ICS 11.120
CCS C 04

CNPPA

T/CNPPA3018—2021

Guidance for Classification and Application of Pharmaceutical Glass Containers

Issued on 2021-08-02 Effective on 2021-08-02

Issued by **China National Pharmaceutical Packaging Association**

Contents

Preface

This document is drafted according to the rules provided in GB/T 1.1-2020 “Directives for Standardization – Part 1: Rules for the Structure and Drafting of Standardizing Documents”.

Please not that some content in this document may be related to patent. The issuing organizing of the document is not liable to identify patent.

This document is under the centralized management of China National Pharmaceutical Packaging Association.

Drafting companies and organizations of this document: Shandong Linuo Technical Glass Co.,Ltd.、Shandong province pharmaceutical glass Co.,Ltd、SCHOTT TUBING （ZHEJIANG) CO., LTD、Corning (Shanghai) Co., LtdShuangfeng Pharmaceutical Packaging Co., Ltd. (Zhenjiang)、Cangzhou Four Stars Glass Co.,Ltd.、SHANDONG WEGO PREFILLS PHARMACEUTICAL PACKAGING CO., LTD.、NINGBO ZHENGLI PHARMACEUTICAL PACKAGING CO.,LTD、Triumph Junheng Co., Ltd.、Ompi Pharmaceutical Packing Technology (China) Co., Ltd.、Nipro PharmaPackaging (Shanghai) Co., Ltd.、SGD PHARMA、Chongqing Zhengchuan Pharmaceutical Packaging Co.,Ltd.、Shandong Zhengxin Pharmaceutical Glass Co., Ltd.、Qilu Pharmaceutical CO., LTD.、Shandong Luye Pharmaceutical Co., Ltd.、 Changzhou Siyao Pharmaceutical CO., LTD、Shijiazhuang No.4 Pharmaceutical CO., LTD、Huiyu Research Institute of Pharmaceutical Packaging Technology.

Main drafter of this document: Yang Zhongchen, Zhang Haixiang, Yuan Hengxin, Xue Junming, Guan Ziqiu, Yao Wenzhen, Song Xiaolong, Yu Shili, Ye Huan, Wang Lisheng, Li Yuntao, Qin Wenwen, Peng Weiwei, Fan Yong, Li Daoguo, Yu Chunmei, Qu Cuijuan, Jiang Qiong, Wu Yuxuan, Zhang Jinyun, Wang Wensong, Teng Jianzhong, Zhou Aime, Xu Guoxin, Geng Lixin, Lin Weihui, Shen Donglin, Xu Ningbo, He Ruiling, Jin Hong, Ji Wei, Sun Yi, Cai Hong

Introduction

Pharmaceutical Glass Containers are commonly used packaging containers in direct contact with drugs.

This guidance comprehensively considers the characteristics, development trend and influencing factors on drug quality of pharmaceutical glasses and selects five ways to classify pharmaceutical glass containers according to material, performance, forming process, surface treatment after forming and shape. These classification ways and corresponding application scenarios are based on existing products and cognition, which shall have limitations and irrationality, It will make corresponding adjustments with the development of science, technology and industry.

This guidance is willing to provide theoretical basis, ideas and practical path reference for promoting the R&D of pharmaceutical glass products, promoting the progress of production technology and meeting new application requests.

When pharmaceutical glass manufacturers design, develop and name new products and formulate product standards according to this guidance, they should fully understand and pay attention to the types, characteristics and requirements of drugs. When pharmaceutical companies select pharmaceutical glass containers through this guidance, they should comprehensively consider the classification and application of various pharmaceutical glass containers according to the characteristics of drugs, drug production processes, drug dosage form and so on, select the appropriate product type. When carrying out necessary compatibility study, the quality stability and uniformity of products, such as the fluctuation range of linear thermal expansion coefficient of glass and boron trioxide content should also be paid attention to.

After selecting the glass containers, pharmaceutical companies shall sign a quality agreement with pharmaceutical glass manufacturer. Quality agreement generally includes:

- Content of Quality Audit
- Product Standard (Including: Cosmetic defects, geometric shape, dimension & deviation, physical & chemical performance, principle of batch definition and acceptable AQL);
- Product quality monitoring protocol of glass manufacturer;
- When changes of process, formulation, manufacturing site, product standard happened, related studies shall be performed, and notification shall be reached to customers timely.

Guidance for Classification and application of Pharmaceutical Glass Containers

1 Scope

This document provides Guidance for Classification and application of Pharmaceutical Glass Containers.

This guidance applies to the glass containers in direct with drugs.

2 Normative References

The contents in the following documents constitute essential clauses of this document through normative references. Among them, for dated references, only the version corresponding to the date is applicable to this document; for undated references, the latest version (including all amendments) is applicable to this document.

<Pharmacopoeia of the People Republic of China> Ver. Y2020

<National Pharmaceutical Packaging Materials Standard> - Ver. Y2015 – 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**

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 of glass is drawn into glass tubes for manufacturing of tubular glass containers, that are put under secondary processing into glass containers of certain geometric shape. Tubular forming is secondary forming process.

3.3 **Moulded glass containers**

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

3.4 **interior surface durability of glass containers**

Interior surface resistance refers to the ability of the interior surface of glass container to withstand the physical and chemical erosion of water, acid, alkali and other chemical substances, as well as the action of environmental factors such as temperature and pressure when any content is packaged in glass container.

3.5 delamination

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

3.6 light protection

In order to avoid the influence of light on the content of drugs, the glass container has the performance of protecting the packaged drugs from the light transmission of a 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 siliconization.

3.8 outer surface treatment

It refers to the treatment process of outer surface of glass containers aimed to improve pharmaceutical glass containers 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

Used to reduce the release of alkali metal ions on the interior surface of glass, sulfurization is often used.

3.10 siliconizing

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

3.11 SiO_2 coating

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

3.12 glass chemical strengthening

Chemical strengthening is to heat the glass container in the melt of some salts and exchange the alkali metal ions (such as sodium ions) with larger ion radius (such as potassium ions) with the alkali metal ions (such as sodium ions) with smaller radius in the glass. Because the large ions occupy the smaller holes in the glass network structure, they produce extrusion, resulting in permanent compressive stress on the glass surface and improving the performance of the glass surface.

3.13 the cold end coating

In order to improve the 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

In order to significantly improve internal pressure strength of glass containers, chemical vapor deposition method is used to spray coating material onto outer surface of the containers that are under high temperature after forming.

3.15 shape

Represents the shape and structure of manufactured product.

4 Classification

4.1 General

Pharmaceutical glass containers are classified by materials, performance, forming processes, post-forming surface treatments and shape.

4.2 Classification by material

Pharmaceutical glass is classified by material into 4 types: quart glass, borosilicate glass, aluminosilicate glass and soda-lime glass. The chemical composition of each glass type is not fixed and may vary within certain range. However, the difference in chemical composition of the same glass type is allowed. The main chemical composition and main performance can be referenced in Table 1.

Table 1 Classification and Performance of Pharmaceutical Glass Materials

Chemical composition and performance	Glass type			
	Quartz glass	Borosilicate glass	Aluminosilicate glass④	Soda-lime glass
SiO_2 (%)	>99	≈71～81	≈72～75	≈70
B_2O_3 (%)①	/	≥5	/	<5
Al_2O_3 (%)	/	≈2～7	≈9～12	≈0～4
Alkali metal oxide	/	≈4～12	≈10～13	≈12～16
Alkali earth metal oxide （CaO、MgO、BaO）(%)	/	0～5	0～5	≈12
Coefficient of mean linear thermo expansion ×$10^{-6}/K^{-1}$（20～300℃）② （$10^{-6}/K^{-1}$）	<1	3.2～7.5	6.0～7.0	7.6～9.0
Hydrolytic resistance of glass grain at 121℃③	Level I	Level I	/	Level II

① Refer to the B_2O_3 determination method in 4009, Volume IV of Chinese Pharmacopoeia Ver. Y2020;

② Refer to the method for determination of coefficient of mean linear thermo expansion (YBB00202003-2015);

③ Refer to the method for determination of hydrolytic resistance of glass grain under 121℃ in 4001, Volume IV of Chinese Pharmacopoeia Ver. Y2020;

④ Aluminosilicate glass　Generally used after chemical strengthening process.

4.3 Classified by performance

4.3.1 Classified by hydrolytic resistance of glass interior surface

Pharmaceutical glass container is classified by hydrolytic resistance of interior surface in Type I, Type II and Type III glass. As listed in table 2.

Table 2 Classification of pharmaceutical glass containers by hydrolytic resistance of glass interior surface

Glass type	Hydrolytic resistance of glass interior surface①
Type I glass	With high hydrolytic resistance
Type II glass	With high hydrolytic resistance after neutralization
Type III glass	With medium hydrolytic resistance without neutralization treatment
① Specific data of the hydrolytic resistance of glass interior surface can be referenced in 4006, Volume IV of Chinese Pharmacopoeia Ver. Y2020	

4.3.2 Classified by light resistance

Pharmaceutical glass containers are classified as colorless and colored types. Colored glass has light resistance characteristic, such as amber glass.

4.4 Classified by forming process

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

Tubular pharmaceutical glass containers include injection vial (vial), ampoule, glass barrel for pen-injector (cartridge), glass barrel for prefilled syringe, oral liquid bottle and tubular medicinal bottle.

Moulded pharmaceutical glass containers include infusion bottle, injection vial (vial) and medicinal bottle.

4.5 Classified by post-forming surface treatment

In order to improve some properties, the surface treatment of formed pharmaceutical glass containers can be divided into neutralization, siliconization, silica coating, chemical strengthening, cold end coating and hot end coating.

4.6 Classified by shape

Pharmaceutical glass container are classified by shape into ampoule, injection vial (vial), infusion bottle, glass barrel for prefilled syringe, glass barrel for pen-injector (cartridge), tubular oral liquid bottle and medicinal bottle.

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 are listed in tables 3-8.

Table 3 Characteristics & application of glass types

Glass type	Characteristics & application
Quartz glass	Melted with pure SiO_2 (content over 99%) , it features high temperature resistance and acid corrosion resistance, sound thermal stability and good light transmission. With simple source of component, it is more suitable for packaging of drugs sensitive to metal ion.
Borosilicate glass	Containing certain amount of boron oxide, it features high chemical and thermal stability and is widely used in pharmaceutical packaging.
Soda lime silica glass	With main component of sodium oxide, calcium oxide and silicon trioxide,features certain chemical stability and thermal stability, and is generally suitable for the packaging of medicines with weak glass corrosion.
Aluminum silicon glass	Containing certain amount of alumina, it features high mechanical strength after surface strengthening treatment.

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

Classification by hydrolysis resistance	Characteristics & application
Type I glass	High hydrolytic resistance, suitable for packaging of most injectable and non-injectable drugs.
Type II glass	High hydrolytic resistance of inner surface after neutralization treatment, it is suitable for the packaging of most acidic and neutral injectable and non injectable drugs.
Type III glass	Medium hydrolysis resistance, suitable for packaging of non-injectable drugs. Applicability to injection drugs is to be proved by proper stability data.

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

Classification by light resistance	Characteristics & application
Clear glass	Colorless, transparent, easy for observation of content, suitable for

	packaging medicines insensitive to light.
Colored glass	Light transmission reduced by glass coloring, suitable for the packaging of drugs with requirements for light resistance.

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

Forming process	Characteristics & application
Molded vial	With the adoption of primary forming process, it features good wall thickness, high mechanical strength, good uniformity, and a wide range of product specification. It can be used for packaging of small-volume and large-volume preparations.
Tubular vial	With the adoption of secondary forming process, it features uniform wall thickness and light weight. It is 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 & application
Neutralization treatment	With the neutralization treatment, the alkali metal ion concentration is decreased and hydrolysis resistance of inner surface of glass containers is improved.
Siliconizing	With the siliconization treatment, the hydrophobicity and lubricity property of the inner surface of glass containers is increased, and the residual liquid on the wall is reduced, thus availing slide of piston inside glass syringe.
SiO_2 coating treatment	With the adoption of ion pulse chemical deposition, a dense and uniform layer of SiO_2 coating is formed on the inner surface of glass containers. This helps to improve the barrier property of migration of glass components and reduce extract leaching.
Chemical strengthening	Through the chemical strengthening process, the mechanical strength of the glass container can be improved significantly, and the breakage, damage and cracks of the glass containers can be reduced.
Cold end coating/hot end coating	By coating the outer surface of glass containers, it can decrease the surface friction coefficient, prevent outer surface from scratching, reduce microcracks, and improve the strength of glass containers.

Table 8 Characteristics and application of glass containers classified by shape

Classification by shape	Characteristics & application
Ampoule	With the adoption of fusion sealing process, it features good airtightness. As it is a kind of single-component packaging system, it is easy to open and use, so it is generally used for the packaging of hydro-injection preparations.
Injection vial	Sealed with a rubber plug and a combination cap or an aluminum cap, it is generally used for packaging of small-volume injection.
Infusion bottle	Sealed with a rubber plug and a combination cap or an aluminum cap, it is generally used for packaging large-volume injection.
Prefilled syringes	It adopts a closed system composed of stainless steel needles, protective caps, pistons and push rods with functions of drug storage and injection. It can reduce the residual liquid during the transfer of the liquid medicine from pharmaceutical glass containers to syringes, and reduce the risk of secondary contamination risk during injections. It is portable and easy to use. It is a kind of medicine packaging material that requires no cleaning and no sterilization. It is generally used in the packaging of high-value medicines and most frequently used for first-aid medicines.
Pen-injector sleeve (cartridge)	Adopting a closed system composed of glass beads, pistons, gaskets and aluminum caps, it is used for pen injectors with functions of drug storing and injection. It can reduce the residual liquid during transfer of the liquid medicine from pharmaceutical glass containers to syringes, and reduce the risk of secondary contamination during injection. It is portable and easy to use. It is generally used for preparations available for fractionated accurate control of injection dosage.
Tubular oral liquid bottle	Sealed with rubber gasket, combination cap or aluminum cap, it is transparent and features ease in sterilization,, resistance to sterilization and corrosion, and good airtightness. It is generally used for the packaging of single-dose oral preparations.
Vial	Sealed with rubber gasket, plastic or aluminum cap, it is generally used for the packaging of oral and external preparations. It is easy for filling and opening and has, various shapes. It can be sealed with pharmaceutical atomizing pump,. It is used for packaging of inhalation or spray single-dose or multi-dose preparations. It is easy for drug administration and 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. When selecting a pharmaceutical glass container, it is necessary to pay attention to the mutual effect of pharmaceutical glass container system , drug characteristics (see Table 9), drug manufacturing process (see Table 10), and drug dosage form (see Table 11).

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

Drug characteristics	Key points of selecting pharmaceutical glass containers
Agents that are easy to complex alkaline earth metals contained	● Attention should be paid to the risk of corrosion 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
Sensitive to acid, alkali and pH	● Category Ⅰ glass containers preferred ● If category II glass containers selected, effect of the chemical resistance of the inner surface on drug stability to be provided; ● 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; ● Pay attention to the effect of metal ions in the glass on the stability of the drug; ● For large-volume injections and long-term administration of parenteral nutrition, the daily allowable amount for aluminum is aluminum is 25 ug/L
[a] The components that easy to complex with alkaline earth metals in the prescription usually include acetate, citrate, gluconate, malate, succinate, tartrate and other organic acids; phosphate buffer; ethylenediamine tetraacetic acid and other commonly used complexing agents.	

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 tolerance 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 requirements for freezing resistance. ● Focus on bottom thickness, 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 the sealing performance of containers to avoid impact of moisture and reactive gases; ● Acceptable glass containers free of cleaning and sterilization suggested
Irradiation sterilization	● Suitable for prefilled syringes and other glass containers sterilized by irradiation; ● Glass containers with zirconium element added in the formulation suggested
Container cleaning	● Focus on matching of bottle openings 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 the 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 preparation	● Focus on integrity of the container sealing system to avoid microbial invasion;

	● Focus on interaction of propellant and the inner surface of glass containers to avoid affecting the drug ingredients and injection function of drug delivery system; ● For preparation of administration route of the highest risk, chemical stability and safety of the glass container to be confirmed; ● Meeting the requirements for pressure container
Injections and ophthalmic preparations	● Focus on integrity of the container sealing system to avoid the microbial invasion; ● Focus on the 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 lyophilized preparations)	● Focus on integrity of container sealing system to avoid the 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 drug stability
Oral preparations	● Meet requirements for the corresponding drugs
Biological agents (vaccines)	● 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 transportation; ● Focus on migration of aluminum ion, tungsten and other elements and substances on inner surface of glass containers under long-term erosion that may lead to protein polymerization or effect on immunogenicity of the product.

5.3 Comprehensive evaluation

5.3.1 General

When selecting glass packaging containers, the whole life cycle of drugs should be considered. According to the concept of risk assessment and the principle of quality sourced from design, a comprehensive evaluation should be performed for selection and application of glass containers. The comprehensive evaluation should not only cover the characteristics and application of glass types and the points of focus of selecting glass containers for pharmaceutical preparations, but also other evaluations that are listed in sections 5.3.2 ~ 5.3.6.

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 capacity of continuous and stable supply of products

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

5.3.4 Evaluation of adaptability to cleaning, filling and sterilization equipment

Pharmaceutical glass containers should meet the requirements for intelligent drug 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 ampoules, etc.

5.3.5 Evaluation of inner surface durability of glass containers

Test results of hydrolysis resistance of inner surface is a part of the chemical resistance evaluation of glass container surface. While hydrolysis resistance of inner surface is improved, neutralization and other chemical treatment of glass containers may reduce the chemical resistance of the inner surface of the glass containers, 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 the direct contact between the drug and the glass container may affect each other, it is not only required to perform evaluation of inner surface durability of glass containers, but also to carry out necessary compatibility studies in accordance with relevant guiding principles to ensure critical quality attributes and safety of drug within the acceptable range.

References

[1] YBB 00202003-2015 Test Methods for Coefficent of Mean Liner Thermal Expansion [S].
[2] Pharmaceutical Administration Law of the People's Republic of China.2019.
[3] National Standard for Pharmaceutical Packaging Materials [S]. China Medical Science and Technology Press .2015-10 .
[4] Compilation of International Standards for Pharmaceutical Packaging[J].China Pharmaceutical Packaging Association.2020.
[5] Technical Guidelines for Compatibility of Chemical Injection and Pharmaceutical Glass Packaging Container [S].National Medical Products Administration .2015-07-28(40).
[6] Chinese Pharmacopoeia Commission & China National Pharmaceutical Packaging Association Compiled:European, American and Japanese Pharmacopoeia and Standards of Pharmaceutical Packaging Materials [J].Chemical Industry Press.2019-8.
[7] Provisions of Drug Registration [M].State Administration for Market Regulation .2020(27).
[8] Yingliang Tian, Shibing Sun. New Glass Technology [J]. China Light Industry Press.2013-08.
[9] Yingliang Tian. Pharmaceutical glass [J]. Chemical Industry Press.2015-05.
[10]Yunan Ma , Cai Hong, Hongyu Luo , Theory and Practice Compatibility of Pharmaceutical Products and Packaging [J]. Chemical Industry Press. 2019-10.