Workshop on Metals in Pharmaceuticals and Dietary Supplements

USP Headquarters
Rockville, Maryland
April 28-29, 2009

Final Summary Session

The content of this presentation reflects the ideas and suggestions of the participants at the Metal Impurities Workshop, April 28-29, 2009. These deliberations are advisory and are not binding in any way to the Council of Experts, its Expert Committees and Advisory Panels, or USP staff.

U.S. PHARMACOPEIA
The Standard of Quality℠

Workshop on Metals in Pharmaceuticals and Dietary Supplements

USP Headquarters
Rockville, Maryland
April 28-29, 2009

Final Summary: Limits

Moderator: Doug Templeton

U.S. PHARMACOPEIA
The Standard of Quality℠

Metals and Limits

What metals?

- As, Cd, Pb, Hg - consensus
- Sb, Cr(VI) - further evaluation
- Catalysts - Later stages if necessary
- “No safe limit for Pb” (?)
- Botanicals - individual elements (e.g., Cd)

Metals and Limits

What Limits?

- Separate limits from implementation.
- Data, data, data! Base on solid scientific toxicoloical data - a vast literature on As, Cd, Hg, Pb wrt. PDE, NOE, etc.
- Good data, safety data, education and rationales, transparency.
- Staged approach - soundest data first, standard population first.
- How much data do we need to generate??? Historical data in Pharmaceuticals maybe not very useful (due to limitations of methods used), but lots of toxicity data.

Thank You

Workshop on Metals in Pharmaceuticals and Dietary Supplements

USP Headquarters
Rockville, Maryland
April 28-29, 2009

Final Summary: Methodology

Moderator: Michael Wierer

U.S. PHARMACOPEIA
The Standard of Quality℠

Participant Feedback—Methodology

- Participants requested allowing further use of either specific wet chemical metal tests or and improved (sample preparation, sensitivity) version of the (231) test. However capabilities to be determined.
- ICP-MS or GF-AAS and cold vapor AAS were considered suitable for analyzing the “big 4”
- ICP-OES considered less suitable
- Allow flexibility in choice of any validated method or other approaches demonstrating compliance with the limits
- Some preference for performance based approach vs. referee methods

Participant Feedback—Methodology

- Sample preparation seems to be most crucial point
- Possible approaches
  - Dilute and shoot
  - Sample digestion by microwave digestion techniques
  - Validation/ verification needed
- Tests should be validated as limit tests
- Reference standards only to be established where they are not available from or traceable to NIST

Thank You

Workshop on Metals in Pharmaceuticals and Dietary Supplements

USP Headquarters
Rockville, Maryland
April 28-29, 2009

Final Summary: Risk Assessment and Implementation

Moderator: Scott Lyon

U.S. PHARMACOPEIA
The Standard of Quality℠

Metals Impurities Implementation Summary

General issues

- Implementation cannot be fully determined until limits and method are finalized.
- FDA guidance is a critical aspect to implementation issues
- A second *Stimuli* article is a recommendation to import ideas for methods and limits generated in this conference

Metals Impurities Implementation Summary

Material Sources

- Look at finished drug products differently than excipients (<467> approach)
- Obtaining information from suppliers may be difficult mainly natural source variation
- Focus on the big four elements
- Broadening list of elements beyond big four and EMEA metal catalysts is a possibility as an “above 1000” informational chapter
- Focus on “what is likely to be present” although this may be difficult to specifically define

Metals Impurities Implementation Summary

Manufacturer Responsibilities/Supply Chain

- For proprietary issues, supplier can work directly with the FDA
- Excipient manufacturers will need to generate more background data
- If regulatory burden is too high, suppliers may not supply the product

Metals Impurities Implementation Summary

Regulatory Considerations

- Evaluation of historical data and comparison to current data may guide regulators on long-term testing requirements
- Key questions:
  - Would regulators require individual filing updates for every drug, DMF, etc.?
  - What would be the extent and format of data required?
  - What is the expectation of suppliers to report and what is the extent of information required?
  - Will the new requirements be considered tightening of limits (i.e., annually reportable)

Metals Impurities Implementation Summary

Test Reduction

- This is a regulatory issue vs. a compendial issue
- Key issue is extent of routine testing required
- Will additional supplement require FDA buy-in

Metals Impurities Implementation Summary

Alternative Technologies

- Would the proposed method be considered a referee method?
- Would the <467> model be acceptable?
- How will Performance Based Methods be viewed by FDA?

Metals Impurities Implementation Summary

Phased Approach

- There may be issues for smaller non-global and non-IPEC firms
- Considering coordinating phased approach with ICH/PDG to assure consistent global implementation

Metals Impurities Implementation Summary

Implementation Time

- Obtain FDA's regulatory expectations first, then determine timeline
- Five-years after publishing, but more time may be necessary
- Adherence to timelines will improve the harmonization process (i.e., ICH)

Thank You

Workshop on Metals in Pharmaceuticals and Dietary Supplements

USP Headquarters
Rockville, Maryland
April 28-29, 2009

Overall Summary

Moderator: Matthew Borer

U.S. PHARMACOPEIA
The Standard of Quality℠

Original Problem Statement

- We are committed to advancing the current standards (<231>) so that widely agreed upon safe limits for key metal impurities are properly measured, thereby protecting the public health.
- **There has been significant debate about how to achieve this goal.**

Limits/Methods/Implementation

- We want to set limits for appropriate metal impurities
  - (of known toxicity, that are sufficiently likely to be present)
- We want analytical techniques that measure selected metal impurities at the limits that we set
- We want an implementation approach that addresses concerns raised in the public response to the stimuli article in *Pharmacopeial Forum*, Vol. 34(5) [Sept.–Oct. 2008]

What Did We Achieve?

- Captured a full range of valuable perspectives on this topic
- Built communication channels to promote ongoing process
- A number of valuable proposals

Meeting Summary

- The new <231> should focus on the top four metal impurities
  - inorganic arsenic, cadmium, lead, methyl mercury
- We need to implement based on the assumptions that metal impurities are assessed as part of the **composition profile** of a test article, not a **random contamination**

Meeting Summary

- Consider a new general chapter for expected metal contaminants (e.g., catalysts and organometallic reagents) that is aligned with the EMEA Guideline (EMEA/CHMP/SWP/4446/2000)

Meeting Summary

- Propose methodology but allow flexibility to apply any validated test method (for example, as stated in <467> … “the following methods are useful…”)

Meeting Summary

- Provide clarity that other metal impurity contamination must be handled as Foreign Substances and Impurities (per USP General Notices, Tests and Assays)

Meeting Summary - Regulatory

- Implementation process requires FDA position
  - Acceptance of strategy
  - Define “likely to be present”
  - Define expectations associated with regulatory filings
- Desire for discussion between Industry, FDA, and USP

What We Expect

- The input collected will be used to revise the proposed General Chapter
- The rationale for how the discussion points were (or were not) addressed will be made clear
- USP will communicate the approaches prior to PF publication
- Assure global harmonization
- Further engage Heavy Metals Project Team to advance these efforts

Thank You