Leak Tests for Packaging of Sterile Products

(無菌医薬品包装の漏れ試験法)

This General Information describes test methods to measure the entry and escape of gases and liquids in packages and containers of sterile pharmaceuticals, and to recognize their unintentional fluid transfer due to leakage. The measured values may indicate the presence, location and size of leak channels as well as leak amount.

The leak tests are classified to qualitative leak tests and quantitative leak tests. This General Information describe liquid immersion test, liquid leak test, tracer liquid test (dye penetration test) and sniffing method (helium leak test method 1) as qualitative leak tests, and 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) and laser-based gas headspace analysis as quantitative leak tests.

Test methods should be selected according to the characteristics of samples and the purpose of the test[1-6]. Samples, the configuration of test apparatus, and conditions such as temperature, pressure and time, are set appropriately based on various technical data, because they affect the validity of results and the safety of operations. It is desirable to use the apparatus that has been calibrated by a standard traceable to the national measurement standard as needed. The leak tests are applied to stoppered rigid or flexible packages and containers, which are empty or contain liquid or solid sterile pharmaceuticals. Specifically, ampoules, vials, syringes, containers for ophthalmic solutions, plastic bags, etc. are subject to the tests.

1. Qualitative leak tests

The qualitative leak tests are test methods to directly observe or measure the leak phenomena, and are used to confirm the presence, position(s) and conditions of leakage.

1.1. Liquid immersion test

The liquid immersion test method is used to detect the presence and locations of leaks by observation of gas emission occurred from defect regions as bubbles, when a sample containing gas in its inside is immersed in liquid and the headspace of the liquid tank is depressurized. In many cases, water is used as the liquid, and in that case it is also called a water immersion test. It observes the generation of gas bubbles after the completion of reduced pressure until the prescribed time, and evaluate the location(s) of leak(s), the size and the occurrence frequency of the gas bubbles. In some cases, bubbles are observed in a liquid tank using a sample pressurized with gas. The amount of leakage can be quantified by collecting the generated gas bubbles in a liquid tank with a measuring cylinder etc. for defined time and measuring the amount. The amount of leakage can be expressed as a function of the sampling time for collecting gas bubbles and the collected quantity being corrected with a reference pressure or one atmospheric pressure. The test is performed at prescribed temperature as required, and the value of reduced pressure and measurement time of the headspace of a liquid tank are set according to the pressure resistance of a sample and assumed defects. It is applied to rigid or flexible packages and containers

1.2. Liquid leak test

The liquid leak test methods are test methods to visualize and observe the transfer of liquid due to leakage using an additive or a developer. The liquid leak test methods include the method that adds liquid containing a fluorescent dye to a sample to detect the leaked liquid by irradiation with ultraviolet light, and the method that coats the surface of a sample with a developer to observe an indication pattern generated by a chemical reaction of the leaked liquid and the developer (Table 1).

Table 1 Types of liquid leak tests

	Methods	Excipients added to liquid	Developers	Observation	Indication pattern
Using an additive	Fluorescent dye method	Fluorescent dye	no	under ultraviolet light (in a dark place)	fluorescence
Using a developer	White development method	no	White developer	under white light	gray color
	Color forming development method	no	Color-forming developer	under white light	red color
	Fluorescence development method	no	Fluorescence developer	under ultraviolet light (in a dark place)	fluorescence

In the fluorescent dye method, liquid containing fluorescent dye is injected inside a sample, or is dissolved in liquid inside a sample, and leakage is detected under ultraviolet light in a dark place. The inside of the sample is pressurized, as necessary, and change due to leakage is observed. In the test methods using a developer, the adequately stirred developer is applied evenly on the surface of a sample by a spray or a brush. After drying of the developed coating film, an indication pattern due to leakage is observed under white light in the cases of the white development method and the color development method. In the fluorescent development method, an indication pattern due to leakage is observed under ultraviolet light in a dark place. Record the indication pattern due to leakage as the description of position, size

and number, etc. or as an image. These test methods are applied to rigid or flexible packages and containers.

1.3. Tracer liquid test (dye penetration test)

The tracer liquid test method is a method to observe the inflow or outflow of tracer liquid by immersing a sample in liquid. The test method is used to detect leak location and to evaluate the relative amount of leakage in non-porous rigid or flexible containers. A dye solution or a solution containing metal ions is used as the tracer liquid. The transfer of the dye is observed visually or measured using instruments. The test method is applied to clear, pressure-tight or other, stoppered rigid or flexible packages and containers which are empty or contain contents (liquid or solid).

a) In the test method where a tracer liquid is introduced, immerse a sample containing no tracer liquid in a chamber filled with the tracer liquid, cover the chamber, and pressurize or depressurize the chamber so that the head space part has a prescribed pressure, and hold. After prescribed time has elapsed, the head space part is opened to the atmosphere and left for prescribed time. Then the sample is taken out, and the surface is cleaned. The tracer liquid which has invaded into the sample is observed visually or measured by chemical analysis.

b) In the test method where a tracer liquid is flowed out, immerse a sample containing a tracer liquid in a chamber filled with a solution containing no tracer liquid. Then cover the chamber, pressurize or depressurize so that the head space part becomes a prescribed pressure, and hold for prescribed time to flow out the tracer liquid. After the head space part is left for a prescribed time under the atmospheric pressure, the sample is taken out, and the transfer of the tracer liquid is measured by observation of the liquid inside the chamber or by chemical analysis. The test method is applied to rigid containers.

1.4. Sniffer method (Helium leak test method 1)[7)]

The helium leak test method by the sniffer method is also called the suction method. This test method is a method to detect leakage by filling helium gas in a sample under normal pressure or pressurized condition and sucking the helium gas that leaks into the outside by a suction probe. In addition, some methods that apply a suction probe to measurement regions or scan with the probe to detect the presence and the position of leakage are also used. The test method is applied to rigid or flexible packages and containers.

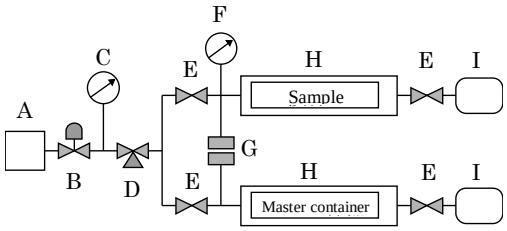
2. Quantitative leak tests

The quantitative leak test methods provide the amount of leakage in numerical physical quantities. Because measured values are affected by conditions (sample temperature, testing time, etc.) and environmental factors (air temperature, humidity, atmospheric pressure, etc.) of the test method, it is necessary to use them with sufficient consideration of these factors.

2.1. Sealed chamber method (Pressure change leak test 1)[8)]

The sealed chamber pressure change leak test method is used to measure the leakage of a stoppered sample by pressure change after pressurizing or depressurizing the chambers which contain the sample and a master container (a leak-free container having same structure as the sample), respectively. The method may be destructive or non-destructive depending on the pressure resistance of the sample and the pressure setting of a chamber. It is applied to rigid or flexible packages and containers.

In this test method, use an apparatus shown in Fig. 1, place a sample and a master container in each chamber, close valves after pressurizing or depressurizing the chambers, and measure pressure difference between the chambers after prescribed time. To detect large leaks, measure pressure difference after releasing the pressure of the inside of both chambers into discharge containers. The amount of leakage is expressed as a function of the value of the pressure difference between the chambers, the space volume of the sample and the chamber, the volume ratio of the chamber and the discharge container, etc.



A : Pressurizing or depressurizing apparatus
B : Pressure regulating valve
C : Pressure gauge
D : Pressure and exhaust valve
E : Shut-off valve
F : Vacuum gauge
G : Differential pressure gauge
H : Chamber
I : Release container

Fig. 1 Example of apparatus configuration for the sealed chamber method (pressure method)

2.2. Vacuum decay method (Pressure change leak test method 2)

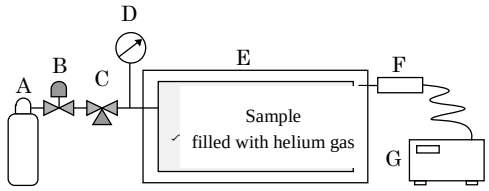
The vacuum decay pressure change leak test is applied to test samples containing liquids. An apparatus similar to that used in the sealed chamber method is used for this test. In the operation, a sample and a master container are placed in chambers, respectively, pressure in the chambers are depressurized below the vapor pressure of the liquid. Changes in the chamber pressure due to the evaporation of the leaked

liquid is measured by a vacuum gauge or a differential pressure sensor. The degree of pressure rise is expressed as a function of gap volume between the sample and the chamber and the measurement time, and is affected by the amount of leaked liquid, vapor pressure, degree of vacuum and the temperature of the liquid. This method is applied to rigid or flexible packages and containers that contain liquid and have no head space.

2.3. Pressure integration method (Helium leak test method 2)

In the pressure integration method, the sample filled with helium gas under normal or pressurized pressure is hold in a chamber or a cover with hood (coating material) to collect helium gas leaked to space between the hood and the sample for a prescribed time. Measure the leakage by sucking the collected gas using a suction probe.

For this test method, an apparatus shown in Fig. 2 is used, and the amount of leakage is expressed as a function of the concentration of helium gas, the gap volume between the hood and the sample, the time for collecting helium gas, the amount of suction by a suction probe, etc. This method is capable of measuring leakage from a whole sample, and is less susceptible to the concentration of surrounding helium. This method is applied to non-stoppered rigid containers without contents.



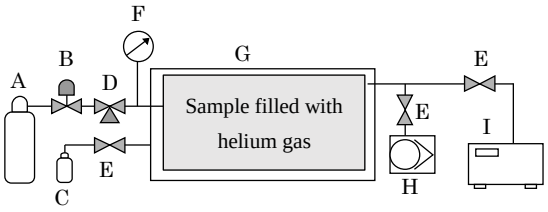
A : Helium cylinder
B : Pressure regulating valve
C : Pressure and exhaust valve
D : Pressure gauge
E : Chamber or cover
F : Suction probe
G : Helium leak detector

Fig. 2 Example of apparatus configuration for pressure integration method

2.4. Vacuum chamber method (Helium leak test method 3),

The vacuum chamber method helium leak test is also called the vacuum container method. This test measures helium gas leaked from a sample filled with helium gas in the chamber maintained at high degree of vacuum by exhausting. High detection sensitivity is obtained compared to the pressure integration method. This method is applied to non-stoppered rigid containers without contents.

For this test method, use an apparatus shown in Fig. 3, set a sample filled with pressured helium gas in a vacuum chamber, close the chamber, and depressurize. The value of leakage is obtained from the difference between the amount of helium in the chamber, in the presence and absence of the sample, at the time when the inside of the chamber reaches prescribed vacuum.

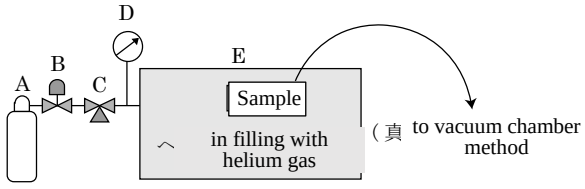


A : Helium cylinder
B : Pressure regulating valve
C : Calibration leak
D : Pressure and exhaust valve
E : Shut-off valve
F : Vacuum gauge
G : Vacuum chamber
H : Auxiliary exhaust apparatus
I : Helium leak detector

Fig. 3 Example of apparatus for the vacuum chamber method

2.5. Immersion method (Helium leak test method 4)

The immersion method helium leak test is also called the bombing method. This test measures outflow due to leakage by the vacuum chamber method after introducing helium gas into the space inside a sample through defects in a chamber filled with helium gas and then taking out the sample, using an apparatus shown in Fig. 4. A sample having space inside is placed in a chamber pressured with helium gas and the concentration of helium inside the sample is increased by immersing helium gas through defect holes from the outside. Then the leakage of the sample is measured by the vacuum chamber method. This method cannot be applied to samples having large leaks. The degree of leakage is expressed as a function of leaving-time in the air, inside volume of a sample, time for filling, pressure for filling, etc. This method is applied to stoppered rigid containers having space inside a sample.



A : Helium cylinder
B : Pressure regulating valve
C : Pressure and exhaust valve
D : Vacuum gage
E : Helium gas filling chamber

Fig. 4 Example of apparatus configuration for immersion method

2.6. High-voltage leak test (Pinhole test)

The high voltage leak test is used to detect pinholes which allow leakage, in the area between where electrodes are applied. The electric current that flows upon application of the high voltage to the sample is measured. Rapid non-destructive tests are possible in appropriate measurement

conditions. This method is applied to rigid or flexible packages and containers with non-conductive packaging materials, containing conductive contents that are not affected by applied voltage.

2.7. Laser-based gas headspace analysis

The laser-based headspace gas analysis is a method that detect changes in the headspace gas of a sample due to leakage from the absorbance or frequency modulation of specific frequency bands in the transmission of a laser light. Information such as the concentration of oxygen, carbon dioxide or water vapor and an internal pressure are obtained by irradiating a sample held between a light source and a detector with a light having a wavelength suitable for the gas to be measured. The possibility of leakage is judged by comparing the measurement value with the value obtained for a reference sample having controlled defects. Non-destructive tests are possible in appropriate measurement conditions, however, it is necessary to perform the tests under environment suitable for the purpose because temperature and humidity affect the results. This method is applied to light-transmitting containers that have a headspace gas.

3. References

1) JIS Z 2330:2012, Non-destructive testing-Selection of leak testing method.
2) The Japanese Society for Non-Destructive Inspection, Leak testing I, 2012.
3) The Japanese Society for Non-Destructive Inspection, Leak testing II, 2012.
4) The Japanese Society for Non-Destructive Inspection, Leak testing III, 2016.
5) US Pharmacopeia 40 (2017), <1207.1> Package Integrity Testing in The Product Life Cycle—Test Method Selection and Validation.
6) US Pharmacopeia 40 (2017), <1207.2> Package Integrity Leak Test Technologies.
7) JIS Z2331:2006, Method for helium leak testing.
8) JIS Z2332:2012, Leak testing method using pressure change.