerously-contaminated#:~:text=Heavy%20metals%2C%20which%20are%20known,1%25%20had%20too%20much%20mercury.

Economic Adulteration

Intentional & Economic Adulteration

- Undeclared drug ingredients (sildenafil, sibutramine)
- Cut actives with cheaper ingredients (bilberry v blueberry)
- Boost nutrient content in testing (melamine in pet food)
- Cheaper plant part used but less potent (leaf v. root)

Economic Adulteration: Undeclared Drugs



WFMY NEWS2

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2 WANTS TO KNOW

Hidden drugs in supplements found on Amazon & eBay

Consumer Reports and the FDA are warning consumers & helping them find the list of tainted supplements.

If improving your wellness is part of your plan, maybe you're thinking about taking dietary supplements. But before you click the "buy" button, Consumer Reports has an important warning about potentially dangerous substances found in some supplements sold online.

Sildenafil, Tadalafil, and Fluoxetine are not only hard to pronounce, but they're also active ingredients in popular prescription drugs. Sildenafil is in Viagra, Tadalafil is in Cialis, and Fluoxetine is in Prozac.

You may be surprised to hear that the Food and Drug Administration also found those ingredients in some weight-loss and sexual-enhancement supplements sold on eBay and Amazon. Some of the tainted products sold on Amazon were even labeled Number-One-Best Seller or Amazon's Choice, according to a press release from the FDA.

It's against the law for a dietary supplement to contain any drugs, and the ingredients must be accurately listed on the label. But what the FDA found were essentially "hidden" drugs in many of these supplements.

Ebay responded to Consumer Reports by saying it was "reviewing the site" and would be removing the tainted products. Amazon said it was "reviewing the information from the FDA" and would take action accordingly.

Even if the companies take down the tainted supplements identified by the FDA, that might not solve the larger problem. This is just the latest in a string of studies that have found undeclared and potentially dangerous drugs in dietary supplements.

If you take a supplement, be sure to check the FDA's database on tainted products to make sure isn't listed. And even if the supplement you take isn't on the list, you should still be cautious.

Feb 9, 2021. https://www.wfmynews2.com/article/news/local/2-wants-to-know/consumer-reports-warns-of-hidden-drugs-in-supplements-found-on-amazon-and-ebay/83-44c4b964-d9ec-406c-ac7d-04da165a9992

Economic Adulteration: Bilberry

Several tests of bilberry found adulteration with other plants, in attempt to increase yields:

- Blueberry
- Mulberry
- Chokeberry
- Soybean
- Black rice
- Red dye amaranth
- Synthetic dyes

J Agric Food Chem. 2014 Nov 12;62(45):10998-1004. doi: 10.1021/jf504078v. Epub 2014 Nov 3.

Bilberry adulteration: identification and chemical profiling of anthocyanins by different analytical methods

Claudio Gardana [1], Salvatore Ciappellano, Laura Marinoni, Christian Fachechi, Paolo Simonetti

Affiliations + expand

PMID: 25365784 DOI: 10.1021/jf504078v

Abstract

Extracts of the bilberry fruit have protective effects against retinopathy and vascular complications; therefore, they are important ingredients in food supplements. Recently, there have been several reported cases of adulteration. Thus, to characterize the anthocyanin profile, and the relative percentages of these pigments, this study analyzed bilberry fruits from different countries by liquid chromatography coupled to a diode array detector and a mass spectrometer detector. A total of 15 anthocyanins were identified, and a fingerprint profile was used for the quality control of the target material. Fourteen bilberry extracts and 12 finished products labeled as bilberry from different marketing manufacturers were analyzed. Approximately 50% of these extracts differed significantly from the reference bilberry, suggesting possible adulteration. Approximately 60% of the extracts and 33% of the food supplements presented a lower anthocyanin content than declared. The adulterations were observed mainly with extracts of mulberry and chokeberry.

Gardana C, Ciappellano S, Marinoni L, Fachechi C, Simonetti P. Bilberry adulteration: identification and chemical profiling of anthocyanins by different analytical methods. *J Agric Food Chem.* 2014;62(45):10998-11004. doi:10.1021/jf504078v.
Penman KG, Halstead CW, Matthias A, et al. Bilberry adulteration using the food dye amaranth. *J Agric Food Chem.* 2006;54(19):7378-7382. doi:10.1021/jf061387d.
https://www.herbalgram.org/resources/herbalgram/issues/96/table-of-contents/hg96-feat-bilberry/

Economic Adulteration: Melamine

- You may remember in early 2000s, melamine in pet food added to boost protein content
- Has also been found in milk sold to humans

Share: Tweet Like 12 Share

Pet owners receive $12.4 million in melamine case

Legal, other expenses claim the rest in class-action settlement

October 12, 2011 (published)
By Edie Lau

Owners of animals affected by food contaminated with melamine received slightly more than half of the money in a $24-million fund established to settle legal claims stemming from the largest pet food recall in North America.

The balance of the fund went to lawyers' fees and expenses, claims administration and public notices.

In all, $12,357,277 was paid on 20,229 claims from the United States and Canada, according to information provided by the claims administrator, the accounting firm Heffler, Radetich & Saitta LLP in Philadelphia.

A total of $27,793,975.36 in claims was judged eligible for compensation. However, the collective payout was significantly less — amounting to 45 cents on the dollar. The claims administrator cited several factors for the reductions: Some claims had been reimbursed before the court action. Some exceeded the $900 limit for undocumented damages. Most significantly, most were reduced pro rata because the fund was not big enough to pay all approved claims in full.

Like most pet owners affected by the melamine contamination and pet food recall of 2007, Karl

https://www.dropbox.com/s/bymsugpetze68ef/Screen%20Shot%202021-02-15%20at%202.55.49%20PM.png?dl=0

Economic Adulteration: Ashwagandha

- 10 commercial products reviewed found concentrations of active constituent withaferin A per g of ashwagandha between 0.02 and 2.34 mg
- Study using HPLC-UV (high performance liquid chromatography with UV detection) to analyze ashwagandha leaf, aerial parts, and roots from 28 authenticated samples of ashwagandha (from growers) and 10 commercial extract samples
- 8/10 commercial samples labeled “root” contained markers for aerial parts
- No authenticated root samples contained flavonol glycosides, the marker of aerial parts.
- A US Lab (Alkemist Labs) reported to American Botanical Council that of 584 commercial raw material samples of ashwagandha sent to the lab, 20.4% were not composed solely of authentic root material.

Mundkinajeddu D, Sawant LP, Koshy R, et al. Development and validation of high-performance liquid chromatography method for simultaneous estimation of flavonoid glycosides in *Withania somnifera* aerial parts. *ISRN Analytical Chemistry*. 2014;2014:351547. doi:10.1155/2014/351547.
Sangwan RS, Chaurasiya ND, Misra LN, et al. Phytochemical variability in commercial herbal products and preparations of *Withania somnifera* (ashwagandha). *Curr Sci*. 2004;86(3):461-465.
Shalini R, Eapen JK, Deepa MS. Macroscopic evaluation of genuine and market samples of ashwagandha (Withania somnifera (Linn.) Dunal) in Kerala. *J Pharmacogn Phytochem*. 2017:6(6);2283-2288.

Massive Testing Challenges!

- In 2015, the NY attorney general filed a cease and desist against several retailers of dietary supplements (GNC, Target, Walgreens, and Walmart)
- Based upon DNA testing of finished products
- Is the DNA of herbs expected in finished extract products?
- Could it have been damaged in processing/extraction?
- Is the testing sophisticated enough?
- Do other ingredients in the finished product interfere with testing?

http://www.documentcloud.org/documents/1532311 -supplements.html#document/p1
https://www.nutraingredients-usa.com/Article/2015/09/11/The-NY-AG-s-herbal-probe-so-far-From-GNC-to-devil-s-claw#

Ingredient/Supply Chain Challenges

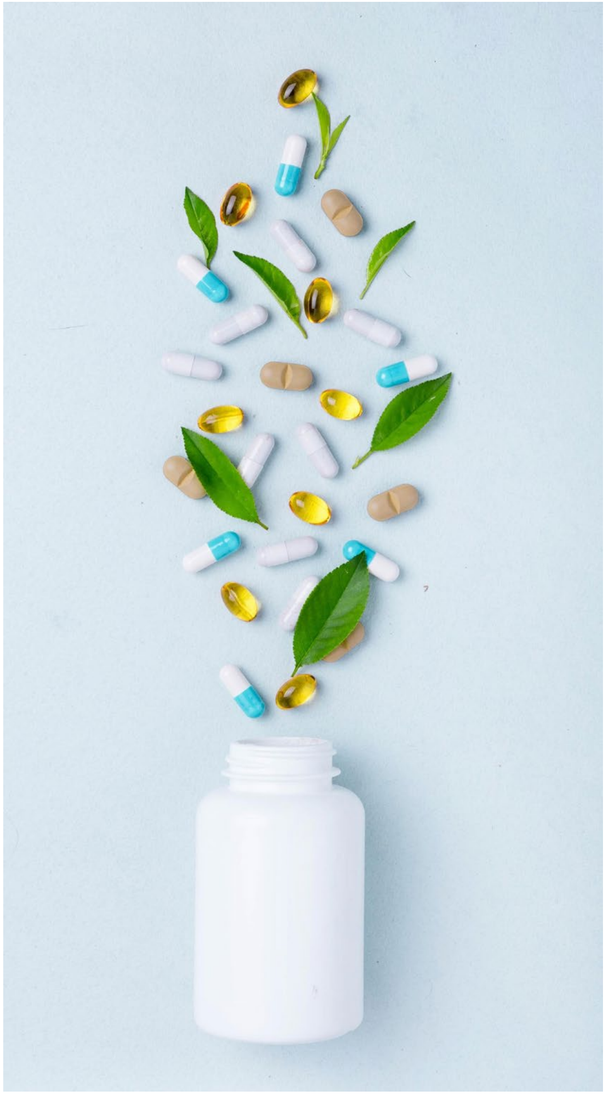
Ingredient and Supply Chain Verification

- Ingredient quality can decline
- The biggest area of true risk today

How does a brand qualify a new raw material supplier?

How often is testing performed once a supplier is qualified?

How often (and how) does requalification occur?



Improper Claims Requalifying Supplements as Drugs

FDA looks at the intended use of the product and ensures that it meets definition of dietary supplement:

- Cannot state or imply used to prevent, treat, mitigate, or cure illness (some are obvious)
- “Cure your cancer!” “Prevent diabetes!” “Fix your erectile dysfunction!”

Others may not be:

- Immune support product containing image of someone sneezing
- Testimonials on a website, social media, etc. not written by the company
- Citing research in literature that refers to research in a disease state

Easy for FDA since they never have to leave the office!

Assuring Quality
in the Production Process

Quality Is GOOD for a Brand!

- Reputation with customers
- Minimize waste
- Maximize productivity in the manufacturing facility
- Good quality is good for business, reducing…
  - Product complaints and internal investigations
  - Recalls
  - Adverse events
  - Litigation
  - Regulatory attention and associated fines/penalties

Supplement Manufacturing: Quality Elements

	Raw Material Ingredients	Manufacturing Processes	Finished Product
Scope of Quality Control	Raw material sourcing and specifications: identity, potency, purity	Current good manufacturing practices (cGMPs) per CFR part 111	Finished goods testing: potency, stability, contaminants
Methods	NIR, TLC, UV-Spec, HPLC, GC, mass spec, organoleptic, macro- and microscopic	QC unit, written SOPs, quality training, process controls, self-audits, plant sanitation, adverse event reporting	TLC, UV-Spec, HPLC, GC, mass spec, retained samples, lot number identification, real-time stability program
Considerations	• Supplier qualification • Specifications • Testing methodology • Testing frequency (every batch v. skip-lot)	• Process validation (cGMP compliance) • In-process sampling • Self-audits • Third party cGMP certification	• Testing methodology • Frequency (every batch v. skip-lot)

Standard Operating Procedures (SOPs)

Essential for good quality and a key part of cGMP guidelines, SOPs must include procedures for the following:

- Raw material receipt, handling, storage, and testing
- Manufacturing process (blending, cleaning, weighing and measuring, checks, etc.)
- Where quality team signoffs are required (“critical control points”) for each process
- Much more!

Key Quality Checks: Audits

Audits are a key step to ensure brands are operating according to their SOPs and ensure that SOPs are written in a clear way to ensure quality:

- Audits may be completed internally on a regular basis (preventive) and also in the case of an error (corrective)
- Review written procedures to ask, “Does this make sense?”
- Verify that those procedures are happening consistently
  - Employee training records
  - Batch records and supportive lab testing
  - Facility walk-through

Audit Overview: The Walkthrough

Evidence of sanitation throughout facility:

- Evidence and logs of daily inspection, floor, ceilings, air vents, cleaners used, etc.
- Evidence of frequent and routine equipment cleaning, maintenance, calibration
- Highly controlled production floor
  - Segregated areas for different processes
  - Signage clearly identifies each manufacturing phase occurring in an area
  - Protection against airborne contamination or adulteration in processing
  - Strict sanitation procedures

An Example of Transparency

One manufacturer offers 24-hour live streaming of their production facility!

COATING ROOM

THE DRYER

PACKAGING

Audit Overview: Other

- Evidence-based specifications established for all steps of production: ingredients, finished product, packaging, labeling
- Logs for frequent in-process checks
  - Double checking weighing, mixing, capsulation, tableting, packaging, cleaning, etc.
  - Usually, 15-minute intervals
- Quality sign-off on finished product, packaging, labels, lab testing
- Testing at various steps in production to verify quality along the way

Lab Testing

- Lab must be qualified to do the testing
- Testing is completed at both the raw material stage and the finished product stage
  - Identity
  - Potency/strength
  - Composition
  - Purity/contamination
    - Microbial contamination
    - Adulterants
    - Residues (i.e., solvents, pesticides/herbicides, etc.)

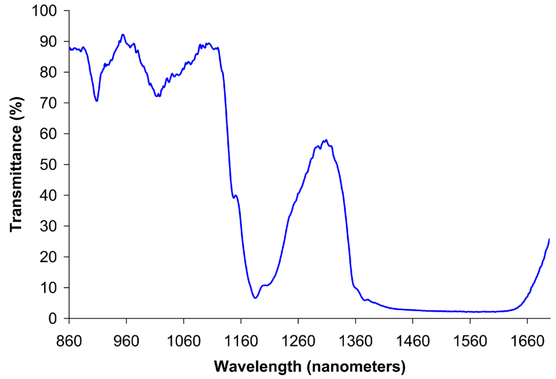
Lab Testing: Sample Methods

- Organoleptic
- Microscopy
- Mass Spectrometry
- Thin-Layer Chromatography (TLC)
- High-Performance Liquid Chromatography (HPLC)
- Fourier Transform Infrared (FTIR) or Near Infrared (NIR)
- DNA Sequencing or ELISA
- UV/VIS (UV spectroscopy)
- Others

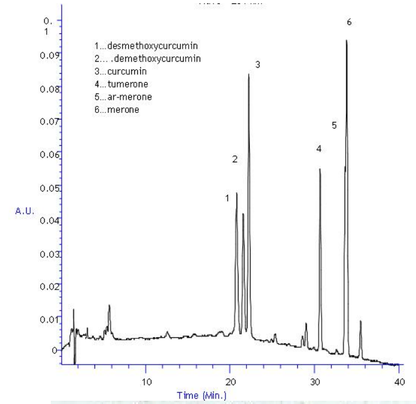
Manufacturing Hot Spots: Raw Materials

- Identity and potency testing (identity required for every receipt)
  - Organoleptic testing for powdered botanicals
  - NIR v. HPLC or TLC for botanical extracts and nutritional compounds
- **NIR** = NIR spectroscopy is the measurement of the wavelength and intensity of the absorption of near-infrared light by a sample
- **HPLC** = High-performance liquid chromatography is a form of liquid chromatography used to separate compounds that are dissolved in solution; used to separate, identify, and quantitate the compounds present in any sample that can be dissolved in a liquid
- **TLC** = Thin-layer chromatography is the only chromatographic method offering the option of presenting the result as an image and the only technique in which all the components of the sample are included in the chromatogram

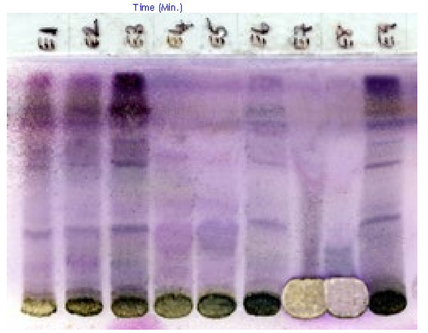
NIR



HPLC



TLC



Examples of Identity/Potency Challenges

Ingredient	Common Adulterants	Primary Analytical Method of Choice	Methods That Are Not Acceptable	Other Comments
Bilberry	Amaranth dye, black soy hull	USP HPLC method covers both identity and potency	FTIR/NIR for identity; UV spectrophotometric for potency	Just because the product may meet "total anthocyanin" specs does not mean the material is in fact bilberry if the right i.d. methods were not used
5-HTP	Unidentified	Specific HPLC methods with a primary standard	HPLC methods not traceable to an authentic primary standard	Market shortage of 5-HTP causes price increases, which leads to economically motivated adulteration (EMA)
Pomegranate	Ellagic acid	Specific HPLC methods to punicalagins	HPLC or UV for "total" ellagic acids	EMA

Industry Hot Spot: Supplier Qualification

- Ingredient suppliers are not bound by 21 CFR part 111 and are only subject to food cGMPs
- CRN SIDI working group is developing supplier qualification
  - Identity method that does not permit adulterated goods
  - Straightforward analyses to be able to confirm Certificate of Analysis (CoA)
  - Adequate CoA: contain place of origin, actual test results, specifications, methodologies, date, signature
- In order to qualify suppliers, CoAs must be confirmed
- Manufacturer should conduct a document audit, on-site audit, have a contract with each supplier and revalidate CoAs after initially verified
- Many manufacturers have long historical relationships with their suppliers that can substitute for initial qualification—ongoing validation of CoA is still necessary
- Suppliers who are brokers present significant quality challenges to the manufacturer

Industry Solution: Irreparable Ingredient SOP

- In 2018, the ABC- AHP-NCNPR Botanical Adulterants Prevention Program (BAPP) has issued draft “Best Practices Standard Operating Procedure (SOP) for Disposal/Destruction of Irreparably Defective Articles”
- Creates agreements whereby brands will destroy adulterated material
- Still in draft form but offers a great potential solution

Purity Hot Spots and Solutions

- Purity Testing (on Raw Material and/or Finished Product)
- Methodology (Limits of Detection), Specifications, Frequency
  - Heavy Metals
  - Herbicide/Fungicide/Pesticide Residues (Botanicals)
  - Chemical Solvent Residues
  - Melamine

Heavy Metals

- Includes lead (Pb), mercury (Hg), cadmium (Cd), arsenic (As), and chromium (Cr)
- DSHEA does not provide a specific list of heavy metal contaminants that could potentially adulterate a dietary supplement
  - Manufacturers determine what, if any, heavy metal specifications are appropriate under cGMP for their ingredients and finished products, and what heavy metal tests are needed, whether to meet established specifications
- Heavy metals are naturally occurring components of the earth's crust that are, as a rule, neither created nor destroyed, but are simply redistributed
- Each of the heavy metals can be absorbed into many plants as they grow, and some plants have been reported to accumulate specific metals (e.g., *Hypericum spp*. and cadmium)

American Herbal Products Association, Heavy Metals: Analysis and Limits in Herbal Dietary Supplements, Dec. 2009

Heavy Metals: Specifications

Specifications are determined by daily dose of the supplement.

	Arsenic (inorganic)	Cadmium	Lead	Methylmercury
Limit (µg/day)	10	4.1	10	2.0

Serving size in relation to presence of heavy metals

	Limit (µg)	Maximum concentration (ppm) at highest labeled daily consumption rate										
		.25g	.5g	1g	2g	2.5g	3g	4g	5g	6g	8g	10g
Arsenic (inorganic)	10	<40	<20	<10	<5.0	<4.0	<3.0	<2.5	<2.0	<1.7	<1.2	<1.0
Cadmium	4.1	<16	<8.2	<4.1	<2.0	<1.6	<1.3	<1.0	<0.82	<0.68	<0.51	<0.41
Lead	10	<40	<20	<10	<5.0	<4.0	<3.0	<2.5	<2.0	<1.7	<1.2	<1.0
Methylmercury	2.0	<8.0	<4.0	<2.0	<1.0	<0.80	<0.67	<0.50	<0.40	<0.33	<0.25	<0.20

American Herbal Products Association, Heavy Metals: Analysis and Limits in Herbal Dietary Supplements, Dec. 2009

Heavy Metals: Analytical Methodology

- Colorimetric analytical methods (**USP <231>**) have been in use for over 100 years and are based on measuring color changes of solutions that arise from specific chemical interactions
  - The current test creates a chemical reaction that is compared with a standard prepared from stock lead nitrate and relies on the ability of lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum to react with thioacetamide-glycerin base TS at a pH of 3.5 to produce a color that is then compared with the standard preparation
- There are disadvantages:
  - The detection limit for colorimetric methods is in the 10–20 ppm range
  - All the responding metals, including some beneficial elements such as copper, molybdenum, tin, and silver are also measured as lead equivalents
  - The test does not measure mercury
- USP recognizes the limits in USP 231 and has been very active in updating the methodology

American Herbal Products Association, Heavy Metals: Analysis and Limits in Herbal Dietary Supplements, Dec. 2009

Heavy Metals: Analytical Methodology

Atomic Absorbance Spectroscopy (Gas Furnace AA)

- Older technique that relies upon the electrochemical properties of metals that allow them to absorb energy from light of specific wavelengths

Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES)

- Uses argon inductively coupled plasma maintained by the interaction of a radio frequency field and ionized argon gas to excite atoms to unstable energy configurations while excess atomic energy is released as emitted light when the atoms return to more stable configurations—the wavelengths of the energy released are specific to the elements in the sample

Inductively Coupled Plasma-Mass Spectroscopy (ICP-MS)

- Similar to ICP-AES but the atomic ions produced by the argon plasma are directed into a mass spectrometer (MS) that separates the ions introduced from the ICP according to their mass-to-charge ratio

It is possible that with widespread implementation of better methodology, certain ingredients that are ingrained in the dietary supplement supply chain would no longer be available.

American Herbal Products Association, Heavy Metals: Analysis and Limits in Herbal Dietary Supplements, Dec. 2009

Heavy Metals: Analytical Methodology

Detection Limit, parts per billion (ppb)

	GFAAS	ICP-AES [ideal for intended minerals]	ICP-MS [ideal for heavy metal contaminant metals]
Arsenic	1	20	<0.05
Cadmium	0.002	0.1	<0.05
Lead	0.5	1	<0.05
Mercury	0.6	1	<0.05

American Herbal Products Association, Heavy Metals: Analysis and Limits in Herbal Dietary Supplements, Dec. 2009

Hot Spot: Herbicides/Pesticides

- The *Pesticide Analytical Manual* (PAM) is published by the FDA as a repository of the analytical methods used in FDA laboratories to examine food for pesticide residues for regulatory purposes (40 CFR 180.101)
- Many manufacturers do not routinely test for herbicides/pesticides
  - Minimally at-risk products should be tested (i.e., non-organic botanical materials)
  - Industry alerts should be tested for
    - Quintozene (Korean ginseng)
    - Aldicarb (ginger root)

Herbicides/Pesticides

- Pesticide screens
  - Some European labs looking at over 800 pesticides
  - FDA looking at ~400 for the future
- Three major classes of pesticides
  - Chlorinated organic pesticides
  - Organophosphates
  - Pyrethroids

- Articles of botanical origin: USP <561> limits range from 0.02 ppm to 4 ppm
- Pesticide testing done using HRGC-ECD with HRGC-MS/MS confirmation
- Also, newer interest in glyphosate testing

Hot Spot: Solvents

- Many manufacturers do not routinely test for solvents
  - Botanical extracts
  - Certain nutraceuticals
  - Fish oil: polychlorinated biphenyl (PCB) and dioxins
- Chemical solvent residue Class I, II, III (when organic solvents are used)
- Methodology per USP <467> GC

Hot Spot: Melamine

- Melamine is non-toxic, but in the presence of cyanuric acid, it associates to form melamine-cyanuric acid complex that can accumulate in the body and cause kidney failure
- Melamine adulteration: added to starting materials to boost their apparent protein content
- At-risk materials are those derived from milk or animal products or those that contain more than 2.5% nitrogen by weight
- HPLC with UV detection determines melamine down to 2.5 ppm (FDA recommended limit)

Melamine: At-Risk Materials

Adenine (USP)
Albumin (IID)
Ammonium salts
Calcium pantothenate(USP)
Caseinate or sodium caseinate (IID)
Chorophyllin copper complex sodium (USP)
Colloidal oatmeal (USP)
Copovidone (USP/NF)
Crospovidone (USP/NF)
Dihydroxyaluminum aminoacetate (USP)
Gelatin (IID)
Glugan (USP)
Guar gum (USP.NF)
Hyalurinidase (USP)
Imidurea (USP/NF)
Amino Acids derived from casein protein by hydrolysates
Lactose (USP/NF, IID)
Melphalan (USP)
Povidone (USP/NF)
Povidone-Iodine (USP)
Protamine sulfate (USP)
Protein hydrolysate powder for injection (USP)
Taurine (USP)
Thioguanine (USP)
Urea (USP)
Wheat bran (USP)
Zein (USP/NF)

Guidance for Industry: Pharmaceutical Components at Risk for Melamine Contamination (August 2009). www.fda.gov

Validating a CoA (Certificate of Analysis)

- Ingredient suppliers will provide a Certificate of Analysis, stating the product conforms to specifications
- How does a brand test against this to confirm?

TRUST BUT VERIFY

Hot Spot: Testing Frequency

- Supplier and Certificate of Analysis qualification justify skip-lot testing
- How often is sufficient?
  - No guidelines and per 21 CFR part 111, any frequency satisfies the requirements
  - Emerson Quality Program requires…
    - Analytical testing be completed at a justified frequency with written rationale for EQP Partners
    - On at least every 5th batch/lot, or if less than 5 lots, at least once annually for EQP Silver Partners
    - On every lot for EQP Gold partners

Hot Spot: Finished-Product Stability

- Some suppliers do not do stability testing (not specifically required by 21 CFR part 111)
- Some suppliers do accelerated stability testing only
  - Accelerated stability assesses the shelf life of a product, but the conditions of storage are harsher (i.e., higher temperature and increased humidity)
  - This provides an estimated shelf life of the product in a shorter time period than “real time” stability (e.g., a 6-month accelerated stability trial may support a 12-month shelf life)
    - However, the correlation has not been validated for most natural products
- Real-time stability tests for potency and microbiological contamination typically every 3–6 months for the duration of the shelf-life or 3 years (typically)
  - Multi-ingredient products may be tested for potency using several marker compounds
    - The most unstable and/or the most testable

Troublesome Ingredients: Concerns and Solutions

Ingredient	Quality Concerns	Quality Solutions
Probiotics	Misidentified bacterial species; inadvertent inclusion of pathogenic bacteria, inclusion of non-viable strains, subpotent products	Bacterial identification based upon DNA fingerprinting; finished product potency with cell enumeration studies and microbiologica contaminant testing; strain-specific human viability data
CoQ10	Adulteration by idebenone substitution; oxidation of ubiquinol into inactive form	ID and potency testing for all-trans natural form of CoQ10 per USP monograph; testing for adulterants against idebenone reference standard; use of branded, stabilized ubiquinol to prevent oxidation
Omega 3	Contamination with excessive levels of PCB, anisidine, and dioxins; Oxidative rancidity (peroxide, anisidine: used to calculate totox value); excessive heavy metals (Hg); EPA ar DHA potency	Low heat, chemical-free extraction process; heavy-metal testing using ICP-MS or AA methodology; full peroxide, PCB, dioxin, anisidine screening; finished-product potency testing using GOED GC methodology
Chondroitin sulfate	One of the most commonly adulterated ingredients yielding a subpotent final product and containing excessive lead	AOAC Enzymatic digest HPLC testing methodology for identity and potency; heavy-metal testing using ICP-MS or AA methodology

What Drives Quality Within a Brand?

- Ethics: a desire and intent to do good
- Knowledge: understanding of…
  - FDA regulations
  - Ongoing changes in the industry
  - Scientific and clinical best practices
  - Their own SOPs (standard operating procedures)
- Investment
  - The spending required to manufacture and test with quality in mind
  - Equipment, experienced personnel, facility, lab testing, ingredient costs

We Appreciate Your Time!

Any Questions?

Thank You!

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