PSEHB/PED Notification No. 1228-7
December 28, 2020

To: Director of Prefectural Health Department (Bureau)

Director of Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Handling of Elemental Impurities in Prescription Drugs

The rules for handling of elemental impurities in new drug products were set forth by the notification "Guideline for Elemental Impurities in Drug Products" issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW) (PFSB/ELD Notification No. 0930-4, September 30, 2015; hereinafter called "Guideline Notification"). Section 5 of the Guideline Notification states: "Application of the guidelines to existing drug products will be discussed in the future."

Meanwhile, the notification "Handling of Application for Marketing Approval of Drug Products Associated with the Enactment of the Second Supplement to the 17th edition of the Japanese Pharmacopoeia" issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW (PSEHB/PED Notification No. 0628-1, June 28, 2019) states in its Section 8(2): "The control rules based on the Guidelines for Elemental Impurities in Drug Products (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-Q3D) will be set forth in the 18th edition of the Japanese Pharmacopeia."

Currently, the General Notice 34 is going to be newly added in the 18th edition of the Japanese Pharmacopeia (hereinafter called "new Pharmacopeia") and the existing General Test <2.66> Elemental Impurities - Procedures is going to be revised, requiring control of elemental impurities in JP-listed drug products on the basis of ICH-Q3D. In the new Pharmacopoeia, the permitted daily exposure levels set forth in the revised General Test <2.66> Elemental Impurities have been corrected to correspond to the notification "Amendment of the Guideline Notification" issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW (PSEHB/PED Notification No. 0626-1, June 26, 2020).

In addition, we plan to expand the application of the Guideline Notification to also include the other non-JP prescription drug products, requiring equivalent control on them.

Basic views underlying the above-mentioned handling policy have been summarized in the

attachment. Your understanding and appropriate dissemination to the related companies and organizations under your jurisdiction will be appreciated concerning the information about this topic.

1. Basic Views underlying the Control of Elemental Impurities

(1) Scope

The JP-listed prescription drug products (hereinafter called "JP-listed products") and JP-non-listed prescription drug products ("non-JP products") are defined to encompass the following products.

[1] JP-listed products

The products defined in the General Test <2.66> Elemental Impurities I.2. of the new Pharmacopoeia.

[2] Non-JP products

The products encompassed in the "2. SCOPE" in the Attachment of the Guideline Notification. Regarding the statement given in that document: "Application of Q3D to existing products is not expected prior to 36 months after publication of the guideline by ICH," these products are considered to be encompassed in the scope because 36 months have elapsed after its publication.

(2) Timing of Application

For both JP-listed products and non-JP products, the control of elemental impurities based on the ICH-Q3D complying with the Guideline Notification and the provisions of the new Pharmacopoeia should be started by 36 months after ministerial announcement and enforcement of the new Pharmacopoeia.

(3) Control Required

Drug marketing authorization holders (hereinafter called "MAH") are required to conduct appropriate control of elemental impurities in drug products in compliance with the Guideline Notification and the General Test <2.66> Elemental Impurities and to be prepared to give an explanation about the status of their control. Suppliers of drug substances, excipients, container/closure systems, etc. (hereinafter called "Suppliers") are also required to conduct appropriate control of elemental impurities on the basis of risk assessment and to provide relevant information as far as possible to contribute to the control of elemental impurities by the MAH.

In the case where the total level of elemental impurities from all sources in the drug product is expected to be less than 30% of the established, permitted daily exposure (PDE) (hereinafter called "control threshold"), routine control is not required as long as the MAH has appropriately assessed the data and provided adequate control on elemental impurities. If the elemental impurity level exceeds the control threshold, it is required to establish adequate control on the basis of the Guideline Notification or the General Test <2.66> Elemental Impurities I.4.1. of the new Pharmacopoeia.

(4) Handling of Elemental Impurities Specified in the Official Monographs of the Japanese Pharmacopeia

If the action set forth above in 1 (3) has been taken, it is not required to implement control on the elemental impurities such as heavy metals and arsenic (specified in the Official

Monographs and other General Chapters, etc.) which overlap with the purpose of such an action according to the General Notice of the new Pharmacopoeia.

(5) Handling of Elemental Impurities Listed in Other Standards for Drugs.

The handling described above in 1 (3) and (4) shall be applied also to the items listed in the following standards, etc. whose purpose overlaps with that mentioned in 1 (3).

[1] Attachment to the Notification "The Japanese Pharmaceutical Codex 2002" issued by the Director of the Pharmaceutical and Food Safety Bureau, MHLW (PFSB Notification No. 0920001, September 20, 2002)

[2] Attachment to the Notification "Creation of Part 4 of the Japanese Pharmaceutical Codex (Partial Revision of the Japanese Pharmaceutical Codex 1997)" issued by the Director of the Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare (PFSB Notification No. 1117, September 22, 1999).

[3] Attachment to the Notification "Japanese Pharmaceutical Excipients 2018" issued by the Director of the Pharmaceutical Safety and Environmental Health Bureau, MHLW (PSEHB Notification No. 0329-1, March 29, 2018)

2. Handling of the Products Approved before the Ministerial Announcement of the New Pharmacopoeia

(1) Case where the control based on in 1 (3) has been implemented, allowing confirmation that the level is consistently less than the control threshold by the data, etc. from an appropriate number of lots evaluated during commercial production or pilot-scale production, thus allowing a judgment that routine analytical control is unnecessary.

[1] Case where only the "Specifications" column overlapping with the purpose of the control based on 1 (3) is to be deleted

Submission of a notification of minor changes in the approved product information (hereinafter called "minor change notification") is possible pursuant to Article 14 Paragraph 14 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter called "the Law") [in case of the drug master file (hereinafter called "DMF"), the notification of minor changes in the DMF registered item (hereinafter called "DMF minor change notification") is submitted pursuant to Article 80-8 Paragraph 2 of the Law]. The data etc. concerned need to be stored appropriately so that they may be submitted upon request as the supporting data for the judgment leading to application for partial change of the approved product information (hereinafter called "partial change application") pursuant to Article 14 Paragraph 13 of the Law (this application is called "DMF registration change application" if the change pertains to DMF and the application is filed pursuant to Article 80-8 Paragraph 1 of the Law) or at other occasions. If it is difficult to judge the action to be taken, consultation should be sought to the regulatory authority. When a minor change notification or a DMF minor change notification is submitted, a description "Notification based on 'Handling of Elemental Impurities in

Prescription Drugs' (PSEHB Notification No. 1228-7, December 28, 2020)" needs to be entered in the Remarks column, accompanied by a statement that control of elemental impurities such as heavy metals and arsenic set forth in official compendia or standards is skipped.

[2] Case where deletion of the "Specifications" column overlapping with the purpose of the control based on 1 (3) causes a change in the "Manufacturing Methods" column

A partial change application or a DMF registration change application needs to be submitted, with care taken of the following points.

A. In principle, a photocopy of the marketing approval document of the drug product concerned needs to be attached. In addition, submission is needed of the documents listed in B-3 of Table 1 of the Notification "Application for Approval of Drugs" issued by the Director of the Pharmaceutical and Food Safety Bureau, MHLW (PFSB Notification No. 2, November 21, 2014), accompanied as needed by the document listed in C-3 or E-5 of Table 1 of the same notification.

B. The entry into the "Change" column and the "Remarks" column of the partial change application form or the DMF registration change application form should be made in compliance with "How to Fill in the Approval Application Form related to JP Drug Products" attached to the notification "Handling of Application for Approval/License of Manufacture or Importation of JP Drug Products" issued by the Director of the Drug Evaluation and Licensing Division and the Director of the Biological Products Division of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (PAB/ELD Notification No. 1462, October 9, 1980), thereby describing in the Remarks column that the partial change application (or the DMF registration change application) is based on the notification "Handling of Elemental Impurities in Prescription Drugs" (PSEHB Notification No. 1228-7, December 28, 2020).

(2) Case where the level exceeds the control threshold after the control described in 1 (3)

Change to the excipients, modifications of the manufacturing processes, etc. should be conducted or a partial change application or a DMF registration change application should be filed after setting the specifications and test methods or in-process tests which correspond to the potential risk involved.

(3) Case where the level exceeds the preset PDE level after the control described in 1 (3)

After change to the excipients, modifications of the manufacturing processes, etc. are conducted and necessary measures such as filing of a partial change application, a DMF registration change application or the like are taken, it is necessary to control based on the revised standards without delay by 36 months after ministerial announcement of the new Pharmacopoeia, assuring no violation of Article 50 (information described on the direct

container, etc.), Article 55 (prohibition of selling and providing, etc.) and Article 56 (prohibition of selling and manufacturing, etc.) of the Law (Law No. 145, 1960).