USP Dietary Supplements Stakeholder Forum
Wednesday, June 1, 2016

USP Tools for the Prevention of Adulteration

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Scientific Liaison

Adulteration and its Detection as Old as Trade

A

TREATISE

ON

ADULTERATIONS OF FOOD,

AND CULINARY POISONS.

EXHIBITING

The Fraudulent Sophistications of

BREAD, BEER, WINE, SPIRITOUS LIQUORS, TEA, COFFEE, CREAM, CONFECTIONERY, VINEGAR, MUSTARD, PEPPER, CHEESE, OLIVE OIL, PICKLES,

AND OTHER ARTICLES EMPLOYED IN DOMESTIC ECONOMY.

AND

METHODS OF DETECTING THEM.

By Frederick Accum,

OPERATIVE CHEMIST, AND MEMBER OF THE PRINCIPAL ACADEMIES AND SOCIETIES OF ARTS AND SCIENCES IN EUROPE.

Philadelphia:

PRINTED AND PUBLISHED BY AB'M SMALL.

1820.

1820

TSIOLOGY;

A DISCOURSE ON TEA.

BEING

AN ACCOUNT OF THAT EXOTIC;

BOTANICAL, CHYMICAL, COMMERCIAL, & MEDICAL,

WITH

NOTICES OF ITS ADULTERATION,

THE MEANS OF DETECTION.

Tea Making,

WITH A BRIEF HISTORY OF

THE EAST INDIA COMPANY,

&c. &c.

BY A TEA DEALER. [illegible]

Lotia olim—necessaria nunc.

IN ONE VOL.

THIRD EDITION.

LONDON:

PUBLISHED BY WM. WALKER, LEATHER-SELLER'S BUILDINGS, LONDON WALL; AND MAY BE HAD OF ALL OTHER BOOKSELLERS.

1827.

Typical Modes of Dietary Ingredient Adulteration

- Species substitution – intentional and unintentional (*e.g.*, Chinese-grown *Actaeae* spp. for the American Black Cohosh, *Actaea racemosa*; cheaper berries for more expensive, *e.g.*, blueberry for bilberry; or cheaper oils for more expensive ones, *e.g.*, fish for krill; different animal sources of chondrotin sulfate)
- Removal/depletion of native plant components (*e.g.*, essential oil from cinnamon)
- Boosting of nonspecific assay values (*e.g.*, synthetic dyes added to berries, hexametaphosphate in chondroitin sulfate), or addition of specific chemical markers (rutin and quercetin to *Ginkgo biloba*, synthetic salicin to willow bark, synthetic caffeine to guarana)
- Dilution – addition of water, silica, neutral fillers (e.g., starch)
- Functional spiking – addition of undeclared components conferring specific functional properties otherwise absent (preservatives and antimicrobials in grapefruit seed extract; sildenafil in *T. terrestris*)

USP Resources

- General Chapters
- USP Authentic Reference Materials
- Individual Dietary Ingredient and Dietary Supplement Monographs
- USP Adulterants Database

Essential General Chapters for Addressing Adulteration

- Non-Specific Adulteration:
  - Foreign Organic Matter, Total Ash, Acid-Insoluble Ash <561>
  - Excessive Water (e.g., Chondroitin Sulfate) <731>
  - Excessive Content of Residual Solvents <467>
  - Presence of Undeclared Fillers (*e.g.*, starch <561>)
- Elemental Impurities <561>, <2232>
- Pesticide Residue Analysis <561>
- Excessive bioburden or prohibited microorganisms <2021>,<2022>

Essential General Chapters for Addressing Adulteration, *cont.*

- Macroscopic and microscopic procedures <563>
- DNA-Based Techniques <563>
  - DNA Barcoding
  - Sanger Sequencing
- Detection of Irradiated Dietary Supplements <2250>
- Adulteration of Dietary Supplements with Drugs and Drug Analogs <2251>

USP Authenticated Reference Materials

- Authentic Chemical Compounds:
  - Plant components and markers (e.g., rutin, quercetin)
  - Chemically and stereochemically pure vitamins, amino acids
- Authentic Reference Materials – Botanical and Nonbotanical
  - USP Powdered Asian Ginseng Extract
  - USP Powdered Red Clover Extract
  - USP Fish Oil
- Impurity and Contaminant Standards:
  - Aflatoxins
  - Residual solvents and their mixtures
  - Specific impurities (e.g., L-Tyrosine for *N*-Acetyl-L-Tyrosine)
  - Increasingly, pharmaceutical API

Monograph Approach to Analysis

- USP Monographs should be utilized in their entirety: individual tests cannot guarantee correct identification of the dietary ingredient or supplement article.
- It may be possible to "trick" an individual test, while it is virtually impossible – or economically (!) unfeasible – to obviate a battery of orthogonal tests. USP monographs commonly include:
  - 1 or 2 identification tests (qualitative)
  - 1 or 2 composition tests (quantitative)
  - Specific Tests: botanical characteristics (macroscopic and microscopic), loss on drying, limit tests (e.g., sorbitol and sucrose in Cranberry Liquid Preparation, rutin and quercetin in Ginkgo Extract), specific rotation, refractive index, *etc*.
  - Contaminants (elemental, microbial, pesticides)

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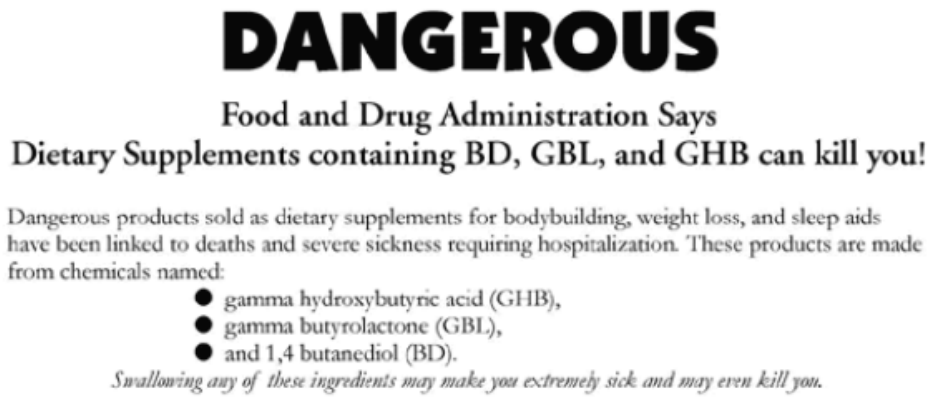
Products Marketed as Dietary Supplements



DANGEROUS

Food and Drug Administration Says
Dietary Supplements containing BD, GBL, and GHB can kill you!

Dangerous products sold as dietary supplements for bodybuilding, weight loss, and sleep aids have been linked to deaths and severe sickness requiring hospitalization. These products are made from chemicals named:

- gamma hydroxybutyric acid (GHB),
- gamma butyrolactone (GBL),
- and 1,4 butanediol (BD).

Swallowing any of these ingredients may make you extremely sick and may even kill you.

Adulteration Paradigm


DIRECTIONS: Take 1-2 capsules 40 minutes before an intimate encounter.
The effects of Arize may last up to 4 days.

Supplement Facts

Serving Size: 1-2 capsules
Servings Per Container: 5

Amount Per Capsule

Arize Men's Sexual Performance Proprietary Blend **500mg***

Muira Puama (Ptychopetalum), Rhodiola Rosea Root Extract (standardized to 3% rosavins and 1% saldrosides), Korean Red (Asian) Ginseng Root Extract (panax ginseng) Standardized to 10% ginosides, Gingko Biloba Leaf Extract (Standardized to 24% flavone glycosides and 6% terpene lactones), Tongkat Ali (Eurycoma Longifolia) Root Extract (200:1)

* Daily Value Not Established

OTHER INGREDIENTS: Vegetable cellulose capsule

Adulteration Paradigm, *cont.*

Analytical Challenges for Products Marketed as Dietary Supplements:

1. The nature of the analyte is not known in advance. Furthermore, it is not known whether there is an adulterant or not; the number of adulterants, or even which therapeutic category the adulterants may belong to. The analyte may not have been even encountered previously.

2. There is no prior knowledge of the adulterant amount. However, as follows from surveying numerous adulterated samples, adulterants are generally present in the pharmacologically meaningful dose. With ED drugs, the content is far from trace; if present, the adulterants are in significant, frequently excessive amounts.

3. There are no usable data about the dietary supplement matrix surrounding the adulterant. Analyst should be prepared for working with the placebo specifically formulated to compromise and disrupt analysis.

Adulteration Paradigm, *cont.*

4. Technically, everything may change from one “production” run to the next: the nature of the adulterant, the number of adulterants, the amount(s), the matrix, or even presence / absence of it. Everything is in flux, and adulterators are intent on keeping it changing (within reason).

5. Extreme differences in content between production “lots”. Also, significant disparity may exist between individual dosage units within a single production lot, even a single pack.

Dose-to-dose variations with single packages of counterfeit medicines

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USP General Chapter <2251>

General Chapter <2251> – Title History

- Intentional Adulteration of Dietary Supplements with Drugs (July 2013 – Jan 2014)
- Adulteration of Dietary Supplements with Drugs and Drug Analogs (January 2014 – May 31, 2016)
- Screening for Undeclared Drugs and Drug Analogues – Official June 1, 2016

USP Adulterants Database

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U.S. Department of Health & Human Services

a A A

FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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Tainted_Supplements_CDER

FDA Home › Tainted_Supplements_CDER

FDA's Medication Health Fraud Page

Disclaimer

This list only includes a small fraction of the potentially hazardous products with hidden ingredients marketed to consumers on the internet and in retail establishments. FDA is unable to test and identify all products marketed as dietary supplements on the market that have potentially harmful hidden ingredients. Even if a product is not included in this list, consumers should exercise caution before using certain products. To learn more about how to reduce your risk of encountering a product marketed as a dietary supplement with a hidden ingredient please visit FDA's Medication Health Fraud webpage linked above.

Click on this link to download all data from the selected searchable database in Excel format. If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players .

Search Criteria

Show Items | Reset

Sort by: Date DESC | Go | Reset

No. of Records Found: 721

Date	Product Name	Company	Hidden Ingredient	Product Category	Lot
05/06/2016	Step 2	Various Distributors	sibutramine	Weight Loss	N/A
04/26/2016	Black Gold X Advanced	Various Distributors	sibutramine	Weight Loss	N/A
04/26/2016	3rd Degree	Various Distributors	sibutramine	Weight Loss	N/A
04/26/2016	Black Label X	Various Distributors	sildenafil	Sexual Enhancement	N/A
03/29/2016	Propell Platinum	Various Distributors	sibutramine	Weight Loss	N/A

Overview of the General Chapter <2251>

- This focus of the chapter is on products marketed as dietary supplements to which pharmaceutically active compounds have been extraneously added to elicit a pharmacological response.
- Adulteration of dietary ingredients with other ingredients, substitution of a cheaper component for a more valuable one, or adulteration directed at inflating the assay value (e.g., amaranth dye in cranberry, or alginate in chondroitin sulfate), and other modes of EMA are outside the scope of this chapter.
- The purpose of the chapter is to point out the existing analytical resources, inform the analyst and the logic of the analysis, suggest a variety of methodologies; in other words, equip the analyst for conducting thoughtful independent work.
- What this chapter is not: a prescribed rigid set of instructions that must be precisely followed to declare the product “adulteration-free as defined by USP.”

Overview of the General Chapter <2251>

- The chapter currently addresses only one segment of adulteration: **Sexual Enhancement** products with PDE5 Inhibitors. Weight Loss and Sports Performance Enhancement products will be added later.
- Appendix A of the chapter details six analytical methods**:**
  - LC-UV
  - LC-MS^n
  - NMR
  - HPTLC – visual, UV densitometry, MS
  - API-MS (DART)
  - Bioassay
- Two informational tables: 64 known adulterants, chromatographic data for 34 compounds, mass-spectral data with fragmentation, chemical structures.
- UV spectra acquired under experimental conditions specified in the chapter.

PF 41(3) (May 2015), USP 39 S1 (Feb 2016), RB (June 1, 2016), Official Aug 2016

USP Adulterants Database

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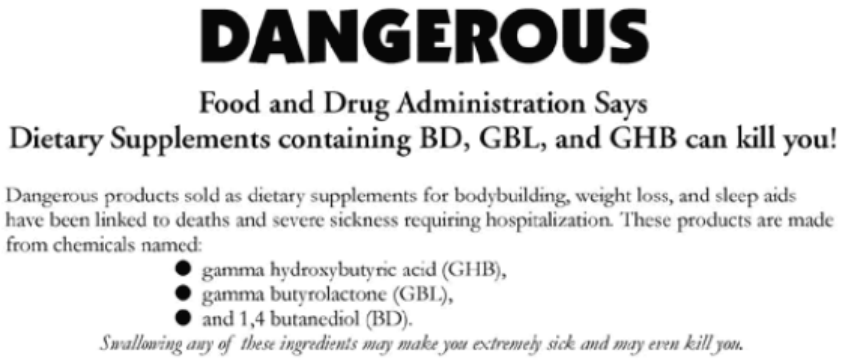
USP Adulterants Database



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Adulterants Database

Welcome, Anton
YOUR ACCOUNT

Home | Search Reports | Search Substances | Submit Reports | Administration

Welcome to the USP Adulterants Database

View | Edit

Dietary supplements, essential to maintaining health and well-being for millions, are being increasingly utilized in fraudulent schemes where rare and expensive ingredients are substituted with substandard and inefficient ones, and synthetic pharmaceutical components are clandestinely added to the formulations without declaration.

USP has assembled reports of dietary supplement adulteration into the USP Adulterants Database, which is intended as a cumulative resource to the laboratory analysts, enforcement agencies and consumers worldwide by raising awareness of ongoing adulteration practices. USP General Chapter <2251>, Screening for Undeclared Drugs and Drug Analogues, is another valuable resource focusing on modern analytical screening methodologies.

Currently developed as a three-component entity:

1. Finished Product Adulteration – focuses on screening methods for drugs and drug-like compounds in finished dosage forms. Will aggregate information from publicly available resources (*e.g.,* FDA, Health Canada, TGA, HSA), draw on both peer-reviewed publications and media reports. Similar to the USP Food Fraud Database.

2. Dietary Ingredient Adulteration – typical adulteration modes involve substitution, component removal, and attempts to trick the analytical methods to boost the assay value. Typical examples: chondroitin sulfate, cranberry, etc.

3. Adulterant Analytical Data – compilation of chromatographic, spectroscopic and other adulterant characterization data which would enable the users to utilize and exchange analytical information. Creation of instrumental libraries (LC-UV, NMR, but particularly, LC-MS/MS) could be the most desirable feature to practicing chemists.

1. Finished Product Adulteration:

a. 1006 references from peer-reviewed literature, media reports. The included articles are read by a human, and thoroughly indexed.

b. 1800 unique pharmaceutical adulterants – extensively indexed, with analogues, synonyms, brand and trade names, chemical attributes, unique identifiers: CAS, UNII, KEGG, InChi, ATC, PubChem – all linking to external resources with plethora of additional information about the adulterants, means of their detection, links within the database to the scientific literature.

c. 1473 records derived from enforcement reports (FDA, TGA, HSA, Health Canada, etc.), recalls, public notifications. Includes expanded recall information: recalling company, manufacturing company, distribution company, product UPC codes – whenever available.

2. Dietary Ingredient Adulteration:

a. About 180 peer-reviewed papers.

b. References to existing Internet resources, e.g., Botanical Adulterants Program (ABC), Known Adulterants (AHPA), etc.

c. Ingredient Information: Name, Latin binomial, Plant part, Synonyms, Taxonomic resources (The Plant List, ITIS, CAS, UNII), availability of USP monographs and reference standards, links.

d. Adulterant Information: same as above, plus: functionality (e.g., dye, preservative), chemical data for molecular entities.

3. Adulterant Analytical Data:

a. Assembling data from existing resources – e.g., compiling adulterant analytical "data packets". Currently, over 300 data packets are available for common finished product adulterants.

b. Partnerships with data generators: individual analytical labs, government and enforcement chemists, independent research institutes and agencies, specialized academic institutions, and reference material manufacturers.

c. Joining forces and prospective data exchange and other collaborative initiatives with existing similar databases (e.g., SWGDRUG, ForensicDB, Designer Drugs Online), analytical instrumentation manufacturers.

d. Design of USP own LC-MS/MS instrumental libraries.

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In memoriam

Mark Roman, Ph.D.
1968 - 2014

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Discussions

Thank You