Packaging Integrity Evaluation of Sterile Products

（無菌医薬品包装の完全性評価）

1. Introduction

Package integrity for sterile pharmaceutical products is ability to prevent microbial ingress and the entry or escape of substances, which is required for the packaging for sterile preparations to maintain their quality products.

This General Information is used to evaluate the package integrity of the primary packaging or the secondary packaging of sterile pharmaceutical products that are required to have a barrier function from microorganisms, reactive gases and other substances that affect quality, from the viewpoint of protection of products. A packaging defect is defined as the situation that unexpected leakage caused by incorrect design or by some abnormality occurred during manufacturing processes or storage up to the shelf life of preparations induces the loss of the intended barrier function of the packaging resulting in the unsustainability of the quality of the preparation including sterility. .

The package integrity testing is applied throughout the product life cycle by product stability programs after the launch, beginning from the development of preparations.

2. Package integrity and testing

2.1. Concept of package integrity

Package integrity for sterile pharmaceutical products is necessary to ensure the quality of products before use. Primary packaging for sterile pharmaceutical products should ensure no ingress of microorganisms from the outside. In addition, if a gas such as water vapor or oxygen affects the quality of products by its moving between in and out of the primary packaging, the quality should be maintained by controlling the amount of gas transfer in the primary packaging, or combining multiple packaging materials including secondary packaging.

It is necessary to recognize that most packaging have gas leakage and permeation depending on their type. In many cases, it is difficult to distinguish between leakage and permeation for qualified packaging. Therefore, complete packaging is to prevent the ingress of microorganisms and to prevent the quality deterioration of the product due to the ingress/transfer of gas/other substances by conforming to the maximum allowable leakage limit of individual preparation packaging, and the product should be ensured to meet physicochemical and microbiological specifications by data. The package integrity test methods include a physicochemical method to find leaks (leak test), a method to ensure that no leakage occurs by confirming the qualification of the sealed part of a package (seal quality test), and a method to confirm a barrier property against microorganisms by biological methods (microbial challenge test). For sterile pharmaceutical products, package integrity is guaranteed by any one or more of these tests.

The application of the leak test or seal quality test requires optimization according to the characteristics of the package of each preparation. In addition, validation is required to demonstrate the detection limit, accuracy and precision of the test method to be set.

2.1.1. Leak test

The leak test guarantees ability to maintain the integrity of packaging by qualitatively detecting or quantitatively measuring holes or pathways, where leaks occur, by a physicochemical method. There are two types of leak tests; qualitative leak test and quantitative leak test.

Since the results of the qualitative leak test are accompanied by uncertainty, the test requires a large sample size and rigorous control of test conditions to obtain reliable results. The qualitative leak test is a useful mean to detect leaks, but is not suitable for the deterministic verification of package integrity. On the other hand, it is an effective test to locate leak positions correctly.

The quantitative leak test is a test to evaluate quantitatively the physicochemical changes accompanied with leaks and to obtain objective data to set a maximum allowable leakage limit and control.

Examples of qualitative and quantitative leak test methods are listed below. Other methods may be used according to a purpose.

< Qualitative leak test methods >

Liquid immersion test

Liquid leak test

Tracer liquid test (dye penetration test)

Sniffer method (helium leak test method 1)

< Quantitative leak test methods >

Sealed chamber method (pressure change leak test method 1)

Vacuum decay method (pressure change leak test method 2)

Pressure integration method (helium leak test method 2)

Vacuum chamber method (helium leak test method 3)

Immersion method (helium leak test method 4)

High-voltage leak test (pinhole test method)

Laser-based gas headspace analysis

2.1.2. Seal quality test

The seal quality test is used to indirectly ensure ability to maintain package integrity by confirming that parameters related to the container seal or fitting are valid. Conducting the seal quality test set based on evidence is useful for the continuous understanding of the characteristics required for closure and maintaining package integrity. In addition to

examples shown as the seal quality test methods (Table 1), various methods are used.

2.1.3. Microbial challenge test

The microbial challenge test is a biological test to estimate qualitatively package integrity by using live microorganisms or microbial spores. The microbial challenge test is useful for acquiring the direct evidence of preventing microbial ingress. Microbial ingress evaluated in the test includes the passage through pathways by microbial growth or movement and the passive transport of microorganisms via liquid.

Conducting the microbiological test is effective when appropriate physicochemical leak test methods, which obtain the evidence of preventing microbial ingress, have not been established, or when the maximum allowable leakage limit depends on the possibility of microbial ingress.

The recommended general practices are as follows. For the test, microorganisms of which quality are controlled should be used. Other scientifically appropriate methods can also be used.

Put a fluid medium aseptically in the primary package of a preparation to be tested, and immerse the preparation in a bacterial solution of 10^6 CFU/ml for at least 30 minutes or more. Cultivate the preparation and confirm the presence or absence of turbidity in the medium.

2.2. Package integrity and testing in the development and manufacturing of preparations

Selection of test methods according to the stage of the product lifecycle is important to ensure package integrity for sterile pharmaceutical products.

2.2.1. Design of packaging

In the packaging design of the product development stage, the maximum allowable leakage limit is required to be set based on evaluations of not only the risk of sterility failure due to microbial ingress but also the effect of various gases passing through the primary packaging on the quality. For the evaluation, it is desirable to use the quantitative leak test method that has been verified to be able to detect leaks that affect product quality.

Samples used for the evaluation should be prepared assuming the worst case in design.

If influence of other than microorganisms can be ignored, the allowable leak limit to be controlled is set by considering the risk of microbial ingress. This can be set by verifying by the microbial challenge test, or by proving that there is logically no ingress of microorganisms by leak tests. On the other hand, the allowable leakage limit should be set to control the passage of substances in addition to preventing microbial ingress for products that require to keep low headspace oxygen concentration to maintain the quality of preparations etc. Verification only by the qualitative microbial challenge test should not be sufficient. Other qualitative tests are also valuable to obtain information appropriate for the purposes.

2.2.2. Manufacturing of preparations

Package integrity testing in the manufacturing of content-filled products is important to prevent the release of incompletely packaged pharmaceuticals. Based on packaging defects recognized in the development stage and initial process validation, tests are established by leak tests, seal quality tests and appropriate combination of visual inspections during manufacturing to obtain supplemental information.

Examples of leak tests used for package integrity evaluation of preparations in manufacturing processes include liquid immersion test, liquid leak test, tracer liquid test (dye ingress method), sealed chamber method (pressure change leak test method 1), vacuum decay method (Pressure change leak test method 2), high voltage leak test (pinhole test method), laser-based gas headspace analysis. Moreover, examples of the seal quality test methods are shown in Table 1.

Tests using a part of a production lot as a sample provide means to verify package integrity. In contrast, non-destructive leak tests for a whole production lot provide continuous and greater guarantees of package integrity. If relevance between seal quality test results and package integrity is verified in advance, the conduction of the seal quality test can indirectly ensure the package integrity. Manufacturers are required to set the necessary number of samples and demonstrate its validity based on the results of statistical process controls obtained in the process validation stage and the trend analysis of product quality after the start of production. For the glass or plastic ampoules that are sealed by sealing or welding the opening, nondestructive leak tests are usually performed with all samples.

The main purpose of package integrity testing in process validation is to obtain high quality product packaging in the process which is operated with no problem within operating parameters set and to reduce sufficiently the incidence of serious packaging defects. Package integrity testing of in-process and final products complements complete packaging design, therefore cannot replace confirmation at initial design, even if performed.

2.2.3. Evaluation of package integrity in stability tests and stability monitoring

In order to assess the risk of new leaks generated during storage of pharmaceuticals, it is necessary to evaluate package integrity as a part of a stability program. It is recommended that test methods with detection ability as close as possible to the maximum allowable leakage limit are used after the understanding of the mechanism and the rationale for ensuring no contamination.

The amount of sample required for the package integrity test in stability tests should be the amount that can achieve the purpose of the test in consideration of the past development and validation tests. If the test is a non-destructive test, the package integrity of a sample to be tested for preparation stability can be inspected prior to the stability test.

In the case of applying a physicochemical leak test method or any other test method that can appropriately evaluate the ingress of microorganisms with a certain level, it can be substituted for a sterility test in stability tests. On the contrary, if only a sterility test is performed as a test to ensure package integrity over the shelf life of products in a stability program, it is necessary to provide the reason accounting that the sterility test alone is sufficient.

2.3. Criteria for the selection of test methods

The method of an individual leak test or seal quality test cannot cover all of the packaging of products. Depending on preparation packaging, multiple test methods may be required during the product life cycle. Therefore, for ensuring package integrity, it is necessary to select appropriate test methods, set parameters, and verify that the selected test methods can be applied to the product. The following product properties are taken into consideration for the choice of test methods.

Contents of package: Physical state (liquid, solid), electrical conductivity of liquid, presence or absence and type of headspace gas, and compatibility with test materials/test conditions.

Package structure and physicochemical properties: Package hardness, presence or absence of mobility, effect of volatiles added to a polymer, electrical conductivity and capacitance of materials, and the amount of passed gas that is not a leak.

Impact on packaging and contents (destructive tests and non-destructive tests): For example, package integrity testing for ampoules, etc. requiring total inspection should be a nondestructive test that does not affect the quality of packaging and contents.

2.4. Setting and verification of test methods

The optimization of test conditions is required to ensure highly sensitive, accurate, robust, highly reproducible leak detection for individual product packaging systems to which leak or seal quality tests are applied. For the design and verification of test methods, the design of a package closure system, packaging materials, the nature of package leaks to be predicted, and the effect of the contents of products on the test results should be taken into account, and positive controls (packages with intentional or known leaks) and negative controls (packages with no known leak) are used. For quantitative evaluation, it is necessary to make an opening with a certain diameter in consideration of the type and structure of materials that compose packages.

3. Glossary

The definitions of terms used in this General Information are as follows.

Package integrity: Package integrity is the ability of a package to prevent the loss of preparations, to prevent microorganism ingress, and to limit entry of detrimental gases or other substances, thus ensuring that the product meets all necessary safety and quality standards. "Container closure system integrity" and "container integrity" mean "package integrity".

Quantitative leak test method: In the quantitative leak test method, the leak to be detected or measured is based on a phenomenon caused by a predictable series of events. Furthermore, the means of leak detection can be easily controlled and monitored, and is based on the physicochemical techniques that can obtain concrete quantitative data.

Qualitative leak test method: The qualitative leak test method is essentially probabilistic. Qualitative tests depend on a series of continuous or simultaneous events, each of which is accompanied by a random result represented by a probability distribution. Therefore, the results have uncertainty and require a large sample size and the rigorous control of test conditions to obtain meaningful results.

Leakage: The transfer of liquid or gas through a breach in a package wall or through a gap between package materials. Leakage is expressed in the measure (in mass or volume units) of the flow rate of gas that pass through leakage pathways under specified temperature and pressure conditions. The leak rate has the dimension of pressure multiplied by volume, divided by time. For example, the international standard SI nomenclature is pascal cubic meter per second ($Pa \cdot m^3 \cdot s^{-1}$).

Leak: A leakage, or a hole, or a pathway where a leakage occurs.

Permeation: The passage of substances through a package walls. Permeation of gases, including water vapor, can usually occurs in the packaging of sterile pharmaceuticals. The "water vapor permeability test" applies to the permeation of water vapor in plastic containers (mainly aqueous injection containers).

Maximum allowable leakage limit: A maximum leakage rate (or hole, or pathway size) allowable for a product package that can assure no risk to product safety and no or negligible impact on product stability.

Positive and negative controls: A positive control is a package having holes or pathways that cause known and intentional leaks. Positive controls are used to test large size defects (used during the development of test methods) and minimum size defects (used for the development of test methods and for validation studies), according to the type

of defects. Negative controls are packages having no hole or pathway that cause known leaks. The negative controls used in the development of leak test methods and validation studies represent packages optimally assembled using normally processed packaging materials. Positive and negative controls should be able to be measured under same test conditions.

Table 1 Examples of seal quality test methods

Name of seal quality test method	Packaging applied	Contents of test
Tensile strength test	Bag, blister pack, etc.	Measure force required to separate two bonded surfaces.
Closure (opening and closing) torque test	Packaging closed by screws	Measure torque required for opening or closing a plug.
Package burst test	Bag, blister pack, etc.	Apply pressure to a package seal to rupture and open, and measure the pressure or force at the rupture.
Residual seal force test	Vial, etc.	Push a cap downward at a constant speed from the top of a vial, and measure the repulsive force when the plot of the transfer distance - repulsive force reaches the inflection point. Non-destructive testing is possible.
Rubber closure depression test	Vial, etc.	Push a rubber closure downward at a constant rate from the top of a vial, and measure intensity to the depression.
Rotation resistance test of winding cap	Vial, etc.	Measure an initial resistance value when idling a cap. Similar to the residual seal strength test, it is possible to estimate the seal property due to the elastic force of rubber closures.
Airbone ultrasound method	Packaging joined by welding/crimping	Pass an ultrasonic signal through the seal area of a package or an article, and inspect the seal quality by measuring the signal strength. The ultrasonic energy of an area with a bad seal decreases compared with a suitable package seal. Non-destructive testing is possible.