ICS 11.120
CCS C 08

Group Standard

T/CNPPA 3016—2021

Technical guide for co-injection closure for intravenous container

一体成型输液容器用密封件技术指南

（*English Translation*）

Issue date：2021-02-25 **Implementation date**：2021-02-25

Issued by China Pharmaceutical Packaging Association

Foreword

This standard is drafted in accordance with the rules given in the GB/T 1.1—2020.

This standard was proposed by China Pharmaceutical Packaging Association.

Technical guide for co-injection closure for intravenous container

1 Scope

This standard 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 theco-injection closures).

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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*

GB 8368, *Infusion sets for single use, gravity feed*

GB 15811, *Sterile hypodermic needles for single use*

YBB 0012003—2015, *Test method for cytotoxicity*

YBB 0022002—2015, *Polypropylene infusion bottle*

YBB 00232004, *Pharmaceutical synthetic polyisoprene liners*

YBB 00242004, *Pull-off PPcap for plastic intravenous container*

YBB 00302004—2015, *Measure of volatile sulfide compounds*

Chinese Pharmacopoeia 2020

Good Manufacturing Practice for Medicinal Products (2010 version)

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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 components. This thermoplastic material is usually polypropylene, polyethylene, etc., which has good welding performance with intravenous containers

3.3
elastomer components

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

3.4
thermoplastic elastomer; TPE

the elastomer which choosed in this co-injection application is non-chemical crosslinking elastomer. It is kinds of polymer between plastic and rubber. Within chemical construction, it's including the plastic chains and the rubber chains. Amongthat, the plastic chains establish physical crosslinking through acting force between these chains. This physical crosslinking is belong to reversible change. The rubber chains is high flexible chains which make TPE have machinability as plastic in high temperature and flexibilityas rubber in normal temperature

NOTE Normal TPE includes styrene (SBS, SIS, SEBS, SEPS), olefin (TPO, TPV) and so on.

3.5
protective components

a kind of sealing material which is bonded with the cap components to ensure that the elastomer components 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 cov-

er components by hot pressing (high frequency)

3.7
break-off (pull-off)

using break-off or pull-off design on the surface of the cover components during the manufacturing of the cap components

4 Co-injection closures technical characteristics

Co-injection closures, the main components 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 shouldmeet 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:

a) Cap components: materials selected should meet the requirements of safety and suitability, and should have space to accommodate elastomer components.

b) Elastomer components: material selected should meet the requirements of safety and suitability. The elastomer components can closely match with the cap components, 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. The puncture site on the elastomer part should be clearly marked.

c) Protective components: can be designed as part of the cover components. The protective components 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.

d) Isolation componet: it is used for separate the elastomer components and Ⅳ solution, used for plastic infusion bottle, vertical soft bag and infusion bag.

Illustrations for above components see Figure 1 and Figure 2.

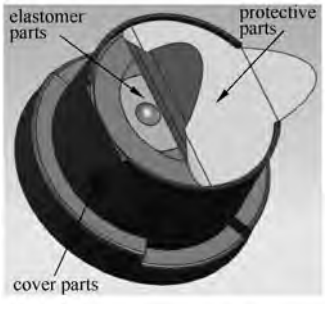


Figure 1—The structure of tear-off foil

Figure 2—The structure of infusion isolation components

5.2 Design requirement of suitability

The co-injectionco-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

5.4.1 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.

5.4.2 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 Prod-

ucts(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.

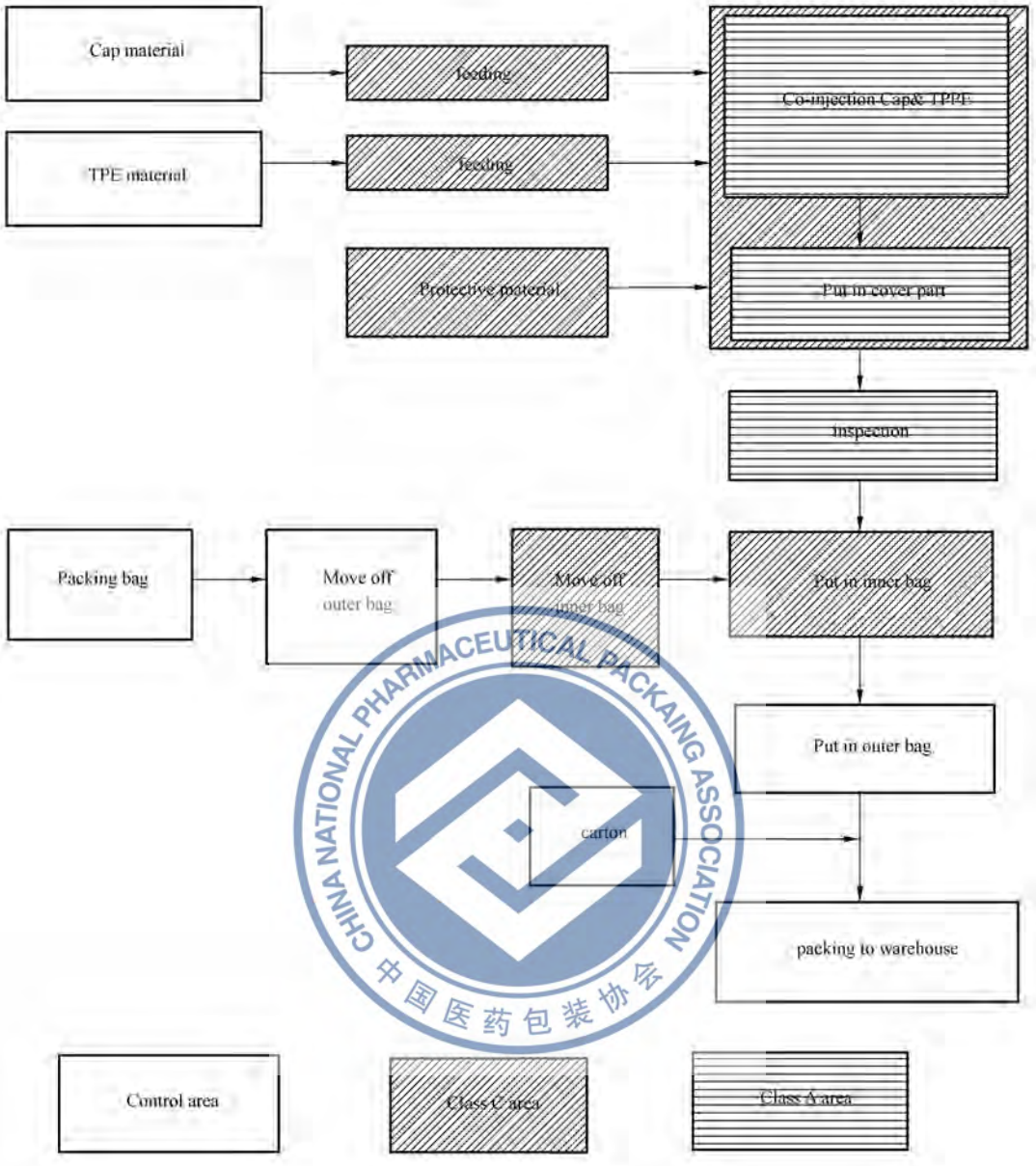
The production of co-injection closures shall be carried out in accordance with the batch management requirements of《Good Manufacturing Practice for Medicinal Products (2010version)》, and the mixed batch shall be strictly prevented.

6.4 Equipment and mould

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

Following please find production technological process of co-injection closures:



6.6 Quality control of co-injection closure

Co-injection closures shall accord with the provisions of Clause 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.

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 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

7.1.2 Adaptability test

Sample preparation: Take several integral molding samples, and perform the following adaptability tests after damp-heat sterilization (standard sterilization F0 value≥8, if the cover is made of polypropylene, the sterilization should be at 121 ℃ for 30 min).

7.1.2.1 Appearance after sterilization

Take 5 above-mentionedsamples and place them at −25 ℃ ± 2 ℃ for 24 h, then at 50 ℃ ± 2 ℃ for 24 h, then at 23 ℃ ± 2 ℃ for 24 h, the samples should not be deformed or cracked. For Foil, it should not find following problem such as layered, color change, break, open in welding area.

7.1.2.2 Leakage and tightness

Leakage: After sterilization, take 10 above-mentioned samples, fill them to 2/3 height with penetrant (65% ethanol : 10 g/L methylene blue solution is 100 : 5) let ethanol solution cover the foil area, keep 60 min, take out then clean it, open the foil, all the closure are should no any color.

Tightness 1 (applicable to the tear-off film type): take 10 above-mentioned samples, remove the easy-tear film, fill them to 2/3 height with penetrant (65% ethanol : 10 g/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 pull-off and break-off type): take 10 above-mentioned samples and put them upside down in the container with penetrant (65% ethanol : 10 g/L methylene blue solution is 100 : 5), vacuumized at −75 kPa for 60 min, then take out and clean the penetrant on the outer wall of the samples, open the protective components, 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 components. Use the puncture apparatus in accordance with Figure 3 and the puncture needle with an outer diameter of 0.8 mm in accordance with GB 15811 to puncture the marked site and then pull out the puncture apparatus and puncture needle at the speed of 200 mm/min ± 20 mm/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 5.0 N; the pull-off force of metal puncture needle should not be less than 1.0 N.

Static holding force of puncture apparatus: take 10 above-mentioned samples, and remove the protective components, 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 3 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 0.3 kg for 4 h.

Unit: mm

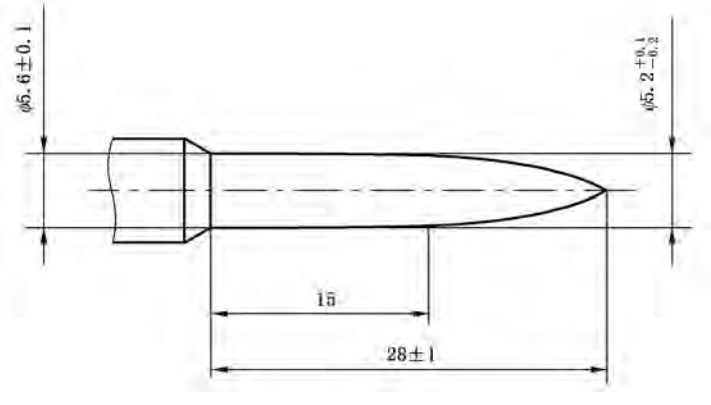


Figure 3—Plastic spike dimension

7.1.2.4 Opening force

Opening force 1(applicable to the tear-off 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 mm/min ± 20 mm/min, and the bigge stopening force of each sample should be between 5 N-30 N, the surface should not found any drawbench or layered in the opening area.

Opening force 2 (applicable to pull-off 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 mm/min ± 20 mm/min at an angle of 23° to vertical, and the opening force should not exceed 80 N. (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 twist-off 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 mm/min ± 20 mm/min at an angle of 23° to vertical, and record the opening force of the valve piece. The opening force should not exceed 80 N. (During the test, other areas around the puncture area should not be torn, and the whole valve plate should not be broken.)

7.1.2.5 Puncture force and puncture fragments

Puncture force: take 10 above-mentioned samples, remove the protective components, and use the plastic puncture apparatus in accordance with Figure 3 to puncture the marked components vertically at the speed of 200 mm/min ± 20 mm/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 75 N, and the maximum puncture force should not exceed 80 N.

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 3 and the puncture needle with an outer diameter of 0.8 mm in accordance with GB 15811, which is connected with a piece of hose at the end, to puncture vertically the marked site removing protective components once time. A total of 30 marked sites are punctured. Before pulling out the puncture apparatus, inject 5 mL 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 25 cm, and the number of fragments on the fast filter paper (fragment' diameter equals to or greater than 50 μm) 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≥8, if the cover is made of polypropylene, it should be damp-heat sterilized at 121 ℃ for 30 min).

Test method: take 10 above-mentioned samples, use the same injection needle with outer diameter of 0.8 mm in accordance with GB 15811 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 20 kPa holding for 15 s).

7.2 Chemical requirements

7.2.1 Elastomer part

7.2.1.1 Identification

Take appropriate amount of sample, test it according tothe Method Ⅳ infrared spectrophotometry for packaging materials《Chinese Pharmacopoeia 2020》, 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)》.

7.2.1.2 Extractable test

Preparation of test solution: take the elastomer with a surface area of 200 cm^2 into the wild-mouth bottle, boil it for 5 min, wash it with cold purified water for 5 times, and cover the bottle with a borosilicate glass beaker. Add 400 mL of purified water and weigh. Heat it to 121 ℃ ± 2 ℃ within 20 min to 30 min, and keep at this temperature for 30 min for sterilization. Cool it to room temperature within 30 min. 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 400 mL of purified water as blank solution.

a) pH variety: add 1 mL of potassium chloride (1→1 000) in 20 mL of test solution, and test it according to the general rule of《Chinese Pharmacopoeia 2020》, the pH value should be within 5.0-7.0.

b) UV absorption: test should be perform within 5 h after preparation of test solution. Filter the test solution using the paper filter with 0.45 μm 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 220 nm to 360 nm, and the absorption should not exceed 0.2.

c) Reducing substance: test should be performed within 4 h after preparation of test solution. Measure precisely 20 mL of test solution, add exact 20 mL of potassium permanganate titration solution (0.002 mol/L) and 1 mL of dilute sulfuric acid solution, heat and boil for 3 min, cool down to room temperature. Add 1 g of potassium iodide, place it in dark place for 5 min, and titrate with sodium thiosulfate solution (0.01 mol/L) to light brown, then add 0.25 mL of starch indicator solution and continue titrate to colorless. In the same time, perfrom 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 3.0 mL.

d) Heavy metals: measure precisely 20 mL of the test solution, add 2 mL of acetate buffer (pH 3.5), and test it according to the Heavy metals test method《Chinese Pharmacopoeia 2020》, the heavy metals' concent should be no more than 2 ppm.

e) Residue on evaporation: measure precisely 50 mL 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 ℃ to constant weight, the weight difference between test solution and blank control should not be more than 2.0 mg.

f) Volatile substance: take the sample and test it according to the determination of volatile sulfide YBB 60052012, the test result should meet the specification.

7.2.2 Cap part

7.2.2.1 Identification

Take appropriate amount of the sample, test it according to the infrared spectrophotometry Method Ⅳ for packaging materials《Chinese Pharmacopoeia 2020》, and the result should correspond with the reference spectrum.

7.2.2.2 Extractable test (plastic cover part)

Preparationof test solution: take 40.0 g of sample, wash and dry at room temperature, and put it into a 500 mL conical flask, add 200 mL of water and seal it. Sterilized it at 121 ℃ for 30 min, 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:

a) Non-volatile constituents: take precisely 50 mL 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 ℃, the weight difference between the two solution should not exceed 12.5 mg.

b) Oxidizable constituents: take precisely 20 mL of test solution, add exact 20 mL of potassium permanganate titration solution (0.002 mol/L) and 1 mL of dilute sulfuric acid solution, heat and boil it for 3 min, and then cool down to room temperature quickly. Add 0.1 g of potassium iodide, place it in dark for 5 min, and titrate with sodium thiosulfate solution (0.01 mol/L) to light brown, then add 5 drops of starch indicator solution and continue titrate to colorless. In the same time, perfrom 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 3.0 mL.

c) Heavy metals: take precisely 10 mL of the test solution, add 2 mL of acetate buffer (pH 3.5), and test it according to the general rule of 《Chinese Pharmacopoeia 2020》, heavy metal content should be no more than 1 ppm.

7.2.3 Tear-off foil

7.2.3.1 Identification

Take appropriate amount of sample, according to the Method Ⅳ infrared spectrophotometry for packaging materials 《Chinese Pharmacopoeia 2020》, the test results of the inner and outer layers should be correspond with the reference spectrum.

7.2.3.2 Extractable test

Preparation of test solution: take the film with a surface area of 600 cm^2 (the same batch of film are OK), wash and dry it at room temperature, and put it into a 500 mL conical flask, add 200 mL of water and seal it. Sterilized it at 121 ℃ for 30 min, cool down to room temperature, as the test solution. Treat water in the same way as the blank solution, and perform the following tests:

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

b) Oxidizable constituents: take precisely 20 mL of test solution, add exact 20 mL of potassium permanganate titration solution (0.002 mol/L) and 1 mL of dilute sulfuric acid solution, heatand boil for 3 min, cool to room temperature quickly. Add 0.1 g of potassium iodide, and titrate with sodium thiosulfate solution (0.01 mol/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 3.0 mL.

c) Heavy metals: take precisely 10 mL of the test solution, add 2 mL of acetate buffer (pH 3.5), and

test it according heavy metals test method《Chinese Pharmacopoeia 2020》, heavy metal content should be no more than 1 ppm.

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《Chinese Pharmacopoeia 2020》, the test result should correspond with the reference spectrum.

The extractable test can refer to the project and requirements of YBB 0002202—2015.

7.3 Microbiological limit and bacterial endotoxin

7.3.1 Microbiological limit

Take several samples, separate and expose all the surface of the closure by sterile operation, add 100 mL 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 of《Chinese Pharmacopoeia 2020》. Microbiological Limit: no more than 10 CFU/piece. Thermophilic bacteria: thermophilic bacteria whose D value exceeds 5 min at 110 ℃ 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 trypsin soybean peptone liquid medium (TSB), and culture at 30 ℃-35 ℃ 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: 50 mL of water, shake it for 1 min, heat it to 121 ℃ ±2 ℃ and sterilize it by damp-heat sterilization for 30 min, cool it to room temperature, as the test solution. Test it according to《Chinese Pharmacopoeia 2020》, the amount of endotoxin in each 1 mL 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 YBB 00012003—2015. The medium containing serum should be used as extraction medium; the ratio of sample surface area to extraction medium is 6 cm^2/mL, the test result should meet the requirement.