4214　药包材元素杂质测定法

本方法适用于药品包装容器及组件在生产加工过程中因原材料引入、工艺残留的元素杂质的检测。基于各品类药包材的材质及生产工艺，所包装药品质量要求及参考 ICH　Q3D 元素杂质指导原则进行风险管理，控制元素杂质总量和（或）元素杂质浸出量。

第一部分　供试液的制备

一、元素杂质总量

1. 塑料类

主要包含与药品直接接触的塑料容器及组件，如注射剂用塑料容器及组件、吸入制剂用塑料瓶及组件、滴眼剂用塑料瓶及组件等。重点关注的元素杂质包括但不限于钡、铜、镉、铅、锡、铬。

1.1　炽灼残渣法

将供试品剪碎，取 5.0g，精密称定，置坩埚中，缓缓炽灼至完全炭化，放冷，在 500～600℃炽灼使完全灰化，冷却后取出，加盐酸溶液（1→2）5ml 溶解，低温加热至盐酸蒸气除尽后，加 2%硝酸溶液使残渣溶解，分次将溶解液转移至 25ml 量瓶中，并用 2%硝酸溶液稀释至刻度，摇匀，即得。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

1.2　微波消解法

将供试品剪碎，取 0.2g，精密称定，置消解管中，加硝酸 6ml 和浓过氧化氢溶液（30%）2ml，旋紧消解管，静置过夜，置微波消解仪中，参照表 1 设置参数，进行微波消解（可根据实际情况调整参数设置）。

表 1 微波消解程序

步骤	功率（W）	设置温度（℃）	爬坡（min）	保持时间（min）
1	1600	120	5	3
2	1600	150	8	5
3	1600	190	10	30

消解完全后，消解液应澄清，将消解液赶酸至约 1ml。用 2%硝酸溶液将消解液转移至 25ml 量瓶中，稀释至刻度，摇匀，即得。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

2.含纸类

主要包含药用铝塑封口垫片的纸板、固体药用纸袋装硅胶干燥剂所用的纸袋。重点关注的元素杂质包括但不限于砷、铅。

2.1 炽灼残渣法

（1）砷

取经高温分离后的纸板或除去干燥剂的纸袋（必要时剪碎），取 2.0g，精密称定，置坩埚中，加氧化镁 1g 及 15%硝酸镁溶液 10ml，混匀，浸泡 4 小时。置水浴锅上蒸干，缓缓炽灼至完全炭化，放冷，在 500～600℃炽灼使完全灰化，冷却后取出。加水 5ml 使润湿，用细玻棒搅拌，再用少量水洗涤玻棒上附着的灰分至坩埚内。置水浴蒸干后再于 500～600℃炽灼 2 小时，冷却后取出。加水 2ml 润湿，再缓慢加入盐酸溶液（1→2）5ml，将溶液移入检砷装置中，坩埚用盐酸溶液（1→2）洗涤 3 次，每次 2ml，再用水洗 3 次，每次 5ml，合并洗液并转移至检砷装置中。

（2）铅

取经高温分离后的纸板或除去干燥剂的纸袋（必要时剪碎），取 1.0g，精密称定，置坩埚中，缓缓炽灼至完全炭化，放冷，在 500～600℃炽灼使完全灰化，冷却后取出。再加入硝酸-高氯酸溶液（4:1）1ml，小火加热，必要时反复处理，直至残渣中无炭粒，待坩埚稍冷，加 2%硝酸溶液溶解残渣后，将试液转移至 25ml 量瓶中，坩埚用少量水洗涤，洗液并入量瓶，用水稀释至刻度，作为供试液。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

2.2 微波消解法

取经高温分离后的纸板或除去干燥剂的纸袋，将供试品剪碎，取 0.2g，精密称定，置消解管中，加硝酸 6ml 和浓过氧化氢溶液（30%）2ml，旋紧消解管，100℃预消解 1 小时，置微波消解仪中，推荐参照表 2 参数设置升温程序，进行微波消解（可根据实际情况调整参数设置）。

表 2 微波消解程序

步骤	功率（W）	设置温度（℃）	爬坡（min）	保持时间（min）
1	1600	80	15	30

2	1600	120	20	30
3	1600	160	20	30
4	1600	180	15	25

消解完全后，消解液应澄清，将消解液赶酸至约 1ml。用 2%硝酸溶液将消解液转移至 25ml 量瓶中，稀释至刻度，摇匀，即得。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

二、元素杂质浸出量

1.塑料类及弹性体类

主要包含与药品直接接触的塑料类及弹性体类容器或组件，如注射剂用塑料容器及组件、注射剂用的弹性体、吸入制剂用塑料瓶及组件、眼用制剂用塑料瓶及组件、预灌封注射器等。重点关注的元素杂质包括但不限于钡、铜、镉、铅、锡、铬、铝。

参照药包材溶出物测定法（通则 4204）项下或各品种项下溶出物试验的方法制备的供试液及空白液进行测定。

2.玻璃类

2.1　玻璃容器

重点关注的元素杂质包括但不限于砷、锑、铅、镉。浸出量测定结果以 mg/L 表示。

供试品为容器时，按照表 3 的取样数量取样，将供试品清洗干净，并用 4%醋酸溶液灌装至满口容量的 90%，对于安瓿等容量较小的容器，则灌装至瓶身缩肩部，用倒置烧杯（用平均线热膨胀系数 α（20～300℃）约为 $3.3\times10^{-6}K^{-1}$ 的硼硅玻璃制成，新烧杯须经过老化处理）或其它惰性材料盖住口部。98℃±1℃蒸煮 2 小时。冷却后取出，溶液即为供试液。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

表 3 玻璃容器容量与取样数量

容量（ml）	数量（支）
≤ 10	30
＞10～50	10

＞50～250	2
＞ 250	1

2.2 玻璃管

重点关注的元素杂质包括但不限于砷、锑、铅、镉。浸出量测定结果以 mg/dm^2 表示。

供试品为玻璃管时，取总表面积（包括每截管的内、外表面及两端的截面）约为 $100cm^2$ 的玻璃管，两端截面细工研磨后清洗干净，置装有 4%醋酸溶液 200ml 的容器中（必要时取样面积与浸提液体积等比例放大），98℃±1℃蒸煮 2 小时，冷却后取出，溶液即为供试液。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

2.3 预灌封玻璃组件

重点关注的元素杂质包括但不限于砷、锑、铅、镉。

（1）预灌封注射器用硼硅玻璃针管：按 2.1 玻璃容器项下的方法制备供试液。

（2）笔式注射器用硼硅玻璃套筒：取供试品，选用适宜的瓶塞物（如硅橡胶），封住套筒的小口端，按 2.1 玻璃容器项下的方法制备供试液。

（3）笔式注射器用硼硅玻璃珠：取供试品，按每 5 粒玻璃珠加浸提液 2ml 的比例（建议浸提液总体积不少于 50ml），取玻璃珠适量，置装有 4%醋酸溶液适量的容器中，98℃±1℃保持 2 小时，制备供试液。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

3.陶瓷类

重点关注的元素杂质包括但不限于铅、镉。

按表 4 的要求取供试品，清洗干净，用 4%醋酸溶液灌装至距容器溢出口 5mm 处，若内部有装饰颜色或容积小于 20ml，灌装至溢出口沿，必要时测定浸泡液的体积，准确到±2%。在 22℃±2℃浸提 24 小时，用不含铅、镉的硼硅玻璃或惰性材料铝箔等盖住供试品口部，以防溶液蒸发。浸泡结束后，将浸提液搅拌均匀，立即移入聚乙烯或聚丙烯容器中，浸提液即为供试液。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

表 4 药用陶瓷容器容量与取样数量

容量（ml）	数量（支）
≤ 10	30
＞10～50	10
＞50～250	2
＞ 250	1

4.金属类

主要包含直接接触药品的药用金属组件和容器，重点关注的元素杂质包括但不限于砷、汞、铅、镉、钴、镍、钒、铬、铜、钼、铝。

4.1　片材类金属药包材

取完整供试品适量（表面积约 200cm^2），参照药包材溶出物测定法（通则 4204）表 1 方法四制备供试液和空白液。必要时用 0.45μm 微孔滤膜过滤。

4.2　金属容器

取完整供试品适量，加水或 4%醋酸溶液（或其它所需浸提溶液）至标示容量，密闭，在 70℃±2℃下浸提 24h，放冷至室温，浸提液即为供试液。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

4.3　预灌封注射器不锈钢针

将 25 支除去护帽和玻璃针管的供试品，加水（或其它所需浸提溶液）250ml，在 37~40℃下浸提 1 小时，浸提液即为供试液。必要时用 0.45μm 微孔滤膜过滤。同法制备空白液。

第二部分　标准溶液的制备

各品种分别制备相应的标准溶液，标准溶液的介质和酸度应与供试液保持一致，标准曲线应至少包含 5 个浓度水平。可根据待测元素的含量调整系列标准溶液的浓度。

第三部分　测定法

第一法　电感耦合等离子体质谱法

照电感耦合等离子体质谱法（通则 0412）测定。

第二法　电感耦合等离子体原子发射光谱法

照电感耦合等离子体原子发射光谱法（通则 0411）测定。

第三法　原子吸收分光光度法

照原子吸收分光光度法（通则 0406）测定。

第四法　原子荧光光谱法

本法可测定的元素杂质包括但不限于砷、锑。

1.　砷浸出量

试验原理　在酸性条件下，供试液加入硫脲和抗坏血酸使五价砷预还原为三价砷，再与还原态氢生成砷化氢，由氩气载入原子化器中分解为原子态砷，在砷空心阴极灯的发射光激发下产生原子荧光，其荧光强度与被测液中的砷浓度成正比，与系列标准溶液比较定量。

测定法　精密量取砷标准品适量，用 4%醋酸溶液稀释制成每 1ml 中含砷 0~30ng 的标准系列溶液。分别精密取供试液与标准溶液 20 ml，加入盐酸 1ml，加入预还原剂溶液 5ml（分别称取硫脲 5.0g 与抗坏血酸 5.0g，加水适量使溶解，用水稀释至 100ml，临用新制），室温放置 30 分钟后测定，同时取 4%醋酸溶液 20ml 自“加入盐酸 1ml……”起，依法制得标准空白液。

将系列标准溶液由低浓度到高浓度依次导入原子荧光光度计后测定其荧光强度值，以浓度为横坐标，荧光强度值为纵坐标，制作标准曲线，计算供试液中砷的浓度。

可根据仪器的灵敏度、线性范围及浸提液中砷的实际浓度确定标准曲线线性范围。

2.　锑浸出量

试验原理　浸出液在盐酸介质中，用硫脲将试液中的五价锑还原为三价锑，再加入硼氢化钾与三价锑还原生成锑化氢，以氩气为载气，将锑化氢导入原子化器中原子化，用原子荧光光谱法测定锑的含量。

测定法　取锑标准品适量，用4%醋酸溶液稀释制成每1ml中含锑0~30ng的系列标准溶液。分别精密取供试液与标准溶液20ml，加入盐酸1ml，加入预还原剂溶液5ml（分别称取硫脲10.0g与抗坏血酸10.0g，加水适量使溶解，用水稀释至100ml，临用新制），放置30分钟后进行测定，同时取4%醋酸溶液20ml自“加入盐酸1ml….”起，依法制得标准空白液。

将系列标准溶液由低浓度到高浓度依次导入原子荧光光度计后测其荧光

强度值，以浓度为横坐标，荧光强度值为纵坐标，制作标准曲线，计算供试液中锑的浓度。

可根据仪器的灵敏度、线性范围及浸提液中锑的实际浓度确定标准曲线线性范围。

第五法　砷盐检查法

本法适用于“2.含纸类 2.1 炽灼残渣法（1）砷”，照砷盐检查法（通则 0822 第一法）测定。

【附注】(1)注意实验器皿对测定结果的影响，所用器皿均应经10%～20%硝酸溶液浸泡过夜，再用去离子水洗净并晾干后使用。（2）经陶瓷坩埚炽灼的样品不得用于铝元素的测定。（3）根据可获得的试验条件，微波消解法可调整预消解过程。

起草单位：四川省药品检验研究院（四川省医疗器械检测中心）联系电话：028-64020264

参与单位：中国食品药品检定研究院、湖南省药品检验检测研究院、广东省医疗器械研究所、上海市食品药品包装材料测试所、江苏博生医用新材料股份有限公司、山东省医疗器械和药品包装检验研究院、中国医药包装协会、江阴市海华橡塑有限公司

药包材元素杂质测定法起草说明

一、制定的目的意义

1. 药品包装容器及组件在生产加工过程中因原料引入、工艺残留的有害元素杂质可能影响药品质量和安全，因此对其进行控制是非常有必要的。

2. 形成“药包材元素杂质测定法”方法标准，科学有效指导药品包装容器及组件元素杂质的测定。

二、制修订的总体思路

遵循药典委对药包材标准体系的架构思路，基于《国家药包材标准》中塑料类、玻璃类、橡胶类包材金属元素及金属离子的测定方法，以及国内外药典中关于元素杂质的测定方法，制定本测定法。

三、需说明的问题

1. 本标准分为三个部分，第一部分为供试液的制备，包括“元素杂质总量”和“元素杂质浸出量”，按各品类制样法分别制备供试液；第二部分为标准溶液的制备；第三部分为测定法，包括电感耦合等离子体质谱法、电感耦合等离子体原子发射光谱法、原子吸收分光光度法、原子荧光光谱法、砷盐检查法。

2. 供试品的制备：“元素杂质总量”项下塑料类及含纸类的制样方法按照 YBB 标准中相关方法，增加了微波消解法。“元素杂质浸出量”项下塑料类及弹性体类、金属类参照药包材溶出物测定法（通则 4204）项下或各品种项下溶出物试验的方法制备样品；玻璃类、陶瓷类的制样方法按照 YBB 标准中相关方法。

3. 测定法：本方法收载了《中国药典》2020 版四部通则中电感耦合等离子质谱法、电感耦合等离子体原子发射光谱法、原子吸收分光光度法、砷盐检查法。新增了原子荧光光谱法测定砷、锑浸出量，未收录前处理复杂、污染环境的紫外-分光光度法。本方法中各测试方法项下载明的元素杂质已经过方法学验证，本方法中未载明的元素杂质如采用上述方法进行测定，需进行方法学验证。

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.

Drafting unit: Sichuan Institute for Drug Control (Sichuan Medical Device Testing Center)

Contact number: 028-64020264

Participating units: China Institutes for Food and Drug Control, Hunan Institute for Drug Control and Testing, Guangdong Institute of Medical Devices, Shanghai Institute for Food and Drug Packaging Materials Testing, Jiangsu Best New Medical Material Co., Ltd., Shandong Institute of Medical Device and Pharmaceutical Packaging Inspection, China National Pharmaceutical Packaging Association, and Jiangyin Haihua Rubber & Plastic Co., Ltd.