IMPLEMENTATION OF ICH Q3D – INDIA

4th PQRI Workshop on ICH Q3D Elemental Impurities Requirements
November 9-10, 2020 / Live Virtual Event

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The views and opinions expressed in this presentation are only of the author, and should not be construed to represent IPEC India, IPEC Federation or other IPEC member views or policies.

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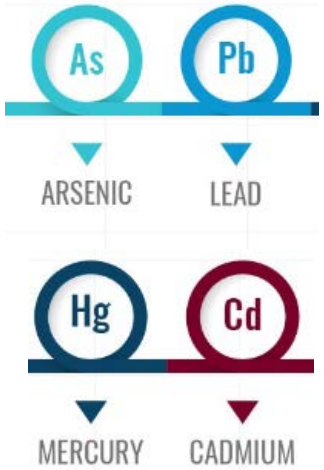
CONTENT

- Background of Elemental impurities control in India
- Indian Pharmacopoeia – plans –complete Update
  - Elemental Impurities Chapter in IP
  - Harmonization with ICH Q3D
  - IP Commission – implementation timelines
- ICH Q3D implementation - Domestic Drug Products
- ICH Q3D implementation - Export Drug Products

BACKGROUND – Elemental Impurities Control in India

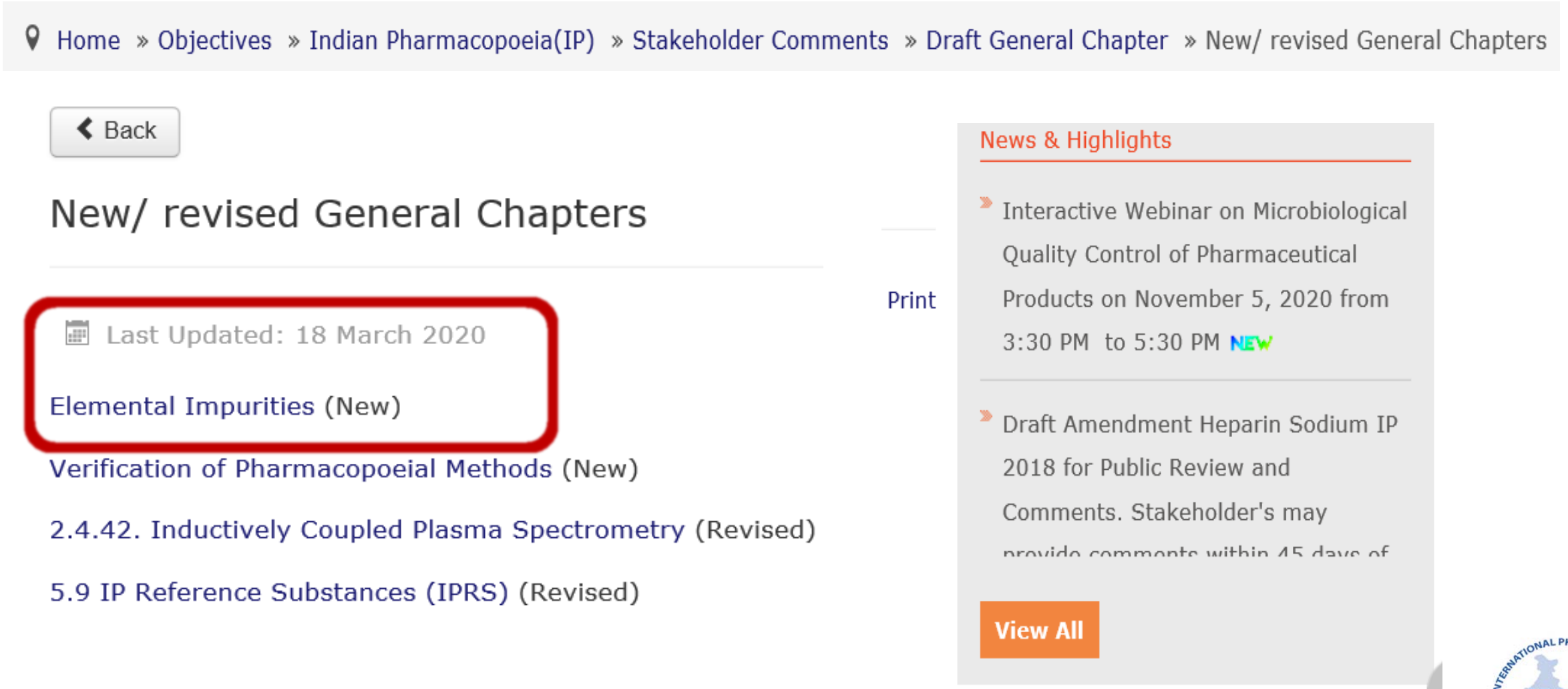


- Only Heavy metals (Lead, Arsenic, Cadmium, Mercury) and certain other metal impurities like Iron, Molybdenum are included in many monographs of the Indian Pharmacopoeia (IP) – Drug products and Excipients.
- Currently NO regulation on Elemental impurities in India,
- **After** the introduction of ICH Q3D and the USP Chapter <232>, <233> in 2016 & 2018, the Pharma industry, especially generic pharma exporting to US and EU started implementation to comply with these.
  - Though they did not apply this to their products for Domestic use.
- Pharma companies manufacturing Drugs exclusively for Domestic use were not affected by this.
- However in 2019 the IP commission decided to introduce a similar chapter in the IP Addendum to IP 2018.

Indian Pharmacopoeia – General Chapter – Elemental Impurities

- IP Commission (IPC) created an awareness about this initiative in FDA & IPC events for Pharma industry.
  - Noted comments from participants attending these events.
  - It appeared that EI would be implied to Excipients also.
  - An IPEC India representative attending one of these events explained to the panelists about the impact on Excipients and why it should not be applied to Excipients
  - Cognizance was taken of this comment
- The Draft Chapter for EI was posted on IP commission website on 18 March 2020 – Not for public comments yet

Indian Pharmacopoeia Website Post – Elemental Impurities (NEW)



Indian Pharmacopoeia – Elemental Impurities - Chapter 5.10 - NEW

Elemental Impurities (New)
http://www.ipc.gov.in/mandates/indian-pharmacopoeia/monographs/draft-general-chapter/8-category-en/744-new-revised-general-chapters.html

5.10. Elemental Impurities

This chapter specifies limits for the amounts of elemental impurities in drug products. Regardless of the approach used, compliance with the limits specified is required for all drug products unless otherwise specified in an individual monograph or specifically excluded in this chapter.

Elemental impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. These impurities may occur naturally, be added intentionally, or be introduced inadvertently (e.g., by interactions with processing equipment and the container–closure system). 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. A risk-based control strategy may be appropriate when analysts determine how to assure compliance with this standard. Due to the ubiquitous nature of arsenic, cadmium, lead, and mercury, they (at the minimum) must be considered in the risk assessment.

This chapter does not apply to radiopharmaceuticals; articles intended only for veterinary use; vaccines; cell metabolites; DNA products; allergenic extracts; cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives; products based on genes (gene therapy); cells (cell therapy); tissue (tissue engineering); dialysate solutions not intended for systemic circulation; total parenteral nutritions (TPNs); elements that are intentionally included in the drug product for therapeutic benefit and neutraceuticals.

The limits presented in this chapter do not apply to excipients and drug substances, except where specified in an individual monograph. However, manufacturers of pharmaceutical products need certain information about the content of elemental impurities in drug substances or excipients in order to meet the criteria of this chapter. Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance or excipient manufacturers, who may provide test data, or if applicable, risk assessments. Elemental impurity data generated by a qualified supplier of drug product components are acceptable for use by a drug product manufacturer

Applies to DRUG PRODUCTS

DO NOT apply to EXCIPIENTS and Drug substances

Risk Based Approach

Harmonization with ICH Q3D

- Classification of elements - 24 Elements only –no mention of any other elements
  - Class 1: As, Cd, Hg, Pb
  - Class 2A: Co, Ni V.
  - Class 2B: Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, Tl
  - Class 3: Ba, Cr, Cu, Li, Mo, Sb, Sn
- Route of Administration – Oral, Parenteral, Inhalation
- Permissible Daily Exposure Limits – ug/ml -
- Compliance Options – Component & Finished product approach
- Analytical Testing – Test Method – ICP-MS, ICP-OES
- Sample Preparation

IP commission plans for implementation

- **Impact on heavy metals/ other metal tests in IP**
  - IPC plans on removal or retaining of Heavy metals tests is not known at this time.

- **Implementation timeline**
  - The Elemental Impurities chapter was scheduled for implementing in IP after the IP Addendum 2021 which itself has been postponed to Jan 2021
  - IPC confirmed that once the draft is finalized it will be published for comments for a 45 day period before implementing in the IP.
  - It is definitely in progress for implementing but the target timeline is not known – Probably in the next addendum or Edition – year 2022 -23

ICH Q3D implementation - Domestic Drug Products

- In absence of a regulation for control of Elemental Impurities many Domestic Pharma companies and Excipient suppliers may not be aware of ICH Q3D guidance.
- Any analysis of heavy metals or other metal impurities is conducted by conventional Chemical methods or Atomic Absorption Spectrometry (AAS).
- Many of these pharma companies engage services of contact laboratories for it.
- Local Excipient manufacturers not following IP would not even be aware of the Metal impurities testing of the IP (inspite selling to Pharma) – **Elemental Impurities ??**

ICH Q3D implementation - Domestic Drug Products

- Implementing EI regulations as per ICH Q3D could cause concern to the domestic manufacturers – Drugs & Excipient both.

  i. Testing Equipment cost

  ii. Ability of contract labs to test EI

  iii. Increase in cost of product

  iv. Complying to Drug Price Control.

ICH Q3D implementation - Export Drug Products

- Generic Pharma industry has now fully implemented ICH Q3D.
- Although there are concerns regarding interpretation
  i. Excipients treated similar to Drug Product
  ii. Force suppliers to comply with PDE levels of EI.
  iii. Desire to have specifications for EI as per levels in individual Drug product
  iv. Demand for 3 batch data – very often
  v. Suggest for reporting EI levels on COA
  vi. Desire to use OPTION 1 for compliance
  vii. In case of exceeding 30 % PDE levels – supplier is directed to reduce EI levels or apply specification limits, instead of implementing a control strategy
  viii. Do not agree to using Option 3 if exceeding PDE Levels
  ix. Mixed Excipients treated as individual excipients
  x. Rejection threats in case of non agreement with requirements
- Regulatory agency deficiencies demanding compliance to ICH Q3D for Excipient

ICH Q3D implementation - Export Drug Products

- Analytical and Purchase personnel dominate all discussions with Excipient suppliers. Regulatory personnel also act in accordance to them.
- Ability to support varies with suppliers but that is utilized to force similar support from all suppliers.

  e.g. 3 batch data or blanket statements or agree to testing EI periodically or every batch.
- Lack of proper audit by Pharma company leads to such misinterpretation and setting improper precedences.
- IPEC India regularly does seminars to educate the industry on EI guidance and its rational implementation.

Summary

- Currently no regulation on Elemental Impurities Indian Pharmacopoeia (IP)
- IP Commission (IPC) to introduce a Chapter on Elemental Impurities in future addendum or Edition of Indian Pharmacopoeia
- Currently a Draft initiated – appears to be harmonized with ICH Q3D
  - Available on IPC website. Not for public comments yet.
  - Awareness created with Pharma industry , need to focus on Excipient industry also.
- Domestic Suppliers & Drug Manufacturers concerned about testing equipment cost and increase in Product cost.
- ICH Q3D Implemented by Pharma industry for Export Drugs – Although concerns exists due to varied interpretations of the guidance
- IPEC India is involved in helping rational implementation of the guidance through regular seminars & monitoring the situation

IMPLEMENTATION IS COMING THROUGH –

HARMONIZATION WITH ICH Q3D IN VIEW.

INDUSTRY AWARENESS & UNDERSTANDING IS ENHANCING

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THANK YOU