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Guidance for Classification and Application of Pharmaceutical Glass Containers

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Contents

Preface

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Introduction

Pharmaceutical glass containers are commonly-used packaging containers in direct contact with drugs. Pharmaceutical glass manufacturer may design, develop and name new products and formulate product standards according to the guidance, and pharmaceutical manufacturer may understand classification and performance of glass containers and select proper packages for different drugs in reference to the guidance.

After selection of glass containers, pharmaceutical manufacturer should sign a quality agreement with pharmaceutical glass manufacturer: content of quality audit; complete product standard, including appearance defect, geometric shape, dimensions, deviation, physical and chemical properties, principle of division of batches and acceptable quality level etc. Glass manufacturer will effectively monitor over variation of product quality, and timely notify customers of changes in process, formulation, manufacturing site and product standard as well as relevant research.

Guidance for Classification and Application of Pharmaceutical Glass Containers

1 Scope

This document provides the guidance for classification and application of pharmaceutical glass containers.

The guidance is applicable to glass containers in direct contact with drugs.

2 Normative References

The following standards contain provisions which, through reference in this text, constitute provisions of this document. For dated references, the corresponding editions of the date shall apply to this document. For undated references, the latest editions (including all amendments) shall apply to this standard.

Chinese Pharmacopoeia 2020

National Standard for Pharmaceutical Packaging Materials-2015-Determination of Coefficient of Mean Linear Thermal Expansion

3 Terms and Definitions

The following terms and definitions are applicable to this document.

3.1 **Pharmaceutical glass containers**

It refers to the glass containers with good chemical stability and transparency that are in direct contact with drugs and able to store drugs stably.

3.2 **Tubular glass containers**

After smelting by glass furnace into liquid glass conforming to the requirement for forming, the mixture or glass batch is drawn into glass tubes for manufacturing of tubular bottles that are put under secondary processing into glass containers of certain geometric shape. Tubular forming is a secondary forming process.

3.3 **Molded glass containers**

After the mixture is smelted by glass furnace into liquid glass conforming to the requirement for forming, forming equipments and molds of different shapes are used to make liquid glass into glass containers of certain shape. Molded forming is a primary forming process.

3.4 **Inner surface durability of glass containers**

It refers to the inner surface resistance to physical/chemical erosion of water, acid, alkali and other substances, and to temperature, pressure and other environmental factors when any content is packaged in glass containers.

3.5 **Delamination**

It refers to the 50μm- 200μm snowflake-shape (or flake-like) sheets falling from inner surface of glass containers due to interaction of the packaged content and glass containers.

3.6 **Light resistance**

It refers to glass container performance of protecting the packaged drugs from transmission of light of specific wavelength.

3.7 **Internal surface treatment**

It refers to the treatment process aimed to improve certain performance of internal surface of glass containers, such as neutralizing treatment and siliconizing.

3.8 **Outer surface treatment**

It refers to the treatment process of outer surface of glass containers aimed to improve pharmaceutical bottle strength and protect from scratching, such as the hot end coating and cold end coating of outer surface of glass containers.

3.9 **Neutralizing treatment**

It refers to sulfidizing and other treatment to reduce alkali metal ion release of glass inner surface.

3.10 **Siliconizing**

It refers to the process aimed to improve hydrophobicity or lubricating property of inner surface of glass containers, such as silicone oil (emulsion) treatment and solidifying of inner surface of glass containers.

3.11 **SiO_2 coating**

It is used to reduce migration of glass components. For instance, the plasma impulse chemical vapor deposition (PICVD) method may be used to enable plasma reaction of inner surface of glass containers and silicon-containing gas (hexamethyldisiloxane) and form SiO_2 coating of uniform density in the form of covalent bond.

3.12 **Glass chemical strengthening**

Pharmaceutical glass container is put into salt bath over 260℃ for hot dipping for hours, during which potassium ion in the salt bath and sodium ion in glass will be exchanged to form a strengthening layer that can improve mechanical strength of glass containers.

3.13 **The cold end coating**

To improve impact strength and resistance to friction and scratching of glass containers, compressed air is used to spray polymer onto outer surface of glass containers that are under low temperature after annealing, so as to form a thin coating.

3.14 **The hot end coating**

To significantly improve internal pressure strength of glass containers, chemical vapor deposition (CVD) method is used to spray coating material onto outer surface of the containers that are under

high temperature after forming.

4 Classification

4.1 General

Pharmaceutical glass containers are classified by material, performance, forming process, post-forming surface treatment and shape.

4.2 Classification by material

Pharmaceutical glass is classified by material into four types, namely quartz glass, borosilicate glass, aluminosilicate glass and soda-lime glass. Chemical composition of each glass type is not fixed and may vary within certain range. However, difference in chemical composition of the same type of glass is allowed. Refer to table 1 for chemical composition and main properties of various glass types.

Table 1 Classification of pharmaceutical glass by material

Chemical composition	Glass type			
	Quartz glass	Borosilicate glass	Aluminosilicate glass ③	Soda-lime glass
SiO_2 (%)	>99	Appr. 71～81	Appr. 72～75	Appr. 70
B_2O_3 (%)	/	≥5	/	<5
Al_2O_3 (%)	/	Appr. 2～7	Appr. 9～12	Appr. 0～4
Alkali metal oxide (Na_2O+K_2O) (%)	/	Appr. 4～12	Appr. 10～13	Appr. 12～16
Alkali earth metal oxide (CaO, MgO, BaO)	/	0～5	0～5	Appr. 12
Coefficient o f mean linear thermal expansion $\times10^{-6}/K^{-1}$ (20～300℃) ① ($10^{-6}/K^{-1}$)	<1	3.2～7.5	6.0～7.0	7.6～9.0
Hydrolytic resistance of glass grain @ 121℃	Type I	Type I	/	Type II
Note: Refer to the diboron trioxide determination method in general technical requirements 4009, part IV, Chinese Pharmacopoeia 2020.				
① Refer to the method for determination of coefficient of mean linear thermal expansion (YBB00202003-2015); ② Refer to the method for determination of hydrolytic resistance of glass grain under 121℃ in general technical requirements 4001, part IV, Chinese Pharmacopoeia 2020. ③ Aluminosilicate glass is generally used after chemical strengthening process.				

4.3 Classification by performance

4.3.1 Classification by hydrolytic resistance of glass inner surface

Pharmaceutical glass is classified by hydrolytic resistance of inner surface into category 1 glass, category II glass and category III glass, as listed in table 2.

Table 2 Classification of hydrolytic resistance of pharmaceutical glass containers

Glass type	Hydrolytic resistance of inner surface①
Category I glass	High hydrolytic resistance
Category II glass	High hydrolytic resistance after neutralizing treatment
Category III glass	Medium hydrolytic resistance without neutralizing treatment
① Refer to the method for determination of inner surface hydrolytic resistance in general technical requirements 4006, part IV, Chinese Pharmacopoeia 2020 for specific value of hydrolytic resistance of inner surface.	

4.3.2 Classification by light resistance

Pharmaceutical glass containers are classified into two types, namely colorless type and colored type. Colored glass, such as brown glass, has light resistance.

4.4 Classification by forming process

Pharmaceutical glass containers are classified into tubular bottle and molded bottle by the forming process.

Tubular pharmaceutical glass containers include tubular injection bottle (penicillin bottle), ampoule, pen-injector sleeve (card bottle), prefilled syringe, tubular oral liquid bottle and tubular vial.

Molded pharmaceutical glass containers include infusion bottle, injection bottle (penicillin bottle) and vial.

4.5 Classification by post-forming surface treatment

Pharmaceutical glass containers that are put under surface treatment after forming for performance improvement include glass containers of neutralizing treatment, siliconizing, SiO_2 coating, chemical strengthening, cold end coating and hot end coating.

4.6 Classification by shape

Pharmaceutical glass containers are classified by shape into ampoule, injection bottle (penicillin bottle), infusion bottle, prefilled syringe, pen-injector sleeve (card bottle), tubular oral liquid bottle and vial.

5 Guide of Application

5.1 Application and characteristics of pharmaceutical glass containers of different types

Pharmaceutical glass containers of various types have different characteristics and certain

difference in application. Main characteristics and application of glass containers of different types are listed in tables 3-8.

Table 3 Characteristics and application of glass types

Glass type	Characteristics and application
Quartz glass	Melted with pure SiO_2 (content over 99%); resistant to high temperature and acid corrosion, sound thermal stability and good light transmission, single component, suitable for packaging of drugs sensitive to metal ion
Borosilicate glass	Containing certain amount of boron oxide, high chemical stability and thermal stability, widely used in pharmaceutical packaging
Soda-lime glass	Main components sodium, calcium and silicon, certain chemical stability and thermal stability, generally used for packaging of drugs with weak glass corrosion
Aluminosilicate glass	Containing certain amount of aluminum oxide, high mechanical strength after chemical strengthening process

Table 4 Characteristics and application of glass containers classified by hydrolytic resistance

Classification by hydrolytic resistance	Characteristics and application
Type I glass	High hydrolytic resistance, suitable for packaging of most injection and non-injection drugs
Type II glass	High hydrolytic resistance of inner surface after neutralizing treatment, suitable for packaging of most acid and neutral injection and non-injection drugs
Type III glass	Medium hydrolytic resistance, suitable for packaging of non-injection drugs; applicability to injection drugs to be proved by proper stability data

Table 5 Characteristics and application of glass containers classified by light resistance

Classification by light resistance	Characteristics and application
Colorless glass	Colorless, transparent, easy for observation of content, suitable for packaging of drugs insensitive to light
Colored glass	Light transmission reduced by glass coloring, suitable for packaging of drugs with requirement for light resistance

Table 6 Characteristics and application of glass containers classified by forming process

Forming process	Characteristics and application
Molded vial	Primary forming process, good uniformity of surface performance, wide range of product specification, used for packaging of small-volume and large-volume preparations
Tubular vial	Secondary forming process, uniform wall thickness, generally used for packaging of small-volume preparations

Table 7 Characteristics and application of glass containers classified by post-forming surface treatment

Classification by post-forming surface treatment	Characteristics and application
Neutralizing treatment	Alkali metal ion concentration on glass inner surface decreased, hydrolytic resistance of inner surface improved
Siliconizing	Hydrophobicity and lubricating property of inner surface improved, residual liquid drug on the wall reduced, thus availing slide of piston inside glass syringe
SiO_2 coating	PICVD method used to form SiO_2 coating of uniform density on inner surface of glass containers, barrier property of migration of glass components improved, and extract reduced
Cold end coating/ hot end coating	Surface friction coefficient decreased, outer surface protected from scratching, strengthen of glass containers improved
Chemical strengthening	Mechanical strength of glass containers improved significantly, and breakage reduced

Table 8 Characteristics and application of glass containers classified by shape

Classification by shape	Characteristics and application
Ampoule	Sealing process adopted, well sealed, packaging system of single component, easy for opening, generally used for packaging of water injection preparations
Injection vial (penicillin vial)	Sealed with rubber plug and combination cap or aluminum cap, suitable for packaging of small-volume injection
Infusion bottle	Sealed with rubber plug and combination cap or aluminum cap, generally used for packaging of large-volume injection
Prefilled syringes	Closed system composed of stainless steel needle, protective cap, piston and push rod with the functions of drug storage and injection; transfer of liquid drug from pharmaceutical glass containers to syringe, liquid residue and secondary contamination risk of injection reduced, easy for use; belonging to packaging material free of cleaning and sterilization, generally used for packaging of drugs of high value, and more frequently used for first-aid medicine
Pen-injector sleeve (Cartridge)	Closed system composed of glass bead, piston, gasket and aluminum cap with the functions of drug storage and injection, used for pen-injector, transfer of liquid drug from pharmaceutical glass containers to syringe, liquid residue and secondary contamination risk of injection reduced, portable and easy for use; generally used for preparations available for fractionated accurate control of injection dosage
Tubular oral liquid bottle	Well sealed with rubber gasket, combination cap or aluminum cap, transparent, easy for disinfection, resistant to sterilization and erosion, generally used for packaging of single-dose oral preparations
Vial	Sealed with rubber gasket, plastic or aluminum cap, easy for filling and opening, various shapes, generally used for packaging of oral and external preparations; or sealed with pharmaceutical atomizing pump, easy for drug administration, used for packaging of inhalation or spray single-dose or multi-dose preparations, and able to avoid drug contamination during use

5.2 Points of focus of Selecting glass containers for pharmaceutical preparations

Drugs should be adequately analyzed and determined based on the concept of risk management and life cycle, pharmaceutical glass containers be selected as per characteristics (table 9), manufacturing process (table 10) and dosage form (table 11) of drugs, and attention be paid to mutual effect of pharmaceutical glass container system and drugs.

Table 9 Characteristics of drugs and key points of selecting pharmaceutical glass containers

Drug characteristics	Key points of selecting pharmaceutical glass containers
High ionic strength/complexing agent contained	· Prescription containing acetate, citrate, phosphate buffer and organic acid salts, such as gluconate, malate, succinate and tartrate; high ionic strength, such as citric acid and edetate sodium; containing complexing agent, such as EDTA; attention to be paid to the risks of erosion and delamination of glass containers; category I glass containers generally used, and sufficient research required
Sensitive to light	· Colored glass with light resistance preferred, and light resistance measures for outer package suggested ·Multiple components generally included in active ingredients of extract from TCM oral liquid or injection, some components being isomer, drug activity related to spatial configuration that may be changed by photocatalysis
Sensitive to pH	· Category I glass containers preferred · If category II glass containers selected, effect of chemical resistance of inner surface on drug stability to be evaluated · Focus on chemical resistance of inner surface and delamination risk of containers
Sensitive to metal ion	· Focus on extract risk of glass components and impurity element, and risk control measures to be provided ·Permitted daily exposure of aluminum 25mg/L in case of long-term large-amount administration of large-volume injection and parenteral nutrition; aluminum residue of human albumin and freeze-dried human albumin no more than 200μg/L

Table 10 Manufacturing process of drugs and key points of selecting pharmaceutical glass containers

Drug manufacturing process	Key points of selecting pharmaceutical glass containers
Moist heat sterilization	· Focus on surface damage and crack of containers ·Focus on overall dimensions of the fitting part of containers and other subassembly to ensure seal integrity of packaging system and avoid impact of moisture · Focus on internal pressure resistance of containers · Focus on stability of inner surface coating of glass containers after inner surface treatment
Hot filling	· Focus on thermal shock resistance of glass containers
Lyophilization	· Focus on coefficient of mean linear thermal expansion of glass containers to meet the requirement for freezing resistance · Focus on bottom thickness and wall thickness uniformity and bottle opening integrity of glass containers · Wall thickness to be increased properly in case of freeze-dried filling volume over 1/3
Aseptic filling	· Focus on dimensional specification of containers to avoid leakage and solvent loss · Focus on surface damage and scratch of containers to avoid microbial contamination of preparations · Focus on sealing performance of containers to avoid impact of moisture and reactive gas · Acceptable glass containers free of cleaning and sterilization suggested
Irradiation sterilization	· Suitable for prefilled syringe and other glass containers sterilized by irradiation · Glass containers with zirconium element added in the formulation suggested

Container cleaning	· Focus on matching of bottle opening and volume to ensure smooth drainage of cleaning solution
Accurate dosing (including drugs with narrow therapeutic window, high requirement for therapeutic dose, cytotoxicity and high added value)	· Focus on accuracy of dosage · Focus on flatness of glass containers, hydrophobicity of siliconized inner surface, adsorption of inner surface and configuration of containers (such as V-shaped bottom) · Focus on mechanical strength of glass containers

Table 11 Dosage form of drugs and key points of selecting pharmaceutical glass containers

Drug dosage form	Key points of selecting pharmaceutical glass containers
Inhalation preparations and nasal sprays	· Focus on integrity of container sealing system to avoid microbial invasion · Focus on interaction of propellant and inner surface of glass containers to avoid effect on drug ingredients and injection function of drug delivery system · For preparations of administration route of the highest risk, chemical stability and safety of glass containers to be confirmed · Meeting the requirements for pressure vessels
Injection and ophthalmic preparations	· Focus on integrity of container sealing system to avoid microbial invasion · Focus on inner surface resistance to water, sudden change of temperature and glass element leaching · Focus on arsenic limit in extractable solution
Sterile powder and injection powder (including freeze-dried preparations)	· Focus on integrity of container sealing system to avoid invasion of moisture and microbe · Focus on freezing resistance of glass containers ·For freeze-dried preparations after redissolution, focus on hydrolytic resistance of container inner surface to avoid effect on drug stability
Oral preparations	· Meeting requirements for the corresponding drugs
Vaccine and biological products	· Focus on inner surface resistance to water and glass element leaching ·Focus on integrity of container sealing system to avoid invasion of moisture and microbe ·Focus on durability of glass containers during low-temperature storage and transport ·Focus on migration of aluminum ion, tungsten, silicone oil and other elements and substances on inner surface of glass containers under

	long-term erosion that may lead to polymerization of protein or effect on immunogenicity of product

5.3 Comprehensive evaluation

5.3.1 General

The whole life cycle of drugs should be considered, and the concept of risk assessment and the principle of quality sourced from design be followed, and comprehensive evaluation be performed for selection and application of glass containers. Besides the content of sections 5.3.2- 5.3.6, comprehensive evaluation should cover characteristics and application of glass types, and the points of focus of selecting glass containers for pharmaceutical preparations.

5.3.2 Evaluation of production quality management system

A pharmaceutical glass container manufacturer should establish the corresponding production quality management system.

5.3.3 Evaluation of the capability of continuous and stable supply of products

A pharmaceutical glass container manufacturer should have the capability of continuous and stable supply and the emergency response mechanism.

5.3.4 Evaluation of applicability to cleaning, filling and sterilizing equipments

Pharmaceutical glass containers should meet the requirements for intelligent production line, high-speed filling and continuous production of drugs, including the requirements for appearance, defect, outer diameter and deviation of glass containers, vertical axis deviation of glass bottles and circular runout of glass ampoule.

5.3.5 Evaluation of inner surface durability of glass containers

Test result of hydrolytic resistance of inner surface is a part of chemical resistance evaluation of glass container surface. While hydrolytic resistance of inner surface is improved, sulfidizing and other chemical treatment of glass containers may reduce chemical resistance of inner surface, and increase glass particles or the risk of delamination for filling of certain drugs.

5.3.6 Evaluation of mutual effect of drugs and glass containers after direct contact

When direct contact of drugs and glass containers may cause mutual effect, it is not only required to perform evaluation of inner surface durability of glass containers, but also to carry out necessary compatibility study according to relevant guiding principles to ensure critical quality attributes and safety of drugs within an acceptable range.

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