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20 March 2024

Reference: Chinese Pharmacopeial Chapter <9653> Guidelines for Microbial Testing of Pharmaceutical Packaging Materials

Dear Madam or Sir,

PDA appreciates the opportunity to provide feedback to the Chinese Pharmacopeia on Chapter <9653> Guidelines for Microbial Testing of Pharmaceutical Packaging Materials. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this important Chapter.

PDA is a non-profit international professional association with over 10,000 individual members, including scientists, industry professionals, and consultants who have an interest in pharmaceuticals, biologics, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in the Public Docket on behalf of PDA's Science Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,

Glenn E. Wright
President and CEO

cc. Josh Eaton,PDA; Carrie Horton,PDA; Jessie Lindner, PDA; Danielle Bretz, PDA

PDA Comments to Chinese Pharmacopeial Guidance Document *"9653 Guidelines for Microbial Testing of Pharmaceutical Packaging Materials"*

General Comments		
Comment to Text	**Proposed Change**	**Rationale for Change**
This document exclusively requires a product sterility test (with reference to Chinese Pharmacopeial Chapter <1101> *Sterility Test Method*) on each batch to support the sterile release of drug products. The shortcomings and limitations of the product sterility test[1] are well-known, and global regulatory standards and guidance documents support the use of parametric release, dosimetric release, and ethylene oxide (EO) biological indicator (BI) test for sterility release as superior alternatives to the sterility test. Please see the table provided below which summarizes examples of the various international regulatory standards and guidance documents that provide recommendations on sterile product release mechanism alternatives to the sterility test. [1]Sadowski MJ, and Langille SE, *Parametric Release of Moist Heat Sterilized Products:* History and Current State, PDA JPST, Vol. 78, Issue 1, November/December 2022.	PDA recommends that Chinese Pharmacopeia (ChP) include the release approaches summarized in the table provided below as acceptable alternatives to the product sterility test.	By expanding the scope of accepted mechanisms for sterile release of drug products, this guidance document will be more aligned to internationally accepted sterile product release approaches.

List of References to Support General Comments		
Sterilization Modality	**Sterile Product Release Approach**	**Reference**
Moist Heat	Parametric Release	U.S. Food and Drug Administration. *Guidance for Industry: Submission of Documentation in Application for Parametric Release of Human and Veterinary Drug Products Terminally*

		Sterilized by Moist Heat Processes; Center for Drug Evaluation and Research (CDER). 2010.
Moist Heat	Parametric Release	U.S. Food and Drug Administration. *Compliance Policy Guide: Sec. 490.200 Parametric Release of Parenteral Drug Products Terminally Sterilized by Moist Heat*; Center for Drug Evaluation and Research (CDER). 2012.
Moist Heat	Parametric Release	*Technical Report No.30 (Revised 2012): Parametric Release of Pharmaceuticals and Medical Device Products Terminally Sterilized by Moist Heat*; Parenteral Drug Association: 2012. www.pda.org/bookstore
Moist Heat	Parametric Release	*EudraLex — Volume 4 — EU Guidelines to Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use*, Annex 1: Manufacture of Sterile Medicinal Products ; European Commission: 2022. https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf
Moist Heat	Parametric Release	PI 005-3 PIC/S Recommendation on Guidance on Parametric Release, September 2007
Moist Heat	Parametric Release	Annex 17, Parametric Release (PIC/S) – Guide to Good Manufacturing Practice for Medicinal Products and Annexes
Moist Heat	Parametric Release	EMA/CHMP/QWP/811210/2009-Rev1, Guideline on Release Time Release Testing (formerly Guideline on Parametric Release)
Moist Heat	Parametric Release	ISO17665-1: 2006 (R) 2014 Sterilization of health-care Products- Moist Heat -- Requirements for the development, validation and routine control of a sterilization process for medical devices
Ethylene Oxide	Parametric Release and BI Test for Sterility Release	ISO11135:2014 Sterilization of health-care products – Ethylene Oxide –Requirements for the development, validation and routine

		control of a sterilization process for medical devices
Radiation	Dosimetric Release	ISO11137-1:2006 (AMD 2018) Sterilization of health care products -- Part 1 -- Requirements for the development, validation and routine control of a sterilization process for medical devices

Section 1: Scope					
Line Numbers-Original Guidance	**Line Numbers-Translated Guidance**	**Current Text**	**Comment to Text**	**Proposed Change**	**Rationale for Change**
4-6	5-7	"This guiding principle provides guidance for selection of microbiological tests, method development, acceptance criteria, and testing frequency in the quality control for finished products of pharmaceutical packaging materials."	PDA recommends adding a statement describing the type of packaging materials and their level of criticality regarding product interaction that is covered under the scope of this guidance. By providing this clarification, it will aid the reader in developing a risk-based approach to microbial testing focusing on the materials that have the most significant impact on the product's microbial quality.	"This guiding principle provides guidance for selection of microbiological tests, method development, acceptance criteria, and testing frequency in the quality control for finished products of pharmaceutical packaging materials **adopting a risk-based approach, on any pharmaceutical primary packaging materials that are in direct contact with drugs**."	By including this clarifying statement, this guidance will be aligned with the application of the International Council for Harmonisation (ICH) Q9 Quality Risk Management (QRM) principles. Additionally, this verbiage clarifies the scope of this document to be applicable to primary pharmaceutical packaging materials that are in direct contact with drugs.

Section 2: Standards of Reference					
Line Numbers-Original Guidance	**Line Numbers-Translated Guidance**	**Current Text**	**Comment to Text**	**Proposed Change**	**Rationale for Change**
11-17	13-18	"1101 *Sterility Test method* 1105 *Microbial Limit Test for Non-sterile Products: Microbial Enumeration Method* 1106 *Microbial Limit Test for Non-sterile Products: Objection Microbials* 9203 *Guiding Principle for Quality Management of Pharmaceutical Microbiology Labs* GB/T19973.1 " *Sterilization of Healthcare Products Microbiological Method Part 1 ：Total Microbial Enumeration for Products*"	PDA recommends adding reference to Chinese Pharmacopeia Chapter 9201 "Guidelines for Validation of Alternative Microbiological Methods for Pharmaceutical Products". Additionally, PDA recommends updating reference "GB/T19973.1 " *Sterilization of Healthcare Products Microbiological Method Part 1 ：Total Microbial Enumeration for Products*"" to adopt the ISO standard 11737-1.	"1101 *Sterility Test method* 1105 *Microbial Limit Test for Non-sterile Products: Microbial Enumeration Method* 1106 *Microbial Limit Test for Non-sterile Products: Objection Microbials* **9201 *Guidelines for Validation of Alternative Microbiological Methods for Pharmaceutical Products*** 9203 *Guiding Principle for Quality Management of Pharmaceutical Microbiology Labs* **ISO11737-1** " *Sterilization of Healthcare Products Microbiological Method Part 1:* ***Determination of a Population of Microorganisms on Products***""	Reference 9201 provides guidance regarding the validation of alternative microbiological detection methods which is discussed in this guidance in Section 4: Testing Methods. By adding this reference, the reader will have a resource to refer to if more information is needed on this topic. By adopting the ISO standard number in place of "GB/T19973.1", it will eliminate potential confusion on which guidance document the reader is being directed to.

Section 3: Table 1. Testing items for finished pharmaceutical packaging materials					
Line Numbers-Original Guidance	**Line Numbers-Translated Version**	**Current Text**	**Comment to Text**	**Proposed Change**	**Rationale for Change**
25-26	27-28	**"Testing Items:** Sterility Test"	PDA proposes recognition of parametric release, ethylene oxide (EO) biological indicator (BI) test for sterility, and dosimetric release as alternatives for sterility testing to include additional globally recognized sterile product release methods.	**"Testing Items:** Sterility Test **NOTE: The product sterility test is not required when parametric release, ethylene oxide (EO) biological indicator (BI) test for sterility, or Dosimetric release sterile product release approaches are employed."**	It is common for parametric release, EOBI test for sterility or dosimetric release (radiation) to be used across the globe to support sterile product release in lieu of finished product test for sterility. Please see comment in Section 1: Scope above.

Section 3: Test Items					
Line Numbers-Original Guidance	**Line Numbers-Translated Guidance**	**Current Text**	**Comment to Text**	**Proposed Change**	**Rationale for Change**
30-32	32-33	"Pharmaceutical packaging material manufacturers should ideally perform sterility test for finished pharmaceutical packaging materials."	PDA encourages the addition of "sterile" to this statement to eliminate confusion for the reader. Additionally, PDA suggests clarifying the sterile product release approaches that can be used by the pharmaceutical packaging material manufacturer (i.e.,	"Pharmaceutical packaging material manufactures **(i.e., suppliers)** should **confirm the sterility of sterile packaging materials using a sterility test or an alternative approach such as parametric release, ethylene oxide (EO) biological indicator (BI) release, or dosimetric release. As an effective**	Parametric release, ethylene oxide (EO) biological indicator (BI) release, and dosimetric release are well-recognized alternatives to the sterility test that can be used by pharmaceutical packaging material manufactures (i.e., suppliers) to support product sterility. Including specific sterile product confirmation

			supplier) in addition to providing a summary of approaches that can be used by the pharmaceutical finished product manufacturer to ensure sterility of these materials prior to use.	**alternative to the sterility test, the contamination control strategy of the pharmaceutical finished product manufacturer should ensure that the packaging material microbial barrier has been validated inclusive of sterilization, transport, and storage over shelf life in addition the use of a risk-based visual inspection program and other controls to ensure the detection and elimination of microbial barrier defects."**	requirements for the pharmaceutical finished product manufacturer in this guidance would be of great benefit to the reader. However, PDA feels it is important to clarify in the guidance that if a packaging material is demonstrated to be sterile by the pharmaceutical packaging material manufacture (i.e., supplier), a breach in the sterile barrier is the only risk that can lead to non-sterility of these materials. The most effective approach to mitigate this risk is to develop an effective contamination control strategy that ensures validation of microbial barrier properties inclusive of sterilization, transport, and storage over the stated shelf life and to deploy a risk-based inspection approach and other controls that detects and eliminates microbial barrier defects.
33-49	34-50	"For non-sterile finished packaging materials used for sterile drugs, bioburden measurement is the process of measuring the total number of viable	PDA recommends adding this statement as a lead into the sections on bioburden testing and microbial limit testing to ensure the reader is aware	**"The necessity of the bioburden test and microbial limit test can be evaluated by referring to relevant domestic and international**	By relocating this sentence earlier in the document and explicitly calling out both bioburden testing and microbial limit testing, it will clarify the scope of

		microorganisms. Bioburden measurement data is helpful for the development, validation, and routine control of cleaning and/or sterilization processes in drug manufacturing enterprises. The necessity of including bioburden measurement for finished pharmaceutical packaging materials is generally stipulated by both the supplier and user in the company standard or quality agreements. Both the supplier and user should comprehensively evaluate the necessity of bioburden measurement based on product characteristics, contamination control measures, historical data, etc., in accordance with the requirements of quality risk management. It should be pointed out that based on the specific purpose of using the bioburden data, further microbial identification is sometimes necessary in addition to the bioburden measurement. Introduction of microbial limit test for finished non-sterile pharmaceutical	that ICH Q6A guidelines apply to both testing methods.	**technical guidelines such as ICH Q6A.** For non-sterile finished packaging materials used for sterile drugs, bioburden measurement is the process of measuring the total number of viable microorganisms. Bioburden measurement data is helpful for the development, validation, and routine control of cleaning and/or sterilization processes in drug manufacturing enterprises. The necessity of including bioburden measurement for finished pharmaceutical packaging materials is generally stipulated by both the supplier and user in the company standard or quality agreements. Both the supplier and user should comprehensively evaluate the necessity of bioburden measurement based on product characteristics, contamination control measures, historical data, etc., in accordance with the requirements of quality risk management. It should be pointed out that based on the specific purpose of using the bioburden data, further	application of the ICH Q6A guidance.

		packaging materials used for non-sterile drugs is generally stipulated by both the supplier and user in the company standard or quality agreements. The necessity of microbial limit test can be evaluated by referring to relevant domestic and international technical guidelines such as ICH Q6A."		microbial identification is sometimes necessary in addition to the bioburden measurement. Introduction of microbial limit test for finished non-sterile pharmaceutical packaging materials used for non-sterile drugs is generally stipulated by both the supplier and user in the company standard or quality agreements."	
42-44	42-44	"It should be pointed out that based on the specific purpose of using the bioburden data, further microbial identification is sometimes necessary in addition to the bioburden measurement."	PDA encourages clarifying how a risk-based approach can be leveraged regarding microorganisms to ensure product quality and safety.	"It should be pointed out that based on the specific purpose of using the bioburden data, further microbial identification may be necessary in addition to the bioburden measurement. **A risk-based approach for assessing microbiological flora is essential to ensuring product quality."**	A risk-based approach for assessing microbiological flora commensurate with the packaging format ensures an enhanced level of control based on the evaluation of the organisms found and the individual microbe's impact on dosage form.

Section 4: Testing Methods					
Line Numbers-Original Guidance	**Line Numbers-Translated Guidance**	**Current Text**	**Comment to Text**	**Proposed Change**	**Rationale for Change**
52-56	53-57	"With the rapid development of microbial analysis technology, some	PDA suggests adding in-text citation directing reader to "9201 Guidelines for	"With the rapid development of microbial analysis technology, some fast or real-	By providing this reference, the reader will be directed to a guidance that provides

		fast or real-time testing techniques can be introduced into microbial quality control. When adopting new testing technologies, alternative methods should be validated based on relevant guiding principles for different application scenarios. Validation results are subjective to evaluation."	Validation of Alternative Microbiological Methods for Pharmaceutical Products".	time testing techniques can be introduced into microbial quality control **(General Chapter 9201).** When adopting new testing technologies, alternative methods should be validated based on relevant guiding principles for different application scenarios. Validation results are subjective to evaluation."	recommendations on how to perform the validation of alternative microbiological methods. Please see related comment in Section 2: Standards of Reference.

Section 4.1: Sterility Test					
Line Numbers-Original Guidance	**Line Numbers-Translated Guidance**	**Current Text**	**Comment to Text**	**Proposed Change**	**Rationale for Change**
63-64	64-65	"Generally the inner and outer surfaces of the test sample are subjective to sterility testing."	PDA encourages clarifying which responsibilities are owned by the pharmaceutical packaging material supplier or pharmaceutical manufacturer.	"Generally the inner and outer surfaces of the test sample are subjected to sterility testing **(where required), which is performed by the pharmaceutical packaging material manufacture (i.e., supplier)**."	This update clarifies the responsibilities of the pharmaceutical packaging material manufacture (i.e., supplier) and those of the pharmaceutical manufacturer.

Section 4.2: Bioburden Testing					
Line Numbers-Original Guidance	**Line Numbers-Translated Guidance**	**Current Text**	**Comment to Text**	**Proposed Change**	**Rationale for Change**

112-113	111-112	"If the test sample has high bacterial count, the amount of the test solution can be reduced as appropriate."	PDA proposes moving away from directing the reader to reduce the solution to an alternative method that would yield and equivalent and/or superior result.	"If the test sample has high bacterial count, the amount of the test solution can be **serially diluted** as appropriate."	By stating "serially diluted" this will clarify the method that should be used in this circumstance. Original statement of "solution can be reduced" could mislead the reader to perform a method that is not suitable for yielding accurate bacterial counts.

9653 Guiding Principle for Microbial Testing of Pharmaceutical Packaging Materials

1 Scope

This guiding principle provides guidance for selection of microbiological tests, method development, acceptance criteria, and testing frequency in the quality control for finished products of pharmaceutical packaging materials.

2 Standards of reference

The contents of the following documents constitute essential provisions through referring to the relevant standards. Their latest versions (including all supplements, errata, etc.) are applicable to this guiding principle.

1101 *Sterility Test method*

1105 *Microbial Limit Test for Non-sterile Products: Microbial Enumeration Method*

1106 *Microbial Limit Test for Non-sterile Products: Objection Microbials*

9203 *Guiding Principle for Quality Management of Pharmaceutical Microbiology Labs*

GB/T19973.1 " *Sterilization of Healthcare Products Microbiological Method Part 1：Total Microbial Enumeration for Products*"

3 Testing items

As pharmaceutical packaging materials and containers have direct contact with drugs, microbial control of pharmaceutical packaging materials is of great significance for controlling microbial contamination of drugs. The microbiological testing items for finished pharmaceutical packaging materials generally include sterility testing, bioburden testing, and microbiological limit testing. The corresponding testing items for different forms of pharmaceutical packaging materials are reflected in Table 1.

Table 1. Testing items for finished pharmaceutical packaging materials

Type of packaging materials		**Testing Items**
Sterile pharmaceutical packaging materials		Sterility test
Non-sterile pharmaceutical packaging materials	For sterile drugs	Bioburden test (determined by the supplier and user)
	For non-sterile drugs	Microbial limit test (determined by the supplier and user)

Sterile pharmaceutical packaging materials are generally ready-to-use for the manufacturing of sterile drugs by aseptic processes. Pharmaceutical packaging material manufacturers should fully validate and precisely control the sterilization process to ensure the sterility of each batch of released products. Pharmaceutical packaging material manufacturers should ideally perform sterility test for finished pharmaceutical packaging materials.

For non-sterile finished packaging materials used for sterile drugs, bioburden measurement

is the process of measuring the total number of viable microorganisms. Bioburden measurement data is helpful for the development, validation, and routine control of cleaning and/or sterilization processes in drug manufacturing enterprises. The necessity of including bioburden measurement for finished pharmaceutical packaging materials is generally stipulated by both the supplier and user in the company standard or quality agreements. Both the supplier and user should comprehensively evaluate the necessity of bioburden measurement based on product characteristics, contamination control measures, historical data, etc., in accordance with the requirements of quality risk management. It should be pointed out that based on the specific purpose of using the bioburden data, further microbial identification is sometimes necessary in addition to the bioburden measurement.

Introduction of microbial limit test for finished non-sterile pharmaceutical packaging materials used for non-sterile drugs is generally stipulated by both the supplier and user in the company standard or quality agreements. The necessity of microbial limit test can be evaluated by referring to relevant domestic and international technical guidelines such as ICH Q6A.

4 Testing methods

The testing method specified in this guideline is a traditional microbial growth method. With the rapid development of microbial analysis technology, some fast or real-time testing techniques can be introduced into microbial quality control. When adopting new testing technologies, alternative methods should be validated based on relevant guiding principles for different application scenarios. Validation results are subjective to evaluation.

4.1 Sterility test

The sterility test of pharmaceutical packaging materials can be carried out in accordance with the general sterility test method (General Chapter 1101).

The number of samples generally follow the requirement for medical devices in the general sterility test method (General Chapter 1101).

Sterile pharmaceutical packaging materials are to be introduced into the aseptic drug manufacturing process in the clean room. Generally the inner and outer surfaces of the test sample are subjective to sterility testing. Considering the shape and other characteristics of pharmaceutical packaging materials that are different from those of drugs, the following methods or other validated methods can be used for sample processing and inoculation into the culture media. These methods serve as a reference for those products not listed.

Prefilled syringes, ointment tubes, rubber seals, etc. Take the test sample, disassemble or chop it into pieces as appropriate. Inoculate an equal amount of the sample fragments into a suitable volume of culture medium that is sufficient to immerse the test sample in each tube.

Plastic bottles, eye drop bottles, flexible bags, etc. Take the test sample, thoroughly rinse the inner and outer surfaces of the test sample with rinsing solution, pool the rinsing solution, and then follow the method of "Water soluble liquid test sample" in the sterility test method (General Chapter 1101).

4.2 Bioburden testing

4.2.1 Method design

4.2.1.1 Sample quantity

The routine monitoring of bioburden levels usually requires 3-10 test samples.

4.2.1.2 Sample volume

Generally, the entire sample is used for bioburden test. In the case where the laboratory container is too small to accommodate the entire test sample, representative parts can be used. For example, for sheet-like packaging materials, a portion of the sample can be taken based on the surface area.

4.2.1.3 Microbial collection

Considering the form of packaging materials, commonly used microbial collection methods include shaking method (mechanical or manual), rinsing method, ultrasonic elution method, bag peristaltic method, etc. Among them, shaking method and rinsing method are the most commonly used. Generally, pH 7.0 sterile sodium chloride peptone buffer, 0.9% sterile sodium chloride solution, and when appropriate, eluents containing surfactants (polysorbate 80 or lecithin) can be used for microbial collection from pharmaceutical packaging materials.

4.2.1.4 Inoculation into the culture medium

The methods for inoculating culture media generally include: membrane filtration method, pour plate method, and plate streaking method. Considering the low bioburden nature of pharmaceutical packaging materials, the membrane filtration method is preferred for inoculating into culture media. After filtering the eluent, transfer the filter membrane on top of a suitable culture medium with the bacteria surface upwards.

4.2.1.5 Microbial culture

The cultivation conditions should be selected with consideration on the potential types of microorganisms. Pharmaceutical packaging materials are unlikely to be contaminated by obligate anaerobic bacteria, so anaerobic test may not be considered. Generally, aerobic bacteria, fungi, and yeast tests can be combined. All the test solution shouldbe filtered onto a filter membrane and placed on a suitable general culture medium (such as TSA). Culture at two different temperatures (such as 30 ° C to 35 ° C, 20 ° C to 25 ° C), or other validated culture conditions. The preparation, sterilization, storage, and quality control of the culture medium should comply with the requirements of microbial limit testing for non-sterile products: Microbial Enumeration Method (General Chapter 1105) and the Guidelines for Quality Management of Pharmaceutical Microbiology Laboratory (9203).

4.2.1.6 Microbial enumeration

When membrane filtration method is used for microbial enumeration, the number of CFU on each filter membrane should not exceed 50. If the test sample has high bacterial count, the amount of the test solution can be reduced as appropriate. Report the measurement results with a colony count equivalent to one test sample.

4.2.2 Method validation

There are two aspects to consider in the validation of bioburden measurement method. One is to evaluate the suitability of the testing method to demonstrate that the testing process has no inhibitory effect on microbial growth. Reference can be made to the microbial limit test for non-sterile products: Microbial Enumeration method (General Chapter 1105). The second is to evaluate the recovery of the testing method, and use the correction factor of the recovery rate to correct the results to compensate for the amount of microorganisms that cannot be completely collected from the product and/or microbial culture. The recovery study of the method is generally carried out by manually inoculating the product with microbials,

and can refer to GB/T19973.1 " Sterilization of Healthcare Products Microbiological Method Part 1：Total Microbial Enumeration for Products"

4.3 Microbial limit test

The microbial limit test for pharmaceutical packaging materials may refer to the microbial limit test for non-sterile products: Microbial Enumeration Method (General Chapter 1105), and the microbial limit test for non-sterile products: Objection Microorganism Test method (General Chapter 1106). Membrane filtration method is preferred.

The sample amount of containers and solid materials shall not be less than 5. The sample amount of sheet materials shall not be less than 500cm^2 (as single side) in 5 replicates with each of 100 cm^2.

Report the total aerobic bacterial count, mold and yeast count results with a CFU count of 1 unit or 100 cm^2 of the test sample. Report the objection microorganism test results as positive or negative of any objection microorganism of 1 unit or 100 cm^2 of the test sample.

Considering the differences of form and other characteristics of pharmaceutical packaging materials, the preparation of the test solution can be carried out according to the following methods or other validated methods. These methods serve as a reference for those products not listed.

Containers (bottle, tube, etc.) Take the test sample and use the rinsing method. Add a certain volume (in proportion to the labeled capacity of the test sample) of flushing solution to each sample, shake for a certain period of time to thoroughly rinse the inner lumen of the test sample, and pool the rinsing solutions to be the test solution. Before shaking, seal the test sample as appropriate (such as tightening the bottle cap, sealing the end of the tube with a clamp, etc.).

Solid materials (seals, gaskets, etc.). Test samples are taken for shaking method. The test samples are combined and placed in a sterile container containing a certain volume (in proportion to the number of test samples) of rinsing solution. The test solution is obtained by shaking for a certain period of time and thoroughly rinsing the test samples. If necessary, the sample can be cut beforehand. When necessary, the test samples can be rinsed separately, and the rinsing solution can be pooled to make the test solution.

Sheet materials (such as aluminum foil, film, hard sheet, etc.) Test samples are taken for shaking method. Each sample is placed in a sterile container containing a certain volume (in proportion to the surface area of the sample) of rinsing solution. Shake for a certain period of time to thoroughly rinse the sample. The rinsing solution is then combined to obtain the test solution. If necessary, the sample can be cut beforehand. When necessary, the test samples can be rinsed separately, and the rinsing solution can be pooled to make the test solution.

6 Limits

6.1 Limits for sterility testing

The acceptance criteria for sterility testing should comply with the provisions of the Sterility Testing Method (General Chapter 1101). No growth should be observed.

6.2 Bioburden level

The acceptable level of bioburden is established based on historical data collected under normal operating conditions of the manufacturing process, reflecting the risk control

requirements and limits of the production process. Meanwhile, the established bioburden levels should also consider the economic viability of subsequent cleaning and/or sterilization processes, as well as the impact on drug endotoxin levels. When drug safety, efficacy, etc., are met, it is now generally stipulated by both the suppliers and users in the company standards or quality agreements. It should be pointed out that some special pharmaceutical packaging materials need to be further processed by drug manufacturers, such as co-extrusion film processing into infusion bags, etc. The processing technology may make a difference to the bioburden level of pharmaceutical packaging materials upon release. Drug manufacturers should reasonably evaluate the changes in biological load levels caused by the processing technology.

6.3 Microbial limits

Microbial limit testing generally includes microbial enumeration and objection microorganism testing. Microbial enumeration should cover total aerobic bacterial count, total mold and yeast count. The corresponding limits include the limits for the total number of aerobic bacteria, the limits for the total number of molds and yeast, and the type of objection microorganism. The formulation of microbial limits for pharmaceutical packaging materials should comprehensively consider factors such as the source and properties of raw materials, manufacturing process conditions, usage, drug administration routes, drug specification, and potential risks of microbial contamination to patients. The limits, which are generally specified by both supplier and users in the company standards or quality agreements, should be adequate for drug safety and efficacy. It should be pointed out that some special pharmaceutical packaging materials need to be further processed and used by drug manufacturers, such as processing hard sheets into blisters, etc. The processing technology may change the microbial level of the pharmaceutical packaging materials upon release. Drug manufacturers should conduct a reasonable evaluation of the changes in microbial level caused by the processing technology.

7 Test frequency

Pharmaceutical packaging material manufacturers should ideally conduct test for each batch of pharmaceutical packaging material products that require sterile testing.

The frequency of bioburden testing should be based on risk assessment, reflecting changes in bioburden caused by seasonal changes, production changes, or material changes. The testing frequency can be based on principles such as time (such as monthly, quarterly) or production volume (such as to skip some batches). The suppliers and users should specify in company standards or quality agreements, and ensure that the bioburden of each batch of products meets acceptable levels.

The frequency of microbial limit testing may refer to ICH Q6A and relevant domestic and international technical guiding principles. The suppliers and users shall specify in the company standards or quality agreements to ensure that each batch meets the microbial limit requirements.

Notes on the Drafting of 9653 Guiding Principle for Microbial Testing of Pharmaceutical Packaging Materials

1. The objective and significance of the revision

This guiding principle is based on the concept of risk management and provides guidance for selection of microbiological testing items, method development, acceptance criteria, and testing frequency in the quality control of finished pharmaceutical packaging materials so as to meet the needs of quality standard formulation and microbiological control in pharmaceutical packaging material manufacturers.

2. Key issues to be highlighted

2.1. Notes on the scope of the standard

This guiding principle focuses on addressing what to test, how to test, what is the target limit, and typical testing strategies for microbial testing of various finished pharmaceutical packaging materials. By supporting the construction of various general chapters in the pharmaceutical packaging material standard system, it provides guidance for the establishment of quality standards for pharmaceutical packaging material manufacturers. The general microbial testing and monitoring techniques for settling bacteria, planktonic bacteria, surface microorganisms in the manufacturing environment of pharmaceutical packaging materials and microbial test for utility water/gas are not included in the scope of this guiding principle.

2.2. Notes on testing items

The requirements for sterility testing and microbial limit testing are basically the same as those for drugs. In order to effectively validate and routinely control the cleaning and sterilization process, this guiding principle introduces bioburden testing to enhance the quality control of pharmaceutical packaging materials and provide assurance for the quality control of sterile drugs. It should be pointed out that the bioburden concept in this guiding principle does not cover the bioburden in the process control of sterile drug packaging material manufacturers.

2.3. Notes on testing methods

Due to the enormous varieties of pharmaceutical packaging materials, it is difficult to provide specific and distinct test methods and parameters for each variety. At the same time, considering the personalized and autonomous needs of manufacturers, this guiding principle provides guidelines for the design and validation of sterility testing, bioburden determination, and microbial limit testing methods. Different types of pharmaceutical packaging material manufacturers can develop and validate methods according to this guideline for routine quality control testing.

2.4. Notes on the limits

· Sterility testing is a qualitative test.

· Unlike microbial limits, the determination of bioburden mainly provides information for subsequent cleaning and/or sterilization. Microorganisms carried by pharmaceutical packaging materials will be killed during the sterilization process and will not be carried over to the drug. However, the bioburden limit should also consider the economy of subsequent sterilization processes and the impact on endotoxin levels in the formulation. The determination of bioburden is mainly based on historical data collected under normal

operating conditions of the production process, and is also specified by both suppliers and users in company standards or quality agreements.

For microbial limit testing, as the microorganisms carried by pharmaceutical packaging materials may come into contact with patients through the drug, the limit should comprehensively consider factors such as the source and properties of raw materials, production process conditions, drug administration routes, and potential risks of microbial contamination to patients. Generally, the total count of aerobic bacteria, mold and yeast, and the detection of objection bacteria should be considered based on the drug. On the basis of meeting the considerations of drug safety, efficacy, etc., it is generally stipulated by both suppliers and users in company standards or quality agreements.

2.5. Notes on conventional testing strategies

At present, the raw materials for pharmaceutical packaging products are mostly plastics, glass, rubber, metals, etc. As they are from non-natural sources, these materials have low water activity and high barrier to the growth of microorganisms. Moreover, the processing technology of pharmaceutical packaging materials is mostly hot processing, which can reduce the initial bioburden of the raw materials themselves, so pharmaceutical packaging materials generally have relatively low bioburden. However, even so, if the initial bioburden of pharmaceutical packaging materials is too high or the production process control of pharmaceutical packaging materials is insufficient, microorganisms may still be introduced into pharmaceutical packaging products. Pharmaceutical packaging material manufacturers should develop appropriate testing strategies based on risk assessment to avoid over control and loss of control.

2.6. Others

This guiding principle only represents the current views and understanding of drug regulatory authorities. With the advancement of scientific research, the relevant content in this guiding principle will be subjective to continuous improvement and updating.