

**STEAM STERILIZABLE CONTAINER AND RELATED STERILIZATION
METHOD
DESCRIPTION**

Technical field

- 5 This invention relates to a superheated steam sterilisable container used for filling and closing primary aseptic containers, by means of a process suitable for sterile pharmaceutical items (injectable products, ophthalmics, etc.), such as bottles, syringes and carpules, which are used as primary containers for manufacturing and distributing parenteral pharmaceutical
- 10 items. The patent also relates to a system made with such containers as well as the sterilising method actuated in the containers.

Background art

- The process for filling bottles or vials, syringes or carpules in aseptic conditions with pharmaceutical, biological and vaccine substances and
- 15 finishing the packaging process for distribution (the so-called “fill-finish”) is one of the most critical points of the entire pharmaceutical production process relative to the aspects relating to the safety of sterility.

- The bottles, syringes and carpules, in fact, are used as primary containers for the manufacture and distribution of parenteral pharmaceutical items and
- 20 require high guarantees of sterility. However, unlike those processes in which it is possible to carry out final sterilisation, the drug, or in its final liquid formulation, or in freeze-dried preparations, or in the form of powders to be reconstituted, is dispensed in open contexts and is exposed to the risk of losing sterility.

- 25 Since the injectable drug must be strictly sterile, the filling and finishing (or closing) steps must take place within designed and qualified environments in order to avoid creating risks to the sterility of the product and risks of its contamination.

- In the context of injectable production processes, the safeguarding and
- 30 quality of the pharmaceutical product – and hence of the patient – is achieved through national or international guidelines and regulations.

Specifically, the regulations require the manufacturer of parenteral drugs to carry out a series of requirements from the point of view of the industrial production and qualification of machinery, as well as the usual control procedures.

- 5 In particular, aseptic production requires greater guarantees than an approach with terminal sterilisation with regard to the filling systems and the environment in which this must occur. In addition to this, it is essential that this is also ensured with regard to the monitoring methods, so as to have a safety of the sterility and avoid microbiological (so-called "viable") and
10 particle (non-viable) contamination.

According to the prior art, the aseptic fill-finish systems are installed inside restricted access barrier systems ("RABS") or isolators. These apparatuses are configured to obtain a confined environment in which the step of filling and closing the container occurs. The RABS and isolators are therefore
15 usually integrated with automatic filling machines.

The requirements set out in the legislation, from the particle and microbiological point of view, are very strict. By way of example, strict limits on particle contamination are imposed in the area in which the most delicate processes occur, both at rest and in operation. The complete absence of
20 microbiological contamination is also required. Moreover, all parts in direct contact (dispensing circuits, gas cover system on the bottle or syringe, etc.) or indirect contact (cap feeding systems) must be sterile to ensure there is no risk of pollution of the pharmaceutical product.

For this reason, the filling machines integrated in insulators or RABS have
25 to manage the parts in direct and indirect contact and the relative operating procedures (which together have been defined as "aseptic techniques") in order to reach the required environmental conditions.

The insulators are closed systems (completely closed) or open systems (provided with a mouse-hole, that is to say, points of entry and exit towards
30 the "cleanrooms") specially designed to reach the conditions of maximum sterile safety in such a way as to correctly execute the aseptic techniques.

They consist of large chambers in which the ventilation is achieved by a high efficiency filtration system (HEPA) and they are conditioned through heating, ventilation and air conditioning systems (HVAC), or the like. The insulators are built to be small "cleanrooms", which are verified and able to reach a controlled atmosphere aseptic condition and are qualified in a similar way. Air is diffused inside the insulators without risks from the particulate point of view thanks to the efficient filtration system. The embodiment comprises the use of materials such as stainless steels or plastic which are certified for the aseptic areas, and a meticulous configuration which allows a correct cleaning and sanitising. A fundamental point is that the insulators are provided with decontamination systems, usually based on vaporised hydrogen peroxide, which is used before the production step to reduce the microbiological charge.

Although these solutions are currently the most advanced and consolidated solutions provided by the market, they have some problems.

Firstly, the most commonly used standard for reducing the microbiological charge is the hydrogen peroxide or vaporised hydrogen generator (VPHP or VHP) which is considered the fundamental process for achieving the aseptic condition.

However, it is not possible to put this process on the same level as saturated steam sterilisation systems, for example used in autoclaves, with ionizing radiation (gamma or beta) and chemical sterilisation with ethylene oxide (ETO). In fact, the VPHP system is defined as a "decontamination" system and not a sterilisation system. In this regard, several limitations have been highlighted regarding the use of VHP, highlighting its weakness; while reaching high levels of reduction of the microbiological charge, decontamination with the hydrogen peroxide generator in the vapour phase is purely superficial and has a low penetration: no deep gaps or areas that are not perfectly clean are decontaminated, especially where dust or residues may have accumulated, as the microbiological contamination is "protected" and VHP loses its effectiveness. For this reason, this process is

not designed for sterilising parts in direct and indirect contact with the product which are present in the closing-filling machines.

For this reason, in order to sterilise the parts in direct and indirect contact before production with other systems, they are removed from the machine

5 and moved into an autoclave, normally located in the rooms adjacent to the production area which houses the isolator. The direct contact parts which are reusable and not sterilised beforehand are placed in bags and then transferred to the isolator without losing their sterility. This results in very high production times which, for obvious reasons, affect the costs of the individual filled and capped bottle.

Since the transfer occurs inside an area normally at a lower sterility level, the contact of these components with the air or their handling causes the loss of sterility. Consequently, the material is introduced either by means of specific transfer systems (Rapid Transfer Port - RTP) or safely transferred and mounted using the special isolator gloves, behind closed doors. It is clear, however, that these methods are complicated and risky, since they are carried out manually, and are also carried out using gloves which are considered an extremely critical element by the regulations.

Moreover, there are residual risks from contact during assembly with non-sterile gloves, procedural errors, violation of the first air criterion inside the aseptic area.

It is even more critical and serious with very large components, such as vibrating cups and hoppers. These items are put in an autoclave and then put into bags, but they are often so large that they cannot be handled with gloves with the doors closed, so they are usually mounted with doors open with protective methods which cannot guarantee, however, the maintenance of sterility.

The result is therefore a risk-mitigated system, but not completely safe from the sterility point of view.

30 **Summary of the Invention**

The aim of the invention is to overcome the above-mentioned drawbacks

and provide an alternative solution to insulators decontaminated with hydrogen peroxide or similar systems.

In the context of the above-mentioned purpose, an aim of the invention is to provide a container which can be sterilised by superheated steam which
5 guarantees the safety of the sterility of the machine and all its parts.

Another aim of the invention is to provide a system for filling and finishing bottles, syringes and carpules which is more efficient than prior art processes.

Yet another aim of the invention is to provide a container which can be
10 sterilised by superheated steam which, whilst guaranteeing maximum quality and sterility, is also economically competitive.

This purpose, as well as these and other aims, which are described in more detail below, are achieved, according to the invention, comprising the technical features described in one or more of the appended claims. The
15 dependent claims correspond to possible different embodiments of the invention.

In particular, according to a first aspect, this invention relates to a container which can be sterilised by superheated steam, which comprises: a process chamber designed to be sterilised with superheated steam coming from a
20 vaporisation duct; at least a first compensated pressure compensation chamber, for housing the operational instruments of the container; a first partition hermetically interposed between the process chamber and the first compensation chamber; and accesses for the connection between the process chamber and its adjacent zones, regulated during opening and
25 closing by means of respective valves.

The term “zones adjacent” to the process chamber means those zones designed to be connected to the same process chamber by the valves for regulating the accesses.

The zones adjacent to the processing chamber designed to be connected
30 to it by regulating these accesses may be, amongst others:
other process chambers, also belonging to separate sterilisable containers;

and/or process chambers arranged one after another, each of them being of other sterilisable container systems; and/or insulators designed to be connected upstream and/or downstream of the sterilisable container according to this invention.

- 5 Obviously, the filling of the bottles, syringes or carpules may only proceed after reaching a sterile condition thanks to the saturated steam sterilisation cycle described below.

The Applicant has developed a superheated steam sterilisable container, for filling and finishing bottles, syringes and carpules, as well as for
10 distributing caps for these bottles and covers for the syringes and carpules, without the use of insulators or similar means which force the operator to remove and refit the components or to intervene with sterile gloves. The container also allows the sterilisation of the instrumentation components, so as to ensure a total disinfection and decontamination of all the parts.

- 15 It is also clear that the process chamber is sterilised by means of superheated steam and therefore becomes sterile and allows a process for aseptic filling of the bottles, syringes and carpules.

Advantageously, in order to prevent the pressure differential between the process chamber and the chamber in which the apparatuses inside the
20 container are housed from causing damage to the apparatuses, there is a pressurising device and, if necessary, a device for generating a vacuum, preferably with alternating cycles. The device is configured for changing the internal pressure of the first compensation chamber from a standard pressure, corresponding to the external pressure, to an operating pressure,
25 variable between a substantially zero value of the operating pressure and a value equal to the pressure of the superheated steam inside the process chamber.

In other words, the operating pressure can vary substantially between 0.2 and 3 bar.

- 30 Similarly, the container includes a second compensated pressure compensation chamber, with inspection means for controlling the process

chamber, separated from this in a sealed fashion by a second partition.

Moreover, the second compensation chamber has an upper access to control the inside of the sterile process chamber, in such a way as to allow the operator to operate easily inside the chamber.

- 5 Thanks to this compensation system, it is possible to perform a saturated steam sterilisation process at high pressures without damaging the instrumentation in the compensation chamber.

Preferably, the process chamber is positioned between the first and the second compensation chamber along the vertical direction of extension of
10 the container, coinciding substantially with the axis of symmetry of the container. Consequently, the first partition lies in a horizontal plane normal to this vertical direction.

Obviously, in an identical way to that seen in the first compensation chamber, the pressurising device of the second compensation chamber, by
15 injecting compressed air, varies the internal pressure of the second compensation chamber between the standard pressure and the operating pressure, advantageously keeping a small pressure differential relative to the process chamber.

According to a first embodiment, a first container is used for the sterile filling
20 and finishing of bottles, syringes and carpules, which enter and leave from the container; for that purpose, inside it, there will be means for filling bottles, syringes or carpules.

In practice, the apparatuses for filling bottles, syringes or carpules are integrated inside this first container provided with an upper process
25 chamber and a first and a second compensation chamber. The first compensation chamber is basically a service compartment, separated in a sealed fashion from the process chamber (where the medical elements are filled and closed), but which is able to compensate for the pressure difference with respect to the upper chamber to prevent deformation of the
30 blowers and a mechanical stress between the two compartments at higher pressures. In the same way, the second compensation chamber, where

inspection means are preferably provided, is also provided with a hermetic separation.

In this document, the terms “upper” and “lower” or “above” and “below” refer to the position of an element, or a part of it, relative to one of the horizontal
5 planes on which the first or the second partition lies.

According to an example embodiment, not necessarily in place of the second compensation chamber; an access chamber is made which allows the operator to inspect the inside of the process chamber using a door which can be opened and hermetically closed.

10 Preferably, the access chamber can be separated from the process chamber by means of a third partition, with hermetic separation. The partition therefore allows the above-mentioned access chamber to be considered to be another compensation chamber to all intents and purposes.

15 In this case, in order to allow inspection inside the process chamber, this third partition is made of optically transparent material, for example Plexiglas or glass.

Advantageously, the access chamber is, similarly to the other compensation chambers, pressurised in such a way that the third glass partition can
20 withstand the very high pressure coming from the process chamber during sterilisation.

Due to the question of practicality, the access chamber is preferably positioned laterally, along the horizontal direction, with respect to the process chamber, in such a way as to facilitate the use by the operator.

25 The making of such an access chamber, for the inspection inside the process chamber, offers a construction advantage (simpler than the window of the second access chamber for the first container) and visual advantage (since the operator is not forced to follow the process from above but can do so in line).

30 According to an alternative embodiment, a second container can be sterilised by superheated steam in which the sterile caps for bottles,

syringes or carpules are distributed. The process chamber of the second container is a chamber for feeding the caps, separated from a first and a second compensation chamber. The upper compensation chamber is provided with at least one transparent portion for inspecting the process chamber, whilst the lower compensation chamber houses the system of vibrating the cup. The caps are fed by a caps storage unit, from which caps already sterilised come, upstream of the container, whilst the vibrating cup distributes the caps towards the process chamber of the first container.

Advantageously, the two containers are connected aseptically by a pipe intercepted by an opening and closing valve, in such a way that the caps or the covers are transported without problems of contamination between the two containers, that is to say, between the second container for sterilising the vibrating cup and the distribution of the caps and the covers and the first container, that is to say, the sterile filling and finishing container of bottles, syringes and carpules, where robotic hands will pick up the caps or the covers and close the respective bottles, syringes and carpules.

The vaporisation duct of the process chamber of the container for the sterile filling and finishing of bottles, syringes and carpules is connected to a vaporisation device extending, inside the process chamber, along a horizontal direction substantially normal to the vertical direction. The vaporisation duct advantageously has a longitudinal cut along the horizontal direction which makes it possible to produce a sheet of sterile air above the train of bottles, syringes and carpules, for maintaining the aseptic condition of the filling zone during the entire time necessary to complete the finish.

The vaporisation duct may, in effect, dispense sterilised air.

The second container which can be sterilised using superheated steam for distributing the caps and the closing elements of the primary containers, preferably comprises the following accesses: an upper opening - adjusted when opening and closing by means of an upper valve - for the entrance of the caps falling towards a vibrating cup positioned in the process chamber, and a lower opening - adjusted when opening and closing by means of a

lower valve - for transferring the caps coming from the vibrating cup towards the container for the sterile filling and finishing of bottles, syringes and carpules, which is also connected to the process chamber.

According to an example of this second container, the first compensation
5 chamber is defined inside the process chamber, in such a way that the first partition corresponds to the perimeter wall of said first compensation chamber and therefore acts as a dividing wall between the two chambers. In practice, in this case, in a single space, the outer walls of the first compensation chamber are enclosed by the inner walls of the process
10 chamber and the compensation chamber is simply a pocket of the same process chamber.

Advantageously, the Applicant has understood that, by positioning a dosing valve inside the process chamber, between the upper opening and the vibrating cup, it would be possible to intercept the caps, already sterilised
15 and coming from the cap storage system, falling inside the process chamber, in such a way as not to engulf the vibrating cup which distributes the caps for closing the bottles.

Another aspect of the invention relates to a system of at least two sterilisable pressurised containers, a first and a second container interconnected with
20 each other by a pipe, wherein the first container is used for filling and finishing bottles, syringes, carpules and other medical elements, inside the relative sterile process chamber, and the second container is used for the distribution of caps and covers for the above-mentioned primary containers, which will then be sent to the first container where the filling will be
25 performed.

In other words, the system comprises one or more process chambers in which it is possible to use a superheated steam sterilisation in place of decontamination with VHP. In these sterilisable chambers, both pressure and temperature can be raised so that a true sterilisation is possible without
30 compromising filling automation and the instrumentation inside the chambers themselves. In this way, the system can no longer be likened to

a traditional insulator, but it is an environment which is able to withstand more than three absolute bars of pressure and at a temperature higher than that of sterilisation, as per regulations.

The Applicant has in fact understood that a system configured in this way is
5 a valid example for overcoming the problems due to the limits of the VHP decontamination processes and the consequent procedures for introducing “autoclaved” parts, but it is also a good solution, with low complexity, to allow outdated production sites to comply with the current guidelines.

Moreover, as this system can rise in pressure and temperature, it can be
10 sterilised with superheated steam and is suitable for the so-called “cleaning in place” (CIP) (that is to say, the process for cleaning the inside of a process apparatus without the removal or removal of parts of the apparatus), both hot and cold. And since it is sterilisable, it is no longer necessary to decontaminate with VHP but, above all, it is no longer necessary to insert
15 and manage the parts in direct and indirect contact with the product, removing them and reassembling them in aseptic condition after “autoclaving”.

A further protection is required for a method for sterilising a container for filling and finishing parenteral drugs which comprises the step of:

- 20 - closing the accesses by acting on the respective valves;
- isolating, relative to the surrounding environment, a process chamber designed to be sterilised with superheated steam, by the closing of system valves;
- changing to a vacuum the isolated process chamber and,
25 simultaneously, the first compensation chamber in such a way as to avoid damage to the components of the instruments which interface between the process and compensation (and/or access) chambers due to the pressure gradient which would otherwise be present;
- injecting saturated steam into the vacuum process chamber until
30 temperature sensors positioned close to system valves detect a predetermined sterilisation temperature;

- injecting saturated steam into the process chamber until completion of the validated sterilisation cycle.

If there is the access chamber, both in the presence of the corresponding second compensation chamber and in its absence, the method for compensating the pressure also in this chamber is the same as that just described: after having isolated and hermetically sealed it thanks to the special door, it is changed to a vacuum, together with the inside of the process chamber which is also isolated.

The cycle is validated in accordance with current regulations.

For clarity, the system valves are those which separate the inner compartments of the container (process and compensation chambers) from the outside and are positioned at the periphery of the apparatus.

The Applicant perceived that, by compensating the vacuum and the pressure created in the process chamber, the mechanical parts of the apparatuses in the compensation chambers and in the access chamber would not risk damage, guaranteeing the correct operation of the container and creating a sterile island around the zone for filling bottles, syringes or carpules, which is fully automated, without the need for external intervention by an operator.

If necessary, saturated steam may be injected into the vacuum process chamber with alternating vacuum-steam cycles until suitable temperature sensors located in the proximity of the system valves detect a predetermined sterilisation temperature. Therefore, compressed air is injected into the compensation chamber with alternating vacuum-compressed air cycles keeping the pressure differential between the compensation chamber and the process chamber below the structural limit identified (typically approximately 10 mbar), to avoid damage to the process apparatuses.

Advantageously, after having injected superheated steam into the vacuum process chamber, the latter can again be changed to a vacuum and then superheated steam can again be injected. This process may be repeated

cyclically until the process chamber is gradually and completely saturated. After completing the sterilisation cycle, the Applicant has, in order to maintain the sterility of the process chamber, kept the chamber under overpressure by means of a flow of air, preferably sterile, through the above-mentioned accesses. The flow may be variable on the basis of the pressure difference between the inside of the process chamber and the zones adjacent to it.

Advantageously, the Applicant has noticed that by making a container sterilisable with superheated steam inside which there are all the processing operations (filling of the bottles, syringes and carpules and closing them with caps and covers), it is possible to sterilise the pipes for conveying the needles for filling the bottles, syringes or carpules inside the process chamber. The pipes, through which the fluid passes to be injected in bottles, syringes or carpules, and which connect the final part of the duct by means of a peristaltic or volumetric pump, are cleaned in-situ and sterilised by superheated steam together with the entire process chamber.

This allows the sterilisation of the needles, the system pumps and the various ducts together with the steam sterilisation of the chamber, avoiding risks of VHP residue on the needles or residual particulate due to the cap extractor of steam from the needles.

The process chamber of the first container is advantageously provided with two valves upstream and downstream of the guides for moving the bottles, syringes or carpules, allowing the entrance and exit of the container. During the washing or sterilisation step, the valves are closed and isolate the process chamber from the outside environment. Once the sterility has been reached, the valves are opened and, thanks to an overpressure, the chamber maintains its sterility thanks to the presence of a positive pressure gradient. The valves, by opening, put in communication the various zones of the container and allow the alignment of the guides for movement of the bottles, creating a unique path for the bottle which will enter the filling chamber.

Detailed description

Further features and advantages of the invention are more apparent in the detailed description below, with reference to a preferred, non-limiting embodiment of the superheated steam sterilisable container illustrated by way of example and without limiting the scope of the invention, with the aid of the accompanying drawings, in which:

Figure 1 is a perspective view of the system 100 of containers 1 and 101 for filling and distributing main containers (bottles F and related caps T);

Figure 2 is a second perspective view of the system 100 of containers 1 and 101, cross-sectioned along a plane XY substantially normal relative to the vertical direction Z;

Figure 3 shows an enlargement of the first container 1 of Figure 2;

Figure 4 shows the system 100 of Figure 1, cross-sectioned with a plane passing through the vertical direction Z and normal relative to the plane XY which encounters the first container 1;

Figure 5 shows the system 100 of Figure 1, cross-sectioned with another plane passing through the vertical direction Z and normal relative to the plane XY;

Figure 6 shows the second container 101 of the system 100 of Figure 1, cross-sectioned with a further plane passing through the vertical direction Z and normal relative to the plane XY;

Figure 7 is a plan view from above of a variant of the first container 1;

Figure 8 shows the cross section VIII-VIII of the container 1 of Figure 7;

Figure 9 illustrates an enlarged detail of Figure 8 showing the access chamber 7;

Figure 10 is a plan view from above of a variant of the second container 101;

Figure 11 shows the cross section XI-XI of the container 1 of Figure 10;

Figure 12 is a perspective view of the second container 101.

The above-mentioned drawings show a preferred embodiment of a container, according to the invention, which is denoted in its entirety by the

numeral 1 or 101 and which comprises a process chamber 2 or 102 designed to be sterilised by superheated steam using a vaporisation duct 20 or 120.

In general, the process chamber 2 or 102 is interposed between a first
5 compensation chamber 3 or 103, at compensated pressure, for housing the instruments 10 or 110 for operating the container 1 or 101, below, and a second compensation chamber 5 or 105, also at compensated pressure.

Following the vertical direction Z of extension of the container which can be sterilised by superheated steam 1 and substantially coinciding with the axis
10 of symmetry of the container 1, the first chamber 3 or 103 is positioned below the process chamber 2 or 102, whilst the second chamber 5 or 105 is mounted above the process chamber 2 or 102.

The process chamber 2 or 102 is hermetically separated from the first compensation chamber 3 or 103 by a first partition 4 or 104 and, from the
15 second chamber 5 or 105, by a second partition 6 or 106. All the partitions 4, 6, 104 or 106 are hermetically sealed.

As shown in Figures 8 and 9, according to the variant of the first process chamber 1, in place of the second compensation chamber 5 there is an access chamber 7 at compensated pressure which is separated from the
20 process chamber 2 by a third partition 71 made of glass or other optically transparent material.

The access chamber 7 is positioned laterally, along the horizontal direction X, relative to the process chamber 2: in practice, it is a sort of protuberance of the process chamber 2.

25 The access chamber 7 is provided with a door 72 – of per se known type - for hermetically closing the access chamber 7 towards the outside, which can be opened and closed using the knobs 73a, 73b and 73c.

Therefore, the first partition 4 or 104 lies in a horizontal plane XY normal with respect to the vertical direction Z, as well as with respect to the axis of
30 symmetry of the container 1 or 101.

Suitable bellows 24 are fixed to the separators 4, 6, 104 or 106, which

isolate the components (of the instruments 10, 110) immersed in the process chamber 2 or 102.

There is also a pressurising device 30 (not illustrated for the container 101) which allows the pressure inside the first 3 and 103, the second
5 compensation chamber 5 and 105 and the access chamber 7 to be changed to a value between a minimum operating pressure and a maximum operating pressure, where the minimum operating pressure is that which corresponds almost to the pneumatic vacuum; and the maximum operating pressure substantially compensates for the pressure of the superheated
10 steam inside the process chamber 2 and 102.

As described below, alternating vacuum/steam cycles may be performed to guarantee the complete extraction of the air from the chamber 2 and 102 and alternating air-vacuum cycles may be performed for the compensation chambers 3 and 103 and 5 and 105 and for the access chamber 7.

15 The process chamber 2 or 102 also has accesses which allow the connection with the adjacent zones, regulated during opening and closing by means of respective valves.

A first embodiment, illustrated in Figures 4 and 5, relates to a container 1 for sterilising the process chamber 2.

20 In the container 1, the vaporisation duct 20 is connected to a vaporisation device (not illustrated) and extends along a horizontal direction X substantially at right angles to the vertical direction Z. The vaporisation duct 20 has a longitudinal cut 20a along the horizontal direction X, in practice on the plane XY. Sterilised air may escape from the duct at ambient
25 temperature for lowering the temperature inside the process chamber 2 after the sterilisation (which operates at temperatures of at least 120°C).

Thanks to the shape of the longitudinal cut 20a and the advantageous position of the latter just above the zone for filling the bottles F, the flow of sterile air which escapes from the duct 20 is one-way and protects the
30 above-mentioned zone for filling the bottles F.

In the container 1, the accesses are defined in the vertical walls of the

process chamber 2 or, more precisely, in the circular vertical wall which delimits the chamber 2. They comprise: an inlet opening 21 for the bottles F to be filled, an access opening 22 for the caps T which will close the bottles F just filled and an outlet opening 23 for the bottles F capped, preferably
5 positioned, approximately, on the opposite side of the process chamber 2 relative to the axis of symmetry of the container 1. Each of the openings 21, 22 and 23 is adjusted, each independently of the others, when opening and closing by means of a respective inlet valve 25, access valve 26 and outlet valve 27.

10 Figure 2 shows that, if the valves 25 and 27 are positioned on the corresponding openings 21 and 23, the access valve 26 is, on the other hand, mounted in the middle portion of a pipe 14 which connects the first container 1 with a second container 101, generally similar on the basis of the inventive concept expressed here, which has the purpose of allowing
15 the distribution of the caps T for the closing of the bottles F.

The pipe 14 is also labelled 114, with reference to what is stated for the container 101.

In this regard, the bottles F enter from the inlet opening 21 through the inlet valve 25 and are transported towards the outlet opening 23 by a movement
20 guide 81, in this case a pair of helical screws 81, from which they can escape by controlling the outlet valve 27.

On the other hand, the caps T are conveyed inside the process chamber 2 by means of a conveying track 86 which slides inside the pipe 14 and which connects the two containers 1 and 101.

25 Inside the process chamber 2 there is a filling head 82 which supports needles 83 for injecting the fluid selected for filling the bottles F (Figure 3), of per se known type. Also inside the process chamber 2, robotic hands 84, also of essentially known type, are mounted for picking up the caps T to be positioned on the bottles F and for positioning the caps T on the filled bottles
30 F, in such a way as to close them.

The first partition 4, for separating the first compensation chamber 3 below

it and the process chamber 2, above the partition 4, have an outlet 42, preferably provided with a cover (not illustrated); the cover prevents the presence of a hazard in the upper surface of the partition 4. The outlet 42 leads into a drainage channel 41 for discharging the fluids which would otherwise stagnate on the upper surface of the first partition 4 and emptying the condensates which form during sterilisation.

With regard to the second partition 6, which separates in a sealed fashion the second compensation chamber 5, below, from the process chamber 2, above, being separate, it has inspection means designed to control the inside of the process chamber 2, such as a camera in an alternative solution. According to an embodiment, the second partition 6 and the dome 61 which closes the upper access 50 of the second chamber 5, are made – at least partly – of optically transparent material, for example glass, to allow the operator to control inside the process chamber 2 during the filling and finishing of the bottles F.

Moreover, the second partition 6 which, as we have seen, can in practice be a glass sheet which allows the inspection by the operator inside the process chamber 2, is provided with an inflatable seal which allows the removal and the closing.

As an alternative to the dome 61 made of glass, or also together with it, the inspection means comprise the system of the access chamber 7 described above.

During the sterilisation cycle, the access chamber 7 is treated in a similar manner to the other compensation chambers 3, 5, 103 and 105

With reference to Figure 6, the container 101, used to dispense the caps T to the container 1, by means of the conveying track 86, has two accesses: an upper opening 121 and a lower opening 123.

The opening 121 is for the inlet for the caps T falling towards a vibrating cup 108, of per se known type, positioned in the process chamber 102.

The lower opening 123 is defined by the intersection of the cylindrical wall of the pipes 14 and 114 with the other cylindrical wall of the process

chamber 102, and allows the distribution of the caps T, coming out from the vibrating cup 108, towards the first container 1.

Each of the openings 121 and 123 is adjusted, respectively, during opening and closing by an upper valve 125 and a lower valve 126.

- 5 For practical reasons, according to the example described, the lower valve 126 coincides with the access valve 26, since both perform the same function: adjusting the interconnection between the containers 1 and 101 along the pipes 14 and 114. As mentioned, the pipe 14, also denoted by the numeral 114, is basically the set of two half-ducts (14 and 114), relative to
10 the containers 1 and 101, which extend from the respective sealed chambers 2 and 102 and are connected or divided by the valve 26 (coinciding with the valve 126).

- More in detail, the conveying track 86 collects the caps T downstream of the vibrating cup 108 and through the pipes 14 and 114 in which the track 86 is
15 installed, facilitates the guided sliding up to the access opening 22 (if the lower valve 126, that is to say, the outlet valve 26 allow it) of the first container 1.

- Inside the process chamber 102 the superheated steam is injected by a vaporisation duct 120 which passes from a neck 102a defined on the upper
20 part of the chamber 102 and which protrudes centrally, wedging into the volume of the second compensation chamber 105 (Figure 6).

- Positioned on the end portion of the neck 102a there is the upper valve 121 which isolates the process chamber 102 from a caps storage unit 112 for containing the caps T already sterilised which are to be then distributed
25 downstream of the container 101.

- As mentioned above regarding the configuration of the container 101, since the storage system 112 is located above the process chamber 102, the caps T enter in the chamber 102, through the neck 102a, by gravity, feeding the underlying vibrating cup 108.

- 30 In order to dose the requirements of the caps T, which depends on the filling and finishing speed of the bottles F, there is a dosing valve 107, mounted

on the neck 102a.

According to the preferred embodiment, the first compensation chamber 103 is enclosed inside the process chamber 102, in such a way that the first partition 104 also comprises a perimeter wall for containing the compensation chamber 103 (Figures 11 and 12), in such a way as to
5 enclose the compensation chamber 103 inside the process chamber 102. In use, the system 100 consists of the two containers 1 and 101 interconnected, and used, respectively, for filling and finishing bottles F in an aseptic manner and for distributing the closing caps T for the bottles F,
10 comprising firstly the assembly of the components inside the containers 1 and 101.

Each container has a respective hermetically sealed process chamber 2 and 102.

The two containers 1 and 101 are connected to each other by a pipe 14 and
15 114, adjusted by a valve (which coincides with the access 26 and lower 126 valve). They are positioned in such a way that the first container 1 has the process chamber 2 positioned below the process chamber 102, in such a way as to favour the lowering of the caps T on the conveying track 86.

In this regard, the legs 15 of the container 1 are shorter than the legs 115
20 of the container 101.

The bottles F which must be filled, weighed (before and after filling, in a real or statistical manner) and closed with the respective cap T, pass in the process chamber 2 of the first container 1, automatically.

The process chamber 102 of the second container 101 has a device for
25 feeding caps T to the vibrating cup 108, which is able to supply, thanks to the movement guide 81, the caps T to the first container 1.

In particular, when the container 1 is not yet closed by the dome 61 and/or by the door 72, the vaporisation duct 20 must be washed before installing it inside the process chamber 2. The duct 20 is mounted through the upper
30 access 50 inside the process chamber 2, above the zone for filling the bottles F. At this point, the upper access 50 and/or the door 72 is closed in

such a way as to allow the isolation of the second compression chamber 5 and/or the access chamber 7 from the outside environment.

All the parts to be sterilised are insulated: the process chambers 2 and 102, as well as the first compensation chambers 3 and 103, the second
5 compensation chambers 5 and 105 and/or the access chamber 7, by the closing of system valves (not illustrated), those which separate the compartments inside the container 1 and 101 from the outside, and which do not correspond to the valves 25, 26, 27, 125 and 126 described above. The accesses 21, 22 and 23 are closed by closing the valves 25, 26 and 27
10 (126).

The process chambers 2 and 102, the compensation chambers 3, 5, 103 and 105 and/or the access chamber 7, insulated in this way, are changed to a vacuum or alternatively to the operating pressure as prescribed by the validated sterilisation cycle on a case by case basis.

15 In this way, it is possible to vary the pressures of the process chamber 2 (or 102) preventing a deformation of the bellows 24 and a mechanical stress between the areas in connection, for example the chambers 2 and 5.

Also thanks to the pressure compensation system 100, any risk of breakage of the glass of the partition 6 during the sterilising step is eliminated.

20 Superheated, high-temperature steam is then injected into the vacuum process chambers 2 and 102, by means of the vaporisation duct 20 and 120, until suitable temperature sensors (not shown), of per se known type, positioned close to system valves detect a predetermined sterilisation temperature (at least 120°C).

25 The process chamber 2 remains in this state for approximately 10-15 minutes according to the sterilisation cycle validated on a case-by-case basis.

Once the system 100 has been sterilised and the pressures are normalised, the dome 61 may be opened so as to follow the dispensing process and, if
30 necessary, intervene with the controls during the filling and finishing steps.

A one-way flow of sterile air is injected, from the vaporisation duct 20 which

has injected the superheated steam, at ambient temperature in the process chamber 2 previously sterilised.

For a gradual injection of saturated steam, the strategy of alternating cycles for injecting superheated steam in the process chamber 2 may be provided
5 with the creation of a vacuum of the process chamber 2, until complete superheating has been favoured.

In order to maintain the overpressure of the process chamber 2, a flow of air escaping from the chamber 2 is created from the accesses 21, 22 and 23. The output flow will vary according to the pressure difference, detected
10 with appropriate sensors, between the inside of the process chamber and the zones adjacent to it.

The pipes for conveying the needles 83, those used to fill the bottles F, are also sterilised, again inside the process chamber 2. In effect, these pipes connect the needles 83 to a suitable container for the fluid to be introduced
15 in the bottles F by means of a peristaltic or volumetric pump (not illustrated).

Once the sterilisation of the process chamber 102 is completed, the caps T, intended to cap the bottles F inside the process chamber 2, which lie in the sterile caps storage unit 112, are dropped towards the vibrating cup 108 inside the process chamber 102, kept sterile, of the second container 101.

20 The vibrating cup 108 discharges a single cap T onto the conveying track 86 which slides inside the pipes 14 and 114.

If allowed by the access valve 26 (which corresponds to the lower valve 126), the caps T to arrive at the process chamber 2 of the first container 1, which is also kept sterile in the ways described above, from the access
25 opening 22.

In the process chamber 2, the bottles F, to be closed with the caps T, are simultaneously introduced from the inlet opening 22 adjusted when opening and closing by means of the inlet valve 25.

The bottles F, which come from a storage unit area (not illustrated) based
30 on established technologies such as rotary tables and dry air sterilising systems, advance inside the chamber 2 by the action of the movement

guide 81 which extends between the inlet opening 21 and the outlet opening 23. As they travel, the needles 83 are filled and robotic hands 84 pick up the caps T from the conveying track 86 to position them on the filled bottles F which, again by means of the guide 81, are exited from the process chamber 2 from the outlet opening 23, adjusted when opening and closing by means of the outlet valve 27.

More specifically, the valves 25 and 27, upstream and downstream of the movement guide 81 of the bottles F, allow the infeed to and outfeed from the container 1. During the washing or sterilisation step, the valves 25 and 27 are closed and isolate the process chamber 2 from the outside environment. Once it has become sterile, the valves 25 and 27 are opened and, thanks to an overpressure, the chamber 2 maintains its sterility thanks to the presence of a positive pressure gradient relative to the adjacent chambers. The valves 25 and 27, opening, therefore put in communication the various zones of the container and allow the alignment of the movement guide 81, in such a way as to create a single path for the bottle F which will enter the filling chamber.

Downstream of the process chamber 2, the bottles F are directed towards freeze-drying zones (the container 1 is therefore partly open) or directly towards areas with a lower classification, or towards an area with equal sterility classification, but dedicated to the insertion and crimping of the sealing rings for the caps T and the covers.

From the above description it may be seen how the invention achieves the preset purpose and aims and in particular it should be noted that a container which can be sterilised by superheated steam is made, representing a valid alternative to insulators with pressure generators or similar systems, which is simpler to control and easier to use.

In particular, the making of a double container system, which can be sterilised by superheated steam, allows an automatic and autonomous process for sterilising the process instruments. The effect is that it is possible to considerably limit – if not completely eliminate – the need for the

intervention of the operator during normal operation of the system.

The system does not therefore require a supporting autoclave, is not provided with gloves since there are no operations for preparing in an aseptic condition, can be automatically cleaned like traditional systems
5 equipped with CIP/SIP (such as freeze-dried devices, where "SIP" means the sterilisation of the production systems without prior removal operations) and it is possible to diffuse sterile unidirectional air, pre-filtered by sterilising cartridges which are in turn sterilised by steam.

Another advantage of the invention is that it has made an innovative process
10 for filling and closing parenteral drugs, both in liquid or powder form, for bottles, syringes or carpules, using the advantages of "in place" saturated steam sterilisation (SIP) and the "in-place" automatic cleaning processes (CIP) to obtain an increase in the guarantees of sterility compared with traditional systems installed in insulators and RABS.

15 Again thanks to the compensation system it is advantageously possible to avoid breakage of the glass which constitutes the second partition and/or the third partition of the first container and eliminate the mechanical stress between the two compartments during the CIP/SIP steps.

Another advantage of the invention is due to the fact that the sterilised
20 superheated steam containers, as well as guaranteeing an absolute safety of the sterility of the machine and all its parts inside the process chambers, makes the step of filling and finishing the bottles, syringes and carpules extremely efficient, so much so that it is possible to achieve production speeds equal to the traditional filling systems.

25 Another advantage of the invention is due to the fact that having created a series of containers which can be sterilised by superheated steam, all under pressure and designed to be interconnected with each other, has allowed the overall dimensions of the traditional insulators to be reduced; the system is therefore much more compact and less complex than an insulator and
30 conceptually more similar to an autoclave.

Another advantage of the system designed in this way is that it does not

require a supporting HVAC device and can be installed in any “cleanroom” in accordance with the requirements of the guidelines.

Lastly, as mentioned above, this system is economically competitive whilst guaranteeing the maximum quality and sterility, thanks to the absence of
5 operating and loading procedures which require fewer supporting personnel. Consequently, the viable and non-viable monitoring will also be reduced, and, mainly, those risks still present in the prior art will be avoided, such as the loading of large components such as hoppers or vibrating cups for feeding caps.

10 The invention described can be modified and adapted in several ways without thereby departing from the scope of the inventive concept.
Moreover, all the details of the invention may be substituted by other technically equivalent elements.

In practice, the materials used, as well as the dimensions, may be of any
15 type, depending on requirements, provided that they are consistent with their production purposes.

CLAIMS

- 1) A container (1, 101) that can be sterilised by superheated steam comprising:
a process chamber (2, 102) designed to be sterilised by superheated steam
5 using a vaporisation duct (20, 120);
a first compensation chamber (3, 103), at compensated pressure, for housing the instruments (10, 110);
a first partition (4, 104) hermetically interposed between the process chamber (2, 102) and the first compensation chamber (3, 103); and
10 accesses (21, 22, 23, 121, 123) for the connection between the process chamber (2, 102) and zones adjacent to it, designed to be connected with the process chamber (2, 102), adjusted when opening and closing using respective valves (25, 26, 27, 125, 126).
- 2) The container (1, 101) according to claim 1, comprising a pressurising
15 device (30) designed to move the pressure inside the first compensation chamber (3, 103) between a standard pressure and an operating pressure; the standard pressure corresponding to the external pressure; and the operating pressure being variable between a substantially zero value of the operating pressure and a value equal to the pressure of the superheated
20 steam inside the process chamber (2, 102).
- 3) The container (1, 101) according to claim 2, comprising a second compensation chamber (5, 105), at compensated pressure, separated from the process chamber (2, 102) by a second partition (6, 106);
wherein the process chamber (2, 102) is interposed between the first (3,
25 103) and the second (5, 105) compensation chambers;
preferably, the first compensation chamber (3, 103), the process chamber (2, 102) and the second compensation chamber (5, 105) being positioned in succession along the vertical direction of extension (Z) for the container (1).
- 30 4) The container (1) according to any one of claims 1 to 3, wherein the accesses (21, 22, 23) are defined in the walls of the process chamber (2)

and comprise:

an inlet opening (21) for the bottles (F) to be filled, adjusted when opening and closing by means of an inlet valve (25);

an access opening (22) for the caps (T) for closing the filled bottles (F),
5 adjusted when opening and closing by means of an access valve (26);

an outlet opening (23) for the closed bottles (F);

preferably, the inlet opening (21) and the access opening (22) being substantially positioned, relative to each other, on the opposite side of the process chamber (2) relative to the axis of symmetry of the container (1),

10 adjusted when opening and closing by means of an outlet valve (27).

5) The container (1) according to claim 4, comprising, in the process chamber (2):

a filling head (82) holding needles (83) for injecting a fluid in the bottles (F) to be filled;

15 robotic hands (84) for picking up the caps (T) to be positioned on the bottles (F) and for positioning the caps (T) on the filled bottles (F) in such a way as to close them;

the bottles (F) being transported between the inlet opening (21) and the outlet opening (23) by means of a movement guide (81);

20 the caps (T) being conveyed inside the process chamber (2) by means of a conveying track (86) fed from a second container (101) designed to be connected to the process chamber (2).

6) The container (1) according to any one of claims 1 to 5, comprising an access chamber (7) at compensated pressure, which can be hermetically
25 closed towards the outside by means of a door (72) and separated from the process chamber (2) by means of a third partition (71).

7) The container (1) according to claim 6, wherein the third partition (71) is made of optically transparent material.

8) The container (1) according to claim 6 or 7, wherein the access chamber
30 (7) is positioned laterally, along the horizontal direction (X), relative to the process chamber (2).

- 9) The container (101) according to any one of claims 1 to 8, wherein the first compensation chamber (103) is formed inside the process chamber (102), in such a way that the first partition (104) comprises a perimeter wall of the compensation chamber (103).
- 5 10) A system (100) of at least two containers (1, 101) which can be sterilised by superheated steam, according to any one of claims 1 to 5, wherein a first container (1) is used for filling bottles (F), syringes and carpules, designed to be filled and finished inside the relative process chamber (2), and a second container (101) is used for distributing caps (T) and elements for
- 10 sealing bottles (F), syringes and carpules, designed to be distributed to the first container (1);
the first container (1) and the second container (101) being interconnected by a pipe (14, 114).
- 11) A method for sterilising a container (1, 101) which can be sterilised by
- 15 superheated steam, according to any one of claims 1 to 5, comprising the steps of:
- closing the accesses (21, 22, 23, 121, 123)
 - isolating, relative to the surrounding environment, a process chamber (2, 102) of a pressurised container (1, 101), designed to be sterilised with

20 superheated steam, by the closing of system valves;
the process chamber (2, 102) being separated from a first compensation chamber (3, 103) for housing the instruments (10, 110) by means of a first partition (4, 104) hermetically interposed between the process chamber (2, 102) and the first compensation chamber (3, 103);

 - 25 - changing to a vacuum the isolated process chamber (2, 102) and, at the same time, the first compensation chamber (3, 103) in such a way as to prevent damage to the components of the instruments (10, 110) interfacing between the process chamber (2, 102) and the compensation chamber (3, 103) due to the pressure gradient which would otherwise be present;
 - 30 - injecting saturated steam into the vacuum process chamber (2, 102) until the end of the execution of the validated sterilisation cycle.

12) The method according to claim 11, wherein the process chamber (2, 102) is separated from a second compensation chamber (5, 105), positioned above the process chamber (2, 102) relative to a vertical direction of extension (Z) of the container (1, 101), by means of a removable
5 sealed partition (6, 106) and designed to define an upper access (50) to the process chamber (2, 102).

13) The method according to claim 11 or 12, comprising the step of maintaining the overpressure of the process chamber (2) by means of an air flow out from one or more of the accesses (21, 22, 23);
10 the flow of air flowing out is variable depending on the pressure difference between the inside of the process chamber (2, 102) and the zones adjacent to it.

14) The method according to any one of claims 11 to 13, comprising the step of sterilising the pipes for conveying the needles (83) for filling the
15 bottles (F) inside the process chamber (2) at the same time as the steam sterilisation of the process chamber (2);
the pipes being for connecting the fluid to be introduced in the bottles (F) between the needles (83) and a suitable container.

1, 101	container
100	system
10, 110	instrumentation
15, 115	legs
2, 102	process chamber
102a	neck of process chamber 102
112	cap storage system
20, 120	vaporisation duct
20a	longitudinal cut
21	inlet opening for bottles F to be filled
22	access opening for cap guides
23	outlet opening for closed bottles F
24	bellows
25	inlet valve
26	access valve
27	outlet valve
121	upper opening
123	lower opening
125	upper valve
126	lower valve
3, 103	first compensation chamber
30	pressurising device
14, 114	pipe
4, 104	first partition
41	drainage channel
42	outlet
5, 105	second compensation chamber
50	upper access
6, 106	second partition
7	
70	
108	vibrating cup
81	movement guide for bottles (F)
82	filling head
83	needles
84	robotic hands
86	conveying track for caps (T)
F	bottles
T	caps
Z	vertical direction
X	horizontal direction
XY	horizontal plane