

USP <467> Residual
Solvents PF 43(2)
proposed inclusion of
Dietary Supplements

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Multiple
stakeholders;
one objective.



▶ International Pharmaceutical Excipients Council ◀
Collaborative solutions for excipient industry stakeholders

USP <467> Residual Solvents PF 43(2)

Proposed change:

Included language to clarify that these drug requirements are directly applicable to dietary supplements.

ICH Q3C Residual Solvents

- ▶ Introduction: “The objective of this guideline is to recommend acceptable amounts of residual solvents in **pharmaceuticals** for the safety of the patient.”
- ▶ Scope: “Residual solvents in drug substances, **excipients** and in drug products are with the scope of this guideline.”



Industry Response

IPEC-Americas, CRN, CHPA, IFAC

- ▶ Not appropriate to extend <467> to dietary supplements including dietary ingredients.
 - <467> was originally designed as a drug requirement derived from ICH Q3C which is not relevant to dietary supplements.
- ▶ In the U.S. dietary supplements, including dietary ingredients, are regulated as a category of foods not drugs.
 - ICH limits for drugs may not be appropriate for dietary supplements.
 - Use patterns & safety standards are different and must be taken into account when developing residual solvent limits for foods.
 - A separate approach should be taken to establish the applicability of residual solvent limits to dietary supplements.



USP Dietary Supplements Expert Committee Review of Industry Comments

- ▶ Based on USP's policies & General Notices there is no need to change this position because dietary supplements which have monographs in the USP or are covered by the USP Verification program were **always** required to meet these requirements.
- ▶ These requirements are safety based, not something that should be different between drugs and dietary supplements.
- ▶ USP isn't changing any requirements. Dietary supplements which do not claim to meet USP would not be required to meet <467> and USP understands that there is no legal requirement for this by FDA. This chapter would only apply to supplements that claim to meet USP.

Industry Perspective

- ▶ The dietary supplement industry, as a whole, did not think that <467> applied to them.
- ▶ Regardless of whether or not there were misunderstandings about USP's policies, USP should not apply <467> to dietary supplements without having a full interactive discussion with industry on this topic.
- ▶ Residual solvents limits are not a separate regulatory requirement for dietary supplements or their ingredients.
- ▶ USP and NF standards may not even include all the requirements which are legally necessary to be used as a food additive in dietary supplements.

Food Standards as Requirements

- ▶ “Dietary ingredient” is defined in DSHEA and must meet food requirements, e.g. the Food Chemicals Codex (FCC), 21 CFR or GRAS, not the USP-NF or the USP’s Dietary Supplement compendium.
- ▶ Food additive standards in the CODEX/GSFA (Global Standards for Food Additives) are critical to the dietary supplement.
 - FCC standards should be harmonized with CODEX/GSFA wherever possible and use these standards which are legally required for dietary supplements in many parts of the world instead of USP-NF monographs, which may not meet appropriate food additive regulatory requirements in the U.S. and abroad.
- ▶ USP should allow for the use of CODEX/GSFA standards for the food additives ingredients used in dietary supplements which make a USP claim or go through the USP Verification program since it is not appropriate to use USP or NF standards which were designed for drugs.

GMPs



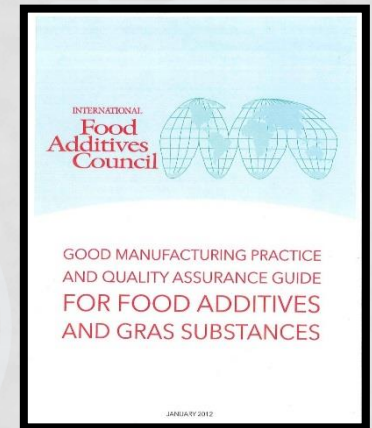
- ▶ Manufacture to appropriate GMPs is a requirement for stating compliance to an article in the USP or NF.
- ▶ Dietary supplement GMPs are defined by FDA in 21CFR 111.
 - For articles in the USP, GMP compliance should be based on ICH Q7 GMPs.
 - For articles in the NF, excipients should be manufactured in accordance with <1078> or other excipient GMP guidelines and standards.
- ▶ Food additives must meet ‘Food GMPs’, i.e. 21CFR117 and requirements in the FSMA (Food Safety Modernization Act).

FDA FOOD SAFETY
MODERNIZATION ACT

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USP Verification Program GMPs

- ▶ Excipient GMPs are not relevant nor appropriate for food additives and excipients often do not comply with FSMA.
- ▶ The International Food Additive Council's (IFAC) *Quality Systems, Food Safety and GMP Guide for Food Additives and GRAS Substances*, which is aligned with FDA's FSMA requirements, should be used when qualifying suppliers of food additives used in dietary supplements.
- ▶ USP should utilize the IFAC GMP guide in the USP Verification Program for food additives.



Industry's Recommendations

- ▶ USP should remove all references to dietary supplements in the proposed revision of <467>.
- ▶ Since ICH Q3C and <467>, which is based on ICH Q3C, were not intended for dietary supplements, further discussion is needed with industry stakeholder groups before extending this to dietary supplements and their ingredients.
- ▶ Industry understands that it may be appropriate to have limits on residual solvents in dietary supplements, but this topic should be discussed at length within the industry with USP.
 - Recommend the development of a separate General Chapter for Residual Solvents in Dietary Supplements much the same way as was done for Elemental Impurities in <2232>.



Thank You

USP Chapter <467> Residual Solvents



PF proposal is NOT intended to:



- ▶ Expand the applicability of <467> to articles not already covered
- ▶ Apply the requirements from ICH Q3C or other pharmaceutical standards to dietary supplements.

Residual Solvents in Dietary Supplements and Dietary Ingredients



- ▶ Processing procedures, such as extraction of plant parts and purification of isolated dietary ingredients, can result in contamination with residual solvents, which may pose a public health risk.
- ▶ Limits for residual solvents are made applicable through a combination of requirements in General Notices, General Chapters and individual monographs.

History of the proposal (PF 31(5) 2005)



- ▶ 467 Organic Volatile Impurities, USP 28 page 2322. It is proposed to change the chapter title to Residual Solvents and to delete the Other Analytical Procedures section (Methods I, IV, V, and VI). These proposals are consistent with revisions to individual monographs. The [Organic volatile impurities 467](#) requirement will be deleted from all USP, NF, and **Dietary Supplements** monographs that currently contain it, and a new requirement for [Residual solvents 467](#) will be added to all appropriate drug substance, excipient, drug product, and dietary supplement monographs. These individual monograph changes will appear in USP 29–NF 24, with a delayed implementation date of January 1, 2007.

Dietary supplements and Residual solvents



- ▶ The application of <467> *Residual Solvents* to all USP-NF official articles is a requirement articulated through the USP-NF General Notices 5.60.20 since its inception:

“All USP and NF articles are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. If solvents are used during production, they must be of suitable quality. In addition, the toxicity and residual level of each solvent shall be taken into consideration, and the solvents limited according to the principles defined and the requirements specified in Residual Solvents <467>, using the general methods presented therein or other suitable methods”
- ▶ The revised text in the chapter’s introduction clarifies the scope of applicability of the current requirements to all USP-NF official articles instrumented through General Notices.

Official Articles include Dietary ingredients and dietary supplements



- ▶ “2.20. *Official Articles*
- ▶ An *official article* is an article that is recognized in *USP* or *NF*. An article is deemed to be recognized and included in a compendium when a monograph for the article is published in the compendium and an official date is generally or specifically assigned to the monograph.
- ▶ *Official articles* include both *official substances* and *official products*. An *official substance* is a drug substance, excipient, **dietary ingredient**, other ingredient, or component of a finished device for which the monograph title includes no indication of the nature of the finished form.
- ▶ An *official product* is a drug product, **dietary supplement**, compounded preparation, or finished device for which a monograph is provided.”



- ▶ Chapter allows a risk based approach
- ▶ Presence of residual solvents in amounts above the MDE represent a risk to health
- ▶ Limits are based on the toxicological principles MDE
- ▶ Toxicity is characteristic of each residual solvent irrespective of the source or regulatory category
- ▶ Dietary supplements \neq Conventional Food



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AHPA prohibits use of class 1 solvents in herbal extracts

The American Herbal Products Association (AHPA) has amended its existing guidance policy on residual solvents in herbal extracts.

The American Herbal Products Association | Aug 05, 2011

- AHPA adopted ICH residual solvents guideline
- CRN cited USP standards to argue against Hexane listing to OEHHA in November 2017
- Chromadex citizen petition to FDA cited safety levels according to <467>
- SIDI document recommends control of Residual Solvents and cites <467>

Conclusions



- ▶ USP does not intend to expand the scope of this General Chapter to impose any new requirements on dietary supplements and dietary ingredients.
- ▶ The revision is intended to add clarity to the current applicability of these requirements to official articles, as currently stated in General Notices.
- ▶ Risk based approach in <467> is aligned with FSMA and is useful to DS industry