Briefing on removing Heavy Metals Test and Individual Metal Impurity Test from Japanese Pharmacopoeia (JP) Official Monographs after transitional period for adopting the Control of Elemental Impurities ends

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Pharmaceuticals and Medical Devices Agency
Office of Review Management

With the publication of the proposed revision drafts on removing the heavy metals tests and individual metal impurity tests such as the arsenic test from the JP official monographs for public consultation, the following background information is provided for your review.

A. In the Japanese Pharmacopoeia 18th Edition (JP18) which was issued and enforced on June 7, 2021, the new General Notice 34 was added, and the General Test "Elemental Impurities <*2.66*>" was revised by integrating with the General Information "G1. Control of Elemental Impurities in Drug Products" which introduces the specifications of ICH-Q3D guideline to assess and control elemental impurities in drug products. Consequently, the requirements for control of elemental impurities based on ICH-Q3D guideline has been applied to the JP Drug Products.

B. In accordance with the notifications "Handling of Application for Marketing Approval of Drug Products Associated with the Enactment of the 18th edition of the Japanese Pharmacopoeia (PSEHB/PED Notification No. 0607-1, June 7, 2021) " and "Handling of Elemental Impurities in Prescription Drugs (PSEHB/PED Notification No. 1228-7, December 28, 2020)," the applicable drug products which are within the scope of the notifications shall be controlled by the General Test "Elemental Impurities <*2.66*>" on and after July 1, 2024.

C. On the other hand, as the provision in the General Notice 34 "When elemental impurities in the drug products are appropriately controlled in accordance with the direction (i.e. the direction under the Elemental Impurities of the General Tests), 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.", control of elemental impurities of prescription drugs and their constituents such as drug substance and excipients based on the

requirements for heavy metals and individual metal impurities such as arsenic in the JP monographs is not necessary on and after July 1, 2024.

Considering the above statuses A, B and C, the draft revision of the official monographs from which the heavy metals tests and the individual metal impurity tests were removed are published for public consultation towards revision in the Supplement I to the JP18 based on the draft policy shown on the attachment. If you have any proposals about the draft revision, please specify the name of the monographs and the test name, and submit the data and evidence for your proposals.

As for the individual metal impurity tests in the JP monographs for pharmaceutical excipient, other pharmacopoeias[*1,*2] have been assessing whether these tests are removable from their pharmaceutical excipient monographs on a case by case basis. Considering such situation, the public consultation will be conducted for the individual metal impurity tests in the JP monographs for pharmaceutical excipient after the assessment of the necessity of the individual metal impurity tests in the JP on a case by case basis.

[*1] Update on the European Pharmacopoeia policy on elemental impurities – Excipient of natural origin: https://www.edqm.eu/en/news/update-european-pharmacopoeia-policy-elemental-impurities-excipients-natural-origin

[*2] First Draft of Roadmap for Addressing Element-Specific Chapters and Tests in Excipient Monographs: https://www.uspnf.com/notices/elemental-impurities-in-excipients-20200803

Attachment

Basic Approach for removing Heavy Metals Tests and Individual Metal Impurity Tests from JP Monographs, accompanying the application of Control of Elemental Impurities in the Japanese Pharmacopoeia 18th Edition (JP18)

○ Heavy Metals Test

- JP official monographs applied to prescription drugs:
  The heavy metals tests in the JP official monographs of all the drug products and their constituents (including pharmaceutical excipients) which are within the scope of the General Test "Elemental Impurities <*2.66*>" will be removed. However, the monographs which are applied to behind-the-counter drugs, pharmacy-only drugs and over-the-counter drugs (hereinafter referred to as "OTC drugs") still require control of elemental impurities in accordance with the General Notice 33 and, thus, still require the control based on the heavy metals tests and individual metal impurity tests specified in the monographs of the JP18. Announcement by a notification about handling of such monographs is under consideration[*1].
- JP official monographs applied only to OTC drugs[*2]:
  The heavy metals tests will not be removed from the JP official monographs.

○ Individual Metal Impurity Test

- JP official monographs which specify individual metal impurity tests (the tests for the elemental impurities) within the scope of the General Test "<2.66> Elemental Impurities"

  Chemicals[*3], Antibiotics, and Biologicals;

  - JP official monographs applied to prescription drugs:
    The individual metal impurity tests will be removed from the official monographs. However, the monographs which are applied to OTC drugs still require control of elemental impurities in accordance with the General Notice 33 and, thus, still require the control based on the heavy metals tests and individual metal impurity tests specified in the monographs of the JP18. Announcement by a notification about handling of such monographs is under consideration.
  - JP official monographs applied only to OTC drugs:

The individual metal impurity tests will not be removed from the JP official monographs.

Pharmaceutical Excipients[*3]

Even if the individual metal impurity tests (the tests for the elemental impurities) are within the scope of the General Test "Elemental Impurities <*2.66*>," control of elemental impurities based on the specification of the individual metal impurity tests in the JP official monographs in addition to the requirements of the General Test "Elemental Impurities <*2.66*>" may be necessary due to intrinsic nature of elemental impurities in natural origin excipients. Therefore, the JP Expert Committee has been discussing removal of individual metal impurity tests from the JP monographs for pharmaceutical excipient individually. Once the Committee comes to a conclusion, a public consultation for the tests will be conducted accordingly.

- JP official monographs specifying individual metal impurity tests (the tests for the elemental impurities (i.e. iron, sodium)) which are out of the scope of the General Test "<2.66> Elemental Impurities" (e.g. the iron limit test in the JP Official Monograph "Acetylcysteine")

  As the General Test "Elemental Impurities <2.66>" does not cover the control of such elemental impurities, these individual metal impurity tests will not be removed.

[*1] Handling the JP official monographs from which the heavy metals impurity tests and individual impurity tests are removed, for OTC drugs or drugs that are out of scope of the ICH-Q3D guideline.

As described in QA-3 of the Administrative Notice "Question an Answer (Q&A) about Handling of Elemental Impurities in Prescription Drugs" by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, the requirements of the General Notice 34 are not applied to behind-the-counter drugs and over-the-counter drugs until further notice. Meanwhile, it is necessary to control impurities such as heavy metal impurities and arsenic individually in accordance with the General Notice 33, and either of the following control of the elemental impurities will be required.

- Control of elemental impurities based on the General Notice 33
  Measures to prescribe elemental impurity tests such as the heavy metals tests and arsenic tests, which are specified in the official monographs of the JP18, in the regulatory dossier are under discussion.

Control of elemental impurities by applying the General Test "Elemental Impurities <*2.66*>" in accordance with the General Notice 34.

[*2] JP official monographs applied only to OTC drugs

Alminoprofen
Aspirin Aluminum
Berberine Tannate
Methylbenactyzium Bromide

Naphazoline Hydrochloride
Dried Aluminum Potassium Sulfate
Potassium Guaiacolsulfonate
Tocopherol Calcium Succinate
Santonin

Information on over-the-counter drugs and behind-the-counter drugs:
https://www.pmda.go.jp/PmdaSearch/otcSearch/
Information on prescription drugs:
https://www.pmda.go.jp/PmdaSearch/iyakuSearch/

*3 Distinction of the JP Official Monographs between Chemicals and Pharmaceutical Excipients

As the JP official monographs of the chemicals and pharmaceutical excipients in Tables 1 and 4 which are the drafts for a public consultation were developed for the intended use when being drafted, these JP official monographs are categorized in these Tables based on the expert committee in charge of the past draft development or revision.

For the revision drafts of the chemicals and pharmaceutical excipients in Tables 1 and 4, if you have any proposals on the revision or further individual examination, please specify the name of the monographs and the test name, and submit the data and evidence for your proposals.