4214 Determination of Elemental Impurities in Drug Packaging Materials

This method applies to the detection of elemental impurities caused by the introduction of raw materials and process residues in drug packaging containers and components during production and processing. Based on the materials and manufacturing processes of each variety of drug packaging materials, the quality requirements of the medicinal product to be packaged, and with reference to the ICH Q3D Guideline for Elemental impurities, the risk management will be conducted to control the total elemental impurities and/or the leached elemental impurities.

Preparation of Test Solutions

Part I Preparation of Test Solution for Total Elemental Impurities

1. Plastics

Mainly including plastic containers and components that come into direct contact with the medicinal product, such as plastic containers and components for injections, plastic bottles and components for inhaled preparations, and plastic bottles and components for eye drops. Key elemental impurities include but are not limited to barium, copper, cadmium, lead, stannum, and chromium.

1.1 Residue on ignition method

Cut the test sample into small pieces, place 5.0 g, accurately weighed, into a crucible, ignite gently until it is thoroughly charred, allow to cool, and ignite at 500-600 °C until incineration is complete. Cool and take the residue, add 5 ml of hydrochloric acid solution(1→2) to dissolve, heat at low temperature until all hydrochloric acid vapor is removed, add 2% nitric acid solution to dissolve the residue, transfer the solution in batches to a 25 ml volumetric flask, dilute with 2% nitric acid solution to volume, and shake well to obtain the test solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same manner.

1.2 Microwave digestion method

Cut the test sample into small pieces, place 0.2 g, accurately weighed, into a digestion tube, add 6 ml of nitric acid and 2 ml of concentrated hydrogen peroxide solution (30%), tightly secure the digestion tube cap, allow to stand overnight, place in a microwave digestion instrument, and set the parameters according to Table 1 for microwave digestion (the parameter settings can be adjusted according to the actual situation).

Table 1 Microwave Digestion Program

Step	Power (W)	Temp Set (°C)	Ramp (min)	Hold Time (min)
1	1600	120	5	3
2	1600	150	8	5
3	1600	190	10	30

After digestion has been completed, the digested solution should be clear and have the acid driven out until about 1 ml is left. Transfer the digested solution with 2% nitric acid solution to a 25 ml volumetric flask, dilute to volume, and shake well to obtain the test solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same manner.

2. Paper-based

Mainly including cardboard for pharmaceutical aluminum plastic sealing gaskets and paper bags for solid silica gel desiccants in pharmaceutical paper bags. Key elemental impurities include but are not limited to arsenic and lead.

2.1 Residue on ignition method

（1）Arsenic Place 2.0 g of cardboard after high-temperature separation or paper bags with desiccant removed (cut into pieces if necessary), accurately weighed, into a crucible, add 1 g of magnesium oxide and 10 ml of 15% magnesium nitrate solution, mix well, and soak for 4 hours. Evaporate to dryness in a water bath, heat gently until thoroughly charred, allow to cool, ignite at 500-600 °C until incineration is complete, cool and take the residue. Add 5 ml of water to moisten, stir with a fine glass rod, and then wash the ash attached to the glass rod with a small amount of water into the crucible. Evaporate to dryness in a water bath, ignite at 500-600 °C for 2 hours, cool and remove. Add 2 ml of water to moisten, then slowly add 5 ml of hydrochloric acid solution (1→2), transfer the solution into the arsenic detection device, wash the crucible with hydrochloric acid solution (1→2) 3 times, 2 ml each time, and then wash with water 3 times, 5 ml each time. Combine the washing solution and transfer it to the arsenic detection device.

（2）Lead Place 1.0 g of cardboard after high-temperature separation or paper bags with desiccant removed (cut into pieces if necessary), accurately weighed, into a crucible, ignite gently until thoroughly charred, allow to cool, ignite at 500-600 °C until incineration is complete, cool and take the residue. Then add 1 ml of nitric acid-perchloric acid solution (4:1), ignite over low heat, repeat if necessary, until there are no carbon particles in the residue. Allow the crucible to cool somewhat, add 2% nitric acid solution to dissolve the residue, and transfer the solution to a 25 ml volumetric flask. Wash the crucible with a small amount of water, add the washing solution to the volumetric flask, dilute with water to volume, and use it as the test solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same method.

2.2 Microwave digestion method

Take the cardboard after high-temperature separation or paper bags with desiccant removed, cut the test sample into small pieces, place 0.2 g, accurately weighed, into a digestion tube, add 6 ml of nitric acid and 2 ml of concentrated hydrogen peroxide solution (30%), secure the digestion tube cap, pre-digest at 100 °C for 1 hour, and place in a microwave digestion apparatus. It is recommended to set the heating program with reference to parameters in Table 2 for microwave digestion (parameter settings can be adjusted according to actual situations).

Table 2 Microwave Digestion Program

Step	Power (W)	Temp Set (°C)	Ramp (min)	Hold Time (min)
1	1600	80	15	30
2	1600	120	20	30
3	1600	160	20	30
4	1600	180	15	25

After digestion has been completed, the digested solution should be clear and have the acid

driven out until about 1 ml is left. Transfer the digested solution with 2% nitric acid solution to a 25 ml volumetric flask, dilute to volume, and shake well to obtain the test solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same manner.

Part II Preparation of Test Solution for Leached Elemental Impurities

1. Plastics and Elastomers

Mainly including plastic and elastomeric containers or components that come into direct contact with the medicinal product, such as plastic containers and components for injections, elastomers for injections, plastic bottles and components for inhaled preparations, plastic bottles and components for eye preparations, and pre-filled syringes. Key elemental impurities include but are not limited to barium, copper, cadmium, lead, stannum, chromium, and aluminum.

Determine with reference to the test solution and blank solution prepared under the dissolution test method for drug packaging materials (General Chapter 4204) or the dissolution test method for each variety.

2. Glasses

2.1 Glass containers

Key elemental impurities include but are not limited to arsenic, antimony, lead, and cadmium. The leaching amount measurement results are expressed in mg/L.

When the test sample is a container, take samples according to the sampling quantity in Table 3, clean the samples thoroughly, and fill with 4% acetic acid solution to 90% of the full capacity or to the shoulder of the bottle body for smaller containers such as ampoules, and cover the mouth with an inverted beaker (made of borosilicate glass with average linear thermal expansion coefficient α (20 to 300 °C) of approximately $3.3\times10^{-6}K^{-1}$, and new beakers must be subjected to aging treatment) or other inert materials. Hold at 98 °C ± 1 °C for 2 hours. Cool and take the residue, and use it as the test solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same manner.

Table 3 Capacity and Sampling Quantity of Glass Containers

Capacity (ml)	Quantity (pieces)
≤10	30
>10 to 50	10
>50 to 250	2
>250	1

2.2 Glass tubes

Key elemental impurities include but are not limited to arsenic, antimony, lead, and cadmium. The leaching amount measurement results are expressed in mg/dm^2.

For the test of glass tubes, take a glass tube with a total surface area (including the inner and outer surfaces of each section and the cross-section at both ends) of about 100 cm^2. Grind the cross-section at both ends carefully and clean thoroughly. Place them in a container containing 200 ml of 4% acetic acid solution (if necessary, scale up the sampling area and the volume of extraction liquid). Hold at 98°C ± 1 °C for 2 hours, cool and take the residue, use it as the test

solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same manner.

2.3 Pre-filled glass components

Key elemental impurities include but are not limited to arsenic, antimony, lead, and cadmium.

Borosilicate glass barrels for pre-filled syringes: Prepare the test solution according to the method described in 2.1 Glass Containers.

Borosilicate glass barrels for syringe pens: Take the test sample, select a suitable stopper (such as silicone rubber) to seal the small mouth end of the barrel, and prepare the test solution according to the method described in 2.1 Glass Containers.

Borosilicate glass beads for syringe pens: Take the test sample, based on 2 ml of extraction liquid added to every 5 glass beads (it is recommended that the total volume of extraction liquid be not less than 50 ml), take an appropriate quantity of glass beads and place in a container containing an appropriate volume of 4% acetic acid solution. Hold at 98 °C± 1 °C for 2 hours to obtain the test solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same manner.

3. Ceramics

Key elemental impurities include but are not limited to lead and cadmium.

Take the test sample according to the requirements of Table 4, clean thoroughly, and fill with 4% acetic acid solution up to 5 mm from the overflow port of the container. If there is decorative color inside or the capacity is less than 20 ml, fill up to the overflow port. If necessary, measure the volume of the soaking solution to an accuracy of ± 2%. Extract at 22 °C ± 2 °C for 24 hours, and cover the mouth of the test sample with borosilicate glass not containing lead or cadmium or inert material aluminum foil to prevent solution evaporation. After soaking has been completed, stir the extraction solution evenly and immediately transfer into a polyethylene or polypropylene container. The extraction solution is used as the test solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same manner.

Table 4 Capacity and Sampling Quantity of Pharmaceutical Ceramic Containers

Capacity (ml)	Quantity (pieces)
≤10	30
>10 to 50	10
>50 to 250	2
>250	1

4. Metals

Mainly including pharmaceutical metal components and containers that come into direct contact with the medicinal product. Key elemental impurities include but are not limited to arsenic, mercury, lead, cadmium, cobalt, nickel, vanadium, chromium, copper, molybdenum, and aluminum.

4.1 Sheet metal drug packaging materials

Take an appropriate quantity of intact test sample (with a surface area about 200 cm^2), and

prepare the test solution and blank solution according to Method IV of Table 1 under the dissolution test method for drug packaging materials (General Chapter 4204). Filter with a 0.45 μm microporous membrane if necessary.

4.2 Metal containers

Take an appropriate quantity of intact test sample, add water or 4% acetic acid solution (or other required extraction liquid) up to the nominal capacity, seal, and extract at 70 °C ± 2 °C for 24 hours. Cool to room temperature, and the extraction solution is used as the test solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same manner.

4.3 Pre-filled syringe stainless steel needle

Remove the protective cap and glass barrel from 25 test samples, add 250 ml of water (or other required extraction liquid) to the needles, and extract for 1 hour at 37-40 °C. The extraction solution is used as the test solution. Filter with a 0.45 μm microporous membrane if necessary. Prepare blank solution using the same manner.

Preparation of Standard Solutions

Prepare corresponding standard solutions for each variety, and the media and acidity of the standard solution should be consistent with those of the test solution. The standard curve should include at least 5 concentration levels. The concentration of the series of standard solutions can be adjusted based on the content of the element to be tested.

Determination Methods

Method I Inductively coupled plasma mass spectrometry

Determine according to Inductively Coupled Plasma Mass Spectrometry (General Chapter 0412).

Method II Inductively coupled plasma atomic emission spectrometry

Determine according to Inductively Coupled Plasma Atomic Emission Spectrometry (General Chapter 0411).

Method III Atomic absorption spectrophotometry

Determine according to Atomic Absorption Spectrophotometry (General Chapter 0406).

Method IV Atomic fluorescence spectroscopy

The elemental impurities that can be determined by this method include but are not limited to arsenic and antimony.

1. Arsenic leaching amount

Test principle Under acidic conditions, thiourea and ascorbic acid are added to the test solution to pre-reduce pentavalent arsenic to trivalent arsenic, which then reacts with NADPH to generate arsine. Arsine is then loaded into an atomizer with argon gas and decomposed into atomic arsenic. Atomic fluorescence is generated under the excitation by the emission light from an arsenic hollow cathode lamp, and its fluorescence intensity is proportional to the arsenic concentration in the tested solution, and is quantified against a series of standard

solutions.

Procedure Accurately measure an appropriate volume of arsenic standard solution and dilute with 4% acetic acid solution to prepare a series of standard solutions containing 0 - 30 ng of arsenic per 1 ml. To 20 ml each of test solution and standard solution, accurately pipetted, add 1 ml of hydrochloric acid, and add 5 ml of pre-reducing agent solution (weigh 5.0 g of thiourea and 5.0 g of ascorbic acid respectively, dissolve with appropriate volume of water, and dilute with water to 100 ml. Prepare the solution just before use. All to stand at room temperature for 30 minutes and determine. At the same time, measure 20 ml of 4% acetic acid solution and prepare the standard blank solutions according to the method from "add 1 ml of hydrochloric acid".

Introduce a series of standard solutions from low to high concentrations into an atomic fluorescence spectrophotometer and measure their fluorescence intensity values. Using concentration as the X-axis and fluorescence intensity as the Y-axis, construct a standard curve and calculate the concentration of arsenic in the test solution.

The linear range of the standard curve can be determined based on the sensitivity, linear range, and actual concentration of arsenic in the extraction solution of the instrument.

2. Antimony leaching amount

Test principle Using the leaching solution in hydrochloric acid media, the pentavalent antimony in the test solution is reduced to trivalent antimony with thiourea. Then, potassium borohydride is added to reduce trivalent antimony to generate stibine. With argon gas as the carrier gas, stibine is introduced into an atomizer for atomization, and the antimony content is determined by atomic fluorescence spectroscopy.

Procedure Measure an appropriate volume of antimony standard solution and dilute with 4% acetic acid solution to prepare a series of standard solutions containing 0 to 30 ng of antimony per 1 ml. To 20 ml each of test solution and standard solution, accurately pipetted, add 1 ml of hydrochloric acid, and add 5 ml of pre-reducing agent solution (weigh 10.0 g of thiourea and 10.0 g of ascorbic acid respectively, dissolve with appropriate volume of water, and dilute with water to 100 ml. (prepare the solution just before use). All to stand for 30 minutes and determine. And measure 20 ml of 4% acetic acid solution and prepare the standard blank solutions according to the method from "add 1 ml of hydrochloric acid".

Introduce a series of standard solutions from low to high concentrations into an atomic fluorescence spectrophotometer and measure their fluorescence intensity values. Using concentration as the X-axis and fluorescence intensity as the Y-axis, construct a standard curve and calculate the concentration of antimony in the test solution.

The linear range of the standard curve can be determined based on the sensitivity, linear range, and actual concentration of antimony in the extraction solution of the instrument.

Method V Arsenic salt test method

This method applies to the determination of arsenic in 2.1 Residue on Ignition Method for the paper-based materials, and determines according to the arsenic salt test method (General Chapter 0822, Method I).

Notes: (1) Pay attention to the impact of experimental utensils on the determination results. All utensils used should be soaked overnight in 10%-20% nitric acid solution, then washed with deionized water and air dried before use. (2) Samples ignited by ceramic crucibles shall not be used for the determination of aluminum element. (3) According to the available test conditions, the pre-digestion process can be adjusted for the microwave digestion method.

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