Residual Solvents: FDA/Regulatory Perspective

PDA/USP Residual Solvents Conference

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Outline

- Laws and regulations governing the compliance requirements of USP chapters
- Compliance Policy Guides pertaining to the compliance requirements of USP chapters
- Applicability
- Basis and Intent
- Specific requirements
Chapter II - Definitions:

- **201(g)(1)(A) -** The term “drug” means (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them.

- **201(j) -** The term “official compendium” means the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them.
Federal Food, Drug, and Cosmetic Act
Chapter V - Adulteration sections:
A drug or device shall be deemed to be adulterated--
501 (b) If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium. Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium, except that whenever tests or methods of assay have not been prescribed in such compendium, or such tests or methods of assay as are prescribed are, in the judgment of the Secretary, insufficient for the making of such determination, the Secretary shall bring such fact to the attention of the appropriate body charged with the revision of such compendium…
Federal Food, Drug, and Cosmetic Act

Chapter V - Adulteration sections:

A drug or device shall be deemed to be adulterated--

501 (a)(2)(B)

If it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. . . .
21 CFR 211.194 (a) (2) - A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, AOAC INTERNATIONAL, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.
Sub Chapter 420 - Compendial /Test Requirements

**Sec. 420.100** - Adulteration of Drugs Under Section 501(b) and 501(c) of the Act.

*Direct Reference Seizure Authority for Adulterated Drugs Under Section 501(b)*

(CPG 7132a.03)

Any official drug which, when tested by compendial methods, fails to conform to compendial standards for quality, strength, or purity, is adulterated unless the differences from such standards are plainly stated on the drug's label.

**Sec. 420.200** - Compendium Revisions and Deletions (CPG 7132.02)

All official articles shipped prior to the date that the current USP/NF became official should be in compliance with the official compendia in effect at the time of shipment.

**Sec. 420.300** - Changes in Compendial Specifications and NDA Supplements (CPG 7132c.04)

Any change in the compendial specifications for an NDA drug will not normally require the submission of an NDA supplement unless there is a relaxation of the acceptance criteria or deletion of a test.
Sec. 420.500 - Interference with Compendial Tests (CPG 7132a.01)

A compendial drug product containing an added substance which interferes with the compendial assay of the product would be adulterated under 501(b) of the Act.
Applicability of <467>

- Processes that use or produce residual solvents
- All Official Articles
  - May be used as guidance for non-official articles.
- Manufacturers of official excipients, official active pharmaceutical ingredients (API), and official drug products.

Note: For the purpose of this presentation whenever excipients, API or drug products are mentioned it refers to official excipients, official active pharmaceutical ingredients (API), and official drug products. Drug substance = API Official = Compendial
Basis and Intent of the Chapter

- Residual solvents do not provide therapeutic benefit
- Should be removed to the extent possible
- Residual solvents are classified in 3 main categories based on toxicity data
- Have some degree of assurance that drug products contain acceptable levels of residual solvents
- May exceed recommended levels but only in “exceptional circumstances”
- Harmonize with Guidance for Industry ICH Q3C Impurities: Residual Solvents
Specific Requirements

Class I Residual Solvents:

- Should be avoided in all drugs
- Their use should be justified
- Levels in drug products should be below the levels in Table 1
- Excipient, API, and drug product manufacturers are expected to identify and quantify using appropriately validated procedures
- Excipient and API manufacturers may report the levels to drug manufacturers. Drug product manufacturers are expected to test incoming components
Specific Requirements

Class II Residual Solvents:

- Should be limited in all drugs.
- Excipient and API manufacturers are expected to identify, quantify, and may report levels over Option 1 (Table 2) to drug product manufacturers. Drug product manufacturers are expected to test incoming components.
- Drug product manufacturers may use Option 1, Option 2, and the drug product manufacturing process to determine compliance with the levels in Table 2.
- Drug product manufacturers should take all necessary steps to reduce the levels to meet Table 2.
- Excipient, API, and drug product manufacturers are expected to identify and quantify using appropriately validated procedures.
Specific Requirements

Class III Residual Solvents:

- Deemed safe to use for all drugs
- Levels of 50mg/day (5000ppm or 0.5% under Option 1) are acceptable
- Excipient and API manufacturers are expected to identify, quantify, and may report levels over Option 1 to drug product manufacturers. Drug product manufacturers are expected to test incoming components
- Excipient, API, and drug product manufacturers are expected to identify and quantify levels over 50mg/day, 5000ppm, or 0.5% under Option 1 using appropriately validated procedures
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