独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Joint MHLW/PMDA-USP Workshop “Role of Quality in Pharmaceuticals”

Session 4 Impurities: Mutagenic impurities and more

Control of elemental impurities and current status in Japan

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Disclaimer

Views expressed in this presentation are solely of the speaker and do not necessarily represent those of the PMDA.

ICH Q3D

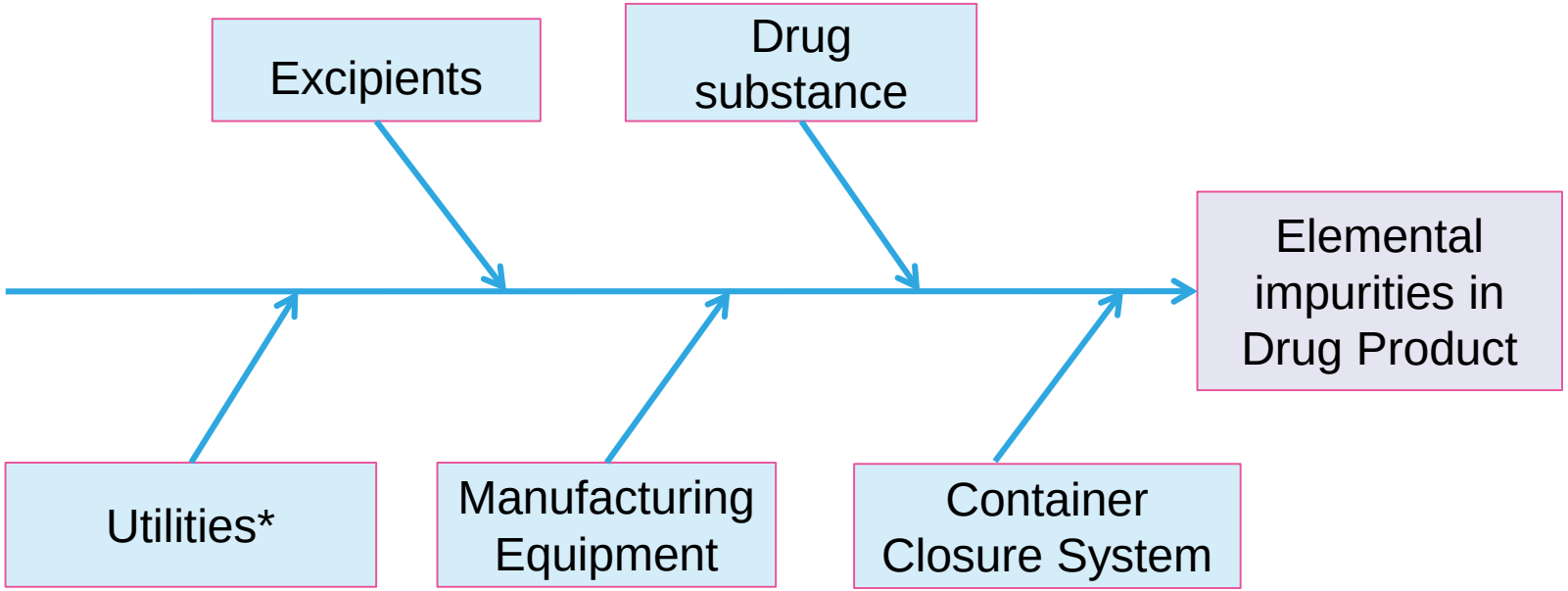
- The Guideline presents a process to assess and control elemental impurities in the drug product using the principles of risk management as described in ICH Q9.

- In Japan, the guideline reached Step 5 on September 30, 2015 and applied to the new drug products submitted after and on April 1, 2017 (PFSB/ELD Notification No. 0930-4 dated September 30, 2015).

Risk assessment process

- Identify known and potential sources of elemental impurities that may find their way into the drug product.
- Evaluate the presence of a particular elemental impurity in the drug product by determining the observed or predicted level of the impurity and comparing with the established PDE.
- Summarize and document the risk assessment. Identify if controls built into the process are sufficient or identify additional controls to be considered to limit elemental impurities in the drug product.

Potential sources of elemental impurities



*Water is the primary utility of potential concern

The product assessment should consider the potential of each of these categories to contribute elemental impurities to the drug product

Implementation of ICH Q3D into JP

Basic Principles for the Preparation of JP18 (October 19, 2016)

Note 3 (2) ⑥. Development of Standards for Control of Impurities in Response to International Trends:

- A roadmap for implementing risk-based control of impurities, especially the ICH Q3D guidelines for elemental impurities, is developed and will be put into practice.

Project for inclusion of ICH-Q3D in the JP

JP17-2
(published on June 28, 2019)

2.66 Elemental Impurities Procedures

G1. Control of Elemental Impurities Procedures in Drug Products (corresponding to the ICH Q3D guideline)

integration

JP18
(published on June 7, 2021)

2.66 Elemental Impurities
Ⅰ. Control of Elemental Impurities Procedures in Drug Products
Ⅱ. Elemental Impurities – Procedures

+ General Notice 34

Application of ICH-Q3D to the JP monographs

General Notice 34

34. In principle, the JP Drug Products are controlled appropriately according to the direction under the Elemental Impurities of the General Tests. When elemental impurities in the drug products are appropriately controlled in accordance with the direction, it is not necessary to perform the tests on elemental impurities such as heavy metals and arsenic in the monographs including but not limited to those of drug products, drug substances and excipients.

Notification and Administrative Notice

- Handling of Elemental Impurities in Prescription Drugs (PSEHB/PED Notification No. 1228-7, December 28, 2020).

- Question and Answer (Q&A) about Handling of Elemental Impurities in Prescription Drugs (Administrative Notice, December 28, 2020)

https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0028.html

Case study 1

Inquiry：

Based on the test results of the 3 exhibit batches, you concluded that the current control measures on drug substance is considered acceptable with no further corrective actions or additional control measures. However, please explain your control strategy that assures that elemental impurities do not exceed the PDEs.

- ✓ A number of factors that can influence the level of the potential impurity and should also have been considered in the risk assessment.
- ✓ An understanding of the manufacturing process and a data obtained from development of the process should be considered.

Case study 2

Inquiry： Please explain the potential for incorporation of elemental impurities from the drug substance manufacturing equipment.

- ✓ Drug substances may be manufactured under severe condition (e.g., use of caustic reagents)
- ✓ Knowledge gained from relevant products may be used in the risk assessment.

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Thank you for your attention.