(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 February 2015 (12.02.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/019374 A1

(51) International Patent Classification:
A61M 5/00 (2006.01) *B65B 31/02* (2006.01)
A61J 1/16 (2006.01) *B65B 5/06* (2006.01)
A61J 1/20 (2006.01) *B65D 81/00* (2006.01)

(21) International Application Number:
PCT/IT2014/000193

(22) International Filing Date:
23 July 2014 (23.07.2014)

(25) Filing Language: Italian

(26) Publication Language: English

(30) Priority Data:
RM2013A000457 5 August 2013 (05.08.2013) IT

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: INTERMEDIATE PRODUCT FOR PRODUCING PRE-FILLED DUAL- CHAMBER SYRINGES OR CARTRIDGES AND METHOD OF PRODUCING SAID INTERMEDIATE PRODUCT

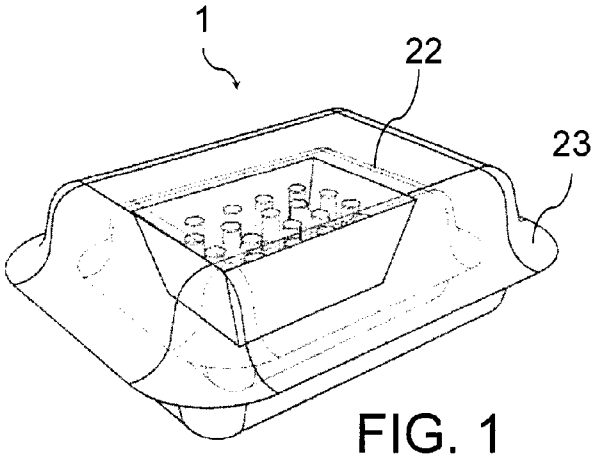

FIG. 1

(57) Abstract: A description is given of an intermediate product (1) for producing a plurality of pre-filled dual-chamber syringes or cartridges, comprising: 5 - a support template (2) comprising an array of support seats; - a plurality of partially pre-filled tubular containment bodies (3), each inserted in a respective support seat, each of the tubular containment bodies (3) 10 extending between a first (4) and a second opening (5); - a sterile package (20-23) inside which the support template (2) and the plurality of tubular containment bodies (3) are enclosed in sterile manner; in which the tubular containment bodies (3) comprise 15 in the interior thereof: - a first (6) and a second stopper (7) arranged in such a manner as to define therebetween a first containment chamber (8) in the tubular containment body (3) and adapted to slide inside the tubular containment 20 body; - a liquid substance contained inside the first filling chamber (8).

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"Intermediate product for producing pre-filled dual-chamber syringes or cartridges and method of producing said intermediate product"

DESCRIPTION

[0001] The present description relates to the technical field of dual-chamber cartridges and syringes and in particular relates to an intermediate product for producing pre-filled dual-chamber syringes or cartridges and method of producing said intermediate product.

[0002] Pre-filled dual-chamber syringes or cartridges have been known for a long time and are today widely used. Said dual-chamber syringes or cartridges comprise a tubular containment body and two substances, of which at least one is a liquid substance, contained in two separate chambers defined inside the containment body.

[0003] The two substances, which are for example a solid substance and a liquid substance, are intended to be mixed one with the other immediately before injection. The liquid substance is for example a solvent for injectable use. For the mixing of the two substances the two chambers are placed in communication one with the other to reconstitute an injectable solution, for example by providing a bypass element in the pre-filled syringe or cartridge.

[0004] WO99/15215 describes, referring to Figure 4 of

this document, a method of filling a dual-chamber syringe shaped like an ampoule, wherein the filling of the two chambers takes place in a sterile chamber 40, in which are provided in sequence:

- the insertion of the middle stopper in the syringe (step indicated as "MIDDLE PLUNGER CHARGING");
- the charging of the front chamber of the syringe with a solution (step indicated as "SOLUTION CHARGING") on the side of the front opening of the syringe;
- lyophilization of the abovementioned solution (step indicated as "LYOPHILIZATION");
- closure of the front opening of the syringe (step indicated as "SEALING");
- filling with the solvent (step indicated as "SOLVENT CHARGING");
- the insertion of the rear stopper in the syringe (step indicated as "REAR PLUNGER CHARGING");

[0005] The need is felt to provide a method of filling of a dual-chamber syringe or cartridge which, compared to filling methods of the prior art, is simple and flexible in relation to the type of substances to be dosed inside the chambers of the syringe or cartridge.

[0006] A general object of the present description is that of making available an intermediate product for the production of pre-filled syringes or cartridges which

allows the abovementioned need to be fulfilled.

[0007] These and other objects are achieved by means of an intermediate product for the production of pre-filled syringes or cartridges as defined in claim 1 in its more general form, and in the claims dependent thereon in some of its particular embodiments.

[0008] The object of the present description is also a method for the production of the intermediate product and a method of pre-filling of a dual-chamber syringe or cartridge.

[0009] The invention will be made clearer by the following detailed description of its embodiments, given by way of an example and therefore in no way limiting in relation to the accompanying drawings, in which:

- Figure 1 shows an intermediate product for producing a plurality of pre-filled dual-chamber syringes or cartridges;
- Figure 2 shows a support template of the intermediate product of Figure 1 comprising an array of support seats and a plurality of partially pre-filled tubular containment bodies, each inserted in a respective support seat, in a configuration in which the support template is inserted inside a containment tray;
- Figure 3 shows the support template of Figure 2 in a condition in which the support template is extracted from

the containment tray;

- Figure 4 shows one of the partially pre-filled containment bodies of Figure 2;

- Figure 5 shows a schematic flow diagram of a method of production of the intermediate product;

- Figure 6 shows a possible starting product of the method of Figure 5;

- Figure 7 shows a tubular container of the starting product of Figure 6;

- Figure 8 shows a step of dosing of the solvent of the method of Figure 5;

- Figure 9 shows a plurality of intermediate products inserted inside an external package;

- Figure 10 shows another step of the method of Figure 5;

- Figure 11 shows a schematic flow diagram of a method of filling of a dual-chamber syringe or cartridge;

- Figure 12 shows the partially pre-filled containment bodies after one of the steps of the method of Figure 11;

- Figure 13 shows a step of dosing of the method of Figure 11;

- Figure 14 shows a part of a pre-filled syringe or cartridge as obtained in output from the method of Figure 11;

- Figure 15 shows some components which can be associated to the part of syringe or cartridge of Figure 14; and

- Figure 16 shows a syringe or cartridge obtained by attaching one to the other the part shown in Figure 14 and the components shown in Figure 15.

[0010] In the accompanying drawings identical or similar elements are to be denoted by the same reference numerals.

[0011] In the accompanying drawings reference numeral 1 denotes overall a preferred and non-limiting embodiment of intermediate product for the industrial production of a plurality of pre-filled dual-chamber syringes or cartridges.

[0012] Referring to Figures 1 to 4, the intermediate product 1 comprises:

- a support template 2 comprising an array of support seats;
- a plurality of partially pre-filled tubular containment bodies 3, each inserted in a respective support seat, each of the tubular containment bodies 3 extending between a first 4 and a second opening 5.

[0013] The abovementioned openings 4,5 are preferably free and are axially spaced one from the other along an axis of main extension of the tubular containment body 3. The first opening 4, or front opening 4, preferably has a smaller diameter with respect to the diameter of the second opening 5, or rear opening 5.

[0014] At the abovementioned openings 4,5 the tubular containment body 3 preferably has respective collars 14, 15 projecting towards the exterior of the body 3. The collar 14 placed at the first opening 4 is preferably an externally threaded collar.

[0015] In accordance with an embodiment the support template 2 has a main body, for example plate-shaped, comprising a plurality of support openings inside of which the containment bodies 3 are inserted. These support openings support the containment bodies 3 for example through interference of their rims against the outer walls of the bodies 3. The support template 2 is preferably made in plastic material.

[0016] The tubular bodies 3 are for example in the form of the containment bodies of a syringe or of a cartridge suitable for containing injectable substances and are for example made in glass or in a transparent or substantially transparent plastic material. The tubular bodies 3 are preferably each made in a single piece.

[0017] The intermediate product 1 also comprises a sterile package 20-23 inside which the support template 2 and the plurality of tubular containment bodies 3 are enclosed in a sterile manner. For example this sterile package 20-23 is a package produced aseptically.

[0018] The tubular containment bodies 3 comprise in the

interior thereof:

- a first 6 and a second stopper 7 arranged in such a manner as to define therebetween in the tubular containment body 3 a first containment chamber 8, or rear chamber 8, and suitable for sliding inside the tubular containment body (for example due to a thrust or traction force);

- a first liquid substance contained inside the first containment chamber 8.

[0019] The abovementioned first liquid substance is preferably a solvent for injectable use, for example a WFI (water for injection) solvent or a solution of lidocaine or a solution of water and benzyl alcohol or a physiological solution of sodium chloride or in general any injectable substance suitable for reconstituting another solid or liquid substance. The first liquid substance can be or contain an API (active pharmaceutical ingredient).

[0020] The stoppers 6,7 are made for example in plastic material, are such as to seal-engage with the internal walls of the tubular body 3 and are such as to be able to slide inside the tubular body 3 under the action of a thrust or traction force.

[0021] The first stopper 6, or middle stopper 6, is spaced from the first opening 4 in such a manner as to

define between the first stopper 6 and the first opening 4 a second containment chamber 9, or rear chamber 9, empty and suitable for being filled with a second substance, solid or liquid, intended to be mixed inside the containment body with said first liquid substance in order to reconstitute an injectable solution. In the case wherein the second substance is solid, it can be crystallized or lyophilized. The version in which the second substance is crystallized and not lyophilized is currently preferred. The second substance is preferably a powder, a substance in granules or a sterile tablet. The abovementioned second substance can be or contain an API. In accordance with an embodiment, the abovementioned second substance comprises two separate substances for example in the form of two separate tablets, each one containing one of said two separate substances.

[0022] The aforesaid second substance is for example a highly active substance, such as for example: a beta-lactam antibiotic or a cytotoxic antitumor agent or a hormone or a biological preparation. The abovementioned second substance can also be a normal active ingredient, i.e. which cannot be defined as a highly active ingredient.

[0023] In accordance with an embodiment the first stopper 6, or middle stopper 6, comprises at least one

bypass channel permanent in a state of closure and adapted for being brought into a state of opening following the stress of an external force, for example a force of pressure acting on the stopper. The stoppers with bypass channels are generally known to a person skilled in the art of dual-chamber injection devices and for this reason will not be described further.

[0024] In accordance with an alternative embodiment the containment body 3 comprises an internal wall provided with a recess 10 adapted to define a bypass channel. This recess is positioned between the first stopper 6 and the first opening 4.

[0025] Preferably the second stopper 7, or rear stopper 7, comprises a fastening element adapted to fasten a plunger to the second stopper 7 in such a manner that the second stopper 7 can slide inside the containment body 3 under the action of the plunger. Said fastening element comprises for example an internally threaded blind hole formed in the thickness of the second stopper 7, inside whereof a complementary threaded end portion of the plunger can be inserted and screwed.

[0026] In accordance with an embodiment the sterile package 20-23 comprises a containment tray 20, and the support template 2 is accommodated and closed in a sterile manner, together with the tubular containers 3,

inside the containment tray 20, for example in a position in which the support template is spaced and parallel to a bottom wall of the containment tray 20. The containment tray 20 is preferably a tray in plastic material.

[0027] In accordance with an embodiment the containment tray 20 comprises an opening rim 25 and the package 20-23 comprises a closure film 21, for example a film in plastic material, fastened flush to said rim 25 and resting on an end portion of the tubular containment bodies 3. For example this film is heat welded to the opening rim 25.

[0028] The package 20-23 preferably comprises a first sterile pouch 22 which contains the containment tray 20. This sterile pouch 22 is for example made in a flexible multilayer laminate. The package 20-23 preferably comprises a second sterile pouch 23 which encloses the first sterile pouch 22. This sterile pouch 22 is for example also made in a flexible multilayer laminate.

[0029] Referring to Figure 5 a description will now be given of a production method 100 for an intermediate product 1, of the type described above, for producing a plurality of pre-filled dual-chamber syringes or cartridges.

[0030] The method 100 comprises a step 101 of providing a starting product comprising a support template 2

comprising an array of support seats. The starting product comprises a plurality of tubular containment bodies 3, each inserted in a respective support seat. The abovementioned starting product takes shape in the assembly 2,3 shown in Figure 6 in which the containment bodies are presented as shown in Figure 7, in which it can be noted that there is only one stopper inserted inside the tubular body 3. Referring to Figure 7, the containment bodies 3 of the starting product 2,3 differ from the containment bodies 3 of the intermediate product 1 already described with reference to Figure 4 due only to the fact that in this case the second stopper 7 and the solvent 8 are not provided. For economy of disclosure the containment bodies 3 of the intermediate product will not be described here in greater detail.

[0031] The method 100 comprises a step of dosing 104 of the first liquid substance, or solvent 8, through the second opening 5. The dosing step 104 is schematically illustrated in Figure 8. The dosing step 104 can be performed simultaneously for more than one or for all the containment bodies 3 of the plurality of containment bodies 3 of the starting product.

[0032] The method 100 comprises a step 105 of inserting a second stopper 7, or rear stopper 7, through the second opening 5 in order to define a first containment chamber

8 of the abovementioned first liquid substance between the first stopper 6 and the second stopper 7. In this way a configuration of the containment body 3 is obtained as already represented in Figure 4 and already described previously. Between the dosing step 104 and the step 105 of inserting the second stopper 7 no step of lyophilization of the first substance is provided.

[0033] The method 100 comprises a step of enclosing 106 the support template 2 and the plurality of tubular containment bodies 3 inside a sterile package 20-23, for example produced aseptically. This step 106 is for example such as to lead to the production of an intermediate product as shown in Figure 1.

[0034] In particular, in accordance with an embodiment, the sterile package 20-23 comprises a containment tray 20, and the step of enclosing 106 the support template 2 comprises a step of inserting the template 2 inside the containment tray 20 and of closing the containment tray 20 in a sterile manner. The containment tray 20 preferably comprises an opening rim 25 and the step of closing the containment tray 20 in a sterile manner comprises a step of fastening a closure film 21 flush with the rim 25. More preferably the enclosing step 106 comprises a step of enclosing the containment tray 20 inside the sterile pouch 22. It may also be foreseen that

the enclosing step 106 comprises a step of enclosing the first sterile pouch 22 in a second sterile pouch 23 to arrive at the configuration of the intermediate product as shown in Figures 1-4.

[0035] Referring to Figure 9, in accordance with an embodiment, a further step 107 can be provided of inserting and closing several intermediate products 1 inside an external package 30.

[0036] In the case wherein the abovementioned starting product also comprises a sterile package 20-23 comprising the abovementioned containment tray 20 and in the case wherein the support template 2 is contained in the containment tray 20 in the starting product, the method 100 can comprise, before the dosing step 104, a step of removing 102 the sterile package 20-23 and a step of extracting 103 the support template 2 from the containment tray 20.

[0037] Referring to Figure 10, in the case wherein also in the abovementioned starting product the containment tray 20 comprises an opening rim 25 whereto a closure film 21 is fastened flush, the step of removing 102 the sterile package 20-23 comprises a step of removing the closure film 21. For example the closure film 21 can be removed by means of a hot roller 31.

[0038] In the case wherein also in the starting product

the sterile package 20-23 comprises one or more sterile pouches 22-23, the removing step 102 provides a step of removing said one or more sterile pouches 22, 23 performed before the removal of the closure film 21.

[0039] The abovementioned steps 103 to 106 of the method 100 can all be performed in a first sterile chamber, for example in a sterile chamber of a liquids dosing machine, in which in fact the first liquid substance or solvent is dosed. As far as step 102 is concerned, the pouches 22-23, if provided, are preferably removed outside of the first sterile chamber while the closure film 21, if provided, is preferably removed inside the first sterile chamber. Moreover the phase of closing 107 in a further package 30 is performed outside of the first sterile chamber.

[0040] The intermediate products as provided in output from steps 106 or 107 can be transported in input to a second sterile chamber separate from the first sterile chamber for performing a method of production of a pre-filled dual-chamber syringe or cartridge. For example and without thereby introducing any limitation, the abovementioned intermediate products can be transported as far as the entrance of the sterile chamber (referred to here as second sterile chamber) of a machine for dosing highly contaminating substances, for example a

dosing machine of antibiotic powders. The second sterile chamber can be located in the same production plant in which the first sterile chamber is located or in another geographically distant production plant.

[0041] An embodiment of the abovementioned method 200 of production of a pre-filled dual-chamber syringe or cartridge is schematically shown in the flow diagram of Figure 11.

[0042] The method of filling 200 of a dual-chamber syringe or cartridge comprises a step of providing 201, for example at the entrance of the second sterile chamber described above, an intermediate product 1 as described with reference to Figures 1-4 in any one of its possible variants and embodiments described and in particular in an orientation of the intermediate product in which the containment bodies 3 have the second opening 5 which is located above the first opening 4.

[0043] The filling method 200 comprises:

- a step 202 of removing the sterile package 20-23;
- a step 204 of turning over the support template 2 such that the first opening 4 is located above the second opening 5;
- a step of dosing 206 through the first opening 4 the second substance, solid or liquid, intended to be mixed inside the containment body 3 with first liquid substance

in order to reconstitute an injectable solution;

-a step of sealing 207 the first opening 4.

[0044] The dosing step 206 for example includes the dosing of a powder or of one or more tablets. In the latter case the second substance can comprise more than one substance and the dosing is provided of one tablet for each substance.

[0045] In accordance with a preferred embodiment, between the dosing step 206 and the sealing step 207 the lyophilization of the second substance is not provided.

[0046] In accordance with an embodiment in which the abovementioned sterile package 20-23 comprises a containment tray 20 which accommodates the support template 2, the method comprises, before the dosing step 206, a step of taking 203 the support template 2 out of the containment tray 20 (as shown in Figure 3). Referring to Figure 12, in the method 200 after the step of turning over the support template 2 and before the dosing step 206 a step of removing 205 the support template 2 is moreover preferably provided, leaving the tubular bodies 3 on a surface or device of resting and/or support provided in the dosing machine.

[0047] The abovementioned steps 203 to 206 are performed inside the second sterile chamber. The phase of removing 202 the sterile package can be performed partly outside

the second sterile chamber and partly inside the second sterile chamber. In particular, in the case wherein the containment tray 20 has an opening rim 25 closed by a closure means 21 fastened flush to the opening rim 25, the step of removing 202 the sterile package 20-23 comprises a step of removing the closure means 21, preferably performed inside the second sterile chamber.

[0048] In the case wherein the sterile package 20-23 comprises at least one sterile pouch 22,23 containing the containment tray 20 and the support template 2, the step of removing 202 the sterile package 20-23 comprises a step of opening and removing said at least one sterile pouch 22,23, preferably performed outside of the second sterile chamber and before removal of the closure means 21.

[0049] Referring to Figure 14, the step of sealing 207 the first opening 4 comprises a step of attaching a closure means 50 to the first opening 4 and fastening a crimp closure 51 to the containment body in the vicinity of the first opening 4 to lock the closure means to the tubular body 3.

[0050] The abovementioned step of sealing 207 the first opening 4 is preferably performed inside the second sterile chamber. Said crimp closure 51 can be such as to engage with the collar 14 of the containment body 3.

[0051] After the step of sealing 207 the step can be provided of packaging the product obtained in this way with a plunger 52, intended to be attached to the second stopper 7, and a needle 53 provided with an attachment flange for example threaded internally, for the fastening to the tubular body 3 once the crimp closure 51 has been removed. A packaged kit of parts is thus obtained which, assembled one with the other, form a pre-filled dual-chamber injection device as for example shown in Figure 16.

[0052] During operation, the pressure of the plunger determines the sliding of the two stoppers 6,7 inside the tubular body 3. In the case wherein the bypass channel 10 is provided, when the first stopper 6 is located at the channel 10, the containment chambers come into communication one with the other and the first liquid substance penetrates the second chamber, mixing with the second substance contained therein to reconstitute an injectable solution.

[0053] On the basis of what is described above it is therefore possible to understand that the intermediate product 1 and the processes proposed allow full achievement of the objects mentioned above with reference to the prior art.

[0054] Referring to Figure 16, it is noted that in the

present description a pre-filled dual-chamber syringe or cartridge was also described, comprising:

- a tubular containment body 3 made in a single piece which extends between a first 4 and a second opening 5;
- a first 6 and a second stopper 7 arranged in such a manner as to define therebetween in the tubular containment body 3 a first containment chamber 8;
- a first liquid substance contained inside the first containment chamber 8;
- a closure means removably attached to the first opening 4;

in which the first stopper 6 is spaced from the first opening 4 in such a manner as to define between the first stopper 6 and the first opening 4 and inside said tubular body a second containment chamber 9 filled with a second highly active substance adapted to be mixed inside the containment body with said first liquid substance in order to reconstitute an injectable solution. For example, the aforesaid second highly active substance is a beta-lactam antibiotic or a cytotoxic antitumor agent or a hormone or a biological preparation.

[0055] Without prejudice to the principle of the invention, its embodiments and its details of manufacture may be widely varied with respect to what has been described and illustrated purely by way of a non-limiting

example, without thereby departing from the scope of protection as defined in the annexed claims.

CLAIMS

1. An intermediate product (1) for producing a plurality of pre-filled dual-chamber syringes or cartridges, comprising:

- a support template (2) comprising an array of support seats;

- a plurality of partially pre-filled tubular containment bodies (3), each inserted in a respective support seat, each of the tubular containment bodies (3) extending between a first (4) and a second opening (5);

- a sterile package (20-23) inside which the support template (2) and the plurality of tubular containment bodies (3) are enclosed in sterile manner;

in which the tubular containment bodies (3) comprise in the interior thereof:

- a first (6) and a second stopper (7) arranged in such a manner as to define therebetween in the tubular containment body (3) a first containment chamber (8) and adapted to slide inside the tubular containment body (3);

- a first liquid substance contained inside the first containment chamber (8);

in which the first stopper (6) is spaced from the first opening (4) in such a manner as to define between the first stopper (6) and the first opening (4) a second containment chamber (9) which is empty and adapted to be

filled with a second substance intended to be mixed inside the containment body with said first liquid substance in order to reconstitute an injectable solution.

2. An intermediate product (1) according to claim 1, in which:

- the first stopper (6) comprises at least one bypass channel; or

- the containment body (3) comprises an internal wall equipped with a recess (10) adapted to define a bypass channel, and in which the recess is located between the first stopper (6) and the first opening (4).

3. An intermediate product (1) according to any one of the preceding claims, in which the tubular containment body (3) is made in a single piece.

4. An intermediate product (1) according to any one of the preceding claims, in which the second stopper (7) comprises a fastening element adapted to fasten a plunger (52) to the second stopper (7) in such a manner that the second stopper (7) can slide inside the containment body (3) under the action of the plunger (52).

5. An intermediate product (1) according to any one of the preceding claims, in which the sterile package (20-23) comprises a containment tray (20), and in which the support template (2) is accommodated inside the

containment tray (20).

6. An intermediate product (1) according to any one of the preceding claims, in which the containment tray (20) comprises an opening rim (25) and in which the sterile package (20-23) comprises a closure film (21) fastened flush to said rim (25) and resting on an end portion of said tubular containment bodies (3).

7. An intermediate product (1) according to claim 5, in which the package (20-23) comprises a first sterile pouch (22) which contains the containment tray (20).

8. An intermediate product (19) according to claim 7, in which the package (20-23) comprises a second sterile pouch (23) which encloses the first sterile pouch (22).

9. A production method (100) for an intermediate product (1) for producing a plurality of pre-filled dual-chamber syringes or cartridges, comprising in sequence the steps of:

- providing (101) a starting product comprising a support template (2) comprising an array of support seats, the starting product comprising a plurality of tubular containment bodies (3) each inserted in a respective support seat, each of the tubular containment bodies (3) extending along a vertical axis between a first (4) and a second (5) opening, the containment bodies (3) comprising a first stopper (6) inserted inside

the containment body (3) between the first (4) and the second (5) opening, the second opening (5) being located at a higher level relative to the first opening (4);

- dosing (104) a first liquid substance through the second opening (5);

- inserting (105) a second stopper (7) through the second opening to define a first containment chamber (8) of the first liquid substance between the first stopper (6) and the second stopper (7);

- enclosing (106) the support template (2) and said plurality of tubular containment bodies (3) inside a sterile package (20-23).

10. A production method (100) according to claim 9, in which the sterile package (20-23) comprises a containment tray (20), and in which the step of enclosing (106) the support template (2) comprises a step of inserting the template (2) inside the containment tray (20) and of closing the containment tray.

11. A production method (100) according to claim 10, in which the containment tray (20) comprises an opening rim (25) and in which the step of closing said containment tray (20) comprises a step of fastening a closure film (21) flush with the rim (25).

12. A production method (100) according to claim 11, in which the enclosing step (106) comprises a step of

enclosing the containment tray (20) inside a sterile pouch (22).

13. A production method (100) according to claim 12, in which the enclosing step (106) comprises a step of enclosing the first sterile pouch (22) in a second sterile pouch (23).

14. A production method (100) according to any one of preceding claims 9 to 13, in which the starting product comprises said containment tray (20), in which the support template (2) is contained in the containment tray (20) in the starting product, and in which the method (100) comprises, before the dosing step (104), a step of extracting (103) the support template (2) from the containment tray (20).

15. A production method (100) according to any one of preceding claims 9 to 14, in which between the dosing (104) and inserting (105) steps there is no lyophilization step.

16. A method for filling (200) a dual-chamber syringe or cartridge, comprising the steps of:

- providing (201) an intermediate product (1) according to claim 1, in which the second opening (5) is located above the first opening (4);
- removing (202) the sterile package (20-23);
- turning over (204) the support template (2) such

that the first opening (4) is located above the second opening (5);

- dosing (206) through the first opening (4) a second substance intended during use to be mixed inside the containment body (3) with said first substance in order to reconstitute an injectable solution;

- sealing (207) the first opening (4).

17. A method for filling (200) a dual-chamber syringe or cartridge according to claim 16, in which the step of sealing (207) the first opening (4) comprises a step of attaching a closure means (50) to the first opening (4) and fastening a crimp closure (51) to the containment body (3) in the vicinity of the first opening (4) to lock the closure means (50) to the tubular body (3).

18. A filling method (200) according to claim 16 or claim 17, in which the sterile package (20-23) comprises a containment tray (20) which accommodates the support template (2) and in which the method (200) comprises, before the dosing step (206), a step of taking (203) the template (2) out of the containment tray (20).

19. A filling method (200) according to claim 17, in which the containment tray (20) has an opening rim (25) closed by a closure means (21) fastened flush to the opening rim and in which the step of removing (202) the sterile package (20-23) comprises a step of removing the

closure means (21).

20. A filling method (200) according to claim 19, in which:

- the sterile package (20-23) comprises at least one sterile pouch (22,23) containing the containment tray (20) and the support template (2);

- the step of removing (202) the sterile package (20-23) comprises a step of opening and removing said at least one sterile pouch (22,23).

21. A production method (200) according to any one of preceding claims 16 to 20, in which between the dosing (206) and sealing (207) steps there is no step of lyophilizing the second substance.

22. A pre-filled dual-chamber syringe or cartridge comprising:

- a tubular containment body (3) made in a single piece which extends between a first (4) and a second opening (5);

- a first (6) and a second stopper (7) arranged in such a manner as to define therebetween in the tubular containment body (3) a first containment chamber (8) and suitable for sliding inside the tubular containment body (3);

- a first liquid substance contained inside the first filling chamber (8);

- a closure means removably attached to the first opening (4);

in which the first stopper (6) is spaced from the first opening (4) in such a manner as to define between the first stopper (6) and the first opening (4) and inside said tubular body a second containment chamber (9) filled with a second highly active substance suitable to be mixed inside the containment body with said first liquid substance in order to reconstitute an injectable solution.

23. A pre-filled dual-chamber syringe or cartridge according to claim 22, in which said second highly active substance is a beta-lactam antibiotic or a cytotoxic antitumor agent or a hormone or a biological preparation.

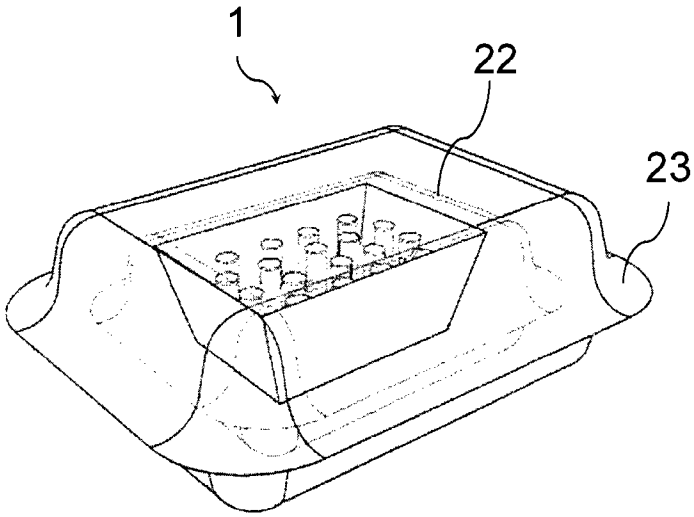

FIG. 1

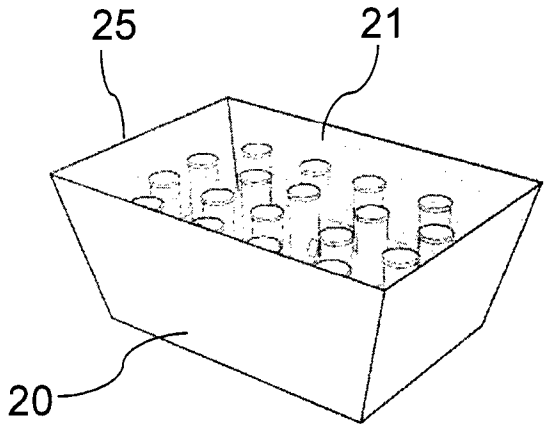

FIG. 2

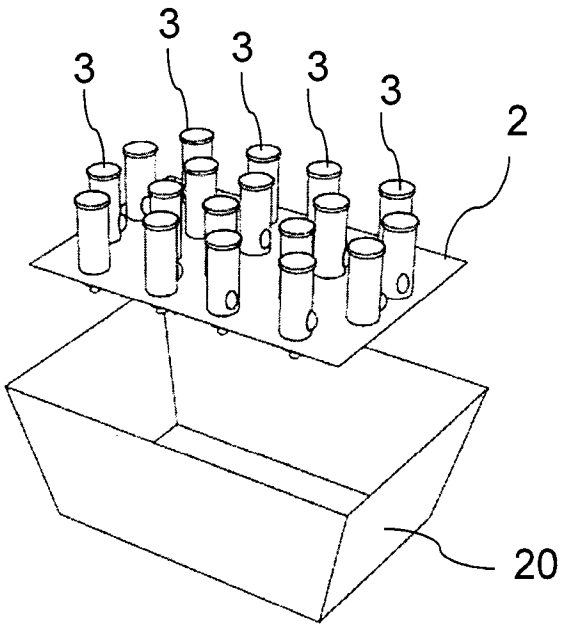

FIG. 3

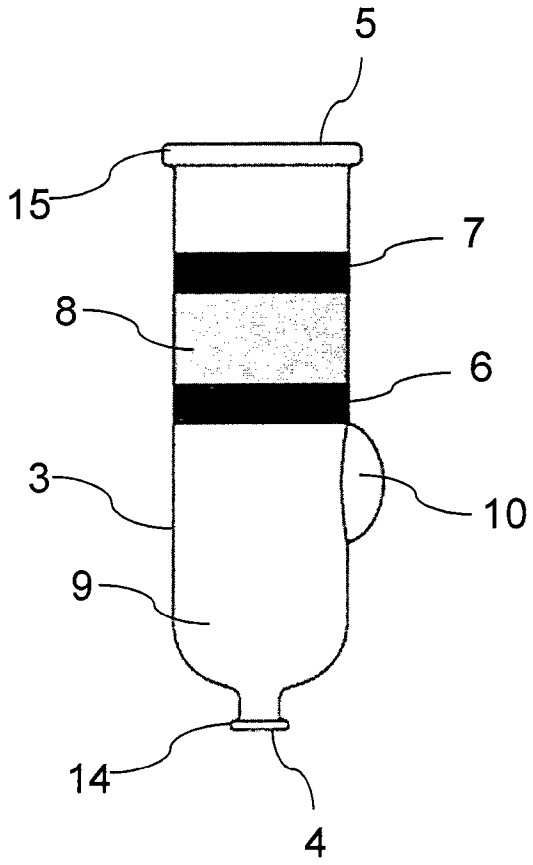

FIG. 4

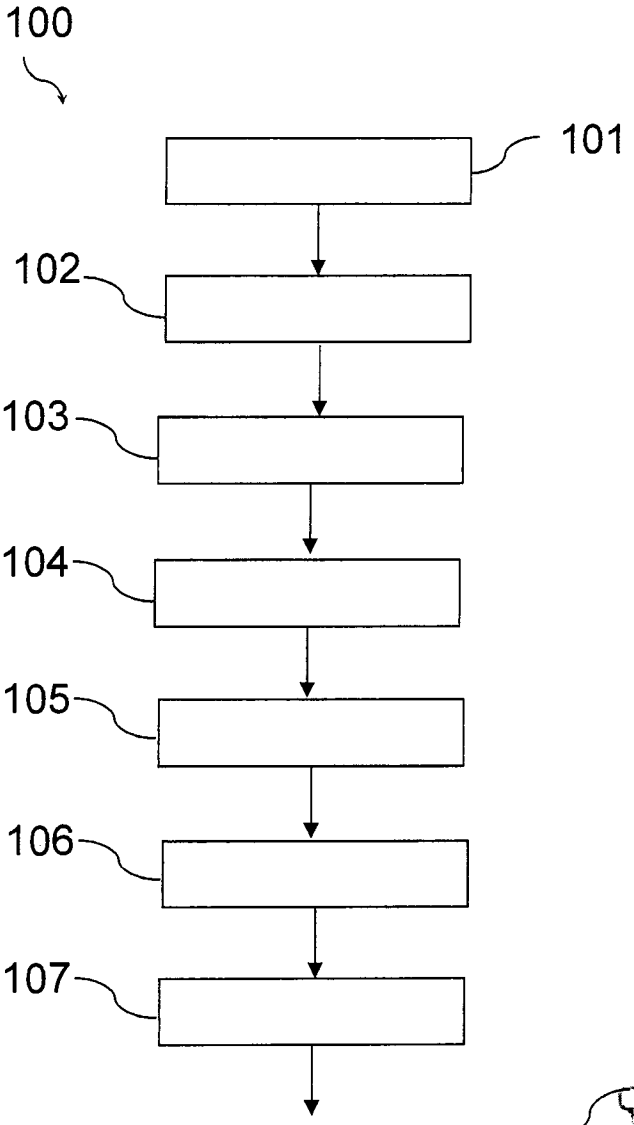

FIG. 5

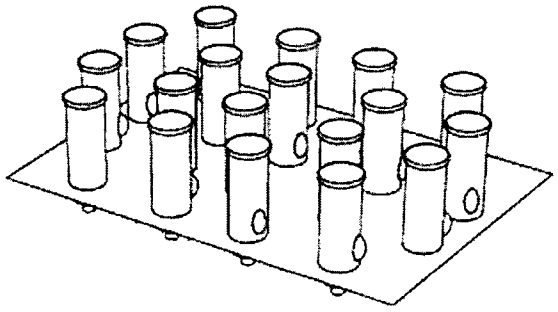

FIG. 6

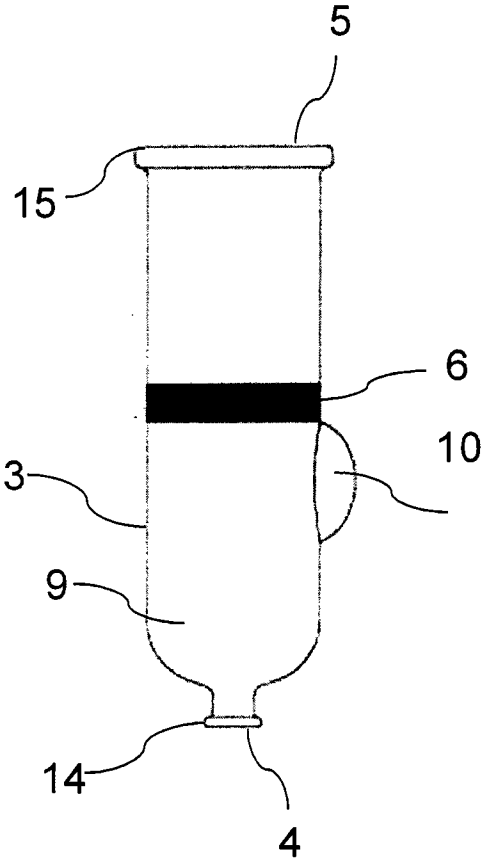

FIG. 7

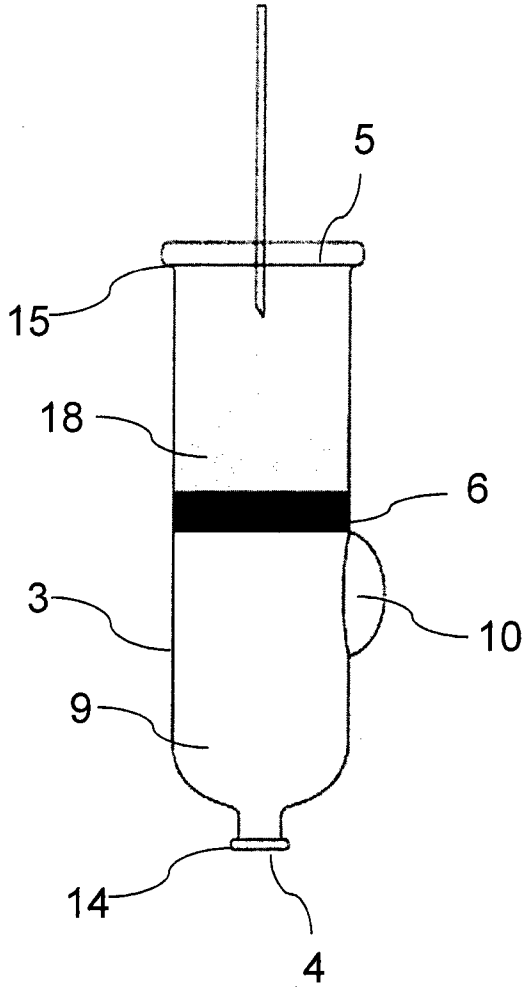

FIG. 8

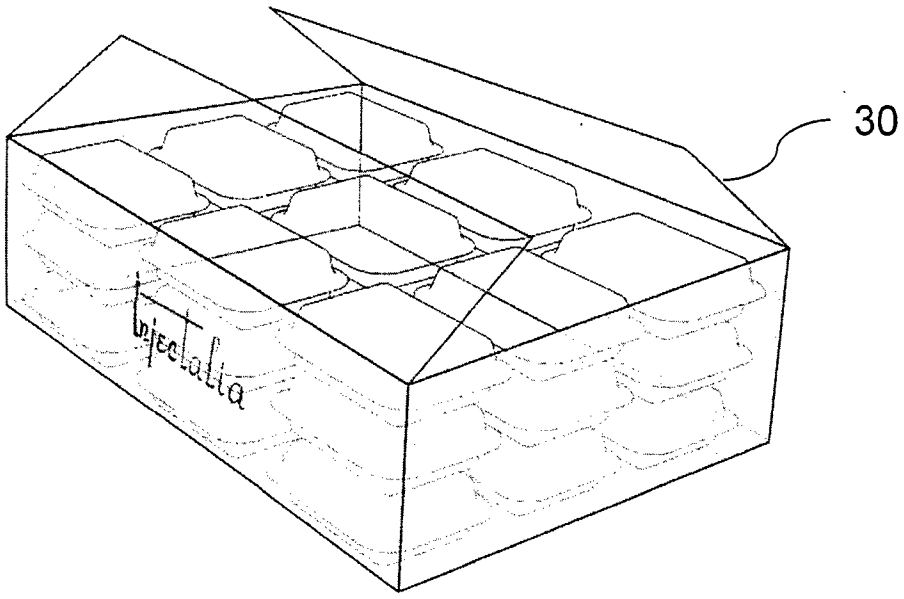

FIG. 9

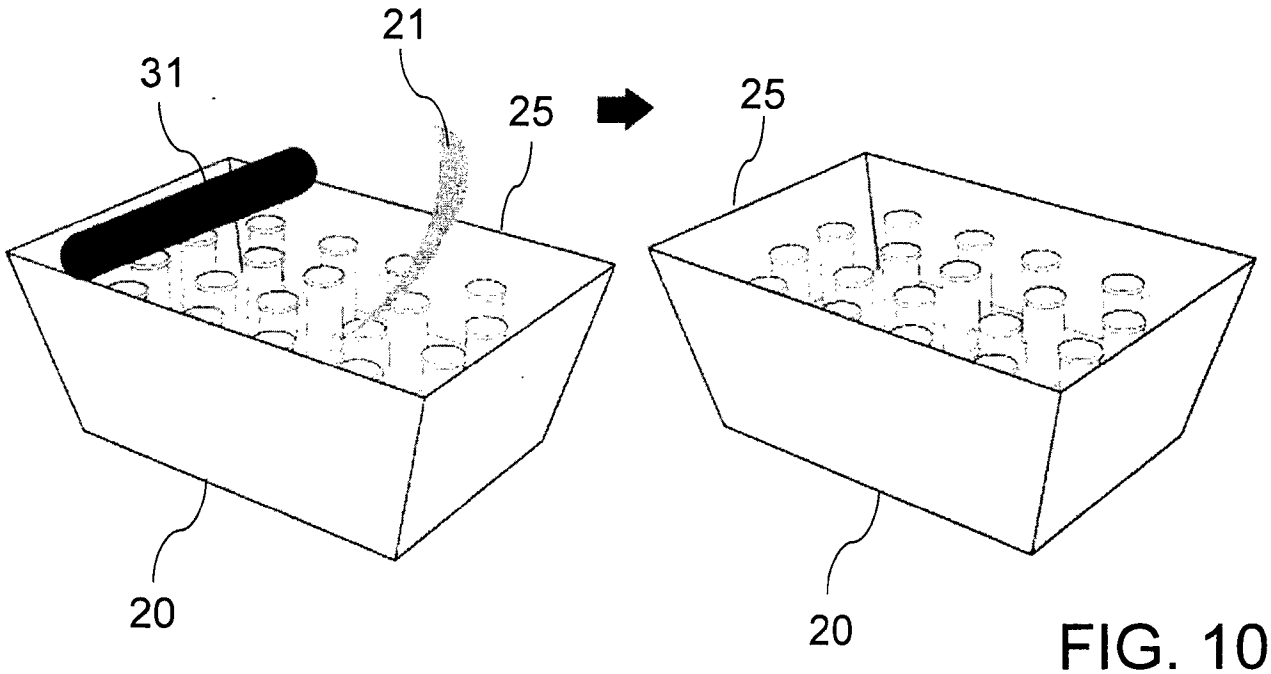

FIG. 10

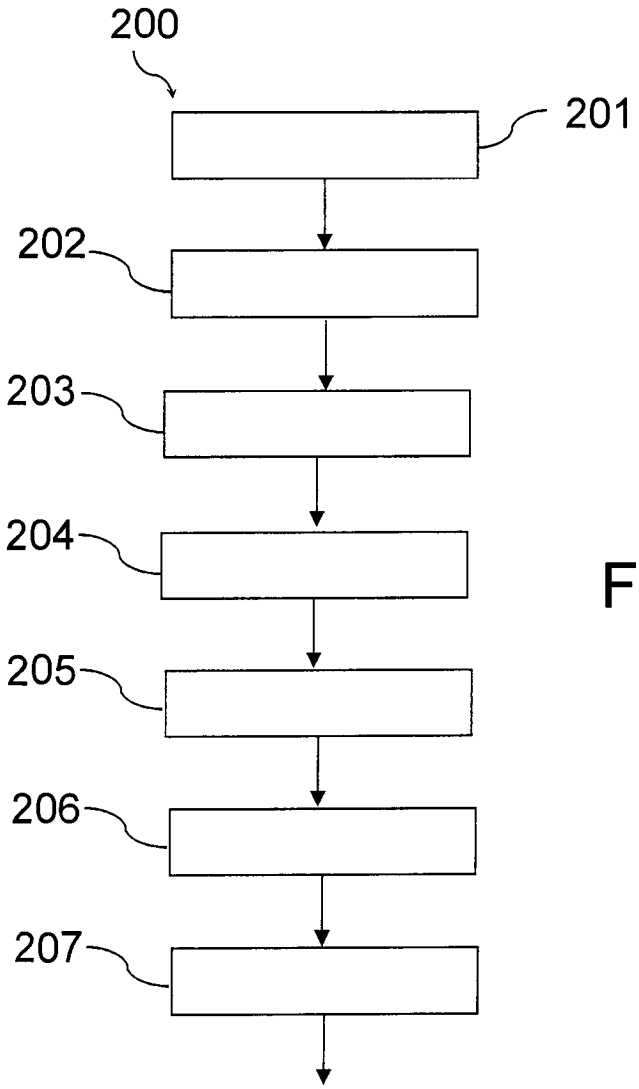

FIG. 11

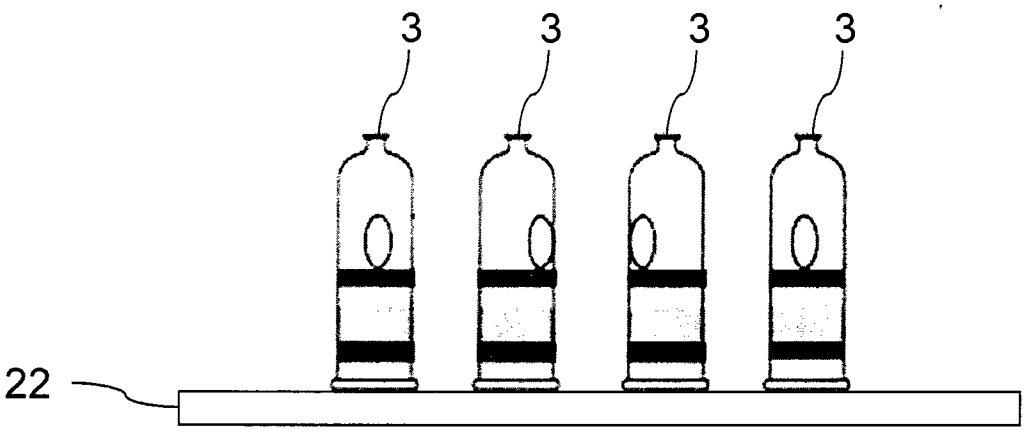

FIG. 12

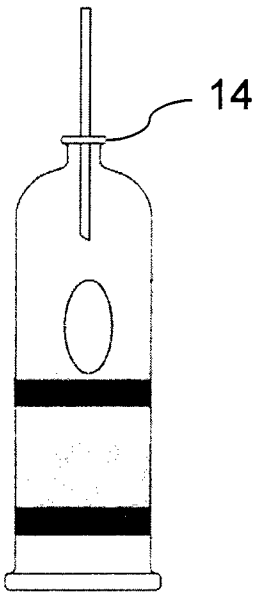

FIG. 13

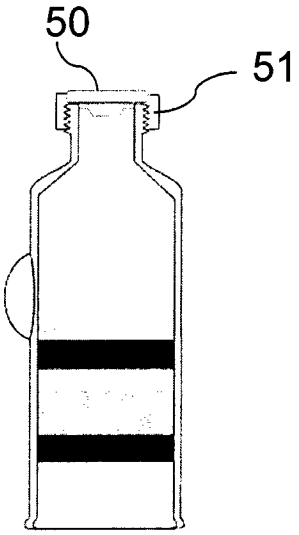

FIG. 14

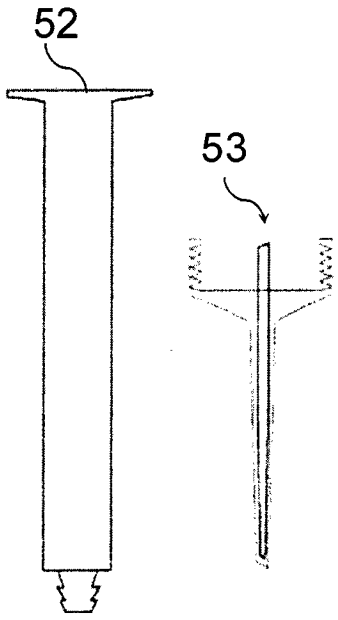

FIG. 15

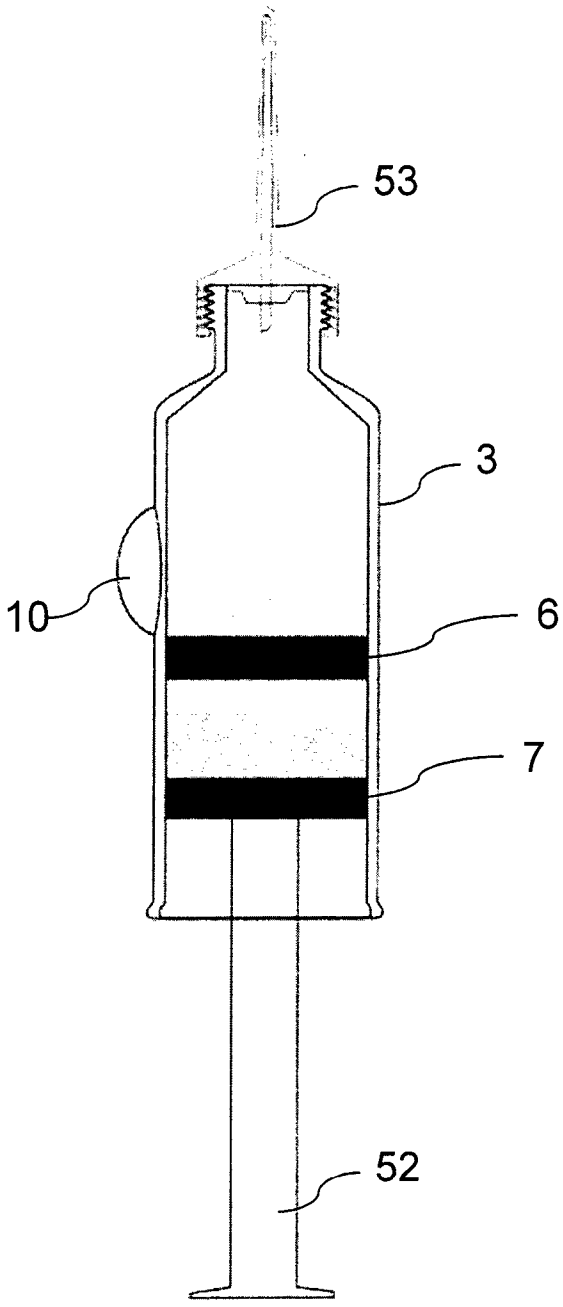

FIG. 16

INTERNATIONAL SEARCH REPORT

International application No
PCT/IT2014/000193

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M5/00 A61J1/16 A61J1/20 B65B31/02 B65B5/06
B65D81/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M A61J B65B B65D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/15215 A1 (PHARMACIA & UPJOHN AB [SE]; FORSBERG MIKAEL [SE]; HJERTMAN BIRGER [SE]) 1 April 1999 (1999-04-01)	1-4,9, 15-17, 21-23
Y	page 7, lines 3-23 page 8, lines 20-21 page 9, lines 1-5,15-18 page 13, lines 11-19 page 15, lines 5-11, 20-23 page 16, lines 9-12 page 20, lines 1-9	5-8, 10-14, 18-20

Y	US 2009/288977 A1 (VANDERBUSH EDWARD [US] ET AL) 26 November 2009 (2009-11-26) figure 7 paragraphs [0002], [0059]	5-8, 10-14, 18-20

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2015	22/01/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Herz, Markus

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IT2014/000193

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No
PCT/IT2014/000193

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