



No. 11-181734- -00000-0000

Fecha: 2011-12-30 13:53:29 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eva: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 71



Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD PATENTE DE
INVENCION

TITULO: DESCONTAMINACIÓN DE SUPERFICIE DE CONTENEDORES
PREVIAMENTE LLENADOS EN EMPAQUE SECUNDARIO

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 30 de Diciembre de 2011

P2011/000216



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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD

PATENTE PCT

ENTRADA EN FASE NACIONAL

P2011/000216

SOLICITUD DE:

1

☒

Patente de Invención.

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Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE
(71)

Nombre: NOVARTIS AG

Dirección: Lichtstrasse 35, CH-4056 Basel

Nacionalidad o Domicilio: Suiza

Lugar de Constitución: Suiza

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número _____

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

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IDENTIFICACIÓN

C.C.

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Otro

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Cual _____

Número 79782747Bta

TP 74.295

INVENTOR (ES)
(72)

Nombre: JÜRGEN SIGG

Dirección: Novartis Pharma AG, Postfach, CH, Basel

Nacionalidad o Domicilio: Alemana

5

PCT (86)

Solicitud Internacional No. PCT/EP2010/060011

Fecha Julio 13, 2010

Publicación Internacional No. WO 2011/006877

Fecha Enero 20, 2011

6

Título (54) DESCONTAMINACIÓN DE SUPERFICIE DE CONTENEDORES
PREVIAMENTE LLENADOS EN EMPAQUE SECUNDARIO

Clasificación Internacional (51) A61L 2/00; A61L 2/20, B65B 55/10, A61L 2/08;
B65B 55/08

Prioridad		(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI	☒	EP	Julio 14, 2009	09165456.6
NO	☐			

9

Comprobante de pago No. 11-

Fecha Diciembre de 2011

10

ANEXOS☒

Comprobante de pago de la tasa de presentación de la solicitud.

☐

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒Poderes, si fuere el caso. *Adjunto copia simple. Ver Exp No. 08-102.832*☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones.

☒

Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

☐

Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

☐

Traducción del examen preliminar internacional efectuado por la IPEA.

☐

De ser el caso, copia del contrato de acceso.

☐

De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

☐

De ser el caso, certificado de depósito del material biológico.

☐

Arte final 12 x 12.

☐

De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

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De ser el caso, modificaciones efectuadas a la solicitud internacional.

☒

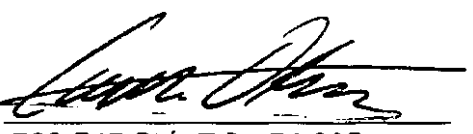
Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTEFIRMA: C.C. 79.782.747 Btá T.P. 74.295

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

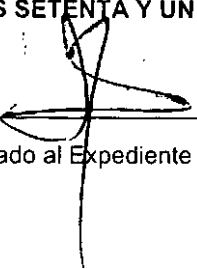
 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 11 - 126955
		Bogotá D.C., Diciembre 29 de 2011 - 10:45:33

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	409132802	28/12/2011	6.677.000.00

*** Conceptos Pagados ***			
CANT.	RENTISTICO	CONCEPTO	Vr. UNIDITARIO Vr. CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	571.000.00 571.000.00
			\$571.000.00
=====			

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE**

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-181734- -00000-0000
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Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambas personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

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E-mail: treseser1@yahoo.com. No. 8346



Traductor Oficial
JORGE E. SIERRA REYES
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OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salazar

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

The undersigned,

domiciled in

NOVARTIS AG

Lichtstrasse 35, CH-4056 Basel / Switzerland

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

domiciliado en

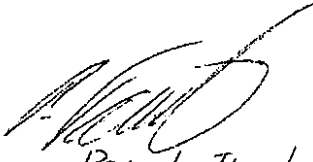
por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Date/Fecha: June 27, 2006

City/Country/Ciudad,País: Basel, Switzerland


Arthur Canonica


Pascal Traub

Attestation

- 1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.
- 2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.
- 3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.
- 4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)



Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven),
2009 (two thousand and nine).

Leg.Prot.Nr. 975/2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)

This official document

2. is signed by H. Staheli

3. in his/her function as Off. Leg.

4. and certified by the seal of the Chancery

Certified 12 May, 2008

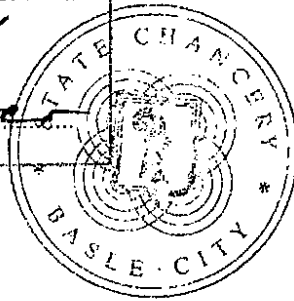
5. in Basel (Bâle) 6. on

7. by the State Chancery of the Canton of Basel-Stadt

8. no. 7049/18584

9. Seal / stamp: 10. Signature: Fischer

Heidi Fischer



VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i v)		an assignment from SIGG, Jürgen to NOVARTIS AG, dated 07 May 2010 (07.05.2010)

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

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International Bureau

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09165456.6 14 July 2009 (14.07.2009) EP

(71) Applicant (for all designated States except US): NO-VARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventor; and

(75) Inventor/Applicant (for US only): SIGG, Jürgen [DE/CH]; c/o Novartis Pharma AG, Postfach, CH-Basel (CH).

(74) Agent: SPINNER, David, Richard; Novartis Pharma AG, Patent Department, CH-4002 Basel (CH).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

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

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

(54) Title: 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

5 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

10 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
15 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.

20 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
25 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.

30 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

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
5 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.

10 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
15 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.

20 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
25 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.

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

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.

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.

5 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.

10 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
15 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.

20 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
25 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.

30 DETAILED DESCRIPTION

The method and system described herein are for the sterilization and surface decontamination of prefilled containers containing sensitive solutions, such as drug products that are otherwise temperature or radiation sensitive or are sensitive to traces of oxidizing substances, and thus not suitable for terminal sterilization by classical methods involving steam, gamma or beta rays or sterilization with oxidizing gases or liquids. The method and system described herein are especially suited for prefilled containers that have been filled under aseptic conditions and been subject to additional processing, such as product labeling and subsequent secondary packaging. Methods include terminal sterilization and surface decontamination by exposing prefilled containers in secondary packaging to tunable-beta radiation and further include terminal sterilization and surface decontamination by exposing prefilled containers to controllable vaporized-hydrogen peroxide, including measures to reduce or prevent the diffusion of vaporized-hydrogen peroxide into prefilled containers. The methods also include an optional step of actively destroying any residual peroxide molecules, for example, by means of gas plasma.

Definitions

In describing and claiming the terminal sterilization and surface decontamination method, the following terminology will be used in accordance with the definitions set forth below.

"Aseptic" conditions refer to conditions free of bacterial or microbial contamination.

"Administration" refers to the method of administering treatment to a subject or patient in need thereof, such as parenteral administration, intravenous administration and intravitreal administration.

"Beta irradiation" refers to sterilization methods using beta rays.

"Cold sterilization" refers to sterilization techniques employing chemical agents, gases, or irradiation. A requirement of cold sterilization is that the technique is carried out at temperatures below those used for steam sterilization, such as autoclavation.

"Container", as used herein, is meant to include vials, syringes, bags, bottles, or other means useful for storage of medical treatments, such as drug products, whether in

solid or liquid form, and other biological agents, such as peptides, proteins or recombinant biologicals, whether in solid or liquid form. Containers may be reusable or disposable, and may have a medical, veterinary or non-medical purpose.

“Prefilled container”, refers to a container, such as a syringe, that is filled with a solution at the time of assembly and packaging and is deliverable for use to an end user, such as a health care professional or a patient needing treatment. This term also refers to prefilled containers integrated into an administration device.

An “instruction” or “instructional material” includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of the method or system of the invention for its designated use. The instruction or instruction material may be presented together as part of the system or provided separately, or independently of the process, to an end user.

“Isolation”, as used herein refers to practices in pharmaceutical production, filling and packaging, wherein a clean, or sterile environment, is separated from a non-sterile environment to limit or prevent the introduction or spread or contamination of infectious agents, such as microorganisms.

“Medical device”, as used herein, refers to a device used for administering medical treatment and whose production or sale must, in part, comply with requirements, such as safety requirements, set forth by a government agency, such as the Food and Drug Administration.

“Solution” as used herein refers to the contents of a container like a vial or a prefilled syringe and includes solutions of biological therapeutics and drug products, protein products, peptide products, biological products, imaging solutions and aqueous solutions. Ideally, solutions are those that are temperature, oxidation or radiation sensitive due to the molecular make-up of the solution.

“Secondary packaging” refers to packaging enclosing the prefilled container, such as plastic wrapping, foil wrapping, paper wrapping or other suitable wrapping, such as blister packs.

“Terminal-antimicrobial-surface treatment” refers to sanitization or sterilization of an assembled container, such as a syringe filled with a solution that is in turn encased in secondary packaging. Terminal-antimicrobial treatment, or sterilization, allows a

secondarily packaged prefilled container to be provided in sterile outside condition at its point of use.

"Vaporized-hydrogen peroxide" refers to hydrogen peroxide in vapor form capable of creating a microbicidal film on a surface, such as the surface of a container or packaging material.

The terms "sterilization", "decontamination", "sanitization", "antimicrobial treatment" are used interchangeably herein.

"Sterility" as used herein is meant to refer to complete absence of microbial life as defined by a probability of nonsterility or a sterility assurance level (SAL). The required SAL for a given product is based on regulatory requirements. For example, required SALs for health care products are defined to be at least 10^{-6} , i.e. a chance of less than 1:1 million of a non-sterile product for aseptically manufactured and terminally sterilized products, respectively.

Reference herein to "one embodiment" or "an embodiment" means that a particular feature, structure, operation or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, the appearances of such phrases or formulations herein are not necessarily referring to the same embodiment. Furthermore, various particular features, structures, operations or characteristics may be combined in any suitable manner in one or more embodiments.

Terminal sterilization and surface decontamination of prefilled containers

Terminal sterilization is the process of sterilizing and/or decontaminating a final packaged product. In contrast, an aseptic packaging process requires individual product components to be sterilized separately and the final package assembled in a sterile environment. Terminal sterilization of a product provides greater assurance of sterility than an aseptic process. Terminal sterilization is also desired and provides a market advantage in some instances for the use of certain medical devices, such as the use of secondarily packaged prefilled syringes for intravitreal administration.

Described herein are terminal-sterilization methods suitable for prefilled containers containing sensitive products, such as biotech (biological) drug solutions, which can otherwise be compromised when using classical terminal sterilization

processes, such as steam, gamma irradiation or cold sterilization processes currently used in pharmaceutical production and assembly lines. While reference is given to drug products, such as heat or radiation-sensitive drug solutions containing biologicals such as peptides or proteins, it will be understood by those skilled in the art that any suitable drug product that is considered a therapeutic agent, whether in solution or solid form, can be housed — or contained — in a prefilled container. Thus, the prefilled container itself is not drug specific.

It has now been discovered that treatment of prefilled containers in secondary packaging by an application of vaporized-hydrogen peroxide, in which vapors are controllable by certain post-treatment measures, and exposure to tunable-beta radiation, in which the depth of penetration of beta rays into secondary packaging are controllable, are ideal for surface decontamination of prefilled containers, yet not harmful to the stability or integrity of the contents of the prefilled container.

The methods and embodiments described herein are suitable for use in pharmaceutical production and packaging in isolation or outside of isolation. Furthermore, the methods described herein are adaptable to different container formats or types, with minimal incremental costs to production plant design. A system is also provided which allows for surface decontamination of prefilled containers in secondary packaging, as well as a kit comprising instructional material for practicing the method and system described herein.

Referring to Fig. 1, a prefilled container 100 previously filled under aseptic conditions is decontaminated on surfaces 102 following encasement or packaging in a secondary package 104 by vaporized-hydrogen peroxide or tunable-beta radiation as described herein. Fig. 1 shows one exemplary prefilled container, however, it will be understood by those skilled in the art that various containers, other than a syringe, are also suitable. Moreover, while the exemplary container shown at Fig. 1 is a syringe in a closed and assembled position, it should be understood that other variants are envisioned. For example, a prefilled container not sealed by a stopper, plunger or other sealing mechanism can be surface decontaminated on interior portions of the container.

In one embodiment, the prefilled container is a syringe. Other suitable prefilled containers include vials, bottles, bags and other medical devices capable of containing a sterile solution or a solution requiring sterilization.

5 In one embodiment, the syringe is filled with a drug product, such as in the form of liquid, solution, powder or solid. In another embodiment the drug product is a solution such as a drug solution or protein solution that is otherwise sensitive to exposure to high temperatures, such as those used in steam sterilization, and ionizing energy, such as gamma or beta rays and oxidizing gasses. In yet another embodiment the drug product is one that has been lyophilized, in other words a solid, and requires reconstitution in
10 liquid or solution prior to use.

In another embodiment, a solution is any drug product having requirements or desirability for sterility of the drug product container surface. In one particular embodiment, the drug product is a protein solution, such as ranibizumab (e.g. 6mg/ml or 10 mg/ml) solution for intravitreal injection.

15 In one embodiment, the container is filled with solution under aseptic conditions, whether by an automated or manual process. Thus, the contents of the container are sterile and unaffected by surface decontamination methods as described herein. The term "filled" is meant to refer to the placement of contents, such as solution, into the container in an appropriate amount, such as an appropriate volume or appropriate
20 concentration. The appropriate amount, volume or concentration will vary depending on the nature of the contents and their intended use.

In one embodiment, the container is considered a primary packaging for the solution contained within. In another embodiment, the prefilled container is packaged within a secondary package or packaging encasing the prefilled container. Suitable
25 secondary packaging includes wrappings, such as paper, plastic or foil, and blister packs impermeable for microbes.

In one embodiment the prefilled container in secondary packaging undergoes decontamination, such that the contents of the secondary packaging, specifically the surfaces of the prefilled container, are decontaminated and terminally sterilized. Thus,
30 prefilled container surfaces enclosed in a secondary packaging decontaminated by the

methods described herein can be presented to, and opened within, a critical or sterile environment, such as a surgical suite.

In one embodiment, terminal sterilization and surface decontamination of prefilled containers within secondary packaging is carried out by treating surfaces of the prefilled container within secondary packaging with vaporized-hydrogen peroxide and applying post-treatment measures, within a decontamination chamber. A suitable decontamination chamber is any chamber, such as an autoclave, that has the means for reversibly sealing a closed environment and equipped with means of manipulating pressure, temperature, inflow and outflow of air within the chamber. Additional elements of a suitable chamber include the means for accommodating treatment by vaporized-hydrogen peroxide and post-treatment measures to reduce or prevent vaporized-hydrogen peroxide from entering into prefilled containers.

In another embodiment, the chamber is configured to accommodate the quantity of containers requiring terminal sterilization. Thus, in large-scale production and assembly lines, the chamber can be configured to accommodate a large quantity of containers, accordingly.

Treatment with vaporized-hydrogen peroxide is brought about by the application or release of hydrogen-peroxide-vapors within the decontamination chamber. In one embodiment, vapors of hydrogen peroxide are controllable, in other words, certain post-treatment measures are applied to manipulate or control the action of vaporized-hydrogen peroxide. In one embodiment, post-treatment measures are applied that direct — or reverse — the direction of vapor diffusion, such that vapors are prevented from entering into the prefilled container. In another embodiment, additionally post-treatment measures are applied that destroy any residual peroxide traces.

In one embodiment, post-treatment measures include reducing or eliminating gas radicals formed by action of vaporized-hydrogen peroxide. In yet another embodiment, post-treatment measures include inactivating vaporized-hydrogen peroxide action, such as oxidative action.

In another embodiment, terminal sterilization and surface decontamination of prefilled containers within secondary packaging is achieved by application of tunable beta ray irradiation. In one embodiment, the surface of a prefilled container in secondary

packaging is decontaminated by an adjustment of accelerator voltage of an irradiation generator to provide beta radiation of a sufficient dose to penetrate secondary packaging without penetrating primary packaging.

In another embodiment, the accelerator voltage required to deliver the appropriate amount of beta radiation to decontaminate the surface of prefilled containers depends on the thickness of secondary packaging materials. For example, in one embodiment, suitable packaging materials are less than or equal to 0.05 mm in thickness. Such materials of less than or equal to 0.05 mm in thickness may be made of foils.

In another embodiment a combination of secondary and primary packaging components, accelerator voltage, irradiation plant design and throughput speed allow surface decontamination of a prefilled container in secondary packaging, while almost completely shielding contents of the prefilled container by primary packaging materials.

In one embodiment, a suitable primary packaging is a syringe capable of shielding irradiation sensitive solution contained within. Shielding can be provided by the thickness of the container walls or the material components of the container. Shielding effectiveness can be determined by adjustment of the accelerator voltage and thus the depth of penetration of the beta rays emitted onto the prefilled container. Furthermore, shielding is determined by measuring the absorbed dosage, such as with a dosimeter.

It is understood by those in the art that a prefilled container is assembled under aseptic conditions, such that the contents of the container are sterile. While contents of the container are sterile, the surface of the container is susceptible to contamination during further packaging and product labeling using standard pharmaceutical packaging protocols. For surface decontamination of prefilled containers, the sterilization methods herein are adaptable to standard production and packaging of pharmaceutical products in isolation or outside of isolation.

In one embodiment, a prefilled container previously filled under aseptic conditions and labeled and packaged into secondary packaging by a manual or automated process is presented to an electron beam tunnel for terminal sterilization and surface decontamination of the final packaged product. In one embodiment, the prefilled

container in secondary packaging is introduced, either by a manual process or automated process, or a combination of the two, into the electron beam tunnel via an inlet and transported for all or a portion of time through the e-beam tunnel to an outlet as the surfaces of prefilled containers in secondary packaging are exposed to low-energy beta radiation. In another embodiment, prefilled containers in secondary packaging remain stationary for all or a portion of time as the surfaces of prefilled containers in secondary packaging are exposed to low-energy beta radiation. In another embodiment, the electron beams are oscillated, e.g. by application of magnetic fields, such that the whole surface of the object is scanned by the electron beam. In another embodiment, the object is passed below the scanning electron beams by means of a transport mechanism like a moving conveyor. In another embodiment, the chamber for electron beam treatment is open, but shielded to the environment by a tortuous path of the objects into and out of the chamber.

15 *Terminal Sterilization of Prefilled Container by Vaporized-hydrogen peroxide (VHP)*

In one embodiment, terminal sterilization of prefilled containers in secondary packaging is carried out by antimicrobial treatment in a chamber with vaporized-hydrogen peroxide, also referred to as "cold sterilization".

The various steps, or operations, involved in the sterilization and surface decontamination process can be performed automatically under the administration of a system manager, such as a microprocessor. Alternatively, operations can be performed separately in manual operations. Furthermore, operations can be performed in a combination of automated and manual processes.

In one embodiment prefilled containers are enclosed in secondary packaging following filling of containers under aseptic conditions. In another embodiment, prefilled containers are labeled with any product information, such as product name, indications; use instructions, etc., prior to encasement of prefilled containers in secondary packaging.

In one embodiment, prefilled containers in secondary packaging are presented either manually or automatically to, and secured within, a decontamination chamber.

A suitable decontamination chamber is any chamber, such as an autoclave, equipped with means for reversibly sealing a closed environment, and equipped with means of manipulating pressure, temperature, inflow and outflow of air within the chamber. Additional elements of a suitable chamber include means for accommodating
5 treatment by VHP and post-treatment measures to reduce or prevent VHP from entering into prefilled containers. A further element of a suitable chamber is means to destroy any remaining peroxide traces.

In one embodiment, hydrogen peroxide vapor is introduced into the chamber, either generated within or released within the chamber for a sufficient time to
10 decontaminate —or treat — the surface of prefilled containers in secondary packaging. In another embodiment, application of vaporized-hydrogen peroxide is carried out at temperatures below those used for steam sterilization.

Hydrogen peroxide in liquid form has long been recognized as a disinfectant. Koubek U.S. Patent No. 4,512,951 describes a method of sterilization with liquid
15 hydrogen peroxide which includes vaporizing an aqueous solution of hydrogen peroxide and passing the resulting hydrogen peroxide-water vapor mixture into an evacuated sterilization chamber where, upon contact with items to be sterilized, the vapor condenses to form a layer of liquid hydrogen peroxide on the items. The items to be sterilized are maintained at a temperature below the dew point of the hydrogen
20 peroxide-water mixture to assure condensation, but the overall chamber temperature must be high enough to prevent condensation of the incoming vapor before it reaches the items. Following a suitable time for sterilization, the condensate is revaporized by passing filtered, preferably heated air over the surface of the items. Sterilization with gaseous hydrogen peroxide is described by Moore et al. U.S. Patent No. 4,169,123 and
25 Forstrom et al. U.S. Patent No. 4,169,124. The methods described in those two patents involve surrounding an article to be sterilized with vapor phase hydrogen peroxide and maintaining contact between the article and the sterilant at temperatures below 80°C until sterility is achieved. The lowest temperature disclosed in either the Moore or Forstrom patents is 20°C.

30 It has been determined that with sensitive solutions, such as protein solutions, leaching of vaporized-hydrogen peroxide into the prefilled container is detrimental to the

molecular integrity of the solutions because hydrogen peroxide vapors that enter the container cause chemical modifications of the solution, such as oxidation.

It has now been discovered that applying post-treatment, or post-application, measures reduces or prevents the adverse effects of VHP on sensitive solutions and preserve the integrity, and thereby therapeutic efficacy, of otherwise sensitive solutions in prefilled containers. Post-application measures are ideally those measures that deactivate the oxidizing action of hydrogen peroxide, whether by removing vaporized-hydrogen peroxide or rendering hydrogen peroxide vapors into an inactive state.

In one embodiment, leaching of VHP into a prefilled container is prevented by application of a vacuum at the end of the antimicrobial treatment in the chamber to inverse the diffusion direction of hydrogen peroxide vapors. By reversing the direction of vapor flow, hydrogen peroxide vapors are prevented from entering the prefilled container, thereby maintaining the integrity of the sensitive solution within the container while the surface of the container is decontaminated.

In yet another embodiment, hydrogen peroxide vapors are inactivated, such that they are incapable of chemically modifying the solution contained in a prefilled container. In another embodiment, post-treatment measures include neutralizing the oxidative ability of hydrogen peroxide vapors. In yet another embodiment, hydrogen peroxide vapors are inactivated by application of ultraviolet rays to the container after a sufficient exposure time of prefilled container to VHP following treatment. Other suitable inactivating agents, such as chemical agents or gas plasma, can be applied post-treatment to inactivate VHP following a sufficient exposure time of the surfaces of prefilled containers to VHP.

At the conclusion of the terminal sterilization process, the prefilled container in secondary packaging may be removed from the chamber, and is suitable for use by an end user.

In one embodiment, the sterilization process may be performed by an automated system. For example, referring to FIG. 2, illustrated is a block diagram of a system 200 for decontaminating a surface of a prefilled container in secondary packaging. System 200 includes a sealed chamber 202 and a control unit 204 coupled, directly or indirectly, to the chamber 202.

In one embodiment, the sealed chamber 202 may be any suitable decontamination chamber. For instance, the chamber 202 may include an autoclave, with the ability to reversibly seal a closed environment. The chamber 202 may also be equipped with mechanisms to manipulate pressure, temperature, and inflow and outflow of air within the chamber 202.

Control unit 204 provides instructions, in the form of signals, to chamber 202 to perform operations associated with sterilizing a prefilled container 100 (such as shown in Fig. 1) in a prescribed-automatic manner. Control unit 204 may transmit signals to chamber 202 to direct chamber 202 (or related parts) to physically enable a vaporized-hydrogen peroxide to come into contact the surface of the prefilled container in the secondary packaging.

For example, in one embodiment, the control unit 204 may transmit a signal to a valve (not shown) associated with a reservoir for passing vaporized-hydrogen peroxide into the chamber. The control unit 204 measures a preset duration-of-time the vaporized-hydrogen peroxide is to remain in contact with the prefilled-container surface. Upon expiration of the preset duration-of-time, the control unit 204 transmits a signal to chamber 202 (or a related device) to cause a post-decontamination measure to occur to reduce the presence of vaporized-hydrogen peroxide in the chamber, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container undergoing surface decontamination.

For example, following surface decontamination, the control unit 204 may transmit a signal to a vacuum (not shown) to reverse the flow of hydrogen-peroxide vapors out of the chamber 202 to remove these vapors from the chamber. Other suitable control mechanisms for controlling hydrogen-peroxide vapors include mechanisms for introducing neutralizing or inactivating agents, such as chemical agents, into the chamber 202, which upon contact with hydrogen-peroxide vapors render the vapors inactive, and thus harmless to the interior solution of a prefilled container.

Reference is made to treatment times that are sufficient to terminally sterilize the prefilled container. In one embodiment, a sufficient treatment time or the duration of the presence of vaporized-hydrogen peroxide within the chamber to sufficiently

decontaminate the container surface is determined by routine validation. For example, containers that have been subjected to treatment by vaporized-hydrogen peroxide are compared to controls and can be checked for bacterial contamination using standard laboratory protocols, such as incubation of suspected contaminated object with bacterial growth medium and then checking for bacterial growth, generally performed by the use of bioindicators. By plotting treatment time against presence of bacterial growth, the treatment time to achieve decontamination, thus the absence of bacterial growth, can easily be determined. Validation techniques apply whether terminal sterilization is carried out by vaporized-hydrogen peroxide as described above or carried out by exposure to beta radiation as described below.

In one embodiment, the control unit 204 is automated, and operates in accordance with code executing on a processor. The implementation of a control unit will be well within the scope of someone skilled in the art. For instance, the control unit may be any personal computer, microprocessor, or other suitable devices, capable of executing code that is programmed to transmit signals to devices associated with physically carrying out the sterilization process.

It will be appreciated that the various steps, or operations, involved in the sterilization and surface decontamination process can be performed automatically under the administration of a control unit as described above. Alternatively, operations can be performed separately in manual operations. Furthermore, operations can be performed in a combination of automated and manual processes.

Terminal Sterilization of Prefilled Containers by Tunable-Beta Irradiation

In one embodiment, terminal sterilization of prefilled containers in secondary packaging is carried out by a decontamination treatment in a chamber equipped with one or more electron beam generators that are tunable to generate an appropriate dose of beta radiation onto the surfaces of the prefilled containers.

The various steps, or operations, involved in the sterilization and surface decontamination process can be performed automatically under the administration of a system manager, such as a microprocessor. Alternatively, operations can be performed

separately in manual operations. Furthermore, operations can be performed in a combination of automated and manual processes.

In one embodiment prefilled containers are enclosed in secondary packaging following filling of containers under aseptic conditions. In another embodiment, prefilled
5 containers are labeled with any product information, such as product name, indications; use instructions, etc, prior to encasement of prefilled containers in secondary packaging.

In one embodiment, prefilled containers in secondary packaging are presented either manually or automatically to a decontamination chamber with an inlet side and an
10 outlet side. In another embodiment the decontamination chamber is an electron beam tunnel. In yet another embodiment, prefilled containers are mechanically moved through the tunnel from the inlet side to the outlet side on a movable mechanism, such as a conveyor. Thus, prefilled containers move through the chamber as the surfaces of prefilled containers are exposed to beta irradiation.

15 In another embodiment, the electron beams are oscillated, e.g. by application of magnetic fields, such that the whole surface of the object is scanned by the electron beam. In another embodiment, the object is passed below the scanning electron beams by means of a transport mechanism like a moving conveyor.

In one embodiment, the surfaces of prefilled containers in secondary packaging
20 are decontaminated during an exposure time of low penetration beta radiation of less than one second, ideally in less than one-half second. Thus, treatment times with tunable-beta radiation as described herein are significantly less than decontamination using gamma rays, which require surface treatment times of several hours or longer for sufficient decontamination and sterilization.

25 In another embodiment, the electron beam tunnel is configured with an electron beam generator, whereby the voltage of energy generated is tunable.

In yet another embodiment, prefilled containers in secondary packaging are transported or moved about in a fashion as to expose all surfaces of the containers to emitted beta radiation within the tunnel.

30 Primary packaging containers for sterile pharmaceutical drug products are often up to about 30-fold thicker than the secondary packaging material. In one embodiment

the thickness of the wall of the primary packaging material is 20 or more times thicker than the thickness of the secondary packaging material, thus allowing a resulting dose absorbed by the contents in the prefilled container to less than 0.1 kGy.

It has been discovered that it is possible to find a combination of packaging components, accelerator voltage, irradiation plant design and throughput speed that allow a surface decontamination or surface sterilization of a prefilled container in secondary packaging, while the contents of the container are essentially shielded by the primary packaging material. Therefore, beta irradiation does not affect sensitive biomolecules, such as biotech drug solutions, inside the primary packaging materials.

In one embodiment, beta irradiation of the prefilled container may be conducted at any dosage useful to provide effective sterilization without degrading the container or its contents, using any known beta irradiation apparatus, such as a low voltage generator or particle accelerator, with the amount of radiation depending on the thickness of the secondary packaging

In one embodiment the minimum sterilizing dose (MSD) of beta radiation is that required to deliver the required SAL for the product. In one embodiment sterilizing doses are measured with Gray (Gy) or Rad (radiation absorbed dose). In another embodiment, absorbed doses are measured by dosimeter, preferably by film dosimeters, calorimeters or cerium dosimeters.

In another embodiment, the amount of radiation depends on the presence of secondary packaging and the thickness of the secondary packaging. For a typical prefilled container, the beta radiation is desirably provided at a dosage of 25 kGy at the surface of the prefilled container.

In one embodiment, a particle accelerator generates beta-particle acceleration through a vacuum tube. In one embodiment, acceleration is by means such as magnetic field, electrostatic charge or by energy transfer from high frequency electromagnetic waves.

At the conclusion of the terminal sterilization process, the prefilled container in secondary packaging leaves the tunnel by the outlet with surfaces decontaminated and is suitable for use by an end user. Because treatment time for surface decontamination is as short as about one second, surface decontamination of prefilled containers in

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secondary packaging offers numerous advantages over sterilization methods involving gamma radiation, which are harmful to container contents, require significantly longer exposure times for decontamination, and require additional shielding along the production line, and cause discoloration of packaging components. Moreover, sterilization techniques involving gamma radiation cause significant bottlenecks in production assembly lines which are eliminated by surface decontamination using tunable-beta radiation in an e-beam tunnel.

In one embodiment, as depicted in Fig. 3, a system 300 — for surface-decontaminating a prefilled container in secondary packaging — includes an electron-beam tunnel 302 equipped with one or more tunable-electron beam generators, shown as voltage generators 304. In another embodiment, the one or more tunable-electron-beam generators 304 of the system are configured to variably generate low-energy beta radiation. Alternatively, electron beams are oscillated, such that the electron beams hit a larger surface of a prefilled container and increase the exposure surface of the container.

In yet another embodiment, the one or more generators 304 apply an accelerator voltage to produce a sufficient amount of beta radiation to decontaminate the surface of the prefilled container, wherein the sufficient amount of beta radiation depends on the thickness of the secondary package and the thickness of the prefilled container. Thus, beta radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

Reference is made to treatment times that are sufficient to terminally sterilize and surface decontaminate the prefilled container. In one embodiment, a sufficient treatment time or the duration of the presence of low-energy beta radiation within the tunnel to sufficiently decontaminate the container surface is determined by routine validation. For example, containers that have been subjected to treatment by beta radiation are compared to controls and can be checked for bacterial contamination using standard laboratory protocols, such as incubation of suspected contaminated object with bacterial growth medium and then checking for bacterial growth. By plotting treatment time against presence of bacterial growth, the treatment time to achieve decontamination, thus the absence of bacterial growth, can easily be determined. Validation techniques

apply whether terminal sterilization is carried out by beta radiation as described above or carried out by exposure to VHP as described above.

Reference is now made to the following examples. These examples are provided for the purpose of illustration only and should in no way be construed as being limited to these examples but rather should be construed to encompass any and all variations, which become evident as a result of the teaching provided herein.

Example 1

In the following experiment, prefilled syringes were treated with a vaporized-hydrogen peroxide sterilization treatment in a chamber, either by a single pass through a VHP sterilization procedure or two passes (shown in the table below as 2 x) through a VHP sterilization procedure. Syringes containing protein solutions treated by VHP were compared to control syringes treated with VHP to determine if the integrity of proteins present in solution was maintained.

A formulation as described in U.S. Patent No. 7,060,269 was tested for protein degradation following treatment by VHP.

Approximately 10 mL of solution was filtered through a 0.22 µm syringe filter. (Millex GV filter available from Millipore, Billerica, MA USA.) Filling of 0.5 mL syringes was performed in a sterile lab for hydrogen peroxide treatment.

Analysis after the treatment with VHP revealed the following protein contents, visualized by HPLC analysis: byproducts and degradation products by HPLC (IEC) and by-products and degradation products by HPLC (SEC).

Table 1: Protein Stability Following Treatment with VHP.

Batch	IEC (% main peak)	IEC (% basic peak)	SEC (% monomer)
Control			
9823.01 CSi	98	2	100
9823.02 CSi	98	2	100
1 x treatment			
9823.04 CSi	98	2	100

9823.05 CSi	98	2	100
2 x treatment			
9823.07	98	2	100
9823.08	98	2	100

The results seen were within the requirement; there were no differences between the results of the untreated syringes and with hydrogen-peroxide treated syringes. Analysis can also be carried out at different time points following treatment, such as 1 month, 3 months and six months following treatment by VHP, or over the shelf-life of the product of the prefilled container. Analysis can be carried out to determine continued stability of the protein solution, including tests by HPLC for presence of by-products using standard HPLC laboratory protocols. Analysis can also be carried out by the presence of physical changes, such as measuring the concentration of H₂O₂ in solution by a fluorescence test using an over-the-counter commercially available kit in conjunction with an apparatus with fluorescence detection.

Example 2

The following experiment was carried out to determine the effectiveness of surface decontamination using beta irradiation. A commercially available e-beam tunnel for outside decontamination of containers, equipped with KeVAC accelerators from Linac Technologies (Orsay, France), was used to investigate the penetration depth of the electron beam in different materials. For example, penetration was measured in a polyethylene bag with foil thickness of 50 µm, an aluminum bag with foil thickness of 0.1 mm and a glass slide of 1 mm thickness.

To increase sensitivity of the study, multiple passes of the samples through the tunnel were investigated. Far West 60 Film dosimeters, available from Far West Technologies (Santa Barbara, CA, USA) were used to record the radiation absorbed.

Table 2: Beta Irradiation Absorption by Packaging Materials:

Number of passes through decontamination tunnel	Absorbed dose		
	Dosimeter in	Dosimeter in	Dosimeter shielded by

	Polyethylene bag	aluminum bag	1 mm glass slide
1 pass	30 kGy	1.3 kGy	<LOQ(0.1 kGy)
3 passes	97 kGy	64 kGy	<LOQ(0.1 kGy)
5 passes	207 kGy	105 kGy	<LOQ (0.1 kGy)

The feasibility study showed that already with these not optimized settings of the electron beam decontamination tunnel a surface sterilization could be obtained (≥ 25 kGy) when the product was packaged into plastic bags. Even after 5 times passing through the electron beam treatment tunnel, the absorbed dose within the packaging material (behind a 1 mm thick glass wall) was far below the limit of quantitation which was 1 kGy for the dosimeters used.

Additionally, the oxidative stress exerted on a 0.5% Polysorbate 20 solution in prefilled glass syringes (1mL long, ISO) was investigated by measurement of peroxides according to standard protocols. The total amount of peroxides was measured by the Ferrous Oxide Oxidation (FOX) test, according to a standard protocol.

Table 3: Peroxide Levels Following Beta Irradiation of Prefilled Containers:

Number of passes through E-beam tunnel	Peroxide content of 0.5% Polysorbate 20 solution in water in 1mL long glass syringe (ISO) [μ Mol/mL]
Reference (not treated)	0.04
1 pass	0.04
3 passes	0.03
5 passes	0.05

No significant influence of the electron beam treatment on the peroxide content of the solution enclosed in glass syringes could be observed. Thus, beta irradiation proved safe to solutions within prefilled containers:

Additionally, the oxidative stress exerted on protein solution in prefilled glass vials was investigated by measurement of degradation products according to standard protocols.

A formulation as described in U.S. Patent No. 7,060,269 was tested for protein degradation following treatment by electron beam irradiation. Approximately 0.3 mL of

solution was filtered through a 0.22 µm filter and aseptically filled into pre-sterilized glass vials, aseptically closed with a sterile rubber stopper and secured with an aluminum crimp cap.

The containers were passed through the above described e-beam tunnel with identical settings as for the other experiments mentioned above. Containers were analyzed after the treatment with electron beam radiation to determine protein contents, visualized by HPLC analysis for byproducts and degradation products by HPLC (IEC), as performed above in Example 1.

Table 4: Protein Stability Following Beta Irradiation of Prefilled Containers

Number of passes through E-beam tunnel	IEC (% main peak)	IEC (% basic peak)
Reference (not treated)	98 (97.8)	1 (1.2)
1 pass	98 (97.8)	1 (1.3)
3 passes	98 (97.5)	2 (1.5)
5 passes	98 (97.6)	1 (1.4)

There were no differences between the results of the untreated syringes and with electron beam sterilized vials, following 1 pass, 3 passes or 5 passes through the e-beam sanitization process, as shown in the results at Table 4. Thus, tunable-beta radiation as described herein proved safe to solutions within prefilled containers.

The described embodiments are to be considered in all respects only as exemplary and not restrictive. The scope of the invention is, therefore, indicated by the subjoined claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS

We claim:

- 5 1. A method for surface decontamination of a prefilled container in secondary packaging, comprising:
- applying vaporized-hydrogen peroxide to the surface of the prefilled container in secondary packaging;
- allowing vaporized-hydrogen peroxide to remain in contact with the
- 10 prefilled container surface for a sufficient time to decontaminate the prefilled container surface; and
- causing a post-decontamination measure to occur to reduce the presence of vaporized-hydrogen peroxide, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container.
- 15 2. The method of claim 1, wherein the prefilled container is a syringe containing a drug product otherwise sensitive to sterilization treatment by gamma radiation, sterilization treatment by exposure to steam, and sterilization treatment by exposure to vaporizing agents and gases.
- 20 3. The method of claim 1 or claim 2, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.
- 25 4. The method of any previous claim, wherein sufficient time to decontaminate the surface of the prefilled container is determined by validation of treatment times and compared to a control standard.
- 30 5. The method of any previous claim, wherein the post-decontamination measure includes applying a vacuum following the duration of treatment with vaporized-hydrogen peroxide, thereby reversing the direction of diffusion of vaporized-hydrogen peroxide and preventing intrusion of vaporized-hydrogen peroxide into the prefilled container.

- 5 6. The method of any of claims 1-4, wherein the post-decontamination measure includes applying ultraviolet rays following the duration of treatment with vaporized-hydrogen peroxide, thereby inactivating oxidative action of hydrogen peroxide vapors.
7. The method of any of claims 1-4, wherein the post-decontamination measure includes gas plasma treatment.
- 10 8. A method for surface decontamination of a prefilled container in secondary packaging, comprising:
- 15 presenting a prefilled container in a secondary package to an electron beam tunnel equipped with one or more tunable electron beam generators capable of variably generating low-energy beta radiation, and capable of oscillating electron beams such that a larger surface of the prefilled container is exposed to beta radiation during decontamination; and
- 20 applying an accelerator voltage of the one or more tunable electron beam generators to produce a sufficient amount of beta radiation to decontaminate the surface of the prefilled container, wherein the sufficient amount of beta radiation depends on the thickness of the secondary package and the thickness of the prefilled container, such that beta radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.
- 25 9. The method of claim 8, wherein the thickness of the wall of the primary packaging material is 20 or more times thicker than the thickness of the secondary packaging material, thus reducing the dose absorbed by the product in the container to less than 0.1 kGy.
- 30 10. The method of claim 8 or claim 9, wherein the prefilled container is a vial filled with a solution or solid otherwise sensitive to sterilization treatment by gamma

radiation, sterilization treatment by exposure to steam, and sterilization treatment by exposure to vaporizing agents, gases or peroxide forming substances.

5 11. The method of any one of claims 8-10, wherein the prefilled container is a syringe filled with a solution otherwise sensitive to sterilization treatment by gamma radiation, sterilization treatment by exposure to steam, and sterilization treatment by exposure to vaporizing agents and gases or peroxide forming substances.

10 12. The method of any one of claims 8-11, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

13. The method of any one of claims 8-12, wherein the penetration depth is measured by dosimetry.

15 14. The method of any one of claims 8-13, wherein sufficient energy to decontaminate a surface of a prefilled container is that which provides a dose of beta radiation of at least approximately 25 kGy to the container surface.

20 15. The method of any one of claims 8-14, wherein sufficient energy to decontaminate a surface of a prefilled container is that which provides a dose of beta radiation yielding a 10^{-6} Sterility Assurance Level of the outside of the container surface.

25 16. A system for decontaminating a surface of a prefilled container in secondary packaging, the system comprising:

a sealed chamber; and

30 a control unit coupled to the chamber, the control unit configured to automatically (i) enable a vaporized-hydrogen peroxide to contact the surface of the prefilled container in the secondary packaging; (ii) allow the vaporized-hydrogen peroxide to remain in contact with the prefilled-container surface for a

predetermined time; and (iii) cause a post-decontamination measure to occur to reduce the presence of vaporized-hydrogen peroxide in the chamber, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container.

5

17. A system for surface-decontaminating a prefilled container in secondary packaging, the system comprising: an electron-beam tunnel equipped with one or more tunable-electron beam generators, the tunable-electron-beam generators, configured to (i) variably generate low-energy beta radiation, (ii) oscillate the
10 electron beams such that a larger surface of a prefilled container is exposed to electron beams; and (iii) apply an accelerator voltage to produce a sufficient amount of beta radiation to decontaminate the surface of the prefilled container, wherein the sufficient amount of beta radiation depends on the thickness of the secondary package and the thickness of the prefilled container, such that beta
15 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

18. A kit for decontaminating the surface of a prefilled container in secondary packaging in a sealed chamber, the kit comprising: an instruction for using the
20 sealed chamber to (i) apply a vaporized-hydrogen peroxide to contact the surface of the prefilled container in the secondary packaging; (ii) allow the vaporized-hydrogen peroxide to remain in contact with the prefilled-container surface for a predetermined time within the sealed chamber; and (iii) cause a post-decontamination measure to occur to reduce the presence of vaporized-
25 hydrogen peroxide in the chamber, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container.

19. A kit for surface-decontaminating a prefilled container in secondary packaging,
30 the kit comprising: an instruction for (i) variably generating low-energy beta radiation to contact the surface of the prefilled container; and (ii) produce a

sufficient amount of beta radiation to decontaminate the surface of the prefilled container, wherein the sufficient amount of beta radiation depends on the thickness of the secondary package and the thickness of the prefilled container such that beta radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

20. A system according to claim 16 or a kit according to claim 18, wherein post-decontamination measure includes gas plasma treatment.

1/1

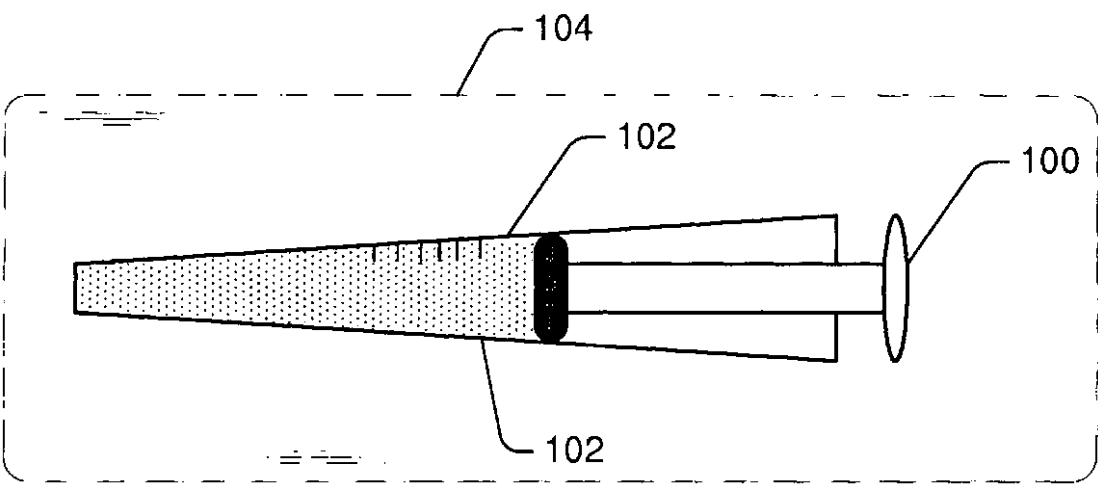


Fig. 1

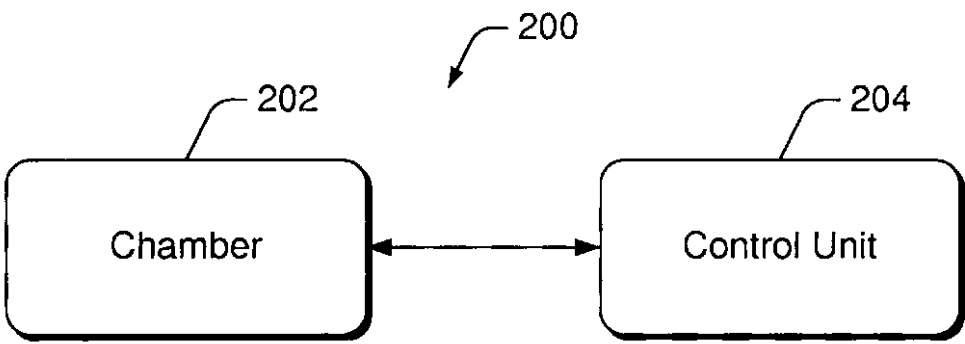


Fig. 2

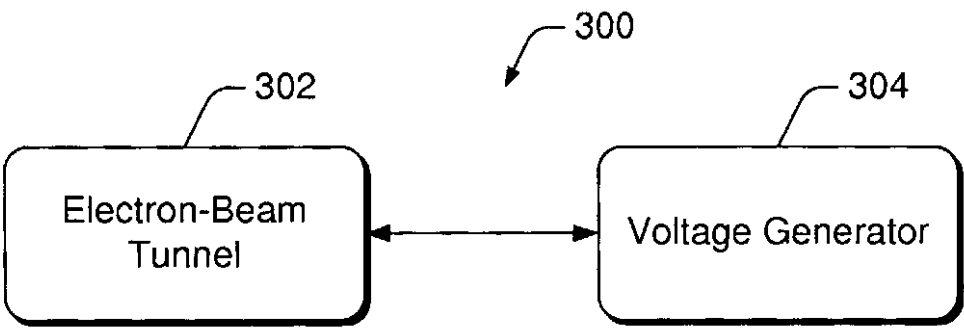


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/060011

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61L2/00 A61L2/20 B65B55/10 A61L2/08 B65B55/08
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L B65B

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)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 779 973 A (EDWARDS STEVEN JAY [US] ET AL) 14 July 1998 (1998-07-14)	1,5,16
Y	column 4, line 3 - line 30 column 5, line 6 - column 6, line 24; figures 1,2,5	2-7,18
Y	----- WO 2008/077155 A (GENENTECH INC [US]; LAM XANTHE M [US]; NGUYEN TUE [US]) 26 June 2008 (2008-06-26)	3
A	page 13, line 10 - line 15	12
Y	----- EP 1 433 486 A (CLOSURE MEDICAL CORP [US]) 30 June 2004 (2004-06-30)	1,2,4,5, 16,18
A	paragraphs [0008], [0024], [0032], [0033], [0035], [0042]; example 3. ----- -/--	8,17

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/060011

G(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/020847 A (COOK BIOTECH INC [US]; HILES MICHAEL C [US]; HODDE JASON P [US]; ERNST) 10 March 2005 (2005-03-10)	6
A	page 23, line 25 - line 30 page 26, line 1 - page 27, line 22	8,17
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Y	EP 1 944 044 A1 (BECTON DICKINSON FRANCE [FR]) 16 July 2008 (2008-07-16) paragraphs [0006], [0009], [0010], [0042], [0045], [0051], [0054]	8-11, 13-15,17
A	US 6 189 292 B1 (ODELL ROBERT B [US] ET AL) 20 February 2001 (2001-02-20) column 11, line 23 - line 27; claim 1	8,17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2010/060011

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7, 16, 18, 20

Independent method claim 1 defines a method for surface decontamination of a prefilled container in a secondary packaging comprising the steps of a) applying vaporised hydrogen peroxide (VHP) to the surface of the prefilled container, b) allowing sufficient decontamination contacting time and c) reducing the presence of VHP to prevent it from diffusing into the prefilled container.

2. claims: 8-15, 17, 19

Independent method claim 8 defines a method for surface decontamination of a prefilled container in a secondary packaging comprising the steps of a) presenting a prefilled container in one or more tunable e-beam generators capable of generating variable low-energy beta radiation and oscillating electron beams and b) applying a sufficient acceleration voltage to decontaminate the surface of the prefilled container, such that beta radiation penetrates the secondary package, while the container thickness shields the contents from the beta radiation.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/060011

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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B65B 55/10 (2006.01)

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13 July 2010 (13.07.2010)

(25) Filing Language:

English

(26) Publication Language:

English

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(75) Inventor/Applicant (for US only): SIGG, Jürgen [DE/CH]; c/o Novartis Pharma AG, Postfach, CH-Basel (CH).

(74) Agent: SPINNER, David, Richard; Novartis Pharma AG, Patent Department, CH-4002 Basel (CH).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

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

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

(54) Title: 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.

Surface Decontamination of Prefilled Containers in Secondary Packaging

FIELD OF THE INVENTION

5 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

10 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
15 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.

20 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
25 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.

30 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

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
5 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.
10 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
15 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.

20 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
25 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.

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

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.

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.

5 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.

10 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
15 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.

20 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
25 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.

30 DETAILED DESCRIPTION

The method and system described herein are for the sterilization and surface decontamination of prefilled containers containing sensitive solutions, such as drug products that are otherwise temperature or radiation sensitive or are sensitive to traces of oxidizing substances, and thus not suitable for terminal sterilization by classical methods involving steam, gamma or beta rays or sterilization with oxidizing gases or liquids. The method and system described herein are especially suited for prefilled containers that have been filled under aseptic conditions and been subject to additional processing, such as product labeling and subsequent secondary packaging. Methods include terminal sterilization and surface decontamination by exposing prefilled containers in secondary packaging to tunable-beta radiation and further include terminal sterilization and surface decontamination by exposing prefilled containers to controllable vaporized-hydrogen peroxide, including measures to reduce or prevent the diffusion of vaporized-hydrogen peroxide into prefilled containers. The methods also include an optional step of actively destroying any residual peroxide molecules, for example, by means of gas plasma.

Definitions

In describing and claiming the terminal sterilization and surface decontamination method, the following terminology will be used in accordance with the definitions set forth below.

"Aseptic" conditions refer to conditions free of bacterial or microbial contamination.

"Administration" refers to the method of administering treatment to a subject or patient in need thereof, such as parenteral administration, intravenous administration and intravitreal administration.

"Beta irradiation" refers to sterilization methods using beta rays.

"Cold sterilization" refers to sterilization techniques employing chemical agents, gases, or irradiation. A requirement of cold sterilization is that the technique is carried out at temperatures below those used for steam sterilization, such as autoclavation.

"Container", as used herein, is meant to include vials, syringes, bags, bottles, or other means useful for storage of medical treatments, such as drug products, whether in

solid or liquid form, and other biological agents, such as peptides, proteins or recombinant biologicals, whether in solid or liquid form. Containers may be reusable or disposable, and may have a medical, veterinary or non-medical purpose.

5 "Prefilled container", refers to a container, such as a syringe, that is filled with a solution at the time of assembly and packaging and is deliverable for use to an end user, such as a health care professional or a patient needing treatment. This term also refers to prefilled containers integrated into an administration device.

10 An "instruction" or "instructional material" includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of the method or system of the invention for its designated use. The instruction or instruction material may be presented together as part of the system or provided separately, or independently of the process, to an end user.

15 "Isolation", as used herein refers to practices in pharmaceutical production, filling and packaging, wherein a clean, or sterile environment, is separated from a non-sterile environment to limit or prevent the introduction or spread or contamination of infectious agents, such as microorganisms.

20 "Medical device", as used herein, refers to a device used for administering medical treatment and whose production or sale must, in part, comply with requirements, such as safety requirements, set forth by a government agency, such as the Food and Drug Administration.

25 "Solution" as used herein refers to the contents of a container like a vial or a prefilled syringe and includes solutions of biological therapeutics and drug products, protein products, peptide products, biological products, imaging solutions and aqueous solutions. Ideally, solutions are those that are temperature, oxidation or radiation sensitive due to the molecular make-up of the solution.

"Secondary packaging" refers to packaging enclosing the prefilled container, such as plastic wrapping, foil wrapping, paper wrapping or other suitable wrapping, such as blister packs.

30 "Terminal-antimicrobial-surface treatment" refers to sanitization or sterilization of an assembled container, such as a syringe filled with a solution that is in turn encased in secondary packaging. Terminal-antimicrobial treatment, or sterilization, allows a

secondarily packaged prefilled container to be provided in sterile outside condition at its point of use.

"Vaporized-hydrogen peroxide" refers to hydrogen peroxide in vapor form capable of creating a microbicidal film on a surface, such as the surface of a container or packaging material.

The terms "sterilization", "decontamination", "sanitization", "antimicrobial treatment" are used interchangeably herein.

"Sterility" as used herein is meant to refer to complete absence of microbial life as defined by a probability of nonsterility or a sterility assurance level (SAL). The required SAL for a given product is based on regulatory requirements. For example, required SALs for health care products are defined to be at least 10^{-6} , i.e. a chance of less than 1:1 million of a non-sterile product for aseptically manufactured and terminally sterilized products, respectively.

Reference herein to "one embodiment" or "an embodiment" means that a particular feature, structure, operation or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, the appearances of such phrases or formulations herein are not necessarily referring to the same embodiment. Furthermore, various particular features, structures, operations or characteristics may be combined in any suitable manner in one or more embodiments.

Terminal sterilization and surface decontamination of prefilled containers

Terminal sterilization is the process of sterilizing and/or decontaminating a final packaged product. In contrast, an aseptic packaging process requires individual product components to be sterilized separately and the final package assembled in a sterile environment. Terminal sterilization of a product provides greater assurance of sterility than an aseptic process. Terminal sterilization is also desired and provides a market advantage in some instances for the use of certain medical devices, such as the use of secondarily packaged prefilled syringes for intravitreal administration.

Described herein are terminal-sterilization methods suitable for prefilled containers containing sensitive products, such as biotech (biological) drug solutions, which can otherwise be compromised when using classical terminal sterilization

processes, such as steam, gamma irradiation or cold sterilization processes currently used in pharmaceutical production and assembly lines. While reference is given to drug products, such as heat or radiation-sensitive drug solutions containing biologicals such as peptides or proteins, it will be understood by those skilled in the art that any suitable drug product that is considered a therapeutic agent, whether in solution or solid form, can be housed — or contained — in a prefilled container. Thus, the prefilled container itself is not drug specific.

It has now been discovered that treatment of prefilled containers in secondary packaging by an application of vaporized-hydrogen peroxide, in which vapors are controllable by certain post-treatment measures, and exposure to tunable-beta radiation, in which the depth of penetration of beta rays into secondary packaging are controllable, are ideal for surface decontamination of prefilled containers, yet not harmful to the stability or integrity of the contents of the prefilled container.

The methods and embodiments described herein are suitable for use in pharmaceutical production and packaging in isolation or outside of isolation. Furthermore, the methods described herein are adaptable to different container formats or types, with minimal incremental costs to production plant design. A system is also provided which allows for surface decontamination of prefilled containers in secondary packaging, as well as a kit comprising instructional material for practicing the method and system described herein.

Referring to Fig. 1, a prefilled container 100 previously filled under aseptic conditions is decontaminated on surfaces 102 following encasement or packaging in a secondary package 104 by vaporized-hydrogen peroxide or tunable-beta radiation as described herein. Fig. 1 shows one exemplary prefilled container, however, it will be understood by those skilled in the art that various containers, other than a syringe, are also suitable. Moreover, while the exemplary container shown at Fig. 1 is a syringe in a closed and assembled position, it should be understood that other variants are envisioned. For example, a prefilled container not sealed by a stopper, plunger or other sealing mechanism can be surface decontaminated on interior portions of the container.

In one embodiment, the prefilled container is a syringe. Other suitable prefilled containers include vials, bottles, bags and other medical devices capable of containing a sterile solution or a solution requiring sterilization.

5 In one embodiment, the syringe is filled with a drug product, such as in the form of liquid, solution, powder or solid. In another embodiment the drug product is a solution such as a drug solution or protein solution that is otherwise sensitive to exposure to high temperatures, such as those used in steam sterilization, and ionizing energy, such as gamma or beta rays and oxidizing gasses. In yet another embodiment the drug product is one that has been lyophilized, in other words a solid, and requires reconstitution in
10 liquid or solution prior to use.

In another embodiment, a solution is any drug product having requirements or desirability for sterility of the drug product container surface. In one particular embodiment, the drug product is a protein solution, such as ranibizumab (e.g. 6mg/ml or 10 mg/ml) solution for intravitreal injection.

15 In one embodiment, the container is filled with solution under aseptic conditions, whether by an automated or manual process. Thus, the contents of the container are sterile and unaffected by surface decontamination methods as described herein. The term "filled" is meant to refer to the placement of contents, such as solution, into the container in an appropriate amount, such as an appropriate volume or appropriate
20 concentration. The appropriate amount, volume or concentration will vary depending on the nature of the contents and their intended use.

In one embodiment, the container is considered a primary packaging for the solution contained within. In another embodiment, the prefilled container is packaged within a secondary package or packaging encasing the prefilled container. Suitable
25 secondary packaging includes wrappings, such as paper, plastic or foil, and blister packs impermeable for microbes.

In one embodiment the prefilled container in secondary packaging undergoes decontamination, such that the contents of the secondary packaging, specifically the surfaces of the prefilled container, are decontaminated and terminally sterilized. Thus,
30 prefilled container surfaces enclosed in a secondary packaging decontaminated by the

methods described herein can be presented to, and opened within, a critical or sterile environment, such as a surgical suite.

In one embodiment, terminal sterilization and surface decontamination of prefilled containers within secondary packaging is carried out by treating surfaces of the prefilled container within secondary packaging with vaporized-hydrogen peroxide and applying post-treatment measures, within a decontamination chamber. A suitable decontamination chamber is any chamber, such as an autoclave, that has the means for reversibly sealing a closed environment and equipped with means of manipulating pressure, temperature, inflow and outflow of air within the chamber. Additional elements of a suitable chamber include the means for accommodating treatment by vaporized-hydrogen peroxide and post-treatment measures to reduce or prevent vaporized-hydrogen peroxide from entering into prefilled containers.

In another embodiment, the chamber is configured to accommodate the quantity of containers requiring terminal sterilization. Thus, in large-scale production and assembly lines, the chamber can be configured to accommodate a large quantity of containers, accordingly.

Treatment with vaporized-hydrogen peroxide is brought about by the application or release of hydrogen-peroxide-vapors within the decontamination chamber. In one embodiment, vapors of hydrogen peroxide are controllable, in other words, certain post-treatment measures are applied to manipulate or control the action of vaporized-hydrogen peroxide. In one embodiment, post-treatment measures are applied that direct — or reverse — the direction of vapor diffusion, such that vapors are prevented from entering into the prefilled container. In another embodiment, additionally post-treatment measures are applied that destroy any residual peroxide traces.

In one embodiment, post-treatment measures include reducing or eliminating gas radicals formed by action of vaporized-hydrogen peroxide. In yet another embodiment, post-treatment measures include inactivating vaporized-hydrogen peroxide action, such as oxidative action.

In another embodiment, terminal sterilization and surface decontamination of prefilled containers within secondary packaging is achieved by application of tunable beta ray irradiation. In one embodiment, the surface of a prefilled container in secondary

packaging is decontaminated by an adjustment of accelerator voltage of an irradiation generator to provide beta radiation of a sufficient dose to penetrate secondary packaging without penetrating primary packaging.

In another embodiment, the accelerator voltage required to deliver the appropriate amount of beta radiation to decontaminate the surface of prefilled containers depends on the thickness of secondary packaging materials. For example, in one embodiment, suitable packaging materials are less than or equal to 0.05 mm in thickness. Such materials of less than or equal to 0.05 mm in thickness may be made of foils.

In another embodiment a combination of secondary and primary packaging components, accelerator voltage, irradiation plant design and throughput speed allow surface decontamination of a prefilled container in secondary packaging, while almost completely shielding contents of the prefilled container by primary packaging materials.

In one embodiment, a suitable primary packaging is a syringe capable of shielding irradiation sensitive solution contained within. Shielding can be provided by the thickness of the container walls or the material components of the container. Shielding effectiveness can be determined by adjustment of the accelerator voltage and thus the depth of penetration of the beta rays emitted onto the prefilled container. Furthermore, shielding is determined by measuring the absorbed dosage, such as with a dosimeter.

It is understood by those in the art that a prefilled container is assembled under aseptic conditions, such that the contents of the container are sterile. While contents of the container are sterile, the surface of the container is susceptible to contamination during further packaging and product labeling using standard pharmaceutical packaging protocols. For surface decontamination of prefilled containers, the sterilization methods herein are adaptable to standard production and packaging of pharmaceutical products in isolation or outside of isolation.

In one embodiment, a prefilled container previously filled under aseptic conditions and labeled and packaged into secondary packaging by a manual or automated process is presented to an electron beam tunnel for terminal sterilization and surface decontamination of the final packaged product. In one embodiment, the prefilled

container in secondary packaging is introduced, either by a manual process or automated process, or a combination of the two, into the electron beam tunnel via an inlet and transported for all or a portion of time through the e-beam tunnel to an outlet as the surfaces of prefilled containers in secondary packaging are exposed to low-energy beta radiation. In another embodiment, prefilled containers in secondary packaging remain stationary for all or a portion of time as the surfaces of prefilled containers in secondary packaging are exposed to low-energy beta radiation. In another embodiment, the electron beams are oscillated, e.g. by application of magnetic fields, such that the whole surface of the object is scanned by the electron beam. In another embodiment, the object is passed below the scanning electron beams by means of a transport mechanism like a moving conveyor. In another embodiment, the chamber for electron beam treatment is open, but shielded to the environment by a tortuous path of the objects into and out of the chamber.

15 *Terminal Sterilization of Prefilled Container by Vaporized-hydrogen peroxide (VHP)*

In one embodiment, terminal sterilization of prefilled containers in secondary packaging is carried out by antimicrobial treatment in a chamber with vaporized-hydrogen peroxide, also referred to as "cold sterilization".

The various steps, or operations, involved in the sterilization and surface decontamination process can be performed automatically under the administration of a system manager, such as a microprocessor. Alternatively, operations can be performed separately in manual operations. Furthermore, operations can be performed in a combination of automated and manual processes.

In one embodiment prefilled containers are enclosed in secondary packaging following filling of containers under aseptic conditions. In another embodiment, prefilled containers are labeled with any product information, such as product name, indications; use instructions, etc., prior to encasement of prefilled containers in secondary packaging.

In one embodiment, prefilled containers in secondary packaging are presented either manually or automatically to, and secured within, a decontamination chamber.

A suitable decontamination chamber is any chamber, such as an autoclave, equipped with means for reversibly sealing a closed environment, and equipped with means of manipulating pressure, temperature, inflow and outflow of air within the chamber. Additional elements of a suitable chamber include means for accommodating
5 treatment by VHP and post-treatment measures to reduce or prevent VHP from entering into prefilled containers. A further element of a suitable chamber is means to destroy any remaining peroxide traces.

In one embodiment, hydrogen peroxide vapor is introduced into the chamber, either generated within or released within the chamber for a sufficient time to
10 decontaminate —or treat — the surface of prefilled containers in secondary packaging. In another embodiment, application of vaporized-hydrogen peroxide is carried out at temperatures below those used for steam sterilization.

Hydrogen peroxide in liquid form has long been recognized as a disinfectant. Koubek U.S. Patent No. 4,512,951 describes a method of sterilization with liquid
15 hydrogen peroxide which includes vaporizing an aqueous solution of hydrogen peroxide and passing the resulting hydrogen peroxide-water vapor mixture into an evacuated sterilization chamber where, upon contact with items to be sterilized, the vapor condenses to form a layer of liquid hydrogen peroxide on the items. The items to be sterilized are maintained at a temperature below the dew point of the hydrogen
20 peroxide-water mixture to assure condensation, but the overall chamber temperature must be high enough to prevent condensation of the incoming vapor before it reaches the items. Following a suitable time for sterilization, the condensate is revaporized by passing filtered, preferably heated air over the surface of the items. Sterilization with gaseous hydrogen peroxide is described by Moore et al. U.S. Patent No. 4,169,123 and
25 Forstrom et al. U.S. Patent No. 4,169,124. The methods described in those two patents involve surrounding an article to be sterilized with vapor phase hydrogen peroxide and maintaining contact between the article and the sterilant at temperatures below 80°C until sterility is achieved. The lowest temperature disclosed in either the Moore or Forstrom patents is 20°C.

30 It has been determined that with sensitive solutions, such as protein solutions, leaching of vaporized-hydrogen peroxide into the prefilled container is detrimental to the

molecular integrity of the solutions because hydrogen peroxide vapors that enter the container cause chemical modifications of the solution, such as oxidation.

It has now been discovered that applying post-treatment, or post-application, measures reduces or prevents the adverse effects of VHP on sensitive solutions and preserve the integrity, and thereby therapeutic efficacy, of otherwise sensitive solutions in prefilled containers. Post-application measures are ideally those measures that deactivate the oxidizing action of hydrogen peroxide, whether by removing vaporized-hydrogen peroxide or rendering hydrogen peroxide vapors into an inactive state.

In one embodiment, leaching of VHP into a prefilled container is prevented by application of a vacuum at the end of the antimicrobial treatment in the chamber to inverse the diffusion direction of hydrogen peroxide vapors. By reversing the direction of vapor flow, hydrogen peroxide vapors are prevented from entering the prefilled container, thereby maintaining the integrity of the sensitive solution within the container while the surface of the container is decontaminated.

In yet another embodiment, hydrogen peroxide vapors are inactivated, such that they are incapable of chemically modifying the solution contained in a prefilled container. In another embodiment, post-treatment measures include neutralizing the oxidative ability of hydrogen peroxide vapors. In yet another embodiment, hydrogen peroxide vapors are inactivated by application of ultraviolet rays to the container after a sufficient exposure time of prefilled container to VHP following treatment. Other suitable inactivating agents, such as chemical agents or gas plasma, can be applied post-treatment to inactivate VHP following a sufficient exposure time of the surfaces of prefilled containers to VHP.

At the conclusion of the terminal sterilization process, the prefilled container in secondary packaging may be removed from the chamber, and is suitable for use by an end user.

In one embodiment, the sterilization process may be performed by an automated system. For example, referring to FIG. 2, illustrated is a block diagram of a system 200 for decontaminating a surface of a prefilled container in secondary packaging. System 200 includes a sealed chamber 202 and a control unit 204 coupled, directly or indirectly, to the chamber 202.

In one embodiment, the sealed chamber 202 may be any suitable decontamination chamber. For instance, the chamber 202 may include an autoclave, with the ability to reversibly seal a closed environment. The chamber 202 may also be equipped with mechanisms to manipulate pressure, temperature, and inflow and outflow of air within the chamber 202.

Control unit 204 provides instructions, in the form of signals, to chamber 202 to perform operations associated with sterilizing a prefilled container 100 (such as shown in Fig. 1) in a prescribed-automatic manner. Control unit 204 may transmit signals to chamber 202 to direct chamber 202 (or related parts) to physically enable a vaporized-hydrogen peroxide to come into contact the surface of the prefilled container in the secondary packaging.

For example, in one embodiment, the control unit 204 may transmit a signal to a valve (not shown) associated with a reservoir for passing vaporized-hydrogen peroxide into the chamber. The control unit 204 measures a preset duration-of-time the vaporized-hydrogen peroxide is to remain in contact with the prefilled-container surface. Upon expiration of the preset duration-of-time, the control unit 204 transmits a signal to chamber 202 (or a related device) to cause a post-decontamination measure to occur to reduce the presence of vaporized-hydrogen peroxide in the chamber, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container undergoing surface decontamination.

For example, following surface decontamination, the control unit 204 may transmit a signal to a vacuum (not shown) to reverse the flow of hydrogen-peroxide vapors out of the chamber 202 to remove these vapors from the chamber. Other suitable control mechanisms for controlling hydrogen-peroxide vapors include mechanisms for introducing neutralizing or inactivating agents, such as chemical agents, into the chamber 202, which upon contact with hydrogen-peroxide vapors render the vapors inactive, and thus harmless to the interior solution of a prefilled container.

Reference is made to treatment times that are sufficient to terminally sterilize the prefilled container. In one embodiment, a sufficient treatment time or the duration of the presence of vaporized-hydrogen peroxide within the chamber to sufficiently

decontaminate the container surface is determined by routine validation. For example, containers that have been subjected to treatment by vaporized-hydrogen peroxide are compared to controls and can be checked for bacterial contamination using standard laboratory protocols, such as incubation of suspected contaminated object with bacterial growth medium and then checking for bacterial growth, generally performed by the use of bioindicators. By plotting treatment time against presence of bacterial growth, the treatment time to achieve decontamination, thus the absence of bacterial growth, can easily be determined. Validation techniques apply whether terminal sterilization is carried out by vaporized-hydrogen peroxide as described above or carried out by exposure to beta radiation as described below.

In one embodiment, the control unit 204 is automated, and operates in accordance with code executing on a processor. The implementation of a control unit will be well within the scope of someone skilled in the art. For instance, the control unit may be any personal computer, microprocessor, or other suitable devices, capable of executing code that is programmed to transmit signals to devices associated with physically carrying out the sterilization process.

It will be appreciated that the various steps, or operations, involved in the sterilization and surface decontamination process can be performed automatically under the administration of a control unit as described above. Alternatively, operations can be performed separately in manual operations. Furthermore, operations can be performed in a combination of automated and manual processes.

Terminal Sterilization of Prefilled Containers by Tunable-Beta Irradiation

In one embodiment, terminal sterilization of prefilled containers in secondary packaging is carried out by a decontamination treatment in a chamber equipped with one or more electron beam generators that are tunable to generate an appropriate dose of beta radiation onto the surfaces of the prefilled containers.

The various steps, or operations, involved in the sterilization and surface decontamination process can be performed automatically under the administration of a system manager, such as a microprocessor. Alternatively, operations can be performed

separately in manual operations. Furthermore, operations can be performed in a combination of automated and manual processes.

In one embodiment prefilled containers are enclosed in secondary packaging following filling of containers under aseptic conditions. In another embodiment, prefilled
5 containers are labeled with any product information, such as product name, indications; use instructions, etc, prior to encasement of prefilled containers in secondary packaging.

In one embodiment, prefilled containers in secondary packaging are presented either manually or automatically to a decontamination chamber with an inlet side and an
10 outlet side. In another embodiment the decontamination chamber is an electron beam tunnel. In yet another embodiment, prefilled containers are mechanically moved through the tunnel from the inlet side to the outlet side on a movable mechanism, such as a conveyor. Thus, prefilled containers move through the chamber as the surfaces of prefilled containers are exposed to beta irradiation.

15 In another embodiment, the electron beams are oscillated, e.g. by application of magnetic fields, such that the whole surface of the object is scanned by the electron beam. In another embodiment, the object is passed below the scanning electron beams by means of a transport mechanism like a moving conveyor.

In one embodiment, the surfaces of prefilled containers in secondary packaging
20 are decontaminated during an exposure time of low penetration beta radiation of less than one second, ideally in less than one-half second. Thus, treatment times with tunable-beta radiation as described herein are significantly less than decontamination using gamma rays, which require surface treatment times of several hours or longer for sufficient decontamination and sterilization.

25 In another embodiment, the electron beam tunnel is configured with an electron beam generator, whereby the voltage of energy generated is tunable.

In yet another embodiment, prefilled containers in secondary packaging are transported or moved about in a fashion as to expose all surfaces of the containers to emitted beta radiation within the tunnel.

30 Primary packaging containers for sterile pharmaceutical drug products are often up to about 30-fold thicker than the secondary packaging material. In one embodiment

the thickness of the wall of the primary packaging material is 20 or more times thicker than the thickness of the secondary packaging material, thus allowing a resulting dose absorbed by the contents in the prefilled container to less than 0.1 kGy.

It has been discovered that it is possible to find a combination of packaging components, accelerator voltage, irradiation plant design and throughput speed that allow a surface decontamination or surface sterilization of a prefilled container in secondary packaging, while the contents of the container are essentially shielded by the primary packaging material. Therefore, beta irradiation does not affect sensitive biomolecules, such as biotech drug solutions, inside the primary packaging materials.

In one embodiment, beta irradiation of the prefilled container may be conducted at any dosage useful to provide effective sterilization without degrading the container or its contents, using any known beta irradiation apparatus, such as a low voltage generator or particle accelerator, with the amount of radiation depending on the thickness of the secondary packaging

In one embodiment the minimum sterilizing dose (MSD) of beta radiation is that required to deliver the required SAL for the product. In one embodiment sterilizing doses are measured with Gray (Gy) or Rad (radiation absorbed dose). In another embodiment, absorbed doses are measured by dosimeter, preferably by film dosimeters, calorimeters or cerium dosimeters.

In another embodiment, the amount of radiation depends on the presence of secondary packaging and the thickness of the secondary packaging. For a typical prefilled container, the beta radiation is desirably provided at a dosage of 25 kGy at the surface of the prefilled container.

In one embodiment, a particle accelerator generates beta-particle acceleration through a vacuum tube. In one embodiment, acceleration is by means such as magnetic field, electrostatic charge or by energy transfer from high frequency electromagnetic waves.

At the conclusion of the terminal sterilization process, the prefilled container in secondary packaging leaves the tunnel by the outlet with surfaces decontaminated and is suitable for use by an end user. Because treatment time for surface decontamination is as short as about one second, surface decontamination of prefilled containers in

secondary packaging offers numerous advantages over sterilization methods involving gamma radiation, which are harmful to container contents, require significantly longer exposure times for decontamination, and require additional shielding along the production line, and cause discoloration of packaging components. Moreover, sterilization techniques involving gamma radiation cause significant bottlenecks in production assembly lines which are eliminated by surface decontamination using tunable-beta radiation in an e-beam tunnel.

In one embodiment, as depicted in Fig. 3, a system 300 — for surface-decontaminating a prefilled container in secondary packaging — includes an electron-beam tunnel 302 equipped with one or more tunable-electron beam generators, shown as voltage generators 304. In another embodiment, the one or more tunable-electron-beam generators 304 of the system are configured to variably generate low-energy beta radiation. Alternatively, electron beams are oscillated, such that the electron beams hit a larger surface of a prefilled container and increase the exposure surface of the container.

In yet another embodiment, the one or more generators 304 apply an accelerator voltage to produce a sufficient amount of beta radiation to decontaminate the surface of the prefilled container, wherein the sufficient amount of beta radiation depends on the thickness of the secondary package and the thickness of the prefilled container. Thus, beta radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

Reference is made to treatment times that are sufficient to terminally sterilize and surface decontaminate the prefilled container. In one embodiment, a sufficient treatment time or the duration of the presence of low-energy beta radiation within the tunnel to sufficiently decontaminate the container surface is determined by routine validation. For example, containers that have been subjected to treatment by beta radiation are compared to controls and can be checked for bacterial contamination using standard laboratory protocols, such as incubation of suspected contaminated object with bacterial growth medium and then checking for bacterial growth. By plotting treatment time against presence of bacterial growth, the treatment time to achieve decontamination, thus the absence of bacterial growth, can easily be determined. Validation techniques

apply whether terminal sterilization is carried out by beta radiation as described above or carried out by exposure to VHP as described above.

Reference is now made to the following examples. These examples are provided for the purpose of illustration only and should in no way be construed as being limited to these examples but rather should be construed to encompass any and all variations, which become evident as a result of the teaching provided herein.

Example 1

In the following experiment, prefilled syringes were treated with a vaporized-hydrogen peroxide sterilization treatment in a chamber, either by a single pass through a VHP sterilization procedure or two passes (shown in the table below as 2 x) through a VHP sterilization procedure. Syringes containing protein solutions treated by VHP were compared to control syringes treated with VHP to determine if the integrity of proteins present in solution was maintained.

A formulation as described in U.S. Patent No. 7,060,269 was tested for protein degradation following treatment by VHP.

Approximately 10 mL of solution was filtered through a 0.22 µm syringe filter. (Millex GV filter available from Millipore, Billerica, MA USA.) Filling of 0.5 mL syringes was performed in a sterile lab for hydrogen peroxide treatment.

Analysis after the treatment with VHP revealed the following protein contents, visualized by HPLC analysis: byproducts and degradation products by HPLC (IEC) and by-products and degradation products by HPLC (SEC).

Table 1: Protein Stability Following Treatment with VHP

Batch	IEC (% main peak)	IEC (% basic peak)	SEC (% monomer)
Control			
9823.01 CSi	98	2	100
9823.02 CSi	98	2	100
1 x treatment			
9823.04 CSi	98	2	100

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9823.05 CSi	98	2	100
2 x treatment			
9823.07	98	2	100
9823.08	98	2	100

The results seen were within the requirement; there were no differences between the results of the untreated syringes and with hydrogen-peroxide treated syringes. Analysis can also be carried out at different time points following treatment, such as 1 month, 3 months and six months following treatment by VHP, or over the shelf-life of the product of the prefilled container. Analysis can be carried out to determine continued stability of the protein solution, including tests by HPLC for presence of by-products using standard HPLC laboratory protocols. Analysis can also be carried out by the presence of physical changes, such as measuring the concentration of H₂O₂ in solution by a fluorescence test using an over-the-counter commercially available kit in conjunction with an apparatus with fluorescence detection.

Example 2

The following experiment was carried out to determine the effectiveness of surface decontamination using beta irradiation. A commercially available e-beam tunnel for outside decontamination of containers, equipped with KeVAC accelerators from Linac Technologies (Orsay, France), was used to investigate the penetration depth of the electron beam in different materials. For example, penetration was measured in a polyethylene bag with foil thickness of 50 µm, an aluminum bag with foil thickness of 0.1 mm and a glass slide of 1 mm thickness.

To increase sensitivity of the study, multiple passes of the samples through the tunnel were investigated. Far West 60 Film dosimeters, available from Far West Technologies (Santa Barbara, CA, USA) were used to record the radiation absorbed.

Table 2: Beta Irradiation Absorption by Packaging Materials:

Number of passes through decontamination tunnel	Absorbed dose		
	Dosimeter in	Dosimeter in	Dosimeter shielded by

	Polyethylene bag	aluminum bag	1 mm glass slide
1 pass	30 kGy	1.3 kGy	<LOQ(0.1 kGy)
3 passes	97 kGy	64 kGy	<LOQ(0.1 kGy)
5 passes	207 kGy	105 kGy	<LOQ (0.1 kGy)

The feasibility study showed that already with these not optimized settings of the electron beam decontamination tunnel a surface sterilization could be obtained (≥ 25 kGy) when the product was packaged into plastic bags. Even after 5 times passing through the electron beam treatment tunnel, the absorbed dose within the packaging material (behind a 1 mm thick glass wall) was far below the limit of quantitation which was 1 kGy for the dosimeters used.

Additionally, the oxidative stress exerted on a 0.5% Polysorbate 20 solution in prefilled glass syringes (1mL long, ISO) was investigated by measurement of peroxides according to standard protocols. The total amount of peroxides was measured by the Ferrous Oxide Oxidation (FOX) test, according to a standard protocol.

Table 3: Peroxide Levels Following Beta Irradiation of Prefilled Containers:

Number of passes through E-beam tunnel	Peroxide content of 0.5% Polysorbate 20 solution in water in 1mL long glass syringe (ISO) [$\mu\text{Mol/mL}$]
Reference (not treated)	0.04
1 pass	0.04
3 passes	0.03
5 passes	0.05

No significant influence of the electron beam treatment on the peroxide content of the solution enclosed in glass syringes could be observed. Thus, beta irradiation proved safe to solutions within prefilled containers.

Additionally, the oxidative stress exerted on protein solution in prefilled glass vials was investigated by measurement of degradation products according to standard protocols.

A formulation as described in U.S. Patent No. 7,060,269 was tested for protein degradation following treatment by electron beam irradiation. Approximately 0.3 mL of

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solution was filtered through a 0.22 µm filter and aseptically filled into pre-sterilized glass vials, aseptically closed with a sterile rubber stopper and secured with an aluminum crimp cap.

The containers were passed through the above described e-beam tunnel with identical settings as for the other experiments mentioned above. Containers were analyzed after the treatment with electron beam radiation to determine protein contents, visualized by HPLC analysis for byproducts and degradation products by HPLC (IEC), as performed above in Example 1.

Table 4: Protein Stability Following Beta Irradiation of Prefilled Containers

Number of passes through E-beam tunnel	IEC (% main peak)	IEC (% basic peak)
Reference (not treated)	98 (97.8)	1 (1.2)
1 pass	98 (97.8)	1 (1.3)
3 passes	98 (97.5)	2 (1.5)
5 passes	98 (97.6)	1 (1.4)

There were no differences between the results of the untreated syringes and with electron beam sterilized vials, following 1 pass, 3 passes or 5 passes through the e-beam sanitization process, as shown in the results at Table 4. Thus, tunable-beta radiation as described herein proved safe to solutions within prefilled containers.

The described embodiments are to be considered in all respects only as exemplary and not restrictive. The scope of the invention is, therefore, indicated by the subjoined claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS

We claim:

- 5 1. A method for surface decontamination of a prefilled container in secondary packaging, comprising:
- applying vaporized-hydrogen peroxide to the surface of the prefilled container in secondary packaging;
- allowing vaporized-hydrogen peroxide to remain in contact with the
10 prefilled container surface for a sufficient time to decontaminate the prefilled container surface; and
- causing a post-decontamination measure to occur to reduce the presence of vaporized-hydrogen peroxide, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container.
- 15 2. The method of claim 1, wherein the prefilled container is a syringe containing a drug product otherwise sensitive to sterilization treatment by gamma radiation, sterilization treatment by exposure to steam, and sterilization treatment by exposure to vaporizing agents and gases.
- 20 3. The method of claim 1 or claim 2, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.
- 25 4. The method of any previous claim, wherein sufficient time to decontaminate the surface of the prefilled container is determined by validation of treatment times and compared to a control standard.
- 30 5. The method of any previous claim, wherein the post-decontamination measure includes applying a vacuum following the duration of treatment with vaporized-hydrogen peroxide, thereby reversing the direction of diffusion of vaporized-hydrogen peroxide and preventing intrusion of vaporized-hydrogen peroxide into the prefilled container.

- 5 6. The method of any of claims 1-4, wherein the post-decontamination measure includes applying ultraviolet rays following the duration of treatment with vaporized-hydrogen peroxide, thereby inactivating oxidative action of hydrogen peroxide vapors.
7. The method of any of claims 1-4, wherein the post-decontamination measure includes gas plasma treatment.
- 10 8. A method for surface decontamination of a prefilled container in secondary packaging, comprising:
- 15 presenting a prefilled container in a secondary package to an electron beam tunnel equipped with one or more tunable electron beam generators capable of variably generating low-energy beta radiation, and capable of oscillating electron beams such that a larger surface of the prefilled container is exposed to beta radiation during decontamination; and
- 20 applying an accelerator voltage of the one or more tunable electron beam generators to produce a sufficient amount of beta radiation to decontaminate the surface of the prefilled container, wherein the sufficient amount of beta radiation depends on the thickness of the secondary package and the thickness of the prefilled container, such that beta radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.
- 25 9. The method of claim 8, wherein the thickness of the wall of the primary packaging material is 20 or more times thicker than the thickness of the secondary packaging material, thus reducing the dose absorbed by the product in the container to less than 0.1 kGy.
- 30 10. The method of claim 8 or claim 9, wherein the prefilled container is a vial filled with a solution or solid otherwise sensitive to sterilization treatment by gamma

radiation, sterilization treatment by exposure to steam, and sterilization treatment by exposure to vaporizing agents, gases or peroxide forming substances.

5 11. The method of any one of claims 8-10, wherein the prefilled container is a syringe filled with a solution otherwise sensitive to sterilization treatment by gamma radiation, sterilization treatment by exposure to steam, and sterilization treatment by exposure to vaporizing agents and gases or peroxide forming substances.

10 12. The method of any one of claims 8-11, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

13. The method of any one of claims 8-12, wherein the penetration depth is measured by dosimetry.

15 14. The method of any one of claims 8-13, wherein sufficient energy to decontaminate a surface of a prefilled container is that which provides a dose of beta radiation of at least approximately 25 kGy to the container surface.

20 15. The method of any one of claims 8-14, wherein sufficient energy to decontaminate a surface of a prefilled container is that which provides a dose of beta radiation yielding a 10^{-6} Sterility Assurance Level of the outside of the container surface.

25 16. A system for decontaminating a surface of a prefilled container in secondary packaging, the system comprising:

a sealed chamber; and

30 a control unit coupled to the chamber, the control unit configured to automatically (i) enable a vaporized-hydrogen peroxide to contact the surface of the prefilled container in the secondary packaging; (ii) allow the vaporized-hydrogen peroxide to remain in contact with the prefilled-container surface for a

predetermined time; and (iii) cause a post-decontamination measure to occur to reduce the presence of vaporized-hydrogen peroxide in the chamber, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container.

5

17. A system for surface-decontaminating a prefilled container in secondary packaging, the system comprising: an electron-beam tunnel equipped with one or more tunable-electron beam generators, the tunable-electron-beam generators, configured to (i) variably generate low-energy beta radiation, (ii) oscillate the
10 electron beams such that a larger surface of a prefilled container is exposed to electron beams; and (iii) apply an accelerator voltage to produce a sufficient amount of beta radiation to decontaminate the surface of the prefilled container, wherein the sufficient amount of beta radiation depends on the thickness of the secondary package and the thickness of the prefilled container, such that beta
15 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

18. A kit for decontaminating the surface of a prefilled container in secondary packaging in a sealed chamber, the kit comprising: an instruction for using the
20 sealed chamber to (i) apply a vaporized-hydrogen peroxide to contact the surface of the prefilled container in the secondary packaging; (ii) allow the vaporized-hydrogen peroxide to remain in contact with the prefilled-container surface for a predetermined time within the sealed chamber; and (iii) cause a post-decontamination measure to occur to reduce the presence of vaporized-
25 hydrogen peroxide in the chamber, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container.

19. A kit for surface-decontaminating a prefilled container in secondary packaging,
30 the kit comprising: an instruction for (i) variably generating low-energy beta radiation to contact the surface of the prefilled container; and (ii) produce a

sufficient amount of beta radiation to decontaminate the surface of the prefilled container, wherein the sufficient amount of beta radiation depends on the thickness of the secondary package and the thickness of the prefilled container such that beta radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

20.A system according to claim 16 or a kit according to claim 18, wherein post-decontamination measure includes gas plasma treatment.

1/1

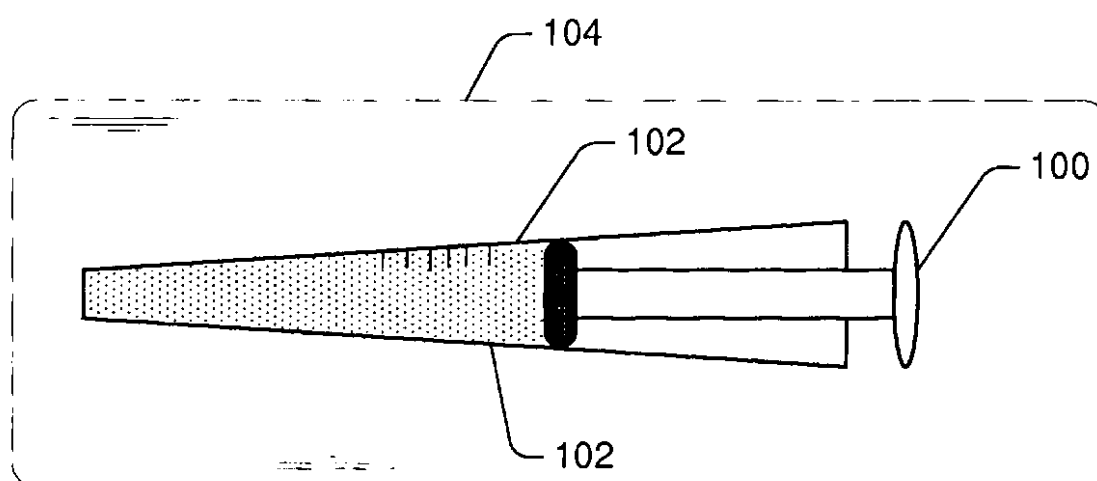


Fig. 1

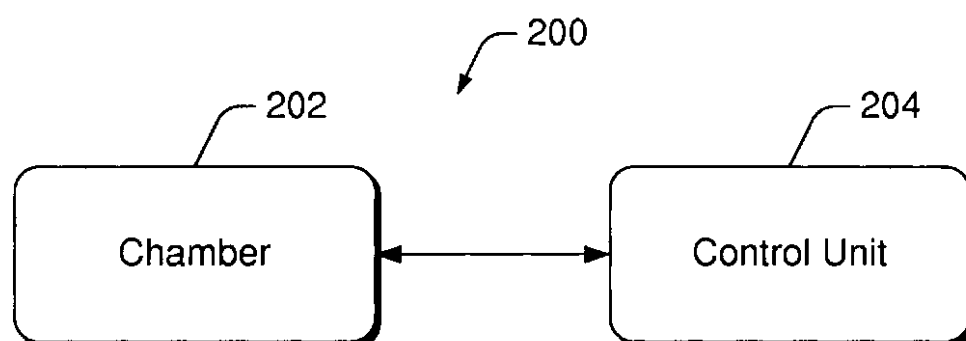


Fig. 2

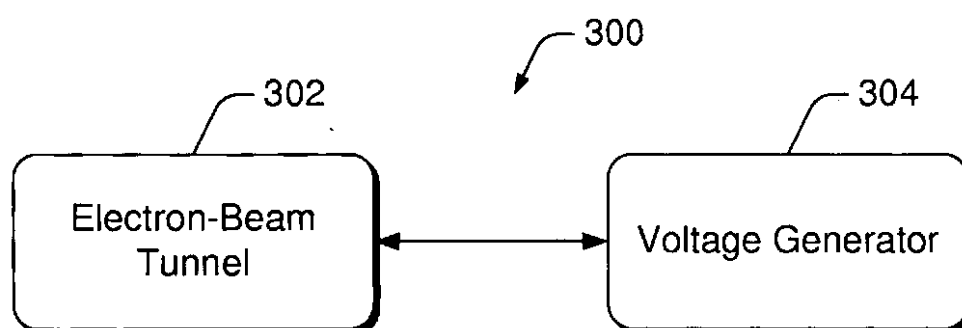


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/060011

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61L2/00 A61L2/20 B65B55/10 A61L2/08 B65B55/08
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L B65B

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 779 973 A (EDWARDS STEVEN JAY [US] ET AL) 14 July 1998 (1998-07-14)	1,5,16
Y	column 4, line 3 - line 30 column 5, line 6 - column 6, line 24; figures 1,2,5	2-7,18
Y	----- WO 2008/077155 A (GENENTECH INC [US]; LAM XANTHE M [US]; NGUYEN TUE [US]) 26 June 2008 (2008-06-26)	3
A	page 13, line 10 - line 15	12
Y	----- EP 1 433 486 A (CLOSURE MEDICAL CORP [US]) 30 June 2004 (2004-06-30)	1,2,4,5, 16,18
A	paragraphs [0008], [0024], [0032], [0033], [0035], [0042]; example 3 ----- -/-	8,17

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

9 December 2010

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20/12/2010

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Katsoulas, K

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/060011

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/020847 A (COOK BIOTECH INC [US]; HILES MICHAEL C [US]; HODDE JASON P [US]; ERNST) 10 March 2005 (2005-03-10)	6
A	page 23, line 25 - line 30 page 26, line 1 - page 27, line 22	8,17
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Y	EP 1 283 061 A (TAISEI KAKO JP) 12 February 2003 (2003-02-12) paragraph [0007]	7
Y	US 4 652 763 A (NABLO SAMUEL V [US]) 24 March 1987 (1987-03-24) column 1, line 30 - line 38 column 2, line 4 - line 63 column 4, line 56 - column 5, line 68 column 7, line 20 - column 8, line 34	8-11, 13-15,17
Y	EP 1 944 044 A1 (BECTON DICKINSON FRANCE [FR]) 16 July 2008 (2008-07-16) paragraphs [0006], [0009], [0010], [0042], [0045], [0051], [0054]	8-11, 13-15,17
A	US 6 189 292 B1 (ODELL ROBERT B [US] ET AL) 20 February 2001 (2001-02-20) column 11, line 23 - line 27; claim 1	8,17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2010/060011

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7, 16, 18, 20

Independent method claim 1 defines a method for surface decontamination of a prefilled container in a secondary packaging comprising the steps of a) applying vaporised hydrogen peroxide (VHP) to the surface of the prefilled container, b) allowing sufficient decontamination contacting time and c) reducing the presence of VHP to prevent it from diffusing into the prefilled container.

2. claims: 8-15, 17, 19

Independent method claim 8 defines a method for surface decontamination of a prefilled container in a secondary packaging comprising the steps of a) presenting a prefilled container in one or more tunable e-beam generators capable of generating variable low-energy beta radiation and oscillating electron beams and b) applying a sufficient acceleration voltage to decontaminate the surface of the prefilled container, such that beta radiation penetrates the secondary package, while the container thickness shields the contents from the beta radiation.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/060011

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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**SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE
COOPERACIÓN EN MATERIA DE PATENTES (TCP)**

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B65B 55/10 (2006.01) B65B 55/08 (2006.01)

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(74) Agente : SPINNER, David, Richard; Novartis Pharma AG, Departamento de Patentes, CH-4002 Basilea (CH).

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(84) Estados (Países) Designados (a menos que se indique de otra manera, para cada tipo de protección regional disponible): ARIPO (BW, GI, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiáticos (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europeos (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones de acuerdo con la Regla 4.17:

-- con respecto al derecho de la solicitante de solicitar y otorgársele una patente (Regla 4.17(ii))

Publicada:

-- con reporte de búsqueda internacional (Art. 21(3))

-- antes del vencimiento del límite de tiempo para enmendar las reivindicaciones, y para volverse a publicar en el caso de recibirse las enmiendas (Regla 48.2(h))

(54) Título : DESCONTAMINACIÓN DE SUPERFICIE DE CONTENEDORES PREVIAMENTE LLENADOS EN EMPAQUE SECUNDARIO

(57) Resumen:

Métodos y sistemas para la esterilización terminal y la descontaminación de superficie de los contenedores previamente llenados que contienen productos de fármacos sensibles, tales como los productos de fármacos de biotecnología que de otro modo son sensibles a la temperatura o a la radiación, y de este modo no son convenientes para la esterilización terminal mediante métodos clásicos que involucren vapor o rayos gamma. Los métodos y sistemas son especialmente convenientes para los contenedores previamente llenados en empaques secundarios. Los métodos incluyen la esterilización terminal exponiendo los contenedores previamente llenados en empaque secundario a radiación beta-sintonizable y además incluyen la esterilización terminal exponiendo a los contenedores previamente llenados a peróxido de hidrógeno vaporizado controlable, incluyendo la aplicación de medidas para reducir o prevenir la difusión del peróxido de hidrógeno vaporizado dentro de los contenedores previamente llenados.

WO 2011/006877 A1

DESCONTAMINACIÓN DE SUPERFICIE DE CONTENEDORES
PREVIAMENTE LLENADOS EN EMPAQUE SECUNDARIO

Campo de la Invención

5 Esta invención se relaciona con un método y sistema para la
esterilización terminal de la superficie externa y/o la
descontaminación de superficie de los contenedores previamente
llenados en empaque secundario, en donde el contenedor
previamente llenado contiene un producto farmacéutico o fármaco
10 biológico.

Antecedentes

Los contenedores previamente llenados son de un tipo de
dispositivo médico que son llenados por el fabricante en el momento
del montaje y se proporcionan al usuario final, generalmente un
15 proveedor de cuidados para la salud o un paciente que requiere
tratamiento, en una condición estéril.

Los contenedores previamente llenados ofrecen varias ventajas
sobre los empaques tradicionales de sustancias terapéuticas,
incluyendo la facilidad de uso, el riesgo reducido de contaminación,
20 la eliminación de errores de dosificación, el aumento de suministro
de fármaco y el desperdicio reducido. De los distintos tipos de
contenedores previamente llenados, las jeringas previamente
llenadas son las más comunes y más convenientes para la
administración parenteral de los productos terapéuticos.

25 Se conocen varios métodos de esterilización de dispositivos

médicos, pero no todos los métodos funcionan con jeringas, especialmente las jeringas previamente llenadas con un fármaco o solución de proteínas.

Comúnmente se emplea la esterilización mediante vapor para
5 esterilizar los dispositivos médicos, lo cual típicamente incluye calentar el dispositivo en una autoclave de vapor. El calor y la presión generados en la autoclave, sin embargo, pueden tener un efecto adverso en el dispositivo y, más importante, en la integridad del producto de fármaco llenado en el dispositivo. La esterilización
10 mediante vapor puede comprometer la estética del producto debido a la degradación del empaque debido al tratamiento de vapor a alta temperatura. Más aún, las altas temperaturas del proceso (por ejemplo 120°C – 132°C) obstaculizan su uso con materiales sensibles al calor, tales como los productos de los fármacos
15 biotecnológicos, específicamente las proteínas u otras soluciones biológicas.

Para esterilizar los dispositivos médicos, también se emplea comúnmente la exposición a la radiación, en la cual se somete el producto a una radiación ionizante, tal como la irradiación gamma.
20 La exposición a la radiación da como resultado un daño perjudicial a las soluciones sensibles, específicamente causando la destrucción a los productos biológicos sensibles como las proteínas, así como la generación de cantidades masivas de peróxidos en soluciones acuosas que en una reacción secundaria pueden dañar más al
25 ingrediente activo. Además, las dosis esterilizantes de los rayos

gamma causan una decoloración café de las partes de vidrio del dispositivo, y son propensas a dañar los materiales elastoméricos como los topes del émbolo. Esta destrucción de los elastómeros conduce a un aumento de la rigidez de los componentes, deshabilitando la funcionalidad del sistema. Así, la radiación no es un medio apropiado para esterilizar los contenedores previamente llenados, tales como las jeringas, que contienen un producto de fármaco biotecnológico.

La esterilización en frío es un término colectivamente usado para los métodos de esterilización llevados a cabo a temperaturas sustancialmente por debajo de las del proceso de vapor; se han hecho intentos para usar óxido de etileno y vapores de peróxido de hidrógeno como esterilizantes para este tratamiento. Sin embargo, el tratamiento con gases esterilizantes tiene el riesgo de que se remueve insuficiente gas oxidante. La difusión del gas en el contenedor del producto afecta la estabilidad del producto de fármaco a través de la modificación química por los vapores del gas, tales como son la alquilación y la oxidación.

Las jeringas previamente llenadas, aunque se llenen en condiciones asépticas, no se empaquetan en su empaque secundario en un ambiente aséptico y por lo tanto probablemente su exterior se contaminará microbiológicamente. La esterilización terminal de los contenedores previamente llenados en el empaque secundario es una manera de proporcionar el dispositivo a un usuario final con poca carga biológica y poco riesgo de contaminantes, para una

aplicación segura del producto para el usuario final. Más aún, hay una gran necesidad en el mercado de dispositivos médicos tratados antimicrobianamente de manera terminal, tales como las jeringas previamente llenadas usadas para las inyecciones intravítreas.

5 Debido a la naturaleza sensible de ciertos productos de fármacos, tales como las proteínas, no es posible realizar la esterilización terminal y la descontaminación de superficie de los contenedores rellenos con estos productos usando los métodos habituales, como vapor, irradiación o esterilización en frío.
10 Específicamente, se sabe que las altas temperaturas desnaturalizan las proteínas y se ha demostrado que la radiación gamma modifica químicamente las soluciones biológicas. Las técnicas de radiación, tales como la esterilización usando radiación gamma o beta causa la decoloración del material de empaque y afecta la estabilidad a largo
15 plazo de los agentes terapéuticos tales como las soluciones de proteínas o de péptidos. Como se comentó anteriormente, los gases oxidantes, aunque eficientes para eliminar la contaminación bacteriana, también dañan a las moléculas biológicas en las soluciones terapéuticas sensibles.

20 Ya que las proteínas y las moléculas biológicas cada vez se desarrollarán más para el uso terapéutico, en un futuro cercano aumentará continuamente la necesidad de una esterilización terminal de superficie y de un método de descontaminación de superficie que no sean dañinos al producto de fármaco. Más aún, ya que las
25 dependencias reguladoras pueden requerir altos niveles de garantía

de esterilidad, las compañías farmacéuticas y de biotecnología buscarán procedimientos alternativos para enfrentar o satisfacer los niveles de pureza microbiológica obligatorios, sin comprometer la seguridad y la eficacia de las preparaciones farmacéuticas.

5 **Breve Descripción de la Invención**

En la presente se describe un tratamiento de esterilización terminal y descontaminación de superficie de los contenedores previamente llenados, específicamente para la esterilización de los contenedores previamente llenados que contienen soluciones
10 sensibles, tales como un producto de fármaco o terapéutico biológico, dentro de un empaque secundario. En una modalidad, se logra la esterilización terminal tratando los contenedores previamente llenados dentro del empaque secundario con peróxido de hidrógeno vaporizado (VHP) controlable. El principio es la
15 formación de un vapor de peróxido de hidrógeno en contención y una posterior remoción o inactivación de los vapores de una manera controlada. Antes de la remoción o la inactivación, el vapor de peróxido de hidrógeno se condensa sobre todas las superficies, creando una película microbicida que descontamina la superficie del
20 contenedor.

Se ha descubierto que variando los parámetros del tratamiento antimicrobiano, por ejemplo – la temperatura, la humedad, la duración del tratamiento, la presión, etcétera, se generan las condiciones que evitan la lixiviación del vapor de peróxido de
25 hidrógeno en las jeringas. Como un ejemplo, la aplicación de un

GA

vacío al final del tratamiento invertirá la dirección de la difusión y se reducirá, si es que no se para, la lixiviación del peróxido de hidrógeno a través de los hules. Además, la inclusión de un tratamiento de plasma de gas después de terminar el ciclo de peróxido de hidrógeno vaporizado degradará adicionalmente todos los residuos potencialmente restantes de peróxido de hidrógeno. La prevención o reducción de la lixiviación de concentraciones perjudiciales de peróxido de hidrógeno en la solución de proteína en la jeringa, ya sea removiendo los vapores o por la inactivación de los vapores, asegura que no se comprometa la estabilidad a largo plazo de la proteína. Además se ha encontrado que entre los componentes de empaque primario comercialmente disponibles, solamente hay pocas combinaciones de materiales de empaque que proporcionan la hermeticidad requerida del sistema para evitar el ingreso de gases esterilizantes en el líquido farmacéutico encerrado por el contenedor previamente llenado.

También se describe en la presente el saneamiento terminal o la esterilización y la descontaminación de superficie de los contenedores previamente llenados dentro de empaque secundario mediante tecnologías de radiaciones de rayo de electrón sintonizable (rayo beta de baja energía) como una alternativa a las operaciones de inspección aséptica y empaque secundario aséptico.

En una modalidad, el uso de la radiación de poca profundidad de penetración a partir de una generador de rayo de electrones para una nueva aplicación para esterilizar la superficie de contenedores

de productos de fármacos empacados secundariamente evita el empaque aséptico. En otra modalidad, la profundidad de penetración de la radiación de rayo de electrones es sintonizable mediante el ajuste del voltaje acelerador del generador de radiación.

5 Generalmente, los conceptos presentados en la presente son aplicables a todos los productos de fármacos que tienen requerimientos o deseabilidad de ausencia de organismos viables en la superficie del contenedor del producto de fármaco. El método y sistema descrito en la presente descontamina o, más
10 preferiblemente, vuelve estéril una superficie exterior de los productos de fármacos empacados primariamente dentro de un empaque secundario, mejorando mediante esto la seguridad de los productos para la administración crítica (por ejemplo, el uso en una sala quirúrgica o para inyecciones intravítreas).

15 El anterior resumen proporciona una vista general de ejemplo de algunos aspectos de la invención. No pretende ser extensiva, ni requiere en absoluto algún elemento clave/crítico de la invención.

Breve Descripción de los Dibujos

La descripción detallada se explica con referencia a las figuras
20 acompañantes. En las figuras, el o los dígitos más hacia la izquierda de un número de referencia identifican la figura en la cual aparece por primera vez el número de referencia.

La Figura 1 muestra un contenedor previamente llenado
ejemplar en empaque secundario que se descontamina en las
25 superficies de acuerdo con los métodos detallados en la presente.

La Figura 2 ilustra un diagrama en bloques de un sistema ejemplar para la descontaminación de superficie de los contenedores previamente llenados usando peróxido de hidrógeno vaporizado.

5 La Figura 3 ilustra un diagrama en bloques de un sistema ejemplar para la descontaminación de superficie de los contenedores previamente llenados usando una radiación beta-sintonizable.

Descripción Detallada de la Invención

El método y sistema descritos en la presente son para la
10 esterilización y descontaminación de superficie de los contenedores
previamente llenados que contienen soluciones sensibles, tales como
los productos de fármacos que de otro modo son sensibles a la
temperatura o a la radiación o son sensibles a trazas de sustancias
oxidantes, y de este modo no son convenientes para la esterilización
15 terminal mediante los métodos clásicos que involucran vapor, rayos
gamma o beta o la esterilización con gases o líquidos oxidantes. El
método y el sistema descritos en la presente son especialmente
convenientes para los contenedores previamente llenados que han
sido llenados bajo condiciones asépticas y han sido sometidos a un
20 procesamiento adicional, tal como etiquetamiento del producto y
empaquetamiento secundario posterior. Los métodos incluyen la esterilización
terminal y la descontaminación de superficie exponiendo a los
contenedores previamente llenados en empaque secundario a una
radiación beta sintonizable y además incluyen una esterilización
25 terminal y descontaminación de superficie exponiendo los

contenedores previamente llenados a peróxido de hidrógeno vaporizado controlable, incluyendo medidas para reducir o evitar la difusión del peróxido de hidrógeno vaporizado en los contenedores previamente llenados. Los métodos también incluyen un paso
5 opcional de destruir activamente cualquier molécula residual de peróxido, por ejemplo, por medio de plasma de gas.

Definiciones

Para describir y reivindicar el método de esterilización terminal y descontaminación de superficie, se usará la siguiente terminología
10 de acuerdo con las definiciones presentadas enseguida.

Condiciones "asépticas" se refiere a condiciones libres de contaminación bacteriana o microbiana.

"Administración" se refiere al método de administrar tratamiento a un sujeto o paciente que lo necesite, tal como la
15 administración parenteral, administración intravenosa y administración intravítrea.

"Irradiación beta" se refiere a los métodos de esterilización usando rayos beta.

"Esterilización en frío" se refiere a las técnicas de
20 esterilización que emplean agentes químicos, gases, o irradiación. Un requerimiento de la esterilización en frío es que la técnica se lleve a cabo a temperaturas por debajo de las usadas para la esterilización mediante vapor, tales como el uso de autoclave.

"Contenedor", como se usa en la presente, se entiende que
25 incluye frascos, jeringas, bolsas, botellas, u otros elementos útiles

para el almacenamiento de los tratamientos médicos, tales como los productos de fármacos, ya sea en forma sólida o líquida, y otros agentes biológicos, tales como los péptidos, las proteínas o los productos biológicos recombinantes, ya sea en forma sólida o líquida. Los contenedores pueden ser reutilizables o desechables, y pueden tener un propósito médico, veterinario o no médico.

"Contenedor previamente llenado" se refiere a un contenedor, tal como una jeringa, que está llena con una solución en el momento del montaje y empaque y es entregable para su uso a un usuario final, tal como a un profesional de cuidados para la salud o a un paciente que necesita tratamiento. Este término también se refiere a los contenedores previamente llenados integrados en un dispositivo de administración.

Una "instrucción" o "material de instrucciones" incluye una publicación, una grabación, un diagrama, o cualquier otro medio de expresión que se puede usar para comunicar la utilidad del método o sistema de la invención para su uso designado. La instrucción o el material de instrucciones puede estar presente adjunto como parte del sistema o se puede proporcionar por separado, o independientemente del proceso, a un usuario final.

"Aislamiento", como se usa en la presente se refiere a las prácticas en la producción farmacéutica, el llenado y el empaque, en donde un ambiente limpio, o estéril, se separa de un ambiente no estéril para limitar o evitar la introducción o diseminación o contaminación de agentes infecciosos, tales como microorganismos.

"Dispositivo médico", como se usa en la presente, se refiere a un dispositivo usado para administrar un tratamiento médico y cuya producción o venta debe, en parte, cumplir con los requerimientos, tales como los requerimientos de seguridad, establecidos por una dependencia gubernamental, tal como la Administración de Alimentos y Fármacos (FDA).

"Solución", como se usa en la presente se refiere al contenido de un contenedor como un frasco o una jeringa previamente llenada e incluye soluciones de productos terapéuticos biológicos y productos de fármacos, productos de proteínas, productos de péptidos, productos biológicos, soluciones para la formación de imágenes y soluciones acuosas. Idealmente, las soluciones son aquellas que son sensibles a la temperatura, la oxidación o la radiación debido a la conformación molecular de la solución.

"Empaque secundario" se refiere a un paquete que encierra al contenedor previamente llenado, tal como una envoltura de plástico, envoltura de hoja de aluminio, envoltura de papel, u otra envoltura conveniente, tal como los paquetes de ampollas.

"Tratamiento de superficie antimicrobiano terminal" se refiere a el saneamiento o la esterilización de un contenedor montado, tal como una jeringa rellena con una solución que a su vez está empacada en un empaque secundario. El tratamiento antimicrobiano terminal, o la esterilización, permite que se proporcione un contenedor previamente llenado empacado de manera secundaria en

condición de exterior estéril en su punto de uso.

"Peróxido de hidrógeno vaporizado" se refiere al peróxido de hidrógeno en forma de vapor capaz de crear una película microbicida en una superficie, tal como la superficie de un contenedor o material
5 de empaque.

Los términos "esterilización", "descontaminación", "saneamiento", "tratamiento antimicrobiano" se usan intercambiablemente en la presente.

"Esterilidad" como se usa en la presente significa la ausencia
10 completa de vida microbiana, como se define por una probabilidad de no-esterilidad o un nivel de garantía de esterilidad (SAL). El nivel de garantía de esterilidad requerido para un producto dado se basa en requisitos reglamentarios. Por ejemplo, los niveles de garantía de esterilidad requeridos para los productos de cuidados para la salud
15 se definen como cuando menos 10^{-6} , es decir, una oportunidad de menos de 1:1 millón de un producto no estéril para los productos fabricados asépticamente y terminalmente esterilizados, respectivamente.

La referencia en la presente a "1 modalidad" o "una modalidad"
20 significa que un aspecto, estructura, operación o característica particular descrita en relación con la modalidad se incluye en cuando menos una modalidad de la invención. De este modo, las apariciones de estas frases o formulaciones en la presente no se refieren necesariamente a la misma modalidad. Además, varios aspectos,
25 estructuras, operaciones o características se pueden combinar de

cualquier manera conveniente en una o más modalidades.

***Esterilización terminal y descontaminación de superficie de los
contenedores previamente llenados***

La esterilización terminal es el proceso de esterilizar y/o
5 descontaminar un producto empacado final. En cambio, un proceso
de empaque aséptico requiere que los componentes individuales del
producto se esterilicen por separado y el paquete final se ensamble
en un ambiente estéril. La esterilización terminal de un producto
proporciona una seguridad mayor de esterilidad que un proceso
10 aséptico. La esterilización terminal también se desea y proporciona
una ventaja en el mercado en algunos casos para el uso de ciertos
dispositivos médicos, tales como el uso de jeringas previamente
llenadas empacadas de manera secundaria para la administración
intravítrea.

15 Se describen en la presente métodos de esterilización terminal
convenientes para los contenedores previamente llenados que
contienen productos sensibles, tales como las soluciones de
fármacos biotecnológicos (biológicos), que de otro modo pueden
comprometerse cuando se usan procesos de esterilización terminal
20 clásicos, tales como vapor, irradiación gamma o los procesos de
esterilización en frío actualmente usados en las líneas de producción
y ensamble de los productos farmacéuticos. Aunque se hace
referencia a los productos de fármacos, tales como las soluciones de
fármacos sensibles al calor o a la radiación que contienen productos
25 biológicos tales como péptidos o proteínas, los expertos en la

técnica entenderán que cualquier producto terapéutico se considera un agente terapéutico, ya sea en solución o en forma sólida, se puede alojar – o contener- en un contenedor previamente llenado. De este modo, el contenedor previamente llenado mismo no es
5 específico del fármaco.

Se ha descubierto ahora que el tratamiento de los contenedores previamente llenados en empaque secundario mediante la aplicación de peróxido de hidrógeno vaporizado, en el cual los vapores son controlables por ciertas medidas después del
10 tratamiento, y la exposición a una radiación beta-sintonizable, en la cual se controla la profundidad de penetración de los rayos beta en el empaque secundario, son ideales para la descontaminación de superficie de los contenedores previamente llenados, y al mismo tiempo no son dañinos a la estabilidad o la integridad del contenido
15 del contenedor previamente llenado.

Los métodos y modalidades descritos en la presente son convenientes para su uso en la producción y empaque de los productos farmacéuticos en aislamiento o fuera de aislamiento. Además, los métodos descritos en la presente son adaptables a
20 diferentes formatos o tipos de contenedores, con incrementos mínimos de los costos del diseño de la planta de producción. También se proporciona un sistema que permite la descontaminación de superficie de los contenedores previamente llenados en empaque secundario, así como un kit que comprende un material de
25 instrucciones para practicar el método y el sistema descritos en la

presente.

Haciendo referencia a la Figura 1, un contenedor previamente
llenado 100 previamente llenado bajo condiciones asépticas es
descontaminado en las superficies 102 después del envoltorio o
5 empaque secundario 104 mediante peróxido de
hidrógeno vaporizado o radiación beta sintonizable como se describe
en la presente. La Figura 1 muestra un contenedor previamente
llenado ejemplar, sin embargo, los expertos en la técnica entenderán
que varios contenedores, distintos de las jeringas, también son
10 convenientes. Más aún, aunque el contenedor ejemplar mostrado en
la Figura 1 es una jeringa en una posición cerrada y ensamblada,
deberá entenderse que se pueden vislumbrar otras variantes. Por
ejemplo, un contenedor previamente llenado no sellado por un tapón,
émbolo u otro mecanismo de sello puede ser descontaminado de
15 superficie en porciones interiores del contenedor.

En una modalidad, el contenedor previamente llenado es una
jeringa. Otros contenedores previamente llenados convenientes
incluyen frascos, botellas, bolsas y otros dispositivos médicos
capaces de contener una solución estéril o una solución que requiera
20 esterilización.

En una modalidad, la jeringa se llena con un producto de
fármaco, tal como en la forma de líquido, solución, polvo o sólido. En
otra modalidad el producto de fármaco es una solución tal como una
solución de fármaco o solución de proteína que de otro modo es
25 sensible a la exposición a altas temperaturas, tales como las usadas

SL

en esterilización de vapor, y energía ionizante, tal como rayos gamma o beta y gases oxidantes. En todavía otra modalidad, el producto de fármaco es uno que ha sido liofilizado, en otras palabras un sólido, y requiere la reconstitución en líquido o solución antes del
5 uso.

En otra modalidad, una solución es cualquier producto de fármaco que tiene requerimientos o deseabilidad para la esterilidad de la superficie del contenedor del producto de fármaco. En una modalidad particular, el producto de fármaco es una solución de
10 proteína, tal como una solución de ranibizumab (por ejemplo 6 miligramos/mililitro o 10 miligramos/mililitro) para inyección intravítrea.

En una modalidad, el contenedor se llena con solución bajo condiciones asépticas, ya sea mediante un proceso automatizado o
15 manual. De este modo, el contenido del contenedor es estéril y no es afectado por los métodos de descontaminación de superficie como se describe en la presente. El término "llenado" se refiere a la colocación del contenido, tal como una solución, en el contenedor en una cantidad apropiada, tal como un volumen apropiado o
20 concentración apropiada. La cantidad, volumen o concentración apropiada variará dependiendo de la naturaleza del contenido y de su uso destinado.

En una modalidad, el contenido se considera un empaque primario para la solución contenida dentro. En otra modalidad, el
25 contenido previamente llenado se empaca dentro de un empaque

secundario o se empaca encajando el contenedor previamente llenado. El empaque secundario incluye envolturas, tales como papel, plástico u hoja de aluminio, y empaques de ampollas impermeables para los microbios.

5 En una modalidad el contenedor previamente llenado en empaque secundario se somete a la descontaminación, de manera que el contenido del empaque secundario, específicamente las superficies del contenedor previamente llenado, son descontaminadas y terminalmente esterilizadas. De este modo, las
10 superficies del contenedor previamente llenado encerradas en un empaque secundario descontaminado por los métodos descritos en la presente se pueden presentar, y abrir, dentro de un ambiente crítico o estéril, tal como una sala quirúrgica.

 En una modalidad, la esterilización terminal y la
15 descontaminación de superficie de los contenedores previamente llenados dentro de empaques secundarios se lleva a cabo tratando las superficies del contenedor previamente llenado dentro del empaque secundario con peróxido de hidrógeno vaporizado y aplicando medidas después del tratamiento, dentro de una cámara de
20 descontaminación. Una cámara de descontaminación es cualquier cámara, tal como una autoclave, que tiene los medios para sellar reversiblemente un ambiente cerrado y equipado con medios para manipular la presión, la temperatura, el flujo hacia dentro y el flujo hacia fuera del aire dentro de la cámara. Los elementos adicionales
25 de una cámara conveniente incluyen los medios para adaptar el

tratamiento mediante peróxido de hidrógeno y medidas después del tratamiento para reducir y prevenir que el peróxido de hidrógeno entre en los contenedores previamente llenados.

En otra modalidad, la cámara se configura para acomodar la
5 cantidad de contenedores que requieren la esterilización terminal. De este modo, en la producción a gran escala y en las líneas de montaje, la cámara se puede configurar para acomodar una gran cantidad de contenedores, de acuerdo con lo anterior.

El tratamiento con peróxido de hidrógeno vaporizado se logra
10 mediante la aplicación o liberación de vapores de peróxido de hidrógeno dentro de la cámara de descontaminación. En una modalidad, los vapores de peróxido de hidrógeno son controlables, en otras palabras, se aplican ciertas medidas para manipular o controlar la acción de peróxido de hidrógeno vaporizado. En una
15 modalidad, se aplican las medidas después del tratamiento que dirigen – o invierten – la dirección de la difusión del vapor, de manera que se evita que los vapores entren en el contenedor previamente llenado. En otra modalidad, se aplican medidas después del tratamiento adicionalmente que destruyen cualquier traza de
20 peróxido residual.

En una modalidad, las medidas después del tratamiento incluyen reducir o eliminar los radicales de gas formados por la acción de peróxido de hidrógeno vaporizado. En todavía otra modalidad, las medidas después del tratamiento incluyen inactivar la
25 acción del peróxido de hidrógeno vaporizado, tal como la acción

oxidativa.

En otra modalidad, se logra la esterilización terminal y la descontaminación de superficie de contenedores previamente llenados dentro del empaque secundario mediante la aplicación de irradiación de rayos beta sintonizables. En una modalidad, la superficie de un contenedor previamente llenado en empaque secundario se descontamina mediante un ajuste del voltaje acelerador de un generador de irradiación para proporcionar radiación beta de una dosis suficiente para penetrar en el empaque secundario sin penetrar en el empaque primario.

En otra modalidad, el voltaje acelerador requerido para aplicar la cantidad apropiada de radiación beta para descontaminar la superficie de los contenedores previamente llenados depende del grosor de los materiales del empaque secundario. Por ejemplo, en una modalidad, los materiales de empaque convenientes tienen un grosor menor o igual que 0.05 mm. Estos materiales con un grosor menor o igual que 0.05 milímetros pueden estar hechos de hojas de aluminio.

En otra modalidad, una combinación de componentes de empaque secundario y primario, voltaje acelerador, diseño de planta de irradiación y velocidad de rendimiento permiten la descontaminación de un contenedor previamente llenado en empaque secundario, aunque los materiales del empaque primario protegen casi completamente el contenido del contenedor previamente llenado.

En una modalidad, un empaque primario conveniente es una jeringa capaz de proteger la solución sensible a la radiación contenida adentro. La protección se puede proporcionar por medio del grosor de las paredes del contenedor o por los componentes del material del contenedor. La efectividad de la protección se puede determinar ajustando el voltaje acelerador y así la profundidad de penetración de los rayos beta emitidos sobre el contenedor previamente llenado. Además, la protección se determina midiendo la dosis absorbida, tal como con un dosímetro.

Los expertos en la técnica entienden que un contenedor previamente llenado se ensambla bajo condiciones asépticas, de manera que el contenido del contenedor es estéril. Aunque el contenido del contenedor sea estéril, la superficie del contenedor es susceptible a la contaminación durante el empaque adicional y etiquetamiento del producto usando protocolos estándares de empaque de productos farmacéuticos. Para la descontaminación de superficie de los contenedores previamente llenados, los métodos de esterilización en la presente son adaptables a la producción y empaque estándar de los productos farmacéuticos en aislamiento o fuera de aislamiento.

En una modalidad, un contenedor previamente llenado previamente lleno bajo condiciones asépticas y etiquetado y empacado en empaque secundario mediante un proceso manual o automatizado se presenta a un túnel de rayos de electrones para la esterilización terminal y la descontaminación de superficie del

producto empacado final. En una modalidad, el contenedor previamente llenado en empaque secundario se introduce, ya sea por un proceso manual o un proceso automatizado, o una combinación de los dos, en el túnel de rayos de electrones vía una entrada y es transportado durante todo el tiempo o una parte del tiempo a través del túnel de rayo de electrones a una salida conforme las superficies de los contenedores previamente llenados en empaque secundario se exponen a la radiación beta de baja energía. En otra modalidad, los contenedores previamente llenados en empaque secundario permanecen estacionarios durante todo o una porción del tiempo conforme las superficies de los contenedores previamente llenados en empaque secundario se exponen a la radiación beta de baja energía. En otra modalidad, los rayos de electrones son oscilados, por ejemplo, mediante la aplicación de campos magnéticos, de manera que la superficie entera del objeto es barrida por el rayo de electrones. En otra modalidad, el objeto se pasa por debajo de los rayos de electrones del barrido por medio de un mecanismo de transporte como un transportador de movimiento. En otra modalidad, la cámara para el tratamiento por rayo de electrones es abierta, pero protegida del ambiente por una trayectoria tortuosa de objetos dentro y fuera de la cámara.

Esterilización terminal de contenedores previamente llenados con peróxido de hidrógeno vaporizado (VHP)

En una modalidad, la esterilización terminal de los contenedores previamente llenados en empaque secundario se lleva

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a cabo mediante un tratamiento antimicrobiano en una cámara con peróxido de hidrógeno vaporizado, también conocido como “esterilización en frío”.

Los distintos pasos, u operaciones, involucradas en el proceso de esterilización y descontaminación de superficie se pueden realizar automáticamente bajo la administración de un administrador del sistema, tal como un microprocesador. Alternativamente, se pueden realizar por separado en operaciones manuales. Además, se pueden realizar las operaciones en una combinación de procesos automatizados y manuales.

En una modalidad los contenedores previamente llenados se encierran en empaques secundarios después de llenar los contenedores bajo condiciones asépticas. En otra modalidad, los contenedores previamente llenados se etiquetan con cualquier información del producto, tal como el nombre del producto, indicaciones; instrucciones de uso, etcétera, antes de envolver los contenedores previamente llenados en empaques secundarios.

En una modalidad, los contenedores en empaques secundarios se presentan ya sea manualmente o automáticamente, y se aseguran, dentro de una cámara de descontaminación.

Una cámara de descontaminación conveniente es cualquier cámara, tal como una autoclave, equipada con medios para sellar reversiblemente un ambiente cerrado, y equipada con medios para manipular la presión, la temperatura, el flujo hacia dentro y el flujo hacia fuera del aire dentro de la cámara. Los elementos adicionales

de una cámara conveniente incluyen medios para acomodar el tratamiento mediante vapor de peróxido de hidrógeno y medidas después del tratamiento para reducir o evitar que el vapor de peróxido de hidrógeno entre en los contenedores previamente
5 llenados. Otro elemento de una cámara conveniente es un medio para destruir cualquier traza remanente de peróxido.

En una modalidad, se introduce el vapor de peróxido de hidrógeno en la cámara, ya sea generado dentro o liberado dentro de la cámara durante un tiempo suficiente para descontaminar – o tratar
10 – la superficie de los contenedores previamente llenados en empaque secundario. En otra modalidad, se lleva a cabo la aplicación de peróxido de hidrógeno vaporizado a temperaturas por debajo de las usadas para la esterilización con vapor.

El peróxido de hidrógeno en forma líquida ha sido reconocido
15 desde hace mucho tiempo como un desinfectante. La Patente de los Estados Unidos de América Número 4,512,951 para Koubek describe un método de esterilización con peróxido de hidrógeno líquido el cual incluye vaporizar una solución acuosa de peróxido de hidrógeno y pasar la mezcla de vapor agua y de peróxido de hidrógeno resultante
20 a una cámara de esterilización evacuada donde, después del contacto con los artículos que se van a esterilizar, el vapor se condensa para formar una capa de peróxido de hidrógeno líquido sobre los artículos. Los artículos que se van a esterilizar se mantienen a una temperatura por debajo del punto rocío de la mezcla
25 de agua y peróxido de hidrógeno para asegurar la condensación,

pero la temperatura global de la cámara debe ser lo suficientemente alta para evitar la condensación del vapor entrante antes de que alcance a los artículos. Después de un tiempo conveniente para la esterilización, el condensado se re-evapora al pasar aire filtrado, de preferencia calentado, sobre la superficie de los artículos. La esterilización con peróxido de hidrógeno gaseoso se describe en la Patente de los Estados Unidos de América Número 4,169,123 para Moore y colaboradores y la Patente de los Estados Unidos Número 4,169,124 para Fostrom y colaboradores. Los métodos descritos en esas dos patentes involucran rodear un artículo que se va a esterilizar con peróxido de hidrógeno en fase vapor y mantener el contacto entre el artículo y el esterilizante a temperaturas por debajo de 80° hasta que se logre la esterilidad. La temperatura más baja descrita ya sea en la patente de Moore o en la de Fostrom es de 20°C.

Se ha determinado que con soluciones sensibles, tales como las soluciones de proteínas, la lixiviación del peróxido de hidrógeno vaporizado en el contenedor previamente llenado es perjudicial para la integridad molecular de las soluciones debido a que los vapores del peróxido de hidrógeno que entran al contenedor causan modificaciones químicas de la solución, tales como la oxidación.

Ahora se ha descubierto que aplicando medidas después del tratamiento, o después de la aplicación se reducen o evitan los efectos adversos del vapor de peróxido de hidrógeno en las soluciones sensibles y se preserva la integridad, y por lo tanto la

eficacia terapéutica, de las soluciones de otro modo sensibles en los
contenedores previamente llenados. Las medidas después de la
aplicación idealmente son las medidas que desactivan la acción
oxidante del peróxido de hidrógeno, ya sea removiendo el peróxido
5 de hidrógeno vaporizado o volviendo los vapores de peróxido de
hidrógeno a un estado inactivo.

En una modalidad, se evita la lixiviación del vapor de peróxido
de hidrógeno en un contenedor previamente llenado por medio de la
aplicación de un vacío al final del tratamiento antimicrobiano en la
10 cámara para invertir la dirección de la difusión de los vapores del
peróxido de hidrógeno. Invirtiendo la dirección del flujo del vapor, se
evita que los vapores de peróxido de hidrógeno entren al contenedor
previamente llenado, manteniendo mediante esto la integridad de la
solución sensible dentro del contenedor mientras que se
15 descontamina la superficie del contenedor.

En todavía otra modalidad, se inactivan los vapores del
peróxido de hidrógeno, de manera que sean incapaces de modificar
químicamente la solución contenida en un contenedor previamente
llenado. En otra modalidad, las medidas después del tratamiento
20 incluyen neutralizar la capacidad oxidante de los vapores del
peróxido de hidrógeno. En todavía otra modalidad, se inactivan los
vapores de peróxido de hidrógeno mediante la aplicación de rayos
ultravioleta al contenedor después de un tiempo de exposición
suficiente del contenedor previamente llenado al vapor de peróxido
25 de hidrógeno después del tratamiento. Se pueden aplicar otros

agentes inactivadores, tales como agentes químicos o plasma de gas, después del tratamiento para inactivar el vapor del peróxido de hidrógeno después de un tiempo de exposición suficiente de las superficies de los contenedores previamente llenados al vapor de peróxido de hidrógeno.

En la conclusión del proceso de esterilización terminal, el contenedor previamente llenado en empaque secundario se puede remover de la cámara, y es conveniente para que lo use un usuario final.

En una modalidad, se puede realizar el proceso de esterilización mediante un sistema automatizado. Por ejemplo, haciendo referencia a la Figura 2, se ilustra un diagrama en bloques de un sistema 200 para descontaminar una superficie de un contenedor previamente llenado en empaque secundario. El sistema 200 incluye una cámara sellada 202 y una unidad de control 204 acoplada, directamente o indirectamente, a la cámara 202.

En una modalidad, la cámara sellada 202 puede ser cualquier cámara de descontaminación conveniente. Por ejemplo, la cámara 202 puede incluir una autoclave, con la capacidad de sellar reversiblemente un ambiente cerrado. La cámara 202 también puede estar equipada con mecanismos para manipular la presión, la temperatura, y el flujo hacia dentro y el flujo hacia fuera de aire dentro de la cámara 202.

La unidad de control 204 proporciona instrucciones, en la forma de señales, a la cámara 202 para realizar las operaciones asociadas

con esterilizar un contenedor previamente llenado 100 (tal como el
mostrado en la Figura 1) de una manera automática prescrita. La
unidad de control 204 puede transmitir señales a la cámara 202 para
dirigir la cámara 202 (o las partes relacionadas) para físicamente
5 habilitar que el peróxido de hidrógeno vaporizado se ponga en
contacto con la superficie del contenedor previamente llenado en el
empaquete secundario.

Por ejemplo, en una modalidad, la unidad de control 204 puede
transmitir una señal a una válvula (no mostrada) asociada con un
10 recipiente para pasar peróxido de hidrógeno vaporizado hacia la
cámara. La unidad de control 204 mide una duración de tiempo
prefijada en la que el peróxido de hidrógeno vaporizado va a
permanecer en contacto con la superficie del contenedor
previamente llenado. Al expirar la duración de tiempo prefijada, la
15 unidad de control 204 transmite una señal a la cámara 202 (o a un
dispositivo relacionado) para hacer que se presente una medida
después de la descontaminación para reducir la presencia de
peróxido de hidrógeno vaporizado en la cámara. Mediante esto se
evita que el peróxido de hidrógeno vaporizado se difunda en el
20 contenedor previamente llenado sufriendo descontaminación de
superficie.

Por ejemplo, después de la descontaminación de superficie, la
unidad de control 204 puede transmitir una señal a un vacío (no
mostrado) para invertir el flujo de los vapores de peróxido de
25 hidrógeno fuera de la cámara 202 para remover estos vapores de la

cámara. Otros mecanismos de control convenientes para controlar los vapores de peróxido de hidrógeno incluyen mecanismos para introducir agentes neutralizantes o inactivantes, tales como agentes químicos, en la cámara 202, lo cual al contacto con los vapores del peróxido de hidrógeno vuelve inactivos los vapores, y así inofensivos a la solución interior de un contenedor previamente llenado.

Se hace referencia a los tiempos de tratamiento que son suficientes para esterilizar terminalmente el contenedor previamente llenado. En una modalidad, un tiempo suficiente de tratamiento o la duración de la presencia del peróxido de hidrógeno vaporizado dentro de la cámara para descontaminar suficientemente la superficie del contenedor se determina por validación de rutina. Por ejemplo, los contenedores que han sido sometidos a tratamiento por peróxido de hidrógeno vaporizado se comparan con los controles y se puede verificar la contaminación bacteriana usando protocolos de laboratorio estándares, tales como la incubación de un objeto sospechoso de estar contaminado con medio de cultivo bacteriano y luego verificar el crecimiento bacteriano, generalmente realizado mediante el uso de bioindicadores. Al graficar el tiempo de tratamiento contra la presencia del crecimiento bacteriano, fácilmente se puede determinar el tiempo de lograr la descontaminación, y así la ausencia de crecimiento bacteriano. Las técnicas de validación se aplican si la esterilización terminal se lleva a cabo mediante peróxido de hidrógeno vaporizado como se describe anteriormente, o si se lleva a cabo mediante la exposición a

radiación beta como se describe más adelante.

En una modalidad, la unidad de control 204 se automatiza y opera de acuerdo con la ejecución del código en un procesador. La implementación de una unidad de control estará bien dentro del alcance de algún experto en la técnica. Por ejemplo, la unidad de control puede ser cualquier computadora personal, microprocesador, u otros dispositivos convenientes, capaces de ejecutar el código que está programado para transmitir señales a los dispositivos asociados con llevar a cabo físicamente el proceso de esterilización.

Se apreciará que los distintos pasos, u operaciones, involucrados en el proceso de esterilización y descontaminación de superficie se pueden realizar automáticamente bajo la administración de una unidad de control como se describe anteriormente. Alternativamente, se pueden realizar las operaciones por separado en operaciones manuales. Además, se pueden realizar las operaciones en una combinación de procesos automatizados y manuales.

Esterilización terminal de contenedores previamente llenados mediante irradiación beta-sintonizable

En una modalidad, se lleva a cabo la esterilización de contenedores previamente llenados en empaque secundario mediante un tratamiento de descontaminación en una cámara equipada con uno o más generadores de rayos de electrones que son sintonizables para generar una dosis apropiada de radiación beta sobre las superficies de los contenedores previamente llenados.

Los distintos pasos, u operaciones, involucradas en el proceso de esterilización y descontaminación de superficie se pueden realizar automáticamente bajo la administración de un administrador del sistema, tal como un microprocesador. Alternativamente, se pueden
5 realizar las operaciones por separado en operaciones manuales. Además, se pueden realizar las operaciones en una combinación de procesos automatizados y manuales.

En una modalidad los contenedores previamente llenados se encierran en empaques secundarios después de llenar los
10 contenedores bajo condiciones asépticas. En otra modalidad, se etiquetan los contenedores previamente llenados con cualquier información del producto, tal como el nombre del producto, indicaciones, instrucciones de uso, etcétera, antes de envolver los contenedores previamente llenados en empaques secundarios.

15 En una modalidad, se presentan contenedores previamente llenados en empaque secundario ya sea manualmente o automáticamente a una cámara de descontaminación con un lado de entrada y un lado de salida. En otra modalidad la cámara de descontaminación es un túnel de rayo de electrones. En todavía otra
20 modalidad, se mueven los contenedores previamente llenados mecánicamente a través del túnel desde el lado de entrada al lado de salida sobre un mecanismo movable, tal como un transportador. De este modo, los contenedores previamente llenados se mueven a través de la cámara conforme las superficies de los contenedores
25 previamente llenados se exponen a la irradiación beta.

En otra modalidad, los rayos de electrones oscilan, por ejemplo, mediante la aplicación de campos magnéticos, de manera que la superficie entera del objeto es escaneado por el rayo de electrones. En otra modalidad, el objeto se pasa por debajo del
5 barrido de los rayos de electrones por medio de un mecanismo de transporte como un transportador móvil.

En una modalidad, las superficies de los contenedores previamente llenados en empaque secundario se descontaminan durante un tiempo de exposición de radiación beta de poca penetración de menos de un segundo, idealmente en menos de
10 medio segundo. De este modo, los tiempos del tratamiento con radiación beta sintonizable, como se describe en la presente, son significativamente menores que la descontaminación usando rayos gamma, que requiere tiempos de tratamiento de superficie de varias
15 horas o más tardados para una descontaminación y esterilización suficiente.

En otra modalidad, el túnel de rayo de electrones se configura con un generador de rayo de electrones, mediante el cual es sintonizable el voltaje de la energía generada.

20 En todavía otra modalidad, los contenedores previamente llenados en empaque secundario se transportan o mueven alrededor de una manera que exponga todas las superficies de los contenedores para emitir radiación beta dentro del túnel.

Los contenedores de empaque primario para los productos de
25 fármacos farmacéuticos estériles frecuentemente son

aproximadamente 30 veces más gruesos que el material de empaque secundario. En una modalidad el grosor de la pared del material de empaque primario es 20 o más veces más grueso que el grosor del material de empaque secundario, permitiendo de este modo una
5 dosis resultante adsorbida por el contenido en el contenedor previamente llenado a menos de 0.1kGy.

Se ha descubierto que es posible encontrar una combinación de componentes de empaque, voltaje acelerador, diseño de planta de irradiación y velocidad de rendimiento que permita la
10 descontaminación de superficie o la esterilización de superficie de un contenedor previamente llenado en empaque secundario, mientras el contenido del contenedor está esencialmente protegido por el material del empaque primario. Por lo tanto, la irradiación beta no afecta las biomoléculas sensibles, tales como las soluciones de
15 fármacos de biotecnología, dentro de los materiales del empaque primario.

En una modalidad, la irradiación beta del contenedor previamente llenado se puede conducir a cualquier dosis útil para proporcionar la esterilización efectiva sin degradar el contenedor o
20 su contenido, usando cualquier aparato de irradiación beta conocido, tal como un generador de bajo voltaje o acelerador de partículas, con la cantidad de radiación dependiente del grosor del empaque secundario.

En una modalidad la dosis mínima esterilizante (MSD) de la
25 radiación beta es la requerida para entregar el nivel de garantía de

esterilización requerida por el producto. En una modalidad se miden las dosis esterilizantes con Gray /Gy) o Rad (dosis absorbida de radiación). En otra modalidad, las dosis absorbidas se miden por dosímetro, preferiblemente por dosímetros de película, calorímetros o dosímetros de cerio.

En otra modalidad, la cantidad de radiación depende de la presencia del empaque secundario y el grosor del empaque secundario. Para un contenedor previamente llenado típico, la radiación beta deseablemente se proporciona a una dosis de 25 kGy en la superficie del contenedor previamente llenado.

En una modalidad, un acelerador de partículas genera aceleración de partículas beta a través de un tubo de vacío. En una modalidad, la aceleración es por medios tales como campo magnético, carga electrostática o por transferencia de energía a partir de ondas electromagnéticas de alta frecuencia.

En la conclusión del proceso de esterilización terminal, el contenedor previamente llenado en empaque secundario deja el túnel por la salida con superficies descontaminadas y es conveniente para su uso por un usuario final. Debido a que el tiempo de tratamiento para la descontaminación de superficie es tan corto como aproximadamente un segundo, la descontaminación de superficie de los contenedores previamente llenados en empaque secundario ofrece numerosas ventajas sobre los métodos de esterilización que involucran a la radiación gamma, la cual es dañina al contenido del

contenedor, requiere tiempos de exposición significativamente más largos para la descontaminación, y requiere protección adicional a lo largo de la línea de producción, y causa decoloración de los componentes de empaque. Más aún, las técnicas de esterilización que involucran la radiación gamma causan cuellos de botella significativos en las líneas de ensamble de producción que son eliminadas por la descontaminación de superficie usando radiación beta sintonizable en un túnel de rayo de electrones.

En una modalidad, como se representa en la Figura 3, un sistema 300 – para descontaminar de superficialmente un contenedor previamente llenado en empaque secundario – incluye un túnel de rayo de electrones 302 equipado con uno o más generadores de rayos de electrones sintonizables, mostrados como los generadores de voltaje 304. En otra modalidad, el uno o más generadores de rayos de electrones sintonizables 304 del sistema se configuran para generar variablemente radiación beta de baja energía. Alternativamente, los rayos de electrones se oscilan, de manera que los rayos de electrones aciertan sobre una superficie más grande de un contenedor previamente llenado y aumentan la superficie de exposición del contenedor.

En todavía otra modalidad, el uno o más generadores 304 aplican un voltaje acelerador para producir una cantidad suficiente de radiación beta para descontaminar la superficie del contenedor previamente llenado, en donde la cantidad suficiente de radiación beta depende del grosor del empaque secundario y el grosor del

contenedor previamente llenado. De este modo, se permite que la radiación beta penetre en el empaque secundario mientras el grosor del contenedor previamente llenado protege al contenido en el mismo de la radiación beta.

- 5 Se hace referencia al tiempo de tratamiento que es suficiente para esterilizar terminalmente y descontaminar la superficie del contenedor previamente llenado. En una modalidad, un tiempo de tratamiento suficiente o la duración de la presencia de radiación beta de baja energía dentro del túnel para descontaminar suficientemente
- 10 la superficie del contenedor se determina mediante una validación de rutina. Por ejemplo, los contenedores que se han sometido a tratamiento por radiación beta se comparan con controles y se puede verificar la contaminación bacteriana usando protocolos de laboratorio estándares, tales como la incubación del objeto
- 15 sospechoso de estar contaminado con medio de cultivo bacteriano y luego verificar si hay crecimiento bacteriano. Graficando el tiempo de tratamiento contra la presencia de crecimiento bacteriano, el tiempo de tratamiento para lograr la descontaminación, de este modo la ausencia de crecimiento bacteriano, se puede determinar fácilmente.
- 20 Las técnicas de validación aplican si la esterilización terminal se lleva a cabo por radiación beta como se describe anteriormente o si se lleva a cabo por exposición a vapor de peróxido de hidrógeno como se describe anteriormente.

- 25 Ahora se hace referencia a los siguientes ejemplos. Estos ejemplos se proporcionan con el propósito de ilustración solamente y

no deberán considerarse de ningún modo como limitados a estos ejemplos sino de otro modo deberán considerarse que abarcan cualquiera y todas las variaciones lo cual será evidente como un resultado de las enseñanzas proporcionadas en la presente.

5

Ejemplo 1

En el siguiente experimento, jeringas previamente llenadas fueron tratadas con un tratamiento de esterilización de peróxido de hidrógeno en una cámara, ya sea mediante una sola pasada a través de esterilización mediante vapor de peróxido de hidrógeno o dos pasadas (mostrados en la tabla que sigue como 2X) a través de un procedimiento de esterilización. Las jeringas que contenían soluciones de proteína tratadas por vapor de peróxido de hidrógeno se compararon con jeringas de control tratadas con vapor de peróxido de hidrógeno para determinar si se mantiene la integridad de las proteínas presentes en la solución.

15

Una formulación como se describe en la Patente de los Estados Unidos de América Número 7,060,269 se probó para ver la degradación de la proteína después del tratamiento con vapor de peróxido de hidrógeno.

20

Aproximadamente 10 mililitros de solución se filtraron a través de un filtro de jeringa de 0.22 micras. (filtro Millex GV disponible de Millipore, Billerica, MA, EUA). El llenado de jeringas de 0.5 mililitros se realizó en un laboratorio estéril para el tratamiento con peróxido de hidrógeno.

25

El análisis después del tratamiento con vapor de peróxido de

hidrógeno reveló los siguientes contenidos de proteínas visualizados por análisis de HPLC: subproductos y productos de degradación por HPLC (IEC) y subproductos y productos de la degradación por HPLC (SEC).

5 **Tabla 1: Estabilidad de la proteína después del tratamiento con vapor de peróxido de hidrógeno**

Lote	IEC (% pico principal)	IEC (% pico básico)	SEC (% monómero)
Control			
9823.01 CSi	98	2	100
9823.02 CSi	98	2	100
Tratamiento 1X			
9823.04 CSi	98	2	100
9823.05 CSi	98	2	100
Tratamiento 2X			
9823.07	98	2	100
9823.08	98	2	100

Los resultados vistos estuvieron dentro del requerimiento, no hubo diferencias entre los resultados de las jeringas no tratadas y

con las jeringas tratadas con peróxido de hidrógeno. El análisis también se puede llevar a cabo en diferentes puntos de tiempo siguiendo el tratamiento, tales como 1 mes, 3 meses y seis meses después del tratamiento por vapor de peróxido de hidrógeno, o sobre la vida en el estante del producto del contenedor previamente llenado. El análisis se puede llevar a cabo para determinar la estabilidad continuada de la solución de proteína, incluyendo pruebas por HPLC para determinar la presencia de productos secundarios usando protocolos de laboratorio estándares de HPLC. El análisis también se puede llevar a cabo por la presencia de cambios físicos, tales como medir la concentración de H_2O_2 en solución mediante una prueba de fluorescencia usando un kit disponible comercialmente sin necesidad de receta junto con un aparato con detección de fluorescencia.

Ejemplo 2

El siguiente experimento se llevó a cabo para determinar la efectividad de la descontaminación de superficie usando irradiación beta. Se usó un túnel de rayos de electrones disponible comercialmente para la descontaminación afuera de los contenedores, equipado con aceleradores KeVAC de Linac Technologies (Orsay, Francia), para investigar la profundidad de penetración del rayo de electrones en diferentes materiales. Por ejemplo, se midió la penetración en una bolsa de polietileno con grosor de hoja de 50 micras, una bolsa de aluminio con grosor de hoja de 0.1 milímetro y un portaobjetos de vidrio de 1 milímetro de

grosor.

Para aumentar la sensibilidad del estudio, se investigaron múltiples pasadas de las muestras a través del túnel. Se usaron dosímetros de Película Far West 60, disponibles en Far West Technologies (Santa Bárbara, CA, USA) para registrar la radiación absorbida.

Tabla 2: Absorción de irradiación beta por los materiales de empaque:

Número de pasadas a través del túnel de descontaminación	Dosis Absorbida		
	Dosímetro en Bolsa de polietileno	Dosímetro en bolsa de aluminio	Dosímetro protegido por un portaobjetos de vidrio de 1 mm
1 pasada	30 kGy	1.3 kGy	<LOQ(0.1 kGy)
3 pasadas	97 kGy	64 kGy	<LOQ(0.1 kGy)
5 pasadas	207 kGy	105 kGy	<LOQ (0.1 kGy)

El estudio de factibilidad mostró que ya con estas referencias no optimizadas del túnel de descontaminación de rayo de electrones pudo obtenerse una esterilización de superficie (>025 kGy) cuando el

producto se empacó en bolsas de plástico. Aún después de pasar 5 veces a través del túnel de tratamiento de rayo de electrones, la dosis absorbida dentro del material de empaque (detrás de una pared de vidrio de 1 milímetro de grosor) fue muy por debajo del
5 límite de cuantificación la cual fue de 1 kGy para los dosímetros usados.

Adicionalmente, se investigó la tensión oxidante ejercida sobre una solución de Polisorbato 20 al 0.5% en jeringas de vidrio previamente llenadas (de 1 mililitro de largo, ISO) midiendo
10 peróxidos de acuerdo con los protocolos estándares. Se midió la cantidad total de peróxidos mediante la prueba de Oxidación de óxido ferroso (FOX), de acuerdo con un protocolo estándar.

**Tabla 3: Niveles de peróxido después de la irradiación beta de
15 contenedores previamente llenados:**

	Número de pasadas a través del túnel de rayo de electrones	Contenido de peróxido de solución de Polisorbato 20 al 0.5% en agua en jeringa de vidrio de 1mL de largo (ISO) [µMol/mL]
20	Referencia (no tratado)	0.04
	1 pasada	0.04
25	3 pasadas	0.03

5

Número de pasadas a través del túnel de rayo de electrones	Contenido de peróxido de solución de Polisorbato 20 al 0.5% en agua en jeringa de vidrio de 1mL de largo (ISO) [$\mu\text{Mol/mL}$]
5 pasadas	0.05

10

No se pudo observar una influencia significativa del tratamiento de rayo de electrones sobre el contenido de peróxido de la solución encerrada en jeringas de vidrio. De este modo, la irradiación beta demostró ser segura para las soluciones dentro de contenedores previamente llenados.

15

Adicionalmente, se investigó la tensión oxidante ejercido sobre la solución de proteínas en frascos de vidrio previamente llenados midiendo los productos de la degradación de acuerdo con protocolos estándares.

20

Se probó una formulación como se describe en la Patente de los Estados Unidos Número 7,060,269 para determinar la degradación de proteínas después del tratamiento por irradiación de rayo de electrones. Aproximadamente 0.3 mililitros de solución se filtraron a través de un filtro de 0.22 micras y se llenaron asépticamente frascos de vidrio previamente esterilizados, asépticamente cerrados con tapón de hule estéril y asegurados con una tapa engarzada de aluminio.

25

Los contenedores se pasaron a través del túnel de rayos de

electrones descrito anteriormente con valores de referencia idénticos que para los otros experimentos mencionados anteriormente. Los contenedores fueron analizados después del tratamiento con radiación de rayo de electrones para determinar el contenido de proteína, visualizado por análisis de HPLC para los subproductos y productos de la degradación por HPLC (IEC), como se realizó anteriormente en el Ejemplo 1.

Tabla 4: Estabilidad de la proteína después de irradiación beta de los contenedores previamente llenados

10	Número de pasadas a		
	través de	IEC (% pico	IEC (% pico
	túnel de rayo de	principal)	básico)
	electrones		
15	Referencia (no tratado)	98 (97.8)	1 (1.2)
	1 pasada	98 (97.8)	1 (1.3)
20	3 pasadas	98 (97.5)	2 (1.5)
	5 pasadas	98 (97.6)	1 (1.4)

No hubo diferencias entre los resultados de las jeringas no tratadas y los frascos esterilizados con rayo de electrones, después

de 1 pasada, 3 pasadas ó 5 pasadas a través del proceso de saneamiento de rayo de electrones, como se muestra en los resultados en la Tabla 4. De este modo, la radiación beta sintonizable como se describe en la presente demostró ser segura para las soluciones dentro de contenedores previamente llenados.

Las modalidades descritas se considerarán en todos los aspectos solamente como ejemplos y no como restricciones. El alcance de la invención, por lo tanto, se indica por las reivindicaciones anexas, en vez de por la anterior descripción. Todos los cambios que vienen dentro del significado e intervalo de variación de equivalencia de las reivindicaciones se considerarán dentro de su alcance.

18

REIVINDICACIONES

1. Un método para la descontaminación de superficie de un contenedor previamente llenado en empaque secundario, que
5 comprende:

aplicar peróxido de hidrógeno vaporizado a la superficie del contenedor previamente llenado en empaque secundario;

permitir que el peróxido de hidrógeno vaporizado permanezca en contacto con la superficie del contenedor
10 previamente llenado durante un tiempo suficiente para descontaminar la superficie del contenedor previamente llenado; y

hacer que se presente una medida después de la descontaminación para reducir la presencia del peróxido de hidrógeno vaporizado, previniendo mediante esto que el peróxido de
15 hidrógeno vaporizado se difunda en el contenedor previamente llenado.

2. El método de la reivindicación 1, en donde el contenedor previamente llenado es una jeringa que contiene un producto de fármaco de otro modo sensible al tratamiento de esterilización
20 mediante radiación gamma, al tratamiento de esterilización mediante exposición al vapor, y al tratamiento de esterilización mediante exposición a agentes y gases vaporizantes.

3. El método de la reivindicación 1 o de la reivindicación 2, en donde el contenedor previamente llenado es una jeringa que
25 contiene una cantidad terapéuticamente efectiva de ranibizumab.

4. El método de cualquier reivindicación anterior, en donde se determina el tiempo suficiente para descontaminar la superficie del contenedor previamente llenado mediante la validación de los tiempos de tratamiento y se compara con un estándar de control.

5 5. El método de cualquier reivindicación anterior, en donde la medida después de la descontaminación incluye aplicar un vacío después de la duración del tratamiento con peróxido de hidrógeno vaporizado, mediante lo cual se invierte la dirección de la difusión del peróxido de hidrógeno vaporizado y se evita la intrusión del
10 peróxido de hidrógeno vaporizado en el contenedor previamente llenado.

6. El método de cualquiera de las reivindicaciones 1 a 4, en donde la medida después de la descontaminación incluye aplicar rayos ultravioleta después de la duración del tratamiento con
15 peróxido de hidrógeno vaporizado, mediante lo cual se inactiva la acción oxidante de los vapores del peróxido de hidrógeno.

7. El método de cualquiera de las reivindicaciones 1 a 4, en donde la medida después de la descontaminación incluye un tratamiento con plasma de gas.

20 8. Un método para la descontaminación de superficie de un contenedor previamente llenado en empaque secundario, que comprende:

presentar un contenedor previamente llenado en un empaque secundario a un túnel de rayo de electrones equipado con
25 uno o más generadores de rayos de electrones sintonizables capaces

de generar de manera variable radiación beta de baja energía y capaces de oscilar rayos de electrones de manera que se exponga una superficie mayor del contenedor previamente llenado a la radiación beta durante la descontaminación; y

5 aplicar un voltaje acelerador del uno o más generadores de rayos de electrones sintonizables para producir una cantidad suficiente de radiación beta para descontaminar la superficie del contenedor previamente llenado, en donde la cantidad suficiente de radiación beta depende del grosor del empaque secundario y del
10 grosor del contenedor previamente llenado, de manera que se permite que la radiación beta penetre en el empaque secundario mientras que el grosor del contenedor previamente llenado protege al contenido en el mismo de la radiación beta.

9. El método de la reivindicación 8, en donde el grosor de la
15 pared del material de empaque primario es 20 o más veces más grueso que el grosor del material del empaque secundario, reduciendo de este modo la dosis absorbida por el producto en el contenedor a menos de 0.1 kGy.

10. El método de la reivindicación 8 o de la reivindicación 9,
20 en donde el contenedor previamente llenado es un frasco relleno con una solución o sólido de otro modo sensible al tratamiento de esterilización mediante radiación gamma, al tratamiento de esterilización mediante exposición a vapor, y al tratamiento de esterilización mediante exposición a agentes o gases vaporizantes o
25 sustancias que forman peróxido.

11. El método de cualquiera de las reivindicaciones 8 a 10, en donde el contenedor previamente llenado es una jeringa llena con una solución de otro modo sensible al tratamiento de esterilización mediante radiación gamma, al tratamiento de esterilización mediante exposición a vapor, y al tratamiento de esterilización mediante exposición a agentes o gases vaporizantes o sustancias que forman peróxido.

12. El método de cualquiera de las reivindicaciones 8 a 11, en donde el contenedor previamente llenado es una jeringa que contiene una cantidad terapéuticamente efectiva de ranibizumab.

13. El método de cualquiera de las reivindicaciones 8 a 12, en donde la profundidad de penetración se mide por dosimetría.

14. El método de cualquiera de las reivindicaciones 8 a 13, en donde la energía suficiente para descontaminar una superficie de un contenedor previamente llenado es la que proporciona una dosis de radiación beta de cuando menos aproximadamente 25 kGy a la superficie del contenedor.

15. El método de cualquiera de las reivindicaciones 8 a 14, en donde la energía suficiente para descontaminar una superficie de un contenedor previamente llenado es la que proporciona una dosis de radiación beta que produce un Nivel de Aseguramiento de Esterilidad de 10^{-6} del exterior de la superficie del contenedor.

16. Un sistema para descontaminar una superficie de un contenedor previamente llenado en empaque secundario, comprendiendo el sistema:

una cámara sellada; y

una unidad de control acoplada a la cámara, configurada la unidad de control para automáticamente (i) permitir que el peróxido de hidrógeno vaporizado haga contacto con la superficie del contenedor previamente llenado en el empaque secundario; (ii) 5 permitir que el peróxido de hidrógeno permanezca en contacto con la superficie del contenedor previamente llenado durante un tiempo predeterminado; y (iii) hacer que se presente una medida después de la descontaminación para reducir la presencia de peróxido de hidrógeno vaporizado en la cámara, mediante lo cual se evita que el 10 peróxido de hidrógeno vaporizado se difunda dentro del contenedor previamente llenado.

17. Un sistema para descontaminar la superficie de un contenedor previamente llenado en empaque secundario, 15 comprendiendo el sistema:

un túnel de rayo de electrones equipado con uno o más generadores de rayos de electrones sintonizables, los generadores de rayos de electrones sintonizables configurados para:

(i) 20 variablemente generar radiación beta de baja energía,

(ii) oscilar los rayos de electrones de manera que se exponga una superficie mayor del contenedor previamente llenado a los rayos de electrones; y

(iii) aplicar un voltaje acelerador para producir 25 una cantidad suficiente de radiación beta para descontaminar la

superficie del contenedor previamente llenado, en donde la cantidad suficiente de radiación beta depende del grosor del empaque secundario y del grosor del contenedor previamente llenado, de manera que se permite que la radiación beta penetre en el empaque secundario mientras que el grosor del contenedor previamente llenado protege al contenido en el mismo de la radiación beta.

18. Un kit para descontaminar la superficie de un contenedor previamente llenado en empaque secundario en una cámara sellada, comprendiendo el kit:

10 una instrucción para usar la cámara sellada para:

(i) aplicar un peróxido de hidrógeno vaporizado para hacer contacto con la superficie del contenedor previamente llenado en el empaque secundario;

(ii) permitir que el peróxido de hidrógeno vaporizado permanezca en contacto con la superficie del contenedor previamente llenado durante un tiempo predeterminado dentro de la cámara sellada; y

(iii) causar que ocurra una medida después de la descontaminación para reducir la presencia del peróxido de hidrógeno vaporizado en la cámara, evitando de este modo que el peróxido de hidrógeno vaporizado se difunda dentro del contenedor previamente llenado.

19. Un kit para descontaminar la superficie de un contenedor previamente llenado en empaque secundario, comprendiendo el kit:

25 una instrucción para:

(i) variablemente generar radiación beta de baja energía para hacer contacto con la superficie del contenedor previamente llenado, y

(ii) producir una cantidad suficiente de radiación beta para descontaminar la superficie del contenedor previamente llenado, en donde la cantidad suficiente de radiación beta depende del grosor del empaque secundario y del grosor del contenedor previamente llenado de manera que la radiación beta puede penetrar en el empaque secundario mientras que el grosor del contenedor previamente llenado protege al contenido en el mismo de la radiación beta.

20. Un sistema de acuerdo con la reivindicación 16, o un kit de acuerdo con la reivindicación 18, en donde la medida después de la descontaminación incluye el tratamiento por plasma de gas.

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RESUMEN

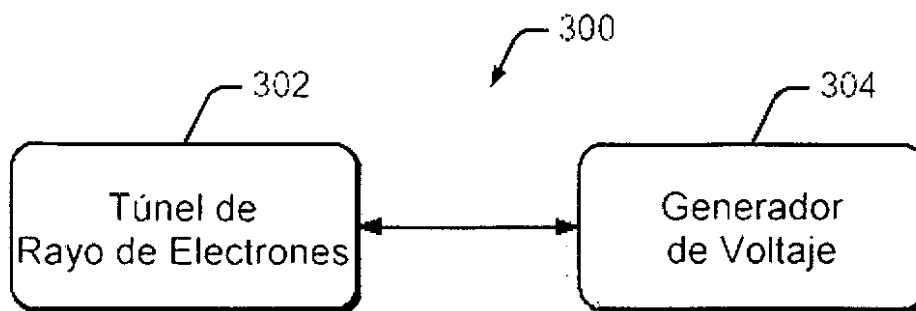
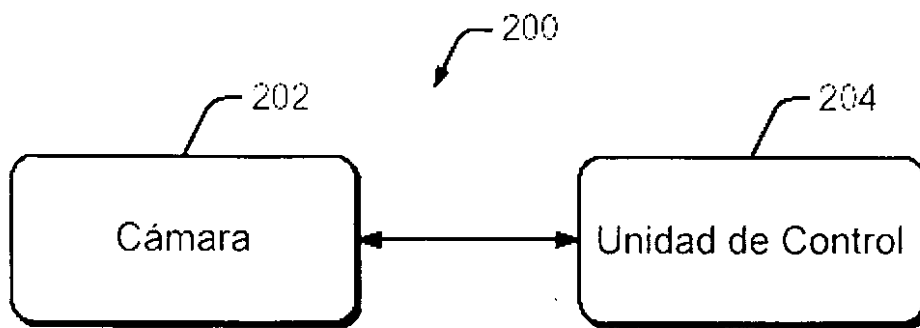
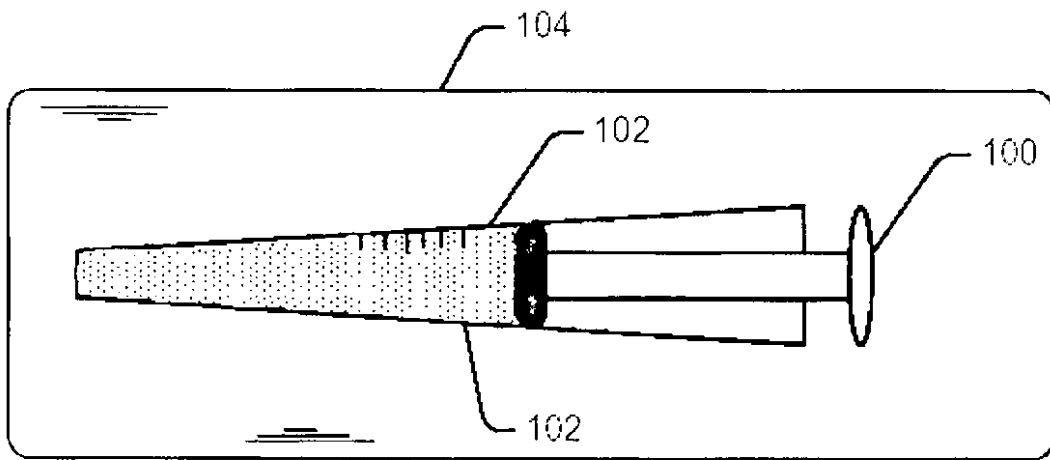
Métodos y sistemas para la esterilización terminal y la descontaminación de superficie de los contenedores previamente
5 llenados que contienen productos de fármacos sensibles, tales como los productos de fármacos de biotecnología que de otro modo son sensibles a la temperatura o a la radiación, y de este modo no son convenientes para la esterilización terminal mediante métodos clásicos que involucran vapor o rayos gamma. Los métodos y
10 sistemas son especialmente convenientes para los contenedores previamente llenados en empaques secundarios. Los métodos incluyen la esterilización terminal exponiendo los contenedores previamente llenados en empaque secundario a radiación beta-sintonizable y además incluyen la esterilización terminal exponiendo
15 a los contenedores previamente llenados a peróxido de hidrógeno vaporizado controlable, incluyendo la aplicación de medidas para reducir o prevenir la difusión del peróxido de hidrógeno vaporizado dentro de los contenedores previamente llenados.

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PATENTE DE INVENCION ☐

MODELO DE UTILIDAD ☐

Art 33 Decisión 486/00

☐	Indicación que se solicita una patente.
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Descripción de la invención
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa ☐	Incompleta ☐

PATENTE DE INVENCION PCT ☐

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

☐	Indicación que se solicita una PCT
☐	Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
Completa ☐	Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

☐	Indicación que se solicita Diseño industrial
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

☐	Indicación que se solicita un esquema de trazado
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica de un esquema de trazado
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐