9624 Guideline for plastic packaging system and components for pharmaceutical packaging

This guideline applies to plastic packaging system and components for contacting directly pharmaceutical packaging. For plastic components that contact indirectly with pharmaceutical preparations but provide additional protection or delivery for pharmaceutical preparations, the guideline can serve as reference.

Classified by material: Common materials used for plastic packaging system and components include polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), polycarbonate (PC), cyclic polyolefin (COC, COP, etc.), polyvinyl chloride (PVC), polyvinylidene chloride (PVDC), ethyl vinyl acetate (EVA), polyamide (nylon PA); Polyoxymethylene (POM) and the composite materials made of above materials by compositing.

Classified by the pharmaceutical delivery route: plastic packaging system and components for injections, for inalation aerosols and sprays, for topical preparations (eye preparations, aural preparations, nasal preparations, external preparation, etc.), for oral preparations, etc.

Classification by dose: Single-dose packaging system for single dose, and multiple-dose packaging system for above single dose.

1 Terms and Definitions

Plastic Abbreviation for plastic polymer materials. It refers to processed and molded plastic materials or cross-linking curing materials, with main component of synthetic resin with high molecular weight, added by appropriate additives, such as plasticizer, stabilizer,antioxidant, lubricant and colorant.

Pellet Broadly speaking, it is a raw material for processing plastic products, and granular compound made of high molecular weight polymers (resin), generally with the melted temperature range and soften temperature range after heating. It has unique number, such as grade number, clear scope of application, certain molecular weight range, melting index, etc.

Plastic Component Any plastic component (or predominantly plastic component) used in the pharmaceutical packaging system, including plastic containers, and products which are shaped through a plasticizing process.

Plastic Container Containers manufactured by plastic (or predominantly plastic) to contain pharmaceutical preparation.

Plastic Packaging system Packaging system composed of plastic packaging components.

Type Sample Products produced with certain formula and stably processes evaluated to meet the use requirements. It is in accordance with the mass-produced formula, processes and purposes.

2 Basic requirements

2.1 Production requirements

2.1.1 Plastic Packaging system and components for packaging drugs shall be manufactured in accordance with relevant production quality specifications.

2.1.2 When selecting plastic pellets, the safety risks of pellets and additives should be evaluated, such as the type and maximum usage of additives, monomer residue, metal residue and test results of related extractable matters. The type and residue of adhesives and solvents in the composite material shall be

controlled.

2.2 Use requirements

2.2.1 The plastic components selected for pharmaceutical preparations shall have good compatibility with the packaging, and must not affect the quality, safety and effectiveness of the pharmaceutical preparations.

2.2.2 When adopting plastic packaging containers and components, the barrier properties shall be investigated according to the quality requirements of the drugs packaged in combination with different materials, processing technologies, material thickness, packaging specifications and shelf life, and be evaluated for the compliance with the needs of drugs according to the quality requirements of pharmaceutical preparations.

2.2.3 The attention shall be paid to the impact of the process on the material, and the test items and limit requirements shall be established. For example, the residue of the sterilizing agent and degradation products shall be controlled during chemical sterilization.

2.2.4 When the plastic components are combined or used with components made of other materials, they shall have good fitness and shall not affect the sealing properties of the packaging system. When necessary, an appropriate method shall be selected for evaluation according to the pharmaceutical risk assessment and the Guidelines for sealing properties of pharmaceutical packaging systems (Guideline 9628). For some plastic components which are easily softened by heat and brittle by supercooling at different temperatures and will swell and easy to deform under the action of solvents in some preparation formulas, the attention shall be paid to the impact of material changes on the integrity when being used for the intended purpose under storage conditions.

2.2.5 Plastic components for pharmaceutical packaging of different materials and purposes should be evaluated or tested for the biological safety in accordance with the Guidlines for biological evaluation and test selection of pharmaceutical packaging materials (Guideline 9651).

2.2.6 The microbial control strategy should be established based on risk management. The Plastic Packaging system and components for drugs packaging in different supply forms should be conducted with the inspection of the sterility, bio-burden limit or microbial limit in accordance with the Guidelines for microbiological testing of pharmaceutical packaging materials (Guideline 9653) and conducted with the bacterial endotoxin test in accordance with the Guideline for Bacterial Endotoxin Test Method Application (Guideline 9251).

3 Product quality control

In order to ensure the quality control of drugs, meet the clinical needs and use safety, the manufacturers and users of Plastic Packaging system and components for drugs packaging shall comply with the enterprise specification or quality agreements for products based on the actual production and use situation in accordance with but not limited to the requirements of the body of the guideline and annexes 1 to 8. The quality control requirements for sterile drug packaging systems using Blow Fill Sealing (BFS) technology can refer to annex 9.

3.1 Identification

Used to identify the material of plastic. In case of any change of the raw material supplier and production technologies of plastic components for drugs packaging or any quality problem of products, the appropriate identification test should be conducted. In addition to the following methods, the differential scanning calorimetry (DSC) may be adopted when necessary.

Infrared radiation (IR) According to the testing of infrared spectroscopy method for packaging materials <4002>, the obtained spectrum should be consistent with that of typical sample.

Density The density shall be determined in accordance with Density Determination Method for pharmaceutical Packaging <4012> and shall comply with the enterprise specification or quality agreements.

3.2 Extractables test

The extractables test is used to evaluate the total extractable matter and specific extractable matter in the plastic components for pharmaceutical packaging and can be used for the preliminary risk assessment of products and to monitor the stability of product quality, and to control the possible impact of containers and components in direct contact with drugs on pharmaceutical preparations quality. The supplier and the demander should select appropriate extractables test items for control in accordance with the Determination of Extractables for Pharmaceutical Packaging Materials and Containers <4204>, according to the risk degree and compatibility study results of the packaged drugs, in combination with different materials and processing technologies. The extractable control requirements of several categories of plastic containers and components commonly used are show in table 1-3. For the applicable scope of various products, please refer to the general chapters of each category. For categories and materials not listed, please refer to and not limited to the following.

In addition to the items in the table below, for the inspection of elemental impurities, also refer to Guideline for Elemental Impurities (Q3D). Identify known or potential sources of elemental impurities according to materials and production technologies of different products, carry out the risk assessment of elemental impurities in combination with the pharmaceutical preparation quality requirements, determine the impurities as per the assessment results and in accordance with the Elemental Impurity Determination Method for Pharmaceutical Packaging <4214> when applicable, and formulate the control requirements in the enterprise specification or quality agreements.

The nonvolatile matters shall be controlled in combination with the expected characteristics and risk degree of packaged pharmaceutical preparations. When applicable, the test solution shall be prepared with appropriate method according to the Determination of Extractables for Pharmaceutical Packaging Materials and Containers <4204> to determine the nonvolatile matters, which shall comply with the enterprise specification or quality agreements.

Table 1 extractables test (plastic products for injections and eye drops)

Product category / Test items	Plastic packaging components for injections	Plastic containers and caps for eye drops
Preparation of test	Regular sample [b]: General Chapter	Bottle: Method V

solution	4204 Method I Irregular sample: General Chapter 4204 Method III	Nozzle and cap: Method VI
Clarity	The test solution should be clear; if it is turbid, it shall not be thicker when compared with No. 2 standard turbidity liquid	The test solution should be clear; if it is turbid, it should not be thicker when compared with No. 2 standard turbidity liquid
Color	Colorless	/
pH or pH variation	5.0-7.0 (pH)	No more than 1.0 (pH variation)
Ultraviolet absorbance [a]	220-240nm: No more than 0.08 241-350nm: No more than 0.05	220~350 nm : No more than 0.10
Reducing substances (volume difference when consuming 0.01mol/L sodium thiosulfate titration solution)	No more than 1.5ml	No more than 1.5ml

a: It is suitable for polyolefin materials, such as polyethylene and polypropylene, and other materials shall comply with enterprise specification or quality agreements.

b: Easy to obtain flat parts and surface area of the sample, such as bottles, bags, etc.

Table 2 extractables test (plastic products for topical liquid preparations and ointments)

Product category / Test items	Plastic composite tubes and components (tube shoulders and caps) for topical ointments	Plastic bottles and caps for topical liquid preparations
Preparation of test solution	Tube body: General Chapter 4204 Method VII Tube shoulder / cap: General Chapter 4204 Method VIII (if necessary, each shoulder / cap can be crossly cut into four parts)	Bottle: General Chapter 4204 Method VII Cap: General Chapter 4204 Method VIII (if the cap is a combined structure, take the part that is contact with the liquid preparation; if necessary, each cap can be crossly cut into four parts)
Clarity	/	Clear; if it is turbid, it shall not be thicker when compared with No. 2 standard turbidity liquid
pH variation no more than	/	No more than 1.0

Ultraviolet absorbance (220-350 nm)	No more than 0.10	Water test solution: No more than 0.1 50% ethanol test solution[a]: No more than 0.2
Reducing substances (volume difference when consuming 0.01mol/L sodium thiosulfate titration solution)	No more than 1.0ml	No more than 1.5ml

a: It is suitable for bottles containing liquid preparations made of ethanol as a solvent, among which, polyester bottles shall comply with the enterprise specification or quality agreements.

Table 3 extractables test (plastic products for oral preparations)

Product category / Test items	Plastic bottles and caps for oral liquid preparations	Plastic bottles and caps for oral liquid preparations	Composite films and bags for oral solid preparations	Sheets for oral solid preparations
Preparation of test solution	Bottle: General Chapter 4204 Method VII Cap: General Chapter 4204 Method VIII (if the cap is a combined structure, take the part that is contact with the liquid preparation; if necessary, each cap can be crossly cut into four parts)	Bottle: General Chapter 4204 Method VII Cap: General Chapter 4204 Method VIII (if the cap is a combined structure, take the part that is contact with the solid preparation; if necessary, each cap can be crossly cut into four parts)	General Chapter 4204 Method IX	General Chapter 4204 Method X
Clarity	Clear; if it is turbid, it should not be thicker when compared with No.	/	/	/

	2 standard turbidity liquid			
pH variation	No more than 1.0	/	/	/
Ultraviolet absorbance , 220-360 nm	No more than 0.1	/	/	/
Reducing substances (volume difference when consuming 0.01mol/L sodium thiosulfate titration solution)	No more than 1.5ml	No more than 1.5ml	No more than 1.5ml	No more than 1.5ml

Annex 1: Plastic packaging system and components for injections

This annex applies to plastic packaging system and components contact with injection, concentrated solution for injection, etc., which are produced by plastic molding process with plastic pellets as the main raw material. This annex is not applicable to the multi-chamber injection packaging systems. Packaging systems for rinsing preparations can refer to implementation. The quality control requirements for the plastic packaging system for injection using Blow Fill Sealing (BFS) technology can refer to Annex 9.

Classified by the shape and structure of containers, plastic containers for injections are divided into: plastic ampoules, plastic bottles, plastic bags, etc.

Classified by shape and structure, plastic components for injections are divided into sealed caps, interfaces, hoses, etc.

Classified by packaged drug dose: A Single-dose container is designed for use with a single patient as a single injection/infusion. A Multiple-dose container is intended to contain more than one dose of a drug product.

Plastic packaging system for injections shall comply with the requirements of the body of the guideline and the following requirements.

The production management and quality control of Plastic packaging system and components for injections shall comply with the requirements of the relevant quality specification. The production environment should be controlled in accordance with the Good Manufacturing Practice for Drugs. When selecting the material of plastic packaging system and components for injections, the safety risks of materials and additives should be evaluated, such as the type and maximum usage of additives, monomer residue and elemental impurities. The packaging systems for injections should be conducted with the integrity evaluation in all links of product design, process verification, commercial production, and product stability investigation in accordance with Guideline for the Integrity of Sterile Pharmaceutical Packaging

System (Guideline 9628). At the same time, an appropriate sampling scheme should be selected based on the results of risk assessment to formulate the enterprise specification.

Plastic package for injections are high-risk preparations and the sector of using should further carry out relevant evaluation and control based on the principle of risk assessment. 1.The influences of the connection ways between components on the integrity of packaging systems should be evaluated. 2.If the specification and shape have an impact on the protection and function, it should be evaluated. When necessary, a diagram should be established to clarify the control requirements. If there are functional components for improving the protection and function in the packaging systems, relevant performance control items and requirements should be established. 3.Appropriate methods should be used to investigate the impact of the transportation and storage processes on the integrity of the packaging systems for injections, including but not limited to the quality test items of package integrity, such a heat seal strength, drop resistance and leakage rate. 4.When there are special requirements for the preparations and other volatile ingredients need to be added to the formulation and process, further attention should be paid to the requirements for the barrier property of the packaging systems for injections. Outer packaging (secondary packaging) bags with high barrier property should be used if necessary. The evaluation items and limit requirements for the barrier bags, such as oxygen transmission, nitrogen transmission or carbon dioxide transmission, should be added to the enterprise specification in combination with the formulation and process characteristics of the preparations. 5.The requirements for clinical use should set items and requirements according to the characteristics and structural forms of packaging systems, as well as the usage in the instructions. 6.If necessary, the specific extracts obtained from extractable matter research should be controlled in the enterprise specification or quality agreements based on the research results of extractable matters, which shall comply with the enterprise specification or quality agreements.

1 Microbiological control

If applicable, the bioburden shall be determined in accordance with the Guideline for Microbiological Test of Pharmaceutical Packaging (Guideline 9627) and shall comply with the enterprise specification or quality agreements.

If applicable, the test shall be determined in accordance with the sterility test method in the Guideline for Microbiological Test of Pharmaceutical Packaging (Guideline 9627) and shall comply with the enterprise specification or quality agreements.

2 Bacterial endotoxin

If applicable, refer to the Guideline for Bacterial Endotoxin Test Method Application (Guideline 9251) and shall comply with enterprise specification.

3 Physical properties

The attention should be paid to spectral transmission, water vapor transmission, gas permeance, mechanical properties, etc. If applicable, relevant items shall be established in the enterprise specification or quality agreements, which should be tested and comply with the enterprise specification or quality agreements.

4 Insoluble particles

The sample shall be determined according to the method for the Determination of Particulate Matter for Pharmaceutical Packaging Materials and Containers <4206>, which shall comply with the enterprise specification or quality agreements.

5 Use performance

5.1 In accordance with the clinical use ways of infusion bags and bottles, the attention should be paid to clinical use performance items: Penetration force, fragmentation, puncture device retention and insertion point impermeability, injection point airtightness, suspension force (for suspension function), drop resistance and opening force. If applicable, relevant items should be established in the enterprise specification, which should be tested and comply with the enterprise specification.

5.2 Plastic ampoules should be set up opening force item, according to the method specified in the enterprise specification, and should comply with the relevant requirements. Attention should be paid to water vapor transmission and spectral transmission items for the secondary packaging, which should meet the enterprise specification.

5.3 Refer to the functional requirements of Guideline on Rubber Closures for Packaging Injections (Guideline 9623) if the packaging with rubber closures for injections is applicable. Packaging system can also be tested combined with the characteristics according to the methods specified in the enterprise specification or quality agreements, and should comply with the enterprise specification or quality agreements.

5.4 For the packaging systems with special use requirements (such as closed infusion), the attention should be paid to items that may affect the clinical use, such as the residual volume and evacuation time. If applicable, relevant items should be established in the enterprise specification, which should be tested and comply with the enterprise specification.

5.5 For multiple-dose packaging systems, the attention should be paid to items that may affect the clinical use, such as the sealability for multiple use and dose accuracy. If applicable, relevant items should be established in the enterprise specification, which should be tested and comply with the enterprise specification.

Annex 2: Plastic Bottle system and Components for Eye drops

This annex applies to molded plastic bottles and components whose body are made of low-density polyethylene or polypropylene for eye drops.

In terms of bottle material: it can be classified as low-density polyethylene bottles for eye drops, and polypropylene bottles for eye drops.

In terms of the dosage of eye drops: it can be classified as plastic bottles for single-dose eye drops, and plastic bottles for multiple-dose eye drops.

It is advisable that bottle body, bottle nozzle, and bottle cap be packaged separately and stored in a dry and clean place. The packaging of sterile products shall comply with the requirements for sterilization, physical protection, maintenance of sterility state before use, and sterile access.

The plastic bottle system and components for eye drops should comply with the requirements of the main body of this guideline, and meet the following product quality control requirements.

1 General requirements

With the purpose of ensuring the controllable quality of drugs, meeting clinical needs and safety in use, manufacturers and users of plastic bottles and components for eye drops shall develop the enterprise specification or quality agreements. Drug product manufacturers shall pay attention to any change of the functional excipients (e.g., antimicrobial preservatives, etc.) in the formula of their drug products during compatibility studies and barrier property evaluations.

The appearance, spectral transmission, residue on ignition and microbiological control may be controlled according to the requirements of product quality between the manufacturers and users, as well as the results of risk assessment, and shall comply with the enterprise specification or quality agreements.

Bottle caps with additional functions, such as bacterial barrier caps and tamper-evident caps, shall be assessed for the performance of their additional functions, which shall comply with the requirements of the enterprise specification or quality agreements.

2 Decolourization test

Applicable to colour bottle. Carry out the Decolourization Examination Method for Plastics <4205>, any colour produced with the test solution is not more intense than that of the blank solution.

3 Non-volatile matter in n-hexane

Applicable to bottle. Cut 5.0g of the bottle into small pieces of suitable size (eg.3cm×0.3cm) and place them in a round-bottom flask. Add accurately 50ml of n-hexane and boil under reflux conditions for 4 hours. Allow to cool down in an ice water bath and filter the extracting solution. Transfer the filtrate into an evaporating dish previously dried to constant weight, evaporate to dryness on a water bath and dry at 105℃ for 2 hours, then weigh. Perform a blank determination and make any necessary correction. The test result shall comply with the requirements of the enterprise specification or quality agreements.

4 Assembling performance

4.1 Compatibility

Applicable to assessment of the compatibility between the bottle and bottle cap for bottles with screw caps. Assemble the bottle, bottle cap, bottle nozzle (if any) and screw tightly according to the requirements specified in the enterprise specification or quality agreements and, no stripped screw is allowed.

4.2 Sealability between components

Applicable to non-BFS (blowing-filling-sealing) bottles for eye drops. Assemble the bottle body, bottle cap, and bottle nozzle (if any) and seal according to the requirements specified in the enterprise specification or quality agreements. Place the assembled bottle in a container with an evacuation device, mount the partition plates, add water to immerse the bottle (glass beads can be previously added to the bottle or other suitable methods can be used). Evacuate the container to achieve a vacuity of 20kPa and maintain for 2 minutes, no water ingression or continuous bubbling is allowed.

4.3 Water vapor transmission

Assemble the bottle, bottle cap, and bottle nozzle (if any) according to the requirements specified in the enterprise specification or quality agreements. Test according to the Determination of Water Vapor Transmission of Packaging Materials or Containers for Pharmaceutical Use. (see the first method, gravimetric method, in General Chapter 4010, 2 weight loss method, test condition B). And the result shall comply with the enterprise specification or quality agreements.

As for BFS bottles for eye drops, make samples prefilled with labelled quantity of water or drugs. Test according to the Determination of Water Vapor Transmission of Packaging Materials or Containers for Pharmaceutical Use (see the first method, gravimetric method, in General Chapter 4010, 2 weight loss method, test condition B). And the result shall comply with the enterprise specification or quality agreements.

5 Visible particles

Applicable to non-BFS bottles to be sterilized. Fill the bottle with 0.9% sodium chloride injection or injection water to labelled quantity, then assemble the bottle, bottle cap, and bottle nozzle (if any) and seal according to the requirements specified in the enterprise specification or quality agreements. Shake for 1 minutes and examine according to the Test for Visible Particles <0904>. And the result shall comply with the enterprise specification or quality agreements.

6 Drop volume

Applicable to plastic bottles for multi-dose eye drops. BFS bottles for multi-dose eye drops shall be opened according to the method specified in the enterprise specification or quality agreements before test. Fill the bottle with 0.9% sodium chloride solution to labelled quantity. If there is a bottle nozzle, it shall be combined according to the requirements specified in the enterprise specification or quality agreements. Wipe dry the bottle mouth. Discard a few drops firstly to avoid the influence of bubbles. Then collect 50 drops of the solution (10drops/min) and obtain accurate weight (m). Calculate the mean drop volume (V) by the following expression. The results shall comply with the enterprise specification or quality agreements.

$$V=\frac{m}{50\rho}$$

where V is the mean drop volume, ml;

m is the mass of dripped solution, g;

ρ is the density of 0.9% sodium chloride solution, calculated as 1.0g/ml.

Note: It is acceptable to reduce the number of drops to be collected for small volume plastic bottles for eye drops, in that case, replace 50 in the expression with the corresponding number of collected drops.

7 Residual ethylene oxide

Applicable to components sterilized with ethylene oxide. Test according to the Determination of Ethylene Oxide for Pharmaceutical Packaging Materials and Containers <4209>. The residual ethylene oxide in test solution shall not exceed 0.6μg/ml.

Annex 3: Pharmaceutical Plastic Composite Tubes System for Topical Ointments

The topical ointments refer to the ointments in General 0109 in ChP., including the composite tubes for creams, gels and semi-solid preparation for eyes etc.

This annex applies to the following: The tubes are produced by polyethylene, aluminum, copolymer, etc., the tube caps and shoulders (tips) are mainly produced by polypropylene, polyethylene, etc., which are used for pharmaceutical plastic composite tubes system for topical ointments, while the tubes are produced by a composite process, the tube caps and shoulders (tips) are mainly produced by composite or single materials.

The components are generally tube shoulders (tips) and tube caps without sealing film. For plastic composite tubes with sealing film in topical ointments, the quality control of tubes, tube shoulders (tips) and tube caps can be carried out according to this annex. In addition, it is necessary to combine the use, the material of sealing film and the way of sealing to control the quality of sealing film and compatibility.

The packaging bag shall comply with the requirements for pharmaceutical use. It should be sealed and stored at dry, clean place without squeezed.

Pharmaceutical Plastic Composite Tubes System and Components for Topical Ointments should meet the requirements of the body of the guideline and the following requirements for product quality control.

1 Requirements

Appearance, thermal sealing strength of tube body and tube tail, microbial limit or sterility can be controlled according to the requirements of the manufacturers and the users and the result of risk assessment, in accordance with the enterprise specification or quality agreement. The risk of use of preparations should be assessed in necessity for example: preparations with different pH levels, interaction of oil-based preparation with pharmaceutical packaging materials.

2 Barrier performance

2.1 Water Vapor Transmission

Take the composite tube with the same batch number of the production sample and carry out the test according to the Determination of Water Vapor Transmission of packaging materials or containers for pharmaceutical use< 4010 method 2 condition B or method 3 condition B> which shall comply with the enterprise specification or quality agreements.

2.2 Oxygen transmission

Take the composite tube with the same batch number of the production sample and carry out the test according to the Determination of Gas Permeance of packaging materials or containers for pharmaceutical use< 4007 method 1 or method 2>, which shall comply with the enterprise specification or quality agreements.

3 Bare Aluminum at the Weld Seam

It is suitable for aluminum-plastic composite tube body. Take an appropriate amount of sample, remove the tube cap, immerse into the acidic copper sulfate solution (Take 2 g of copper sulfate, add 100 ml hydrochloride and 0.05 ml glycerin, and add water to 100 ml) to 5 mm of tube tail. Remove it after 5 minutes and cut the wall of the tube. The weld zone should not become black.

4 Residue solvents

Applicable to the outer printed and composite process produced composite tubes. Take an appropriate amount of sample, the total amount of residual solvent should not exceed 5.0 mg/m2, among which benzene as well as its homologues in solvent should not be detected (considering undetected if the result is less than 0.01 mg/m2) according to the Determination of Residual Solvent in Pharmaceutical Packaging Materials < 4207>.

5 Combined Performance

5.1 Tightness of Tube Cap

Take the ointment tube and the matching tube cap, and fasten the tube cap according to the enterprise specification or quality agreements. The tube cap should fit the tube properly without slipping teeth.

Take the above sample, fill it with water, invert it and fasten the tube cap. Observe it after 1 minute. The tube head should not leak water.

5.2 Ethanol Vapor Transmission

Applicable to the composite tubes for ethanol preparations. Take the ointment tube and the matching tube cap carry out the method for Determination of Ethanol Vapor Transmission for Pharmaceutical Plastic Containers < 4212>. The ethanol vapor transmission should not more than 0.5%.

Annex 4: Plastic Bottle system and Components for Topical Liquid Medicines

The topical liquid formulations mentioned in this attachment refer to ointments, lotions, films, and some formulations of gels, liniments, and washes as outlined in the General Chapter for Preparations of Chinese Pharmacopoeia <0100>.This attachment applies to plastic bottle system and components produced by plastic molding processes for packaging topical liquid formulations. The bottles are mainly made of materials such as polyethylene terephthalate/terephthalate G, polyethylene (low-density polyethylene is only applicable for specific drugs), and polypropylene. The bottle caps are mainly made of materials such as polyethylene and polypropylene, with the addition of opacifying agent, colorants, etc. The bottle cap is a single cap or combined cap , excluding gaskets.

For plastic bottle system and components for topical liquid medicines that use gaskets, quality control of bottles and caps may refer to this attachment. Furthermore, considering the purpose, gasket material, and sealing method, quality control of gaskets and compatibility shall be ensured.

For plastic bottle system and components for topical liquid medicines containing inner plugs, quality control of the bottle may refer to this attachment. Furthermore, considering the material and purpose of the inner plug, quality control of the inner plug and compatibility shall be ensured.

The bottle and bottle cap should be packaged separately. The packaging bags shall meet pharmaceutical requirements, be sealed, and stored in a dry and clean place.

The plastic bottle system and components for topical liquid shall comply with the requirements of the body of these guidelines and the following product quality control requirements.

1 General requirements

Caps have additional features such as child stopper caps, elderly easy-to-open caps, the opening should meet the requirements of enterprise standards or quality agreements, including and not limited to the claimed function of the inspection.

The appearance, ignition residue, oil permeability and microbial limits (or sterility) of the plastic bottle system and components for topical liquid may be controlled according to the requirements of product quality between the manufacturers and users, as well as the results of risk assessment, and shall meet enterprise specification or quality agreements.

2 Acetaldehyde

Applicable to PET bottles/caps. According to the Plastic Acetaldehyde Determination <4208>, the content of acetaldehyde shall not exceed 0.2ppm.

3 Ethylene Glycol

Applicable to PET bottles/caps. According to the Determination of Ethylene Glycol and Total Terphthaloyl Moieties for Plastic Containers <4213, Method 1>, the absorbance of the test solution shall not exceed that of the standard solution (equivalent to the ethylene glycol not exceeding one part per million.).

4 Total terephthaloyl moirties

Applicable to PET bottles/caps. According to the Determination of Ethylene Glycol and Total Terphthaloyl Moieties for Plastic Containers <4213, Method 2>, the absorbance of both test solutions shall not exceed 0.150 (equivalent to the total terephthaloyl moirties not exceeding one part per million).

5 Decolorization test

Applicable to colored bottles. According to the Plastic Decolorization Inspection <4205>, the color of each test solution shall not be darker than that of the blank solution.

6 Combination performance

6.1 Seal between bottle and bottle cap

Take the bottle and matching bottle cap, screw the cap tightly (refer to Table 4 for the torque of screw caps), immerse them in water in a container equipped with a vacuum device (glass beads or other suitable methods can be added to the bottle in advance), vacuum the test device, to a vacuum degree of 27 kPa, maintain for 2 minutes, and there shall be no ingress of water or bubbling inside the bottle.

Table 4 Torque for Bottle and Cap

Cap Diameter（mm）	Torque（N·cm）
15～20	25～110
21～30	25～145
31～40	25～180

6.2 Drop resistance

Take the bottle and matching bottle cap, screw the cap tightly (refer to Table 4 for the torque of screw caps), according to the Examination Method of Drop for Plastics Containers <4025>, there shall be no breakage.

6.3 Water vapor transmission

Applicable to bottles containing liquid formulations with water as the solvent. Take the bottle and matching bottle cap, according to the Determination of Water Vapor Transmission (Method 1, weight loss

method, test condition B in General Chapter 4010). The weight loss for each set shall not exceed 0.2% (when the cap is tightened, refer to Table 4 for the torque of screw caps).

6.4 Ethanol transmission

Applicable to bottles containing liquid formulations with ethanol as the solvent. Take the bottle and matching bottle cap, according to the Determination of Ethanol Vapor Transmission for Pharmaceutical Plastic Containers <4212>, the weight loss shall not exceed 0.5%.

Annex 5: Plastic Bottle system and Components for Oral Liquid Preparations

This annex applies to plastic bottle system which mainly use polyester, high-density polyethylene, polypropylene, etc. as the primary materials for bottles, use polyethylene, polypropylene, etc. as the primary materials for caps, can be added with opacifying agents and colorants, are manufactured using plastic molding processes and are used for packaging multi-dose oral liquid preparations. Bottle caps are single caps or combined-structured caps, excluding closure liners.

For plastic bottle system for oral liquid preparations that have closure liners, the quality of bottle bodies and caps can be controlled with reference to this annex; the quality and fitting performance of closure liners shall be additionally controlled based on the purpose, liners material, sealing method, etc.

Bottle bodies and caps shall be packaged separately. Pouches for packaging shall comply with pharmaceutical requirements and be preserved in sealed packaging pouches in a dry and clean place.

Plastic Bottle system and Components for Oral Liquid Preparations should meet the requirements of the body of the guideline and the following requirements for product quality control.

1 Requirements

If the bottle caps have additional functions, such as child-resistant caps and senior-friendly caps, the opening method shall comply with the enterprise specification or quality agreements, including but not limited to the investigation of the declared functions. Appearance, ignition residue, oil permeability, microbial limits (or sterility) for Plastic Bottle system and Components for Oral Liquid Preparations should be controlled according to the requirements of product quality between the manufacturers and users, as well as the results of risk assessment, and shall meet the enterprise specification or quality agreements.

2 Acetaldehyde

Applicable to polyester materials. Carry out the test as directed in Determination of Acetaldehyde in Plastics <4208>. The content of acetaldehyde shall be no more than 0.2 ppm.

3 Ethylene glycol

Applicable to bottles/bottle caps of PET materials. According to the Determination of Ethylene Glycol and Total Terphthaloyl Moieties for Plastic Containers <4213, Method 1> the absorbance of the test solution shall be no more than that of the standard solution (equivalent to ethylene glycol no more than 1 ppm).

4 Total terephthaloyl moirties

Applicable to bottles/bottle caps of PET materials. According to the Determination of Ethylene Glycol and Total Terphthaloyl Moieties for Plastic Containers<4213, Method 2>, the absorbance of both test solutions shall not exceed 0.150 (equivalent to the total terephthaloyl moirties not exceeding one part per million).

5 Decolorization test

Applicable to colored bottles. Take samples and carry out the test as instructed in Examination Method of Decolourization for Plastics<4205>. The color of each test solution shall not be deeper than that of the blank solution.

6 Combination performance

6.1 Seal between bottle and bottle cap

Take the bottle and matching bottle cap, screw the cap tightly (refer to Table 1 for the torque of screw caps), immerse them in water in a container equipped with a vacuum device (glass beads or other suitable methods can be added to the bottle in advance), vacuum to a vacuum degree of 27 kPa, maintain for 2 minutes, and there shall be no ingress of water or bubbling inside the bottle.

Table 5 Torque for Bottle and Cap

Cap Diameter (mm)	Torque (N·cm)
15～20	25～110
21～30	25～145
31～40	25～180

6.2 Drop resistance

Take the bottle and matching bottle cap, screw the cap tightly (refer to Table 5 for the torque of screw caps), according to the Plastic Drop Resistance Test Method < 4025>, there shall be no breakage.

6.3 Water vapor transmission

Take the bottle and the matching cap, and carry out the test as instructed in Determination of Water Vapor Transmission of packaging materials or containers for pharmaceutical use<4010, weight loss method 2 in method 1 gravimetric method, condition B>. The weight loss of each combination shall be no more than 0.2%. (Refer to Table 1 for the torque of screw caps when caps are tightened).

Annex 6: Plastic Bottle system and Components for Oral Solid Preparations

This annexapplies to plastic bottles which mainly use high-density polyethylene, polypropylene, polyester, etc. as the primary materials for bottles, use high-density polyethylene, polypropylene, low-density polyethylene, etc. as the primary materials for caps, can be added with opacifying agents, colorants and reinforcing agents, are manufactured using plastic molding processes and are used for packaging multi-dose oral solid preparations.

Bottle caps are equipped with closure liners or desiccants, and have various structures and functions.

The products with sealing gaskets in this annex are composed of aluminum-plastic laminated films and cardboards.

Bottles、caps (which may include closure liners) and closure liners (if any) shall be packaged separately. Pouches for packaging shall comply with pharmaceutical requirements and be preserved in sealed packaging pouches in a dry and clean place. The caps containing desiccant shall be sealed with high-barrier-performance laminated pouches that meet the pharmaceutical requirements, such as laminated pouches containing an aluminum layer.

Plastic Bottle system and Components for Oral Solid Preparations should meet the requirements of the body of the guideline and the following requirements for product quality control.

1 Requirements

The aluminum-plastic laminated films for closure liners shall meet the requirements in annex 7 on Plastic laminated Films and Pouches for Oral Solid preparations

If there are different combinations of bottle bodies and caps, such as combination by screw and press, the influence of mouth shape and structure on the protection and function of solid preparations shall be evaluated, and illustrations shall be provided if necessary to facilitate control.

If the bottle caps have additional functions, such as child-resistant caps and senior-friendly caps, the opening method shall comply with the enterprise specification or quality agreements, including but not limited to the investigation of the declared functions.

The sealing methods for liners mainly include heat sealing, compression and adhesion. The opening performance should be concerned according to the sealing method including but not limited to the investigation of opening force, declared function, etc. (For example, heat sealing methods should pay attention to high-temperature separability and heat seal strength)，the stability of the formulation should be combined (the investigation of in-use product stability shall be carried out for the packaging form of the product and the usage and dosage in the instructions) to control its re-protection function, not limited to the investigation of water vapor transmission before opening. The result shall comply with the enterprise specification or quality agreements.

For the caps with moisture-proof function, moisture content of desiccant and moisture content of cardboard etc. should be controlled combining with the construction of combination caps and the variety of desiccant, moisture absorption rate should be controlled not limited to the following standard methods and requirement complying with the enterprise specification or quality agreements. Appearance, residue on ignition and limit of microorganisms for plastic bottle system and components for oral solid preparations may be controlled according to the requirements of product quality between the manufacturers and users, as well as the results of risk assessment, and shall comply with the enterprise specification or quality agreements.

2 Acetaldehyde

Applicable to polyester materials. Carry out the test as directed in Determination of Acetaldehyde in Plastics < 4208>. The content of acetaldehyde shall be no more than 0.2 ppm.

3 Fluorescent of cardboard

Applicable to heat sealing liners composed of aluminum-plastic laminated films and cardboards. Take a cardboard with the surface area of 100 cm^2, place the cardboard under the UV lamp, and observe at 254 nm and 365 nm. There shall be no flake fluorescence.

4 Moisture absorption rate of desiccant

Applicable to moisture-proof combinational caps. Carry out the test as instructed in Determination of Moisture Content and Moisture Adsorption Rate of Desiccants in Moisture-proof Combinational Caps. <4211>. The saturated moisture absorption rates of silica gel, large molecular sieve and a mixture of 40%

silica gel and 60% large molecular sieve shall be no less than 30%, 19% and 24%, respectively. Their short-term moisture absorption rates shall be no more than 3%, 4.5% and 3.5%, respectively.

5 Combination performance

5.1 Tightness of bottles and caps

Take the bottle and the matching cap, and close the cap tightly (for screw caps, using the torque that is specified in Table 6), For the packaging system with closure liners, heat seal separately with reference to the heat sealing process for pharmaceutical packaging, and then immerse in water in a container with an air extractor.(glass beads can be added into the bottle in advance or other suitable methods can be adopted),and evacuate to a vacuum level of 27 kPa, and maintain for 2 minutes. There must be no water or bubble in the bottle.

Table 6 Torque between bottle and cap

Cap diameter (mm)	Torque (N·cm)
15～22	59～78
23～48	98～118
49～70	147～176

5.2 Water vapor transmission

For packaging systems without closure liners Take the bottle and the matching cap, and carry out the test as instructed in Determination of Water Vapor Transmission of packaging materials or containers for pharmaceutical use <4010, weight loss method 2 in Method 1 gravimetric method, condition C> and place for 72 hours (3 days). The weight loss of each combination shall be no more than 100 mg/24 h·L. (Refer to Table 6 for the torque of screw caps when caps are tightened).

For packaging systems with heat sealed closure liners Take the bottle and the matching cap (with a closure liner), carry out the method as instructed in Determination of Water Vapor Transmission of packaging materials or containers for pharmaceutical use<4010, weight loss method 2 in Method 1 gravimetric method, condition C>, and place for 336 ± 1 hour (14 days). The result of each combination shall be no more than 25 mg/24 h·L.

Annex 7: Oral solid Laminated film and Pouches for pharmaceutical Packaging

This annex requirement applies to the production of oral solid laminated film and pouches for pharmaceutical Packaging using welding processes on different base materials and the pouches. Its thickness generally does not exceed 0.25mm.

The Laminated film referred to in this annex is mainly composed of base material (plastic film, aluminized plastic film, aluminum foil, paper, etc.), ink, adhesive, etc.

Oral solid laminated film and pouches for pharmaceutical packaging shall meet the medicinal requirements, be sealed and stored in a dry and clean place.

Oral solid laminated film and pouches for pharmaceutical packaging should meet the requirements of the body of the guideline and the following requirements for product quality control.

1 Requirements

Oral solid laminated film and pouches for pharmaceutical packaging have various materials and structural compositions (Note 1. Schedule A). The materials and structures of the laminated films will affect the safety and protective functions of pharmaceutical preparations. The laminated films should be evaluated based on the use requirements. Materials and structures are selected and evaluated. Its design needs to consider the possible impact of the contruction and process on the packaging preparation.

Appearance and microbial limits of oral solid laminated film and pouches for pharmaceutical packaging can be controlled according to the product quality requirements of the manufacturers and users; when necessary, the type of adhesive used and the risk assessment results of residual amounts shall be controlled and meet the enterprise specification or quality agreements.

2 Barrier performance

Barrier performance is one of the key indicators for evaluating laminated film to ensure drug quality. When used for the first time, the material structure composition should be clarified. Unless otherwise specified by enterprise specification or quality agreements, relevant project selected methods and indicators shall meet the requirements. The user should fully evaluate the barrier performance risks of the laminated pouch in the form of packaging based on the special requirements of the preparation, such as oxygenation (oxygen sensitivity), etc., and conduct verification and control if necessary.

2.1 Oxygen transmission rate

It is measured according to the Determination of Gas Permeance of packaging materials or containers for pharmaceutical use< 4007 Method 1 or Method 2>. During the test, the heat seal faces the oxygen low-pressure side, oxygen permeability should not more than 0.5 cm3/(m2·24h·0.1MPa) (High oxygen resistance) or not more than 10.0cm3/(m2·24h·0.1MPa) (Medium oxygen resistance). For the specific products with low oxygen resistance, it needs to combine the characteristic of the material construction and the requirements of the quality control and shall comply with the enterprise specification or quality agreements.

2.2 Water vapor transmission rate

It is measured according to the Determination of Water Vapor Transmission of packaging materials or containers for pharmaceutical use<4010, Method1(1), Method 2 and Method3, condition B>. During the test, the welding surface is facing the low humidity side, water vapor transmission rate should not more than 0.5 g/(m2·24h) (High water resistance) or not more than 2.0 g/(m2·24h) (Medium water resistance). For the specific products with low water resistance, it needs to combine the characteristic of the material construction and the requirements of the quality control and shall comply with the enterprise specification or quality agreements.

3 Peel strength (applicable to adhesive laminated process for inner layer and sub-inner layer)

It is measured according to the Standard of Peel Strength Test<4004>. During the test, the inner layer and the sub-inner layer and above are regarded as one layer when the co-extrusion laminated process is used. The average value of the longitudinal and transverse peel strength shall comply with the regulations of the corresponding level in Table 7.

Table 3 Peel strength classification and requirements

Classification	Peel strength of inner layer and sub-inner layer（N/15mm）
1	≥2.5
2	≥1.0
3	≥0.5

Note: 1. When the dimensions of the sample in either longitudinal or transverse direction cannot meet the sampling requirements stipulated in the method standard, the peel strength test does not need to be conducted in that direction;

2. *Only applicable to laminated film/pouches for packaging small-sized preparations (such as ≤0.2g etc.).

4 Welding strength

Measure according to the requirements of the relevant material (laminated film) or pouches (laminated pouches) in the welding strength determination method <4008>. Welding strength is related to the inner material and the thickness, the average value is usually not less than 12.0 or 7.0 (N/15mm) (can be selected according to the material); the welding strength of easy-to-remove laminated film is not less than 3(N/15mm).

5 Solvent residual amount

Take an appropriate amount of sample, cut out an inner surface area of 0.02m2, and measure it according to the Determination of Residual Solvent in Pharmaceutical Packaging Materials <4207>. The total solvent residues shall not exceed 5.0 mg/m2, and the residual amounts of benzene and benzene solvents shall not be tested (considering undetected if the result is less than 0.01 mg/m2).

[Note] 1. The material and construction of oral solid laminated film and pouches for pharmaceutical packaging are various, which can be divided into paper-plastic film, plastic film-plastic film, plastic film -aluminized film, paper or plastic film-aluminum foil, multi-layer plastic film-aluminum foil, oxide coating film-plastic film or multi-layer plastic film, etc. 2. The English abbreviations of the constituent materials are commonly used in the naming and specifications of laminated film. Therefore, the names of commonly used constituent materials and their corresponding English abbreviations are listed in Schedule 8.

Schedule 8 Common abbreviations for membrane materials

abbreviation	Full name of material
ABS	Acrylonitrile butadiene styrene
AL	Aluminum foil
ALOx-BOPET	Aluminum oxide coated - biaxially oriented polyester
ALOx-BOPP	Aluminum oxide coated - biaxially oriented polypropylene
AS	Acrylonitrile-styrene copolymer
BOPA	Biaxially oriented polyamide
BOPET	Biaxially oriented polyester
BOPP	Biaxially oriented polypropylene
CPE	Cast polyethylene
CPP	Cast Polypropylene
EAA	Ethylene-acrylic acid copolymer
EEA	Ethylene-ethyl acrylate copolymer

EMA	Ethylene-methacrylic acid copolymer
EVA	Ethylene-vinyl acetate copolymer
EVOH	Ethylene-vinyl alcohol copolymer
LDPE	Low density polyethylen
MBS	Methacrylate-butadiene-styrene copolymer
OPA	Oriented polyamide
OPP	Oriented polypropylene
PAPER	Paper
PC	Polycarbonate
PE	Polyethylene
PO	Polyolefin
PT	Plane Transparent Cellophane
PVA	Polyvinyl alcohol
SiOx-BOPET	Silicon oxide coated - biaxially oriented polyester
SiOx-BOPP	Silicon oxide coated - biaxially oriented polypropylene
SiOx-OPP	Silicon oxide coating - oriented polypropylene
VMBOPP	Vacuum aluminum plated biaxially oriented polypropylene
VMCPP	Vacuum aluminum plated cast polypropylene
VMPET	Vacuum aluminized polyester

Note: Materials not listed above shall comply with the material name and English abbreviation of the specification.

Annex 8: Sheet for Oral Solid Preparations

This annex applies to sheet and composite sheet utilized in blister packaging for oral solid Preparations (tablets, capsules, etc.).

In terms of the component, sheet can be classified as single-layer sheet and multi-layer (composited) sheet.

In terms of the forming process of the blister, sheet can be classified as thermal-formed sheet and cold-formed sheet.

The products should be sealed and stored in dark, dry and clean place while the pouches and bags for packaging should meet the operating requirements of pharmaceutical products.

Sheet for Oral Solid Preparations should meet the requirements of the body of the guideline and the following requirements for product quality control.

1 Requirements

During the forming process, the properties of sheet for oral solid Preparations, including barrier properties, mechanical properties will be degraded due to tensile deformation, the tendency of degradation is related to the shape and size of the formed blisters. The risks associated with the degradation should be adequately evaluated by the utilizer on the basis of the characteristics of the preparations. Validation and control should be introduced if necessary.

Appearance and microbiological limit of sheet for oral solid Preparations may be controlled according to the requirements of product quality between the manufacturers and users, as well as the results of risk

assessment, and shall meet the enterprise specification or quality agreements.

2 Barrier properties

2.1 Water vapor transmission

Select appropriate test methods and conditions with the sealed surface facing the low-humidity side during the test. The result shall meet the enterprise specification or quality agreements according to the Determination of Water Vapor Transmission of packaging materials or containers for pharmaceutical use <4010>.

2.2 Oxygen transmission

Select appropriate test methods with the sealed surface facing the oxygen low-pressure side during the test. The result shall meet the enterprise specification or quality agreements according to the Determination of Gas Permeance of packaging materials or containers for pharmaceutical use<4007>.

3 Tensile strength

Determine the tensile strength with the test speed being 100 ± 10 mm/min and the specimen being Type I. The result shall meet the enterprise specification or quality agreements according to the Test for Tensile Properties<4005>.

4 Heat seal strength

Prepare test specimens for testing. If the product is sealed to homogeneous material, cut 4 specimens in 100mm×100mm, laminate the sealed surfaces, and seal them along the transverse direction and longitudinal direction. If the product is sealed to pharmaceutical aluminum foil (or other materials), cut 2 specimens in 100mm×100mm, then laminate the heat seal surface with the pharmaceutical aluminum foil (or other materials) with the same size and seal them along the transverse direction and longitudinal direction. Specimens should be sealed in the condition of (155 ± 5) ℃, 0.2 MPa, and 1 s. Alternatively, the condition can be customized on the basis of the characteristics of the product, technology and manufacturing equipment. The result shall meet the enterprise specification or quality agreements according to the Test for Heat Seal Strength <4008>.

5 Thermal tensile ratio (not applicable to cold stamped sheet)

The result shall meet the enterprise specification or quality agreements according to the Determination for Thermal Tensile Ratio of Pharmaceutical Sheets<4027>.

6 Polyvinylidene chloride (PVDC) coating weight

Applicable to products coated with polyvinylidene chloride (PVDC). Prepare five test specimens in 100 cm2 accurately for testing. Immerse specimens in acetone (or other suitable solvent) until the specimens can be separated (heating if necessary). Take out specimens and carefully isolate the polyvinylidene chloride (PVDC) layers. The layers should be dried in the condition of 80 ℃ ± 2 ℃ for 2 hours (or using equivalent drying method) and be stored at room temperature (23 ℃ ± 2 ℃) for 30 minutes. Subsequently, weigh each polyvinylidene chloride (PVDC) layer precisely and calculate the polyvinylidene chloride (PVDC) coating weight (expressed in g/m2). The deviation from the nominal value shall meet the enterprise specification or quality agreements.

7 Peel strength

Applicable to cold-formed sheet containing aluminum. The peel strength between the aluminum layer and the polymer layer shall meet the enterprise specification or quality agreements according to the Standard of Peel Strength Test<4004>.

8 Residual solvent

Applicable to composite sheet. Prepare test specimens with an inner surface area of 0.02 m2 for testing. The total amount of residual solvent should not exceed 5.0 mg/m2, among which benzene as well as its homologues in solvent should not be detected (considering undetected if the result is less than 0.01 mg/m2) according to the Determination of Residual Solvent in Pharmaceutical Packaging Materials <4207>.

9 Residual monomer

For the sheet containing polyvinyl chloride (PVC): Prepare test specimens for testing, the residual amount of vinyl chloride monomer should not exceed 1 μg/g according to the Determination of Vinyl Chloride Monomer and Vinylidene Chloride Monomer in Plastics <4210>.

For the sheet coated with polyvinylidene chloride (PVDC): Prepare test specimens for testing, the residual amount of vinylidene chloride monomer should not exceed 3 μg/g according to the Determination of Vinyl Chloride Monomer and Vinylidene Chloride Monomer in Plastics <4210>.

Annex 9: Aseptic Pharmaceutical Packaging Systems Produced Using Blow-Fill-Seal (BFS) Technology

This attachment provides guidance for the quality control of aseptic pharmaceutical packaging systems produced using blow-fill-seal technology (BFS technology).

BFS technology refers to an automated production process using integrated equipment to heat and extrude plastic granules, complete the blow molding of packaging containers, fill the pharmaceuticals, and seal the containers within the same equipment, guaranteeing the aseptic level.

Blow-Fill-Seal equipment (BFS equipment) is fully automated machinery that blows thermoplastic materials into containers and performs filling and sealing operations. The BFS equipment can continuously carry out blow molding, filling, and sealing processes. BFS equipment comes in two forms: open-type parison and closed-type parison.

BFS technology is suitable for filling injections, inhalation solutions, eye drops, nasal drops, rinsing solutions, and other formulations. The packaging containers produced by BFS technology operate continuously from molding, filling to sealing, reduce personnel interference, less time exposure to the environment, so as to obtain a high level of aseptic protection. The key processes of BFS technology are divided into five parts : (1) **Extrusion**: Plastic granules are heated and extruded to form a parison, which enters the open blow mold. (2) **Molding**: The main mold closes, sealing the bottom of the container. The parison is blown into the container shape using sterile compressed air or a vacuum system. (3) **Filling**: The accurately measured pharmaceutical is filled into the container through a special mandrel unit. (4) **Sealing**: After filling the pharmaceutical, the head mold closes to seal the container. (5) **Mold Opening**: The mold opens, and the container is conveyed out of the equipment, starting the next production cycle. Containers are transported to the next process through a transmission system.

1. Technical Requirements

1.1 Selection Requirements for Plastic Granule

Plastic granules used in BFS technology should be non-toxic, harmless, compatible with the type of pharmaceutical packaging container and route of administration, and suitable for BFS equipment extrusion processing. Commonly used plastic granules for BFS technology are polyethylene and polypropylene. When selecting plastic granules, safety risks of granules and additives should be evaluated. Additionally, based on the characteristics of the pharmaceutical packaging container, product stability, and final user needs, the following elements should be evaluated, including but not limited to: (1) Compatibility with the drug. (2) Mechanical properties of the packaging container. (3) Processing characteristics. (4) Performance in use. (5) Sterilization resistance.

1.2 Design Requirements for Pharmaceutical Packaging Containers

The design of pharmaceutical packaging containers should consider aspects such as shape, rigidity, toughness, wall thickness, barrier properties, light-blocking (light-transmitting) properties, and heat resistance (if needed) to meet the intended use.

1.3 BFS Technology Confirmation and Validation

Confirmation and validation of BFS technology should be determined based on quality risk management principles and the characteristics of BFS technology. The lifecycle approach should be implemented to achieve contamination control objectives through continuous improvement throughout the process.

2. Quality Control

The aseptic pharmaceutical packaging system produced by BFS technology should meet the requirements of the main body of this guidance document. The appearance, specifications, dimensions, wall thickness, sealing, light transmittance, barrier performance, mechanical performance of the pharmaceutical packaging system should meet design and usage requirements.

Depending on the use of the pharmaceutical packaging system, quality control items should be determined and meet relevant requirements to ensure the quality of pharmaceuticals is controllable, meets clinical needs, and is safe to use. The aseptic pharmaceutical packaging system produced by BFS technology should focus on the following items. For items already included in the finished product quality control, testing of the packaging system may be exempted if applicable.

2.1 Microbial Control

Biological load testing should be conducted according to the Principles of Microbiological Examination of Pharmaceutical Packaging Materials (Guideline 9653) and should meet the requirements for plastic packaging systems and components for injections, plastic bottle system, and components for eye drops, and other related preparation packaging systems.

2.2 Bacterial Endotoxins

Bacterial endotoxin testing should be conducted according to the Principles of Bacterial Endotoxin Test Application (Guideline 9251) and should meet the requirements for plastic packaging systems and components for injections and other related preparation packaging systems.

2.3 Insoluble Particles

Testing should be conducted according to the Determination Method of Insoluble Particles in Pharmaceutical Packaging Materials <4206>, and results should meet the requirements for plastic packaging systems and components for injections and other related preparation packaging systems.

2.4 Visible Foreign Matters

Inspection should be conducted according to the Inspection Method for Visible Foreign Matters<0904>, and results should meet the requirements for related preparation packaging systems.