

Technical guide for Co-injeciton closure for Intravenous container

1 Scope

This guide specifies the terms and definitions, technical characteristics, design requirements, manufacturing process, in process control and technical requirements of the co-injection closures for intravenous container (hereinafter referred to as the co-injection closures).

2 Normative References

The following documents are necessary for the application of this document. For dated referenced documents, only dated versions are applicable to this document. For cited documents without date, the latest versions (including all modification lists) are applicable to this document.

Chinese Pharmacopoeia 2015

《*Good Manufacturing Practice for Medicinal Products (2010 version)*》

Annex 1: Manufacture of Sterile Medicinal Products.

GB/T 2828.1-2012 Sampling procedures for inspection by attributes – Part 1 :

Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection

GB8368 Infusion sets for single use - Gravity feed

GB15811 Sterile hypodermic needles for single use

YBB00232004 Pharmaceutical synthetic polyisoprene liners

YBB00242004 Pull-off PPcap for plastic intravenous container

3 Term and Definition

3.1 co-injection closures

One kind of plastic cap using for intravenous container which have co-injection structure of cap components, elastomer liner and protective components produced by co-injection technology.

3.2 Cap components

Cap components are made of plastic and is used as skeleton material for

combinational structure, and form an co-injection structure with elastomer componets.This thermoplastic material is usually polyolefin, polypropylene, etc., which has good welding performance with intravenous containers.

3. 3Elastomer componets

Elastomer componets provide sealing and spike holding function when dosing and deliverging IV solution. Elastomer componets forms co-injection structure with cap componets through co-injeciton molding process by using TPE (thermoplastic elastomer).

3. 4 TPE ---(Thermoplastic Elastomer)

Thermoplastic Elastomer contains resin segments and rubber segments with different constitution of chemical bonds.The common Thermoplastic Elastomers includes styrene (SBS, SIS, SEBS, SEPS), olefin (TPO, TPV) amino ester TPU and so on.

3. 5Protective componets

A kind of sealing material which is bonded with the cap componets to ensure that the elastomer componets are not contaminated and easy to remove when use. Tear-off foil, break off or pull-off ring can be considered.

3. 6 Tear-off foil

Tear-off foil is multilayer composite barrier film, the inner layer material can be formed with the cover componets by hot pressing (high frequency).

3. 7Break-off (Pull-off)

Using break-off or pull-off design on the surface of the cover componets during the manufacturing of the cap componets.

4. Co-injection closures technical characteristics

Co-injection Closures, the main componets of which is manufactured through one procedure, has advantages over the traditional closures. Based on the design principal, the influence of environment on the quality of products is reduced by avoiding the additional substances during the production process, such as visible foreign matters and insoluble particles. On the other hand, Co-injection Closures improves the leak tightness of each component to ensure the quality of medicines.

4.1 Production system design

The cleanliness level of the production environment of Co-injection Closures should be consistent with the environment where the drug to be packaged. The equipment shall be installed in a Class A clean area with a Class C background, and the production environment, from injection moulding to final package procedure, should be performed under the same conditions too.

The clean compressed air used in direct contact with products during production process shall comply with the requirements of 《*Good Manufacturing Practice for Medicinal Products (2010 version)* 》 *Annex 1: Manufacture of Sterile Medicinal Products*.

4.2 Technological design

Co-injection Closures are formed by one step. The raw material of closures is unpackaged in controlled-not-classified area and enclosed conveyed to injection procedure, which decreases the additional substances of raw material and product, such as foreign matters and particles which are introduced by transportation and combination and reduces risks of product quality.

On-line in-process control is contained in the production process of Co-injection Closures to ensure product quality.

5. Design requirement

Co-injection closures, combining with the intravenous container by BFS process, plastic infusion bottle, vertical soft bag, infusion bag, etc. forms the infusion packaging system (hereinafter referred to as the infusion packaging system). For the co-injection closures, the material of each part should meet the requirements of safety and suitability; the design should be able to provide safety and convenience to the production, storage of the infusion packaging system and the use of the medical care personnel, and prevent the infusion packaging system from contamination in production, storage and transportation. The co-injection closures are components of the infusion packaging system, which has functions of infusion, dosing, connection and hold with the infusion device, and maintain a sealing status throughout the infusion process.

5.1 Design requirement of co-injection closures

The composition of co-injection closures is as follows:

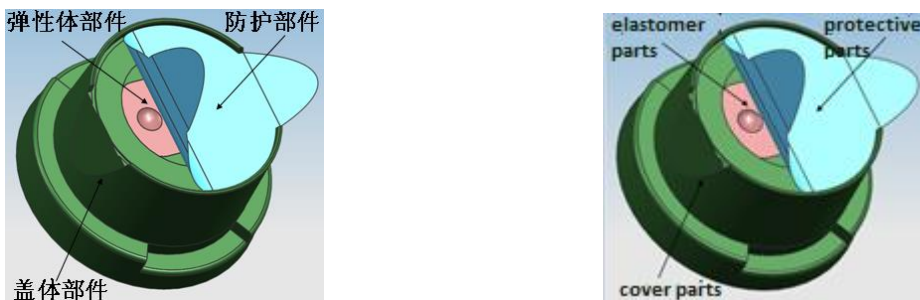
Cap componets: materials selected should meet the requirements of safety and suitability, and should have space to accommodate elastomer componets;

Elastomer componets: material selected should meet the requirements of safety and suitability. The elastomer componets can closely match with the cap componets, and form co-injection structure together. The size of the puncture site should match with the plastic puncture device which meets the requirements of *GB 8368* and the injection needles which meets the requirements of *GB 15811* (Sterile hypodermic needles for single use). The puncture site on the elastomer part should be clearly marked.

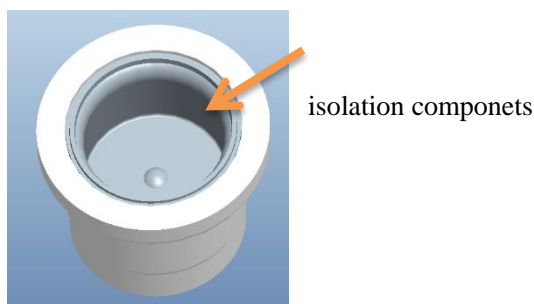
Protective componets: can be designed as part of the cover componets. The protective componets should provide sealing function to the puncture part, and can be easy to open and use. Tear-off foil structure, break-off or pull-off ring structure can be adopted

Isolation componet: it is used for seperate the elastomer componets and IV solution, used for plastic infusion bottle, vertical soft bag and infusion bag.

Illustrations for above componets are attached below:



Pic. 1 The structure of Tear-off Foil



Pic. 2 The structure of infusion isolation componets

5.2 Design requirement of suitability

The co-injection closures should be designed with suitable structure and size, which can fit with the infusion packaging conveniently and fast, to form a closure system.

5.3 Design requirement of material and structure

The co-injection closures should be designed with suitable materials, which can meet the requirements of safety and suitability (e.g. Moist Heat Sterilization), to ensure the completeness of functions during manufacturing, storage, transportation and use.

The co-injection closures should be designed with suitable structure, which can prevent the insoluble particles produced during the packaging, transportation and drug packaging process, and reduce the puncturing exfoliation when use. The protective components should have good barrier performance after filling the medicine.

5.4 Design requirement of package

The co-injection closures should be designed with suitable package, which can meet the demands of the users and ensure it free from contamination in storage and transportation, or cross-contamination in use.

The information on the package label of the co-injection closures shall refer to the relevant requirements listed in the General Rules of State Pharmaceutical Packaging Materials.

6 Production process and Process control

6.1 Production conditions

Water, compressed air and other media and production environment involved in the manufacturing process of co-injection closure shall accord with 《Good Manufacturing Practice for medicinal products(2010 version) 》 .

The co-injection closure production needs to be processed and formed in C + A Clean Level Environment.

The raw materials shall be transported by pipeline or confined vacuum to ensure

clean production environment.

6.2 The raw materials control

The co-injection closure usually consists of polyethylene / polypropylene (forming the cap part), thermoplastic elastomer TPE (forming the elastomer part) and aluminum foil / plastic foil / plastic cap (forming the protective part), shall accord with the requirements of relevant regulations and enterprise control standards of drug packaging materials.

6.3 Production process control

The production process of the co-injection closure shall be evaluated and verified to confirm that the production process conditions will not affect the physical and chemical properties of the co-injection closure.

The co-injection closure production process has process control over the appearance quality, specification and size of products.

The reliability of the protective components should be controlled in the production process of the co-injection closure.

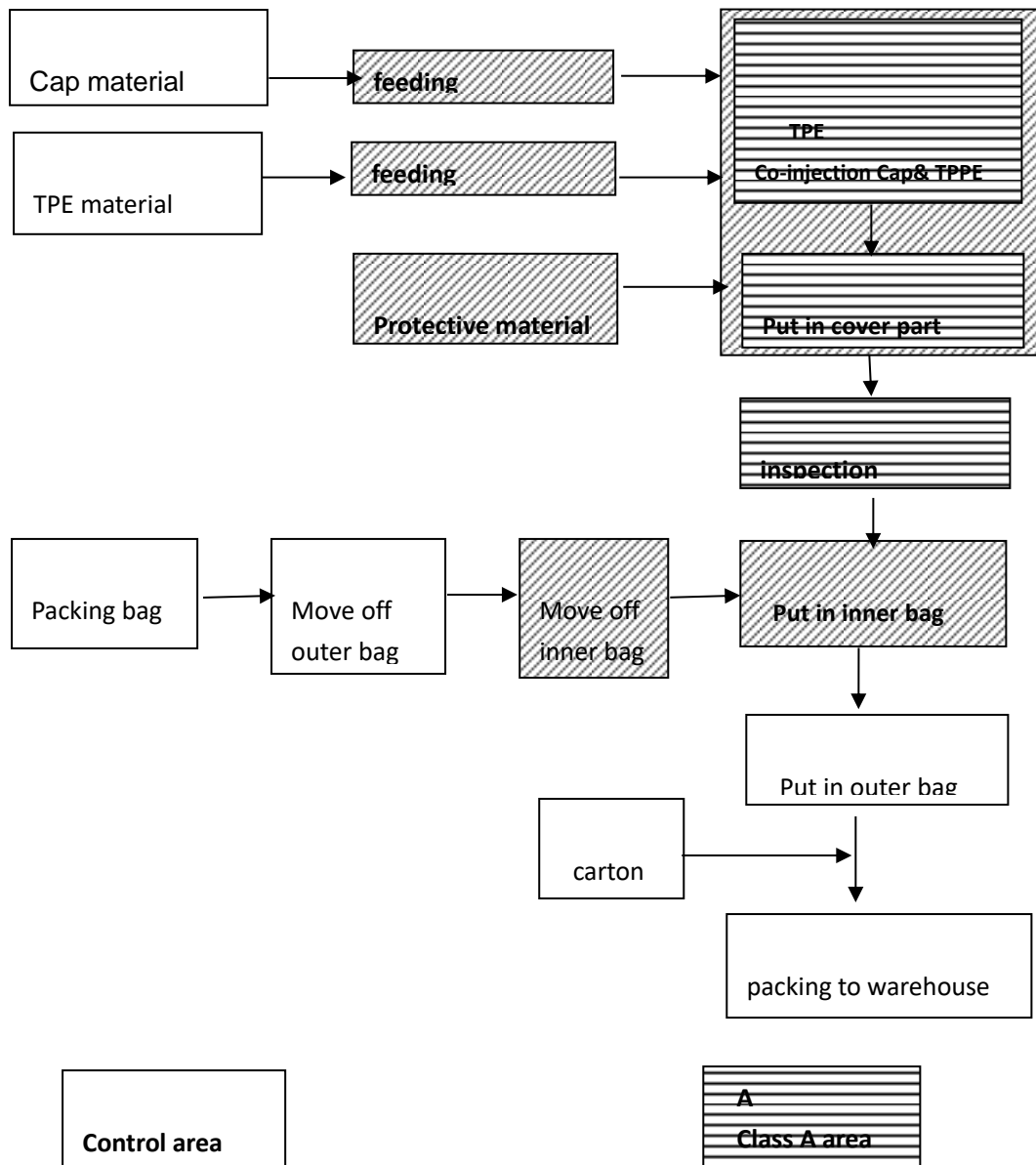
The production of co-injection closures shall be carried out in accordance with the batch management requirements of GMP, and the mixed batch shall be strictly prevented.

6.4

The co-injection molding machine can be used, and one set of molds is composed of two molds with good interchangeability, The two injection molds can realize the continuous production of the co-injection closures through continuous exchange.

6.5

Production process



6.6 Quality control of co-injection closure

Co-injection closures shall accord with the provisions of Article 7 of this guide and the provisions of enterprise standards.

6.7 Packaging, storage and transportation

The packaging of the co-injection closure shall ensure the effective prevention of pollution during storage and transportation.

The inner packaging materials of direct contact co-injection closure shall be double-layer packaged with pharmaceutical grade packaging materials.

The co-injection closure shall be stored and transported under the appropriate

temperature and humidity conditions, and shall accord with the relevant national regulations.

Chapter 7 Appendix

7. 1 Physical requirements

7. 1. 1 Appearance

7.1.1.1 125 samples shall be visually inspected under the bright natural light, and there should be no scars, cracks, bubbles, foreign matters, burrs, etc. unqualified samples should be no more than 10.

7.1.1.2 Inspection according to quality contract. Appearance defects are classified into critical defects and minor defects, and the inspection are carried out according to the Sampling Procedures Part 1: sampling plan for lot by lot inspection (GB / T 2828.1-2012) indexed by acceptance quality limit (AQL).

Typical defects are as follows:

Critical defects

- Broken, unfilled, cracked, filamented;
- Elastomer and cover are not sticky together, etc;
- Foreign matter visible on drug contact surface;

Minor defects

- Foreign matters visible on the external surface of cover
- Uneven color of the same lot

For normal one-time sampling, the acceptance quality limit (AQL) shall be determined by both the supplier and the customer. For example, the AQL for critical defects should ≤ 0.04 , and the AQL for minor defects should ≤ 0.65 .

7. 1. 2 Adaptability test

Sample Preparation: Take several integral molding samples, and perform the following adaptability tests after damp-heat sterilization (standard sterilization F_0 value ≥ 8 , if the cover is made of polypropylene, the sterilization should be at 121°C for 30minutes).

7. 1. 2. 1 Appearance after sterilization

Take 5 above-mentioned samples and place them at $-25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 24 hours, then at $50^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 24 hours, then at $23^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 24 hours, the samples should not be deformed or cracked.

7.1.2.2 Tightness

Tightness 1 (applicable to the easy-tear film type) : Take 10 above-mentioned samples, remove the easy-tear film, fill them to $2/3$ height with penetrant (65% ethanol:10g/L methylene blue solution is 100:5) then place them on paper filter for 60 minutes, there should be no leakage.

Tightness 2 (applicable to ring pulling and plate bending type): take 10 above-mentioned samples and put them upside down in the container with penetrant (65% ethanol:10g / L methylene blue solution is 100:5), vacuumized at -75kpa for 60 minutes, then take out and clean the penetrant on the outer wall of the samples, open the protective componets, and the seal part should not be dyed.

7. 1. 2. 3 Retention force

Dynamic retention force of puncture apparatus: take 10 above-mentioned samples and remove the protective componets. Use the puncture apparatus in accordance with figure 1 and the puncture needle with an outer diameter of 0.8mm in accordance with GB15811 to puncture the marked site and then pull out the puncture apparatus and puncture needle at the speed of $200\text{mm}/\text{min} \pm 20\text{mm}/\text{min}$. The pull-off force should meet the corresponding requirements, for example, the pull-off force of plastic puncture apparatus should not be less than 5.0N; the pull-off force of metal puncture needle should not be less than 1.0N

Static holding force of puncture apparatus: take 10 above-mentioned samples, and remove the protective componets, and make appropriate combination (for example, assemble them on the matched plastic infusion containers, fill the containers to the nominal capacity with injection water, and then seal them). Use the plastic puncture apparatus in accordance with figure 1 to puncture the marked part vertically, hang the container upside down, hang a certain weight on the puncture apparatus vertically, keep it for a certain time, the puncture apparatus should not be pulled out, and there should be no leakage at the puncture part. The weight and holding time of

the weight should meet the corresponding requirements:such as 0.3Kg for 4 hours.

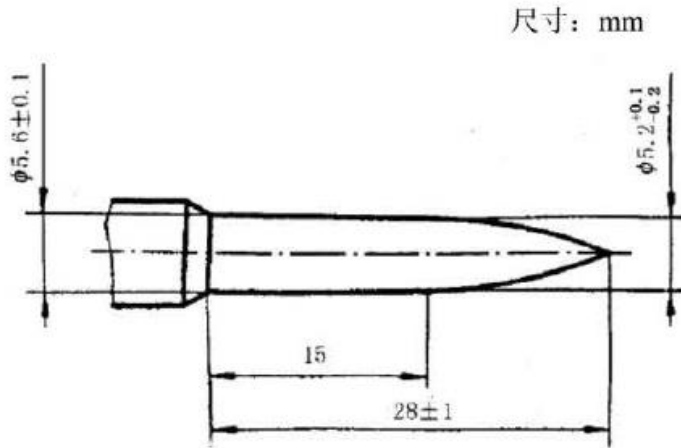


图 1 塑料穿刺器尺寸

7. 1. 2. 4 Opening force

Opening force 1 (applicable to the easy-tear film type): take 10 above-mentioned samples, fix the outer cover horizontally on the lower fixture of the tester, fix the lamination film on the upper fixture, peel off the lamination film at the speed of $200\text{mm}/\text{min} \pm 20\text{mm}/\text{min}$, and the opening force of each sample should be between 5-12.5N.

Opening force 2 (applicable to ring pulling type): take 10 above-mentioned samples, fix the outer cover horizontally on the lower fixture of the tester, and fix the pull ring on the upper fixture. Pull the pull ring at the speed of $200\text{mm}/\text{min} \pm 20\text{mm}/\text{min}$ at an angle of 23° to vertical, and the opening force should not exceed 80N. (During the test, other areas around the puncture area should not be torn, and the pull ring should not be broken).

Opening force 3 (applicable to plate bending type): take 10 above-mentioned samples, fix the outer cover horizontally on the lower fixture of the tester, and fix the wrench on the upper fixture. Pull the valve piece at a speed of $200\text{mm}/\text{min} \pm 20\text{mm}/\text{min}$ at an angle of 23° to vertical, and record the opening force of the valve piece. The opening force should not exceed 80N. (During the test, other areas around the puncture area should not be torn, and the whole valve plate should not be broken.)

7. 1. 2. 5Puncture force and Puncture fragments

Puncture force:take 10 above-mentioned samples, remove the protective componets, and use the plastic puncture apparatus in accordance with figure 1 to puncture the marked componets vertically at the speed of 200mm/min \pm 20mm/min. Record the puncture force imposed on the integrated molding samples, and make sure all samples are punctured once time. The determinant standard should meet the corresponding requirements, such as the average puncture force should not exceed 75N, and the maximum puncture force should not exceed 80N.

Puncture fragment: take above-mentioned samples and make a proper combination (for example, assemble them on the matched plastic infusion containers, fill the containers to the nominal capacity with injection water, and then seal them)). Use the puncture apparatus in accordance with figure 1 and the puncture needle with an outer diameter of 0.8mm in accordance with GB15811, which is connected with a piece of hose at the end, to puncture vertically the marked site removing protective componets once time . A total of 30 marked sites are punctured. Before pulling out the puncture apparatus, inject 5ml of water into the puncture apparatus through the hose. Repeat the above steps until all the integrated molding samples are punctured, remove the samples, and filter all the water in the container through the fast filter paper and make sure that there is no fragment left in the container. Under general conditions, the distance between the eye and the filter paper is 25cm, and the number of fragments on the fast filter paper (fragment' diameter equals to or greater than 50um) is observed by naked eyes. The determinant standard should meet the corresponding requirements, such as the number of puncture fragments of plastic and metal puncture apparatus shall not exceed 10.

7. 1. 3 Sealing of injection point

Take the plastic infusion container intended using for assembling, fill the container to the nominal capacity with injection water and then seal. Perform the following tests after damp-heat sterillization (standard sterilization F0 value \geq 8, if the cover is made of polypropylene, it should be damp-heat sterilized at 121 °C for 30 minutes).

Test method: take 10 above-mentioned samples, use the same injection needle with

outer diameter of 0.8mm in accordance with GB15811 to puncture vertically 3 different points of the puncture area removing protective components, and then pull out the injection needle, place the plastic infusion container between two parallel plates, apply a certain internal pressure and hold for a certain period of time, and there should be no liquid leakage at the insertion point. (the specific parameters should be determined according to the contract and service conditions, such as the internal pressure applied is 20KPa holding for 15s).

7.2 Chemical requirements

7.2.1 Elastomer part

Identification : take appropriate amount of sample, test it according to the Method IV infrared spectrophotometry for packaging materials (Ch.P 2019 2nd published version

<http://www.chp.org.cn/upload/userfiles/20190930/35301569812590231.pdf> or YBB00262004), and the result should correspond with the reference spectrum.

Monomer and specific migration substance (according to the formula and confirm if applicable, such as polyphenylene ether): take appropriate amount of sample, and perform the test according to the conditions of extractable research project in the Technical Guidelines for Compatibility Research of Chemicals and Elastomeric Seals (Trial).

Preparation of test solution: take the elastomer with a surface area of 200cm² into the wide-mouth bottle, boil it for 5 minutes, wash it with cold purified water for 5 times, and cover the bottle with a borosilicate glass beaker. Add 400ml of purified water and weigh. Heat it to 121 ± 2 °C within 20 to 30 minutes, and keep at this temperature for 30 minutes for sterilization. Cool it to room temperature within 30 minutes. Add purified water to original weight. Shake and pour the water immediately to separate the solution from the stopper. Shake the sample solution before each test.

Preparation of blank solution: take 400ml of purified water as blank solution.

pH variety: add 1 ml of potassium chloride (1→1000) in 20ml of test solution, and test it according to the General Rule 0631 of Ch.P2015, the pH value should be within 5.0-7.0.

UV absorption: test should be performed within 5 hours after preparation of test solution. Filter the test solution using the paper filter with 0.45µm fine holes, and discard the initial several milliliters of filtrate. Take the blank solution as the reference, measure the absorption of filtrate between the wavelength of 220nm and 360nm, and the absorption should not exceed 0.2.

Reducing substance: test should be performed within 4 hours after preparation of test solution. Measure precisely 20 ml of test solution, add exact 20ml of potassium permanganate titration solution (0.002mol/L) and 1 ml of dilute sulfuric acid solution, heat and boil for 3 minutes, cool down to room temperature. Add 1g of potassium iodide, place it in dark place for 5minutes, and titrate with sodium thiosulfate solution (0.01mol/L) to light brown, then add 0.25ml of starch indicator solution and continue titrate to colorless. In the same time, perform the same steps for blank solution. The difference of consumption of sodium thiosulfate solution (0.01 mol/L) between test solution and blank solution should not exceed 3.0ml.

Heavy metals: measure precisely 20ml of the test solution, add 2ml of acetate buffer (pH3.5), and test it according to the General Rule 0821 method I of Ch.P2015, the heavy metals' concentration should be no more than 2ppm.

Residue on evaporation: measure precisely 50ml of the test solution and blank solution, put them in the constant weighted evaporating dishes respectively, evaporate them in water bath, and dry at 105 °C to constant weight, the weight difference between test solution and blank control should not be more than 2.0mg.

Volatile substance: take the sample and test it according to the determination of volatile sulfide (YBB60052012), the test result should meet the specification.

7. 2. 2Cap part

Identification : take appropriate amount of the sample, test it according to the infrared spectrophotometry Method IV for packaging materials (Ch.P 2019 2nd published version <http://www.chp.org.cn/upload/userfiles/20190930/35301569812590231.pdf> or YBB00262004), and the result should correspond with the reference spectrum.

Preparation of test solution: take 40.0g of sample, wash and dry at room temperature,

and put it into a 500ml conical flask, add 200ml of water and seal it. Sterilize it at 121 °C for 30 minutes, cool down to room temperature, as the test solution. Treat water in the same way as the blank solution, and then perform the following tests:

Non-volatile constituents: take precisely 50ml of test solution and blank solution and put them in constant weighted evaporating dishes respectively, evaporate them in a water bath and dry them to constant weight at 105 °C, the weight difference between the two solutions should not exceed 12.5mg .

Oxidizable constituents: take precisely 20ml of test solution, add exact 20ml of potassium permanganate titration solution (0.002mol/L) and 1ml of dilute sulfuric acid solution, heat and boil it for 3 minutes, and then cool down to room temperature quickly. Add 1g of potassium iodide, place it in dark for 5 minutes, and titrate with sodium thiosulfate solution (0.01mol/L) to light brown, then add 5 drops of starch indicator solution and continue titrate to colorless. In the same time, perform the same steps for blank solution. The difference of consumption of sodium thiosulfate solution (0.01 mol/L) between test solution and blank solution should not exceed 3.0ml.

Heavy metals: take precisely 10ml of the test solution, add 2ml of acetate buffer (pH3.5), and test it according to the General Rule 0821 method I of Ch.P 2015, heavy metal content should be no more than 1ppm.

7. 2. 3 Tear-off Foil

Identification : take appropriate amount of sample, according to the Method IV infrared spectrophotometry for packaging materials (Ch.P 2019 2nd published version <http://www.chp.org.cn/upload/userfiles/20190930/35301569812590231.pdf> or YBB00262004), the test results of the inner and outer layers should be correspond with the reference spectrum.

Extractable test

Preparation of test solution: take the film with a surface area of 600cm² (the same batch of film are OK), wash and dry it at room temperature, and put it into a 500ml conical flask, add 200ml of water and seal it. Sterilize it at 121 °C for 30 minutes, cool down to room temperature, as the test solution. Treat water in the same way as the blank solution, and perform the following tests:

Non-volatile constituents: take precisely 50ml of test solution and blank solution in constant weighted evaporating dishes respectively, evaporate them in a water bath, dry them at 105 °C to constant weight, the weight difference between the two solution should not exceed 12.5mg

Oxidizable constituents: take precisely 20ml of test solution, add exact 20ml of potassium permanganate titration solution (0.002mol/L) and 1ml of dilute sulfuric acid solution, heat and boil for 3 minutes, cool to room temperature quickly. Add 0.1g of potassium iodide, and titrate with sodium thiosulfate solution (0.01mol/L) to light brown, then add 5 drops of starch indicator solution and continue titrate to colorless. In the same time, perform the same steps for blank test. The difference of consumption of sodium thiosulfate solution (0.01 mol/L) between test solution and blank solution should not exceed 3.0ml

Heavy metals: take precisely 10ml of the test solution, add 2ml of acetate buffer (pH3.5), and test it according to the General Rule 0821 method I of Ch.P 2015, heavy metal content should be no more than 1ppm.

7. 2. 4 Isolation part (If applicable)

It should include but not limited to the following items and limits:

Identification : take appropriate amount of the sample, test it according to the Method IV infrared spectrophotometry for packaging materials (Ch.P 2019 2nd published version

<http://www.chp.org.cn/upload/userfiles/20190930/35301569812590231.pdf> or

YBB00262004), the test result should correspond with the reference spectrum.

The extractable test can refer to the project and requirements of Polypropylene Infusion Bottle(YBB0002202-2015).

7.3 Microbiological Limit and Bacterial endotoxin

7. 3. 1 Microbiological Limit

Take several samples, add 100ml of aseptic pH 7.0 sodium chloride peptone buffer and mix well, as the test solution. Filtrate test solution and then test it according to general rule 1105 of Ch.P 2015. Microbiological Limit: no more than 10 CFU/piece. Thermophilic bacteria: thermophilic bacteria whose D value exceeds 5 minutes at

110 °C can not be detected.

7.3.2 Microbiological requirements under protective components

Remove the protective components under aseptic condition, use aseptic cotton swab to wipe the surface of the puncture site of samples, put the cotton swab into the test tube of tryptic soybean peptone liquid medium (TSB), and culture at 30°C-35°C for 3-5 days, the test result should be no microbial growth.

7.3.3 Bacterial endotoxin

Take several samples, put it in a certain volume of bacterial endotoxin inspection water according to the proportion of each sample:50ml of water, shake it for 1 minute, heat it to 121°C±2°C and sterilize it by damp-heat sterilization for 30 minutes, cool it to room temperature, as the test solution. Test it according to the General Rule 1143 of Ch.P 2015, the amount of endotoxin in each 1ml of test solution should not exceed 0.25EU.

7.4 Biological evaluation

The part in direct contact with the solution should include not limited to the following items and limit requirements.

Cytotoxicity

Take several samples and test them according to the fourth method of Test for Cytotoxic (YBB00012003-2015). The medium containing serum should be used as extraction medium; the ratio of sample surface area to extraction medium is 6cm²/ml, the test result should meet the requirement.