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Inside the mind of the FDA

A Summary of Current & Future Implications of the

USP General Chapter <232>
&
ICH-Q3D Heavy Metal Guidelines

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What Does The FDA Want From **You** Now?

The USP revised general chapter <232> states:

"The concentration of elemental impurities in drug products, drug substances and excipients must be known, documented and made available upon request.

What does this require?

Test Everything

Every component, every process, every final product and their packaging for the presence of heavy metals.

Document Everything

Assess & document the existence of these metals at any level.

Develop Control Programs

To ensure compliance and consistency both for you and your suppliers.

FDA
U.S. Department of Health and Human Services
Food and Drug Administration

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What Does The FDA Want From **You** Now?

USP <232> goes on to state:

"When elemental impurities are known to be present, have been added, or have the potential for introduction, assurance of compliance to the specified levels is required."

Meaning: You must (at the very least) be in compliance with the limits set forth in Table 1

Further to that…

"The acceptable levels for these impurities depend upon the material's ultimate use. Therefore, drug product manufacturers must **determine the acceptable levels** of elemental impurities in the drug substance and excipients used to produce their products."

Meaning: This statement is a significant indicator regarding the expectations of the FDA as to how they want Drug Companies to control their suppliers not just their final drug products.

Meaning: The FDA wants drug companies to develop more stringent internal standards for their suppliers. Table 2 is to be considered a "suggested limit" and basis for discussion not a final requirement.

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Why is the FDA so concerned with Heavy Metals?

It's a Consumer Issue:

The average US citizen is becoming more aware of Arsenic (As), Lead (Pb), Cadmium (Cd) and Mercury (Hg) contamination highlighted by media exposure.

It's the FDA's Federal Mandate to "protect" Americans from exposure to toxic substances in the Food and Drug supply.

There is already a substantial grass-roots movement against heavy metals in vaccines, with momentum building through various consumer groups. Yet, the general public remains relatively unaware of the existence of heavy metals in the drug supply and drug supply chain. What will be the result of increased awareness?

What is the acceptable level of heavy metals in your child's drug?

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What is the FDA's Ultimate Agenda for Heavy Metals?

To enforce more stringent mandates on the Pharmaceutical industry that will either eliminate heavy metals in the drug supply or develop a body of scientific data acceptable to the consumer that identifies the levels reported to be deemed as "safe."

The FDA will adopt similar guidelines to ICH-Q3D that will require companies to:

- Develop toxicological data for each metal impurity.
- Establish Permissible Daily Exposure Limits (PDE's) for each metal of toxicological concern in every drug product.
- Fully disclose impurity levels and toxic affects to the public!

Is 5 ppm Cd and 30 ppm of Hg* acceptable levels of Impurities in your child's daily oral dose of drug?

* As per USP <232> (table 1.)

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How the FDA will Enforce these Mandates

1.) Over time

2.) Through You, the Pharmaceutical Companies

3.) Upon you through enforcement of cGMP

The FDA wants to strengthen cGMP requirements for drug manufacturers, and can use the USP <232> to support that initiative.

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How the FDA will Enforce these Mandates

FDA will ultimately require Drug Manufacturers to enforce these "themes" on the entire supply chain for each drug with:

- **More extensive testing throughout the entire manufacturing process and supply chain.**

- **Validation of results through the entire supply.**

- **The goal to drive the use of higher quality raw materials for themselves, API Manufacturers and Excipient Suppliers.**

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What Is Your Posture?

The FDA is only at the beginning phase of a multi-year incremental enforcement of these (and possibly additional) standards

Highest Purity Ethanol

Meets USP, ACS, FCC, EP, BP and JP Monographs.
Kosher and Sterile

Custom Solvent Blends

Clean/White Room
Batching Capabilities
From Kilo's to Metric Tons

Pharma Process Solvents

Meets / Exceeds USP <232>
EMA (EP) Ch. 5.2 and ICH-Q3D
Heavy Metal Requirements

Pharmco-Aaper: Your First Line of Defense!

FDA (USP) <232> & ICH-Q3D Heavy Metal Mandates

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Are you working to Reduce the Risk of Non-Compliance?

PHARMCO-AAPER Produces the **Highest Purity Ethanol in the World** with the **lowest levels of heavy metal impurities** of any process solvent. We have the data to prove it!

Each Lot of our World Grade Ethanol is **fully tested** for **ALL** heavy metal mandates along with many other (global) monographs.

We manufacture a full line of **Process Solvents** that are also **multi-compendia certified** and tested for all Heavy Metal Mandates: **FDA (USP) <232>**
EMA (EP) Ch. 5.2 and ICH-Q3D.