

**A process for preparing an injectable preparation
and device for implementing same**

The present invention provides a process for preparing an injectable pharmaceutical preparation, a device for implementing said process and the product obtained by implementing the process by means of the device.

- 5 It is known that injectable forms are immediately bioavailable and constitute a potential passive mode of administration for the patient and an ideal treatment in urgent cases.

10 Another important reason for the development of parenteral forms is the use of active principles (AP) which are degraded and/or not significantly absorbed by the oral route.

15 Of all these AP which, for various reasons, require an injectable form, many of them are unstable in aqueous media, whether in solution, suspension or dispersion.

20 In order to avoid hydrolysis and all the physico-chemical problems associated with a liquid presentation (precipitation, aggregation, adsorption, crystallisation), a presentation is often used in which the AP is preserved in a solid, dried or freeze-dried form.

The preparation of the liquid form required for injection then takes place extemporaneously, just prior to injection.

- 25 This preparation consists in hydrating the solid form with the liquid medium for solubilisation or suspension of the AP.

30 Traditionally, this operation is carried out in a sealed bottle which contains the solid form. The liquid is introduced into the bottle by a syringe, the needle of which is capable of piercing a stopper-septum.

The liquid form is then recovered in the syringe so that it can be injected.

35 The time required for this delicate operation and the risks of contamination it involves led experts in medical technology to devise devices for making

extemporaneous preparation simpler and more reliable, and for using the fewest possible components.

5 Along such lines, the patents EP-A-0 664 136, DAIKYO SEIKO, EP-0 599 649 PHARMACIA, WO-95 11051 disclose a bicompartmental or "by-pass" syringe which combines in the same syringe the liquid medium and the solid form which will be directly rehydrated in the syringe before injection.

10 Similarly, certain producers propose devices which combine the bottle with the syringe and control the satisfactory execution of the preparation (French patents DEBIOTECH 2 705 898, 2 715 311, 2 717 086).

15 Certain faults in the traditional systems are not, however, solved by said new devices, which pose problems of loss of preparation in their dead volumes, which do not render rehydration automatic and static but keep it manual and dynamic, that is, the flow of liquid and the transfers after hydration displace the solid form and, in particular, the AP. The injectable form does not, therefore, necessarily have the same distribution or homogeneity as the dry form. This constitutes a problem, particularly in the case of suspensions.

20 The fact that preparation is dynamic and carried out manually may lead to important differences depending on the operator, the speed with which he acts, the manner in which he loads the liquid and controls the evacuation of the air. Finally, the force with which the solid AP is hydrated is likely to lead to a relatively
25 substantial emulsion of microbubbles of air.

The time allowed for solubilisation or suspension and agitation of the liquid medium determines the homogeneity of the preparation.

30 In the case of suspensions, poor homogeneity or the onset of sedimentation may lead to dose and administration problems.

The object of the invention is to propose a process for overcoming these various
35 disadvantages.

According to the invention, the process for preparing an injectable preparation is characterised in that a dry form of an active principle under vacuum and a liquid

are prepared, and said liquid is introduced into the dry form by suction by virtue of the action of the vacuum in order to form the said injectable preparation.

5 The process of preparation and packing under vacuum according to the invention avoids the above-mentioned problems (dead volume, manual activation, injectability) and at the same time the problems of injected liquid formulation (homogeneity, degassing).

10 According to a characteristic of the process, the dry form under vacuum occupies the same volume as the final form obtained after automatic hydration by a corresponding, exactly pre-determined volume of liquid.

15 According to an embodiment of the process of the invention, a layer of excipient is added to the dry form, said layer being used subsequent to the injectable preparation as a liquid piston in order to push the other layers and to reduce the losses of active principle during injection.

20 According to another embodiment of the process of the invention, the dry form is packed in a syringe fixed to an automatic rehydration device; in order to prepare the dry form, a liquid containing the active principle is frozen, a specific quantity of excipient solution is added to the surface of the frozen liquid, this excipient solution is frozen, the whole unit is freeze-dried so as to obtain, between the piston of the syringe and the solid of active principle under vacuum, a volume of freeze-dried product containing only the excipient which, after automatic rehydration and
25 movement of the piston in order to empty the syringe, occupies a dead volume at the bottom of the syringe and of the injection needle at the end of injection.

This process of preparation and packing leads to automatic rehydration: it is sufficient for the user to activate the device for the liquid to restore the solid form to
30 the state it was in prior to drying or freeze-drying. Activation of the device consists in bringing into contact the liquid volume and the solid volume under vacuum. After activation, extemporaneous preparation is automatic, that is, the components of the device move solely under the action of the liquid which is drawn by suction by the vacuum under which the solid formulation is placed.

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This property of vacuum packing is independent of the operator, and hydration leads to an immediate return to the situation of the liquid form prior to drying or freeze-drying.

The solid form and active principle remain static during this hydration, that is, they are not displaced by the liquid.

- 5 This immediate preparation is thus directly injectable without the need to agitate it, transfer it or expel the air before injection.

10 This process of preparation and packing may use certain devices or containers currently available, provided that they ensure that the form under vacuum is kept under vacuum until rehydration. The component(s) of the device must allow this rehydration whilst avoiding contact with the ambient air.

15 This feature also leads to certain specific devices or components for this process of preparation and packing. These devices and components will be described below.

The techniques for vacuum packing the solid form in the device and the packaging are derived from existing techniques (blood sampling tube, packing under a plastic film). This vacuum packing of the solid form and of the AP is, moreover, capable of replacing inert gas blanketing (nitrogen) and improving the stability of the preparation particularly at high temperatures (thermal insulation) and the compatibility with the container (contact insulation).

25 The above-mentioned advantages of the process and of the devices of the invention, which will be explained below, are particularly important for certain preparations:

- For a solid, readily solubilised preparation, the advantage is that of obtaining immediately a degassed liquid preparation without air bubbles.
- 30 - For a solid preparation which is more difficult to solubilise, either due to its viscosity or due to the time required for solution, the formulation under vacuum avoids the emulsion of air in the liquid, simplifies and accelerates solubilisation.
- For a suspension and, more especially, for a sustained-release suspension
35 of microspheres (Décapeptyl 3.75 B.1), the formulation under vacuum avoids the problems of dehomogenisation and the risks of precipitation, hence blocking off whilst reducing the time required for reconstitution.

The pharmaceutical preparation under vacuum and the preloaded device make it possible to reduce considerably the dead volume and hence the losses of active principle.

- 5 - Finally, for a dispersion and more particularly for semi-solid forms, the very high viscosity of the hydrated form makes it practically indispensable to use a process of preparation and packing under vacuum for the dry form.

10 The non-liquid or semi-solid aqueous form obtained after hydration under vacuum is, moreover, likely to have salting out properties which are different to and better than those of a form hydrated in air. The fact of not having trapped air in the dispersion makes it possible to reduce the volume for the same quantity (which improves salting out) and avoids rupture of the in situ depot structure which may also modify salting out.

15 The process, packing and devices are described here for aqueous liquid forms. It goes without saying that the whole of the invention applies with the same advantages to liquid forms (solution, suspension or dispersion) which are reconstituted from a mixture of water-organic solvent, from an organic solvent, or
20 from other liquids such as injectable oils.

The speed of the process of preparation and its realisation in a hermetic packing compensates for the viscosity or the risks of evaporation of certain liquids.

25 The device for implementing the process according to the invention is characterised in that it comprises means of vacuum packing a dry form, means of packing an extemporaneous rehydration liquid, and of connection between the said means in order to add, by suction, the liquid to the dry form.

30 According to a preferred embodiment, the means of vacuum packing the dry form are a gastight syringe and the means of packing liquid are a reservoir containing a piston.

35 The syringe is preloaded with the solid form under vacuum, the packing of which allows immediate injection after hydration without agitation, and avoiding the transfer of the solution or suspension through a needle from the preparation reservoir of the liquid to the syringe.

Another advantage of the vacuum-packed devices is that it is thus possible to reduce the volumes of the reservoirs of the liquid and solid whilst increasing the precision of the volume injected.

- 5 In fact, the absence of air makes it possible to fill completely the compartment containing the solid. The volume contained in the liquid compartment may be calculated exactly in order to occupy the volume left empty in the preparation plus losses of the device. But this volume may also be in excess because it is the volume of the empty space in the solid that will determine exactly the quantity of
10 liquid required for rehydration.

The device containing the rehydration liquid is advantageously contained in an leakproof reservoir, the volume of which may fall freely as the liquid is transferred to the reservoir of the solid form under vacuum.

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This may be obtained easily, in particular, with a cartridge or with a pre-filled syringe, the piston of which moves with the movement of the liquid.

- The reservoir may also be composed of a pre-filled flexible plastic bag, the flexible
20 walls of which will follow the movement of the liquid.

The connecting element of the liquid and the vacuum shielded from the ambient air may be composed of a septum, a gate, valve or tap.

- 25 One of the characteristics of the method and of the devices is to reduce the dead volumes. This is achieved not only by reducing the volume of the connecting components (liquid-vacuum) or injection components (needle-syringe) but also by virtue of the static rehydration process which makes it possible to occupy the dead volumes with liquid without active principle, and hence without loss of injection.

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Thus, the connecting component and/or the needle may be loaded with liquid without active principle in order to eliminate losses.

- Moreover, it is possible, by virtue of the same static process, to provide the "liquid
35 piston" without active principle mentioned above, which will occupy the dead volumes of the injection syringe and of the needle after administration, thus making it possible to reduce even further the losses of active principle. This is simply obtained by adding, after freezing the liquid formulation containing the active

principle, a calculated volume of a solution of excipient such as mannitol, which will be frozen and freeze-dried at the same time as the formulation. By virtue of static and rapid rehydration, the two liquids, once re-formed, will hardly mix at all and the liquid without active principle will be able to push all the liquid with active principle out of the syringe and the needle (like a "liquid piston"), which will avoid losses.

In all cases (solution, suspension or dispersion), once the solid form has dried or freeze-dried, if the syringe is closed on the injection side by the connecting component, the needle or a septum, the piston is placed under vacuum with or without a blocking system, for example, inside the freeze-dryer. If the syringe is open, it can be vacuum-packed at the time of packaging under plastic film.

Even if the packing of the closed syringe is carried out beforehand under vacuum, it will be best then to pack this syringe under vacuum in such a way that the packaging, and not the syringe, ensures air-tightness during storage. This constitutes a double safety mechanism and also facilitates monitoring of the integrity of the packaging prior to use (opening).

The product or final form obtained after hydration of the solid may take one of the three forms below:

1) Solutions

The active principle combined, for example, with mannitol, is solubilised in water for injectable preparation; the solution is distributed by volume inside the syringes; the syringes are frozen and freeze-dried according to a conventional process and the solid freeze-dried product is vacuum-packed with the syringe, whether or not the said syringe has been fixed beforehand to the other components of the extemporaneous rehydration device.

2) Suspensions

In the case of sustained-release microspheres, for example, the dose of microspheres is weighed into the syringe. The volume of dispersion liquid is added. The microspheres are then dispersed mechanically in the liquid. Ultrasonics are preferably used for this dispersion operation. The dispersion is then frozen rapidly,

preferably in liquid nitrogen to obtain a homogeneous dispersion of the microspheres in the frozen liquid. The liquid contains the matrix of the freeze-dried product, for example, mannitol. Freeze-drying is carried out to obtain a solid in which the microspheres are suspended by the matrix in the ideal state of homogeneous dispersion of the liquid.

This solid, whether or not it is combined with the components of the automatic device for extemporaneous rehydration, is then vacuum-packed.

3) Dispersion

In the case of a semi-solid implant, for example, the semi-solid Autogel BIM 23014 C, the active principle is weighed out inside a gastight metered-dose syringe.

The product obtained by implementing the process and device according to the invention comprises a dry form for parenteral administration and vacuum-packed inside an injection device also containing a liquid volume, ready to be mixed by suction with the dry form in order to reconstitute the injectable preparation.

The dry form may be a freeze-dried form or a powder obtained after removal of a solvent.

Other features and advantages of the invention will become apparent during the description that follows, given with reference to the attached drawings which illustrate a certain number of embodiments thereof by way of non-limiting examples.

Figure 1 is an elevation of a gastight syringe containing an active principle.

Figure 2 illustrates the compression of the active principle in the syringe of Figure 1.

Figure 3 illustrates the placing under vacuum of the active principle of the syringe of Figure 2.

Figure 4 is a longitudinal elevation of the syringe of Figure 3 connected to a liquid reservoir by way of a valve, the latter being in the closed position.

Figure 5 illustrates the suction of the liquid into the syringe containing the solid after the valve has been opened.

Figure 6 represents a complementary phase of mixing between the liquid and solid
5 by suction of said mixture into the reservoir initially filled with liquid.

Figure 7 illustrates a loading stage of a small syringe from the syringe previously filled and separated from the second syringe.

10 Figure 8 is a view of the small syringe of Figure 7 ready to be connected to a liquid reservoir.

Figure 9 is a view of the syringe of Figure 8 connected to a liquid reservoir with an
interposed valve.

15 Figure 10 is a view of the whole syringe-liquid reservoir unit of Figure 9 packed under vacuum.

20 Figures 11 to 14 illustrate the successive stages of implementation of a first embodiment of the process and device according to the invention.

Figures 15 to 17 are elevations similar to Figures 11 to 14 illustrating the implementation of a second embodiment of the device according to the invention.

25 Figures 18 to 21 illustrate the implementation of a third embodiment of the process and device according to the invention.

Figure 22 is a longitudinal elevation of a fourth embodiment of the device according
30 to the invention.

Figures 23 to 25 show the successive stages of the preparation and vacuum packing of a fifth embodiment of the device according to the invention.

35 Figures 26 to 29 are longitudinal elevations and partial sections illustrating the implementation of a sixth embodiment of the device according to the invention.

Figures 30 to 32 are longitudinal elevations illustrating the implementation of a seventh embodiment of the device according to the invention.

Figures 33 to 36 are views illustrating the implementation of an eighth embodiment of the device according to the invention.

- 5 Figures 37, 38 and 39 illustrate the successive stages of implementation of a ninth embodiment of the syringe device according to the invention.

Figures 40, 41 and 42 are partial elevations illustrating three possible variants of execution of the embodiment of Figures 37 to 39.

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Figure 43 is a partial section and elevation of a tenth embodiment of the device according to the invention.

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Figure 44 is a view similar to Figure 40 of an eleventh embodiment of the device according to the invention.

Figure 45 is a longitudinal section and partial elevation of a twelfth embodiment of the syringe device according to the invention.

- 20 Figure 46 is a longitudinal section and partial elevation of a thirteenth embodiment of the packing device provided by the invention.

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With reference to figures 1 to 10, a description will first be given of an embodiment of the process for preparing an injectable preparation according to the invention, and of the rehydration device under vacuum for implementing said process.

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An active principle 3 is loaded into a syringe 1, fitted with a tap or valve 2 in the position of its injection needle, said active principle having been weighed and brought to a volume approximating or equal to that occupied by the semi-solid form by pressure of the piston 4 (Figure 2) of syringe 1 before or after application of a vacuum. In Figures 2 and 3, it may be assumed, for example, that the active principle 3 is compressed by the piston 3 [sic] borne by its spindle 5, prior to application of a vacuum, which operation is carried out at the stage of Figure 3. Spindle 5 is fitted with a piece 26 for retaining the piston 4 resting on the end of syringe 1, and this because of the vacuum in the volume of the active principle 3.

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Active principle 3 may be pretreated in order to adjust to the final volume and/or to promote subsequent hydration. It is thus possible to calculate its particle size

distribution by grinding, spray-drying or by freeze-drying to a determined concentration.

5 Metered-dose syringe 1 containing the active principle under vacuum 3 is then connected (Figure 4) by the leakproof valve 2 with the same syringe 6 containing a volume 7 of liquid for rehydration of the solid 3, for example, water. This liquid volume 7 is contained in the syringe 6 by the piston 8 and the spindle 9 of this syringe.

10 Then valve 2 is opened (Figure 5) with the result that the liquid 7 passes into the solid 3 by suction under the action of the vacuum, plus, possibly, by a mechanical action on the piston 8. The retaining piece 26 may then be removed.

15 The preparation is thus first mixed in syringe 1, then it is mixed again immediately or after a hydration period by the backward and forward motion from one syringe to the other (Figure 6). This backward and forward motion is obtained by mechanical action on piston 8 and on piston 4, for example, with a syringe push or a hydraulic press.

20 Once homogeneous, the mixture is distributed immediately, or after a rest period, inside small syringes such as 11 of the injection device by volumetric metering from one of the two mixing syringes 1 and 6 which are large in size. If the quantity and precision of metering into each syringe 11 does not allow direct distribution from the syringe for preparation of the mixture, particularly if the mixing syringe 6
25 corresponds to a large volume, an intermediate syringe of smaller diameter is used for distribution.

Syringe 11 may be, for example, one such intermediate syringe. The contents of the large syringe 6 are thus distributed in several intermediate syringes 11 of
30 smaller capacity, each of them then being emptied in a final step into several small syringes of small capacity.

For example, from a batch prepared in 200 ml syringes 6, it is possible to use ten 10 ml syringes in order to load single 0.2 ml doses to the final syringes.

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The final syringes 11 or 12 filled with semi-solid 13 and fitted with their pistons 14 and their spindles 15 (Figure 8) are then freeze-dried and vacuum-packed, then combined (Figure 9) with an automatic device 16 for extemporaneous rehydration.

This device 16 may itself be a syringe containing the liquid 17 and connected to syringe 11 or 12 by a leakproof valve 2.

Finally, the device thus obtained (Figure 9) is packed in a vacuum packaging 18 ready to be used for an injection of the injectable preparation which will be obtained by mixing the liquid 17 and the solid 13 by suction by virtue of the action of the vacuum under which the solid 13 is placed.

In the embodiment of Figures 11 to 14, the dry form 18 is packed in a syringe 19 fixed to an automatic rehydration device 21 containing a volume 22 of liquid, composed of a reservoir containing a piston 23. The freeze-dried product or solid 18 is pre-loaded under vacuum inside syringe 19 before the said syringe is connected with the liquid reservoir 21. The means of connection between reservoir 21 and the syringe 19 are, in the example shown, composed of a connection 28 [sic] comprising a septum 24 in which is inserted the end of an injection needle 25 of syringe 19. Said syringe is also fitted with a piece 26 keeping the spindle 27 and its piston 28 in a suitable position, in view of the vacuum under which the solid 18 is placed. The whole device is vacuum-packed in a flexible packaging 31.

In order to obtain the injectable preparation from the device of Figure 11, the packaging 31 is first removed, then the syringe 19 is pushed by its spindle 27 so as to insert the needle 25 in the septum 24 (Figures 12, 13). When the end of the needle 25 penetrates the volume of liquid 22, said liquid is sucked by the vacuum prevailing in the solid 18 with which it mixes without altering the volume occupied by the solid 18, whilst the piston 23 slides in the direction of syringe 19. After which the user removes piece 26, the reservoir 21 and the cap-septum 29 (Figure 14), and the syringe 19 is ready for use for the injection of the preparation which it contains.

In the example illustrated in Figures 15 to 17, the freeze-dried product or solid 18 pre-loaded under vacuum into syringe 19 is connected to the liquid reservoir 21 (here a cartridge as in the example of Figures 11 to 14) by way of a valve 31, for example, of the quarter-turn type. Syringe 19 is vacuum-packed in a flexible packaging 32 and fixed to a connector 33 in communication with the liquid reservoir 21, the connector 33 being fitted with valve 31.

Extemporaneous rehydration preparation then consists in opening valve 31 so that the liquid 22 passes automatically, by suction, from cartridge 21 to syringe 19

(Figure 16) whilst the piston 23 of cartridge 21 travels towards syringe 19. Cartridge 21 and tap 31 (Figure 17) of syringe 19 are then disconnected in order to fix injection needle 25 to said syringe, the mixture obtained in syringe 19 then being ready to be injected.

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In the embodiment of Figures 18 to 21, the syringe 34 is vacuum packed in a flexible packaging 35 and fixed to a connector 36 in communication with liquid reservoir 37 composed of a cartridge. The connector 36 serves to pierce the plastic packaging 35 (Figure 19) and to fix syringe 34 to the reservoir of liquid (water) 37.

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The connector 36 is pierced with an axial channel 39 such that the piercing of the plastic packaging 35 by the connector 36 brings into communication the volume of liquid 38 with the solid dry form 41, which operation draws into the latter, via connector 36, the liquid 38 (Figure 20), the piston 23 accompanying the displacement of the liquid 38. The reservoir 37 thus empties automatically to rehydrate the solid 41. It is then disconnected from syringe 34 (Figure 21) and the injection needle 25 is fitted to syringe 34.

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In the embodiment of Figure 22, the device comprises a syringe 42 connected by a cap 43 to a cartridge-septum 44 containing the liquid 45. The syringe 42 containing the solid (dry form 46) is fitted with an injection needle 47 introduced and kept in place inside the cap 43 in a packing 48 made of a flexible material such as an elastomer, which keeps needle 47 in place inside the cap 43, opposite the septum 49. The needle 47 is then ready to be inserted in the septum 49 to bring about the passage of liquid 45 into the syringe 42 and thus the rehydration of the solid of active principle 46.

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In the embodiment of the device illustrated in Figures 23 to 25, the syringe 51 is provided with an injection needle 52 engaged in a cap 53 inside of which it is able to slide in order to bring into communication the interior volume of syringe 51 containing the solid 54 with the reservoir or cartridge 55 containing the liquid 56. These two elements are prepared independently and then combined in an extemporaneous rehydration device (Figures 24 and 25) by fixing the cap 53 with the end 55a of cartridge 55 by means of a suitable connection 57 (Figure 25).

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The whole unit is vacuum-packed in a flexible packaging 58, ready for use after removal of this packaging 58, insertion of the needle 52 in the end 55a and suction of the liquid 56 into the solid 54.

The needle 52 is inserted in septum 53a which it pierces completely at the moment of rehydration under vacuum of solid 54 by liquid 56.

5 In the device illustrated in Figures 26 to 29, the process to which the invention relates provides for the addition to the dry form 58 of a layer of excipient 59 which is used subsequent to the injectable preparation as a liquid piston to push the other layers and reduce the losses of active principle during injection.

10 The device comprises, apart from syringe 61 containing the solid active principle 58, a reservoir 62 containing a piston 60 and the rehydration liquid 63 and a cap-septum 64 blocking off the reservoir 62 on the side of syringe 61 and in which is engaged the injection needle 25. The syringe 61 is fitted with piece 26 for retaining its piston 65 and its spindle 27, the piece 26 resting against the end of the body of
15 the syringe.

According to the process, after freezing of the liquid containing the active principle and prior to freeze-drying or drying, a specific quantity of solution of excipient such as mannitol is added to the surface of the frozen liquid. This volume is in turn
20 frozen and the whole unit (58, 59) is then freeze-dried. A volume 59 of freeze-dried product containing only the excipient (mannitol) is thus obtained between piston 65 and the solid 58 of active principle under vacuum. This volume 59, after automatic and static rehydration by piercing of the septum 64 by the needle 25 (Figure 27) and separation of the reservoir 62, will be used to push the liquid form 66 of active
25 principle. At the end of injection, the volume 59 occupies the dead volumes 59a (Figure 29) at the bottom of the syringe 61 and of needle 25.

Thanks to liquid piston 59, practically any loss of active principle is avoided, this being an important advantage because of the cost of said active principle.

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The embodiment of the device illustrated in Figures 30, 31 comprises a liquid reservoir composed of a flexible bag 67 containing the volume of rehydration liquid 68. The bag 67 is connected to a syringe 69 by a stopper 71 fitted with a septum 72 ready to be pierced by needle 25. The syringe 69 containing the solid
35 formulation 74 is vacuum-packed in a flexible envelope 73. The needle 25 allows, by pressure on the piston 28, the formulation under vacuum 74 to be connected with its volume of rehydration liquid 68 (Figure 31).

Once mixing has taken place, the packaging envelope 73 is removed, the bag 67 is separated and the stopper-septum 71 removed, the syringe 69 then being ready for use (Figure 32).

- 5 In the embodiment illustrated in Figures 33 to 36, the device comprises a syringe 75 packed in a vacuum packaging 76 and a reservoir 77 of liquid 78 fitted with a stopper 70. The injection needle 25 forming a connector by way of its support 79 is introduced beforehand into a cartridge-reservoir 77 through stopper 70. The reservoir 77 may be connected to syringe 75 by piercing packaging 76 by way of
10 the connection 79 (Figure 34).

- Once this operation has been carried out, the volume of liquid 78 and the solid formulation 81 are brought into communication, with the result that the liquid is drawn into syringe 75 (Figure 35). After which it is sufficient to remove the cartridge
15 77, its stopper 70, and the plastic packaging 76 in order to render the syringe 75 ready for use (Figure 36). In this embodiment, the needle 25 and its support 79 form the connector proper, the needle 25 being introduced beforehand into the stopper 70 of cartridge 77.

- 20 In the embodiment represented in Figures 37 to 39, the vacuum packing and rehydration device for the injectable preparation comprises a syringe 81 with a needle 116 enveloped by a stopper 110. This syringe comprises two compartments 82, 83 containing respectively the liquid 82a and the solid formulation 83a. These compartments are delimited by a first piston 84 integral with an activating spindle
25 85 and by three other independent pistons 86, 87, 88 juxtaposed between the piston 84 and the injection orifice 89. These three pistons 86-88 are independent, that is, not fixed together.

- The syringe 81 is loaded with a liquid containing the active principle 83. The
30 preparation is then freeze-dried and the freeze-dried product 83a is vacuum-packed in the bottom of the syringe with the three flat and independent pistons 86, 87, 88. The volume of rehydration liquid 82a is then added to syringe 81 then the piston 84 with its spindle 85, positioned behind the liquid 82a as for a bicompartmental syringe. Piston 84 is made of a standard non-rigid rubber.

- 35 Drawing on piston 84 by means of its spindle 85 causes suction of the three flat pistons 86-88 (Figure 38) which pivot and bring into communication the solid 83a and liquid 82a forms. During this suction and the sliding of piston 84, the solid and

liquid forms mix and are mixed by the movement of pistons 86-88. The liquid (for example, water) passes automatically into the solid and reconstitutes the preparation to a liquid of the active principle, which may then be immediately injected (Figure 39).

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This system avoids the specific by-pass syringe and may be implemented by means of a standard syringe.

10 A flat positioning of the three independent pistons 86-88 in the syringe could prevent good mixing of the liquid/freeze-dried product but the arrangement of the three pistons avoids this risk. The maximum angle of rotation of the pistons is in relation to the distance between the pistons at rest. Said pistons are sufficiently close to one another to avoid a 90° rotation, and as soon as the two chambers 82, 83 communicate, the pistons 86-88 no longer undergo a force likely to displace
15 them to the extent that they come into contact with the injection piston 84.

However, for greater security, it is possible, as a variant, to provide between the pistons 86-88 flexible bonds which join them in pairs. These bonds may be centred, such as bonds 120 and 121 (Figure 40) or asymmetrical: bonds 122, 123 (Figure
20 41) or situated on the same side of the axis of the syringe 81: bonds 124, 125 (Figure 42).

Such arrangements make it possible to fix the pistons by a flexible bond, whilst leaving each piston free to pivot.

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30 The device represented in Figure 43 comprises a syringe 91 pre-filled with solid under vacuum 92, a cartridge 93 containing the liquid 94 and fitted with a septum 95, and a connector 96 in communication between syringe 91 and the reservoir 93. The injection needle 25 is introduced into connector 96, ready to perforate septum 95.

As soon as the terminal bevel of needle 25 is inserted in septum 95, the solid form 92 and the liquid form 94 are brought into communication and the liquid 94 is sucked into the dry formulation 92 of the syringe 91.

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In the embodiment of Figure 43 shown in Figure 44, the piston 97 of the liquid reservoir 93 is fitted with a spindle 98 after the liquid 94 has been introduced into

said reservoir 93, this arrangement having the advantage of avoiding any risk of faulty handling.

In the embodiment of Figure 45, the device comprises a syringe 99 of the two-compartment type 101, 102 separated by a central by-pass 103 obtained by a local lateral recess of the wall of the syringe leading to an increase in the cross section at that location. One of the two compartments, namely compartment 101 having to contain the rehydration liquid 101_a, contains two independent pistons 104, 105 between which the liquid may be placed.

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The process for implementing the injectable preparation by means of this device is as follows.

15 Into the compartment 102 contained between the by-pass 103 and the injection needle 25, a liquid is loaded and frozen, said liquid containing the active principle 102_a, and a solution of excipient 106 is added at by-pass 103 and then in turn frozen. The excipient may be a cold dilute solution of mannitol. The whole unit is freeze-dried under vacuum, the first piston 104 is arranged on the excipient under vacuum 106, the second compartment 101 is filled with liquid 101_a, the second piston 105 is placed on liquid 101_a, the spindle (not shown) of the second piston 105 is installed.

25 By means of this second piston 105, a pressure is exerted which crushes the excipient freeze-dried under vacuum 106, with the result that the first piston 104 slides and reaches the level of by-pass 103; the liquid 101_a then passes automatically via the by-pass 103 into the first compartment 102 and rehydrates the solid under vacuum 102_a, and finally the preparation ready to be injected is obtained.

30 The advantage of the system compared with the conventional use of by-passes is to avoid non-loaded re-solution or re-suspension volumes and to make it possible to fill the wasted volumes at the by-pass, the pistons at the bottom of the syringe and of the needle with a liquid preparation without active principle, provided that the rehydrated active principle does not become mixed with the rehydrated excipient before injection. This is the case, for example with microspheres of PLGA (polylactic-glycolic acids).

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It is thus possible to load, for example, a quantity of 2 ml and more into a by-pass syringe 99 initially intended only for 1 ml.

5 The device illustrated in Figure 46 comprises a syringe 107 fitted with an injection needle 25 and containing a cartridge-septum 108. This latter is fitted with a short needle 109 blocked off by insertion in an injection piston 111 of syringe 107. The cartridge-septum 108 may contain the rehydration liquid 112 and the syringe 107 may contain the dry form 113.

10 The cartridge-septum 108 is fitted with a piston 114 and a spindle 115 of sufficient length to be able to use the cartridge-septum 108 as a spindle of the injection piston 111. The cartridge-septum 108, which is the equivalent of a small syringe with its short needle 109, is pre-filled with liquid 112 and positioned in the barrel of the syringe 107. The short needle 109 is blocked off by insertion in the injection
15 piston 111. Activation of the device is obtained by inserting the needle 109 of the cartridge-septum 108 in the injection piston 111. This insertion makes it possible to pass the liquid 112 into the reservoir of the syringe 107 contained between the injection piston 111 and needle 25 and which contains the solid under vacuum 113, which operation ends in the reconstitution of the injectable preparation.

20 In this type of embodiment, the injection piston 111 acts as a septum or barrier between the volume of liquid 112 and the solid under vacuum 113. Thus, the device as a whole is in the same syringe 107, and the needle 25 is not used to pierce the septum and to serve as a connecting element.

25 In order to obtain the dry form, in the case of a semi-solid, the liquid dispersion is loaded into the syringe 107, freeze-dried or dried and vacuum-packed with the injection piston 111.

30 The product obtained by implementing the device and the process which have just been described in the various embodiments illustrated in the drawings comprises, in a general manner, a dry form for parental administration and vacuum-packed inside an injection device also containing a liquid volume, ready to be mixed by suction with the dry form in order to reconstitute the injectable preparation.

35 The dry form may be a freeze-dried form or a powder obtained after removal of a solvent.

The dry form may contain the active principle alone, or the active principle and an injectable excipient, for example, mannitol.

5 The volume containing the dry form under vacuum is equal to the volume occupied by the injectable preparation obtained after mixing the dry form with the necessary liquid.

10 The liquid may be water, or an aqueous medium, or an organic solvent with or without water, or an anhydrous liquid or injectable oil.

The injectable preparation obtained may be a liquid solution, or a solid suspension in a liquid, or a gel or a semi-solid dispersion.

15 The vacuum required for the process of preparation according to the invention is a vacuum sufficient to draw a stream of reconditioning liquid prior to injection (hydration or other) into the whole of the volume to be injected without leaving air bubbles, dead spaces or a zone of product that is still dry.

20 According to conventional processes for packing dry or freeze-dried injectable products, it is possible to use a "partial vacuum" of air or inert gas (nitrogen) before closing the reservoir containing the dry form in order to avoid excess pressure after stoppering.

25 This partial vacuum may be offset by stoppering with a return to atmospheric pressure, or a pressure slightly below atmospheric may be maintained in the bottle or in the syringe in order to prevent excess pressure during the addition of the liquid medium.

30 It is possible, of course, to stopper a bottle under a "total vacuum" after freeze-drying, but this does not have any advantage for reconditioning the solid apart from the precise case of the invention where the solid occupies the entire volume under vacuum, and where the liquid comes to occupy exactly this volume under vacuum directly in the injection device (syringe).

35 The partial vacuum may be between 0.9 and 0.6 atmospheres. The total vacuum may be defined as the vacuum corresponding to less than 1/2 atmosphere and advantageously to low pressures of 1/10 atmosphere and less.

This total vacuum may also be defined as the vacuum obtained by a vacuum pump used, for example, for a freeze-dryer. A rotary pump with a two-stage valve may reach $1 \cdot 10^{-3}$ mbar or 1 μ bar.

- 5 The vacuum used for the invention may thus be less than 100 mbar or advantageously less than 10 mbar or even less than 0.1 mbar.



CLAIMS

1. A process for preparing an injectable preparation, characterised in that a dry form (3) of an active principle under vacuum and a liquid (7) are prepared and the said liquid is introduced into the dry form by suction by virtue of the action of the vacuum in order to form the said injectable preparation.

5

2. A process for reconstituting an injectable preparation, characterised in that a volume of dry form of an active principle under total vacuum and a liquid are prepared, and said liquid is introduced into said volume of dry form by suction by virtue of the action of the total vacuum in order to form the said volume of the said preparation.

10

3. A process according to claim 2, wherein the total vacuum is a vacuum lower than 100 mbars.

15

4. A process according to claim 2, wherein the said total vacuum is a vacuum lower than 10 mbars and advantageously lower than 0.1 mbar.

20

5. A process according to one of claims 2 to 4, characterised in that the dry form occupies the entire volume of the means of vacuum packing which constitute an injection device after extemporaneous rehydration.

25

6. A process according to claim 1, wherein a layer of excipient (59) is added to the dry form, said layer being used subsequent to the injection preparation as a liquid piston to push the other layers (58) and to reduce the losses of active principle during injection.

30

7. A process according to claim 6, wherein the dry form (58) is packed in a syringe (61) fixed to an automatic rehydration device (62, 64), characterised in that, in order to prepare the dry form, a liquid containing the active principle is frozen, a specific quantity of excipient solution (59) is added to the surface of the frozen liquid, said excipient solution is frozen, the whole unit is freeze-dried, the result being thus to obtain, between the piston (65) of the syringe and the solid (58) of active principle under vacuum, a volume (59) of freeze-dried product containing only the excipient which, after automatic rehydration and movement of the piston in order to empty the syringe, occupies at the end of injection a dead volume at the bottom of the syringe and of the injection needle (25) (Fig. 26-29).

35





8. A process according to one of claims 1 to 7, wherein the dry form is prepared in a syringe (99) of the by-pass type constituted by an increase (103) in cross-section in a median zone of the syringe, characterised in that a liquid (101a) containing the active principle is loaded into and frozen in a compartment (102) contained between the by-pass and an injection needle, a solution of excipient (106) is added at the by-pass, which solution is then frozen in turn, the whole unit is freeze-dried under vacuum, a first piston (104) is arranged on the excipient under vacuum, the second compartment (101) is filled with liquid (101a), a second piston (105) is placed on the liquid, the spindle of the second piston (105) is installed, a pressure is exerted by this second piston which crushes the freeze-dried excipient with the result that, when the first piston reaches the by-pass, the liquid automatically passes via the by-pass into the first compartment and rehydrates the solid under vacuum, and finally a preparation ready for injection is obtained (Fig. 42).

9. A process according to claim 1, characterised in that the dry form (3) being composed of active principle with or without injectable excipient, the dry form is prepared by removing an aqueous or organic solvent after having distributed the dry form obtained in various precise volumes into the devices (11) which are then closed under vacuum (Fig. 1-7).

10. A process according to claim 9, characterised in that the solvent is mixed beforehand with the constituents of the dry form (3) such that the said constituents occupy the same volume as in the final form, the dry form under vacuum thus occupying the same volume as the final form obtained after automatic hydration by a corresponding volume of liquid, exactly predetermined.

11. A process according to claim 9, characterised in that the liquid and the dry form are mixed by the backward and forward motion between two syringes (11, 16) through a connector (Fig. 8-9).

12. A device for implementing the process according to any one of claims 1 to 11, characterised in that it comprises means of vacuum packing a dry form (18), means of packing a liquid (22) for extemporaneous rehydration and means of connection (29) between the said means in order to add, by suction, the liquid to the dry form.





13. A device according to claim 12, characterised in that the said dry form occupies the entire volume of the said means of vacuum packing, which constitute the injection device after said extemporaneous rehydration.

5

14. A device according to claim 12, characterised in that the means of vacuum packing a dry form are a gastight syringe (11, 12), and said means of liquid packing are a reservoir (16) containing a piston (10).

10

15. A device according to claim 12, characterised in that the means of connection comprise either a septum (29) and an injection needle (25) or a tap (2) (Fig. 10-11).

15

16. A device according to claim 12, characterised in that the syringe is vacuum-packed in a flexible packaging (8, 31) and fixed to a connector in communication with the liquid reservoir (16).

20

17. A device according to claim 12, characterised in that the syringe (19) is provided with an injection needle (25) engaged in a cap (29) inside of which it is able to slide in order to bring the syringe into communication with the liquid reservoir (21) and in that the whole unit is packed in a vacuum packaging (3) (Fig. 11).

25

18. A device according to claim 12, characterised in that the liquid reservoir is a flexible bag (67) linked by a stopper-septum (71) to the syringe (69), this latter being vacuum-packed (Fig. 30-32).

30

19. A device according to claim 14, characterised in that the syringe (75) is packed in a vacuum packaging (76) and provided with an injection needle (25) forming a connector, introduced into the liquid reservoir through a stopper (70) and joined to the syringe through the packaging (76) (Fig. 33-36).

35

20. A device according to claim 14, characterised in that the syringe (81) comprises two compartments (82, 83) delimited by a first piston (84) integral with an activating spindle (85) and by independent pistons, for example three (86, 87, 88) (Fig. 37-39), optionally linked together.

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21. A device according to claim 14, characterised in that the syringe (99) is of the two-compartment type (101, 102) separated by a central by-pass (103) and in that one of the two compartments, designed to contain the rehydration liquid (101a), contains two independent pistons (104, 105) between which may be placed the liquid (Fig. 42).

22. A device according to claim 14, characterised in that the syringe (107) contains a capsule-septum (108) provided with a needle (109) blocked off by insertion in an injection piston (111) of the syringe, the capsule-septum being able to contain the rehydration liquid (112) and the syringe being able to contain the dry form (113) (Fig. 43).

23. A device according to claim 14, characterised in that the cartridge-septum is fitted with a piston (114) and a spindle (115) of sufficient length to be able to use the cartridge-septum as the spindle of the injection piston (111), after insertion of the needle (109) of the cartridge-septum in the injection piston in order to pass the liquid contained in the cartridge-septum into the reservoir of the syringe contained between the injection piston and the injection needle and containing a solid under vacuum, which operation makes it possible to reconstitute the injectable preparation (Fig. 43).

24. A device according to claim 14, characterised in that the syringe (42) is joined by a cap (43) to a cartridge-septum (44) containing the liquid (45), the syringe being fitted with an injection needle (47) introduced and kept in place inside the cap, opposite the septum (49) of the cartridge-septum, ready to be inserted in the septum in order to bring about rehydration of the solid (46) of active principle contained in the syringe (Fig. 22).

25. A product obtained by implementing the process according to one of claims 1 to 11 by means of the device according to any one of claims 12 to 24, comprising a dry form (3) for parenteral administration and vacuum-packed inside an injection device (11, 16) also containing a liquid volume (17) ready to be mixed by suction with the dry form in order to reconstitute the injectable preparation.

26. A product according to claim 25, characterised in that the said dry form occupies the entire volume of the said means of vacuum packing.





27. A product according to claim 25, characterised in that the dry form (13) is a freeze-dried form or a powder obtained after removal of a solvent.

5 28. A product according to claim 25, characterised in that the dry form (13) contains the active principle alone or the active principle and an injectable excipient (59), for example, mannitol

10 29. A product according to one of claims 25 to 28, characterised in that the volume containing the dry form under vacuum (13) is equal to the volume occupied by the injectable preparation obtained after mixing the dry form with the necessary quantity of liquid.

15 30. A product according to one of claims 25 to 29, characterised in that the liquid (17) is water, or an aqueous medium, or an organic solvent with or without water, or an anhydrous liquid, or injectable oil.

31. A product according to one of claims 25 to 29, characterised in that the injectable preparation (20) is a liquid solution, or a solid suspension in a liquid, or a gel, or a semi-solid dispersion.

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