

METHOD FOR INSPECTING A SEAL OF A FLEXIBLE CONTAINER

The present invention relates to a method for inspecting a seal of a flexible container
5 for a fluid, in particular for a fluid medicine, as well as the flexible container for a fluid
medicine itself.

Flexible containers of this type for fluid medicines can, for example, be used as what
are known as single use bags, in order to store and transport very valuable fluid
10 biopharmaceuticals. They can consist of two layers of plastic – in particular plastic
films – which are flexible and heat sealed at the edges („flexible wall“).

Inspecting the seal of these containers is a technical challenge, in particular because
between production of the container and use thereof, the container is exposed to a
15 number of influences which could be the cause of leaks or holes and the like. Such
exposure may occur, for example, during packaging, sterilisation (for example using
gamma radiation), transport, storage, unpacking as well as any manual manipulations
and the like.

20 Thus, the prior art contains an established two-stage inspection method in which,
initially at the production site for the container, a precise inspection is carried out and
secondly, a further inspection is carried out at the point of use.

The inspection at the production site functions by introducing helium into the container.
25 In this regard, it should be noted that this is actually only applicable to the container
itself. Tubes, connectors, filters and the like, if any, are not tested along with it. The
container filled with helium is disposed in a vacuum chamber. By evacuating the
vacuum chamber and detecting helium present in the vacuum chamber which has
escaped through any leaks, a conclusion can be drawn as regards the seal or the
30 presence of a leak. This measurement is highly sensitive. Leaks with sizes of less than 5
 μm can be detected. However, at the same time, a heavy load is placed on the container
because pressurizing with helium causes the container to expand and inflate in the
manner of a balloon. Greater precision at the point of use cannot be achieved using this
prior art method, however, because appropriate equipment for high vacuum and the like is
35 not readily available.

Leaks which only occur after this inspection has been carried out at the production site naturally cannot be detected in this manner.

5 As mentioned, a further inspection is carried out directly at the point of use. In this regard, the container is pressurized with a relatively low pressure (approximately 30 millibar) and monitored for approximately half an hour. A conclusion regarding the escape of a gas from the container can be drawn from the pressure changes. If these are too great, then the presence of a leak can be concluded. However, leaks with a size of 20 μm or less
10 cannot be detected.

At the point of use, it is not practical to employ the prior art method carried out on the containers at the production site because the (industrial) facilities, such as a vacuum chamber and the availability of helium, might not be easy to reproduce at the point of use.

15 However, the sensitivity to leaks greater than 20 μm in size at the point of use is in the end not sufficient, because even holes of more than 3 to 5 μm are considered to be capable of leading to non-sterility inside the container (what is known as "bacterial ingress"). In short, a hole more than 3 to 5 μm in size allows bacteria to gain access to
20 the interior of the container.

Thus, the objective of the invention is to provide a method and a device which can be used to reduce the risk of a failure of the sterility of a flexible container for fluid medicines and similar products, for example from the pharmaceutical production process.

25 In respect of the method, this objective is achieved by means of the features of claim 1. In respect of the device, the objective is achieved by means of the features of claim 10.

Having regard to the method, this objective is achieved by the following:

- 30
- the container (in other words the test specimen) is at least partially – preferably completely – covered with a gas-permeable layer,
 - the container including the gas-permeable layer is disposed in a flexible essentially gas-tight bag (the escape of small quantities of fluid following sealing may be acceptable, depending on the application),
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- the essentially gas-tight bag is evacuated by pumping out via a bag opening,

- the container is filled with a noble gas, and
- the presence of noble gas which escapes via a leak from the container through the gas-permeable layer via the bag opening is detected.

5 By using a gas-permeable layer and an additional essentially gas-tight bag, the vacuum chamber used in the prior art can be dispensed with in the method. This has, on the one hand, the advantage that complicated measuring apparatus as described in connection with the prior art inspection at the production site, is no longer required. At the same time, inflation of the container is prevented and because of this, the
10 introduction of fresh damage, in particular leaks, is avoided.

This is because the evacuation of the space between the container to be inspected and the essentially gas-tight bag means that it is only atmospheric pressure that acts (via the essentially gas-tight bag and the gas-permeable layer) on the flexible container
15 from outside.

When the space between the flexible container and the essentially gas-tight bag has been evacuated, the gas-permeable layer also allows helium, which escapes from the container via a leak, to migrate by pumping it out from the essentially gas-tight bag to a
20 detecting device.

Advantageously and preferably, a nonwoven or the like may be used as the gas-permeable layer.

The gas-permeable layer may be produced from plastic.
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In summary, the method in accordance with the invention has on the one hand the advantage of the necessary precision, because leaks with sizes of less than 3 to 5 μm can be detected, and on the other hand the mechanical load on the flexible container to be tested is smaller, reducing the risk of leaks caused by the inspection.
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The container may be filled with the noble gas before, during or after evacuating the bag.

Regarding the device, the objective is achieved by means of a set formed by a flexible container for a fluid, in particular for a fluid medicine, and a pressurised gas container to
35 accommodate a noble gas. This too reduces the necessity for complicated laboratory

equipment at the inspection site, because the appropriate noble gas is supplied directly along with the flexible container. By pre-packaging the flexible container together with the pressurised gas container, sources of errors when carrying out the inspection, which can easily occur when filling the container with noble gas, can be eliminated. Examples are

5 pressurizing with too high a pressure or incorrect connection of an external source of pressure to the container (for example because the connectors do not fit together well enough or the like).

In this regard, the container comprises an opening which can essentially be sealed in a

10 gas-tight manner (the escape of smaller quantities of fluid after sealing may be acceptable, depending on the application) and which is configured in a manner such that a fluid connection between the container and the pressurised gas container which is gas-tight to the outside can be produced.

15 The bag may also be part of the set in accordance with the invention.

By means of the invention, it is also possible to test the container including accessories such as tubes, connectors, valves and the like.

20 More than one bag opening may be provided, whereupon judicious positioning on the bag, for example on opposite sides, means that paths to the detector for the noble gas which are as short as possible can be obtained.

The container may, for example, consist of polyethylene, ethylene-vinyl acetate,

25 fluoropolymers or blends thereof.

Protection is also sought for the use of a set in accordance with the invention is also protected by the method in accordance with the invention.

30 Further advantageous embodiments of the invention are defined in the dependent claims.

As mentioned, the container may be filled by bringing the container into fluid connection - preferably gas-tight to the outside - with a pressurised gas container filled with the noble gas via an opening.

In a very particularly preferred embodiment, prior to evacuation, the pressurised gas container may be disposed – preferably in its entirety – inside the essentially gas-tight bag. In this regard, no tubes have to be fed out of the bag, the edges of which must be assiduously sealed to the outside. In addition, this allows for a particularly simple
 5 procedure for the method. Activating the pressurised gas container can in this regard be carried out in a remote manner via any type of electromagnetic waves. Because the essentially gas-tight bag may also be flexible or elastic, filling of the container with noble gas may also be initiated by means of a switch on the pressurised gas container which is actuated through the bag.

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Very particularly preferably, in one embodiment, the procedure for producing the fluid connection between the pressurised gas container and the container may be carried out automatically and mechanically.

15 In other words, by disposing the entirety of the pressurised gas container within the bag, this means that the prior art practice of passing tubes from a source of helium into the test chamber and the concomitant additional risk to the seal can be avoided.

Preferably, helium may be used as the noble gas because among the noble gases, this
 20 has the lowest molecular weight and therefore – insofar as this is an indication of the corresponding scale of its size - has the smallest “dimensions” . In this manner, the smallest possible holes or leaks in the container can be detected (because under some circumstances, larger noble gas atoms might not be able to penetrate through the holes in question).

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It may be beneficial to the accuracy of the measurement for the essentially gas-tight bag to be kept evacuated by being continuously pumped out. This means that pumping out can be initiated when a representative signal is delivered by the detection device. Naturally, it is also possible to pump out in pulses or to program and control it in another
 30 manner in order, for example, to save energy.

In order to detect the presence of the noble gas escaping from the bag opening, mass spectrometers, for example, may be used as the detectors.

The fluid is preferably a fluid medicine. However, the invention may also be employed for similar high value products such as, for example, precursors of medicines and other substances which are formed during (bio)pharmaceutical production processes, wherein the small-scale seal of the container is also important. The fluid may also preferably be a liquid. In a most particularly preferred embodiment, the fluid may be a fluid medicine.

The flexible container may – preferably once and once only – be used for the storage and/or transport of a fluid medicine as long as no leaks are detected during the inspection. Thereafter, the container can be disposed of. In this case, they are termed single use bags.

It may be beneficial to the accuracy of the measurement for the method to be carried out on an empty – preferably completely empty – container. Particularly effectively, the method may be employed with containers of the type which are so flexible that they can essentially be completely emptied without the need for the use of a reduced pressure.

In respect of the set, the pressurised gas container may be connected to the container via the sealable opening, wherein preferably, a tube and/or pipe connection is provided.

It may be of particular advantage for the pressurised gas container to be relatively small. This means in particular that its capacity should be such that a quantity of the noble gas which is stored in the pressurised gas container, under normal conditions, i.e. at atmospheric pressure, does not exceed twice the nominal capacity of the container. Particularly preferably, the capacity may be such that this volume does not exceed the nominal volume capacity of the container and more particularly preferably three quarters and in particular half of the nominal volume capacity.

Further advantages and details of the invention will become apparent from the figures as well as the accompanying description of the figures. In the drawings:

Figure 1 shows a diagrammatic representation of the test setup for carrying out the method in accordance with the invention, and

Figures 2a and 2b show diagrammatic images of the set in accordance with the invention as well as the set in accordance with the invention after covering with the gas-permeable layer.

In one embodiment of the method in accordance with the invention, helium is used as the noble gas.

5 The test setup is shown in Figure 1 in a highly diagrammatic manner and may be designed to be so compact that the inspection of the seal may also be carried out reliably at the site where the container 2 is filled. The container 2 is flexible and constructed as shown diagrammatically in Figure 2a, for example. It is at least partially – preferably completely – covered with the gas-permeable layer 3.

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The container 2 is in a set with the pressurised gas container 7. The pressurised gas container 7 is connected to the container 2 by means of a tube connection and the opening 6 on the container 2. The opening 6 can be sealed in a gas-tight manner and is indicated in only a diagrammatic manner in Figure 1 as the intersection of the tube connection with the container 2.

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The container 2 is completely covered by the gas-permeable layer 3, wherein the gas-permeable layer 3 in this embodiment is formed as a nonwoven. The container covered with the gas-permeable layer is disposed in the essentially gas-tight bag 4 together with the tube connection and the pressurised gas container 7. The interior of the bag 4 is connected to the detector 8 via the bag opening 5 (also shown only diagrammatically as the intersection between the bag 4 and a connection of the detector 8 with the bag 4). The detector 8 in this case also comprises a vacuum pump for evacuating the bag 4 as well as the complete hardware and software required for detecting helium in the gas stream brought about by the evacuation.

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During evacuation, the gas-permeable layer 3 reduces any destructive forces on the container 2. At the same time, in the evacuated condition of the outer bag 4, the gas-permeable layer 3 allows helium escaping from a leak in the container 2 to migrate to the bag opening 5. The escaped helium can be pumped out from the bag opening 5 in the direction of the detector 8. In other words, the gas-permeable layer 3 prevents the outer bag 4 from sealing any holes in the container 2 upon evacuation.

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Multiple manifestations of the bag opening 5 may be present in the measurement setup (on container 2), for example on the opposite sides of the container 2. In this manner, escaped helium can take as short as possible a route to the detector 8.

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Naturally, prior to detection, the container 2 has to be filled with noble gas from the pressurised gas container 7. This may be carried out either before, during or after the evacuation. When filling following evacuation, the opening 6 must be correspondingly opened; this may, for example, be carried out contactlessly by the transmission of
10 electromagnetic waves.

The pressurised gas container 7 in this embodiment is dimensioned in a manner such that, after opening the opening 6, the noble gas (helium) takes up approximately half of the nominal volume of the container 2 (at approximately 1 bar atmospheric pressure).

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(Thus, there is a difference in pressure between the interior of the container 2 and the space between the container 2 and the essentially gas-tight bag 4 of approximately 1 bar, because the space has in fact been evacuated).

An embodiment of the set in accordance with the invention formed by the flexible
20 container 2 and the pressurised gas container 7 is shown photographically in Figure 2a. It can be seen here how the pressurised gas container 7 is connected to the container 2 via a small (black) tube. The opening of the container 2 can be sealed, whereupon the sealing mechanism in this embodiment is associated with the pressurised gas container 7 or is disposed in it. The container 2 also has further connections which can be seen on
25 the right hand side of the image and, for example, serve for filling and emptying the container 2.

The container 2 shown by way of example in Figure 2a is designed as what is known as a single use bag, i.e. it is intended to be disposed of after having been used just once.

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Containers of this type may have a nominal volume capacity of 10 litres, for example.

Figure 2b shows the container 2 together with the pressurised gas container 7 in the condition in which it is completely covered or surrounded by the gas-permeable layer 3 and inside the bag 4. After sealing the bag 4, the disposition is as shown in Figure 2b.

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(The detector 8 is not shown in Figure 2b). It should be noted that in the evacuated state,

as a rule, there is of course no longer a space between the gas-permeable layer 3 and the container 2 and the bag 4 respectively. These gaps are only shown in Figure 2b for the sake of clarity.

- 5 The pressurised gas container can then dispense a defined quantity of helium into the container 2. To this end, a special valve may be employed, for example. The pressurised gas container 7 (also known as the "helium applicator") in the present case is also intended for a single use, but naturally may also be designed for repeated use.
- 10 When filling the container 2 with helium from the pressurised gas container 7, a fluid connection which is gas-tight to the outside (i.e. to the space between container 2 and bag 4) is formed between the pressurised gas container and the interior of the container 2.
- 15 Because of the relatively small quantity of helium, an excess pressure (i.e. a pressure far above the normal atmospheric pressure of 1 bar) in the container 2 is avoided.

As already mentioned, evacuation may be carried out before or after introducing the helium into the container 2. Too long an interval between filling the container 2 and
20 detecting the helium by the detector 8 should not pass, however, as if so, diffusion of the helium through the container 2 could falsify the results of the measurement.

In any case, the presence of a leak in the container 2 is concluded if the quantity of the helium detected by the detector 8 exceeds a specific threshold.

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A further advantage of the use of the gas-permeable layer lies in the fact that the volume in the essentially gas-tight bag 4 to be evacuated is smaller, whereupon the ratio of the helium (if a leak is present) to the atmospheric air is increased.

- 30 The presence (because the threshold has been exceeded, for example) or absence of a leak may be output, for example, via a user interface on the detector 8.

Overall, the invention means that a smaller mechanical load is exerted on the container 2 to be inspected, which reduces the safety risk and the test outlay.

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PATENT CLAIMS

1. A method for inspecting a seal of a flexible container (2) for a fluid, in particular a fluid medicine, wherein
 - 5 - the container (2) is at least partially – preferably completely – covered with a gas-permeable layer (3),
 - the container (2) including the gas-permeable layer (3) is disposed in a flexible essentially gas-tight bag (4),
 - the essentially gas-tight bag (4) is evacuated by pumping out via a bag opening (5),
10 - the container (2) is filled with a noble gas, and
 - the presence of noble gas which escapes via a leak from the container (2) through the gas-permeable layer (3) via the bag opening (5) is detected.
- 15 2. The method as claimed in claim 1, characterized in that the container (2) is filled by bringing the container (2) into fluid connection with a pressurised gas container (7) filled with the noble gas via an opening (6).
3. The method as claimed in claim 2, characterized in that prior to evacuation, the
20 pressurised gas container (7) is disposed – preferably in its entirety – inside the essentially gas-tight bag (4).
4. The method as claimed in one of the preceding claims, characterized in that the noble gas is helium.
- 25 5. The method as claimed in one of the preceding claims, characterized in that the essentially gas-tight bag (4) is kept evacuated by being continuously pumped out.
6. The method as claimed in one of the preceding claims, characterized in that a
30 detector (8) is used in order to detect the presence of the noble gas escaping via the bag opening.
7. The method as claimed in one of the preceding claims, characterized in that the
35 flexible container (2) – preferably once and once only – is used for the storage and/or transport of a fluid – preferably a fluid medicine, as long as a quantity of

the detected noble gas escaping from the bag opening (5) does not exceed a threshold.

- 5 8. The method as claimed in claim 7, characterized in that the container (2) is disposed of after use for storage and/or for transport of fluid.
9. The method as claimed in one of the preceding claims, characterized in that the method is carried out on an empty – preferably completely empty – container (2).
- 10 10. A set formed by
- a flexible container (2) for a fluid, in particular for a fluid medicine, and
 - a pressurised gas container (7) to accommodate a noble gas,
- 15 wherein the container (2) comprises an opening (6) which can essentially be sealed in a gas-tight manner and which is configured in a manner such that a fluid connection between the container (2) and the pressurised gas container (7) which is gas-tight to the outside can be produced.
- 20 11. The set as claimed in claim 10, characterized in that the pressurised gas container (7) connected to the sealable opening (6) with the container, wherein preferably, a tube and/or pipe connection is provided.
- 25 12. The set as claimed in claim 10 or claim 11, characterized in that a nominal capacity of the pressurised gas container (7) is such that a volume of the noble gas present at atmospheric pressure does not exceed twice a nominal capacity of the container (2).
- 30 13. The set as claimed in claim 12, characterized in that a nominal capacity of the pressurised gas container (7) is such that a volume of the noble gas present at atmospheric pressure does not exceed the volume capacity of the container (2).
- 35 14. The set as claimed in claim 13, characterized in that a nominal capacity of the pressurised gas container (7) is such that a volume of the noble gas present at atmospheric pressure does not exceed three quarters – preferably half – of the nominal volume capacity of the container (2).

15. The set as claimed in one of claims 10 to 14, characterized in that container (2) is so flexible that it can essentially be completely emptied without the use of a reduced pressure.

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16. The use of a set as claimed in one of claims 10 to 15 in a method as claimed in one of claims 1 to 9.