9622 Guideline on Glass Containers for Pharmaceutical Packaging

This guideline is applicable to glass containers directly contact with drug product

Glass containers commonly used for pharmaceutical packaging are borosilicate glass and soda-lime-silica glass.

According to the different dosage form of the drug product which the glass containers directly contact with and the different usage, pharmaceutical glass containers can be classified as infusion glass bottles, glass ampoules, glass bottles for injection, glass barrel for prefilled syringes, glass components for pen-injector and pharmaceutical glass bottles etc.

1 Terms and Definitions

Borosilicate Glass

Glass containing significant amounts of boric oxide, as well as aluminum oxide, alkali metal oxide and/or alkaline earth metal oxide in addition to the main component of silicon dioxide in its glass network structure. The content of boron trioxide in borosilicate glass is generally above 5%.

Soda-lime-silica Glass

Glass containing alkali metal oxide (mainly sodium oxide) and alkali earth metal oxide (mainly calcium oxide) in addition to the main component of silicon dioxide in its glass network structure. It is also abbreviated as soda-lime glass.

Molded Glass Container

Raw materials are mixed in a certain proportion, melted into glass liquid that meets forming requirements, the glass liquid is made into glass containers with certain shape through the molding equipment with various mold shape, and annealing process. Molding formation is a one-stage molding process.

Tubular Glass Container

Raw materials are mixed in a certain proportion, heated and refined to molten glass mass that meet the tube drawing requirements, the glass liquid is drawn into glass tubing for tubular containers production. The glass tubing is then formed into glass containers with certain shape through secondary processing and annealing. Tubular formation is a two-stage molding process.

2 Basic Requirements

2.1 Production Requirements

The production of pharmaceutical glass containers shall comply with the relevant Good Manufacturing Practice (GMP) to ensure the products meet the pharmaceutical requirements. The composition of pharmaceutical glass containers shall meet the requirements for product performance, the formula proportion uniformity, the mixing and melting quality of the mixtures shall be strictly controlled in production to ensure the uniformity and stability of glass composition. The production process of pharmaceutical glass containers shall be stable to ensure uniformity within batches and consistency between batches. The pharmaceutical glass containers with interior treatment should not affect the quality of the drug products. Glass tubing used for the tubular glass containers shall conform to the related provisions of these Guideline and meet the

quality requirements and processing requirements of pharmaceutical glass containers.

2.2 Application Requirements

To ensure the safety, efficacy and the controllable quality of the drug products, pharmaceutical manufacturer shall select suitable pharmaceutical glass containers according to the specific characteristics of the drug product and it`s manufacturing process. These pharmaceutical glass containers can be made by different material and different forming process. Pharmaceutical manufacturer shall use the glass containers which appearance and size meeting the requirements of the enterprise standards or quality agreement. For drug product with light protection requirements, colored glass containers which with the light-protection performance (such as amber glass containers) can be used. Pharmaceutical manufacturer shall pay attention to the integrity of the glass container and the compatibility between the glass containers with the seals. One shall select suitable glass containers with the influence factors such as process requirements of sterile filling, freeze-drying and terminal sterilization for drug products, as well as storage condition and validity period etc. of the drug products. According to the risk assessment, one shall determine whether to carry out compatibility study and the corresponding study items. For drug products that are sensitive to factors such as metal ions, attention should be paid to the leaching risk of glass composition and elemental impurities. For drugs with high ionic strength/containing complexing agents, mild acidic or slightly alkaline, attention shall be paid to the chemical tolerance and delamination risk of the inner surface of the glass container.

3 Quality Requirements

With the purpose of ensuring the controllable quality of drug products, meeting clinical needs and safety in use, manufacturer and user of the pharmaceutical glass containers shall choose appropriate quality requirements according to the production and use situation of the glass containers, develop the enterprise specification or quality agreements, including but not limited to the provisions of these guidelines and the appendix 1-6, and develop inspection rules based on the risk management of the glass containers during their producing and using.

3.1 Coefficient of Linear Thermal Expansion It is usually used to characterize the quality of glass material and formulation stability. Coefficient of linear thermal expansion as well as its fluctuations should comply with the enterprise specification or quality agreement according to the results of Determination of Coefficient of Mean Linear Thermal Expansion for Glass (General chapter 4022) or Determination of Coefficient of Linear Thermal Expansion for Glass (General chapter 4021).

3.2 Boron Trioxide Content (for borosilicate glass) It is often used to characterize the quality of glass material and formulation stability of borosilicate glass. Tested according to Determination of Boron Trioxide Content for Glass (General chapter 4203), the boron trioxide content, as well as its fluctuation range, should comply with the enterprise specification or quality agreement.

3.3 Hydrolytic Resistance of Glass Grains at 121℃ It is an important indicator of the chemical stability of glass material characterized by the degree of hydrolytic resistance of glass materials,

which can be used to classify the grades of glass material, and can also be used to evaluate the different levels of same glass material through specific indicators. According to the Determination method of Determination of Hydrolytic Resistance for Glass Grains at 121℃ (General chapter 4201). Borosilicate glass shall match grade 1 requirement and soda-lime-silica glass shall match grade 2.

3.4 Hydrolytic Resistance of Interior Surface of Glass Containers It is an important indicator of the chemical stability of glass containers through the degree of hydrolytic resistance of the interior surface of glass containers. According to the Determination of Hydrolytic Resistance of the Inner Surfaces for Glass Containers (General chapter 4202). The hydrolytic resistance of the interior surface for different type glass container shall meet the requirement in Table 1.

Table 1 Requirement for hydrolytic resistance of interior surface

Glass container type		The lowest hydrolytic resistance Grade
Soda-lime glass container	not neutralized	Grade HC3
	neutralized	Grade HC2
Borosilicate glass container		Grade HC1 or Quality Agreements (such as Grade HCB)

Note: Neutralization treatment is a treatment process that using chemical substance to treat the inner surface of the glass container for significantly reducing the release of alkali metal ions or alkaline earth metal ions on its surface.

3.5 Leaching Amount of Arsenic, Antimony, Lead and Cadmium It is used to control the safety of the glass material. According to the Determination Method of Elemental Impurities in Pharmaceutical Packaging (General chapter 4214). The amount of arsenic, antimony, lead and cadmium shall not exceed 0.1 mg, 0.7 mg, 1.0 mg and 0.25mg, respectively, per liter of leaching solution.

3.6 Shading Property (applying to colored glass with shading property) It is used to characterize the ability of a glass container to block light of a particular wavelength, avoiding the effect of light on the drug product. The maximum light transmittance (%) within wavelength range of 290nm ~450nm is determined according to the Determination of Boron Trioxide Content for Glass (General chapter 4023). Ampoules and injection bottles shall meet the requirement in Table 2. The maximum light transmittance of glass containers used for non-injection with shading requirement shall not exceed 10%.

Table 2 Requirements for shading requirement

Size (ml)	Maximum transmittance in the wavelength range of 290nm ~ 450nm (%)	
	Ampoule	Injection vial
≤1	*≤50*	*≤25*
＞1~≤2	*≤45*	*≤20*

＞2~≤5	*≤40*	*≤15*
＞5~≤10	*≤35*	*≤13*
＞10~≤20	*≤30*	*≤12*
＞20	*≤25*	*≤10*

Appendix 1: Infusion Glass Bottles

This Guideline is applicable to infusion glass bottles of large volume.

In terms of glass material, infusion glass bottles can be classified as soda-lime-silica infusion glass bottles and borosilicate infusion glass bottles.

In terms of glass color, infusion glass bottles can be classified normally as colorless infusion glass bottles and amber glass infusion bottles.

Infusion glass bottles shall comply with the text of this guideline , and meet the following quality requirements.

1 Appearance It is used to ensure the appearance quality of infusion glass bottles. Carry out visual inspection by naked eyes under natural and bright light. The appearance quality should meet the requirement of the enterprise specification or quality agreements.

2 Thermal Shock Resistance It is used to control the thermal stability of infusion glass bottles to prevent product breakage due to thermal shock in use. According to the Determination of Thermal Shock and Thermal Shock Endurance for Glass Containers (General chapter 4019), soda-lime-silicate glass infusion bottles should not break when undertaking thermal shock test for temperature difference of 42℃; borosilicate glass infusion bottles should not break when undertaking thermal shock test for temperature difference of 60℃.

3 Internal Pressure Resistance It is used to control the internal pressure resistance of infusion glass bottles to prevent the bottles from breakage due to the increase of internal pressure during production and use. According to the Determination of Internal Pressure Resistance for Glass Containers (General chapter 4017), it shall not break after 0.6 MPa internal pressure test.

4 Internal Stress It is used to control the residual internal stress of infusion glass bottles after annealing and reduce the influence of internal stress on the mechanical strength of the product. According to Determination of Internal Stress for Glass Containers (General chapter 4003). The maximum optical path difference caused by permanent stress shall not exceed 40 nm/mm after annealing process.

Appendix 2: Glass Ampoules

This guideline is applicable to glass ampoules containing injections.

The material of glass ampoules is borosilicate glass

In terms of color, glass ampoules can be classified normally as colorless glass ampoules and amber glass ampoules.

In terms of easy-breaking way, glass ampoules can be classified as easy-breaking glass ampoules with dots and easy-breaking glass ampoules with chromatic circle.

Glass ampoules shall comply with the text of this guideline, and meet the following quality requirements.

1 Appearance It is used to control the appearance quality of glass ampoules. Carry out visual inspection by naked eyes under natural and bright light. The appearance quality shall meet the requirements of the enterprise specification or quality agreement.

2 Internal Stress It is used to control the residual internal stress of glass ampoule after annealing and reduce the influence of internal stress on the mechanical strength of the product. According to Determination of Internal Stress for Glass Containers (General chapter 4003), the optical path difference caused by the maximum permanent stress after annealing shall not exceed 40 nm/mm.

3 Breaking Force It is used to control the easy-breaking property of glass ampoules. According to the Determination of Breaking Force for Glass Ampoules (General chapter 4018), the range of breaking force should be within the level specified in Table 1.

Table 1 Breaking Force of Glass Ampoules

<table>
<tr><td rowspan="2">Size (ml)</td><td colspan="2">Breaking Force (N)</td></tr>
<tr><td>Minimum</td><td>Maximum</td></tr>
<tr><td>1</td><td rowspan="8">25</td><td rowspan="4">80</td></tr>
<tr><td>2</td></tr>
<tr><td>3</td></tr>
<tr><td>5</td></tr>
<tr><td>10</td><td>90</td></tr>
<tr><td>20</td><td rowspan="3">100</td></tr>
<tr><td>25</td></tr>
<tr><td>30</td></tr>
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Appendix 3: Glass Bottles for Injection

This Guideline is applicable to glass bottles containing small volume injection, sterile powder for injection (including freeze-dried) and concentrated solution for injection (commonly known as vials).

In terms of glass material, glass injection vials can be classified as soda-lime-silica injection glass bottles and borosilicate injection glass bottles.

In terms of glass color, glass injection vials can be classified normally as colorless glass bottles for injection and amber glass bottles for injection.

In terms of forming process, glass injection vials can be classified as tubular glass injection vials and molded glass injection vials.

Glass injection vials shall comply with the text of this guideline, and meet the following quality requirements.

1 Appearance It is used to ensure the appearance quality of injection glass bottles. Carry out visual inspection by naked eyes under natural and bright light. The appearance quality shall meet the requirements of the enterprise specification or quality agreement.

2 Thermal Shock Resistant (for molded injection bottles) It is used to control the thermal stability of molded injection bottles to prevent product breakage due to thermal shock in use. According to the Determination of Thermal Shock and Thermal Shock Endurance for Glass Containers (General chapter 4019), Soda-lime-silica glass shall not break when undertaking thermal shock test for temperature difference of 42℃; Borosilicate glass shall not break when undertaking thermal shock test for temperature difference of 60℃.

3 Internal Pressure Resistance (for molded injection bottles) It is used to control the internal pressure resistance of injection glass bottles to prevent the containers from breaking due to the increase of internal pressure during production and use. According to the Determination of Internal Pressure Resistance for Glass Containers (General chapter 4017), it shall not break under 0.6 MPa internal pressure test.

4 Internal Stress It is used to control the residual internal stress of injection glass bottles after annealing and reduce the influence of internal stress on the mechanical strength of the product. According to the Determination of Internal Stress for Glass Containers (General chapter 4003), the optical path difference caused by the maximum permanent stress after annealing shall not exceed 40 nm/mm.

Appendix 4: Glass Barrel for Prefilled Syringes

This guideline is applicable to glass barrel for prefilled syringes containing injections.

Glass barrels for prefilled syringes are normally made of borosilicate glass, and have two forms, one is Glass barrels for prefilled syringes with staked needle, and the other is glass barrels for prefilled syringes with luer cone.

Glass barrels for prefilled syringes shall comply with the text of this guideline, and meet the following quality requirements.

1 Appearance It is used to control the appearance quality of glass barrel for prefilled syringes. Carry out visual inspection by naked eyes under natural and bright light. . The appearance quality shall meet the enterprise specification or quality agreements.

2 Internal stress It is used to control the residual internal stress of glass barrels for prefilled syringe after annealing and reduce the influence of internal stress on the mechanical strength of

the product. According to the Determination of Internal Stress for Glass Containers (General chapter 4003), the optical path difference caused by the maximum permanent stress after annealing shall not exceed 40nm/mm.

Appendix 5: Glass Components for Pen-injector

This guideline is applicable to glass components for pen-injector containing injections.

Glass components for pen-injector are normally made of borosilicate glass, including glass barrels and glass beads.

Glass components for pen-injector shall comply with the text of this guideline, and meet the following quality requirements.

1 Appearance It is used to control the appearance quality of glass components for pen-injector. Take appropriate amount of glass barrel or glass beads, carry out visual examination by observing under natural light. The appearance quality shall conform to the enterprise specification or quality agreement.

2 Internal Stress (applicable to glass barrel) It is used to control the residual internal stress of glass barrels after annealing and reduce the influence of internal stress on the mechanical strength of the products. According to the Determination of Internal Stress for Glass Containers (General chapter 4003), the optical path difference caused by the maximum permanent stress after annealing shall not exceed 40 nm/mm.

Appendix 6: Pharmaceutical Glass Bottles

This guideline is applicable to pharmaceutical glass bottles containing oral or topical drugs.

Pharmaceutical glass bottles can be mainly classified in terms of glass material, forming process and color.

In terms of glass material, pharmaceutical glass bottles can be classified as soda-lime-silica glass bottles and borosilicate glass bottles.

In terms of forming process, pharmaceutical glass bottles can be classified as tubular glass bottles and molded glass bottles.

In terms of color, pharmaceutical glass bottles can be classified normally as colorless glass bottles and amber glass bottles.

Pharmaceutical glass bottles shall comply with the text of this guideline, and meet the following quality requirements.

1 Appearance It is used to control the appearance quality of pharmaceutical glass bottles. Carry out visual inspection by naked eyes under natural and bright light. The appearance quality shall meet the enterprise specification or quality agreements.

2 Thermal Shock Resistant (for molded pharmaceutical bottles) It is used to control the thermal stability of molded pharmaceutical bottles to prevent product breakage due to thermal shock in use. According to the Determination of Thermal Shock and Thermal Shock Endurance

for Glass Containers (General chapter 4019), soda-lime-silica glass shall not break when undertaking thermal shock test for temperature difference of 42℃ Borosilicate glass shall not break when undertaking thermal shock test for temperature difference of 60℃.

3 Internal Stress It is used to control the residual internal stress of glass after annealing, and to prevent the mechanical strength of pharmaceutical glass bottles from decreasing due to the internal stress during production and use. According to the Determination of Internal Stress for Glass Containers (General chapter 4003). The optical path difference caused by the maximum permanent stress after annealing shall not exceed 40nm/mm.

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