Administrative Notice
December 28, 2020

To: Division of Pharmaceutical Affairs, Prefectural Health Department (Bureau)

Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

Question and Answer (Q&A) about Handling of Elemental Impurities in Prescription Drugs

The Q&A about the topic specified above has been prepared as shown in the attachment. Your dissemination of this information to the related companies and organizations under your jurisdiction will be appreciated.

(Attachment)

1. Scope, etc.

Q1:
Which drug products require control of elemental impurities?

A1:
It is required for the prescription drug products described in “2. Scope of the Guideline” in the attachment of the notification “Guidelines for Elemental Impurities in Drug Products” (hereinafter called “Guideline Notification”) issued by the Director of the Evaluation and Licensing Division of the Pharmaceutical and Food Safety Bureau, MHLW (PFSB/ELD Notification No. 0930-4, September 30, 2015) and in “2. Scope” of the General Test <2.66> Elemental Impurities in the 18th edition of the Japanese Pharmacopoeia (hereinafter called “new Pharmacopoeia”). To put it concretely, drug products containing purified proteins and peptides (including proteins and peptides produced from genetic recombinant or non-recombinant origins), their derivatives, and drug products containing the above mentioned components (e.g., conjugates), as well as drug products containing synthetic peptides, polynucleotides, and oligosaccharides are within the scope of the above mentioned documents.

It does not apply to crude drugs, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellar blood components, blood derivatives including plasma and plasma preparations, dialysate solutions not intended for systematic circulation, and drug products based on genes (gene therapy), cells (cell therapy) and tissues (tissue engineering). Also, it does not apply to elements that are intentionally included in the drug product for therapeutic benefit.

Q2:
Is it correct to understand that products falling under the General Notice 4 of the Japanese Pharmacopoeia (hereinafter called “JP”) are out of scope?

A2:
Yes, it is.

Q3:
Is it correct to understand that the General Notice 34 of the new Pharmacopoeia applies only to prescription drugs?

A3:
Yes, it is. 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.

Q4:
The General Test <2.66> Elemental Impurities in the new Pharmacopoeia does not provide PDE levels of elemental impurities in dermal or transdermal products. When such information is given in the ICH draft Guidelines published for public comments,

is it acceptable to use it?

A4:

The information given in the ICH draft Guidelines published for public comments may be used when validity of the information concerned can be explained appropriately while considering that the information is provisional.

Q5:
Is it acceptable to replace the control based on the Guideline Notification or the General Test <2.66> Elemental Impurities of the new Pharmacopoeia with the test on heavy metals, arsenic, etc.?

A5:

Not acceptable. For the products to which this guideline applies, the control based on the Guideline Notification or the General Test <2.66> Elemental Impurities must be implemented by 36 months after ministerial announcement and enforcement of the new Pharmacopoeia.

2. Application for Approval

[1] Documents related to application

Q6:
I would like to know the requirements and points to consider, if any, about the documents to be attached to the approval application form.

A6:

The application for approval needs to be accompanied by the documents such as CTD, explaining, as a result of risk assessment, the process design, and operation and control points to control elemental impurities.

[2] Questions related to the specifications

Q7:
Regarding the specification on elemental impurities, is it acceptable to apply the periodic testing using the principles established in ICH Q6A?

A7:

Yes, it is. It is required to examine the testing frequency taking into account the control strategy devised based on risk assessment and to explain the justification to apply the periodic testing to the specifications. The frequency of the testing needs to be specified in the approval application form.

Q8:
When the risk assessment allows us to judge that manufacturing of products having less than the control threshold is possible, can we regard further control unnecessary unless any change is made in the manufacturing methods adopted by the suppliers of drug substances, excipients, container closure systems, etc.?

A8:

Generally speaking, routine analysis control such as setting of the specifications or in-process tests), periodic analysis or risk re-evaluation is not required if justification of

manufacturing facilities (including deterioration over time) can be explained. If there is any change that has arisen in the drug substances, excipients, etc. or their manufacturing methods, equipment/apparatuses, container closure systems or facilities, it is required to perform a risk management appropriately, to review the need of control on the basis of the risk assessment results and to re-evaluate the control strategy as needed.

[3] Entry into the approval application form and the drug master file (hereinafter called "DMF")

Q9:
When the analytical methods of the General Test <2.66> Elemental Impurities in the new Pharmacopoeia are applied as the specifications for the control of elemental impurities, is it acceptable to simplify the description by filling "According to the JP xxx" in the Specifications column of the approval application form or the DMF as suggested in the administrative notice "Questions and Answers (Q&A) about the Drug Master File (Part 4)" issued by the Evaluation and Licensing Division of the Pharmaceutical and Food Safety Bureau, MHLW (October 29, 2013)?

A9:
The simplified description "According to JP XXX" alone is not acceptable. When the analytical methods of the General Test <2.66> Elemental Impurities of the new Pharmacopoeia are applied as the specifications, it is required to specify the information about the procedures, conditions and criterion values related to the sample preparation methods and analysis together with the description "According to JP xxx" on the approval application form or DMF. Examples of such descriptions are found in the "5.1. ICP-Atomic Emission Spectrometry" or "5.2. ICP-Mass Spectrometry," 2) Purity Test of the notification "Guideline for Preparation of the Draft 18th edition of the Japanese Pharmacopeia (Partial Revision, Part 2)" issued by the Office of Review Management, Pharmaceuticals and Medical Devices Agency (PMDA/ORM Notification No. 1221001, December 21, 2020).

[4] Procedure for Change

Q10:
Is it acceptable that when the control of elemental impurities is changed or newly set following a change or an addition of manufacturing sites or manufacturing methods, the relevant procedure required under the Law is taken in the form of application for partial change in the manufacturing methods, etc.?

A10:
Yes, it is. However, it is necessary to consider that when the control strategy for elemental impurities is changed or newly set, the application is not covered by the expedited review based on the notification "Acceleration of the Procedure regarding Change or Addition of Manufacturing Sites for Prescription Drug Products" issued by the Director of the Evaluation and Licensing Division and the Director of the Compliance and Narcotics Division of the Pharmaceutical and Food Safety Bureau, MHLW (PFSB/ELD Notification No. 1225002 & PFSB/CND Notification No. 1225007, December 25, 2006).

3. Risk Assessment

[1] Main Framework

Q11:
In order to secure the safety of drug products and facilitate smooth drug supply for clinical use, what is desired from drug marketing authorization holders (hereinafter called "MAH") and suppliers of drug substances, excipients, container closure systems, etc. (hereinafter called "Suppliers") respectively in terms of risk assessment of elemental impurities?

A11:
It is desirable that MAH and Suppliers cooperate with each other to get easier access to the information necessary for control of elemental impurities and to improve the quality and effectiveness of such control.

For example, it is desirable for the MAH to provide information they have about the purpose of use, dosage, administration, etc. of their finished products to the Suppliers since such information will facilitate correct understanding of the finished products by the Suppliers. On the other hand, it is desirable for the Suppliers to provide information they have obtained about the outline, results, etc. of risk assessment of elemental impurities in their supplied products to the MAH since such information is needed for appropriate implementation of risk assessment of finished products by the MAH.

The cooperative relation between these two parties concerning the control of elemental impurities in drug products described above is expected to achieve both safety assurance and smooth drug supply for clinical use adequately.

Q12:
When an element such as a catalyst is intentionally added during the manufacturing processes of drug substances, excipients, container closure systems, etc. and if such element remains as an impurity in the drug substances, excipients, container closure systems, etc., would the suppliers of such drug substances, excipients, container closure systems be expected to perform any routine control?

A12:
Manufacturers and suppliers of drug substances, excipients, container closure systems, etc. are required to consider appropriate control by the specifications and/or the process control for the products based on quality risk management. However, the suitability of such control by the suppliers is also closely related to the control strategy for elemental impurities in drug products and is dependent on the degree of information sharing and mutual understanding with the MAH. It is therefore advisable to devise various control strategies, taking into account the content of QA11 given above. For example, Option 1 may be selected for control of the drug product concerned. When information including risk assessment results is shared appropriately between the two parties and consequently it is possible to judge that the control of a given element level constantly not to exceed 30% of the permitted concentration level is constantly feasible, it is possible to consider that routine control of the element concerned in the manufacturing process or product testing of such products is unnecessary.

Q13:
Is it limited to Option 1 as an approach for evaluation of the levels of elemental impurities?

A13:
It is not limited to Option 1. Evaluation of elemental impurities depends on the dosage of individual drug products. The MAH are therefore required to select an option by appropriately judging whether an approach via the components of a product or an approach via the finished product should be taken. However, regardless of the option selected, it is required to practice control so that the level of elemental impurities does not exceed the control threshold throughout the period until the expiration date if the elemental impurity level in the product is anticipated to rise over time due to leachables from the container closure systems, etc.

Q14:
When Suppliers conduct risk assessment based on sufficient understanding of the elemental impurity profile of the drug substances, excipients, container closure systems, etc. followed by appropriate information provision about the risk assessment results to MAH and appropriate control on the basis of the General Notice 34 of the new Pharmacopoeia, is it acceptable to skip the test on elemental impurities such as heavy metals and arsenic specified in the Official Monographs?

A14:
The test may be skipped taking while the content of QA11 given above into account.

Q15:
Is it correct to understand that analysis on each valence is not necessary when the level of each elemental impurity is measured by specifications of finished products or in-process tests for the products?

A15:
It is not necessary to analyze it when the level does not exceed the PDE.

Q16:
For some injections such as products used for dilution of other drug products, the dosage are not predetermined. In such cases, is it acceptable for the applicant to conduct any own approach for the assessment on the basis of the purpose of the Guideline Notification or the General Test <2.66> Elemental Impurities of the new Pharmacopoeia?

A16:
It is considered acceptable when the assumption about the dosage of the product is appropriate.

Q17:
Is it correct to understand that measurement of elemental impurities is not necessary when the product indicates conformity to the JP Monographs of Purified Water or Water for Injection is used for manufacturing processes?

A17:

Yes, it is. However, when these products provided in a container, it is required to control based on the General Test <2.66> Elemental Impurities in the new Pharmacopoeia because it is distributed as a drug product for clinical use.

[2] About justification for the control without of specifications, etc.

Q18**:**
The Guideline Notification states: "If the total elemental impurity level is expected to be consistently less than 30% of the PDE, then additional controls are not required, provided the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities." When evaluating the data from 3 production-scale lots, is it acceptable to justify the above control strategy even for products known to have some variabilities in impurity level?

A18:
The control strategy and the risk should be taken into consideration. For example, if the data from 3 production-scale lots do not allow a judgment of not constantly exceeding 30% of the PDE, the control strategy should be reevaluated and additional lots should be validated as needed.

Q19:
The General Test <2.66> Elemental Impurities, I. Control of Elemental Impurities in Drug Products, 4.5. Summary of Risk Assessment Process of the new Pharmacopoeia states: "For some components that have inherent variability (e.g., mined excipients), additional data may be needed to apply the control threshold." Which data is meant by "additional data" in this statement?

A19:
Sources of variability may include the following.

- Variability of the analytical method
- Variability of the elemental impurity level in the specific sources
- Variability of the elemental impurity level in the drug product

Concerning these cases, it is acceptable to judge elemental impurity levels and their variabilities on the basis of the data obtained from 3 representative production-scale lots or 6 representative pilot-scale lots of the component or the product if there is no other method to demonstrate the justification. However, concerning the components having unique variability (e.g., mined excipients) may require additional data which consider also the site of mining, etc..

[3] Scope of Risk Assessment

Q20:
Elemental impurities which possibly contaminate pharmaceuticals may arise from several sources. To which extent should the applicant trace back the raw materials used in the manufacture of drug products when controlling the intentionally added elemental impurities?

A20:
The scope of risk assessment needs to be set depending on the magnitude of the risk for contamination of the product.

Q21:
Should risk assessment cover the solvents used in the manufacturing processes?

A21:
Risk assessment should cover substances, including solvents, which have the possibility of contamination of elemental impurities.

Q22:
Should risk assessment cover reagents or the like which are used for extensive industrial purposes not limited to pharmaceuticals?

A22:
Yes, it should. The Guideline Notification and the General Test <2.66> Elemental Impurities of the new Pharmacopoeia provide the PDE of elemental impurities in drug products. Also when reagents for industrial use are used for manufacture of pharmaceuticals, it is necessary to evaluate the risk for contamination with elemental impurities originating from such reagents in the drug products.

Q23:
Should risk assessment cover the excipients which are contained in a drug product at a concentration not exceeding 0.1%?

A23:
In principle, risk assessment is needed on each component of a drug product. However, it may be considered to use the amount of the component contained in the product as a reason for judging that risk assessment on the component is unnecessary.

Q24:
When manufacturing sites for drug substances are changed, is it necessary to re-measure for re-evaluation of risk for contamination with elemental impurities derived from the equipment or tap water used during the manufacturing processes?

A24:
The necessity of actual data should be judged on the basis of the magnitude of the impact of the change. The information needed for appropriate implementation of risk assessment should be considered in light of the content of QA11 given above.

Q25:
The General Test <2.66> Elemental Impurities, I. Control of Elemental Impurities in Drug Products, 4.3. Identification of Potential Elemental Impurities of the new Pharmacopoeia states: “the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment.” Is it correct to understand that unlike liquid or semi-solid dosage forms, the solid dosage forms do not require evaluation of migration of elemental impurities from the container to the product by actual data if evaluation of the materials constituting the container closure systems yields no particular concern?

A25:
It is usually unnecessary. However, it is noted that evaluation of such materials alone does not suffice depending on the components of the solid dosage forms or the characteristics of the materials constituting the container closure systems, etc.

Q26:
When control is applied on the basis of the Guideline Notification or the General Test <2.66> Elemental Impurities in the new Pharmacopoeia, is it acceptable to skip the soluble iron test specified in "<7.01> Test for Glass Containers for Injections" and the test on heavy metals, lead, cadmium, etc. specified in "<7.02> Test Methods for Plastic Containers" or "<7.03> Test for Rubber Closure for Aqueous Infusions"?

A26:

After setting appropriate conditions for extraction from the container closure systems, etc., it is acceptable to apply the analytical methods specified in the General Chapter <2.66> Elemental Impurities of the new Pharmacopoeia, by replacing the soluble iron test specified in "<7.01> Test for Glass Containers for Injections" and the tests on heavy metals, lead, cadmium, etc. specified in "<7.02> Test Methods for Plastic Containers" or "<7.03> Test for Rubber Closure for Aqueous Infusions."

Furthermore, it is possible to routinely skip the soluble iron tests specified in "<7.01> Test for Glass Containers for Injections" and the tests on heavy metals, lead, cadmium, etc. specified in "<7.02> Test Methods for Plastic Containers" or "<7.03> Test for Rubber Closure for Aqueous Infusions" if the following requirements are met.

- Risk assessment of the container closure systems, etc. is performed appropriately on the basis of the Guideline Notification or General Test <2.66> Elemental Impurities of the new Pharmacopoeia, resulting in control of elemental impurities based on the Guideline Notification or General Test <2.66> Elemental Impurities of the new Pharmacopoeia is feasible
- Compliance with the specifications with regard to the soluble iron tests specified in "<7.01> Test for Glass Containers for Injections" and the tests on heavy metals, lead, cadmium, etc. specified in "<7.02> Test Methods for Plastic Containers" or "<7.03> Test for Rubber Closure for Aqueous Infusions" is judged consistently possible
- Submission of an explanation of the results of risk assessment, the process design for control of elemental impurities and manipulation/control items at the time of the approval review upon request is possible.

In the above case, if there is any change that has arisen in the raw materials for container closure systems, etc., their manufacturing methods, the equipment/apparatus, container closure systems or the facilities etc., it is required to appropriately perform risk assessment, consider the need of control on the basis of the appropriate risk assessment results and to review the control strategy as needed.

Regarding the procedure for change, it is advisable to seek consultation after evaluation has been made by the applicant.

Q27:
Is it correct to understand that the excipients derived from plants do not require the actions based on the Guideline Notification or the General Test <2.66> Elemental Impurities of the new Pharmacopoeia?

A27:

Such excipients need to be included in risk assessment and actions should be taken.

[4] Documents, etc. used for information sharing among manufacturers and suppliers

Q28:
Which requirements are applicable for the information described in the documents related to control of elemental impurities issued by Suppliers?

A28:
For example, such documents are required to contain the information as to whether or not any elemental impurity has been intentionally added to serve as a metal catalyst etc. during manufacturing processes, whether or not any raw material of natural mineral origin has been used or whether or not the risk for contamination with elemental impurities from the raw materials, container closure systems, manufacturing equipment/apparatus, utility, etc. has been evaluated. In addition, it is desirable that the documents also contain information as to the results of risk assessment conducted with these factors taken into consideration.

Q29:
If information about elemental impurities in pharmaceuticals (ingredients) is available in a document or the like issued by Suppliers, is it acceptable to utilize it when considering control of elemental impurities?

A29:
It is acceptable, assuming that the applicant is aware of the necessity of continuously (or periodically at appropriate intervals) confirming reliability of such a document as one of the control required for users of such information, referring to QA28 given above.

[5] Data Utilization

Q30:
Is it acceptable to use the data of domestic and / or overseas excipient consortia for risk assessment?

A30:
It is acceptable if the data are appropriate. The other useful information has been listed in the 5.5 of the Attachment to the Guideline Notification and the General Test <2.66> Elemental Impurities, I. Control of Elemental Impurities in Drug Products, 4. of the new Pharmacopoeia, although the information useful is not confined to it. When use such information required to explain appropriateness of utilization of the information concerned.

4. Others

Q31:
Is it correct to understand that application for partial change is needed when only the “Specifications” column which the purpose overlaps with the control described in 1. (3) is deleted by applying the General Test <2.66> Elemental Impurities of the new Pharmacopoeia concerning the behind-the-counter drugs and over-the-counter drugs (identical in composition, quantity and manufacturing method) to the prescription drugs on which a minor change notification has been submitted pursuant to 2. (1) [1] of 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)?

A31:

Yes, it is.

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