

USP Open Forum

Impurities and Contaminants

in Dietary Ingredients and Dietary Supplements

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Overview of <2760> Informational General Chapter: Impurities and Contaminants in Dietary Ingredients and Dietary Supplements

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- ▶ Scope of General Chapter
- ▶ Impurities
 - Types of Impurities
 - Control of Impurities
 - Analytical procedures for impurities
 - Setting Acceptance criteria for Impurities
- ▶ Contaminants
 - Elemental contaminants
 - Toxins
 - Pesticides residue
 - Dioxins, Furans and PCBs
 - Polycyclic Aromatic Hydrocarbons (PAH)
- ▶ Risk analysis considerations

Scope of General Chapter



- ▶ Informational chapter only – aid to help industry comply with GMP requirements
- ▶ Provides an overview of the types of impurities and contaminants that are commonly found in dietary ingredients and dietary supplements
- ▶ Includes guidance on methods for identification, quantification and control of impurities and contaminants in dietary ingredients and supplements.
- ▶ This chapter only covers dietary supplements containing dietary ingredients as defined by FDA

- ▶ Impurities are undesirable chemicals that are present in dietary ingredients and supplements arising from normal manufacturing
- ▶ They are not chemicals accidentally or maliciously introduced.
- ▶ Impurities have no health benefit and are potentially harmful.
- ▶ Characterization and quantitation of impurities can help ensure the robustness of the manufacturing process and ensure production of quality dietary ingredients and supplements.

Types and Sources of Impurities



Organic Impurities

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

Inorganic Impurities

- Reagents, ligands and catalysts
- Starting materials
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

Residual Solvents

- **Class 1**- Solvents To Be Avoided
- **Class 2** - Solvents To Be Limited
- **Class 3** - Solvents with Low Toxic Potential

Types of Impurities



- ▶ **Organic impurities** can be present in raw materials or arise during the manufacturing process and/or storage of the dietary ingredients and supplements. They can be identified or unidentified, volatile or nonvolatile.
- ▶ **Inorganic impurities** can result from the manufacturing process. They are normally known and identified.
- ▶ **Residual solvents** are organic volatile chemicals that are used or produced in the manufacturing of dietary ingredients, or in the preparation of dietary supplement products.

Control of Impurities



- ▶ Manufacturers must employ measures for the proper control of unwanted impurities in dietary ingredients and dietary supplements.
- ▶ Manufacturers should consider the chemical characteristics and safety aspects of impurities when they identify and classify impurities in a dietary ingredient or dietary supplement.
- ▶ Acceptance levels of common impurities are set by specifications within a monograph to cover both organic and inorganic impurities.
- ▶ Impurities in a monograph are covered under the tests entitled- Impurities, organic impurities, Related Compounds or Specific tests
- ▶ No monograph can include all of the possible impurities; it is the responsibility of the manufacturer to evaluate impurities in their own products

- ▶ When there are changes to the chemistry, manufacturing, and/or controls of the dietary ingredient described in a monograph, they should be evaluated to determine if the differences affect the impurity profile listed in the existing monograph
- ▶ If the individual monograph does not include a procedure for quantifying an impurity or acceptance criterion for an observed impurity, the manufacturer is responsible for developing and validating analytical procedures and then establishing an appropriate acceptance criterion.

Analytical Procedures for Impurities



- ▶ Manufacturers shall validate or verify, as appropriate, analytical procedures and must demonstrate their suitability for the detection and quantitation of impurities.
- ▶ Analytical procedures for the detection and quantitation of impurities should be verified or validated as per <1225> *Validation of Compendial Procedures* and <1226> *Verification of Compendial Procedures*
- ▶ Instrumental methods are used for the characterization of organic impurities
- ▶ In cases of complex impurity profiles, it may not be feasible to resolve each of the impurities individually or to detect them and quantify them using a single analytical procedure. In such cases, manufacturers should consider alternative approaches such as the use of multiple analytical procedures to test for impurities.
- ▶ For chiral dietary ingredients, enantiomeric Purity by HPLC is the preferred test, as compared to optical rotation

- ▶ Inorganic impurities are usually monitored by tests such as those for *Residue on Ignition* <281>
- ▶ <467> *Residual Solvents*- provides procedures for the analysis of residual solvents or validated alternate methodology can be used
- ▶ The suitability of residual solvent procedures must be verified under actual conditions of use - <1467> *Residual Solvents- Verification of Compendial Procedures and Validation of Alternative Procedures*

Setting acceptance criteria for Impurities



- ▶ 21CFR Part 111- What specifications must you establish? You must establish 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
- ▶ Setting impurity limits in dietary ingredients and supplements should be based on chemistry, quality and safety concerns
- ▶ The basic tenet for setting limits is that levels of impurities in a dietary ingredient and supplement must be controlled throughout its development to ensure its safety and quality for use
- ▶ Manufacturers shall develop acceptance criteria for impurities that are justified by appropriate safety considerations and consistent with current applicable regulatory guidelines
- ▶ The most commonly used acceptance criteria are for each specified impurity, for any unspecified impurity, and for total impurities

Dietary Ingredients

- ▶ Each specified identified impurity
- ▶ Each specified unidentified impurity
- ▶ Any unspecified impurity
- ▶ Total impurities

Dietary Supplements

- ▶ Each specified identified degradation product
- ▶ Each specified unidentified degradation product
- ▶ Any unspecified degradation product
- ▶ Total degradation products

- ▶ Contaminants are substances that have not been intentionally added to dietary ingredients and supplements.
- ▶ These substances may be present from extraneous sources such as presence in the environment or through various stages of production, packaging, transport, or holding.
- ▶ Chemical contaminants pose a potential risk to the safety of dietary supplements, depending on the concentrations present and their respective toxicities.
- ▶ Prolonged and/or combined exposures to contaminants from dietary supplements may lead to deleterious effects on human health.
- ▶ Microbial contaminations are not covered in this chapter- <2021>, <2022> and <2023>

Elemental contaminants



- ▶ Elemental contaminants include catalysts and environmental contaminants that may be present in dietary ingredients and supplements.
- ▶ These contaminants may occur naturally, or be introduced inadvertently (e.g., by interactions with processing equipment and the container–closure system).
- ▶ Due to the ubiquitous nature of arsenic, cadmium, lead, and mercury, they (at the minimum) must be considered in the risk assessment.

Elemental contaminants (continued)



- ▶ *<233> Elemental Impurities-Procedures-* describes analytical procedures for the evaluation of the levels of the elemental impurities. The chapter also describes criteria for acceptable alternative procedures.
- ▶ *<561> Articles of Botanical origin-* Limits of Elemental contaminants
- ▶ *<2232> Elemental contaminants in dietary supplements-* provides limit to the amounts of elemental contaminants in finished dietary supplement dosage forms labeled as conforming to USP or NF standards. The chapter also provides speciation procedures- Inorganic arsenic and Methyl mercury

- ▶ Toxins- Mycotoxins, cyanotoxins and pyrrolizidine alkaloids (PA)
- ▶ **Mycotoxins** are structurally diverse secondary metabolites produced by filamentous fungi like *Aspergillus*, *Penicillium* and *Fusarium* species.
- ▶ These fungi can grow on plants both, in the field and during harvesting, transportation, processing and storage.
- ▶ The contamination of dietary ingredients may result in the occurrence of mycotoxins in botanical dietary supplements.
- ▶ Aflatoxins, ochratoxin A (OTA), zearalenone (ZEN), trichothecenes, fumonisins and citrinin are important mycotoxins due to their occurrence and well-established adverse effects on human.

- ▶ **Cyanotoxins**- produced by cyanobacteria
- ▶ Microcystins, β -methylamino- L-alanine (BMAA) are important cyanotoxins due to the adverse effects on human-hepatotoxic and neurotoxic.
- ▶ **Pyrrolizidine alkaloids (PA)**- Pyrrolizidine alkaloids are secondary metabolites produced by plants as a defense mechanism against insect herbivores
- ▶ PAs can be found as either a contaminant or naturally occurring in botanical ingredients, especially herbal products, thereby posing a potentially serious threat to human health
- ▶ <561> *Articles of botanical origin*- Aflatoxin test method
- ▶ Ph. Eur.- 2.8.22 *Determination of Ochratoxin A in herbal drugs*
- ▶ <1567> *Pyrrolizidine Alkaloids (PAs) As Contaminants*- PF 48(1)
- ▶ *Contaminant pyrrolizidine alkaloids (2.8.26)*- published in *Pharmeuropa* 32.1

Pesticides residues



- ▶ Pesticides are xenobiotics intended to kill other forms of life, including insects (insecticides), vegetation (herbicides) and small rodents (rodenticides).
- ▶ The occurrence of pesticide residues in dietary supplements is due to the presence of such compounds in dietary ingredients.
- ▶ Herbal supplements contain plant materials that are grown using conventional agricultural practices, including the application of pesticides during cultivation and/or storage.
- ▶ Dietary supplements based on fish, vegetable oils may also contain pesticides especially those of lipophilic nature- organochlorine pesticides are contaminant of marine ecosystem.
- ▶ Analysis of pesticides have many technical challenges due to complex matrix.
- ▶ Proper sample preparation methodology is needed to isolate and concentrate target compounds.
- ▶ <561> *Articles of Botanical origin*- Pesticide Residue Analysis- Limits and analytical method

Dioxins, Furans and PCBs



- ▶ Dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) are persistent organic pollutants.
- ▶ These compounds were intentionally produced and used with different applications in the past, such as lubricants, coatings, plasticizers or inks. PCB manufacture is prohibited but their release to environment still occurs from waste disposal.
- ▶ They are highly resistant which leads to their accumulation in the environment and subsequent entry into food chain.
- ▶ Human exposure to these toxic compounds result from consumption of dietary supplements of animal origin with high fat content, due to the high accumulation of these compounds in fatty tissues.
- ▶ The presence of dioxins, furans and PCBs are mainly reported from fish-oil based dietary supplements.
- ▶ Analytical method and limits- polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) - 1613 Current revision of the Environmental Protection Agency. PCBs - 1668 Current revision of the Environmental Protection Agency.

Polycyclic Aromatic Hydrocarbons (PAH)



- ▶ Polycyclic aromatic hydrocarbons (PAHs) are a large group of chemical contaminants, generally occurring in complex mixtures consisting of hundreds of compounds.
- ▶ They are produced by natural and anthropogenic processes, mainly by incomplete combustion of organic matter.
- ▶ PAH is found in food supplements that underwent improper processing (thermal treatment, improper drying process), or in which PAHs accumulated from the environment
- ▶ Commission Regulation (EU) No. 835/2011- high levels of PAHs have been found in some food supplements often containing botanical ingredients such as ginkgo, ginseng, green tea, spirulina, or bee products such as propolis.
- ▶ ΣPAH4 – benz[a] anthracene, benzo[a]pyrene, benzo[b]fluoranthene and chrysene.
- ▶ Method of analysis- pre-treatment of the sample, where the PAHs are extracted from the complex mixtures in which they are present, into a new matrix by liquid/liquid, solid-phase and/or ultrasonic extractions and measured using HPLC or GC with suitable detectors.

Risk analysis considerations



- ▶ **Risk** - an estimate of the probability and severity of the adverse health effects in exposed populations, consequential to hazards in dietary ingredients and supplements
- ▶ **Risk analysis** - risk assessment, risk management, and risk communication
- ▶ The best approach to protect the product from chemical contamination is to identify the hazards in the ingredients before they can affect the final product.
- ▶ It is not realistic to test every lot of ingredient for every contaminant, it is best to develop a testing program for your most risky ingredients.
- ▶ The extent of testing can be determined using a risk-based approach that takes into account the likelihood of contamination.
- ▶ Manufacturers should consider the presence of unexpected contaminants to determine compliance.
- ▶ Contaminants that are inherent in the nature of the material, as in the case of some naturally sourced materials (minerals), must be considered in the risk assessment.

Thank You



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