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(54) Title: SURFACE DECONTAMINATION OF PREFILLED CONTAINERS IN SECONDARY PACKAGING

(57) Abstract: Methods and systems for the terminal sterilization and surface decontamination of prefilled containers containing sensitive drug products, such as biotech drug products that are otherwise temperature or radiation sensitive, and thus not suitable for terminal sterilization by classical methods involving steam or gamma rays. The methods and systems are especially suited for prefilled containers in secondary packaging. Methods include terminal sterilization by exposing prefilled containers in secondary packaging to tunable-beta radiation and further include terminal sterilization by exposing prefilled containers to controllable vaporized-hydrogen peroxide, including application of measures to reduce or prevent diffusion of vaporized-hydrogen peroxide into prefilled containers.

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Surface Decontamination of Prefilled Containers in Secondary Packaging

FIELD OF THE INVENTION

This invention relates to a method and system for terminal sterilization of the outer surface and/or surface decontamination of prefilled containers in secondary packaging, wherein the prefilled container contains a pharmaceutical or biological drug product.

BACKGROUND

Prefilled containers are a type of medical device that are filled by the manufacturer at the time of assembly and provided to the end user, generally a health-care provider or a patient requiring treatment, in a sterile condition.

Prefilled containers offer several advantages over traditional packaging of therapeutics, including ease of use, reduced risk of contamination, elimination of dosing errors, increased drug supply and reduced waste. Of the various types of prefilled containers, prefilled syringes are the most common and best suited for parenteral administration of therapeutic products.

Various methods of sterilization of medical devices are known, but not all methods work with syringes, especially syringes prefilled with a drug or protein solution.

Steam sterilization is commonly employed for sterilizing medical devices, which typically involves heating the device in a steam autoclave. The heat and pressure generated in the autoclave, however, can have an adverse effect on the device and, more importantly, on the integrity of the drug product filled into the device. Steam sterilization may compromise the aesthetics of the product due to packaging degradation from high temperature steam treatment. Moreover, the high temperatures of the process (e.g. 120° C — 132° C) preclude its use with heat sensitive materials, such as biotech drug products, specifically protein or other biological solutions.

Radiation exposure is also commonly employed for sterilizing medical devices, in which the product is subjected to ionizing radiation, such as gamma irradiation. Radiation exposure results in harmful damage to sensitive solutions, specifically causing destruction to sensitive biologicals such as proteins, as well as generation of massive amounts of peroxides in aqueous solutions that in a secondary reaction further

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may damage the active ingredient. Further, sterilizing doses of gamma rays cause a brown discoloration of glass parts of the device, and is prone to damage elastomeric materials like plunger stoppers. This destruction of the elastomers leads to increased stickiness of the components thus impairing the functionality of the system. Thus radiation is not an appropriate means for sterilizing prefilled containers, such as syringes, containing a biotech drug product.

Cold sterilization is a term collectively used for sterilization methods carried out at temperatures substantially below those of the steam process; attempts have been made to use ethylene oxide and hydrogen peroxide vapors as sterilants for this treatment. Treatment with sterilizing gasses, however, bears the risk of insufficient removal of the oxidizing gas. Diffusion of gas into the product container affects the stability of the drug product through chemical modification by gas vapors, such as alkylation and oxidation.

Prefilled syringes, although filled under aseptic conditions, are not packed into their secondary packaging in an aseptic environment and are therefore likely to be microbiologically contaminated at their outside. Terminal sterilization of prefilled containers in secondary packaging is one way to provide the device to an end user with a low bio-burden and low risk of contaminants, for safe application of the product by the end user. Moreover there is a strong market need for terminally antimicrobially-treated medical devices, such as prefilled syringes used for intravitreal injections.

Due to the sensitive nature of certain drug products, such as proteins, it is not possible to perform terminal sterilization and surface decontamination of containers filled with such products using current methods, like steam, irradiation or cold sterilization. Specifically, high temperatures are known to denature proteins and gamma radiation has been shown to chemically modify biological solutions. Radiation techniques, such as sterilization using gamma or beta radiation causes discoloring of packaging material and affects the long term stability of therapeutic agents such as protein or peptide solutions. As discussed above, oxidizing gases, while efficient for killing bacterial contamination, also harm biological molecules in sensitive therapeutic solutions.

As protein and biological molecules will be more and more developed for therapeutic use, the need for a terminal surface sterilization and surface

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decontamination method that is not harmful to the drug product will continually increase in the near future. Moreover, as regulatory agencies may require higher levels of sterility assurance, pharmaceutical and biotech companies will seek alternative procedures to approach or meet mandated-microbiological purity levels, without compromising the safety and efficacy of pharmaceutical preparations.

SUMMARY

Described herein is a terminal sterilization and surface decontamination treatment of prefilled containers, specifically for sterilization of prefilled containers containing sensitive solutions, such as a drug product or biological therapeutic, within secondary packaging. In one embodiment, terminal sterilization is achieved by treating prefilled containers within secondary packaging with controllable vaporized-hydrogen peroxide (VHP). The principle is the formation a vapor of hydrogen peroxide in containment and a subsequent removal or inactivation of vapors in a controlled manner. Prior to removal or inactivation, VHP condenses on all surfaces, creating a microbicidal film that decontaminates the container surface.

It has been discovered that by varying the parameters of the antimicrobial treatment, for example — temperature, humidity, treatment duration, pressure, etc., conditions are generated that prevent the leaching of VHP into the syringes. As an example, the application of a vacuum at the end of the treatment will inverse the diffusion direction and reduce, if not stop, leaching of hydrogen peroxide through the rubbers. Further, inclusion of a gas plasma treatment after completion of the vaporized hydrogen peroxide cycle will further degrade all potentially remaining hydrogen peroxide residues. Prevention or reduction of leaching of detrimental concentrations of hydrogen peroxide into the protein solution in the syringe, either by removal of vapors or inactivation of vapors, ensures that the long-term stability of the protein is not compromised. It further has been found that among the commercially available primary packaging components, there are only very few packaging material combinations that provide the required tightness of the system such as to avoid ingress of sterilizing gasses into the pharmaceutical liquid enclosed by the prefilled container.

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Further described herein is terminal sanitization or sterilization and surface decontamination of prefilled containers within secondary packaging by tunable electron beam (low-energy beta-ray) irradiation technologies as an alternative to aseptic inspection and aseptic secondary packaging operations.

In one embodiment, the use of low penetration depth radiation from a low-energy electron beam generator for a new application to sterilize the surface of secondary packaged drug product containers avoids aseptic packaging. In another embodiment, the penetration depth of electron beam radiation is tunable by adjustment of the accelerator voltage of the irradiation generator.

Generally, the concepts presented herein are applicable to all drug products having requirements or desirability for absence of viable organisms of the drug product container surface. The method and system described herein decontaminate or, more preferably render sterile an outside surface of primary packaged drug products within a secondary pack, thereby improving safety of products for critical administration (e.g. use in a surgical suite or for intravitreal injections).

The foregoing summary provides an exemplary overview of some aspects of the invention. It is not intended to be extensive, or absolutely require any key/critical elements of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The detailed description is explained with reference to the accompanying figures. In the figures, the left-most digit(s) of a reference number identifies the figure in which the reference number first appears.

Fig. 1 shows an exemplary prefilled container in secondary packaging that is decontaminated on surfaces according to the methods detailed herein.

Fig. 2 illustrates a block diagram of an exemplary system for surface decontamination of prefilled containers using vaporized-hydrogen peroxide.

Fig. 3 illustrates a block diagram of an exemplary system for surface decontamination of prefilled containers using tunable-beta radiation.

DETAILED DESCRIPTION

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