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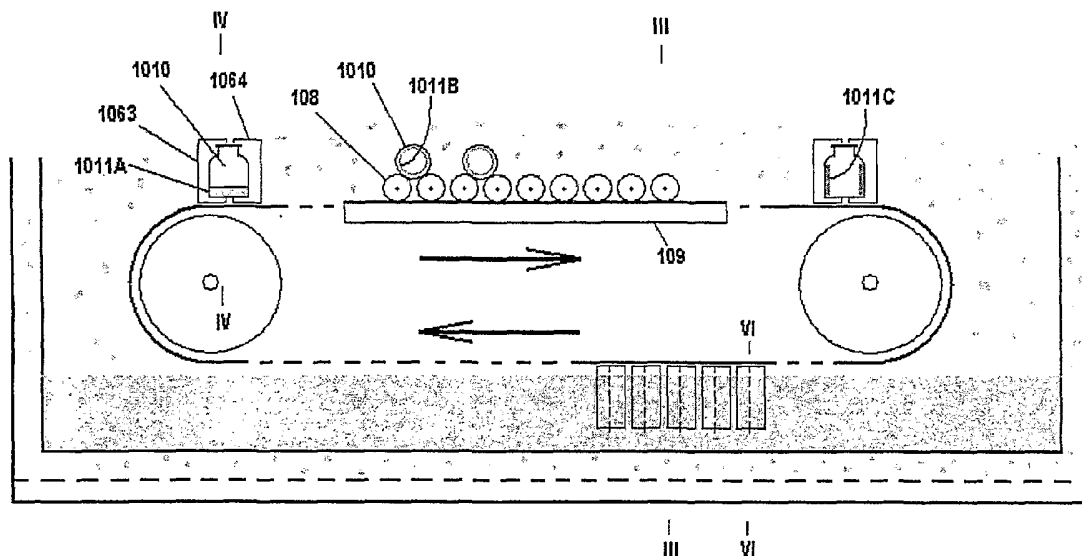
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(54) Title: APPARATUS FOR SHELL FREEZING A LIQUID CONTENT IN A CONTAINER



(57) Abstract: An apparatus for shell freezing a liquid content in a container, comprising an endless loop conveyor (100) having a conveying length (101) adapted to convey plural containers such as pharmaceutical vials (1010), incorporating plural rollers (106) to spin the containers as they are conveyed by the conveyor (100), and a return length (102), along at least part of the return length (102) the rollers (106) are immersed in a cooling liquid at a temperature below the freezing point of the liquid content of the containers, and along the conveying length (101) the rollers (106) are entirely above the surface of the cooling liquid. A preferred cooling liquid is liquid nitrogen (201), the evaporating vapour (203) of which can be used to shield vials (1010) on the conveying length (101).



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

APPARATUS FOR SHELL FREEZING A LIQUID CONTENT IN A CONTAINER

This invention relates to an apparatus for shell freezing medicament products in vials in preparation for lyophilisation, and to a method for shell freezing medicament products in vials in preparation for lyophilisation which can be performed
5 using this apparatus.

Medicament products such as drugs and vaccines are often lyophilised, i.e. an aqueous solution of the product is frozen, then exposed in the frozen state to vacuum (herein the term "vacuum" includes any sub atmospheric pressure sufficient to cause evaporation of frozen liquid content) to evaporate off the water at low temperature to
10 leave a dry product for reconstitution. Often this process is performed with the solution in a vial with an open mouth or a stopper which allows water vapour to escape.

Numerous machines are known for performing lyophilisation or various stages of the lyophilisation process. One such machine is disclosed in WO-A-0812411,
15 which uses shell freezing. EP-A-0048194 discloses the process of so called "shell freezing" in which the vial is spun about its cylindrical axis to spread the liquid content by centrifugal force around the vial sides in a thin layer to create a large surface area before freezing. The large surface area facilitates evaporation. In EP-A-0048194 vials in a horizontal orientation are spun on a roller conveyor, and whilst on
20 the conveyor the vials are partly immersed in cold ethanol.

It is an object of this invention to provide an improved apparatus, and process which can be performed by this apparatus, for shell freezing, suitably as part of a lyophilisation process. Other objects and advantages of the present invention will be apparent from the following description.

25 According to this invention an apparatus for shell freezing a liquid content in a container is provided, the apparatus comprising an endless loop conveyor having a conveying length adapted to convey plural containers in a conveying direction and incorporating plural rollers to spin the containers as they are conveyed by the conveyor, and a return length, characterised in that the return length of the conveyor is
30 configured such that along at least part of the return length at least part of the rollers is immersed in a cooling liquid at a temperature below the freezing point of the liquid

content of the containers, and the conveying length is configured such that along the conveying length the rollers are entirely above the surface of the cooling liquid.

A preferred apparatus of this invention is adapted to convey and spin conveyors being pharmaceutical vials containing a liquid content which is an aqueous solution or suspension of a drug compound or vaccine, to thereby spread the liquid content by centrifugal force around the vial sides in a thin layer to create a large surface area before freezing, and to shell freeze this liquid content in preparation for lyophilisation, i.e. exposure in the frozen state to vacuum to evaporate off the water at low temperature to leave a dry product for reconstitution. Typically a pharmaceutical vial has a cylindrical body and a cylindrical neck region terminating at its mouth opening, with an internal step between the body and the neck, so that when the vial is arranged horizontally it can hold liquid content without it spilling out. Suitable rotation speeds to spread the liquid content of a container such as a vial into a thin layer around the interior of the container by centrifugal force may be determined experimentally.

This preferred form of the apparatus is preferably adapted to convey plural vials of this generally cylindrical shape in a conveying direction which is transverse, e.g. perpendicular, to their longitudinal cylindrical axis. Preferably in this apparatus this axis is horizontal i.e. the vials are conveyed horizontally with their cylindrical axis aligned across the conveying direction.

In this preferred form of the apparatus such vials are preferably spun about their longitudinal cylindrical mouth-base axis as a rotation axis, aligned horizontally across the conveying direction to thereby form the liquid content into a layer around the sides of the vial in a manner conventional in the art of shell freezing.

Rollers are provided in the apparatus of this invention to spin containers such as vials as they are conveyed by the conveyor comprises plural rollers comprising part of the conveyor, which are rotated about a rotation axis as the conveyor conveys the containers, and which are in contact with the containers so as to impart rotation to the containers. Preferably such rollers are arranged with their axis of rotation aligned horizontally across the conveying direction, preferably perpendicular to the conveying direction. For example with the rollers arranged with their rotation axes horizontal, a vial may rest on a roller, preferably on a pair of rollers which are adjacent in the

conveying direction, with the rotation axis of the vial in a plane between the rotation axes of the rollers, and the rotation of the rollers imparts rotation to the vial resting thereon.

In the apparatus of the invention the containers and their liquid content are cooled to below the freezing point of the liquid content by contacting the containers, such as vials, with cold rollers at a temperature below the freezing point of the liquid content, and preferably having a high heat conductivity, e.g. cold metal rollers. For example the rollers may be made of stainless steel. As the cold rollers rotate in contact with the containers, e.g. vials, to spin them, at the same time they withdraw heat from the containers to cool them and their contents and to freeze the liquid content.

Therefore a preferred construction of apparatus of this invention comprises the features that:

the conveyor is adapted to convey plural cylindrical vials containing a liquid content which is an aqueous solution or suspension of a drug compound or vaccine, in a horizontal conveying direction which is perpendicular to their longitudinal cylindrical axis,

the conveyor incorporates plural rollers comprising part of the conveyor, which are rotated about a rotation axis aligned horizontally across the conveying direction as the conveyor conveys the vials, the rollers adapted such that a conveyed vial rests on a pair of rollers which are adjacent in the conveying direction such that the rotation of the rollers imparts rotation to the vial resting thereon,

the rollers are cooled by their immersion in the cooling liquid such that along the conveying length they are at a temperature below the freezing point of the liquid content, to thereby withdraw heat from the containers to cool them and their contents and to freeze the liquid content.

Some preferred features of construction of the apparatus of this invention will now be described.

Construction of the Conveyor

Preferably the conveyor is configured as an endless loop conveyor, having a conveying length which conveys the containers in the conveying direction, and a return length along which the conveyor moves in the opposite return direction to the conveying direction.

Preferably the conveyor is configured so that the conveying length is above the return length, and the return length may also move horizontally below the conveying length. Such a configuration conveniently enables a construction in which along the return length the rollers are immersed in the cooling liquid, and the conveying length
5 is entirely above the surface of the cooling liquid.

Such a conveyor may comprise an endless chain of linked mountings for plural rollers upon which the rollers are rotatably mounted. For example a roller may be provided with a spindle extending in its rotation axis direction, and a mounting may comprise a bearing upon which the spindles are rotatably mounted, aligned transverse
10 to the conveying direction. The spindle or roller may be configured so that as it moves in the conveying direction it engages with a track alongside the conveyor, so that the engagement causes the spindle and hence the roller to rotate. For example the spindle may be provided with a toothed pinion to engage a toothed rack alongside the conveyor. Alternatively the apparatus may be provided with means to drive the rollers
15 to cause them to spin, for example the spindle may be provided with a toothed pinion, and a rack or a driven screw may be arranged alongside the conveyor to engage and drive the pinion. Other ways to cause such rollers to rotate will be apparent to those skilled in the art. As mentioned above the rotation speed of such rollers may be determined experimentally.

20 The conveyor may be supported at upstream and downstream positions by guide wheels in a generally conventional manner, and may be driven in a generally conventional manner so that the upper conveying length moves in the conveying direction by rotating one or more such guide wheels with a motor, typically an electric motor. Such guide wheels are suitably rotatably mounted with their rotation axis
25 horizontal.

Cooling the Rollers.

A suitable cooling liquid is any substance which is liquid at a temperature below the freezing point of the liquid content of the containers, preferably the liquid being non-inflammable, non-toxic and environmentally safe. Suitably the cooling
30 liquid is a liquid gas. A preferred cooling liquid is liquid nitrogen which is typically at a temperature of -196°C. Immersion in liquid nitrogen can cool a metal roller to ca. -196°C.

For example over at least part of the return length the conveyor, or part at least of the rollers, may dip into the cooling liquid such as liquid nitrogen. If the cooling liquid is a liquefied gas such as liquid nitrogen, at least part of the rollers, e.g. along the conveying length, may also be exposed to cold vapour from evaporating cooling liquid. For example a trough may be provided below the conveying length, configured such that the return length, or part at least of the rollers, may dip into cooling liquid such as liquid nitrogen contained therein. Such a trough may be elongate and may extend the entire length of the conveyor. Such a trough may also be configured relative to the conveying length of the conveyor so that cold vapour such as gaseous nitrogen evaporating from liquid nitrogen in the trough forms an atmosphere around the upper conveying length of the conveyor. This configuration allows the vapour, e.g. gaseous nitrogen to shield the conveying length of the conveyor from environmental contamination, which is important if the vials contain pharmaceutical products which are to be maintained sterile. In particular such a shield of cold gaseous vapour can shield the containers from moist ambient atmosphere, and thereby reduce the likelihood of frost formation on and within the containers. This may be achieved by providing the trough with upwardly extending sidewalls of a height sufficient that cold vapour evaporating from the cooling liquid forms a cloud around the upper conveying length. To assist in maintaining sterility a flow of purified air, e.g. Class A or higher may be directed around the conveying length of the conveyor, suitably downwardly, in a well known manner.

Such a trough for containing the cooling liquid, especially a liquefied gas such as liquid nitrogen needs to be insulated from ambient temperature. Numerous methods of insulation are known. In a preferred construction the trough may be double walled with a void between the walls, and cold vapour evaporating from the cooling liquid in the trough may be allowed to flow into this void between the walls, to both provide insulation and provide a means of removal of the vapour. For example such a double walled arrangement may comprise an inner trough containing liquid nitrogen, and an outer trough, with the void between the inner and outer trough, so that nitrogen gas can spill over from the inner trough and descend between the walls of the inner and outer troughs, and an outlet means, e.g., an exhaust manifold may be provided in the outer trough to remove the nitrogen gas.

In a preferred embodiment the conveyor is constructed so that along the return length rollers are immersed into the cooling liquid with their rotation axis vertical. This orientation of the rollers can facilitate the use of a relatively deep but narrow
5 trough of cooling liquid, which can help to reduce evaporation loss of the cooling liquid.

The construction described above provides an advantage over for example EP-A-0048194 that the vials do not contact the cooling liquid, and therefore the risk of contamination of the interior of the vial is reduced. By the use of liquid nitrogen as a
10 cooling liquid the rollers can be made so cold that heat transfer from the vial to the rollers is rapid without any need for the vial to contact the cooling liquid. Further the use of a liquefied gas like liquid nitrogen as cooling liquid enables the shielding of the cooled vials from environmental moisture and other contamination by the cloud of cold vapour.

15 **On-loading and off-loading.**

The conveyor is preferably provided at an upstream end with on-loading means to load containers such as vials onto the conveyor, and at a downstream end with off-loading means to remove the containers, containing their frozen content.

It is preferred that the on-loading means is configured to load containers such
20 as vials onto the conveyor in a vertical orientation, i.e. with their mouth uppermost. Therefore in a preferred construction of the apparatus the conveyor has an on-loading position at which the plural rollers have their rotation axis aligned vertically across the conveying direction, and means to present plural vials to the conveyor, adapted such that a vial presented to the conveyor is received between a pair of rollers which are
25 adjacent in the conveying direction. As the rollers move downstream in the conveying direction from this on-loading position the conveyor may be configured so that the rollers move, e.g. rotate about a rotation axis parallel to the conveying direction and perpendicular to their conveying length, so that their rotation axis becomes aligned horizontally across the conveying direction as described above. This may be achieved
30 by mounting the rollers on the conveyor such that the rollers can pivot about an axis parallel to the conveying direction so that their rotation axis can pivot between the vertical and horizontal alignments.

Whilst the rollers have their rotation axis other than aligned horizontally across the conveying direction the rollers need not rotate about their rotation axis, so that the containers e.g. vials in contact with them do not consequently spin. Preferably the rollers move in the conveying direction at a sufficient speed that all or the bulk of the content of the containers is still liquid by the time the rollers adopt their horizontal orientation.

Whilst the rollers have their rotation axis other than aligned horizontally across the conveying direction it may be necessary to support containers such as vials in contact with the rollers until gravity holds the containers down in contact with the rollers when the rollers assume their horizontal alignment. The apparatus may be provided with a suitable supporting means, such as a rail adjacent to the conveyor.

Suitably containers such as vials may be loaded onto the conveyor at this loading position by a conventional means, preferably for example a rotating star wheel having notches in its perimeter to receive containers such as vials in their vertical orientation from for example a conventional loading tray, and to rotate them into a position where they are adjacent to the conveyor and received by the conveyor. Preferably two such star wheels may be provided in series to receive vials from a loading tray and to present them to the conveyor, i.e. comprising a first star wheel which receives containers from a loading tray, and which presents the containers to a second star wheel which in turn presents the containers to the conveyor. In such an arrangement the second star wheel may be mounted so as to be capable of some limited movement relative to the conveyor so as to accommodate to any stresses experienced by the containers as they are received by the conveyor, so as to avoid breakage of fragile glass vials.

It is preferred that the off-loading means is also configured to off-load containers such as vials from the conveyor in a vertical orientation. Therefore in a preferred construction of the apparatus the conveyor has an off-loading position at which the plural rollers have their rotation axis aligned vertically across the conveying direction, and means to receive plural vials from the conveyor, adapted such that a vial is received from the conveyor from a pair of rollers which are adjacent in the conveying direction. As the rollers move upstream in the conveying direction toward this off-loading position the conveyor may be configured so that the rollers move, e.g.

rotate about a rotation axis parallel to the conveying direction, so that their rotation axis becomes aligned vertically across the conveying direction as described above. As with the on-loading position whilst the rollers have their rotation axis other than aligned horizontally across the conveying direction the rollers need not rotate about their rotation axis, so that the containers e.g. vials in contact with them do not consequently spin. Similarly as at the on-loading position whilst the rollers have their rotation axis other than aligned horizontally across the conveying direction it may be necessary to support containers such as vials in contact with the rollers, and the apparatus may be provided with a suitable supporting means, such as a rail adjacent to the conveyor.

Suitably containers such as vials may be loaded off the conveyor at this off-loading position by a conventional means, preferably for example a rotating receiving star wheel having notches in its perimeter to receive containers such as vials in their vertical orientation from the conveyor and to deliver them to a conventional receiving tray. Preferably a further star wheel is provided on the opposite side of the conveyor from this receiving star wheel, and having radially extending fingers which penetrate between the rollers to push containers such as vials away from the conveyor and into the notches of the receiving star wheel.

To assist continuous operation of the apparatus the apparatus may be provided with plural receiving trays so that when one is full it may be replaced by another. Preferably the receiving tray is kept cool at a temperature below the freezing point of the liquid content so that the liquid content remains frozen whilst the containers are waiting on the receiving tray. Heat exchanger means such as cooling tubes may be used to achieve this. When the apparatus incorporates the above-mentioned trough of a cooling liquid which is a liquid gas such as liquid nitrogen, a suitable construction of cooling means comprises a tray upon which containers such as vials may be received, and means to expose the underside of the tray to cold vapour of the evaporating cooling liquid. For example a plate may be situated underneath but in close proximity to this tray so there is a narrow space between the tray and the plate, and liquid nitrogen may be introduced into this space to thereby cool the tray and maintain the tray at a temperature below the freezing point of the liquid content.

The apparatus of the invention may comprise part of an overall apparatus for lyophilisation of medicament in containers such as vials, wherein the apparatus as described above is provided in combination with a means to apply vacuum to cause evaporation of frozen liquid content. Conventional known vacuum chambers may be used.

The invention also provides a process for shell freezing a liquid content in a container is provided, comprising the use of an apparatus as described above. Suitably in this process plural containers are conveyed on a conveyor adapted to convey plural containers in a conveying direction, the apparatus incorporating means to spin the containers as they are conveyed by the conveyor, and the apparatus incorporating means to cool the containers and their liquid content to below the freezing point of the liquid content. Preferably the process is applied to vials as described above, and preferred features of such an apparatus for use in the process of the invention are as described above.

Preferably the process is one in which plural cylindrical vials containing a liquid content which is an aqueous solution or suspension of a drug compound or vaccine are conveyed by a conveyor adapted to convey such vials in a conveying direction which is transverse, e.g. perpendicular, to their longitudinal cylindrical axis, and is horizontal,

the conveyor incorporating plural rollers comprising part of the conveyor, which are rotated about a rotation axis aligned horizontally across the conveying direction as the conveyor conveys the vials, the rollers adapted such that a conveyed vial rests on a pair of rollers which are adjacent in the conveying direction such that the rotation of the rollers imparts rotation to the vial resting thereon,

the rollers being at a temperature below the freezing point of the liquid content, to thereby withdraw heat from the containers to cool them and their contents and to freeze the liquid content.

The invention will now be described by way of example only with reference to the accompanying drawings in which:

Fig. 1 shows the overall schematic configuration of an apparatus of this invention.

Fig. 2 shows the overall schematic configuration of an apparatus of this invention with vials loaded on the conveyor.

Fig. 3 shows a cross section across the conveyor of Fig. 1

Fig. 4 shows how vials are loaded onto and transported on the conveyor of

5 Figs 1 and 2.

Fig. 5 shows a schematic plan view of the conveyor of Figs. 1 and 2.

Fig. 6 shows the cooling of the rollers of the conveyor.

Fig. 7 shows in more detail the mounting of the rollers.

Fig. 8 shows in more detail the overall construction of the conveyor.

10 Fig. 9 shows a rack and pinion system to spin the rollers

Fig. 10 shows a more detailed plan view.

Parts shown in Figs. 1-10 are identified below.

100 conveyor 100 (generally)

101 upper conveying length

15 101A upstream end

101B downstream end

102 lower return length

103, 104 guide wheels

105 mountings

20 106, 1061, 1062, 1063, 1064 plural rollers

107 spindle

108 toothed pinion gear

109 rack

1010 vial

25 1011 liquid content

1010A vial body

1010B vial neck

1010C vial mouth opening

1010D internal step

30 1011 liquid content

1012 guide rail

1013 guide rail

- 200 trough
- 201 liquid nitrogen
- 202 side walls of trough
- 203 gaseous nitrogen
- 5 204 flow of purified air
- 205 outer wall
- 206 void
- 207 exhaust manifold
- 300 on-loading system
- 10 301 loading table
- 302 first star wheel
- 303 second star wheel
- 400 off-loading system
- 401 receiving star wheel
- 15 402 further star wheel
- 403 receiving tray
- 404 receiving tray
- 405 plate
- 1015 side plates
- 20 1016 drive wheel
- 1017 pivot axle
- 1018 – 1022 motors
- 1023, 1024 support wheels

Referring to Figs. 1, 2 and 3, this shows an overall perspective schematic view of the architecture of an apparatus of this invention. Figs 1 and 2 show a longitudinal section, cut in the conveying direction shown by the arrow, through the conveyor. Fig. 3 shows a cross section through the conveyor cut across the conveying direction at line III – III of Fig. 1. Figs 4 and 6 show part sections cut across the conveying length at points IV- -IV and VI- -VI respectively.

The apparatus comprises a conveyor 100 (generally) which is an endless loop, having an upper conveying length 101 which moves in the conveying direction shown by the arrow and a lower return length 102 which returns in the opposite direction and

is positioned below the conveying length 101. At a respective upstream end 101A and a downstream end 101B are guide wheels 103, 104 rotatably mounted with their rotation axles horizontal, and which are driven in a generally conventional manner by electric motors (not shown). Referring to Fig. 4 the conveyor 100 comprises a series of linked mountings 105 for plural rollers 106 which are rotatably mounted on the conveyor 100. Rollers 106 are generally cylindrical and are arranged with their axis of rotation, i.e. the longitudinal axis of their cylindrical shape, aligned horizontally perpendicularly across the conveying direction. Each roller 106 is integrally made with a spindle 107 extending in its rotation axis direction, and each mounting 105 comprises a bearing through which the spindles are rotatably threaded. These bearings are lubricant-free but have considerable slack to reduce the possibility of jamming. At an end of the spindle 107 opposite the roller 106 is a toothed pinion gear 108 which engages a rack 109 which extends alongside the conveying length 101. Engagement of this rack 109 with pinion 108 causes pinion 108, spindle 107 and roller 106 to rotate.

Figs. 1, 2 and 4 show two rollers 1061 and 1062 which are adjacent in the conveying direction, looking in the direction along the axis of rotation direction of the rollers 1061, 1062 which is horizontal and perpendicular to the conveying direction. With the rollers 1061, 1062 arranged in this way, as seen in Figs. 2 and 4A, a vial 1010, having a cylindrical body and viewed in Fig. 2 looking in its cylindrical axis direction rests on the pair of rollers 1061, 1062 with its axis of rotation in a plane between the rotation axes of the two rollers 1061, 1062. Fig. 2A shows more clearly how the rotation of the rollers 1061, 1062 in the direction as shown by arrows imparts corresponding rotation to the vial 1010 resting thereon, as the rollers 1061, 1062 and the vial 1010 are conveyed in the conveying direction. This causes liquid content 1011 in the vial 1010 to form a thin layer around the sides of the vial 1010. Fig. 4A shows the vial 1010 in a longitudinal section and shows the cylindrical body 1010A and a cylindrical neck region 1010B terminating at a mouth opening 1010C, with an internal step 1010D between the body 1010A and the neck 1010B, so that when the vial 1010 is arranged horizontally it can hold liquid content 1011 without it spilling out.

Rollers 106 are made of stainless steel and are at a temperature below the freezing point of the liquid content 1010. This causes the rollers 106, when they are in contact with the vial 1010 as shown in Fig. 2, to withdraw heat from the vial 1010 and

its liquid content 1010 to freeze the liquid content 1010. The conveying length 101 of the conveyor and its speed in the conveying direction are such that the vial 1010 remains in contact with the cold rollers 106 for sufficient time that the liquid content 1010 is frozen by the time the vial reaches the downstream end 101B.

5 The rollers 106 are cooled to the temperature below the freezing point of the liquid content as follows. The conveyor 101 (shown schematically in Fig. 3) is mounted within a trough 200, which is elongate in the conveying direction. Trough 200 contains liquid nitrogen 201, and is configured such that along the return length 102 of the conveyor the rollers 106 dip into the liquid nitrogen 201. The trough
10 extends the entire length of the conveyor 100. Conveyor 100 and trough 200 are configured so that the conveying length 101 of the conveyor 100 is above the surface of the liquid nitrogen 201, and the trough has upwardly extending sidewalls 202 of a height sufficient that cold nitrogen gas evaporating from the liquid nitrogen 201 forms a cloud 203 around the upper conveying length 101 of the conveyor 100. This cloud of
15 gaseous nitrogen 203 shields the conveying length 101 of the conveyor from environmental contamination, particularly from moist ambient atmosphere, thereby reducing the likelihood of frost formation on and within the vials 1010. To assist in maintaining sterility a flow of purified air 204 of Class A or higher is directed downwardly around the conveying length 101 of the conveyor 100 in a well known
20 manner.

The trough 200 is double walled, having an outer wall 205 with a void 206 between the walls 204,205, and cold nitrogen gas 203 evaporating from the liquid nitrogen 201 in the trough 200 flows over the inner wall and into this void 206 between the walls 202,204, and an exhaust manifold 207 is provided to remove the
25 gaseous nitrogen. This double walled arrangement helps to insulate the trough 200. Trough 200 is supported by a conventional stand (not shown).

Figs. 1, 4 and 5 show how vials 1010 are loaded onto the conveyor 100. Fig. 4B shows a sectional view through the conveyor 100 at the line IV - - IV of Fig. 1 looking opposite to the conveying direction. As seen in Fig 4B the mountings 105 are
30 mounted pivotally on the conveyor 100. In the on-loading position shown in Fig. 4B the mountings are oriented, e.g. by use of guide cams or ramp parts (not shown) positioned adjacent to the conveyor 100, so that the rollers 106 have their cylindrical

axis vertical, shown as roller 1063. With the rollers 106 in this orientation, vials 1010 are presented to the rollers so that a vial 1010 presented to the conveyor is received between a pair of rollers 1063, 1064 which are adjacent in the conveying direction, with the vial 1010 in a vertical configuration mouth uppermost as shown in Fig. 4B.

5 The rack 109 is located so that whilst the rollers 106 are in this vertical orientation the rack 109 is not engaged with pinion 108 so that the rollers do not rotate about their rotation axis, and the vials 1010 in contact with them do not consequently spin. Whilst in this vertical orientation the vials 1010 are supported by a guide rail 1012 adjacent to the conveyor 100.

10 As the rollers 106 move downstream in the conveying direction from this on-loading position the mountings 105 pivot so that the rollers 106 move about a rotation axis parallel to the conveying direction so that their rotation axis becomes aligned horizontally across the conveying direction as seen in Fig 4A, i.e. along length 101C of the conveying length 1010 the vials swing about an axis in the plane of the drawing
15 until they are aligned horizontally with the rollers 106 as in Fig. 4A, and identified as rollers 1061,1062. This too may be achieved by suitably positioned cam or ramp surfaces (not shown).

 When the vials 1010 are in their horizontal orientation 1010 as seen in Fig 4A in the region 101A of the conveying length of the conveyor 100, the rack 109 is
20 engaged with pinion 108 so that the rollers rotate about their rotation axis, and the horizontal vials 1010B in contact with them consequently spin.

 Fig. 2 shows the liquid content 1011 of the vials 1010 in three states: 1011A in a liquid state with the vial 1010 vertical, 1011B with the vial horizontal and spinning, with the liquid content 1011B converting from a liquid to a frozen state as the vial
25 1010 moves in the conveying direction, and 1011C in a frozen state with the vial 1010 again vertical.

 The plan view of Fig. 5 shows in schematic detail the on-loading system 300 and off-loading system 400 of the conveyor 100. Vials 1010 are supplied in a vertical orientation onto a conventional loading table 301, on which they are directed toward
30 the conveyor 100. The vials 1010 are loaded onto the conveyor 100 at this loading position by a first rotating notched star wheel 302 which receives vials 1010 in their vertical orientation from for the loading table 301. First star wheel 302 transfers the

vials 1010 to a second rotating notched star wheel 303 which on rotation moves vials 1010 into a position where they are adjacent to the vertically oriented rollers 106 of the conveyor and received by these as described above. The star wheel 303 is synchronized with the guide wheel 103 so that the vials in the notches of the star wheel 303 are properly aligned with the rollers 106.

The plan view of Fig. 5 also shows the off-loading system 400 of the conveyor 100. Vials 1010 approach the downstream end 101B of the conveyor 100 in their horizontal orientation i.e. as seen in Fig. 4B. As vials 1010 near the end 101B the mountings 105 pivot, e.g. under the action of cam or ramp surfaces (not shown) so that the vials 1010 rotate into the vertical orientation 1010A as shown in Fig. 4B but with their content 1011 in a thin frozen layer around the walls of the vial 1010. Another guide rail 1013, analogous to that 1012 is located at the downstream end 101B to support the vials 1010 whilst in their vertical orientation. At end 101B the vials 1010 are received by a rotating notched star wheel 401 which can receive vials 1010 in their vertical orientation from the conveyor 101 in its notches. A further star wheel 402 is rotatably mounted on the opposite side of the conveyor 101 from star wheel 401 and has radially extending fingers which extend between the rollers 106 in their vertical orientation to push vials 1010 into the notches of star wheel 401. As star wheel 401 rotates it moves the vials 1010 into a position where they are in a position to be delivered to an adjacent receiving tray 403. A guide rail 1014 is provided to guide vials 1010 off the star wheel 401. In a preferred form there are two receiving trays 403 and 404, so that when one of these trays 403,404 is full it may be removed and replaced by the other further vials 1010 may be diverted to the other to thereby maintain continuous operation. The downward flow of sterile air 204 is maintained over the entire area of the conveyor 100 and the on and off loading areas 300, 400.

The receiving trays 403,404 are kept cool at a temperature below the freezing point of the liquid content so that the liquid content remains frozen whilst the containers are waiting on the receiving tray 403. This is achieved by means of a plate 405 positioned beneath trays 403,404 with a narrow space (not shown) vertically between the trays 403,404 and into which liquid nitrogen is introduced. Alternatively there may be heat exchanger pipes arranged beneath the trays 403,404. Additionally or alternatively the trough 200 of liquid nitrogen may be configured so that cold gaseous

nitrogen evaporating from the trough 200 is directed into contact with the underside of the tray 403, to cool and maintain the tray at a temperature below the freezing point of the liquid content 1011.

Thereafter the vials 1010 with their shell frozen content may be taken away by
5 an operator to a conventional vacuum chamber (not shown) where they are exposed to a vacuum to evaporate the frozen content in a conventional lyophilisation system.

Fig 6 shows a part section cut across the return length 102 at points VI- -VI. Here it is seen how the rollers 106 have pivoted into a vertical configuration analogous to Fig. 4B but inverted. In this configuration the rollers 106 are immersed
10 in the liquid nitrogen 201 in trough 200, and thereby cooled. As will be apparent from Fig. 1 and 2, as the rollers 106 in their vertical orientation at the downstream end 101B travel around the guide wheel 104 they roll around the guide wheel 104 and enter the liquid nitrogen 201 in trough 200.

Fig. 7 shows a perspective view of the on-loading end 101A of the conveyor
15 100, parts corresponding to Figs 1-6 being numbered correspondingly. For clarity only some of the rollers 106 and their mountings 105 are shown. It is seen how guide wheel 103 is mounted between side plates 1015, and the conveyor 100 is driven by drive wheel 1016. It can clearly be seen how rollers 106 swing from a vertical orientation 1063 to a horizontal orientation 1061.

20 Fig. 8 shows an overall perspective view of the conveyor 100. It is seen how over most of the central part of the conveying length 101 the rollers 106 are oriented horizontally. It can clearly be seen how rollers 106 swing from a vertical orientation 1063 to a horizontal orientation 1061. Rollers 106 are also clearly seen in their inverted orientation as shown in Fig. 6 on the return length 102 of the conveyor 100.

25 Fig. 9 shows in a perspective view the mountings 105 of the rollers 106, with spindles 107 and pinions 108. The mountings 105 are made of PTFE, being a low friction material, and they are pivotally mounted at pivot axle 1018, about which the rollers 106 can pivot between vertical (see Fig. 4B) and horizontal (see Fig. 4A) orientations. In the construction shown in Fig. 10 the pinions 1020 are driven by
30 means of the toothed rack 109 arranged adjacent to the conveyor 100, with which pinions 108 engage as the pinions 108 move in the conveying direction.

Fig. 10 shows a more detailed plan view similar to Fig. 5. In Fig. 10 two motors 1018, 1019 are shown used for driving the conveyor 100 and the star wheels 302, 303, 401, 402 by appropriate gearing. Two sets of star wheels 302, 303 and 401, 402 are respectively used at the on- and off- loading positions 300, 400. Motors 1020, 1021, and 1022 vibrate the on-loading and receiving trays 301, 403, 404. Support wheels 103 (also seen in Fig. 8) are rotatably mounted at points along the conveyor 100.

In the apparatus shown it is found that liquid content 1011 in vials 1010 freezes solid in 60 – 75 seconds, with an on- and off- loading frequency of ca. 1 vial 1010 per second.

Claims.

1. An apparatus for shell freezing a liquid content in a container, the apparatus comprising an endless loop conveyor having a conveying length adapted to convey
5 plural containers in a conveying direction and incorporating plural rollers to spin the containers as they are conveyed by the conveyor, and a return length, *characterised* in that the return length of the conveyor is configured such that along at least part of the return length at least part of the rollers is immersed in a cooling liquid at a temperature below the freezing point of the liquid content of the containers, and the
10 conveying length is configured such that along the conveying length the rollers are entirely above the surface of the cooling liquid.
2. Apparatus according to claim 1 characterised in that:
the conveyor is adapted to convey plural cylindrical vials containing a liquid
15 content which is an aqueous solution or suspension of a drug compound or vaccine, in a horizontal conveying direction which is perpendicular to their longitudinal cylindrical axis,
the conveyor incorporates plural rollers comprising part of the conveyor, which are rotated about a rotation axis aligned horizontally across the conveying
20 direction as the conveyor conveys the vials, the rollers adapted such that a conveyed vial rests on a pair of rollers which are adjacent in the conveying direction such that the rotation of the rollers imparts rotation to the vial resting thereon,
the rollers are cooled by their immersion in the cooling liquid such that along the conveying length they are at a temperature below the freezing point of the liquid
25 content.
3. Apparatus according to claim 1 or 2 characterised in that the conveyor is configured as an endless loop conveyor, having a conveying length which is above the return length.
30
4. Apparatus according to claim 1, 2 or 3 characterised in that the cooling liquid is a liquefied gas.

5. Apparatus according to claim 4 characterised in that the cooling liquid is liquid nitrogen.
- 5 6. Apparatus according to claim 4 or 5 characterised in that the conveyor is configured that at least part of the rollers along the conveying length are also exposed to cold gaseous nitrogen from evaporating cooling liquid.
7. Apparatus according to claim 4, 5 or 6 characterised in that a trough is
10 provided below the conveying length, the trough configured such that the return length, or part at least of the rollers, dips into the cooling liquid, and the trough is provided with upwardly extending sidewalls of a height sufficient that cold vapour evaporating from the cooling liquid forms a cloud around the upper conveying length.
- 15 8. Apparatus according to claim 7 characterised in that the trough is double walled with a void between the walls, and cold vapour evaporating from the cooling liquid in the trough is able to flow into this void between the walls.
9. Apparatus according to any one of the preceding claims characterised by a
20 conveyor constructed so that along the return length rollers are immersed into the cooling liquid with their rotation axis vertical.
10. Apparatus according to any one of claims 4 to 9 characterised by a
25 downstream end off-loading means to remove the containers, containing their frozen content, and to deliver the containers to a receiving tray wherein the receiving tray is kept cool at a temperature below the freezing point of the liquid content so that the liquid content remains frozen whilst the containers are waiting on the receiving tray by means to expose the underside of the tray to cold vapour of the evaporating cooling liquid.

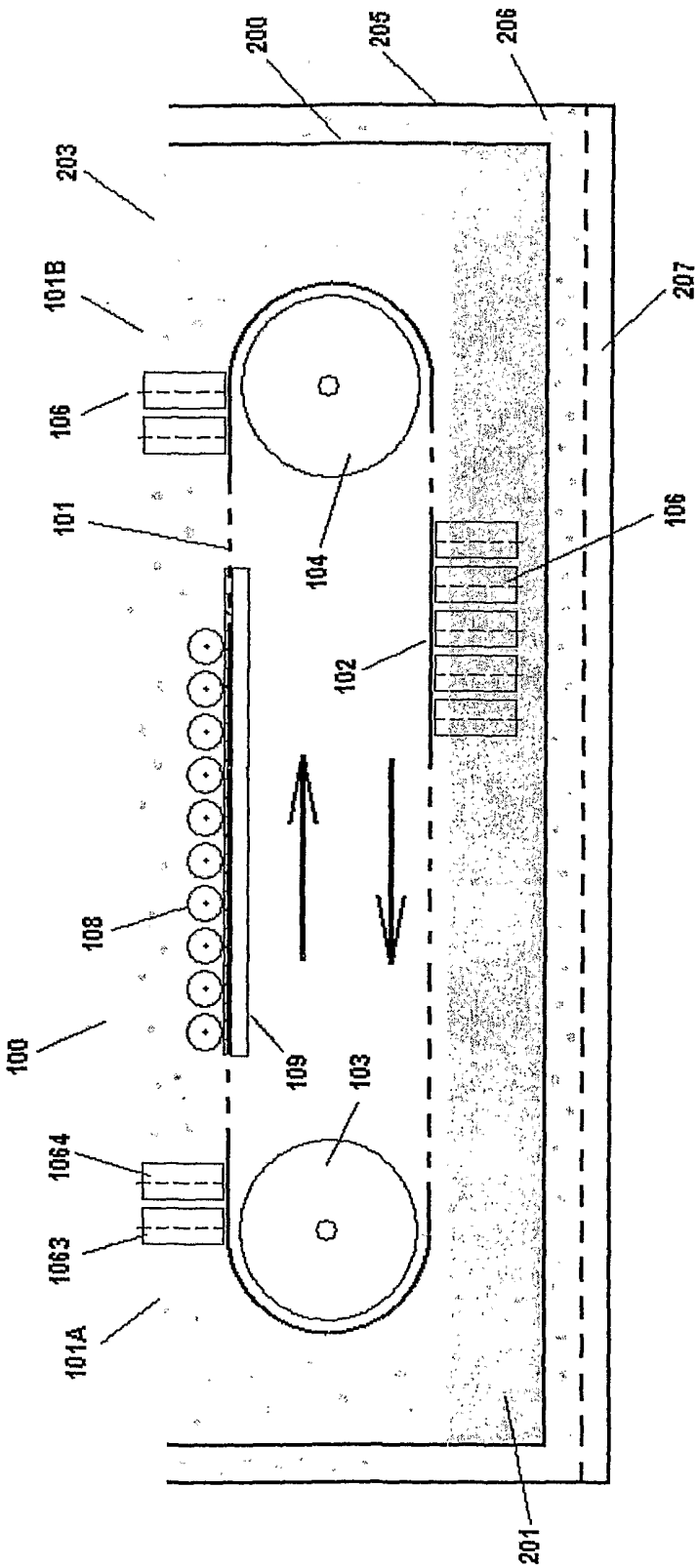
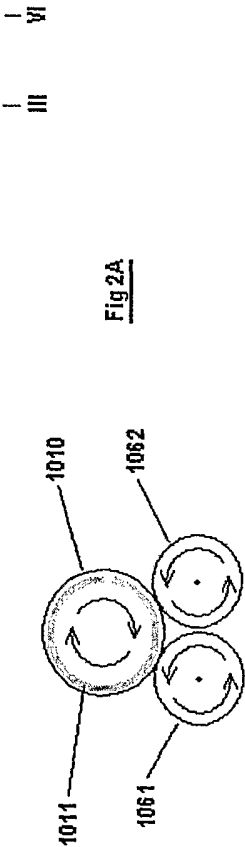
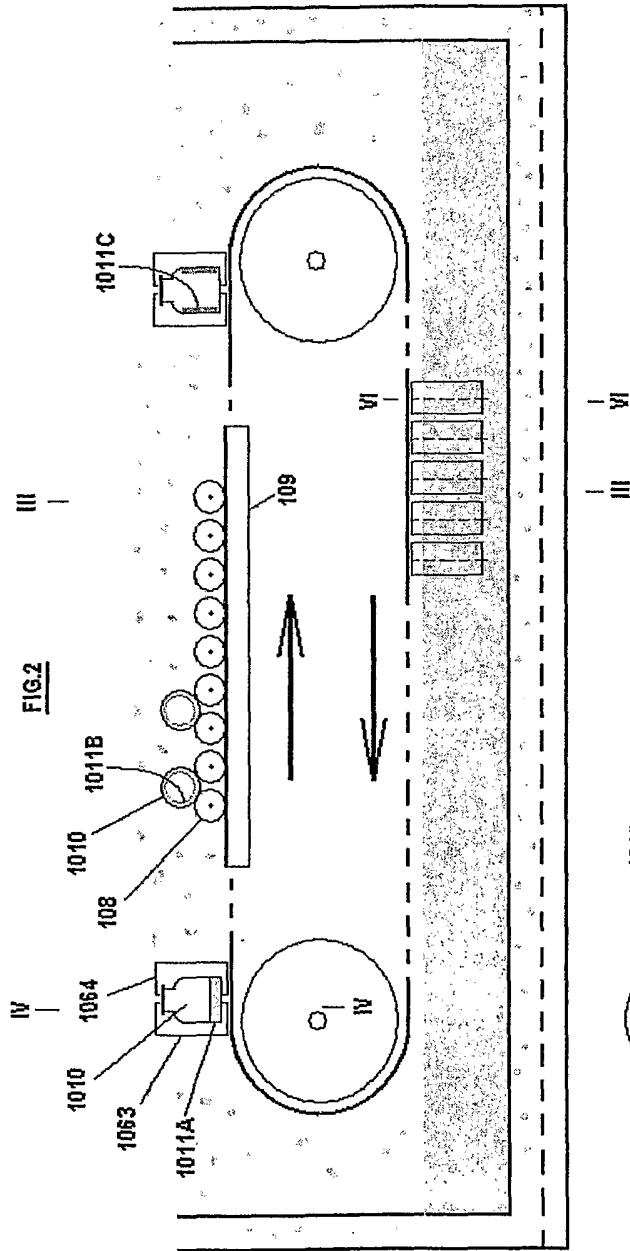
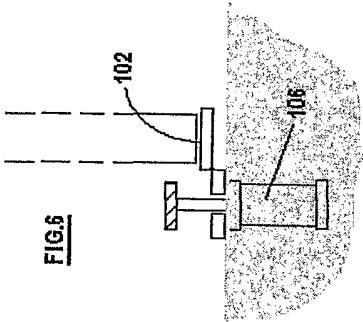
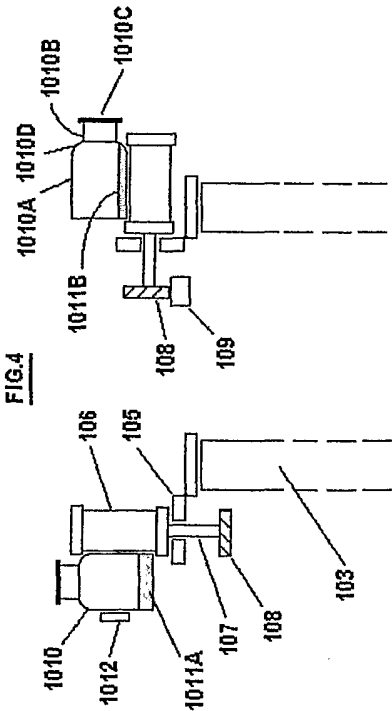
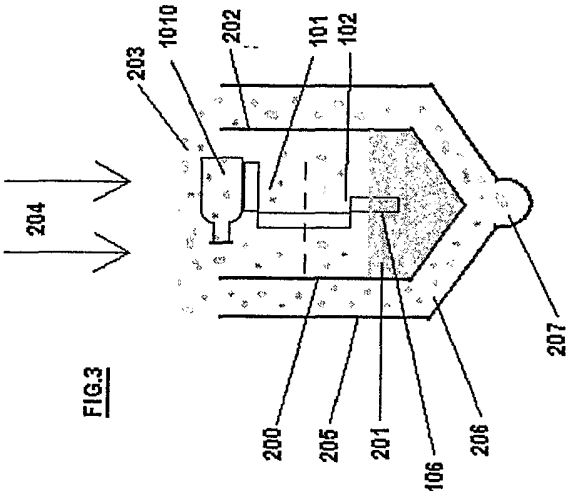


FIG.1





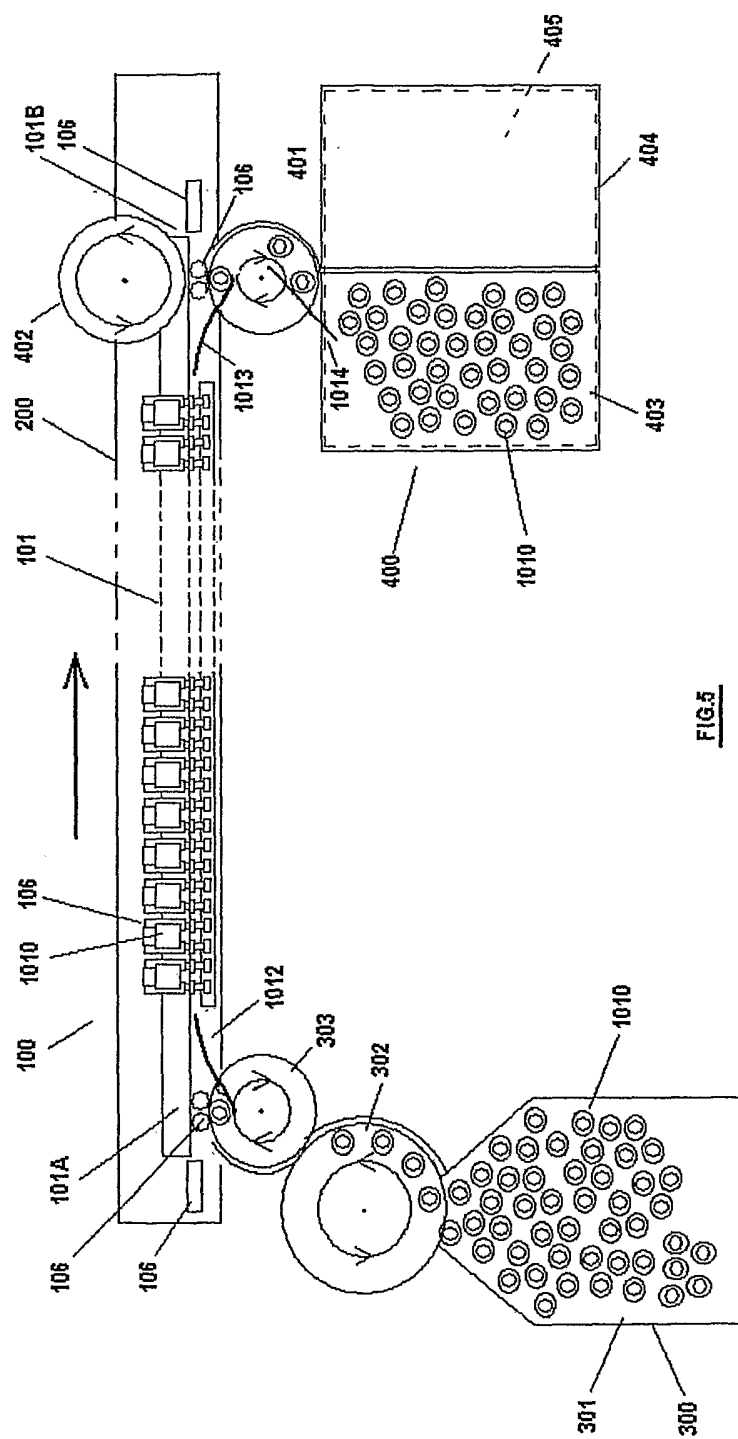


FIG. 5

Fig.7

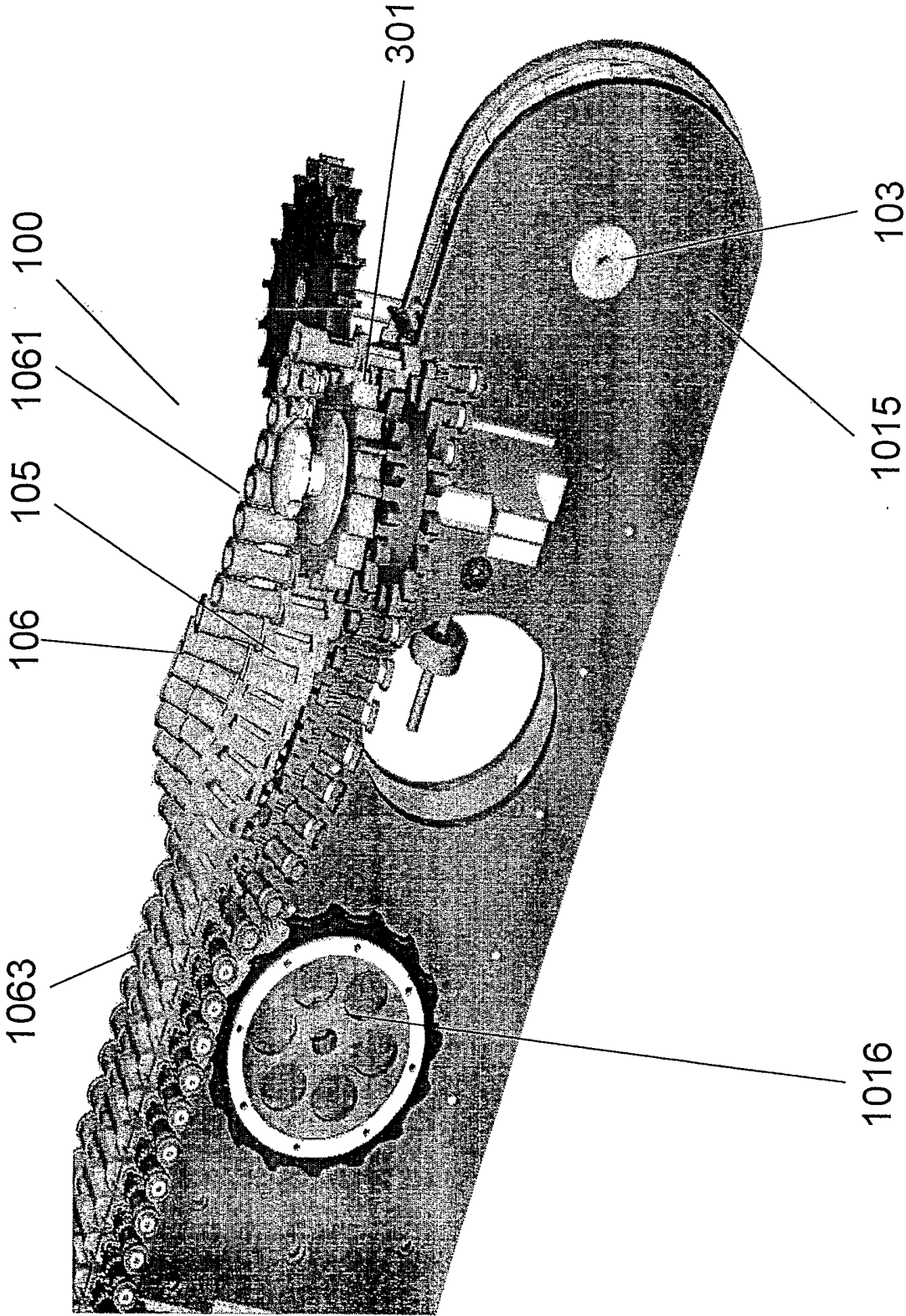


FIG. 8

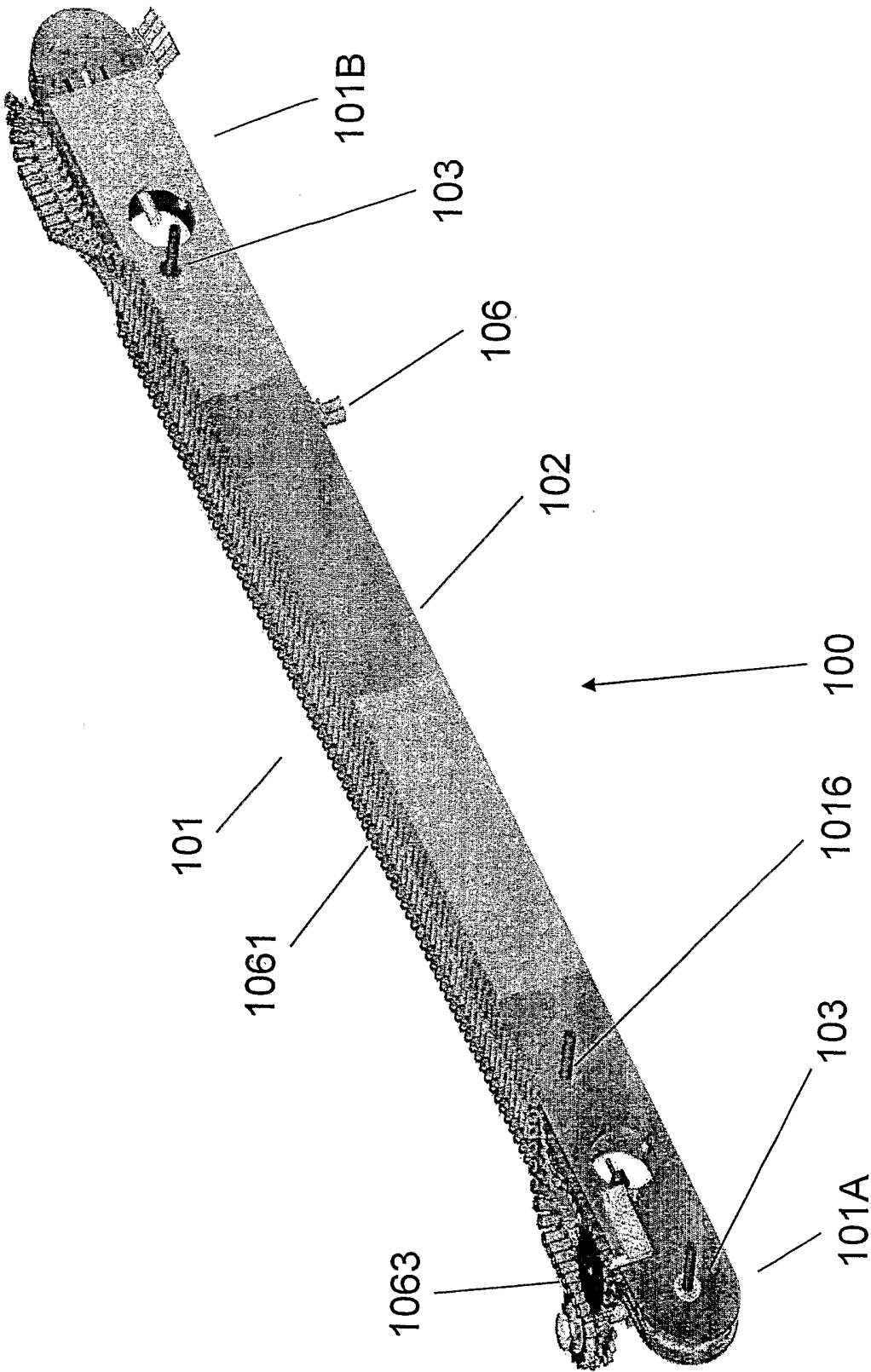


FIG. 9.

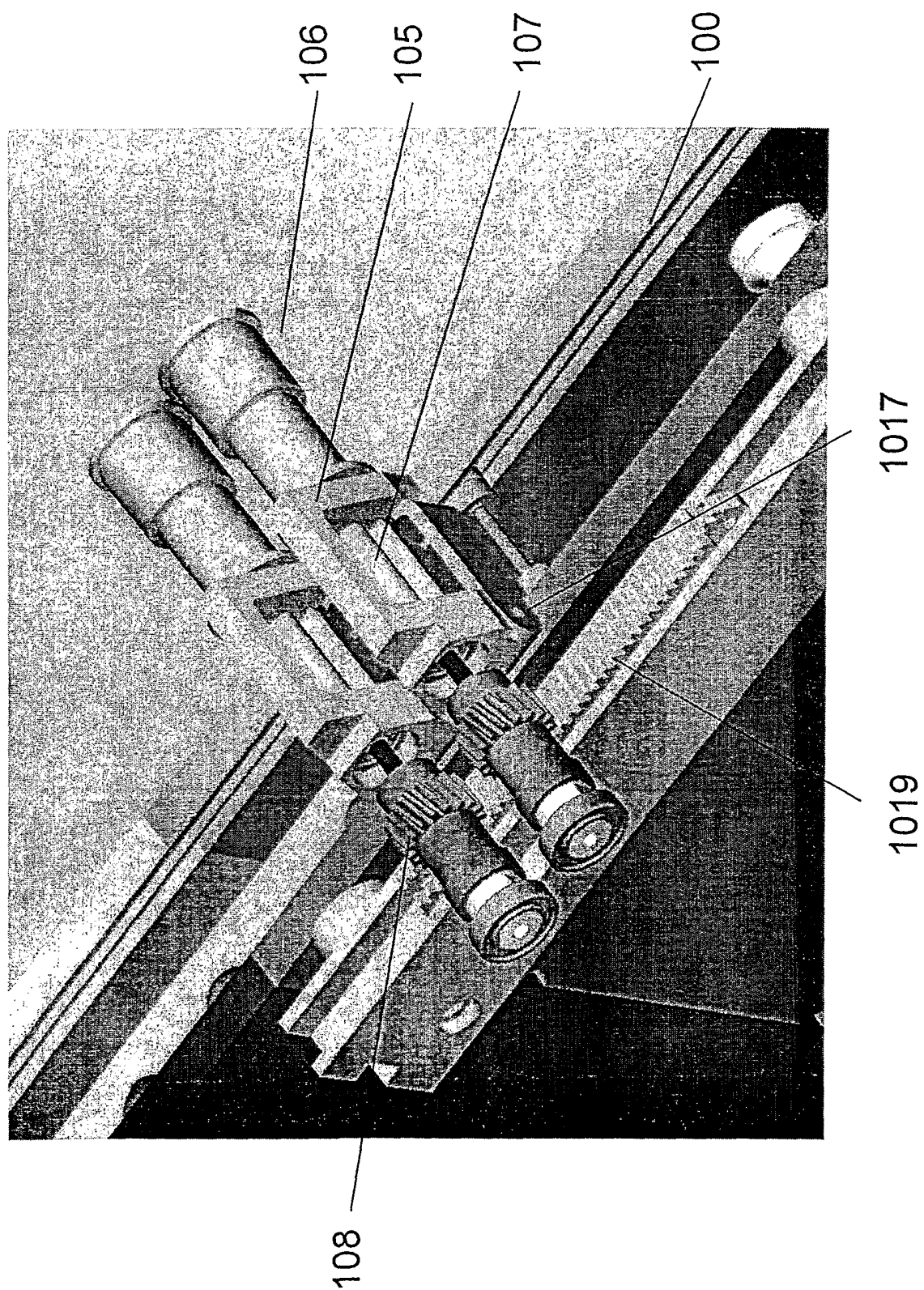
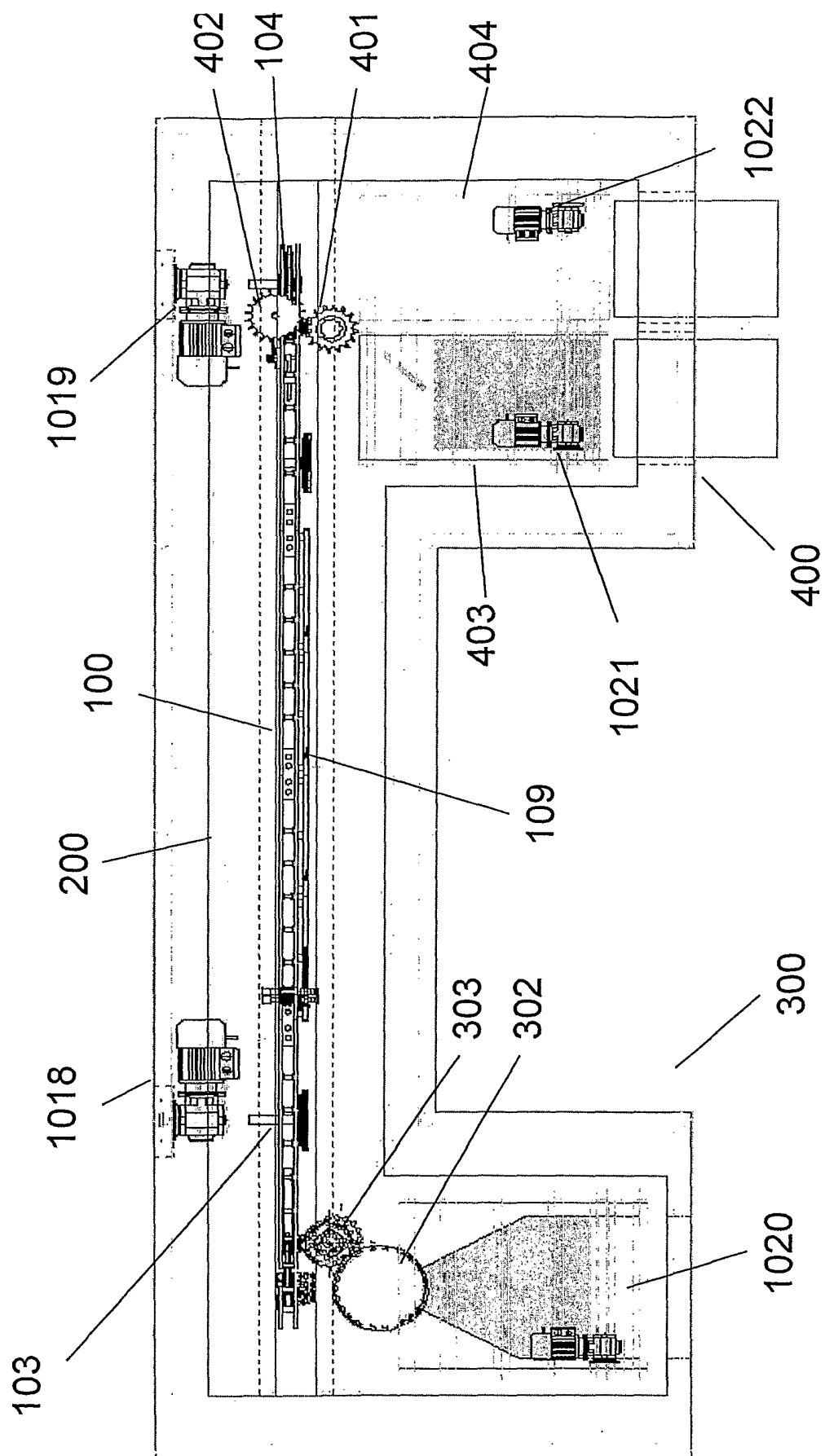


FIG. 10



INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP2005/005124

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 F25D3/11 F26B5/06

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)
IPC 7 F25D F26B

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 practical, search terms used)

EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

2 August 2005

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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