Date: December 11, 2020

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The document is designated as:

- International Application Number: PCT/EP97/02641

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PATENT COOPERATION TREATY (PCT) PUBLISHED INTERNATIONAL APPLICATION

(51) **International patent classification**[6]:
A61L 2/04, 2/06, 2/12, 2/20, A61M 5/00

A1

(11) International publication number: **WO 97/44068**

(43) International Publication date: November 27, 1997 (11/27/97)

(21) International application number: PCT/EP97/02641

(22) International filing date: May 23, 1997 (5/23/97)

(30) Priority dates:
196 22 283.4 May 23, 1996 (5/23/96) DE

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TI, UA, UG, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, Fl, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the period allowed for changes to the claims. Publication will be repeated in case of changes.

(54) Title: METHOD OF TERMINALLY STERILIZING FILLED SYRINGES

(57) Abstract

The invention concerns a method of producing a pre-filled sterile syringe. The syringe comprises a syringe body with a proximal end and a distal end, a syringe-outlet part at the distal end, a seal, a stopper, a fluid medium and a gaseous medium, the fluid medium being a liquid. The method comprises the following steps: preparing the syringe body, seal and stopper which is/are free from germs and/or endotoxins and low in particles; a lubricant is applied; the proximal end is sealed by inserting the stopper into the syringe body; the syringe is filled through the distal end; the syringe outlet part is sealed with the seal; the syringe is sterilized in a sterilizing chamber; the syringe is then packaged and the package container is then sterilized once again.

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Method of terminally sterilizing filled syringes

The invention relates to a method of terminally sterilizing filled syringes. In particular, the focus is a pyrogen-free and germ-free surface of the syringes. These syringes are preferably intended for the use of injectable diagnostic agents, in particular contrast media, which are injected, for example, into blood vessels, organs, organ parts, cavities and other vessels or have an imaging effect there.

Patent specification AT-E 68 979 describes a method of manufacturing a filled, terminally sterilized syringe. The syringe is made of plastic. The syringe has a cylinder with a distal end having a syringe outlet part. The syringe outlet part is closed by a seal. After the syringe is filled, it is closed with a flexible rubber stopper that is slidable in the cylinder. The method begins by removing waste particles or other contaminants from the seal and the plunger. Microbial contaminants on the seal and piston are destroyed. The cylinder is washed with a variety of water jets to remove pyrogens and waste particles. Silicone oil is then applied to the inner wall of the syringe. The seal is then attached to the syringe outlet part. The contrast agent is filled into the syringe through the proximal end of the syringe. The syringe is then closed with the stopper. This assembled and filled syringe is sterilized in an autoclave. In addition to the normal autoclave pressure, an additional support pressure is generated in the autoclave. This makes the pressure on the outer surface of the syringe equal to or greater than the pressure on the inner surface of the syringe.

From the publication by Venten and Heppert (E. VENTEN and J. HOPPERT (1978) Pharm. Ind. Vol. 40, No. 6, pages 665 to 671), a terminal sterilization of pre-filled syringe ampoules is known. The syringe ampoules, which have a stopper at the proximal end, are filled distally through the rolled rim. The rolled rim is then sealed by a sealing disc, with a flange cap fixing the sealing disc to the rolled rim. (M. JUNGA (1973) Pharm. Ind. Vol. 35, No. 11a, pages 824 to 829). The pre-filled syringe ampoules are then transferred to an autoclave. This autoclave is adjustable with respect to temperature and pressure. To prevent the sealing disc from loosening from the syringe ampoule, a support pressure is generated in the autoclave. The support pressure is built up by an additional gas. This makes it possible to keep the pressure on the inside of the sealing disc approximately equal to the pressure on the outside of the sealing disc. This also prevents movement of the piston used. As a result of the good control, it is even possible to terminally sterilize dual chamber syringe ampoules filled with two solutions without any unacceptable stopper movement or sealing disc leakage.

Finnish patent application FI 93 0405 describes a method of terminally sterilizing a pre-filled plastic syringe or glass syringe, the syringe containing a contrast agent. The syringe comprises a syringe cylinder with a syringe outlet part at the distal end. In addition, syringe ampoules in the form previously described by

Venten and Heppert are also listed. The syringes have an open proximal end, which can be closed by a stopper which slides in the syringe. The stopper is connected to a plunger.
When the syringe or syringe ampoule is filled, the stopper is first inserted into the proximal end of the syringe or syringe ampoule. Then the distal end is filled. The distal end is then sealed. In the case of syringe ampoules, a sealing disc is fixed to the rolled rim with a flange cap. The syringes or syringe ampoules are then sterilized, using a support pressure. This keeps the pressure on the outer surface of the syringe lower than the pressure on the inner surface of the syringe or syringe ampoule. In the case of the syringe ampoules, the pressure in the autoclave is equal to, greater than or less than the pressure in the syringe ampoule.

WO 95/12418 describes a terminal sterilization method for pre-filled syringes in which no autoclave is used, but only a pressure-resistant sterilization chamber is used. The distally or proximally filled syringe is placed in this sterilization chamber. The chamber is heated by means of heating gas. At the same time, this heating gas also provides a pressure which is to compensate for the pressure increase in the syringe. In order to prevent evaporation of liquid penetrating through the plastic, water vapor is introduced in addition to the heating gas. It is described in the property right that the same safety is to be achieved as with autoclaving.

WO 95/12482 describes a method for the production of pre-filled plastic syringes filled with a contrast agent. The syringes are comprised of a cylinder, a syringe outlet part at the distal end, which is prepared for a cannula attachment. Further, the syringe includes a stopper that can slide in the cylinder. It seals the proximal end of the syringe. The syringe has been manufactured based on a method that results in pyrogen-free objects. Likewise, no particles are present. The syringe is filled through the proximal end, and the syringe outlet part is sealed with a stopper. The filled syringe is closed with the stopper. The particle status of the spatialities corresponds to the conditions of class 100.
After the syringe parts come out of the mold, they are blown off with gas to remove particles. The syringe is then washed. The syringe is then sterilized so that it can be further processed, stored or transported, as desired.

The task is to offer a syringe which is pre-filled with a medium, whereby the medium is permanently present in the syringe without any loss of quality. Particularly high demands are to be placed on safety with regard to sterility and the absence of particles inside and outside the syringe.

The task is solved by a manufacturing method of a pre-filled, sterile syringe made of glass or plastic or a mixture of glass and plastic, further a glass syringe with a plastic foil connected thereto and a plastic syringe with a glass coating connected thereto, the syringe comprising
a cylindrical syringe body with a closable proximal end and a closable distal end,

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