PSEHB/PED Notification No. 1212-5
December 12, 2022

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 Behind-the-counter/Over-the-counter Drugs

Handling of elemental impurities in prescription drugs is shown in the notification "Handling of Elemental Impurities in Prescription Drugs" issued by the Director of Pharmaceutical Evaluation Division of the Pharmaceutical Safety and Environmental Health Bureau, MHLW (PSEHB/PED Notification No. 1228-7, December 28, 2020) (hereinafter called the Notification issued by the Director).

Meanwhile, as for behind-the-counter drugs and over-the-counter drugs, the Administrative Notice "Question and Answer (Q&A) about Handling of Elemental Impurities in Prescription Drugs" issued by the Pharmaceutical Evaluation Division of the Pharmaceutical Safety and Environmental Health Bureau, MHLW (December 28, 2020) (hereinafter called "Administrative Notice"), QA3 states: "Under the General Notice 34 of the new Pharmacopoeia states that, in principle, the JP-listed Drug Products are controlled appropriately according to the requirement of Elemental Impurities in the General Test. However, this requirement is not applied to behind-the-counter drugs and over-the-counter drugs until further notice."

Currently, basic views underlying the handling policy on elemental impurities in behind-the-counter drugs and over-the-counter drugs 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.

In association with the issuance of this notification, QA3 and QA31 of the Administrative Notice are abolished.

Attachment

1. Basic Views underlying the Control of Elemental Impurities in Behind-the-counter drugs and Over-the-counter drugs

(1) Scope

The JP-listed behind-the-counter drugs and over-the-counter drugs (hereinafter called "JP-listed products") and JP-non-listed behind-the-counter drugs and over-the-counter drugs ("non-JP products") are defined to encompass the following products.

[1] JP-listed products

The products are defined in the General Tests <2.66> Elemental Impurities I.2. of the 18th edition of the Japanese Pharmacopoeia (hereinafter called Pharmacopoeia).

[2] JP-non-listed products that are identical to prescription drugs to which the Notification issued by the Director has already been applied

The same scope is applied as for [1]. The identical drug products refer to drug products that are identical in manufacturing site, manufacturing methods, manufacturing process, manufacturing equipment, specifications, etc. which will be kept unchanged.

[3] JP-non-listed products other than [2]

Not applicable.

(2) Timing of Application

For drug products that are shown in 1 (1) [1] and to which the General Notice 34 of the pharmacopoeia is applied, the control of elemental impurities based on the ICH-Q3D complying with 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") and the provisions of the Pharmacopoeia should be started no later than June 30, 2024 after ministerial announcement and enforcement of Supplement I to the 18th edition of the Japanese Pharmacopoeia (hereinafter called "Supplement I").

(3) Control Required for the Drug Products Shown in 1 (1) [1] and [2]

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 or the General Tests <2.66> Elemental Impurities of the Pharmacopoeia 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 Tests <2.66> Elemental Impurities I.4.1. of the new Pharmacopoeia.

2. Handling of the Products Approved before the Ministerial Announcement of Supplement I

(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 16 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"). 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 15 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 is submitted, a description "Notification based on 'Handling of Elemental Impurities in Behind-the-counter/Over-the-counter Drugs' (PSEHB/PED Notification No. 1212-5, December 12, 2022)" 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 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 columns and the "Remarks" column of the partial 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 is based on the notification "Handling of Elemental Impurities in Behind-the-counter/Over-the-counter Drugs" (PSEHB/PED Notification No. 1212-5, December 12, 2022).

(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 should be filed after setting the specifications and test methods 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 or the like are taken, it is necessary to start to control based on the revised standards without delay no later than June 30, 2024 after ministerial announcement and enforcement of Supplement I, 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.

3. Handling of the products for which a new approval application will be submitted after the announcement of Supplement I

The drug products within the scope of 1 (1) [1] and [2] should be controlled in accordance with 1 (3) of this notification.