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(54) **System and devices for aseptic handling of materials**

(57) A system for aseptic handling of materials comprising an aseptic isolator chamber with arrangements for handling of the materials; an airlock chamber with a pair of airlock doors to the outside and to the isolator chamber, respectively. A HEPA filter system establishes a laminar air flow in the airlock chamber and a higher pressure in the airlock-chamber than outside the airlock chamber. Another HEPA filter system establishes a laminar air flow in the isolator chamber and a higher pressure

in the isolator chamber than in the airlock chamber. A controller is adapted to open a first airlock door to the outside only when the second airlock door to the isolator chamber is closed, to allow transport of the materials between the outside and the airlock chamber, and to open the second airlock door to the isolator chamber only when the first airlock door is closed and aseptic conditions have been established in the airlock chamber, to allow transport of the materials between the airlock chamber and the isolator chamber.

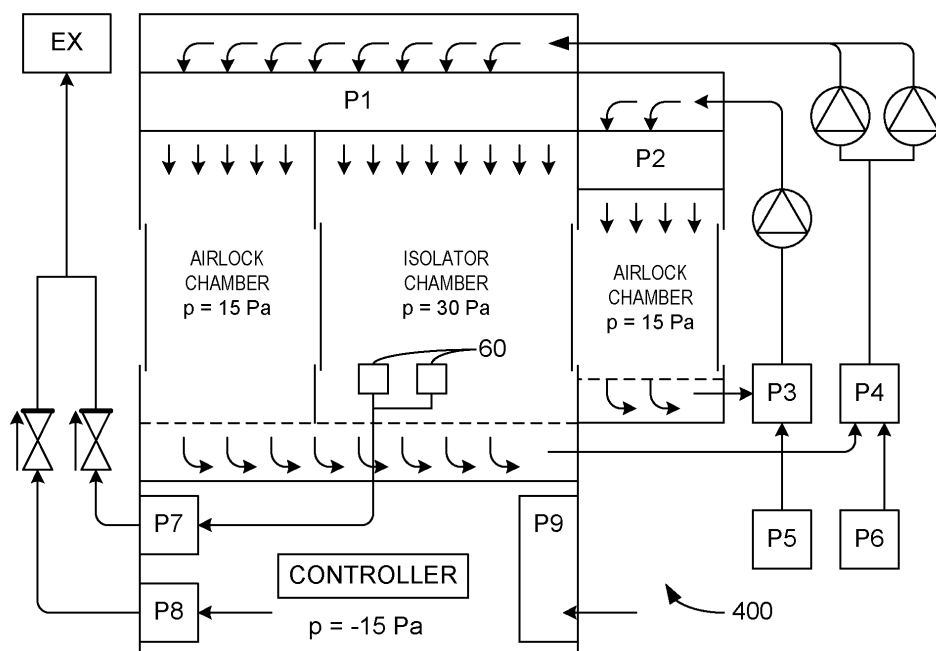


Fig. 4

Description

FIELD OF THE INVENTION

[0001] This invention relates to apparatus and devices for aseptic handling and manipulation of devices used in the pharmaceutical industry and in hospitals when handling sterile substances and devices.

BACKGROUND OF THE INVENTION

[0002] WO 2008/009288 relates to a sterilisable connector device for establishing fluid connection between a container holding a sterile diluent liquid such as isotonic sodium chloride solution, and a vial holding a pharmaceutical compound, so that the diluent liquid and the pharmaceutical compound are mixed to provide a sterile injection fluid.

[0003] The handling of such connector device for establishing interconnection liquid container and vial must take place under aseptic conditions. Reference is made to e.g. the publication Manufacture of Sterile Medicinal Products, an EC Guide to manufacturing Practice by the European Commission, 30 May 2003.

[0004] The use of isolator technology is prescribed to minimise human interventions in processing areas resulting in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. Access for equipment and materials to the isolator takes place through an airlock chamber. Laminar air flow is prescribed, and the content of particles in the air must be kept below specified limits. Isolators for aseptic handling and manipulation of materials are typically specified to Grade A, i.e. having a laminar air flow at a velocity of 0.36 - 0.54 m/s as a guidance value and no more than 3,500 particles of size 0.5 μm per m^3 (100 particles per cu. ft.). This requires that the air outside the isolator has no more than 35,000 such particles per m^3 , i.e. no more than 10 times as many particles as the upper limit for the isolator chamber. In order to achieve this there is usually at least one further, outer airlock system.

[0005] The connector device of WO 2008/009288 has an engagement member with a collar having a rim for receiving the neck of a vial by a lateral movement. In order to prevent the vial from being removed and to prevent contamination of portions to be kept sterile, the engagement member must be rotated 180 degrees whereby a member with an external thread is advanced from the engagement member and brought in contact with the rubber seal, whereby lateral movement is prevented and the vial is locked in its position in the collar of the connector device. For further details reference is made to WO 2008/009288.

[0006] Connecting the connector device of WO 2008/009288 with a vial and a diluent-liquid container can be done manually or automatically using specialised equipment such as robot technology. Many elemental

processes must be performed including the above mentioned rotation of the engagement member of the connector device.

[0007] The vial and the diluent-liquid container each has a neck with a rubber seal to be pierced when their contents are to be mixed. Before connecting the vial and the diluent-liquid container to the connector their rubber seals must be sterilised. Today, such sterilising is done using e.g. a swab containing a sterilising liquid such as ethanol and rubbing the area to be sterilised with the swab. There is a potential risk of contamination and cross contamination transferred by the swab, and therefore there is a need for a method reducing this risk.

[0008] The invention provides a system and devices that solve the above problems. In particular, the isolator and airlock system of the invention can be placed in a room where the air may contain 350,000 0.5 μm particles (10,000 particles per cu. ft.), i.e. 100 times more than the upper limit for the isolator chamber. This reduces the complexity of the entire facility where an isolator system of the invention can be installed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009]

Figure 1 shows a vial connected to a connector device;

Figure 2 shows the vial and the connector device in figure 1 in a configuration where the vial is locked to the connector device;

Figure 3 shows a system for manipulating the vial and the connector device in figure 1;

Figure 4 shows schematically a system according to the invention for aseptic handling of materials;

Figure 5 shows a vial; and

Figure 6 shows schematically the sterilisation of the seal of the vial in figure 5 before being connected to a connector device.

DETAILED DESCRIPTION OF THE INVENTION

[0010] Figures 1 and 2 show the connector device 1 disclosed in WO 2008/009288. The connector device 1 has an engagement member 14 with a collar 17 and a rim 18 on the collar. A vial 23 has a neck 34 that by a lateral movement has been received in the collar 17 and retained by the rim 18. The connector device 1 has a tube member 4 with an external thread, and the engagement member 14 has a bore with an internal thread in engagement with the external thread of the tube member 4. The tube member 4 there is a piercing member for piercing the seal 36 of the vial. A piercable cap 40 covers

the piercing end of the piercing member.

[0011] In figure 1 the end of the piercable cap 40 is flush with the bottom of the cavity defined by the collar 17 which allows the top of the vial to be inserted laterally into the cavity and gripped by the rim 18 of the collar 17.

[0012] In order to prevent the vial 23 from being removed from the collar 17 of the engagement member 14, the engagement member 14 is rotated 180 degrees whereby the tube member 4 and the piercable cap 40 are advanced so that the piercable cap 40 protrudes through the central opening 27 in the metal cap 37 covering the seal 36 and is pressed slightly against the top part 41 of the seal. Reversal of this rotation is prevented by detent means on the threaded parts, and removal of the vial is hereby prevented. This structure and function is disclosed in detail in WO 2008/009288.

[0013] Figure 3 shows how the rotation of the engagement member 14 is carried out in a device according to the invention. An elongate member 301 is rotatable about an axis of rotation 302. The elongate member 301 has two identical ends each of which has a pair of tongues 303 with a pair of opposed walls that define a radially extending and open-ended space between the tongues. The engagement member 14 of a connector device can be received in the space between the tongues in a movement radially relative to the axis of rotation 302. In the system of the invention to be described below the connector device and the attached vial are engaged e.g. by a robot gripping mechanism which places the engagement member 14 as shown in the space between the pair of tongues 303. The vial 23 and the remaining parts of the connector device are held and being prevented from rotation while the entire assembly of the connector device and the vial is moved as indicated by a dashed-line arrow. Hereby the engagement member 14 is rotated 180 degrees relative to the vial and the remaining parts of the connector device. A small "x" on the cap 37 of the vial indicates that the vial is not rotated, and a small "o" on the engagement member 14 indicates that it is rotated together with the rotatable elongate member 301.

[0014] In this embodiment the rotation is 180 degrees and by rotation of the elongate member 301 through this angle the other end is positioned to receive the engagement member of another connecting device. Rotation through other angles than 180 degrees can also be effected if so desired. If the rotation is a fraction $1/n$ of 360 degrees where n is an integer number, the rotatable member can advantageously have n spaces for engaging and rotating the engagement member 14 equidistantly distributed along a circle with its centre on the axis of rotation. Thereby the rotatable member will always be left in a position ready to receive an engagement member when an engagement member leaves the space after having been rotated. The device preferably has a self-aligning mechanism which aligns an empty space for receiving an engagement member to be rotated.

[0015] Figures 5 and 6 show a known vial 23 with a seal 36. A metal cap 37 with a central opening 38 covers

the seal 36. The metal cap 37 is bent around the neck 35 of the vial 23. The top part 41 of the seal is exposed and must be sterilised before being brought into connection with a connector device 1.

[0016] Figure 6 illustrates how a spraying device 60 sprays a sterilising fluid such as ethanol onto the top part 41. By spraying the sterilising fluid the fluid will have a flushing effect whereby possible particles will be removed, and possible remaining bacteria will be killed. During spraying both the spraying pressure and the opening angle of the spraying cone can be varied to obtain both a flushing effect and a desired distribution of the sterilising liquid. The spraying device 60 does not come into contact with any part of the vial but the sterilising liquid is sprayed onto the top part of the vial whereby contamination and cross contamination is prevented.

[0017] In figure 6 the vial 23 is oriented upside down and the spraying device 60 is arranged below the vial, but any orientation can be used.

[0018] An example of spraying devices that can be used is model EFD-781 from Engineered Fluid Dispensing.

[0019] In figure 4 is shown schematically the arrangement of a system 400 according to the invention for aseptic handling of materials, and in particular for aseptically connecting a connecting device 1 as disclosed in WO 2008/009288 to a vial and a diluent-liquid container.

[0020] The system 400 has an isolator chamber with arrangements for aseptic handling of the materials. The handling is preferably done by programmable robots. Two airlock chambers each having two sliding doors allow materials to be transported into and out of the isolator chamber. Such materials include primarily connector devices, vials 23 and diluent-liquid containers to be connected, but also trays and packaging materials.

[0021] The system includes High Efficiency Particulate Arresting, HEPA, filters P1 and p2 and motor-driven blowers for establishing a laminar air flow in the airlock chambers and in the isolator chamber. In the airlock chambers a pressure which is higher than the pressure outside the airlock chambers is established, e.g. 15 Pa, and in the isolator chamber a pressure which is higher than the pressure in the airlock chambers is established, e.g. 30 Pa. This ensures that each of the airlock chambers (with all doors closed) and in the isolator chamber meet the specifications of maximum 100 particles $0.5 \mu\text{m}$ per cu. ft. corresponding to 3,500 particles $0.5 \mu\text{m}$ per m^3 .

[0022] HEPA filters P3 and P4 filter the return air from the airlock chambers and the isolator chamber to ensure that e.g. drugs from vials that are broken inside the airlock chambers or the isolator chamber are filtered and not recirculated.

[0023] Supplemental air for compensating the loss of air through the doors etc. is fed through HEPA filters P5 and P6 where in particular drugs from vials that are broken outside the airlock chambers or the isolator chamber are filtered and are not fed into the airlock chambers or the isolator chamber.

[0024] In the lower compartment of the system a controller is situated. The controller controls the operation of all components of the system. Since this compartment is not a "clean" area the pressure is kept below the pressure outside the system, e.g. -15 Pa. Particle filter P9 filters the air that enters the lower compartment of the system.

[0025] In the isolator chamber two sterilisation stations 60 are arranged. Sterilising fluid is removed through particle filter P7 and led out through an explosion proof exhaust EX together with air from the lower compartment.

[0026] The controller controls the robots handling and manipulation of the materials (connector devices, vials and diluent-liquid containers), the operation of the sliding doors and blower motors. In order to maintain aseptic conditions in the isolator chamber and the airlock chambers the controller is adapted to open an airlock door to the outside only when the corresponding airlock door to the isolator chamber is closed. This allows transport of the materials between the outside and the airlock chamber. Further, the controller will open an airlock door to the isolator chamber only when the corresponding airlock door to the outside is closed and aseptic conditions have been established in the airlock chamber. This allows transport of the materials between the airlock chamber and the isolator chamber.

[0027] The system may have means for monitoring when aseptic conditions actually have been established in individual ones of the airlock chambers and the isolator chamber and open a door to the isolator chamber only when it has been determined based on actual observations that aseptic conditions have been established, or the system may be suitably programmed only to open a door to the isolator chamber after a predefined delay time after the corresponding airlock chamber door to the outside was closed.

[0028] The airlock doors are sliding doors which require less space than traditional hinged doors.

Claims

1. A system for rotating a first part a predetermined angle relative to a second part rotatably coupled to the first part, the device comprising

- a member rotatable at least through the predetermined angle about an axis of rotation, the rotatable member having means for engaging and rotating the first part together with the rotatable member and for disengaging the first part after having been rotated through the predetermined angle, and
- a device for engaging the second part when the first part is received by the rotatable member and for holding the second part non-rotating during the rotation.

2. A system according to claim 1 wherein the device for engaging the second part comprises a robot-controlled device.

3. A rotatable member for use in a system according to claim 1, the rotatable member being rotatable at least through a predetermined angle about an axis of rotation, the rotatable member having means for engaging and rotating the first part together with the rotatable member and for disengaging the first part after having been rotated through the predetermined angle.

4. A rotatable member according to claim 3 wherein the means for engaging and rotating the first part comprises a pair of opposed walls defining a radially extending and open-ended space therebetween for receiving the first part by a movement of the first part in a radial direction relative to the axis of rotation.

5. A rotatable member according to claim 4 wherein the predetermined angle is a fraction $1/n$ of 360 degrees, n being an integer and the rotatable member has n means for engaging and rotating the first part equidistantly distributed along a circle having its centre on the axis of rotation.

6. A device for applying a sterilising fluid to a surface to be sterilised, the device comprising a spraying device for spraying the sterilising fluid onto the surface to be sterilised.

7. A system for aseptic handling of materials, the system comprising

- an isolator chamber with arrangements for aseptic handling of the materials;
- an airlock chamber having a first airlock door between the airlock chamber and the outside, and a second airlock door between the airlock chamber and the isolator chamber, the first and second airlock doors allowing transport of the materials between the isolator chamber and the environment of the system;
- a system including a High Efficiency Particulate Arresting filter for establishing a laminar air flow in the airlock chamber and an airlock-chamber pressure higher than the pressure outside the airlock chamber;
- a system including a High Efficiency Particulate Arresting filter for establishing a laminar air flow in the isolator chamber and an isolator-chamber pressure higher than the airlock-chamber pressure;
- a controller adapted to open the first airlock door only when the second airlock door is closed to allow transport of the materials between the outside and the airlock chamber, and to open

the second airlock door only when the first airlock door is closed and aseptic conditions have been established in the airlock chamber to allow transport of the materials between the airlock chamber and the isolator chamber.

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8. A system according to claim 7 wherein the airlock doors are sliding doors.

9. A system according to any one of claims 7-8 wherein the materials include vials and diluent-liquid containers and a connector device for establishing fluid connection between a vial and a diluent-liquid container, the system further comprising a system according to any one of claims 1-2 and a rotatable member according to any one of claims 3-5.

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10. A system according to claim 9 further comprising a device according to claim 6 for sterilising parts to be connected.

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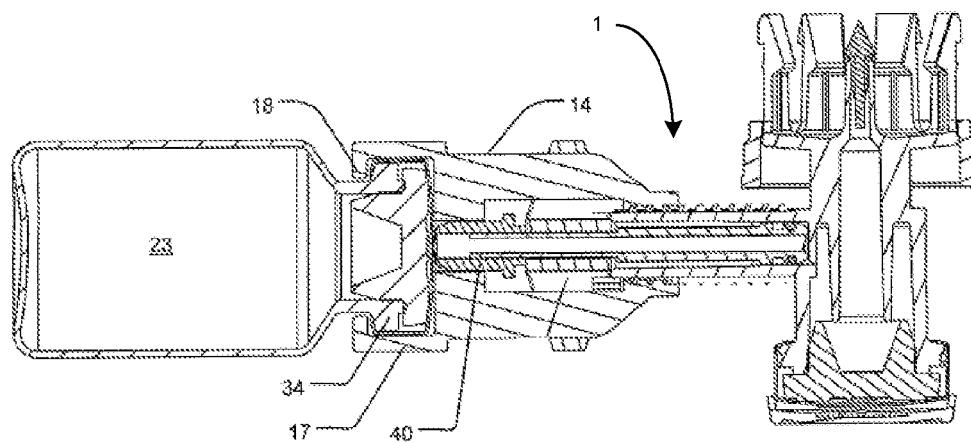


Fig. 1

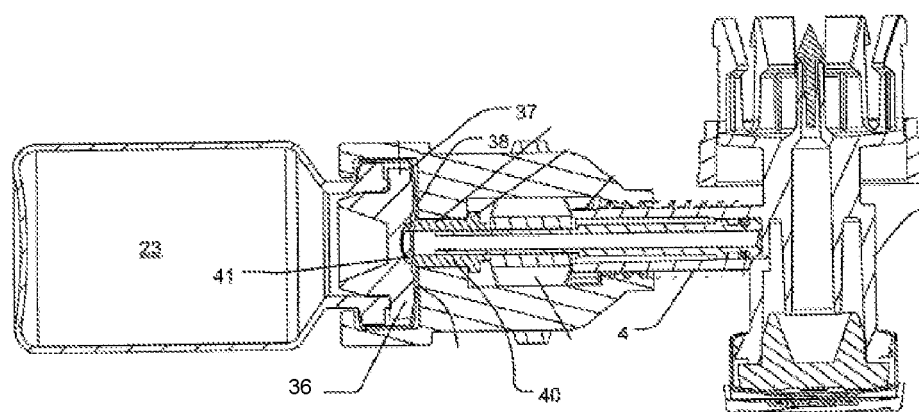


Fig. 2

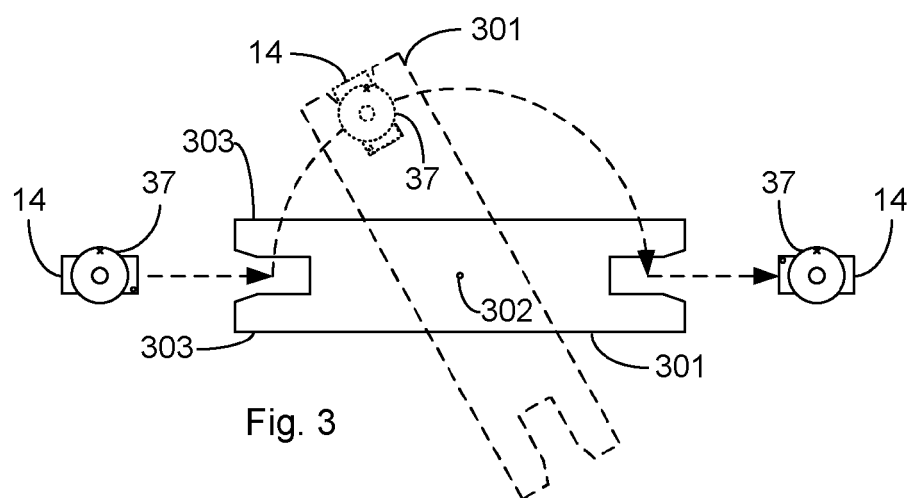


Fig. 3

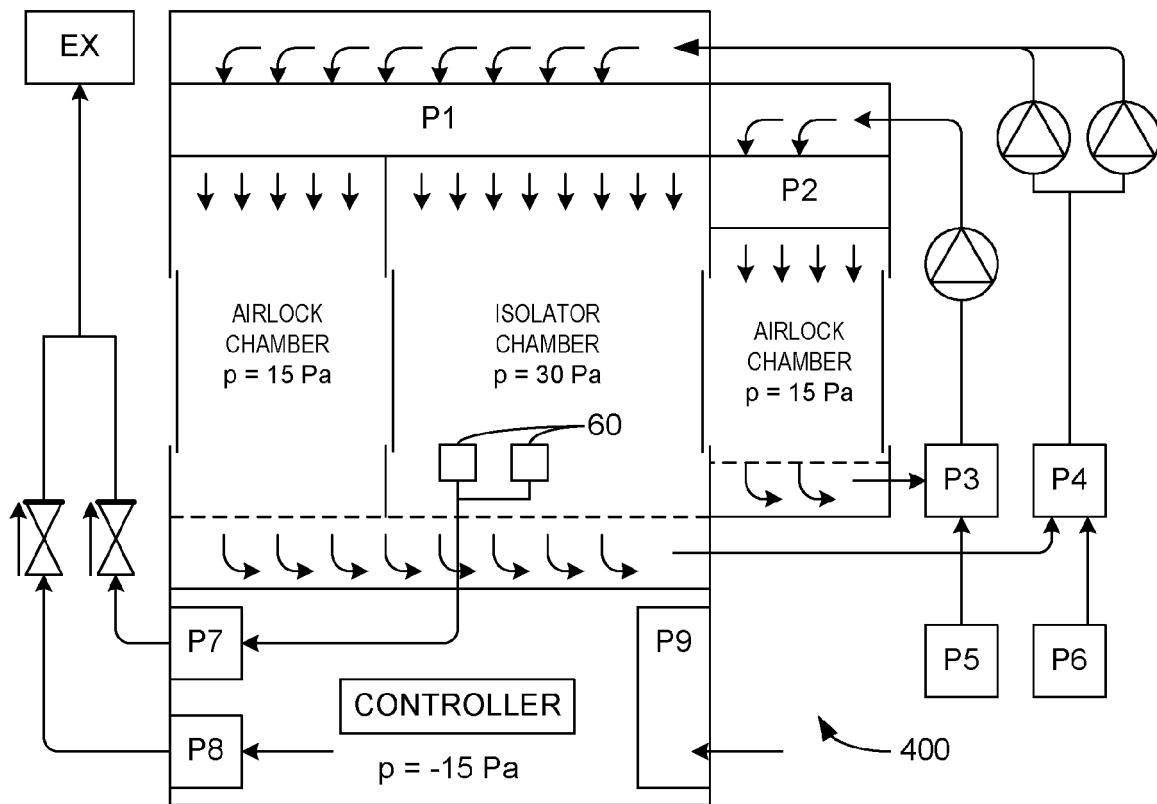


Fig. 4

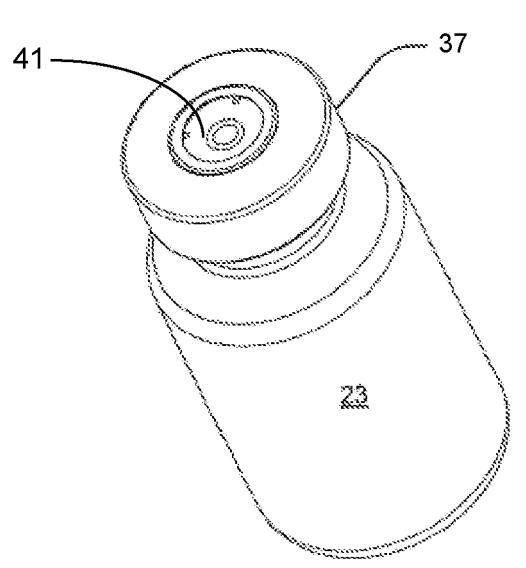


Fig. 5

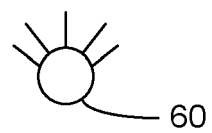
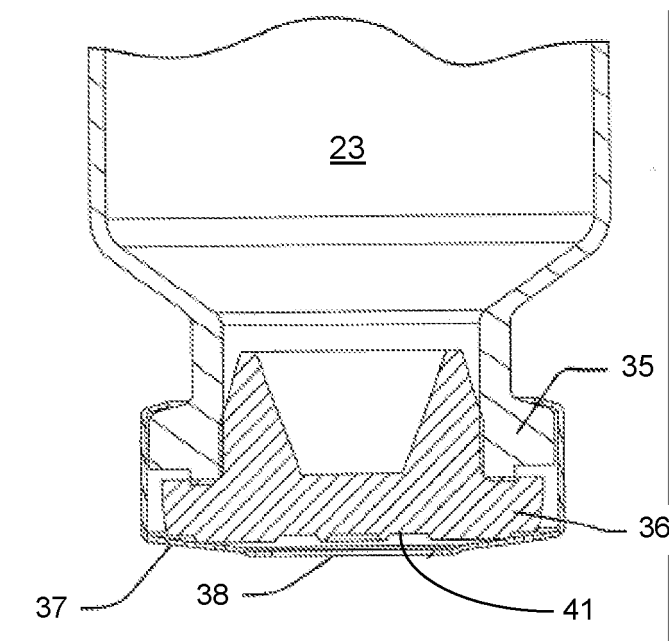


Fig. 6



EUROPEAN SEARCH REPORT

Application Number
EP 09 15 5764

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 2006/259195 A1 (ELIUK WALTER W [CA] ET AL) 16 November 2006 (2006-11-16) * paragraphs [0206], [0207], [0213]; figure 24 *	1-4	INV. A61J3/00 B65B3/00 A61J1/20 B65B55/02
X	* paragraph [0195] *	6	
Y	* paragraphs [0078], [0089] - [0091], [0099], [0264] - [0266]; figures 3,4 *	7-10	
X	US 2008/169043 A1 (OSBORNE JOEL A [US] ET AL) 17 July 2008 (2008-07-17) * paragraph [0045]; figures 2-4 *	3-5	
Y	WO 98/12112 A (AWAX PROGETTAZIONE [IT]; CAPPI ANGELO [IT]; RIMONDI RENATO [IT]) 26 March 1998 (1998-03-26) * page 5, line 1 - page 6, line 2; figure 1 *	7-10	
A	US 2006/003685 A1 (ROTHBAUER JUERGEN [DE] ET AL) 5 January 2006 (2006-01-05) * paragraphs [0029], [0031], [0032]; figure 2 *	7	
A	US 7 146 781 B1 (COLE NATHAN ALBERT [US]) 12 December 2006 (2006-12-12) * column 3, lines 1-53; figure 1 *	7	A61J B65B
A	EP 1 834 878 A (DOVESI PIETRO [IT]) 19 September 2007 (2007-09-19) * paragraphs [0011], [0013], [0016], [0019], [0022]; figures *	7	
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 25 November 2009	Examiner Mammeri, Damya
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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EPO FORM 1503 03.82 (P04C01)



Application Number

EP 09 15 5764

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

☐ The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).



**LACK OF UNITY OF INVENTION
SHEET B**

Application Number

EP 09 15 5764

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-5, 9 partially

a rotatable member

2. claims: 6, 10 partially

a spraying device

3. claims: 7-10

a system for aseptic handling of materials

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 09 15 5764

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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25-11-2009

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REFERENCES CITED IN THE DESCRIPTION

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[0012] [0019]

Non-patent literature cited in the description

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