Copy for (DO-US) 36 PCT/EP2010/060011

PATENT COOPERATION TREATY

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

NOVARTIS PHARMACEUTICALS CORPORATION
Patent Department
One Health Plaza
Building 101
East Hanover, NJ 07936
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
20 September 2011 (20.09.2011)

Applicant's or agent's file reference
53689-WO-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2010/060011

International filing date *(day/month/year)*
13 July 2010 (13.07.2010)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

NOVARTIS PHARMACEUTICALS CORPORATION
Patent Department
One Health Plaza
Building 101
East Hanover, NJ 07936
United States of America

State of Nationality | State of Residence

Telephone No.
+1 862 778 1601

Facsimile No.
+41 61 322 75 32

E-mail address
pip_inbox.phchbs@novartis.com
☒ Notifications by e-mail authorized

3. Further observations, if necessary:
All future correspondence should be sent to the address for correspondence indicated in Box 2. Advance copies of future notifications will also be sent in electronic form via e-mail to the e-mail address indicated above.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

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Form PCT/IB/306 (January 2009) 1/T6MDAEPY11

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

Form PTO-1390 (MOD) U.S. Department of Commerce Patent and Trademark Office (REV 10-96)

ATTORNEY'S DOCKET NUMBER: PAT053689-US-PCT

U.S. APPLICATION NO. (If known, see 37 CFR 1.5):

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP2010/060011	July 13, 2010	14 July, 2009

TITLE OF INVENTION
Surface Decontamination of Prefilled Containers in Secondary Packaging

APPLICANT(S) FOR DO/EO/US
Sigg, Juergen

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau. (See Form PCT/IB/308)
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C.371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau)
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An executed Declaration and Power of Attorney (original or copy) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included.

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☒ An Application Data Sheet under 37 CFR 1.76.

15. ☐ A substitute specification.

16. ☐ A change of power of attorney and/or address letter.

17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821-1.825.

18. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4).

19. ☐ A second copy of the English language translation of the International application under 35 U.S.C. 154(d)(4).

20. ☐ Other items or information:

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
	PCT/EP2010/060011	PAT053689-US-PCT

The following fees are submitted:		CALCULATIONS PTO USE ONLY
21. ☒ Basic national fee ($ 380)	$ 380	
22. Examination Fee		
☐ If International preliminary examination report was prepared by USPTO and all claims satisfy provisions of PCT Article 33(1)-(4) ($ 0)	$ 0	
☒ All other situations ($ 250)	$ 250	
23. Search fee		
☐ If Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ($ 120)	$ 0	
☒ If International Search Report was prepared and provided to the Office ($ 490)	$ 490	
☐ All other situations ($ 620)	$ 0	
TOTAL OF 21, 22 AND 23 =		$ 1120

Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is $ 310 for each additional 50 sheets of paper or fraction thereof.

Total Sheets	Extra sheets	Number of each additional 50 or fraction thereof (round up to a whole number)	RATE	
29 - 100 =	[redacted] /50 =	0	X $ 310	$ 0

Surcharge of $0 for furnishing the oath of declaration later than ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). $ 0

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	22	- 20 =	2	X $ 60	$ 120
Independent claims	5	- 3 =	3	X $ 250	$ 750
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			☐	+ $ 450	$ 0
TOTAL OF ABOVE CALCULATIONS =					$ 1990
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).					$
SUBTOTAL =					$ 1990
Processing fee of $ 130 for furnishing the English translation later than ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	$ 0
TOTAL NATIONAL FEE =					$ 1990
☐ Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31): $ 40 per property				+	$ 0
TOTAL FEES ENCLOSED =					$ 1990
				Amount to be: refunded	$
				charged	$

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $ 1990 to cover the above fees. A duplicate copy of this form is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0134 in the name of Novartis.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to the address associated with Customer No. 001095, which is currently:

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936

Andrew Holmes
Agent for Applicant
Reg. No. 51,813
+1 862 7785816

US Case PAT053669

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

☒ Original ☐ Supplemental ☐ Substitute

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

Surface Decontamination of Prefilled Containers in Secondary Packaging

the specification of which:

☐ is attached hereto.

☐ was filed on _____ as Application No. _____
(day/month/year)

and, if this box (☐) contains an ×

☐ was amended on _____
(day/month/year)

☒ was filed as Patent Cooperation Treaty International Application No.

_____ on _____
(day/month/year)

and, if this box (☐) contains an ×

☐ entered the national stage in the United States and was accorded Application No.

_____

and, if this box (☐) contains an ×

☐ was amended, subsequent to entry into the national stage, on _____
(day/month/year)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) specifically referred to above and, if this application was filed as a Patent Cooperation Treaty international application, by any amendments made during the international stage (including any made under Patent Cooperation Treaty Rule 91, Article 19 and Article 34).

I acknowledge my duty to disclose information which is material to patentability as defined in 37 C.F.R. 1.56, including, for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or Patent Cooperation Treaty international filing date of the continuation-in-part application.

US Case PAT053689

I hereby claim the benefit under 35 U.S.C. 119(a)-(d) or (f) or 365(b) of any foreign application(s) for patent, inventor's certificate or plant breeder's right certificate listed below and under 35 U.S.C. 365(a) of any Patent Cooperation Treaty international application(s) designating at least one country other than the United States listed below and have also listed below any foreign application(s) for patent, inventor's certificate or plant breeder's right certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application the priority of which is claimed for that subject matter:

COUNTRY/REGION (OR P.C.T.)	APPLICATION No.	FILING DATE (day/month/year)	PRIORITY CLAIMED	
EP	08166458.8		☒ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

APPLICATION NO.	FILING DATE (day/month/year)

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s) listed below and under 35 U.S.C. 365(c) of any Patent Cooperation Treaty international application(s) designating the United States listed below:

United States Application No.	United States Filing Date (day/month/year)	Status (Pending, Abandoned or U.S. Patent No.)	International Application No.	and Filing Date (day/month/year)

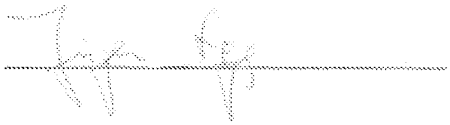
US Case PAT053688

I hereby appoint all of the registered practitioners associated with Customer No. , respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

If this box (☐) contains an x ☒, I hereby authorize the registered practitioners associated with Customer No. and any others acting on my behalf to take any action relating to this application based on communications from Corporate Intellectual Property of Novartis International AG, Basle, Switzerland, or an affiliate thereof or a successor thereto, without direct communication from me.

Please send all correspondence relating to this application to the address associated with Customer No. .

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Full name of sole or first joint inventor	Juergen Sigg
Inventor's signature	 Date 01/07/2010 (day/month/year)
Residence	Lörrach, Germany
Citizenship	Germany
Post Office Address	c/o Novartis Pharma AG Postfach 4002 Basel Switzerland

IMPORTANT: Before this declaration is signed, the patent application (the specification, the claims and this declaration) must be read and understood by each person signing it, and no changes may be made in the application after this declaration has been signed.

Case PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF Art Unit:

Sigg, Juergen Examiner:

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: PCT/EP2010/060011

35 USC §371 DATE:

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed:

☒ within three months of the date of entry of the national stage as set forth in 37 C.F.R. §1.491 of the international application. Therefore, no fees are required.

☒ before the mailing date of a first Office action on the merits, and so under 37 C.F.R. §1.97(b)(3) no fees are required.

If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134 in the name of Novartis.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO/SB/08A/B.

☒ The listed references were cited in the international stage search report and copies are enclosed herewith except for the US patents/applications.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO/SB/08A/B form(s).

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
+1 862 7785816

Andrew Holmes
Agent for Applicant
Reg. No. 51,813

Date: January 5, 2013

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	Not yet Known
Filing Date	Herewith
First Named Inventor	Sigg, Juergen
Art unit	
Examiner Name	
Attorney Docket Number	PAT053689-US-PCT

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-5,779,973	07-14-1998	Edwards et al.	
		US-4,652,736	03-24-1987	Nablo, Samuel	
		US-6,189,292 B1	02-20-2001	Odell et al.	
		US-			
		US-			
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		US-			
		US-			
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
		EP 1 433 486 A1	06-30-2004	Closure Medical Corp		☐
		WO 2005/020847 A2	03-10-2005	Cook Biotech Inc.		☐
		DE 196 22 283 A1 (Equivalent to WO 97/44068)	11-27-1997	Schering AG		☐
		WO 97/44068 (English Abstract)	11-27-1997	Schering AG		
		EP 1 283 061 A1	02-12-2003	Taisei Kako Co., Ltd		☐
		EP 1 944 044 A1	07-16-2008	Becton Dickinson France		☐
		WO 2008/077155 A	06-26-2008	Genetech Inc.		☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

CASE PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF

Sigg, Juergen

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: Not Yet Known

35 USC §371 DATE: Herewith

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

Prior to the examination of the above-referenced patent application, please enter the following preliminary amendments.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of the claims which begins on page 4 of this paper.

Remarks/Arguments begin on page 8 of this paper.

REMARKS/ARGUMENTS

The foregoing amendments to the specification are to insert the cross-reference beneath the title and to place the Abstract on a separate sheet. The amendments to the claims are to place the claims in better form and remove multiple dependencies. No new matter has been added. Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
+1 862 7785816

Andrew Holmes
Agent for Applicant
Reg. No. 51,813

Date: January 5, 2012

INVENTOR INFORMATION

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Family Name:: Sigg
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Country:: Germany
Postal or Zip Code:: 79540
Citizenship Country:: Germany

CORRESPONDENCE INFORMATION

Correspondence Customer Number:: 001095
Fax One:: 973-781-8064

APPLICATION INFORMATION

Title Line One:: Surface Decontamination of Prefilled Con
Title Line Two:: tainers in Secondary Packaging
Total Drawing Sheets:: 1
Formal Drawings?:: No
Application Type:: Utility
Docket Number:: 53689-US-PCT
Secrecy Order in Parent Appl.?:: No

CONTINUITY INFORMATION

This application is a::371 OF
> Application One:: PCT/EP10/060011
 Filing Date:: 07-13-2010

PRIOR FOREIGN APPLICATIONS

Foreign Application One:: 09165456.6
Filing Date:: 07-14-2009
Country:: EP
Priority Claimed:: Yes

Source:: PrintEFS Version 2.0

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 433 486 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
30.06.2004 Bulletin 2004/27

(21) Application number: **03356193.7**

(22) Date of filing: **08.12.2003**

(51) Int Cl.[7]: **A61L 2/02**, A61L 2/08, A61L 2/12, A61L 2/20, B65B 55/02, B65B 55/16, A61L 24/04

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR
Designated Extension States:
AL LT LV MK

(30) Priority: **23.12.2002 US 325912**

(71) Applicant: **Closure Medical Corporation**
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Durham North Carolina 27713 (US)
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(74) Representative: **Guerre, Dominique**
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BP 6153
69466 Lyon Cedex 06 (FR)

(54) Sterilization of medical adhesive kits

(57) Adhesive compositions, particularly medical adhesive compositions, often include several components that may react differently to different sterilization processes, particularly when combined with one another. The present invention is directed to methods of sterilizing different components or groups of components of a final adhesive composition. The different components or groups of components are sterilized in separate containers before packaging the components or groups of components within a kit, and thereafter sterilizing the kit.

EP 1 433 486 A1

Printed by Jouve, 75001 PARIS (FR)

Description

BACKGROUND OF THE INVENTION

1. Field of Invention

[0001] The present invention is directed to the sterilization of liquid and gel or gel-like compositions that are useful as biomedical adhesives and sealants and particularly to sterilization of kits of such liquid and gel or gel-like compositions. In particular, the present invention relates to the application of separate sterilization processes to discrete components of the liquid and gel or gel-like compositions, and kits containing the liquid and gel or gel-like compositions assembled from components treated by the separate sterilization processes.

2. Description of Related Art

[0002] Monomer and polymer adhesives are used in both industrial (including household) and medical applications. Included among these adhesives are the 1,1-disubstituted ethylene monomers and polymers, such as the α-cyanoacrylates. Since the discovery of the adhesive properties of such monomers and polymers, they have found wide use due to the speed with which they cure, the strength of the resulting bond formed, and their relative ease of use. These characteristics have made the α-cyanoacrylate adhesives the primary choice for numerous applications such as bonding plastics, rubbers, glass, metals, wood, and, more recently, biological tissues.

[0003] It is known that monomeric forms of α-cyanoacrylates are extremely reactive, polymerizing rapidly in the presence of even minute amounts of an initiator, including moisture present in the air or on moist surfaces such as animal (including human) tissue. Monomers of α-cyanoacrylates are anionically polymerizable or free radical polymerizable, or polymerizable by zwitterions or ion pairs to form polymers. Once polymerization has been initiated, the cure rate can be very rapid.

[0004] Medical applications of 1,1-disubstituted ethylene adhesive compositions include use as an alternate or an adjunct to surgical sutures and/or staples in wound closure, as well as for covering and protecting surface wounds such as lacerations, abrasions, burns, stomatitis, sores, minor cuts and scrapes, and other wounds. When an adhesive is applied to surfaces to be joined, it is usually applied in its monomeric form, and the resultant polymerization gives rise to the desired adhesive bond.

[0005] When such adhesive compositions are desired to be used in the medical arts, it is often required, or at least preferred, that the adhesive composition be sterile. Likewise, it is often required, or at least preferred, that the applicators used to apply the adhesive composition, also be sterile. A variety of sterilization methods are generally used to sterilize monomeric and polymeric compositions as well as the packaging of such kits. These methods include chemical, physical, and irradiation methods. Examples of chemical methods include exposure to ethylene oxide or hydrogen peroxide vapor. Physical methods of sterilization may include, for example, sterilization by dry or moist heat. Gamma irradiation, electron beam (e-beam) irradiation, and microwave irradiation are some common examples of irradiation methods. Aseptic filling can also be used to provide sterile compositions.

[0006] U.S. Patent No. 6,143,805 to Hickey et al. discloses a method for sterilizing a liquid adhesive composition, and in particular embodiments an α-cyanoacrylate adhesive composition, by e-beam irradiation while it is enclosed in a container. After the container containing the liquid adhesive composition is sterilized, the container may be further subjected to e-beam radiation. The patent also discloses that the container may be placed in a kit with other components that need to be sterilized, after which the entire kit may then be sterilized. In addition to e-beam irradiation, the entire kit may be sterilized by chemical, physical or other techniques such as microwave irradiation or γ-irradiation.

[0007] U.S. Patent No. 6,248,800 discloses a method for sterilizing a polymerizable cyanoacrylate ester composition in a shipping element comprising multiple individual packages of cyanoacrylate compositions. A packaging element, such as an ampoule made of glass, polyalkylene based polymers, metal foils or polyolefins, is filled with a cyanoacrylate ester composition comprising a polymerizable cyanoacrylate ester. These filled packaging elements are then placed into a shipping element and exposed to a sufficient dosage of e-beam radiation maintained at an initial fluence of at least 2 μCurie/cm^2 to sterilize both the packaging elements and the cyanoacrylate ester composition therein without gelling the composition. The average bulk density of the materials comprising all of the packaging elements is less than about 0.2 gm/cm^3. In another embodiment, the patent discloses first exposing the empty ampoule to a gas stream comprising a sufficient amount of ethylene oxide to reduce the level of bioburden on the ampoule, before filling the ampoule with the cyanoacrylate adhesive.

[0008] U.S. Patent No. 5,997,544 discloses a process for producing sterile-packed bone cement, comprising providing a first and a second container connected through a sealing device between the containers. The first container contains a polymer powder and the second contains a monomer. The containers are sterilized by introducing a sterilizing gas, such as ethylene oxide, into the containers via sterile filters attached to both containers.

[0009] U.S. Patent No. 3,954,174 discloses a unitary two-compartment package for sterile surgical articles. The package comprises two separate and sealed containers that are joined to each other. The containers are defined by walls of sheet material permeable to a steri-

lizing agent. The disclosed package permits the packaging of surgical articles that may require diverse means of sterilization in a single package. For example, a germicidal liquid in one container may be sterilized by exposure to cobalt radiation, while surgical drapes or applications in the second container are sterilized via ethylene oxide gas. Once the individual packages have been sterilized, they are joined to form the described package. The reference discloses the package itself as well as the separate sterilization of diverse surgical articles.

[0010] Despite the increasing use of cyanoacrylate adhesives in medical and non-medical applications, the need exists for new and improved liquid and gel or gel-like adhesive compositions, and kits containing such compositions that enable their use in still further and varied applications. At the same time, however, as the formulations of the liquid and gel or gel-like adhesive compositions change to adapt to such further and varied applications, new sterilization techniques are required in order to provide the desired sterilization of the kit and all of its components.

SUMMARY OF THE INVENTION

[0011] The present invention is directed to such new and improved liquid and gel or gel-like adhesive compositions, and processes for effectively sterilizing such compositions. More particularly, the present invention is directed to processes for effectively sterilizing liquid and gel or gel-like adhesive compositions, and kits of such compositions, which otherwise are not amenable to conventional single-step sterilization processes.

[0012] In particular, the present inventors have discovered that as the formulations of the liquid and gel or gel-like adhesive compositions are varied, such changes have presented significant challenges to sterilization of the compositions and kits. It has now been discovered that some adhesive compositions cannot be fully sterilized as a single composition, because various of the component materials react adversely to the sterilization process. For example, adhesive compositions have been prepared to include a plasticizer, which provides desirable elasticity and tensile properties to a polymeric film or article formed from the composition. However, some plasticizer materials in some amounts have been found to react adversely to the even moderate level of irradiation necessary to sterilize the adhesive composition. The irradiation can cause the plasticizers to at least partially degrade, often into byproducts that in turn act as initiators or stabilizers for the liquid and gel or gel-like adhesive. The result is that the sterilization process renders the product unusable. Any initiators created as degradation byproducts can cause the composition to prematurely polymerize. On the other hand, any stabilizers created as degradation byproducts can cause the composition to become "more stable" and more difficult to polymerize completely.

[0013] To overcome this problem, the present inventors conducted extensive investigation into alternative ways to sterilize the liquid and gel or gel-like adhesive compositions, and kits containing such compositions. The present inventors have discovered suitable sterilization processes that provide not only a sterile liquid and gel or gel-like adhesive composition and kits, but such sterile compositions and kits that retain their usefulness for a sufficient time (i.e., a useful shelf-life) for their desired purposes.

[0014] One such process is to sterilize individual components of the composition and/or kit separately from other components of the kit. In this method, components of the composition or kit that can withstand higher or longer sterilization processing are sterilized first. The first components are then combined with the remaining components of the composition or kit, and the combined composition or kit is then subjected to terminal sterilization. In an alternate method, separate components of the composition, or kit, are sterilized separately by respective suitable sterilization processes. The separate components are then combined together into a kit, which is then subjected to terminal sterilization, for example, to sterilize the kit-packaging element itself.

[0015] As used herein, the phrase "terminally sterilize" or variants thereof refers to a process by which a product is sterilized in its final container. For example, a kit may consist of several components. Each component may be individually sterilized by an appropriate means of sterilization. Once all the components are packaged into a kit (in a final container), the kit can be subjected to terminal sterilization where the outer surface of each component will be sterilized. As another example, a first container with solid materials may be irradiated (e-beam) at an initial dose of 10 kGy. This container and the second container (containing adhesive composition) are then assembled into a kit, which is then irradiated (terminal sterilization) at the dose of 15 kGy rendering the outer surfaces of both containers and their contents sterile.

[0016] The present invention is thus directed to methods of sterilizing different components or groups of components of a final adhesive composition. The different components or groups of components may be sterilized in separate containers before packaging the components or groups of components within a kit, and thereafter terminally sterilizing the kit. Different sterilization techniques may be used as determined by the compatibility of each adhesive component and/or its container.

[0017] Thus, a kit may comprise a package containing a mixture of plasticizer, thickening agent, radioopaque agent and initiator sterilized by irradiation. The irradiated package may then be combined in the kit with a second package containing a liquid and gel or gel-like adhesive, such as cyanoacrylate monomer adhesive. The entire kit could then be irradiated a second time, at a dose sufficient to terminally sterilize the kit. Thus, the adhesive is only subjected to a single dose, while the

other package is subjected to both doses, providing a relatively higher irradiation dose.

[0018] A combination of different methods may be used to sterilize the components of a kit. A package containing a mixture of liquid and gel or gel-like adhesive (e.g., cyanoacrylate) and plasticizer can be sterilized, for example, using dry heat, while a second package containing a mixture of thickening agent, radioopaque agent and initiator may be sterilized, for example, by irradiation. The two packages may then be placed together in a kit that is in turn chemically sterilized such as by ethylene oxide or hydrogen peroxide vapor. Other acceptable component combinations and sterilization techniques may be used as appropriate.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0019] The process of the invention comprises separately sterilizing different components or groups of components that, when mixed together, form an adhesive composition. Thus, for example, an adhesive composition that would otherwise contain various components, such as polymerizable monomer, stabilizing agent, thickener, plasticizer, radioopaque agent, colorant, flavorant, medicament, fibrous reinforcement agent, thixotropic agent, natural or synthetic rubber, pH modifier, formaldehyde scavenger, preservative, and/or the like, is separated by components into at least two separate compositions for separate sterilization. The separated components may be combined into a kit, either after the separate components are sterilized, or between sterilization steps.

[0020] Adhesive compositions, particularly medical adhesive compositions, often include several components that may react differently to different sterilization processes, particularly when combined with one another. For example, as described briefly above, it is often desirable to add one or more plasticizing agents into a polymerizable monomer adhesive composition. However, the present inventors have discovered that different plasticizers, and particularly when used in different amounts, react differently to sterilization processing. By way of example only, experiments were conducted using isopropyl myristate or acetyl tri-n-butyl citrate as plasticizers. When isopropyl myristate was used, the plasticizer could be mixed with the monomer composition, and the entire composition could be sterilized by e-beam irradiation as a single composition and without any adverse effects. However, when acetyl tri-n-butyl citrate was used as a plasticizer, particularly in larger amounts to provide its desired effect, it was discovered that the e-beam irradiation caused the plasticizer to degrade into degradation products that interfered with the complete polymerization of the composition when initiated, rendering the product useless.

[0021] The present inventors overcame these problems by developing new sterilization processes for the adhesive compositions and kits thereof. To avoid subjecting the components to a sterilization process with which the component or groups of components of a final adhesive composition may be incompatible, the different components or groups of components may be separately sterilized. Once sterilized, or at a suitable point in the sterilization process, the separate components or groups of components may be packaged in separate containers within a kit. Thereafter, the entire kit itself may be subjected to further sterilization, if desired.

[0022] As used herein, "compatible," as referring to a material being compatible with the adhesive formulation or another component, means that the material does not cause premature polymerization of the adhesive composition, or does not otherwise render the adhesive composition unusable for its intended purpose. Likewise, "incompatible," as referring to a material being incompatible with the adhesive formulation or another component, means that the material does cause premature polymerization of the adhesive composition, or otherwise renders the adhesive composition unusable for its intended purpose.

[0023] As a non-limiting example only, in a first embodiment of the present invention, the adhesive composition generally includes a polymerizable monomer, plasticizer, thickening agent, and radioopaque agent, in addition to such materials as stabilizers and optional colorant. The adhesive composition is generally activated, i.e., initiated, by contact with a separate initiator. However, because the polymerizable monomer cannot withstand as much irradiation sterilization as the other components, the various components of the composition are divided into two separate groups for sterilization. In this embodiment, the kit may include a mixture of plasticizer, thickening agent, radioopaque agent and initiator packaged together, which is sterilized by irradiation (e.g., e-beam or γ irradiation) at a relatively low dose (e.g., 5-15 kGy). A package or container containing the irradiated composition could then be combined in a kit with a second package containing an adhesive, such as cyanoacrylate monomer adhesive. Once combined, both components of the kit may then be sterilized again, using the same or a different sterilization dose. Thus, the adhesive is only subjected to the second low dose, while the other package or container is subjected to both doses, providing a relatively higher level of irradiation dose.

[0024] Alternatively, in a second embodiment of the present invention, where the plasticizer is degraded by irradiation sterilization to render the formulation unsuitable for its intended purpose, the plasticizer can be packaged with the polymerizable monomer for sterilization processing, and other components can be sterilized separately. In this embodiment, a package or container containing a mixture of polymerizable adhesive (e.g., cyanoacrylate) and plasticizer can be sterilized with dry heat, while a package containing a mixture of thickening agent, radioopaque agent and initiator can be sterilized with e-beam or γ-irradiation. The two packages are then

placed together in a kit that is in turn sterilized with ethylene oxide gas or hydrogen peroxide vapor. Other acceptable component combinations and sterilization techniques may also be used in accordance with the invention.

[0025] Accordingly, in embodiments of the present invention, the respective components of an adhesive composition or kit are first considered to determine whether and to what extent they should be separated in order to perform adequate sterilization of all of the components of the composition or kit. Such consideration can be based, for example, on known chemical interaction, experimental observations, product packaging considerations, end use considerations, and the like.

[0026] Known chemical interactions provide the first consideration in determining any separation of composition components. For example, as is known in the art, a suitable initiator can be selected to cause polymerization of the adhesive composition. As used herein, an "initiator" encompasses not only a compound that causes initiation of polymerization of monomer species in the adhesive composition, but also compounds that cause and/or accelerate polymerization or cross-linking of the adhesive composition. When such an initiator is to be used, the initiator should be kept separate from at least the polymerizable species of the adhesive composition until the desired time of use. Other compounds, known to cause adverse reactions with the polymerizable species of the adhesive composition, should also generally be maintained separate from the polymerizable species. Likewise, it is also known that stabilizers, or polymerization inhibitors, can be used to prolong the monomeric form of the adhesive composition. In order for such compounds to serve their intended purpose, it is generally desirable to maintain such stabilizers together with the polymerizable species of the adhesive composition.

[0027] Experimental observations can also be used to determine any separation of composition components. For example, as described above, experiments have shown that some plasticizers, such as acetyl tri-n-butyl citrate, produce degradation products upon e-beam irradiation, which degradation products cause the adhesive composition to become "more stable" and more difficult to polymerize completely. Further, such interactions may be apparent based on different product formulations and/or different sterilization processes. Such experimental observations can thus also indicate a need to separate one or more components from other components of the adhesive composition.

[0028] Still further considerations for assessing any need or desire to separate composition components can be product packaging considerations and end use considerations. For example, in embodiments, it may be desirable to separate one or more components from the remainder of the adhesive composition, to address packaging concerns such as preferences in terms of containers that are used or the like. Likewise, in embodiments, it may be desirable to separate one or more components from the remainder of the adhesive composition, to provide for different uses of the composition, or to allow the end-user to tailor the mixing proportions of different components to meet particular needs.

[0029] In one embodiment of the present invention, the materials are separated based on incompatibility of one component with another component of the composition. That is, where a mixture of the two components together would have an adverse effect on the composition, even in the absence of sterilization, the respective components should be separated.

[0030] In another embodiment of the present invention, the materials are separated based on incompatibility of one component with another component of the composition that arises only due to the sterilization processing. That is, where a mixture of the two components together would otherwise form an acceptable composition, but the mixture would experience an adverse effect as a result of sterilization, the respective components should be separated and sterilized separately and maintained separate in the kit.

[0031] In yet a further embodiment of the present invention, the materials are separated regardless of their compatibility in the composition, both before and after sterilization. That is, in embodiments, it may be desirable to separate two components of the composition although the components would otherwise be compatible with each other, and with other components of the adhesive composition that may be present together, regardless of the selected sterilization procedures.

[0032] After a separation of the components is determined, suitable packaging for each of the respective components can be determined. For example, suitable packaging can include bottles, vials, tubes, pouches, envelopes, sachets, syringes, pipettes, and the like. For example, liquid components of the composition or kit can be packaged in suitable containers, such as bottles, vials, tubes, pouches, envelopes, sachets syringes, pipettes, or the like, that provide any necessary or desirable barrier properties. Likewise, applicators or other solid materials of the composition or kit can be packaged in suitable containers, such as bottles, vials, tubes, pouches, envelopes, sachets, and the like, although in the case of applicators or larger objects, simple envelopes or pouches may be suitable and preferred. Alternatively, as long as the kit packaging is suitably designed, one or more of the separate components of the composition or kit can be packaged loose in the kit, such as in a compartment, well, dimple, recess, or the like. Other variations will be apparent based on the present disclosure.

[0033] Once desired separation and packaging of the components is determined, an appropriate sterilization process sequence can be selected. The sterilization process sequence, as desired or as necessary, can include two or more different sterilization processes, which can be conducted on the respective composition components in series and/or in parallel. That is, when

conducted in parallel, at least two separate components of the adhesive composition or kit are sterilized separated or apart from each other, prior to being placed into a kit. When conducted in series, one of at least two separate components of the adhesive composition or kit is sterilized separated or apart from the other(s); the sterilized component is then placed into a kit with the remaining component(s), and a successive sterilization step is conducted on the kit. Combinations of these approaches can of course be used, especially where the kit includes three or more separate parts (i.e., multiple separated composition components, one or more applicators, and the like).

[0034] Although the present discussion focuses on the adhesive composition being separated into two separate sub-units, the present invention is in no way limited to such embodiments. Rather, the processes of the present invention can be equally and desirably utilized where a kit of three, four, five, six or more separate parts are included. Thus, for example, the processes of the present invention can be used to separately sterilize three or more components of an adhesive composition; to separately sterilize two components of an adhesive composition and a separate applicator; to separately sterilize an adhesive composition, a separate applicator, and a separate other component of the kit; and the like. Such modifications of the process of the present invention will be apparent to one skilled in the art, and are encompassed by the present invention. When such modifications are employed, combinations of the above-described parallel and serial processing are likewise applicable.

[0035] For sterilizing the various components of the kit, any of the suitable sterilization processes can be used. Thus, for example, suitable sterilization processes include, but are not limited to, chemical, physical, and/or irradiation methods. Examples of chemical methods include, but are not limited to, exposure to ethylene oxide or hydrogen peroxide vapor. Examples of physical methods include, but are not limited to, sterilization by heat (dry or moist) or retort canning. Examples of irradiation methods include, but are not limited to, γ-irradiation, e-beam irradiation, and microwave irradiation. A preferred method is e-beam irradiation, as described in U.S. Patent No. 6,143,805, the entire disclosure of which is incorporated herein by reference.

[0036] According to the present invention, the preferred selected sterilization process can also vary depending on the particular component(s) being sterilized. Thus, for example, e-beam or dry heat irradiation may be preferred for sterilizing the polymerizable monomer, optionally in combination with other composition components, and e-beam for other solid materials. However, where applicators or other parts of the kit, or the kit packaging itself, are to be sterilized, chemical methods such as exposure to ethylene oxide or hydrogen peroxide vapor may be preferred.

[0037] Furthermore, in embodiments of the present invention, it may be desirable to conduct a sterilization process on one or more of the containers of the kit, prior to individual adhesive composition components being introduced into the containers. Thus, for example, where solid materials are to be stored in respective vials, syringes, bottles, or the like, it may be desirable to expose the empty containers or the empty kit packaging element to a sterilization process such as ethylene oxide or hydrogen peroxide gas, to reduce the bioburden of the containers. Of course, any other suitable sterilization process can also be used.

[0038] In selecting the sterilization processes, an important consideration is the effect, if any, that the individual and overall sterilization processes have on the respective composition components. For example, it is known that excessive sterilization exposure, particularly to irradiation, can cause polymerization of the polymerizable monomer. Thus, for example, where multiple sterilization cycles are used in series, the multiple cycles should be selected such that either the total sterilization dose is within an acceptable range, or such that the polymerizable monomer is not exposed to all of the successive processes. Similar concerns may also apply to other components in the adhesive composition and/or kit.

[0039] Thus, for example, care must be exercised when sterilizing the polymerizable monomer, particularly by e-beam irradiation. When the polymerizable monomer is to be exposed to only one irradiation process, the irradiation can be in a suitable amount of, for example, from about 10 to about 30 kGy, preferably about 15 to about 25 kGy. However, when the polymerizable monomer is to be exposed to two successive irradiation processes, the total irradiation from both processes should be controlled to be in the above-described amounts. Thus, a first irradiation process could deliver a dose of from about 5 to about 15 kGy, preferably about 10 to about 15 kGy, and the second irradiation process could deliver an additional dose of from about 5 to about 15 kGy, preferably about 10 to about 15 kGy. Similar concerns, and dosage ranges, apply to the use of γ-irradiation, or to combinations of γ and e-beam irradiation.

[0040] Regardless of the sterilization methods used, the respective components of the kit, and preferably the entire kit and its contents, should be sterile. By "sterile" herein is meant that the composition or component is free from viable microorganisms. In preferred embodiments of the present invention, the composition is sterilized to provide a Sterility Assurance Level (SAL) of at least 10^{-3}. In embodiments, the Sterility Assurance Level may be at least 10^{-4}, or may be at least 10^{-5}, or may be at least 10^{-6}.

[0041] As a result of the sterilization processes, there is preferably substantially no initiation of polymerization of the liquid and gel or gel-like adhesive composition. That is, the sterilization processes preferably do not cause polymerization of the composition, which would render the composition unusable for its intended pur-

pose.

[0042] As described briefly above, the kits of the present invention can include one or more containers of material, such as components of an adhesive composition, or one or more compartments containing such materials, and optionally one or more applicators or other parts. Although not limited to any particular construction, the kit container (also referred to as a kit packaging element) itself can be any suitable container, including but not limited to a bottle, jar, carton, box, or the like. The kit container can be formed of any suitable material including, but not limited to, paper, cardboard, plastic, metal, glass, or the like. Suitable kit container designs are disclosed in, for example, U.S. Patent Applications Nos. 09/145,200, filed September 1, 1998, 09/385,030, filed August 30, 1999, 09/987,116, filed November 13, 2001, and 09/559,651, filed April 28, 2000, the entire disclosures of which are incorporated herein by reference.

[0043] The kits can be particularly adapted, in terms of their construction and/or contents, for a wide range of medical procedures. For example, the kits can be used for apposing surgically incised or traumatically lacerated tissues; retarding blood flow from wounds; dressing burns; dressing skin or other superficial or surface wounds (such as abrasions, chaffed or raw skin, ulceration and/or stomatitis); hernia repair; meniscus repair; and aiding repair and re-growth of living tissue. One particular example of a surgical kit that can be prepared includes a kit whose construction and contents is particularly adapted for use in lung volume reduction procedures. Such lung volume reduction procedures, and compositions and kits useful therefor, are described, for example, in U.S. Provisional Patent Application No. 60/231,569, filed September 11, 2000, and U.S. Patent Application No. 09/949,644, filed September 12, 2001, the entire disclosures of which are incorporated herein by reference.

[0044] Furthermore, in embodiments of the present invention, the kits and contents can be used in non-medical procedures, including but not limited to industrial and home applications, for example in bonding rubbers, plastics, wood, composites, fabrics, and other natural and synthetic materials. Although sterilization may not be required for such applications, sterilization may still be preferred to retard bacterial growth and the like, and/or in environments where increased sterility is desired.

[0045] The composition in embodiments of the invention is preferably a monomeric adhesive composition. The monomer (including prepolymeric) adhesive composition may include one or more polymerizable monomers. In embodiments, the monomer is a 1,1-disubstituted ethylene monomer, e.g., an α-cyanoacrylate. Preferred monomer compositions of the present invention and polymers formed therefrom are useful as tissue adhesives, sealants for preventing bleeding or for covering open wounds, and in other biomedical applications. They find uses in, for examples, apposing surgically incised or traumatically lacerated tissues; retarding blood flow from wounds; drug delivery; dressing burns; and aiding repair and regrowth of living tissue.

[0046] Monomers that may be used in this invention are readily polymerizable, e.g., anionically polymerizable or free radical polymerizable to form polymers. Such monomers include those that form polymers, which may, but do not need to, biodegrade. Reference is made, for example to U.S. Patents Nos. 5,328,687, 6,183,593 and 5,928,611, U.S. Patent Application Serial No. 09/430,177, filed on October 29, 1999, which are hereby incorporated by reference in their entirety. Useful 1,1-disubstituted ethylene monomers include, but are not limited to, monomers of the formula:

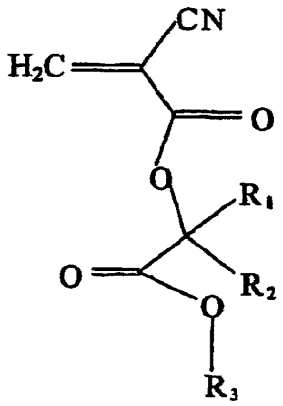
$$(I) \qquad HRC{=}CXY$$

wherein X and Y are each strong electron withdrawing groups, and R is H, $-CH{=}CH_2$ or, provided that X and Y are both cyano groups, a C_1-C_4 alkyl group. Preferred monomers include 1,1-disubstituted ethylene monomers, such as α-cyanoacrylates including, but not limited to, alkyl α-cyanoacrylates having an alkyl chain length of from about 1 to about 20 carbon atoms or more, preferably from about 3 to about 8 carbon atoms.

[0047] The α-cyanoacrylates of the present invention can be prepared according to methods known in the art. U.S. Patents Nos. 2,721,858, 3,254,111, 3,995,641, and 4,364,876, each of which is hereby incorporated in its entirety by reference herein, disclose methods for preparing α-cyanoacrylates.

[0048] Preferred α-cyanoacrylate monomers used in this invention include methyl cyanoacrylate, ethyl cyanoacrylate, n-butyl cyanoacrylate, 2-octyl cyanoacrylate, methoxyethyl cyanoacrylate, ethoxyethyl cyanoacrylate, dodecyl cyanoacrylate, 2-ethylhexyl cyanoacrylate, butyl cyanoacrylate, 3-methoxybutyl cyanoacrylate, 2-butoxyethyl cyanoacrylate, 2-isopropoxyethyl cyanoacrylate, 1-methoxy-2-propyl cyanoacrylate, hexyl cyanoacrylate, or dodecylcyanoacrylate.

[0049] Suitable cyanoacrylates for use in the present invention also include, but are not limited to, alkyl ester cyanoacrylate monomers such as those having the formula



wherein R_1 and R_2 are, independently H, a straight, branched or cyclic alkyl, or are combined together in a cyclic alkyl group, and R_3 is a straight, branched or cyclic alkyl group. Preferably, R_1 is H or a C_1, C_2 or C_3 alkyl group, such as methyl or ethyl; R_2 is H or a C_1, C_2 or C_3 alkyl group, such as methyl or ethyl; and R_3 is a C_1-C_{16} alkyl group, more preferably a C_1 -C_{10} alkyl group, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl or decyl, and even more preferably a C_2, C_3 or C_4 alkyl group. Such alkyl ester cyanoacrylates and other suitable monomers are disclosed in, for example, U.S. Patent Applications Nos. 09/630,437, filed August 2, 2000, and 09/919,877, filed August 2, 2001, the entire disclosures of which are incorporated herein by reference.

[0050] Examples of preferred alkyl ester cyanoacrylates include, but are not limited to, butyl lactoyl cyanoacrylate (BLCA), butyl glycoloyl cyanoacrylate (BGCA), ethyl lactoyl cyanoacrylate (ELCA), and ethyl glycoloyl cyanoacrylate (EGCA). BLCA may be represented by the above formula, wherein R_1 is H, R_2 is methyl and R_3 is butyl. BGCA may be represented by the above formula, wherein R_1 is H, R_2 is H and R_3 is butyl. ELCA may be represented by the above formula, wherein R_1 is H, R_2 is methyl and R_3 is ethyl. EGCA may be represented by the above formula, wherein R_1 is H, R_2 is H and R_3 is ethyl.

[0051] The compositions of the present invention may include at least one plasticizing agent that assists in imparting flexibility to the polymer formed from the monomer. The plasticizing agent preferably contains little or no moisture and should not significantly affect the stability or polymerization of the monomer. Examples of suitable plasticizers include but are not limited to isopropyl myristate, isopropyl palmitate, tributyl citrate, acetyl tri-n-butyl citrate (ATBC), polymethylmethacrylate, polydimethylsiloxane, polyester glutarates; polyester adipates; polyester sebacates; and others as listed in U.S. Patent No. 6,183,593, the disclosure of which is incorporated in its entirety by reference herein.

[0052] Other compositions are exemplified by U.S. Patents Nos. 5,259,835, 5,328,687, 5,981,621, 6,143,352, 6,010,714, 6,217,603, and 5,928,611 and U. S. Patent Application Serial No. 08/909,845, all incorporated by reference herein in their entirety.

[0053] The composition may also optionally include at least one thixotropic agent. Suitable thixotropic agents are known to the skilled artisan and include, but are not limited to, silica gels such as those treated with a silyl isocyanate, and optionally surface treated titanium dioxide. Examples of suitable thixotropic agents and thickeners are disclosed in, for example, U.S. Patent Nos. 4,720,513and 6,310,166, the disclosures of which are hereby incorporated in their entireties by reference herein.

[0054] The composition may optionally also include thickeners. Suitable thickeners may include poly (2-ethylhexy methacrylate), poly(2-ethylhexyl acrylate) and others as listed in U.S. Patent Application Serial No. **09/472,392 [is this correct?]** filed December 23,1999, the disclosure of which is incorporated by reference herein in its entirety.

[0055] The composition may also optionally include at least one natural or synthetic rubber to impart impact resistance. The skilled artisan would know of such suitable rubbers. Such rubbers include, but are not limited to, dienes, styrenes, acrylonitriles, and mixtures thereof. Examples of suitable rubbers are disclosed in, for example, U.S. Patents Nos. 4,313,865 and 4,560,723, the disclosures of which are hereby incorporated in their entireties by reference herein.

[0056] The composition may also optionally include a radioopaque agent to make the polymerized material visible upon x-ray examination. Suitable radioopaque agents may include, but are not limited to, tantalum powder, iodine-containing compounds including ethiodized oil, and barium sulfate.

[0057] The composition may optionally also include one or more stabilizers, preferably both at least one anionic vapor phase stabilizer and at least one anionic liquid phase stabilizer. These stabilizing agents may inhibit premature polymerization. Suitable stabilizers may include those listed in U.S. Patent No. 6,183,593, the disclosure of which is incorporated by reference herein in its entirety. Other suitable stabilizers, which have additional functions in the composition, are disclosed in U. S. Patent Applications Nos. 09/657,913, filed September 8, 2000, and 09/964,415, filed September 28, 2001, the entire disclosures of which are incorporated herein by reference.

[0058] The stability, and thus the shelf-life, of some monomeric adhesive compositions can be further enhanced and extended through careful regulation of the packaging. Treated (e.g., fluorinated polymer) packaging such as that disclosed in copending U.S. Patent Application Serial No. 09/430,289, filed October 29, 1999, which is hereby incorporated by reference herein in its

entirety, is preferred and may reduce the amount of stabilizer that is combined into the composition. Other suitable container constructions are disclosed, for example, in U.S. Patent Application No. 09/657,913, the entire disclosure of which is incorporated herein by reference.

[0059] The compositions may also include pH modifiers to control the rate of degradation of the resulting polymer, as disclosed in U.S. Patent No. 6,143,352, the entire disclosure of which is hereby incorporated by reference herein in its entirety.

[0060] Compositions of the present invention may also include at least one biocompatible agent effective to reduce active formaldehyde concentration levels produced *during in vivo* biodegradation of the polymer (also referred to herein as "formaldehyde concentration reducing agents"). Preferably, this component is a formaldehyde scavenger compound. Examples of formaldehyde scavenger compounds useful in this invention include sulfites; bisulfites; mixtures of sulfites and bisulfites, etc. Additional examples of formaldehyde scavenger compounds useful in this invention and methods for their implementation can be found in U.S. Patents Nos. 5,328,687, 5,514,371, 5,514,372, 5,575,997, 5,582,834 and 5,624,669, all to Leung et al., which are hereby incorporated herein by reference in their entireties.

[0061] To improve the cohesive strength of adhesives formed from the compositions of this invention, difunctional monomeric cross-linking agents may be added to the monomer compositions of this invention. Such crosslinking agents are known. U.S. Patent No. 3,940,362 to Overhults, which is hereby incorporated herein in its entirety by reference, discloses exemplary cross-linking agents.

[0062] The compositions of this invention may further contain fibrous reinforcement and colorants such as dyes, pigments, and pigment dyes. Examples of suitable fibrous reinforcement include PGA microfibrils, collagen microfibrils, and others as described in U.S. Patent No. 6,183,593, the disclosure of which is incorporated by reference herein in its entirety.

[0063] The polymerizable compositions useful in the present invention may also further contain one or more medicaments, preferably one or more non-antioxidant medicaments. Suitable medicaments include, but are not limited to, antibiotics, antimicrobials, antiseptics, bacteriocins, bacteriostats, disinfectants, steroids, anesthetics, antifungal agents, anti-inflammatory agents (other than the dual function stabilizers of the present invention), antibacterial agents, antiviral agents, antitumor agents, growth promoting substances, antioxidants (other than the dual function stabilizers of the present invention), or mixtures thereof. Suitable specific medicaments are disclosed in, for example, U.S. Patent Application No. 09/430,177, filed October 29, 1999, the entire disclosure of which is incorporated herein by reference.

[0064] The polymerizable compositions useful in the present invention may also further contain one or more preservatives. Suitable preservatives, and methods for selecting them and incorporating them into adhesive compositions, are disclosed in U.S. Patent Application No. 09/430,180, the entire disclosure of which is incorporated herein by reference. Such preservatives can be in addition to any anti-fungal agent that may or may not be added to the composition, as described above. Such preservatives can be included irrespective of whether the composition and containers are sterilized.

[0065] In embodiments of the present invention, the composition and/or its applicator may contain materials such as a polymerization initiator, accelerator, rate-modifier, and/or cross-linking agent for initiating polymerization and/or cross-linking of the polymerizable monomer material. Suitable materials and applicators and packaging systems are disclosed in U.S. Patent Nos. 5,928,611, 6,352,704 and U.S. Patent Applications Serial Nos. 09/430,177, 09/430,176, 09/430,289, 09/430,290, and 09/430,180 filed October 29, 1999; 09/385,030 filed August 30, 1999; and 09/176,889 filed October 22, 1998; the entire disclosures of which are incorporated herein by reference.

EXAMPLES

[0066] The following examples illustrate specific embodiments of the invention. These examples are intended to be illustrative only, and the invention is not limited to the materials, conditions, or process parameters set forth in the Examples.

Example 1

[0067] A finished adhesive composition consisting of components of stabilized monomer (2-octyl cyanoacrylate), plasticizer (isopropyl myristate), thixotropic agent (fumed silica), and radioopaque agent (tantalum powder) is desired. The composition is to be initiated using benzalkonium chloride or butyrylcholine chloride. The components are divided into two elements. Element one contains the stabilized monomer packaged in a fluorinated high-density polyethylene bottle. Element two contains the plasticizer, thixotropic agent, radioopaque agent, and an amount of initiator to provide the desired setting time. The components of element two are first mixed to form a homogeneous gel-like material. The element two composition is then packaged into a syringe (glass or plastic).

[0068] Element two is sterilized first using an e-beam or γ-irradiation dose of 5 to 15 kGy. This dose reduces the bioburden in the product. To form the kit, non-sterile element one is added to the sterilized element two in a foil pouch. The foil pouch is sealed. The two elements in the foil pouch are exposed to an e-beam irradiation dose of 15 kGy. Element two has then been exposed to approximately 30 kGy. Element one has been exposed to the single dose of 15 kGy. The sterilization steps are

sequential.

[0069] When it is time to use the composition, element one and element two are mixed. The polymerization time ("working time") is related to the initiator level. The flexibility of the resulting polymer is related to the amount of plasticizer.

[0070] The result is a medical procedure kit that includes compositions 1 and 2, which are both sterilized and substantially retain their original properties in terms of viscosity and appearance. The compositions can be mixed and subsequently applied to a surface. Mixing of the compositions 1 and 2 initiates polymerization of the monomer, providing a polymer film.

Example 2

[0071] The same composition as described in Example 1 is desired. The components are divided into two elements. Element one contains the stabilized monomer and the plasticizer in a fluorinated high-density polyethylene bottle. Element two contains the thixotropic agent, radioopaque agent, and an amount of initiator to provide the desired setting time. The components of element two may be mixed together to form a homogeneously distributed powder (all components are solids), or the components may be added sequentially to the packaging container. The element two components are packaged into a syringe.

[0072] The sterilization steps described in Example 1 are repeated.

[0073] If the plasticizer level and initiator amount are the same for example two as in example one, the polymerization time and the flexibility of the resulting polymer will be very similar to example one.

Example 3

[0074] A finished adhesive composition consisting of components of stabilized monomer (2-octyl cyanoacrylate), plasticizer (acetyl tri-n-butyl citrate, ATBC), thixotropic agent (fumed silica), and radioopaque agent (tantalum powder) is desired. The composition is to be initiated using benzalkonium chloride or butyrylcholine chloride. The components are divided into two elements. Element one contains the stabilized monomer and the plasticizer packaged in a glass vial or ampoule. Element two contains the components of thixotropic agent, radioopaque agent, and an amount of initiator to provide the desired setting time. The components of element two may be mixed together to form a homogeneously distributed powder (all components are solids), or the components may be added sequentially to the packaging container. The element two components are packaged into a syringe.

[0075] Experimentally it was discovered that ATBC degraded at the e-beam irradiation dose required for sterility. To prevent this degradation, element one components are sterilized using dry heat. Element two components are sterilized with an e-beam irradiation dose of approximately 25 kGy. Element two may or may not be placed into a foil pouch before e-beam irradiation. The two sterilization processes occur in parallel. Once both elements are sterilized, they are joined together into a pouch, which is sealed and is then exposed to ethylene oxide gas.

[0076] When it is time to use the composition, element one and element two are mixed. The polymerization time ("working time") is related to the initiator level. The flexibility of the resulting polymer is related to the amount of plasticizer.

[0077] The polymer created in example three can be similar to the polymer created in examples one and two. The plasticizer and initiator levels can be modified so the polymers are similar. Each plasticizer must be evaluated individually in the composition to give the desired amount of flexibility. One plasticizer may or may not be exchanged weight for weight in a composition. Once the plasticizer level is determined the initiator amount can be adjusted to give the desired polymerization time.

[0078] The result is a medical procedures kit that includes compositions 1 and 2, which are both sterilized and substantially retain their original properties in terms of viscosity and appearance. The compositions can be mixed and subsequently applied to a surface. Mixing of the compositions 1 and 2 initiates polymerization of the monomer, providing a polymer film

Example 4

[0079] Example two is repeated with acetyl tri-n-butyl citrate substituted for isopropyl myristate. The same sterilization sequence as described in example one is repeated. When element one and element two are mixed for their intended purpose, the polymerization time is undesirably extended and the resulting polymer does not have the desired physical characteristics.

[0080] While the invention has been described with reference to preferred embodiments, the invention is not limited to the specific examples given, and other embodiments and modifications can be made by those skilled in the art without departing from the spirit and scope of the invention.

[0081] While the invention has been described with reference to preferred embodiments, the invention is not limited to the specific examples given, and other embodiments and modifications can be made by those skilled in the art without departing from the spirit and scope of the invention.

Claims

1. A method for sterilizing an adhesive kit comprising:

providing a first container containing at least a polymerizable monomer of a polymerizable ad-

hesive composition;
providing a second container containing at least one additional component of the polymerizable adhesive composition;
subjecting the second container to a first sterilization process to reduce the bioburden contents of said second container;
combining the first container and the second container in a kit packaging element; and
subjecting the kit packaging element, containing the first and the second containers, to a second sterilization process that terminally sterilizes contents of said first and second containers.

2. The method according to claim 1, wherein the first sterilization process does not terminally sterilize contents of said second container.

3. The method according to claim 1, wherein the first and second sterilization steps cause substantially no initiation of polymerization of the liquid and gel or gel-like adhesive composition.

4. The method according to claim 1, wherein the at least one additional component is at least one of a plasticizer, a thickening agent, a radioopaque agent, and an initiator.

5. The method according to claim 1, wherein the at least one additional component is at least one of an initiator, a thickening agent, and a radioopaque agent.

6. The method according to claim 1, wherein the at least one additional component is an initiator.

7. The method according to claim 1, wherein the polymerizable monomer comprises a 1,1-disubstituted ethylene monomer.

8. The method according to claim 1, wherein the polymerizable monomer is an α-cyanoacrylate.

9. The method according to claim 1, wherein at least one of the first and second containers is sealed to maintain contents of said first container separate from contents of said second container.

10. The method according to claim 1, wherein at least one of the first and second containers is made of glass.

11. The method according to claim 1, wherein at least one of the first and second containers is made of plastic.

12. The method according to claim 1, wherein the first and second containers are independently selected from the group consisting of ampoules, vials, syringes, pipettes, tubes and applicators.

13. The method according to claim 1, wherein the first and second containers are compatible with e-beam.

14. The method according to claim 1, wherein the first container contains said polymerizable monomer, and said second container contains a plasticizer, a thickening agent, a radioopaque agent, and an initiator agent for said polymerizable monomer.

15. The method according to claim 1, wherein the first container contains said polymerizable monomer and at least one of a plasticizer, a thickening agent, and a radioopaque agent, and said second container contains an initiator agent for said polymerizable monomer and at least one other of the plasticizer, the thickening agent, and the radioopaque agent not packaged in the first container.

16. The method according to claim 1, further comprising sealing said kit packaging element prior to said second sterilization process.

17. The method according to claim 16, further comprising, prior to said sealing step, a third sterilization process to sterilize exposed surfaces in said kit packaging element.

18. The method according to claim 17, wherein said third sterilization process comprises exposure to ethylene oxide or hydrogen peroxide vapor.

19. The method according to claim 1, further comprising including at least one applicator for said polymerizable adhesive composition in said kit packaging element.

20. The method according to claim 1, wherein at least one material contained in said first container is incompatible with at least one material contained in said second container, at least prior to said first sterilization process.

21. The method according to claim 1, wherein at least one material contained in said first container is incompatible with at least one material contained in said second container, at least after said first sterilization process but not before said first sterilization process.

22. The method according to claim 1, wherein the first container is a glass ampoule and the second container is a plastic syringe.

23. The method according to claim 1, wherein the first and second sterilization processes are independ-

ently selected from the group consisting of irradiation, physical treatment, or chemical treatment.

24. The method according to claim 1, wherein the first sterilization process comprises e-beam irradiation at a dosage of from about 5-15 kGy.

25. The method according to claim 1, wherein the second sterilization process comprises e-beam irradiation at a dosage of from about 5-15 kGy.

26. The method according to claim 1, wherein at least one of said first sterilization process and said second sterilization process comprises dry heat.

27. The method according to claim 1, wherein said kit is sterilized to provide a Sterility Assurance Level of at least 10^{-3}.

28. The method according to claim 1, wherein the second container contains at least one material that at least partially degrades during sterilization to become incompatible with the polymerizable monomer.

29. The method according to claim 28, wherein said at least one material that at least partially degrades is a plasticizer.

30. An adhesive kit produced by the method of claim 1.

31. A sterile adhesive kit, comprising:

a sterilized outer packaging element containing at least a sterilized first container and a sterilized second container,
the sterilized first container containing at least a polymerizable monomer of a polymerizable adhesive composition,
the sterilized second container containing at least one additional component of the polymerizable adhesive composition.

32. A method for sterilizing an adhesive kit comprising:

providing a first container containing at least a polymerizable monomer of a polymerizable adhesive composition;
subjecting the first container to a first sterilization process to reduce the bioburden or sterilize contents of said first container;
providing a second container containing at least one additional component of the polymerizable adhesive composition;
subjecting the second container to a second sterilization process to reduce the bioburden or sterilize contents of said second container;
combining the first container and the second container in a kit packaging element; and
subjecting the kit packaging element, containing the first and the second containers, to a third sterilization process that terminally sterilizes at least exposed surfaces in said kit packaging element.

33. The method according to claim 32, wherein the first sterilization process sterilizes contents of said first container, and said second sterilization process sterilizes contents of said second container.

34. The method according to claim 32, wherein at least one of (a) said first sterilization process does not terminally sterilize contents of said first container, and (b) said second sterilization process does not terminally sterilize contents of said second container.

35. The method according to claim 32, wherein the first sterilization process does not terminally sterilize contents of said first container, and said second sterilization process does not terminally sterilize contents of said second container.

36. The method according to claim 32, wherein said first and second containers are separately sterilized by different sterilization processes.

37. The method according to claim 32, wherein said third sterilization process terminally sterilizes only exposed surfaces in said kit packaging element.

38. The method according to claim 32, wherein said third sterilization process comprises exposure to ethylene oxide or hydrogen peroxide vapor.

39. The method according to claim 32, wherein the first, second and third sterilization processes cause substantially no initiation of polymerization of the liquid and gel or gel-like adhesive composition.

40. The method according to claim 32, wherein the at least one additional component is at least one of a plasticizer, a thickening agent, a radioopaque agent, and an initiator agent.

41. The method according to claim 32, wherein the at least one additional component is at least one of an initiator, a thickening agent, and a radioopaque agent.

42. The method according to claim 32, wherein the at least one additional component is an initiator.

43. The method according to claim 32, wherein said first container further contains at least one plasticizer, and said second container does not contain any

plasticizing agents.

44. The method according to claim 32, wherein the polymerizable monomer comprises a 1,1-disubstituted ethylene monomer.

45. The method according to claim 32, wherein the polymerizable monomer is an α-cyanoacrylate.

46. The method according to claim 32, wherein at least one of the first and second containers is sealed to maintain contents of said first container separate from contents of said second container.

47. The method according to claim 32, wherein at least one of the first and second containers is made of glass.

48. The method according to claim 32, wherein at least one of the first and second containers is made of plastic.

49. The method according to claim 32, wherein the first and second containers are independently selected from the group consisting of ampoules, vials, syringes, pipettes, tubes and applicators.

50. The method according to claim 32, wherein the first and second containers are compatible with e-beam.

51. The method according to claim 32, wherein the first container contains said polymerizable monomer, and said second container contains a plasticizer, a thickening agent, a radioopaque agent, and an initiator agent for said polymerizable monomer.

52. The method according to claim 32, wherein the first container contains said polymerizable monomer and at least one of a plasticizer, a thickening agent, or a radioopaque agent, and said second container contains an initiator agent for said polymerizable monomer and at least one other of the plasticizer, the thickening agent, or the radioopaque agent not packaged in the first container.

53. The method according to claim 32, further comprising including at least one applicator for said polymerizable adhesive composition in said kit packaging element.

54. The method according to claim 32, wherein at least one material contained in said first container is incompatible with at least one material contained in said second container, at least prior to said first and second sterilization processes.

55. The method according to claim 32, wherein at least one material contained in said first container is incompatible with at least one material contained in said second container, at least after said first and second sterilization processes, but not before said first and second sterilization processes.

56. The method according to claim 32, wherein the first container is glass ampoule and the second container is a plastic syringe.

57. The method according to claim 32, wherein the first, second and third sterilization processes are independently selected from the group consisting of irradiation, physical treatment, or chemical treatment.

58. The method according to claim 32, wherein the first and second sterilization processes are independently selected from the group consisting of e-beam irradiation, γ-irradiation, and dry heat.

59. The method according to claim 32, wherein said kit is sterilized to provide a Sterility Assurance Level of at least 10^{-3}.

60. The method according to claim 32, wherein the first container contains at least one material that at least partially degrades during sterilization to become incompatible with the polymerizable monomer.

61. The method according to claim 61, wherein said at least one material that at least partially degrades is a plasticizer.

62. An adhesive kit produced by the method of claim 32.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 03 35 6193

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 2002/037310 A1 (BOBO JOHN ET AL) 28 March 2002 (2002-03-28)	30-33, 40-42, 44,45, 47-53, 59,62	A61L2/02 A61L2/08 A61L2/12 A61L2/20 B65B55/02 B65B55/16 A61L24/04
A	* paragraphs [0021],[0023]-[0027],[0065]-[0067],[0070], [0071] *	1-29	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	24 March 2004	Jochheim, J

CATEGORY OF CITED DOCUMENTS
X : particularly relevant if taken alone
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A : technological background
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 03 35 6193

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(54) Title: GRAFT MATERIALS CONTAINING BIOACTIVE SUBSTANCES, AND METHODS FOR THEIR MANUFACTURE

(57) Abstract: Described are packaged, sterile medical graft products containing controlled levels of a growth factor such as Fibroblast Growth Factor-2 (FGF-2). Also described are methods of manufacturing medical graft products wherein processing, including sterilization, is controlled and monitored to provide medical graft products having modulated, known levels of a extracellular matrix factor, such as a growth factor, *e.g.* FGF-2. Preferred graft materials are extracellular matrix materials isolated from human or animal donors, particularly submucosa containing extracellular matrix materials. Further described are ECM compositions that are or are useful for preparing gels, and related methods for preparation and use.

GRAFT MATERIALS CONTAINING BIOACTIVE SUBSTANCES, AND METHODS FOR THEIR MANUFACTURE

REFERENCE TO RELATED APPLICATION

This application claims the benefit of United States Patent Application Serial No. 60/497,746 filed August 25, 2003, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

The present invention relates generally to materials useful for tissue grafting, and in particular to such materials derived from extracellular matrices and retaining both collagen and substances such as growth factors that contribute to the beneficial properties of the materials. In one aspect, the invention relates to extracellular matrix tissue graft materials containing one or more growth factors modulated to a predetermined level, and related methods of manufacturing.

Extracellular matrix (ECM) materials, including those derived from submucosa and other tissues, are known tissue graft materials. See, e.g., U. S. Patent Nos. 4,902,508, 4, 956,178, 5,281,422, 5,372,821, 5,554,389, 6, 099,567, and 6,206,931. Tissues from various biological structures can be used for these purposes, including for example small intestine, stomach, the urinary bladder, skin, pericardium, dura mater, fascia, and the like. These sources provide collagenous materials useful in a variety of surgical procedures where tissue support and/or ingrowth are desired.

Submucosa and other ECM materials have been shown to include a variety of components other than collagen that that can contribute to the bioactivity of the materials and to their value in medical grafting and other uses. As examples, ECM materials can include growth factors, cell adhesion proteins, and proteoglycans. However, ECM materials are typically subjected to a battery of manipulations in the manufacture of finished products containing them. This

presents challenges in obtaining finished products that not only possess the necessary physical properties and appropriate levels of biocompatibility and sterility, but also the desired bioactivity. The present invention is addressed to these needs.

SUMMARY OF THE INVENTION

Accordingly, in one aspect, the present invention provides a method for manufacturing a tissue graft material such as a collagenous extracellular matrix containing at least one extractable, bioactive growth factor or other non-collagenous protein material, particularly Fibroblast Growth Factor-2 (FGF-2), at a predetermined amount. The method includes the steps of providing a non-sterile extracellular matrix material; fashioning a plurality of graft products from the extracellular matrix material; packaging the products; subjecting the packaged products to a sterilization procedure that affects the level of extractable bioactive growth factor (FGF-2) or other non-collagenous protein material in the products; and, taking and testing sample products of the sterilized packaged products to determine a level of a growth factor (FGF-2) in the sample products, wherein said determined level is representative of an approximate level of said growth factor in other ones of said products from the lot from which the sample product was taken.

In another aspect, the present invention provides a medical product that comprises a packaged, sterile animal-derived extracellular matrix material comprising FGF-2 at a level of at least about 50 nanograms per gram dry weight. Particularly preferred materials are lyophilized and/or include submucosa.

Another aspect of the invention provides a packaged, sterile extracellular matrix material isolated from animal tissue and including components native to the tissue, the matrix material including collagen, growth factors, proteoglycans, glycosaminoglycans, and having extractable, bioactive FGF-2 at a level of at least about 50 nanograms per gram dry weight.

Another aspect of the invention provides a method for manufacturing a sterile, extracellular matrix material. The method includes isolating an extracellular matrix material from animal tissue, the isolated extracellular matrix material including extractable FGF-2 at a first level; and, sterilizing the isolated extracellular matrix material under conditions to retain the extractable, bioactive FGF-2 in at least 10% of the first level.

Another aspect of the invention provides a method for manufacturing medical products. The method includes providing extracellular matrix material in

non-sterile condition and isolated from animal tissue, the extracellular matrix material comprising extractable, bioactive FGF-2; packaging and sterilizing the extracellular matrix material to provide product lots each containing multiple, packaged extracellular matrix material products; taking sample products from the product lots; and testing the sample products to determine whether they include extractable, bioactive FGF-2 at a level above a predetermined level, e.g. above about 50 nanograms per gram dry weight.

Another aspect of the invention provides a medical product adapted for treating wounds, the product including an extracellular matrix material isolated from animal tissue, the material including bioactive components useful to treat wounds including but not limited to FGF-2. The FGF-2 is present in the extracellular matrix material at a level of at least about 50 nanograms per gram dry weight.

Another aspect of the invention relates to a medical product comprising a dry collagenous powder comprising extracellular matrix material, wherein the dry collagenous powder is effective to gel upon rehydration with an aqueous medium and comprises FGF-2 at a level of at least about 50 ng/g dry weight.

In another aspect, the invention relates to a medical product comprising a fluid composition comprising solubilized or suspended collagenous extracellular matrix material, wherein the fluid composition comprises FGF-2 at a level of about 0.1 ng/ml to about 100 ng/ml.

In another embodiment, the invention provides a method for disinfecting an aqueous extracellular matrix hydrolysate composition. The aqueous extracellular matrix hydrolysate composition is contacted with an oxidizing disinfectant for a period of time and under conditions sufficient to disinfect the aqueous extracellular matrix hydrolysate composition.

Another aspect of the invention relates to a method for preparing a disinfected, extracellular matrix hydrolysate composition. This method comprises forming an aqueous extracellular matrix hydrolysate. A first dialysis step is conducted and includes dialyzing the aqueous extracellular matrix hydrolysate against an aqueous medium containing an oxidizing disinfectant so as to contact

and disinfect the extracellular matrix hydrolysate with the oxidizing disinfectant and thereby form a disinfected extracellular matrix hydrolysate. A second dialysis step includes dialyzing the disinfected extracellular matrix hydrolysate under conditions to remove the oxidizing disinfectant.

In another embodiment, the invention provides an extracellular matrix hydrolysate product having extracellular matrix components disinfected by contact of an aqueous medium containing the extracellular matrix hydrolysate with an oxidizing disinfectant. The extracellular matrix hydrolysate product can take on a variety of forms, including a dry powdery material, a non-gelled aqueous composition, a gel, or a sponge.

Still another embodiment of the invention provides an extracellular matrix graft material that includes an extracellular matrix hydrolysate combined with extracellular matrix particles. In a preferred form, the graft material includes an aqueous medium having said extracellular matrix hydrolysate in a dissolved state with the extracellular matrix particles suspended therein, desirably wherein the medium exhibits gel-forming capacity.

Another embodiment of the invention provides an extracellular matrix graft material that includes a sterile, injectable fluid extracellular matrix composition including an aqueous medium containing an extracellular matrix hydrolysate. The extracellular matrix hydrolysate is present in the composition at a level of at least about 20 mg/ml, for example in the range of about 20 mg/ml to about 200 mg/ml.

Additional aspects as well as features and advantages of the invention will be apparent to those of ordinary skill in the art from the descriptions herein.

DETAILED DESCRIPTION

For the purposes of promoting an understanding of the principles of the invention, reference will now be made to certain embodiments and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such alterations and further modifications in the illustrated device, and such further applications of the principles of the invention as described herein being contemplated as would normally occur to one skilled in the art to which the invention relates.

As disclosed above, in one aspect, the present invention provides packaged, sterile medical products including tissue grafts materials containing one or more growth factors, and methods for manufacturing the same. As for the tissue graft material used, it will desirably be a naturally-derived material such as an extracellular matrix (ECM) material. Preferred are naturally-derived collagenous ECMs isolated from suitable animal or human tissue sources. Suitable extracellular matrix materials include, for instance, submucosa (including for example small intestinal submucosa, stomach submucosa, urinary bladder submucosa, or uterine submucosa, each of these isolated from juvenile or adult animals), renal capsule membrane, amnion, dura mater, pericardium, serosa, peritoneum or basement membrane materials, including liver basement membrane or epithelial basement membrane materials. These materials may be isolated and used as intact natural sheet forms, or reconstituted collagen layers including collagen derived from these materials and/or other collagenous materials may be used. For additional information as to submucosa materials useful in the present invention, and their isolation and treatment, reference can be made to U.S. Patent Nos. 4,902,508, 5,554,389, 5,993,844, 6,206,931, and 6,099,567. Renal capsule membrane can also be obtained from warm-blooded vertebrates, as described more particularly in International Patent Application serial No. PCT/US02/20499 filed June 28, 2002, published January 9, 2003 as WO03002165.

Preferred ECM base materials contain residual bioactive proteins or other ECM components derived from the tissue source of the materials. For example, they may contain Fibroblast Growth Factor-2 (basic FGF), Transforming Growth

Factor-beta (TGF-beta) and vascular endothelial growth factor (VEGF). It is also expected that ECM base materials of the invention may contain additional bioactive components including, for example, one or more of glycosaminoglycans, glycoproteins, proteoglycans, and/or growth factors.

It has been discovered that the sterilization conditions utilized in the manufacture of tissue graft materials can significantly impact the level of one or more of such bioactive components or growth factors, including for example FGF-2. Accordingly, in accordance with the invention, sterilization protocols can be selected and controlled to modulate the level of growth factors, for example by either intentionally reducing growth factor levels to a predetermined level or below, or to retain at least a given percentage or level of one or more growth factors, particularly FGF-2, in the material. In certain embodiments of the invention, the ECM or other graft material is processed to finished, packaged, sterile products containing FGF-2 at a level of at least 50 ng/g dry weight, or even at least about 60, at least about 70, at least about 80, or at least about 100 ng/g dry weight. In other embodiments of the invention, an ECM material will have a first level of a bioactive component, such as FGF-2 or another growth factor, after isolation from the animal or human donor source tissue and rinsing with a rinse agent such as water. The ECM material will thereafter be processed under controlled conditions, including sterilization, to provide packaged, sterile medical products containing at least about 10% of said first level of the FGF-2 or other bioactive component, or even at least 15%, 20%, 30% or even 50% or more of said first level.

Illustratively, it has been found that sterilization protocols including ethylene oxide (EO) sterilization, electron beam (E-beam) radiation and gas plasma sterilization (e.g. Sterrad®) can significantly reduce levels of extractable, bioactive FGF-2. At the same time, these sterilization techniques have significantly lower or essentially no impact on levels of extractable, bioactive TGF-beta. Advantageously, the modulation of growth factors imparted by the sterilization technique can be used to affect and optimize levels of given growth factors, their ratios, etc., to prepare a graft material better suited for a particular medical

indication wherein the retained growth factor or growth factors are beneficial to the indication, and/or wherein eliminated growth factor or growth factors are deleterious to the medical indication.

For example, FGF-2 is known to stimulate angiogenesis, neurite growth, plasminogen activator (PA) secretion, and matrix metalloproteinase 1 (MMP-1) production. Correspondingly, levels of FGF-2 can be retained and optimized for use in the graft material in wound healing (angiogenesis), treatment of nervous tissue (neurite outgrowth) including peripheral nervous tissue and central nervous tissue, modulating adhesion formation (by stimulating PA), and facilitating collagen turnover and degradation (by stimulating MMP-1 production). Thus, FGF-2 levels can be retained in the material as high as possible by selecting and optimizing the sterilization protocol. For instance, it has been found that non-sterile isolated submucosa layers (and in particular isolated from small intestine), contain relatively high levels of extractable, bioactive FGF-2. For example, submucosa tissue isolated from small intestine and minimally treated, e.g. only by rinsing, may be recovered so as to contain in excess of about 100 nanograms per gram of FGF-2 dry weight and potentially even higher levels such as above about 200 or about 400 nanograms per gram. In manufacturing, it may be beneficial to retain as much of this FGF-2 in the material as possible. Thus, intermediate steps between the isolation of the original submucosa material and the finished, packaged medical article, can be selected and controlled so as to maintain as much active FGF-2 in the material as possible.

As one example, an isolated, small intestinal submucosa material disinfected as described in US Patent No. 6,206,931 with peracetic acid may contain from about 70 to about 200 nanograms per gram (dry weight) of FGF-2. It has been found that sterilization treatments using ethylene oxide, E-beam, and gas plasma sterilization techniques significantly reduce the levels of FGF-2 in the disinfected material. Among these, E-beam sterilization had the smallest impact on FGF-2 levels, with E-beam sterilized submucosa having FGF-2 levels ranging from about 75 nanograms per gram dry weight to about 150 nanograms per gram dry weight, and generally retaining greater than about 50% of the FGF-2 level of

the disinfected submucosa material. Gas plasma sterilized material had an FGF-2 level ranging from about 60 nanograms per gram dry weight to about 110 nanograms per gram dry weight, and retaining at least 40% of the FGF-2 level of the disinfected submucosa material. Thus, in embodiments of the invention, materials sterilized using E-beam or gas plasma techniques are used in products configured for and methods for treating patients where relatively high FGF-2 levels are beneficial, for example wound healing, treatment of tissue of the nervous system, modulating adhesions, or facilitating collagen turnover and degradation.

On the other hand, ethylene oxide sterilization at both low temperature and high temperature conditions had a more significant impact in reducing the FGF-2 levels, with products typically having from about 10 to about 40 nanograms per gram of FGF-2 dry weight, and retaining less than about 40% of the FGF-2 level of the disinfected submucosa material (e.g. about 10% to about 40%). In this ethylene oxide work, the high temperature conditions tended to do have a slightly greater effect in reducing the FGF-2 levels than the low temperature conditions. Accordingly, in the ethylene oxide and potentially other sterilization techniques, the temperature may be increased or decreased to provide a respective higher or lower level of reduction of FGF-2 and/or other growth factors or non-collagenous ECM proteins. Similarly, the total dose of sterilant chemical or energy can be increased or decreased to provide a respective higher or lower level of reduction of FGF-2 and/or other growth factors or non-collagenous ECM proteins. Increased doses of sterilant can be achieved, for instance, through a longer, single exposure of the graft material to the sterilant, or through multiple, discreet exposures of the graft material to the sterilant.

In accordance with the invention, in addition to controlling the sterilization protocol, a number of other manufacturing techniques can be undertaken to provide a packaged, sterilized graft product with a controlled level of one or more growth factors, including for example FGF-2. As a first measure, where it is desired to retain as high as possible a level of FGF-2, the animal-derived collagenous ECM can be processed and preserved from the time of harvest to the time at which FGF-2 or other growth factor is protected against further significant

degradation. For these purposes, the harvested tissue from which the ECM material is to be isolated may be placed soon or immediately after harvest in a stabilizing solution that prevents degradation of the product including for example, osmotic, hypoxic, autolytic, and/or proteolytic degradation. This solution can also protect against bacterial contamination. To achieve these effects, the stabilizing material may be a buffered solution of anti-oxidants, antibiotics, protease inhibitors, oncotic agents, or other stabilizing agents.

Illustratively, enzymes (e.g. superoxide dismutase and catalase) may be used to neutralize the superoxide anion and hydrogen peroxide or compounds that can directly react with and neutralize other free-radical species. Antioxidants may be added and include tertiary butylhydroquinone (BHT), alpha tocopherol, mannitol, hydroxyurea, glutathione, ascorbate, ethylenediaminetetraacetic acid (EDTA) and the amino acids histidine, proline and cysteine. In addition to antioxidants, the stabilizing solution may contain agents to inhibit hypoxic alteration to normal biochemical pathways, for example, allopurinol to inhibit xanthine dehydrogenase, lipoxigenase inhibitors, calcium channel blocking drugs, calcium binding agents, iron binding agents, metabolic intermediaries and substrates of adenosine triphosphate (ATP) generation.

The stabilizing solution may also contain one or more antibiotics, antifungal agents, protease inhibitors, proteoglycans, and an appropriate buffer. Antibiotics can be used to inhibit or prevent bacterial growth and subsequent tissue infection. Antibiotics may be selected from the group of penicillin, streptomycin, gentamicin, kanamycin, neomycin, bacitracin, and vancomycin. Additionally, anti-fungal agents may be employed, including amphotericin-B, nystatin and polymyxin.

Protease inhibitors may be included in the stabilizing solution to inhibit endogenous proteolytic enzymes which, when released, can cause irreversible degradation of the ECM, as well as the release of chemoattractant factors. These chemoattractants solicit the involvement of polymorphonuclear leukocytes, macrophages and other natural killer cells which generate a nonspecific immune response that can further damage the ECM. Protease inhibitors can be selected

from the group consisting of N-ethylmaleimide (NEM), phenylmethylsulfonyl fluoride (PMSF), ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis (2-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), leupeptin, ammonium chloride, elevated pH and apoprotinin.

Glycosaminoglycans may be included in the stabilizing solution to provide a colloid osmotic balance between the solution and the tissue, thereby preventing the diffusion of endogenous glycosaminoglycans from the tissue to the solution. Endogenous glycosaminoglycans serve a variety of functions in collagen-based connective tissue physiology. They may be involved in the regulation of cell growth and differentiation (e.g. heparin sulfate and smooth muscle cells) or, alternatively, they are important in preventing pathological calcification (as with heart valves). Glycosaminoglycans are also involved in the complex regulation of collagen and elastin synthesis and remodeling, which is fundamental to connective tissue function. Glycosaminoglycans are selected from the group of chondroitin sulfate, heparin sulfate, and dermatan sulfate and hyaluronan. Non-glycosaminoglycan osmotic agents which may also be included are polymers such as dextran and polyvinyl pyrolodone (PVP) and amino acids such as glycine and proline.

The stabilizing solution can also contain an appropriate buffer. The nature of the buffer is important in several aspects of the processing technique. Crystalloid, low osmotic strength buffers have been associated with damage occurring during saphenous vein procurement and with corneal storage. Optimum pH and buffering capacity against the products of hypoxia damage (described below), is essential. In this context the organic and bicarbonate buffers have distinct advantages. (In red cell storage, acetate-citrate buffers with glycine and glucose have been shown to be effective in prolonging shelf-life and maintaining cellular integrity.) The inventors prefer to use an organic buffer selected from the group consisting of 2-(N-morpholino)ethanesulfonic acid (MES), 3-(N-morpholine)propanesulfonic acid (MOPS) and N-2-hydroxyethylpiperazine-N'-2-ethane-sulfonic acid (HEPES). Alternatively, a low salt or physiological buffer,

including phosphate, bicarbonate and acetate-citrate, may be more appropriate in certain applications.

In another aspect, components of the stabilizing solution address one or more of the events that occur during the harvesting of tissues, such as spasm, hypoxia, hypoxia reperfusion, lysosomal enzyme release, platelet adhesion, sterility and buffering conditions. Involuntary contraction of the smooth muscles can result from mechanical stretching or distension, as well as from the chemical action of certain endothelial cell derived contraction factors, typically released under hypoxic (low oxygen) conditions. This involuntary contraction may result in damage to the adjacent ECM. For this reason, the stabilizing solution can include one or more smooth muscle relaxants, selected from the group of calcitonin gene related peptide (CGRP), papaverine, sodium nitroprusside (NaNP), H7 (a protein Kinase C inhibitor) calcium channel blockers, calcium chelators, isoproterenol, phentolamine, pinacidil, isobutylmethylxanthine (IBMX), nifedepine and flurazine. The harvested tissue can be immediately placed into this stabilizing solution and is maintained at 4°C. during transportation and any storage prior to further processing.

The tissue graft material of the invention can be provided in any suitable form, including substantially two-dimensional sheet form (optionally meshed sheet), or a three-dimensional form such as a tube, valve leaflet, or the like. The tissue graft material may contain a single layer of isolated ECM material, or may be a multilaminate construct sized the same as its component layers (e.g. containing directly overlapped layers) or larger than its component layers (e.g. containing partially overlapped layers), see, e.g., U.S. Patent Nos. 5,885,619 and 5,711,969.

In another embodiment, the invention provides a medical product that includes a dry collagenous powder useful for example to treat wounds or to otherwise induce tissue growth at a desired implant location, and including an ECM material. The powder is desirably effective to gel upon rehydration with an aqueous medium and includes FGF-2 at a level of at least about 50 nanograms per gram dry weight. Illustratively, the powder can include a particulate of ECM

material prepared by drying a fluidized material prepared as described in US Patent Nos. 5,516,533 and 5,275,826. This resulting powder can be used alone or in combination with other powder materials to support gelling of the overall powder upon rehydration with an aqueous medium such as a buffered saline solution. In this regard, in addition to the particulate ECM material, the powder composition may also include powdered, purified collagen, gelatin, or the like, to assist in gelling the product upon rehydration.

In one embodiment, the preparation of the powder will be conducted to include FGF-2 at a level of at least about 50 nanograms per gram dry weight, more preferably at least about 60, 70, 80, or 100 nanograms per gram dry weight. Resultant fluid compositions containing solubilized or suspended collagenous ECM materials will desirably be prepared to contain FGF-2 at a level of about 0.1 nanograms per milliliter or greater, e.g. typically in the range of about 0.1 nanograms per ml to about 100 nanograms per ml. This fluid composition is desirably gelable, for example upon incubation for a time after rehydration, which may be hastened by bringing the fluid composition to a relatively neutral pH and/or to body temperature from room temperature. In other embodiments, the fluidized medical product may contain FGF-2 at a level of about 1 to about 15 nanograms per ml, or may contain FGF-2 at a level of about 10 to about 30 nanograms per ml.

As disclosed above, certain embodiments of the invention provide packaged, sterile medical products. Known packaging techniques and materials can be used in the manufacture of such products, with the packaging being selected to suit the final sterilization technique being employed, e.g. ethylene oxide gas, electron-beam, or gas plasma techniques. In addition, the packaging may contain or otherwise bear indicia relating to the use of the enclosed graft material for a particular medical indication, e.g. wound care, and/or may contain or otherwise bear indicia as to one or more growth factors (e.g. FGF-2) for which the product manufacture has been controlled to modulate its level, e.g. to reflect a minimum level of such growth factor, a maximum level of such growth factor, or a range of such growth factor contained in the enclosed tissue graft product.

In other embodiments, the present invention provides ECM gel compositions and methods and materials for their preparation, which can optionally also be used in conjunction with the techniques described above for modulating the level of one or more bioactive substances in the product, including for example growth factors such as FGF-2. The gel compositions of the invention can be prepared from an isolated ECM material, for example one of those listed above. The ECM material is used to prepare a solubilized mixture including components of the material. This can be achieved by digestion of the ECM material in an acidic or basic medium and/or by contact with an appropriate enzyme or combination of enzymes.

Typically, the ECM material is reduced to particulate form to aid in the digestion step. This can be achieved by tearing, cutting, grinding or shearing the isolated ECM material. Illustratively, shearing may be conducted in a fluid medium, and grinding may be conducted with the material in a frozen state. For example, the material can be contacted with liquid nitrogen to freeze it for purposes of facilitating grinding into powder form. Such techniques can involve freezing and pulverizing submucosa under liquid nitrogen in an industrial blender.

Any suitable enzyme may be used for an enzymatic digestion step. Such enzymes include for example serine proteases, aspartyl proteases, and matrix metalloproteases. The concentration of the enzyme can be adjusted based on the specific enzyme used, the amount of submucosa to be digested, the duration of the digestion, the temperature of the reaction, and the desired properties of the final product. In one embodiment about 0.1% to about 0.2% of enzyme (pepsin, for example) is used and the digestion is conducted under cooled conditions for a period of time sufficient to substantially digest the ECM material. The digestion can be conducted at any suitable temperature, with temperatures ranging from 4-37 °C being preferred. Likewise, any suitable duration of digestion can be used, such durations typically falling in the range of about 2-180 hours. The ratio of the concentration of ECM material (hydrated) to total enzyme usually ranges from about 25 to about 125 and more typically the ratio is about 50, and the digestion is conducted at 4° C for 24-72 hours. When an enzyme is used to aid in the digestion,

the digestion will be performed at a pH at which the enzyme is active and more advantageously at a pH at which the enzyme is optimally active. Illustratively, pepsin exhibits optimal activity at pH's in the range of about 2-4.

The enzymes or other disruptive agents used to solubilize the ECM material can be removed or inactivated before or during the gelling process so as not to compromise gel formation or subsequent gel stability. Also, any disruptive agent, particularly enzymes, that remain present and active during storage of the tissue will potentially change the composition and potentially the gelling characteristics of the solution. Enzymes, such as pepsin, can be inactivated with protease inhibitors, a shift to neutral pH, a drop in temperature below 0° C, heat inactivation or through the removal of the enzyme by fractionation. A combination of these methods can be utilized to stop digestion of the ECM material at a predetermined endpoint, for example the ECM material can be immediately frozen and later fractionated to limit digestion.

The ECM material is enzymatically digested for a sufficient time to produce a hydrolysate of ECM components. The ECM can be treated with one enzyme or with a mixture of enzymes to hydrolyze the structural components of the material and prepare a hydrolysate having multiple hydrolyzed components of reduced molecular weight. The length of digestion time is varied depending on the application, and the digestion can be extended to completely solubilize the ECM material. In some modes of operation, the ECM material will be treated sufficiently to partially solubilize the material to produce a digest composition comprising hydrolyzed ECM components and nonhydrolyzed ECM components. The digest composition can then optionally be further processed to remove at least some of the nonhydrolyzed components. For example, the nonhydrolyzed components can be separated from the hydrolyzed portions by centrifugation, filtration, or other separation techniques known in the art.

Preferred gel compositions of the present invention are prepared from enzymatically digested vertebrate ECM material that has been fractionated under acidic conditions, for example including pH ranging from about 2 to less than 7, especially to remove low molecular weight components. Typically, the ECM

hydrolysate is fractionated by dialysis against a solution or other aqueous medium having an acidic pH, e.g. a pH ranging from about 2 to about 5, more desirably greater than 3 and less than 7. In addition to fractionating the hydrolysate under acidic conditions, the ECM hydrolysate is typically fractionated under conditions of low ionic strength with minimal concentrations of salts such as those usually found in standard buffers such as PBS (i.e. NaCl, KCl, Na_2HPO_4, or KH_2PO_4) that can pass through the dialysis membrane and into the hydrolysate. Such fractionation conditions work to reduce the ionic strength of the ECM hydrolysate and thereby provide enhanced gel forming characteristics.

The hydrolysate solution produced by enzymatic digestion of the ECM material has a characteristic ratio of protein to carbohydrate. The ratio of protein to carbohydrate in the hydrolysate is determined by the enzyme utilized in the digestion step and by the duration of the digestion. The ratio may be similar to or may be substantially different from the protein to carbohydrate ratio of the undigested ECM tissue. For example, digestion of vertebrate ECM material with a protease such as pepsin, followed by dialysis, will form a fractionated ECM hydrolysate having a lower protein to carbohydrate ratio relative to the original ECM material.

In accordance with certain embodiments of the invention, shape retaining gel forms of ECM are prepared from ECM material that has been enzymatically digested and fractionated under acidic conditions to form an ECM hydrolysate that has a protein to carbohydrate ratio different than that of the original ECM material. Such fractionation can be achieved entirely or at least in part by dialysis. The molecular weight cut off of the ECM components to be included in the gel material is selected based on the desired properties of the gel. Typically the molecular weight cutoff of the dialysis membrane (the molecular weight above which the membrane will prevent passage of molecules) is within in the range of about 2000 to about 10000 Dalton, and more preferably from about 3500 to about 5000 Dalton.

In one embodiment of the invention, apart from the potential removal of undigested ECM components after the digestion step and any controlled

fractionation to remove low molecular weight components as discussed above, the ECM hydrolysate is processed so as to avoid any substantial further physical separation of the ECM components. For example, when a more concentrated ECM hydrolysate material is desired, this can be accomplished by removing water from the system (e.g. by evaporation or lyophilization) as opposed to using conventional "salting out"/centrifugation techniques that would demonstrate significant selectivity in precipitating and isolating collagen, leaving behind amounts of other desired ECM components. Thus, in certain embodiments of the invention, solubilized ECM components of the ECM hydrolysate remain substantially unfractionated, or remain substantially unfractionated above a predetermined molecular weight cutoff such as that used in the dialysis membrane, e.g. above a given value in the range of about 2000 to 10000 Dalton, more preferably about 3500 to about 5000 Dalton.

Vertebrate ECM material can be stored frozen (e.g. at about -20 to about -80°C.) in either its solid, comminuted or enzymatically digested forms prior to formation of the gel compositions of the present invention, or the material can be stored after being hydrolyzed and fractionated. The ECM material can be stored in solvents that maintain the collagen in its native form and solubility. For example, one suitable storage solvent is 0.01 M acetic acid, however other acids can be substituted, such as 0.01 N HCl. In accordance with one embodiment the fractionated ECM hydrolysate is dried (by lyophilization, for example) and stored in a dehydrated/lyophilized state. The dried form can be rehydrated and gelled to form a gel of the present invention.

In accordance with one embodiment, the fractionated ECM hydrolysate will exhibit the capacity to gel upon adjusting the pH of a relatively more acidic aqueous medium containing it to about 5 to about 9, more preferably about 6.6 to about 8.0, and typically about 7.2 to about 7.8, thus inducing fibrillogenesis and matrix gel assembly. In one embodiment, the pH of the fractionated hydrolysate is adjusted by the addition of a buffer that does not leave a toxic residue, and has a physiological ion concentration and the capacity to hold physiological pH. Examples of suitable buffers include PBS, HEPES, and DMEM. In one

embodiment the pH of the fractionated ECM hydrolysate is raised by the addition of a buffered NaOH solution to 6.6 to 8.0, more preferably 7.2 to 7.8. Any suitable concentration of NaOH solution can be used for these purposes, for example including about 0.05 M to about 0.5 M NaOH. In accordance with one embodiment, the ECM hydrolysate is mixed with a buffer and sufficient 0.25 N NaOH is added to the mixture to achieve the desired pH. If desired at this point, the resultant mixture can be aliquoted into appropriate forms or into designated cultureware and incubated at 37° C for 0.5 to 1.5 hours to form an ECM gel.

The ionic strength of the ECM hydrolysate is believed to be important in maintaining the fibers of collagen in a state that allows for fibrillogenesis and matrix gel assembly upon neutralization of the hydrolysate. Accordingly, if needed, the salt concentration of the ECM hydrolysate material can be reduced prior to neutralization of the hydrolysate. The neutralized hydrolysate can be caused to gel at any suitable temperature, e.g. ranging from about 4°C to about 40°C. The temperature will typically affect the gelling times, which may range from 5 to 120 minutes at the higher gellation temperatures and 1 to 8 hours at the lower gellation temperatures. Typically, the hydrolysate will be gelled at elevated temperatures to hasten the gelling process, for example at 37°C. In this regard, preferred neutralized ECM hydrolysates will be effective to gel in less than about ninety minutes at 37°C, for example approximately thirty to ninety minutes at 37°C. Alternatively, the gel can be stored at 4°C, and under these conditions the setting of the gel will be delayed, e.g. for about 3-8 hours.

Additional components can be added to the hydrolysate composition before, during or after forming the gel. For example, proteins carbohydrates, growth factors, therapeutics, bioactive agents, nucleic acids, cells or pharmaceuticals can be added. In certain embodiments, such materials are added prior to formation of the gel. This may be accomplished for example by forming a dry mixture of a powdered ECM hydrolysate with the additional component(s), and then reconstituting and gelling the mixture, or by incorporating the additional component(s) into an aqueous, ungelled composition of the ECM hydrolysate

before, during (e.g. with) or after addition of the neutralization agent. In other embodiments, the additional component(s) are added to the formed ECM gel, e.g. by infusing or mixing the component(s) into the gel and/or coating them onto the gel.

In one embodiment of the invention, a particulate ECM material will be added to the hydrolysate composition, which will then be incorporated in the formed gel. Such particulate ECM materials can be prepared by cutting, tearing, grinding or otherwise comminuting an ECM starting material. For example, a particulate ECM material having an average particle size of about 50 microns to about 500 microns may be included in the hydrolysate, more preferably about 100 microns to about 400 microns. The ECM particulate can be added in any suitable amount relative to the hydrolysate, with preferred ECM particulate to ECM hydrolysate weight ratios (based on dry solids) being about 0.1:1 to about 200:1, more preferably in the range of 1:1 to about 100:1. The inclusion of such ECM particulates in the ultimate gel can serve to provide additional material that can function to provide bioactivity to the gel (e.g. itself including FGF-2 and/or other growth factors or bioactive substances as discussed herein) and/or serve as scaffolding material for tissue ingrowth.

In certain embodiments, an ECM hydrolysate material to be used in tissue augmentation, e.g. in functional or cosmetic purposes, will incorporate an ECM particulate material. In these embodiments, the ECM particulate material can be included at a size and in an amount that effectively retains an injectable character to the hydrolysate composition, for example by injection through a needle having a size in the range of 18 to 31 gauge (internal diameters of 0.047 inches to about 0.004 inches). In this fashion, non-invasive procedures for tissue augmentation will be provided, which in preferred cases will involve the injection of an ungelled ECM hydrolysate containing suspended ECM particles at a relatively lower (e.g. room) temperature, which will be promoted to form a gelled composition when injected into a patient and thereby brought to physiologic temperature (about 37°C).

In other aspects of the invention, it has been discovered that processing techniques that involve contacting the ECM material with a disinfecting oxidizing agent compound can significantly affect not only the concentration of bioactive substances but also the gelling quality of the collagen molecules. In particular, it has been found that contacting an ECM material with an oxidizing agent such as peracetic acid prior to digestion to form the ECM hydrolysate can disrupt or impair the ability of ECM hydrolysate to form a gel. On the other hand, contacting an aqueous medium including ECM hydrolysate components with an oxidizing disinfectant such as a peroxy compound provides an improved ability to recover a disinfected ECM hydrolysate that exhibits the capacity to form beneficial gels. In accordance with one embodiment of the invention, an aqueous medium containing ECM hydrolysate components is disinfected by providing a peroxy disinfectant in the aqueous medium. This is advantageously achieved using dialysis to deliver the peroxy disinfectant into and/or to remove the peroxy disinfectant from the aqueous medium containing the hydrolysate. In one preferred embodiment, the aqueous medium containing the ECM hydrolysate is dialyzed against an aqueous medium containing the peroxy disinfectant to deliver the disinfectant into contact with the ECM hydrolysate, and then is dialyzed against an appropriate aqueous medium (e.g. an acidic aqueous medium) to at least substantially remove the peroxy disinfectant from the ECM hydrolysate. During this dialysis step, the peroxy compound passes through the dialysis membrane and into the ECM hydrolysate, and contacts ECM components for a sufficient period of time to disinfect the ECM components of the hydrolysate. In this regard, typical contact times will range from about 0.5 hours to about 8 hours and more typically about 1 hour to about 4 hours. The period of contact will be sufficient to substantially disinfect the digest, including the removal of endotoxins and inactivation of virus material present. The removal of the peroxy disinfectant by dialysis may likewise be conducted over any suitable period of time, for example having a duration of about 4 to about 180 hours, more typically about 24 to about 96 hours. In general, the disinfection step will desirably result in a disinfected ECM hydrolysate composition having sufficiently low levels of endotoxins, viral burdens, and other contaminant

materials to render it suitable for medical use. Endotoxin levels below about 2 endotoxin units (EUs) per gram (dry weight) are preferred, more preferably below about 1 EU per gram, as are virus levels below 100 plaque forming units per gram (dry weight), more preferably below 1 plaque forming unit per gram.

In one embodiment, the aqueous ECM hydrolysate composition is a substantially homogeneous solution during the dialysis step for delivering the oxidizing disinfectant to the hydrolysate composition and/or during the dialysis step for removing the oxidizing disinfectant from the hydrolysate composition. Alternatively, the aqueous hydrolysate composition can include suspended ECM hydrolysate particles, optionally in combination with some dissolved ECM hydrolysate components, during either or both of the oxidizing disinfectant delivery and removal steps. Dialysis processes in which at least some of the ECM hydrolysate components are dissolved during the disinfectant delivery and/or removal steps are preferred and those in which substantially all of the ECM hydrolysate components are dissolved are more preferred.

The disinfection step can be conducted at any suitable temperature, and will typically be conducted between 0°C and 37°C, more typically between about 4°C and about 15°C. During this step, the concentration of the ECM hydrolysate solids in the aqueous medium is typically in the range of about 2 mg/ml to about 200 mg/ml, and may vary somewhat through the course of the dialysis due to the migration of water through the membrane. In certain embodiments of the invention, a relatively unconcentrated digest is used, having a starting ECM solids level of about 5 mg/ml to about 15 mg/ml. In other embodiments of the invention, a relatively concentrated ECM hydrolysate is used at the start of the disinfection step, for example having a concentration of at least about 20 mg/ml and up to about 200 mg/ml, more preferably at least about 100 mg/ml and up to about 200 mg/ml. It has been found that the use of concentrated ECM hydrolysates during this disinfection processing results in an ultimate gel composition having higher gel strength than that obtained using similar processing with a lower concentration ECM hydrolysate. Accordingly, processes which involve the removal of amounts of water from the ECM hydrolysate resulting from the digestion prior to the

disinfection processing step are preferred. For example, such processes may include removing only a portion of the water (e.g. about 10% to about 98% by weight of the water present) prior to the dialysis/disinfection step, or may include rendering the digest to a solid by drying the material by lyophilization or otherwise, reconstituting the dried material in an aqueous medium, and then treating that aqueous medium with the dialysis/disinfection step.

Certain impacts of dialysis processing conditions upon ECM hydrolysate gels are illustrated in specific work to date described more particularly in Examples 2-5 below. Generally, several different submucosa hydrolysates were prepared while varying the acid present during pepsin digestion and varying the concentration of ECM hydrolysate present during dialysis against a peracetic acid (PAA) solution. Specifically, a first gel (A1) was prepared using 0.5 M acetic acid in the pepsin digestion solution, and about 5-15 mg/ml ECM hydrolysate during the PAA disinfection; a second gel (A2) was prepared using 0.5 M acetic acid in the pepsin digestion solution, and about 130-150 mg/ml ECM hydrolysate during the PAA disinfection; a third gel (H1) was prepared using 0.01 M hydrochloric acid in the pepsin digestion solution, and about 5-15 mg/ml ECM hydrolysate during the PAA disinfection; and a fourth gel (H2) was prepared using 0.01 M hydrochloric acid in the pepsin digestion solution, and about 130-150 mg/ml ECM hydrolysate during the PAA disinfection. The processed ECM hydrolysates were provided in a solution of 0.1 M HCl at a concentration of about 30 mg/ml, and then PBS was added and the pH of the mixture was adjusted to 7.5-7.6 with 0.25 M NaOH to gel the composition. The mechanical properties of the various gels were then assessed. The results are summarized in Table 1 below.

Table 1

Gel	Compressive Modulus (kPa)	Compressive Strength (kPa
A1	1	0.5
A2	7	2
H1	10	3
H2	20	7

As can be seen, the gels prepared using high submucosa hydrolysate concentrations during the disinfection step (A2,H2) were relatively stronger than those prepared using low submucosa hydrolysate concentrations (A1, H1). In addition, in cell growth assays, the A2 and H2 gels demonstrated an improved capacity to support the proliferation of primary human dermal fibroblast and primary human bladder smooth muscle cells as compared to the A1 and H1 gels. In other observations, the gels prepared from ECM hydrolysate materials resultant of HCl/pepsin digestion were relatively stronger than the corresponding gels resultant of acetic acid/pepsin digestion. Thus, the conditions used during the preparation and processing of ECM hydrolysate materials can be selected and controlled to modulate the physical and biological properties of the ultimate ECM gel compositions.

In one mode of operation, the disinfection of the aqueous medium containing the ECM hydrolysate can include adding the peroxy compound or other oxidizing disinfectant directly to the ECM hydrolysate, for example being included in an aqueous medium used to reconstitute a dried ECM hydrolysate or being added directly to an aqueous ECM hydrolysate composition. The disinfectant can then be allowed to contact the ECM hydrolysate for a sufficient period of time under suitable conditions (e.g. as described above) to disinfect the hydrolysate, and then removed from contact with the hydrolysate. In one embodiment, the oxidizing disinfectant can then be removed using a dialysis procedure as discussed above. In other embodiments, the disinfectant can be partially or completely removed using other techniques such as chromatographic or ion exchange techniques, or can be partially or completely decomposed to physiologically acceptable components. For example, when using an oxidizing disinfectant containing hydrogen peroxide (e.g. hydrogen peroxide alone or a peracid such as peracetic acid), hydrogen peroxide can be allowed or caused to decompose to water and oxygen, for example in some embodiments including the use of agents that promote the decomposition such as thermal energy or ionizing radiation, e.g. ultraviolet radiation.

In another mode of operation, the oxidizing disinfectant can be delivered into the aqueous medium containing the ECM hydrolysate by dialysis and processed sufficiently to disinfect the hydrolysate (e.g. as described above), and then removed using other techniques such as chromatographic or ion exchange techniques in whole or in part, or allowed or caused to decompose in whole or in part as discussed immediately above.

Peroxygen compounds that may be used in the disinfection step include, for example, hydrogen peroxide, organic peroxy compounds, and preferably peracids. Such disinfecting agents are used in a liquid medium, preferably a solution, having a pH of about 1.5 to about 10.0, more desirably about 2.0 to about 6.0. As to peracid compounds that can be used, these include peracetic acid, perpropioic acid, or perbenzoic acid. Peracetic acid is the most preferred disinfecting agent for purposes of the present invention.

When used, peracetic acid is desirably diluted into about a 2% to about 50% by volume of alcohol solution, perferably ethanol. The concentration of the peracetic acid may range, for instance, from about 0.05% by volume to about 1.0% by volume. Most preferably, the concentration of the peracetic acid is from about 0.1% to about 0.3% by volume. When hydrogen peroxide is used, the concentration can range from about 0.05% to about 30% by volume. More desirably the hydrogen peroxide concentration is from about 1% to about 10% by volume, and most preferably from about 2% to about 5% by volume. The solution may or may not be buffered to a pH from about 5 to about 9, with more preferred pH's being from about 6 to about 7.5. These concentrations of hydrogen peroxide can be diluted in water or in an aqueous solution of about 2% to about 50% by volume of alcohol, most preferably ethanol. Additional information concerning preferred peroxy disinfecting agents can be found in discussions in U.S. Patent No. 6,206,931, which is herein incorporated by reference.

ECM gel materials of the present invention can be prepared to have desirable properties for handling and use. For example, fluidized ECM hydrolysates can be prepared in an aqueous medium, which can thereafter be caused or allowed to form of a gel. Such prepared aqueous mediums can have any

suitable level of ECM hydrolysate therein for subsequent gel formation. Typically, the ECM hydrolysate will be present in the aqueous medium to be gelled at a concentration of about 2 mg/ml to about 200 mg/ml, more typically about 20 mg/ml to about 200 mg/ml, and in some preferred embodiments about 30 mg/ml to about 120 mg/ml. In preferred forms, the aqueous ECM hydrolysate composition to be gelled will have an injectable character, for example by injection through a needle having a size in the range of 18 to 31 gauge (internal diameters of about 0.047 inches to about 0.004 inches).

Furthermore, gel compositions can be prepared so that in addition to neutralization, heating to physiologic temperatures (such as 37°C) will substantially reduce the gelling time of the material. As well, once the material is gelled, it can optionally be dried to form a sponge solid material. It is contemplated that commercial products may constitute any of the these forms of the ECM gel composition, e.g. (i) packaged, sterile powders which can be reconstituted in an acidic medium and neutralized and potentially heated to form a gel, (ii) packaged, sterile aqueous compositions including solubilized ECM hydrolysate components under non-gelling (e.g. acidic) conditions; (iii) packaged, sterile gel compositions, and (iv) packaged, sterile, dried sponge compositions; or other suitable forms. In one embodiment of the invention, a medical kit is provided that includes a packaged, sterile aqueous composition including solubilized ECM hydrolysate components under non-gelling (e.g. acidic) conditions, and a separately packaged, sterile aqueous neutralizing composition (e.g. containing a buffer and/or base) that is adapted to neutralize the ECM hydrolysate medium for the formation of a gel. In another embodiment of the invention, a medical kit includes a packaged, sterile, dried (e.g. lyophilized) ECM hydrolysate powder, a separately packaged, sterile aqueous acidic reconstituting medium, and a separately packaged sterile, aqueous neutralizing medium. In use, the ECM hydrolysate powder can be reconstituted with the reconstituting medium to form a non-gelled mixture, which can then be neutralized with the neutralizing medium for the formation of the gel.

Medical kits as described above may also include a device, such as a syringe, for delivering the neutralized ECM hydrolysate medium to a patient. In this regard, the sterile, aqueous ECM hydrolysate medium or the sterile ECM hydrolysate powder of such kits can be provided packaged in a syringe or other delivery instrument. In addition, the sterile reconstituting and/or neutralizing medium can be packaged in a syringe, and means provided for delivering the contents of the syringe into to another syringe containing the aqueous ECM hydrolysate medium or the ECM hydrolysate powder for mixing purposes. In still other forms of the invention, a self-gelling aqueous ECM hydrolysate composition can be packaged in a container (e.g. a syringe) and stable against gel formation during storage. For example, gel formation of such products can be dependent upon physical conditions such as temperature or contact with local milieu present at an implantation site in a patient. Illustratively, an aqueous ECM hydrolysate composition that does not gel or gels only very slowly at temperatures below physiologic temperature (about 37°C) can be packaged in a syringe or other container and potentially cooled (including for example frozen) prior to use for injection or other implantation into a patient.

In particular applications, ECM hydrolysate compositions that form hydrogels at or near physiologic pH and temperature will be preferred for *in vivo* bulking applications, for example in the treatment of stress urinary incontinence, gastroesophageal reflux disease, cosmetic surgery, vesico urethral reflux, anal incontinence and vocal cord repair. These forms of the submucosa or other ECM gel have, in addition to collagen, complex extracellular matrix sugars and varying amounts of growth factors in other bioactive agents that can serve to remodel tissue at the site of implantation. These ECM hydrolysate compositions can, for example, be injected into a patient for these applications.

ECM gels and dry sponge form materials of the invention prepared by drying ECM gels can be used, for example, in wound healing and/or tissue reconstructive applications, or in the culture of cells.

Generally, it has been found that the manipulations used to prepare ECM hydrolysate compositions and gellable or gelled forms thereof can also have a

significant impact upon growth factors or other ECM components that may contribute to bioactivity. Techniques for modulating and sampling for levels of FGF-2 or other growth factors or bioactive substances can also be used in conjunction with the manufacture of the described ECM hydrolysate compositions of the invention. Illustratively, it has been discovered that the dialysis/disinfection processes of the invention employing peroxy compounds typically cause a reduction in the level of FGF-2 in the ECM hydrolysate material. In work to date as described in Examples 2-5, such processing using peracetic acid as disinfectant has caused a reduction in the level of FGF-2 in the range of about 30% to about 50%. Accordingly, to retain higher levels of FGF-2, one can process for a minimal about of time necessary to achieve the desired disinfection of the material; on the other hand, to reduce the FGF-2 to lower levels, the disinfection processing can be continued for a longer period of time. In one embodiment of the invention, the disinfection process and subsequent steps will be sufficiently conducted to result in a medically sterile aqueous ECM hydrolysate composition, which can be packaged using sterile filling operations. In other embodiments, any terminal sterilization applied to the ECM hydrolysate material (e.g. in dried powder, non-gelled aqueous medium, gelled or sponge form) can also be selected and controlled to optimize the level of FGF-2 or other bioactive substances in the product. Terminal sterilization methods may include, for example, high or low temperature ethylene oxide, radiation such as E-beam, gas plasma (e.g. Sterrad), or hydrogen peroxide vapor processing.

Preferred, packaged, sterilized ECM hydrolysate products prepared in accordance with the invention will have an FGF-2 level (this FGF-2 being provided by the ECM hydrolysate) of about 100 ng/g to about 5000 ng/g based upon the dry weight of the ECM hydrolysate. More preferably, this value will be about 300 ng/g to about 4000 ng/g. As will be understood, such FGF-2 levels can be determined using standard ELISA tests (e.g. using the Quantikine Human Basic Fibroblast Growth Factor ELISA kit commercially available from R&D Systems).

In order to promote a further understanding of the present invention and its features and advantages, the following specific examples are provided. It will be

understood that these examples are illustrative and are not limiting of the invention.

EXAMPLE 1

Small intestinal submucosa material was harvested and disinfected with peracetic acid as described in U.S. Patent No. 6,206,931. The submucosa material was lyophilized, packaged in medical packaging comprised of polyester/Tyvek and sterilized by various methods including ethylene oxide (EO), gas plasma (hydrogen peroxide vapor), and E-beam radiation (20 kGy (plus/minus 2 kGy). The resultant submucosa material was frozen in liquid nitrogen and ground to a powder. The material was then extracted with an extraction buffer containing 2M urea, 2.5 mg/ml heparin, and 50 mM Tris buffer, at pH 7.5 at 4°C under constant stirring for 24 hours. After 24 hours, the extraction medium was transferred to centrifuge tubes and the insoluble fraction pelleted at 12000 X G. The supernatant was transferred to dialysis tubing (MW cutoff 3500) and dialyzed exhaustively against high purity (18 megaohm) water. Following dialysis the dialysate was centrifuged at 12000 X G to remove any additional particulate matter and the resulting soluble extract was lyophilized. Prior to measurement the extract was reconstituted at 10 mg/dry weight per ml in the manufacturer-provided diluent (R&D Systems). Samples were centrifuged to remove any insoluble matter. The resulting supernatents were recovered and assayed for FGF-2 content using the Quantikine *Human Basic Fibroblast Growth Factor* Immunoassay (R&D Systems). The results are summarized in Table 2 below.

TABLE 2

ELISA Summary – CBI Extracted Tissues		
Sterilization	Growth factor range (ng/g)	% of Non-sterile*
NONE	100-210	100
EO (low temp)	28-50	24
EO (high temp)	18-40	18
E-beam	50-150	66
Gas Plasma	30-125	49

* based upon the average of 8 experiments.

As can be seen, E-beam and gas plasma sterilization had a significantly lower impact in reducing the level of extractable, bioactive FGF-2 in the materials. On the other hand, ethylene oxide sterilization at both low and high temperatures had a significant impact in lowering the level of extractable, bioactive FGF-2.

EXAMPLE 2

Raw (isolated/washed but non-disinfected) porcine small intestine submucosa was frozen, cut into pieces, and cryoground to powder with liquid nitrogen. 50 g of the submucosa powder was mixed with one liter of a digestion solution containing 1 g of pepsin and 0.5 M acetic acid. The digestion process was allowed to continue for 48-72 hours under constant stirring at 4°C. At the end of the process, the digest was centrifuged to remove undigested material. The acetic acid was then removed by dialysis against 0.01 M HCl for approximately 96 hours at 4°C. The resulting digest was transferred (without concentration) into a semipermeable membrane with a molecular weight cut off of 3500, and dialyzed for two hours against a 0.2 percent by volume peracetic acid in a 5 percent by volume aqueous ethanol solution at 4°C. This step served both to disinfect the submucosa digest and to fractionate the digest to remove components with

molecular weights below 3500. The PAA-treated digest was then dialysed against 0.01 M HCl for 48 hours at 4°C to remove the peracetic acid. The sterilized digest was concentrated by lyophilization, forming a material that was reconstituted at about 30 mg/ml solids in 0.01 M HCl and neutralized with phosphate buffered NaOH to a pH of about 7.5-7.6 and heated to physiologic temperature to form a submucosa gel.

EXAMPLE 3

A second acetic acid processed submucosa gel was made using a process similar to that described in Example 2 above, except concentrating the digest prior to the PAA treatment. Specifically, immediately following the removal of acetic acid by dialysis, the digest was lyophilized to dryness. A concentrated paste of the digest was made by dissolving a pre-weighed amount of the lyophilized product in a known amount of 0.01 M HCl to prepare a mixture having an ECM solids concentration of about 50 mg/ml. The concentrated paste was then dialysed against the PAA solution for 2 hours and then against 0.01 M HCl for removal of PAA in the same manner described in Example 2. The digest was adjusted to about 30 mg/ml solids and neutralized with phosphate buffered NaOH to a pH of about 7.5-7.6 and heated to physiologic temperature to form a submucosa gel.

EXAMPLE 4

An HCl processed submucosa gel was made using a procedure similar to that described in Example 2, except using 0.01 M of HCl in the pepsin/digestion solution rather than the 0.5 M of acetic acid, and omitting the step involving removal of acetic acid since none was present. The digest was used to form a gel as described in Example 2.

EXAMPLE 5

Another HCl processed submucosa gel was made using a procedure similar to that described in Example 3, except using 0.01 M of HCl in the pepsin/digestion solution rather than the 0.5 M of acetic acid, and omitting the step involving

removal of acetic acid since none was present. The digest was used to form a gel as described in Example 3.

While the invention has been illustrated and described in detail in the drawings and foregoing description, the same is to be considered as illustrative and not restrictive in character, it being understood that only the preferred embodiment has been shown and described and that all changes and modifications that come within the spirit of the invention are desired to be protected. In addition, all publications cited in this application are indicative of the abilities possessed by those of ordinary skill in the pertinent art and are hereby incorporated by reference in their entirety as if each had been individually incorporated by reference and fully set forth.

WHAT IS CLAIMED IS:

1. A medical product, comprising a packaged, sterile animal-derived extracellular matrix material comprising extractable, bioactive Fibroblast Growth Factor-2 (FGF-2) at a level of at least about 50 ng/g dry weight.

2. The medical product of claim 1, wherein the extracellular matrix material comprises submucosa.

3. The medical product of claim 2, wherein the submucosa is small intestinal submucosa.

4. The medical product of claim 2 or 3, wherein the submucosa is porcine.

5. The medical product of any of claims 1-4, wherein the FGF-2 is present at a level of at least about 60 ng/g dry weight.

6. The medical product of any of claims 1-4, wherein the FGF-2 is present at a level of at least about 70 ng/g dry weight.

7. The medical product of any of claims 1-4, wherein the FGF-2 is present at a level of at least about 80 ng/g dry weight.

8. The medical product of any of claims 1-4, wherein the FGF-2 is present at a level of at least about 100 ng/g dry weight.

9. The medical product of any of claims 1-8, wherein the extracellular matrix material has been sterilized with radiation.

10. The medical product of claim 9, wherein the material has been sterilized with e-beam radiation.

11. A medical product, comprising a packaged, sterile extracellular matrix material isolated from animal tissue and comprising components native to said tissue including collagen, growth factors, proteoglycans, and glycosaminoglycans, and having extractable, bioactive Fibroblast Growth Factor-2 (FGF-2) at a level of at least about 50 ng/g dry weight.

12. The medical product of claim 11, wherein the extracellular matrix material comprises submucosa.

13. The medical product of claim 12, wherein the submucosa is small intestinal submucosa.

14. The medical product of claim 12 or 13, wherein the submucosa is porcine.

15. The medical product of any of claims 11-14, wherein the FGF-2 is present at a level of at least about 60 ng/g dry weight.

16. The medical product of any of claims 11-14, wherein the FGF-2 is present at a level of at least about 70 ng/g dry weight.

17. The medical product of any of claims 11-14, wherein the FGF-2 is present at a level of at least about 80 ng/g dry weight.

18. The medical product of any of claims 11-14, wherein the FGF-2 is present at a level of at least about 100 ng/g dry weight.

19. The medical product of any of claims 11-18, wherein the extracellular matrix material has been sterilized with radiation.

20. The medical product of claim 19, wherein the material has been sterilized with e-beam radiation.

21. A method for manufacturing a sterile, extracellular matrix material, comprising:

isolating an extracellular matrix material from animal tissue, the isolated extracellular matrix material comprising a first level of extractable FGF-2;

processing the isolated material to a sterilized extracellular matrix material under conditions to retain said extractable FGF in at least 10% of said first level.

22. The method of claim 21, wherein the extracellular matrix material comprises submucosa.

23. The method of claim 22, wherein the submucosa is small intestinal submucosa.

24. The method of claim 22 or 23, wherein the submucosa is porcine.

25. The method of any of claims 21-24, wherein the FGF-2 is present in said sterilized material at a level of at least about 60 ng/g dry weight.

26. The method of any of claims 21-24, wherein the FGF-2 is present in said sterilized material at a level of at least about 70 ng/g dry weight.

27. The method of any of claims 21-24, wherein the FGF-2 is present in said sterilized material at a level of at least about 80 ng/g dry weight.

28. The method of any of claims 21-24, wherein the FGF-2 is present in said sterilized material at a level of at least about 100 ng/g dry weight.

29. The method of any of claims 21-28, wherein the extracellular matrix material has been sterilized with radiation.

30. The method of claim 29, wherein the material has been sterilized with e-beam radiation.

31. A method for manufacturing medical products, comprising:

providing extracellular matrix material isolated from animal tissue, the extracellular matrix material comprising extractable, bioactive FGF-2 at a first level;

processing the extracellular matrix material to provide product lots each containing multiple packaged, sterile extracellular matrix material products;

taking sample products from said product lots; and

testing said sample products to determine whether they include extractable, bioactive FGF-2 at a level of at least about 10% of said first level.

32. The method of claim 31, wherein the extracellular matrix material comprises submucosa.

33. The method of claim 32, wherein the submucosa is small intestinal submucosa.

34. The method of claim 32 or 33, wherein the submucosa is porcine.

35. The method of any of claims 31-34, wherein said testing comprises testing for FGF-2 at a level of at least about 50 ng/g dry weight.

36. The method of any of claims 31-34, wherein said testing comprises testing said sample products to determine whether they include extractable, bioactive FGF-2 at a level of at least about 15% of said first level.

37. The method of any of claims 31-34, wherein said testing comprises testing said sample products to determine whether they include extractable, bioactive FGF-2 at a level of at least about 20% of said first level.

38. The method of any of claims 31-34, wherein said testing comprises testing said sample products to determine whether they include extractable, bioactive FGF-2 at a level of at least about 30% of said first level.

39. The method of any of claims 31-34, wherein said testing comprises testing said sample products to determine whether they include extractable, bioactive FGF-2 at a level of at least about 50% of said first level.

40. The method of any of claims 31-39, wherein the extracellular matrix material has been sterilized with e-beam radiation.

41. A medical product adapted for treating wounds, comprising:

an extracellular matrix material isolated from animal tissue, said material including bioactive components useful to treat wounds including FGF-2, said FGF-2 present in said extracellular matrix material at a level of at least about 50 ng/g dry weight.

42. The medical product of claim 41, wherein the extracellular matrix material comprises submucosa.

43. The medical product of claim42, wherein the submucosa is small intestinal submucosa.

44. The medical product of claim 42 or 43, wherein the submucosa is porcine.

45. The medical product of any of claims 41-44, wherein the FGF-2 is present at a level of at least about 60 ng/g dry weight.

46. The medical product of any of claims 41-44, wherein the FGF-2 is present at a level of at least about 70 ng/g dry weight.

47. The medical product of any of claims 41-44, wherein the FGF-2 is present at a level of at least about 80 ng/g dry weight.

48. The medical product of any of claims 41-44, wherein the FGF-2 is present at a level of at least about 100 ng/g dry weight.

49. The medical product of any of claims 41-48, wherein the extracellular matrix material has been sterilized with radiation.

50. The medical product of claim 49, wherein the material has been sterilized with e-beam radiation.

51. A medical product, comprising:

a dry collagenous powder comprising extracellular matrix material;

said dry collagenous powder effective to gel upon rehydration with an aqueous medium; and

said dry collagenous powder comprising FGF-2 at a level of at least about 50 ng/g dry weight.

52. The medical product of claim 51, wherein the extracellular matrix material comprises submucosa.

53. The medical product of claim 52, wherein the submucosa is small intestinal submucosa.

54. The medical product of claim 52 or 53, wherein the submucosa is porcine.

55. The medical product of any of claims 51-54, wherein the FGF-2 is present at a level of at least about 60 ng/g dry weight.

56. The medical product of any of claims 51-54, wherein the FGF-2 is present at a level of at least about 70 ng/g dry weight.

57. The medical product of any of claims 51-54, wherein the FGF-2 is present at a level of at least about 80 ng/g dry weight.

58. The medical product of any of claims 51-54, wherein the FGF-2 is present at a level of at least about 100 ng/g dry weight.

59. The medical product of any of claims 51-58, wherein the extracellular matrix material has been sterilized with radiation.

60. The medical product of claim 59, wherein the material has been sterilized with e-beam radiation.

61. A medical product, comprising:

a fluid composition comprising solubilized or suspended collagenous extracellular matrix material;

said fluid composition comprising FGF-2 at a level of about 0.1 ng/ml to about 100 ng/ml.

62. The medical product of claim 61, wherein said fluid composition is a gelable composition.

63. The medical product of claim 61 or 62, comprising FGF-2 at a level of about 1 to about 50 ng/ml.

64. The medical product of claim 61 or 62, comprising FGF-2 at a level of about 10 to about 30 ng/ml.

65. A method for preparing a disinfected, extracellular matrix hydrolysate composition, the method comprising:

forming an aqueous extracellular matrix hydrolysate containing solubilized ECM components;

a first dialysis step including dialyzing said aqueous extracellular matrix hydrolysate against an aqueous acidic medium containing an oxidizing disinfectant so as to contact and disinfect the extracellular matrix hydrolysate with the oxidizing disinfectant and thereby form a disinfected extracellular matrix hydrolysate; and

a second dialysis step including dialyzing the disinfected extracellular matrix hydrolysate under conditions to remove the oxidizing disinfectant.

66. The method of claim 65, wherein the oxidizing disinfectant comprises a peroxy compound.

67. The method of claim 65, wherein the peroxy compound is a peracid.

68. The method of any of claim 67, wherein the peroxy compound is peracetic acid.

69. The method of any of claims 65-68, wherein during said dialysis steps, aqueous ECM hydrolysate has an ECM hydrolysate concentration of about 2 mg/ml to about 200 mg/ml.

70. The method of any of claims 65-67, wherein during said dialysis steps, the aqueous ECM hydrolysate has an ECM hydrolysate concentration of at least about 20 mg/ml.

71. The method of any of claims 65-67, wherein during said dialysis steps, the aqueous ECM hydrolysate has an ECM hydrolysate concentration of about 100 to about 200 mg/ml.

72. The method of any of claims 65-71, wherein the aqueous ECM hydrolysate is concentrated prior to said first dialysis step.

73. The method of claim 72, wherein the aqueous ECM hydrolysate is dried and reconstituted in an aqueous medium prior to said first dialysis step.

74. The method of claim 72, wherein the aqueous ECM hydrolysate is partially dewatered to form a more concentrated aqueous ECM hydrolysate prior to said first dialysis step.

75. A method for disinfecting an aqueous extracellular matrix hydrolysate composition containing solubilized extracellular matrix components, comprising contacting the aqueous extracellular matrix hydrolysate composition with an oxidizing disinfectant for a period of time and under conditions sufficient to disinfect the aqueous extracellular matrix hydrolysate composition.

76. The method of claim 75, wherein the oxidizing disinfectant comprises peracetic acid.

77. The method of claim 75 or 76, also including removing the oxidizing disinfectant from the aqueous extracellular matrix hydrolysate composition.

78. The method of claim 75 or 76, wherein the extracellular matrix comprises vertebrate submucosa.

79. An extracellular matrix hydrolysate composition having extracellular matrix components disinfected by contact in solution with an oxidizing disinfectant.

80. The composition of claim 79 wherein the oxidizing disinfectant comprises a peroxy compound.

81. The composition of claim 80 wherein the oxidizing disinfectant comprises peracetic acid.

82. The composition of claim 79 which is a powder, a non-gelled aqueous composition, a gel, or a sponge.

83. The composition of claim 82, which is a gel, and wherein said extracellular matrix components have been disinfected by dialysis of a liquid medium containing the extracellular matrix components against an aqueous medium containing the oxidizing disinfectant.

84. The composition of claim 83, wherein the oxidizing disinfectant comprises a peroxy compound.

85. The composition of claim 84, wherein the oxidizing disinfectant comprises a peracid.

86. The composition of claim 85 wherein the oxidizing disinfectant comprises peracetic acid.

87. The composition of claim 79, wherein the extracellular matrix components comprise FGF-2.

88. The composition of claim 87, wherein the extracellular matrix components remain substantially unfractionated at molecular weights above a value in the range of about 2000 to about 10000.

89. An extracellular matrix graft material, comprising:

an extracellular matrix hydrolysate; and

extracellular matrix particles.

90. The graft material of claim 89, comprising an aqueous medium including said extracellular matrix hydrolysate in a dissolved state with said extracellular matrix particles suspended therein.

91. The graft material of claim 90 in injectable form.

92. The graft material of any of claims 89-91 wherein said extracellular matrix hydrolysate comprises a submucosa hydrolysate and said extracellular matrix particles comprise submucosa particles.

93. An extracellular matrix graft material, comprising:

a sterile, injectable fluid extracellular matrix composition including an aqueous medium containing an extracellular matrix hydrolysate, said extracellular matrix hydrolysate present in said composition at a level of about 20 mg/ml to about 200 mg/ml.

94. The graft material of claim 93 wherein the extracellular matrix hydrolysate comprises a submucosa hydrolysate.

95. The graft material of claim 93 or 94, wherein said extracellular matrix hydrolysate is present at a level of about 30 mg/ml to about 120 mg/ml.

96. The graft material of any of claims 93-95, also including extracellular matrix particles having an average particle size in the range of about 50 microns to about 500 microns.

97. The graft material of claim 96, wherein the extracellular matrix particles are included in a weight ratio of about 1:1 to about 100:1.

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(54) Bezeichnung: VERFAHREN ZUR TERMINALEN STERILISIERUNG VON BEFÜLLTEN SPRITZEN

(57) Abstract

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

(57) Zusammenfassung

Die Erfindung besteht aus einem Herstellungsverfahren einer vorgefüllten, sterilen Spritze. Die Spritze umfaßt einem Spritzenkörper mit einem proximalen und distalen Ende, ein Spritzenauslaßstück am distalen Ende, einen Verschluß, einen Stopfen und ein fluides und ein gasförmiges Medium. Das fluide Medium ist eine Flüssigkeit. Das Verfahren umfaßt die folgenden Schritte: Bereitstellen von dem Spritzenkörper, Verschluß und Stopfen, der oder die von Keimen und/oder Endotoxinen befreit sowie partikelarm sind. Ein Gleitmittel wird aufgetragen. Das proximale Ende wird durch Einführen des Stopfens in den Spritzenkörper abgedichtet. Die Spritze wird durch das distale Ende befüllt. Das Spritzenauslaßstück wird mit dem Verschluß abgedichtet. In einer Sterilisationskammer wird die Spritze sterilisiert, anschließend verpackt und der Verpackungsbehälter danach noch einmal sterilisiert.

LEDIGLICH ZUR INFORMATION

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Verfahren zur terminalen Sterilisierung von befüllten Spritzen

Die Erfindung betrifft ein Verfahren zur terminalen Sterilisierung von befüllten Spritzen. Dabei wird insbesondere auf eine pyrogenfreie und keimfreie Oberfläche der Spritzen abgestellt. Diese Spritzen sind bevorzugt für den Einsatz von injizierbaren Diagnostika, insbesondere Kontrastmitteln vorgesehen, die zum Beispiel in Blutgefäße, Organe, Organteile, Höhlungen und andere Gefäße gespritzt werden oder dort bildgebende Wirkung entfalten.

In der Patentschrift AT-E 68 979 wird ein Verfahren zum Herstellen einer gefüllten, terminal sterilisierten Spritze beschrieben. Die Spritze besteht aus Kunststoff. Die Spritze weist einen Zylinder auf mit einem distalen Ende mit einem Spritzenauslaßstück. Das Spritzenauslaßstück wird durch einen Verschluß abgedichtet. Die Spritze wird nach dem Befüllen mit einem flexiblen Gummistopfen verschlossen, der in dem Zylinder gleitfähig ist. Das Verfahren beginnt damit, daß Abfallteilchen oder andere Verunreinigungen von dem Verschluß und dem Kolben entfernt werden. Mikrobielle Verunreinigungen auf dem Verschluß und dem Kolben werden zerstört. Der Zylinder wird mit einer Vielzahl von Wasserstrahlen gewaschen, um Pyrogene und Abfallteilchen zu entfernen. Anschließend wird Silikonöl auf die Innenwandung der Spritze aufgetragen. Der Verschluß wird daraufhin auf das Spritzenauslaßstück aufgesteckt. Durch das proximale Ende der Spritze wird das Kontrastmittel in die Spritze gefüllt. Die Spritze wird anschließend mit dem Stopfen verschlossen. Diese zusammengesetzte und befüllte Spritze wird in einem Autoklaven sterilisiert. Dabei wird neben dem üblichen Autoklavendruck noch ein zusätzlicher Stützdruck in dem Autoklaven erzeugt. Dadurch wird der Druck auf der Außenoberfläche der Spritze gleich oder größer als der Druck auf der Innenoberfläche der Spritze.

Aus der Publikation von Venten und Hoppert (E. VENTEN und J. HOPPERT (1978) Pharm. Ind. Vol. 40, Nr. 6, Seiten 665 bis 671) ist ein terminales Sterilisieren von vorgefüllten Spritzampullen bekannt. Die Spritzampullen, die einen Stopfen am proximalen Ende aufweisen, werden distal durch den Rollrand befüllt. Der Rollrand wird anschließend durch eine Dichtscheibe abgedichtet, wobei eine Bördelkappe die Dichtscheibe auf dem Rollrand fixiert. (M. JUNGA (1973) Pharm. Ind. Vol. 35, Nr. 11a, Seiten 824 bis 829) Die vorgefüllten Spritzampullen werden dann in einen Autoklaven überführt. Dieser Autoklav ist bezüglich der Temperatur und des Druckes regelbar. Damit die Dichtscheibe

sich nicht von der Spritzampulle löst wird in dem Autoklav ein Stützdruck erzeugt. Der Stützdruck wird durch ein zusätzliches Gas aufgebaut. Dadurch ist es möglich, den Druck auf der Innenseite der Dichtscheibe annähernd gleich dem Druck auf der Außenseite der Dichtscheibe zu halten. Hierdurch wird auch eine Bewegung des eingesetzten Kolbens vermieden. Infolge der guten Regelung ist es selbst möglich, Zweikammerspritzampullen, die mit zwei Lösungen gefüllt sind, terminal zu sterilisieren, ohne daß eine unzulässige Stopfenbewegung oder Dichtscheibenundichtigkeit auftritt.

In der finnischen Patentanmeldung FI 93 0405 wird ein Verfahren zum terminalen Sterilisieren einer vorgefüllten Plastikspritze oder Glasspritze beschrieben, wobei die Spritze ein Kontrastmittel enthält. Die Spritze besteht aus einem Spritzenzylinder, der ein Spritzenauslaßstück am distalen Ende aufweist. Daneben werden Spritzampullen in der zuvor schon bei Venten und Hoppert beschriebenen Form angeführt. Die Spritzen weisen ein offenes proximales Ende auf, welches durch einem in der Spritze gleitfähigen Stopfen verschließbar ist. Der Stopfen wird mit einem Stempel verbunden.
Wenn die Spritze oder Spritzampulle befüllt wird, wird zuerst der Stopfen in das proximale Ende der Spritze oder Spritzampulle eingeführt. Danach wird über das distale Ende befüllt. Das distale Ende wird anschließend durch einen Verschluß abgedichtet. Bei den Spritzampullen wird eine Dichtscheibe mit einer Bördelkappe am Rollrand fixiert. Die Spritzen oder Spritzampullen werden anschließend sterilisiert, wobei ein Stützdruck verwendet wird. Dadurch wird der Druck auf der Außenoberfläche der Spritze kleiner als der Druck auf der Innenoberfläche der Spritze oder Spritzampulle gehalten. Bei den Spritzampullen ist der Druck in dem Autoklaven gleich, größer oder kleiner als der Druck in der Spritzampulle.

In der WO 95/12418 wird ein terminales Sterilisationsverfahren für vorgefüllte Spritzen beschreiben, bei dem kein Autoklav verwendet wird, sondern lediglich eine druckfeste Sterilisationskammer zum Einsatz gelangt. In diese Sterilisationskammer wird die distal oder proximal befüllte Spritze eingebracht. Die Kammer wird mittels Heizgas erwärmt. Zugleich sorgt dieses Heizgas auch für einen Druck, der den Druckanstieg in der Spritze kompensieren soll. Um ein Verdampfen von Flüssigkeit, die durch den Kunststoff dringt, zu vermeiden, wird neben dem Heizgas auch Wasserdampf eingebracht. Es wird in dem Schutzrecht beschrieben, daß dieselbe Sicherheit wie bei einem Autoklavieren erzielt werden soll.

Die WO 95/12482 beschreibt ein Verfahren zur Herstellung von vorgefüllten Kunststoffspritzen, die mit einem Kontrastmittel gefüllt sind. Die Spritzen bestehen aus einem Zylinder, einem Spritzenauslaßstück am distalen Ende, welches für einen Kanülenansatz vorbereitet ist. Weiterhin umfaßt die Spritze einen Stopfen, der in dem Zylinder gleiten kann. Er dichtet das proximale Ende der Spritze ab. Die Spritze ist nach einem Verfahren hergestellt worden, das zu pyrogenfreien Objekten führt. Ebenso liegen keine Partikel mehr vor. Die Spritze wird durch das proximale Ende befüllt, dabei ist das Spritzenauslaßstück mit einem Verschluß abgedichtet. Die befüllte Spritze wird mit dem Stopfen verschlossen. Der Partikelstatus der Räumlichkeiten entspricht den Bedingungen der Klasse 100.
Nachdem die Spritzenteile aus der Gußform kommen, werden sie mit Gas abgeblasen, um Partikel zu entfernen. Die Spritze wird anschließend gewaschen. Die Spritze wird danach sterilisiert, so daß die Spritze wahlweise weiterverarbeitet, gelagert oder transportiert werden kann.

Es stellt sich die Aufgabe, eine Spritze anzubieten, welche mit einem Medium vorgefüllt wird, wobei sich das Medium dauerhaft ohne Qualitätseinbußen in der Spritze befindet. Besonders hohe Ansprüche sollen an die Sicherheit bezüglich Sterilität und Partikelarmut innerhalb und außerhalb der Spritze gestellt werden.

Die Aufgabe wird gelöst durch ein Herstellungsverfahren einer vorgefüllten, sterilen Spritze aus Glas oder Kunststoff oder eine Mischung aus Glas und Kunststoff, weiterhin einer Glasspritze mit einer damit verbundenen Kunststoffolie und einer Kunststoffspritze mit einer damit verbundenen Glasbeschichtung,
dabei umfaßt die Spritze

- einen zylinderförmigen Spritzenkörper mit einem verschließbaren proximalen und einem verschließbaren distalen Ende,
- ein Spritzenauslaßstück am distalen Ende,
- ein das Spritzenauslaßstück abdichtenden Verschluß,
- einen Stopfen, der in dem Spritzenkörper gleitfähig ist,
  - dabei ist der Stopfen durch einen Stempel bewegbar,

und

- ein fluides und ein gasförmiges Medium,
  - wobei das fluide Medium eine Flüssigkeit, eine Lösung, eine Suspension oder eine Emulsion ist,

wobei das Verfahren die folgenden Schritte umfaßt:

- Bereitstellen von dem Spritzenkörper, der von Keimen, Pyrogenen und/oder Endotoxinen befreit, sowie partikelarm ist,
- Bereitstellen von dem Verschluß, der von Keimen, Pyrogenen und/oder Endotoxinen befreit, sowie partikelarm ist,
- Bereitstellen von dem Stopfen, der von Keimen, Pyrogenen und/oder Endotoxinen befreit, sowie partikelarm ist,
- Auftragen eines Gleitmittels,
- Abdichten des proximalen Endes durch Einführen des Stopfens in den Spritzenkörper und Befüllen der Spritze durch das distale Ende und Verschließen des Spritzenauslaßstückes mit dem Verschluß oder Verschweißen des Spritzenauslaßstückes,

oder alternativ

Abdichten des distalen Endes durch den Verschluß oder Verschweißen des Spritzenauslaßstückes und Befüllen der Spritze durch das proximale Ende und Abdichten des proximalen Endes durch Einführen des Stopfens in den Spritzenkörper,

- thermisches Sterilisieren in einer Sterilisationskammer, insbesondere einem Autoklaven oder Sterilisator, mit Dampf, Heißluft und / oder Mikrowelle,
- gegebenenfalls Aufbau von einem Stützdruck durch ein Gas in der Sterilisationskammer, wobei der Druck auf die Außenoberfläche der Spritze gleich, größer oder kleiner als der Druck auf die Innenoberfläche der Spritze ist.
- Verpacken der sterilisierten Spritze in einem Behälter, insbesondere einem Sekundärpackmittel, und
- Sterilisieren der verpackten Spritze mit einer Substanz, die mindestens Teile des Behälters, insbesondere des Sekundärpackmittels, permeiert.

Der Begriff Spritze umfaßt die Begriffe Kartusche (großvolumige Spritze mit mindestens 100 ml Volumen), Ampullenspritzen, Einmalspritzen, Einmalspritzampullen, Einwegspritzampullen, Einwegspritzen, Injektionsampullen, Spritzampullen, spritzfertige Ampulle, Zylinderampulle, Doppelkammer-Spritzampulle, Zweikammer-Spritze, Zweikammer-Spritzampulle, Zweikammer-Einmalspritze und Sofortspritze.

Glasspritzen und Kunststoffspritzen sind in der Publikation von Junga (M. JUNGA (1973) Pharm. Ind. Vol. 35, Nr. 11a, Seiten 824 bis 829) ausführlich

beschrieben. Eine Mischung aus Glas und Kunststoff wird in WO 96/00098 (Anmeldetag 23.6.1995) dargestellt.

Kunststoffe werden ausführlich in Römpp - Chemie - Lexikon, Herausgeber Jürgen FALBE und Manfred REGITZ, 9. Auflage, Stuttgart, 1990 auf den Seiten 2398 ff dargestellt. Bevorzugt sind COC, PP und Polymethylpenten. [COC = Cycloolefincopolymer mit den Markennamen CZ (Hersteller: Nihon Zeon) und TOPAS (Hersteller: Mitsui Chemicals und Hoechst)] Diese Kunststoffe sind besonders für den Einsatz bei vorgefüllten, terminal sterilisierten Spritzen geeignet, weil deren hoher Schmelzpunkt (mindestens 130 °C) eine Dampfsterilisation (Standardverfahren 121 °C) zulassen. Darüber hinaus sind die optischen Eigenschaften für eine arzneibuchgemäße visuelle einhundertprozentige Inspektion ausreichend.

Die Begriffe proximal und distal definieren sich aus Sicht des behandelnden Arztes. Am distalen Ende befindet sich das Spritzenauslaßstück, an dem zum Beispiel die Kanüle oder ein Schlauch, der zu einer Kanäle führt, angeschlossen ist. Am proximalen Ende befindet sich der Stopfen, der das Medium durch das distale Ende bei der Applikation drückt. Die Bewegung des Stopfens kann manuell oder auch mechanisch erfolgen. Der Ausdruck Stopfen umfaßt auch Kolben. Für die manuelle Betätigung der Spritze ist es für das Bedienungspersonal hilfreich, wenn die Spritze am proximalen Ende Fingerhalterungen trägt. Dabei weisen die Fingerhalterungen üblicherweise mindestens eine Fläche als Widerlager für den Zeigefinger und Mittelfinger auf, wobei die Fläche der Fingerhalterung im wesentlich senkrecht zu der Achse des Spritzenzylinders steht. Bei mechanischen Pumpvorrichtungen sind verschiedene Modell bekannt. Eine Spritze trägt dann bevorzugt eine oder mehrere Gerätehalterungen am vorzugsweise proximalen Ende. Besonders gut ist eine solche mechanische Pumpe in der EP 0 584 531 (Reilly et al. Anmeldetag 21. 07. 1993) beschrieben. Auch Mischformen aus Fingerhalterung und Gerätehalterung sind möglich.

Die Spritzen sind üblicherweise drehsymmetrisch, lediglich die Fingerhalterungen und Gerätehalterungen und bisweilen auch das Spritzenauslaßstück weichen von der Symmetrie ab. So kann das Spritzenauslaßstück exzentrisch angeordnet sein. Besonders bevorzugt ist der Luer - Lock, da er ausschließlich bei der Applikation von Kontrastmitteln dann zum Tragen kommt, wenn mechanische Pumpvorrichtungen eingesetzt werden. Auch bei der manuellen Appli-

kation vermeidet der Luer - Lock und der damit verbundene Schlauch, daß nicht beabsichtigte Bewegungen des Arztes auf die Kanüle direkt übertragen werden. Weiterhin sind der einfache Luer-Ansatz und auch der Record-Ansatz bekannt.

Es ist auch möglich, das Spritzenauslaßstück zu verschweißen und dadurch abzudichten. Vorteilhaft ist dann, daß ein Spritzenauslaßstück eine Sollbruchstellte aufweist, die problemlos ein Öffnen des Spritzenauslaßstückes vor dem Benutzen erlaubt.

Die proximale und das distale Ende der Spritze muß verschließbar sein. Das distale Ende wird durch einen Verschluß abgedichtet, der auf das Spritzenauslaßstück aufsetzbar ist. Das Spritzenauslaßstück umfaßt in diesem Schutzrecht die Decke des Spritzenzylinders. Weiterhin umfaßt das Spritzenauslaßstück eine Röhre, die zu der Nadel oder dem Schlauch führt, ein Endstück, welches mit der Nadel oder dem Schlauch in Kontakt steht und einem Zylinder mit Gewinde auf der Innenseite, wobei der Zylinder das Endstück umgibt und ein Gewinde für einen zum Beispiel Luer - Lock trägt. Dabei kann das Spritzenauslaßstück einstückig oder mehrstückig sein. Die Decke kann gewölbt, eben oder pyramidenförmig sein. Auch Mischformen sind denkbar. Der Stopfen verschließt das proximale Ende der Spritze. Er muß in dem Zylinder gleitfähig sein und muß das Medium sicher von der Umgebung zurückhalten. Er soll möglichst wenig für Gase und Flüssigkeiten permeabel sein. Auch Temperaturschwankungen müssen ohne Funktionsstörung aufzufangen sein. Üblicherweise ist der Stopfen bei dem mechanischen Entleeren der Spritzen nicht mit einem eigenen Stempel versehen. Vielmehr greift ein Stempel, der Teil der Pumpvorrichtung ist, in einen Verschluß im Inneren des Stopfens ein, so daß eine Bewegung des Stopfens problemlos möglich ist. (vgl. EP 0 584 531)

Das Medium in der befüllten Spritze ist eine Mischung aus einem fluiden Medium und mindestens einem Gas. Das Medium kann eine Flüssigkeit, eine Lösung, eine Suspension oder eine Emulsion sein. Diese Erscheinungsformen sind in W. SCHRÖTER et al., (1987) Chemie; Fakten und Gesetze, 14. Auflage, Leipzig auf den Seiten 23 und folgende beschrieben.

Bevorzugt ist ein fluides Medium, welches ein Kontrastmittel ist. Hierbei handelt es sich um die folgenden Kontrastmittel mit den generischen Namen: Ami-

dotrizoesäure, Gadopentetsäure, Gadobutrol, Gadolinium EOB-DTPA, Iopamidol, Iopromid, Iotrolan und Iotroxinsäure.

Eine Spritze muß von Fremdkörpern gereinigt werden. Fremdkörper sind all die Partikel, die nicht aus dem Material der Spritze und dem Medium und die losgelöste Bruchstücke der Spritze sind.
Pyrogene sind Substanzen, die als Fragmente der Bakterien eine Immunantwort des Menschen provozieren. Insbesondere handelt es sich um Lipopolysaccharide.

Sterile und reine Produktionsprozesse sind in DAB 1996 oder Ph.Eur. beschrieben.

Publikationen zum Sterilisieren und zur Keimzahlreduktion sind in den folgenden Fundstellen angeführt:

K.H. WALLHÄUSSER (1990) Die mikrobielle Reinheit von Arzneimittelrohstoffen und Arzneimitteln, Pharma Technologie, Vol 11, Nr. 4, Seiten 2 - 9;

H. SEYFARTH (1990) Kritische Anmerkungen zu den Hygieneanforderungen des EG-Leitfadens einer guten Herstellpraxis für Arzneimittel, Pharma Technologie, Vol 11, Nr. 4, Seiten 10 - 19;

W. Hecker und R. MEIER (1990) Bestimmung der Luftkeimzahl im Produktionsbereich mit neueren Geräten, Pharma Technologie, Vol 11, Nr. 4, Seiten 20 - 28;

G. SPICHER (1990) Möglichkeiten und Grenzen der Sterilisation mit Gasen und ionisierenden Strahlen im Vergleich mit den klassischen Sterilisationsverfahren, Pharma Technologie, Vol 11, Nr. 4, Seiten 50 - 56;

Als chemische Sterilisierungsverfahren sind die Behandlung mit Ethylenoxid, Propan-3-olid und Diethyldikarbonat, weiterhin Wasserstoffperoxid und ein Ozon/Dampfgemisch bekannt. Solche Verfahren werden beschrieben in:

G. SPICHER (1990) Möglichkeiten und Grenzen der Sterilisation mit Gasen und ionisierenden Strahlen im Vergleich mit den klassischen Sterilisationsverfahren, Pharma Technologie, Vol 11, Nr. 4, Seiten 50 - 56;

H. HÖRATH (1990) Rechtliche Rahmenbedingungen der Sterilisation mit Ethylenoxid und Formaldehyd, Pharma Technologie, Vol 11, Nr. 4, Seiten 57 - 64;

J. SCHUSTER (1990) Die Praxis der betrieblichen Ethylenoxid-Sterilisation und Versuche zu ihrer Optimierung, Pharma Technologie, Vol 11, Nr. 4, Seiten 65 - 71;

M. MARCZINOWSKI (1990) Praktische Durchführung der Formaldehyd-Sterilisation, Pharma Technologie, Vol 11, Nr. 4, Seiten 72 - 76;

Besonders bevorzugt ist das Verfahren mit Wasserstoffperoxid.

Ebenso ist ein Sterilisieren mit energiereicher Strahlung möglich. Hier sind Gamma-Strahlen und Röntgenstrahlen bekannt. Ebenso werden Neutronenstrahlen, Beta-Strahlen und Alpha-Strahlen eingesetzt.

Gleitmittel dienen dazu, daß der Stopfen ohne größeren Kraftaufwand innerhalb des Zylinders bewegt werden kann. Bevorzugt ist Silikonöl, welches folgende Eigenschaften aufweist: Viskosität mindestens 1000 cSt; Qualität: medical grade.

Nachdem die Spritze teilweise zusammengesetzt worden ist, ist es eventuell möglich, die Spritze erneut von Fremdkörpern zu reinigen. Fremdkörper sind all die Partikel, die nicht aus dem Material der Spritze und dem Medium sind und die losgelöste Bruchstücke der Spritze sind.

Als Sterilisationsverfahren sind besonders geeignet: Strahlensterilisation beziehungsweise chemische Sterilisationsverfahren.

Als chemische Sterilisierungsverfahren sind die Behandlung mit Ethylenoxid, Propan-3-olid und Diethyldikarbonat, weiterhin Wasserstoffperoxid und ein Ozon/Dampfgemisch bekannt.

Ebenso ist ein Sterilisieren mit energiereicher Strahlung möglich. Hier sind Gamma-Strahlen und Röntgenstrahlen bekannt.

Gegebenenfalls werden die Teile der Spritze in bakteriendichte, aber gasdurchlässige Folie oder Aluminium sterilverpackt. Die Sterilisation erfolgt mit Hilfe von thermischem und/oder chemischem Sterilisieren, mit Gamma-Strahlen oder Röntgenstrahlen, Neutronenstrahlen oder Beta-Strahlen oder einem Gemisch

der zuvor genannten Strahlen. Bevorzugt ist die Behandlung mit Wasserstoffperoxid oder Ozon/Dampfgemisch.

Anschließend wird der Spritzenkörper durch das distale oder proximale Ende befüllt, wobei entweder der Stopfen oder der Verschluß das entgegengesetzte Ende abdichten. Anschließend wird die Befüllungsöffnung durch den Verschluß oder den Stopfen verschlossen.

Das distale Ende wird mit einem Verschluß oder durch Verschweißen des distalen Endes verschlossen. Bei dem Verschweißen weist das distale Ende eine Sollbruchstelle proximal zur Verschweißung auf. Dadurch kann das distale Ende problemlos nach dem Verschweißen geöffnet werden.

Im nächsten Schritt wird die Spritze oder Kartusche im Autoklaven oder Sterilisator mit Heißluft oder mittels Mikrowelle thermisch sterilisiert.
Damit der Stopfen nicht innerhalb des Zylinders wandert, ist es vorteilhaft, wenn der Stopfen während des Sterilisierens fixiert ist.
Gegebenenfalls ist es möglich, einen Stützdruck in dem Sterilisationsraum des Autoklaven oder der Sterilkammer durch ein Gas in dem Sterilisationsraum aufzubauen, wobei der Druck auf die Außenoberfläche der Spritze größer, gleich oder geringer als der Druck auf der Innenoberfläche der Spritze ist. Der Stützdruck ist zu definieren als der Druck, welcher der Summe der Partialdrücke im Sterilisationsraum minus dem Partialdruck des Dampfes entspricht.

Vorteilhaft ist, wenn der Stopfen nach dem Sterilisieren rejustiert wird. Hierdurch wird gewährleistet, daß der Stopfen sich in einer optimalen Position befindet. Bisweilen ist die Reibung zwischen Stopfen und Zylinder so groß, daß ein Einstellen des Stopfens in die stabile Position, bei der keine Druckdifferenz zwischen Innenseite und Außenseite der Spritze besteht, nicht selbständig erfolgt.

An dieser Stelle ist eine optische Kontrolle vorteilhaft. Dadurch wird gewährleistet, daß Partikel, die sich in der Spritze befinden, aufgefunden werden. Spritzen mit Partikel sind dabei zu verwerfen.

Besonders wesentlich ist das Verpacken der sterilisierten Spritze in einem Behälter und das Sterilisieren des gefüllten Behälters. Dieser Vorgang kann in einem Sterilraum erfolgen. Dieser Schritt ist besonders vorteilhaft, weil da-

durch allein eine Sicherheit gegeben ist, dem behandelnden Arzt eine Spritze anzubieten, die auch äußerlich steril ist. Hierdurch kann die Kontaminationsgefahr verringert werden. Auch bei den mechanisch zu entleerenden Spritzen kommt dieser Vorteil zur Geltung, da der Arzt auch hier die Spritze berührt. Häufig werden die mechanisch zu entleerenden Spritzen in sterilen Operationsräumen angewendet. In diese Räume dürfen nur sterile oder desinfizierte Materialien eingebracht werden. Somit muß auch eine mechanisch zu entleerende Spritze äußerlich unbedingt steril sein.

Vorteilhaft ist weiterhin, daß die gefüllte und terminal gefüllte Spritze in sterile Kunststoffolie und / oder Aluminiumfolie unter gegebenenfalls aseptischen Bedingungen verpackt wird. Vorteilhaft ist dabei, daß die Spritze in möglicherweise sterile Blister eingepackt wird, wobei gegebenenfalls aseptische Bedingungen vorherrschen.

Anschließend wird die Spritze, die in dem Behälter liegt, äußerlich erneut sterilisiert, indem die Spritze mit Ethylenoxid, Propan-3-olid und/oder Diethyldikarbonat behandelt wird. Weiterhin sind Wasserstoffperoxid und ein Ozon/Dampfgemisch bekannt.

Eine bevorzugte Ausführungsform wird beispielhaft im weiteren dargestellt.
Eine Spritze gemäß der Erfindung wird in der Figur 1 als perspektivische Zeichnung abgebildet.
In der Figur 2 wird eine Schnittzeichnung der Spritze abgebildet.
In der Figur 3 ist ein Flußdiagramm zu sehen, in dem das Verfahren der Herstellung, Sterilisation, Befüllung und des terminalen Sterilisierens dargestellt ist.

Die Figur 1 und 2 zeigen eine Kunststoffspritze 100, die aus einem Spritzenkörper 1 mit einem Spritzenzylinder 2 besteht. Die Spritze 100 weist ein proximales Ende 3 auf, welches durch einen Stopfen 4 verschlossen ist. Der Stopfen weist ein pyramidenförmigen distalen Stopfenteil 5 und einen zylinderförmigen proximalen Stopfenteil 6 auf, der der Innenwandung des Spritzenzylinders 2 dichtend anliegt. Der Kontakt zwischen dem proximalen Stopfenteil 6 und der Zylinderinnenwandung erfolgt über mehrere Gummiwülste 7.
Am proximalen Ende sind Gerätehalterungen 8 an der Außenwand des Spritzezylinders angeordnet, die aus einem Gerätehalterungsring 9 und zwei Gerätehalterungsvorsprünge 10 und 10´ bestehen. Die Gerätehalterungen 8 dienen zum Einspannen der Spritze in eine mechanische Pumpvorrichtung.
Am distalen Ende 11 der Spritze befindet sich ein pyramidenförmige Spritzenauslaßstück 12, welches eine Röhre 13 und ein Endstück 14 umfaßt. Der pyramidenförmige distale Stopfenteil 5 paßt komplementär in das pyramidenförmige Spritzenauslaßstück 12. Zentrisch von dem Spritzenauslaßstück 12 ist die konisch zulaufende Röhre 13 angeordnet, die in dem Endstück 14 endet. Dieses Endstück 14 ist von einem Zylinder 15 umgeben, der auf der Innenseite ein Gewinde 16 für einen Luer - Lock trägt. Das Endstück 14 ist entweder durch ein Spritzenverschlußteil in Form eines Tip - Cap oder durch ein Spritzenverschlußteil mit Luer - Lock verschließbar. Das Spritzenverschlußteil ist in der Zeichnung nicht abgebildet.

In der Figur 3 ist ein Flußdiagramm abgebildet.

51414AWOM1XX00-P 21.5.1997

Patentansprüche

1. Herstellungsverfahren einer vorgefüllten, sterilen Spritze aus Glas oder Kunststoff oder eine Mischung aus Glas und Kunststoff, weiterhin einer Glasspritze mit einer damit verbundenen Kunststoffolie und einer Kunststoffspritze mit einer damit verbundenen Glasbeschichtung,

dabei umfaßt die Spritze

einen zylinderförmigen Spritzenkörper mit einem verschließbaren proximalen und einem verschließbaren distalen Ende,

ein Spritzenauslaßstück am distalen Ende,

ein das Spritzenauslaßstück abdichtenden Verschluß,

einen Stopfen, der in dem Spritzenkörper gleitfähig ist,

dabei ist der Stopfen durch einen Stempel bewegbar,

und

ein fluides und ein gasförmiges Medium,

wobei das fluide Medium eine Flüssigkeit, eine Lösung, eine Suspension oder eine Emulsion ist,

wobei das Verfahren die folgenden Schritte umfaßt:

- Bereitstellen von dem Spritzenkörper, der von Keimen, Pyrogenen und/oder Endotoxinen befreit, sowie partikelarm ist,
- Bereitstellen von dem Verschluß, der von Keimen, Pyrogenen und/oder Endotoxinen befreit, sowie partikelarm ist,
- Bereitstellen von dem Stopfen, der von Keimen, Pyrogenen und/oder Endotoxinen befreit, sowie partikelarm ist,
- Auftragen eines Gleitmittels,
- Abdichten des proximalen Endes durch Einführen des Stopfens in den Spritzenkörper und Befüllen der Spritze durch das distale Ende und Verschließen des Spritzenauslaßstückes mit dem Verschluß oder Verschweißen des Spritzenauslaßstückes,

oder alternativ

Abdichten des distalen Endes durch den Verschluß oder Verschweißen des Spritzenauslaßstückes und Befüllen der Spritze durch das proximale Ende und Abdichten des proximalen Endes durch Einführen des Stopfens in den Spritzenkörper,

- thermisches Sterilisieren in einer Sterilisationskammer,
- Verpacken der sterilisierten Spritze in einem Behälter und

- Sterilisieren der verpackten Spritze mit einer Substanz, die mindestens Teile des Behälters permeiert..

2. Herstellungsverfahren nach Anspruch 1, wobei die Sterilisationskammer ein Autoklav oder Sterilisator, mit Dampf, Heißluft und / oder Mikrowelle ist.

3. Herstellungsverfahren nach einem der vorherigen Ansprüche, wobei ein Stützdruck durch ein Gas in der Sterilisationskammer aufgebaut wird, wobei der Druck auf die Außenoberfläche der Spritze gleich, größer oder kleiner als der Druck auf die Innenoberfläche der Spritze ist.

4. Herstellungsverfahren nach einem der vorherigen Ansprüche, wobei die Spritzen umfassen: Kartuschen, Ampullenspritzen, Einmalspritzen, Einmalspritzampullen, Einwegspritzampullen, Einwegspritzen, Injektionsampullen, Spritzampullen, spritzfertige Ampullen, Zylinderampullen, Doppelkammer-Spritzampullen, Zweikammer-Spritzen, Zweikammer-Spritzampullen, Zweikammer-Einmalspritzen oder Sofortspritzen.

5. Herstellungsverfahren nach einem der vorherigen Ansprüche, wobei der Kunststoff der Polyolefine aus der Gruppe COC, Polymethylpenten und PP ist.

6. Herstellungsverfahren nach einem der vorherigen Ansprüche, wobei die Spritze einen Luer - Lock am distalen Ende aufweist.

7. Herstellungsverfahren nach einem der vorherigen Ansprüche, wobei das Medium in der befüllten Spritze eine Mischung aus einem fluiden Medium und mindestens einem Gas ist.

8. Herstellungsverfahren nach Anspruch 7, wobei das Medium eine Flüssigkeit, eine Lösung, eine Suspension oder eine Emulsion ist.

9. Herstellungsverfahren nach Anspruch 8, wobei das Medium ein Kontrastmittel ist.

10. Herstellungsverfahren nach Anspruch 9, wobei das Kontrastmittel eine Substanz oder eine Mischung aus der Gruppe der folgenden Substanzen umfaßt: Amidotrizoesäure, Gadopentetsäure, Gadobutrol, Gadolinium EOB-DTPA, Iopamidol, Iopromid, Iotrolan und Iotroxinsäure

11. Herstellungsverfahren nach einem der vorherigen Ansprüche, wobei das Sterilisationsverfahren mit Gas die Behandlung mit Ethylenoxid, Propan-3-olid und Diethyldikarbonat, weiterhin Wasserstoffperoxid und ein Ozon/Dampfgemisch umfaßt.

12. Herstellungsverfahren nach Anspruch 11, wobei die Behandlung Wasserstoffperoxid umfaßt.

13. Herstellungsverfahren nach einem der vorherigen Ansprüche, wobei der Stopfen während des Sterilisierens fixiert ist.

14. Herstellungsverfahren nach einem der vorherigen Ansprüche, wobei der Stopfen nach dem Sterilisieren rejustiert wird.

15, Herstellungsverfahren nach einem der vorherigen Ansprüche, wobei die gefüllte und terminal gefüllte Spritze in sterile Kunststoffolie und / oder Aluminiumfolie unter gegebenenfalls aseptischen Bedingungen verpackt wird.

16. Herstellungsverfahren nach Anspruch 15, wobei die Spritze, die in dem Behälter liegt, äußerlich erneut sterilisiert wird, indem die Spritze mit Ethylenoxid, Propan-3-olid, Wasserstoffperoxid, ein Ozon/Dampfgemisch und/oder Diethyldikarbonat behandelt wird. Weiterhin sind bekannt.

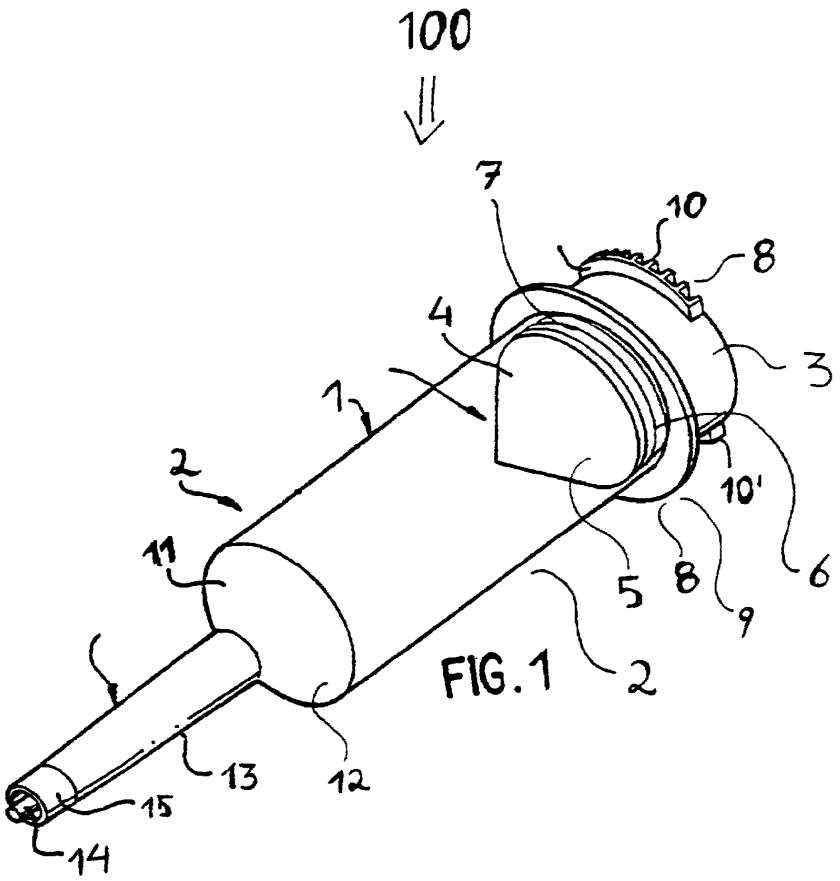

FIG. 1

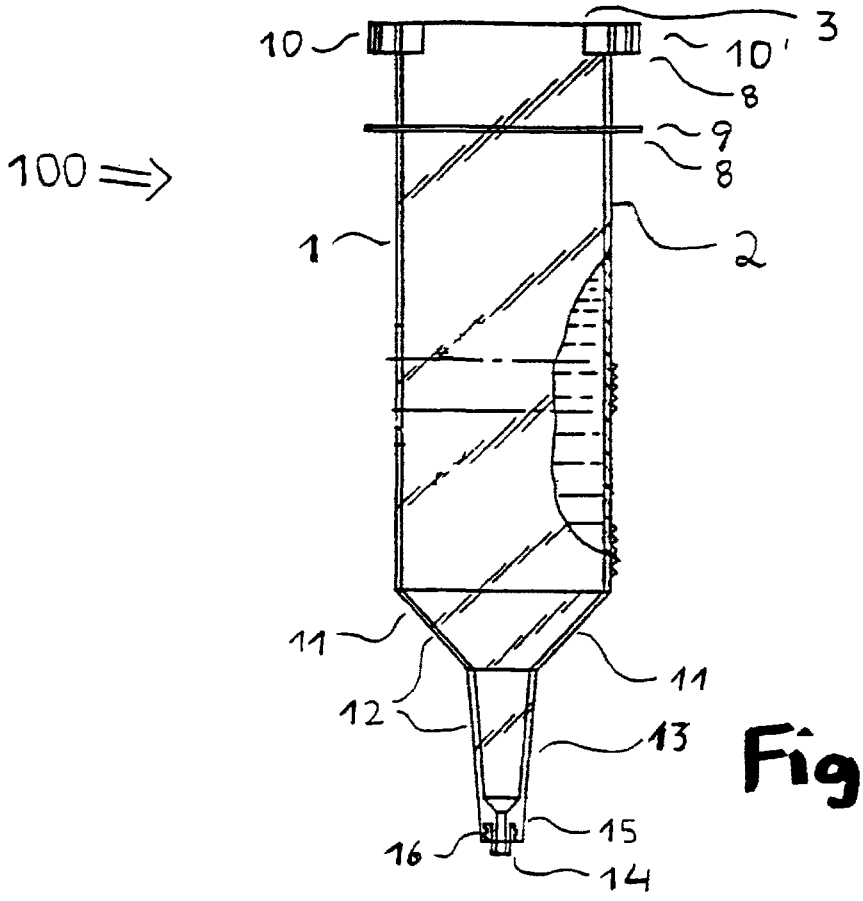

Fig. 2

Figur 3

Herstellung von	Spritzenzylinder mit Spritzenauslaßstück (pyrogenfrei)	Kolben	Verschluß	Medium
	---	Autoklavieren	Autoklavieren	Sterilfiltriert
Einführen des Kolbens in den Spritzenkörper			---	---
Sterilisieren des Kolbens und des Spritzenkörpers			---	---
Weiterverarbeiten, Verpacken und Lagern oder Verpacken und Transportieren				---

Befüllen der Spritze durch das distale Ende
Verschließen der Spritze mit dem Verschluß
Autoklavieren der gefüllten Spritze unter Stützdruck
Abkühlen der Spritze unter Stützdruck
Verpacken der gefüllten Spritze in Behälter
Verschließen der Behälter
Sterilisieren der Behälter mit Gas

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP 97/02641

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L2/04 A61L2/06 A61L2/12 A61L2/20 A61M5/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61M

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 13328 A (MALLINCKRODT MEDICAL INC) 23 June 1994 see abstract see page 4, line 5 - line 9 see page 4, line 15 - line 24 see claims 1-13 see figure 1 ---	1,2,4-16
X Y	WO 95 00180 A (FARCO PHARMA GES MIT BESCHRAEN ;WOLF ERICH (DE)) 5 January 1995 see page 3, line 24 - page 4, line 13 see page 6, line 28 - line 32 see claims 1,4-6 --- -/--	1-8, 13-15 9,10

[X] Further documents are listed in the continuation of box C.

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° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
10 October 1997	17 -10- 1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Heck, G

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP 97/02641

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 628 969 A (JURGENS JR RAYMOND W ET AL) 16 December 1986 see column 1, line 38 - line 64 see column 2, line 24 - line 39 see claims 1-3	9,10
A	US 5 207 983 A (LIEBERT RICHARD T ET AL) 4 May 1993 see column 2, line 8 - line 28 see claims 1,3,4,7,8	1,2,4, 7-9
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International Application No
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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 97/02641

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61L2/04 A61L2/06 A61L2/12 A61L2/20 A61M5/00

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61L A61M

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 94 13328 A (MALLINCKRODT MEDICAL INC) 23.Juni 1994 siehe Zusammenfassung siehe Seite 4, Zeile 5 - Zeile 9 siehe Seite 4, Zeile 15 - Zeile 24 siehe Ansprüche 1-13 siehe Abbildung 1 ---	1,2,4-16
X Y	WO 95 00180 A (FARCO PHARMA GES MIT BESCHRAEN ;WOLF ERICH (DE)) 5.Januar 1995 siehe Seite 3, Zeile 24 - Seite 4, Zeile 13 siehe Seite 6, Zeile 28 - Zeile 32 siehe Ansprüche 1,4-6 ---	1-8, 13-15 9,10
	-/--	

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

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1

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
10.Oktober 1997	17-10-1997
Name und Postanschrift der Internationalen Recherchenbehörde Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	**Bevollmächtigter Bediensteter** Heck, G

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 97/02641

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
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PCT/EP 97/02641

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(19) Europäisches Patentamt
European Patent Office
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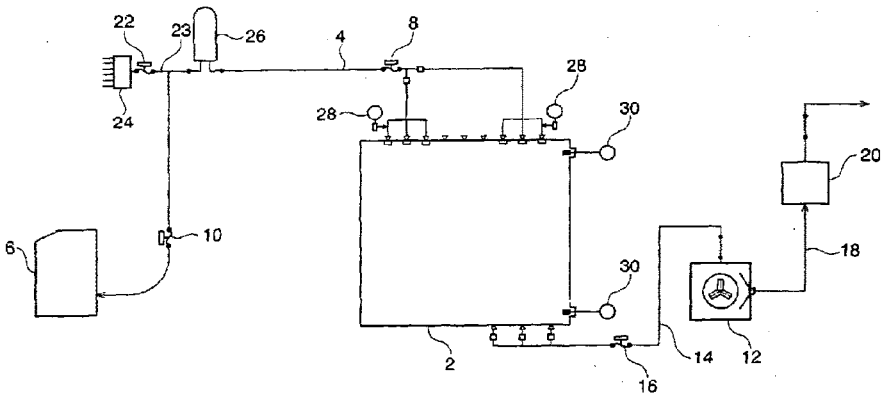
(54) METHOD FOR MANUFACTURING SEALING TOOL STERILIZED WITH GASEOUS HYDROGEN PEROXIDE

(57) It is an object to establish a sterilization condition and means for decreasing the amount of a remaining sterilization agent as much as possible after sterilizing a rubbery sealing tool. In a sterilizing method using gaseous hydrogen peroxide, a filling rate of a sample in a sterilization bag for a normal type is set to 45 % or more and a sterilization condition is set to a hydrogen peroxide treatment of 3 pulses and an aeration pulse of 20 pulses, thereby carrying out a sterilization treatment. Furthermore, it is preferable that a volume rate in a bag of an outer bag accommodating the sterilization bag should be set to 55 to 12 %. By such setting, a survival ratio of 0/10 of a bacteria cell could be realized at first to fifth times of repetition of the sterilization treatment.

Fig. 1



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Description

Technical Field

[0001] The present invention relates to a method for the production of a variety of sealing tools sterilized with gaseous hydrogen peroxide. More specifically, the present invention pertains to a method for the production of a sterilized sealing tool, which comprises the step of sterilizing a sealing tool such as a cap, a gasket for a piston or a plunger head inserted into an injection cylinder such as a syringe, a tool for preventing liquid leakage such as rubber boots and an elastic ring for a bushing or for fitting a joint such as an O-ring, with hydrogen peroxide vapor, a hydrogen peroxide-containing gas, or an aerosol of hydrogen peroxide obtained by, for instance, the atomization of a hydrogen peroxide solution.

Background Art

[0002] Conventionally, the sterilization of, in particular, machinery and tools for medical use have been carried out, for a long time, according to the dry sterilization and the sterilization by boiling in hot water. Thereafter, the level of the sterilization has been further improved because of the development of the pressurized steam-sterilizing device. In this connection, there have been developed and put into practical use the ethylene oxide gas (hereunder abbreviated as "EOG") sterilization, the γ-ray-irradiation sterilization and the electron beam-irradiation sterilization for treating the articles to be processed, to which none of the foregoing sterilization methods can easily be applied.

[0003] In this regard, the treatment with ethylene oxide gas (EOG) is advantageous in that the gas can penetrate even into fine spaces of articles to be processed, but it has been found that this treatment suffers from the following problems:

First, a considerable amount of the sterilization agent and, for instance, ethylene glycol (hereunder abbreviated as "EG") and/or ethylene chlorohydrin (hereunder abbreviated as "ECH") derived from the sterilization agent remain on the articles thus treated even after the sterilization treatment and as a result, a serious problem has been indicated such that this would be involved in the production of cancer.

[0004] Moreover, the γ-ray-irradiation sterilization requires neither the exposure of articles to be processed to any high temperature nor the drying thereof after being wetted with a liquid and is excellent in that this treatment permits the sterilization of an article having a complicated shape and even the shaded portions thereof while making the most use of the high penetrability and that the γ-rays per se is colorless, odorless and tasteless. The electron beam (cathode rays) has a penetrability inferior to that of the γ-rays, but the sterilizing power thereof while making use of the ability of ionizing the object to be treated has sufficiently been highly estimated.
However, the γ-rays and the electron beams belong to the high energy radioactive rays and for this reason, the practical use thereof has been restricted since the irradiation of an article with γ-rays or electron beams may easily deteriorate the surface area or the like of the article and a personnel who handles them must be authorized by the license for the licensed engineer of radiation.
Japanese Un-Examined Patent Publication No. Hei 10-24093 (prior reference 1) discloses a sterilization device, which makes use of gaseous hydrogen peroxide and a sterilization treatment, which makes use of a combination of three members: a transfer box, a sterilization chamber and a sterilized container.
This prior reference 1 discloses in the section entitled "Technical Field of the Invention" as follows: the present invention relates to a sterilization device and more particularly to a sterilization device for sterilizing the surface of an article, for instance, a small-sized container from a synthetic resin such as a container for ophthalmic medicaments or other small-sized molded articles from synthetic resins.

[0005] In addition, the prior reference 1 cites, in the section "[0004]", Japanese Examined Patent Publication No. Sho 60-8826 as a prior art technique for this invention, refers to the following passage from the section of the reference entitled "Method for Washing, Sterilizing and Drying Rubber Stoppers for Vials": the following steps are successively conducted: a degassing step, a washing step, a foreign substance-eluting step, a rinsing and washing step and a highly pressurized steam-sterilization step in which highly pressurized steam maintained at a temperature and pressure at which the rubber stoppers for vials are not deteriorated is introduced into a steam sterilizer to thus sterilize the rubber stoppers for vials and thus indicates that the pressurized steam-sterilization of "the rubber stoppers for vials" is conducted in the invention of the foregoing cited reference.

[0006] However, the prior reference 1 does not directly disclose a method for sterilizing "the rubber stoppers for vials" with gaseous hydrogen peroxide. More specifically, the prior reference 1 neither refers to nor suggests any specific method for sterilizing rubber stoppers (for vials) or rubber caps with gaseous hydrogen peroxide and specific conditions for the sterilization, but the prior reference simply and specifically describes, in the latter half of the specification, the sterilization device using "containers for ophthalmic medicaments".

[0007] As a sterilization technique, which has attracted special interest lately, there may be listed, for instance, a gas-irradiation combined method in which gaseous hydrogen peroxide is injected under a high vacuum (about 0.04 kPa) and thereafter an object is irradiated with plasma beams (charged corpuscular flow).

[Problems That the Invention is to Solve]

[0008] A variety of the foregoing conventional techniques may permit the sterilization of microorganisms attached just to the surface of an article to be processed, with difficulty, but this technique cannot sufficiently kill the microorganisms penetrating into the slightly interior region of the article to be processed. More specifically, there are, in fact, many fine and uneven portions on the surface of a sealing tool such as a rubber stopper and therefore, microorganisms inevitably penetrate into these fine concave portions of the article. However, the conventional sterilization methods using gaseous hydrogen peroxide or hydrogen peroxide vapor cannot kill the microorganisms concealed in these fine concave portions of the article to such an extent that the presence of microorganisms can be neglected.

[0009] The present invention is rather an improved technique of those disclosed in the foregoing prior references 1, 2 and 3, completed by investigating the scope of application thereof on the basis of these prior references. However, the purpose of the present invention is to provide a specific sterilization procedure, a sterilizing condition and the like which use gaseous hydrogen peroxide when applying, to a rubber gasket and other sealing tools, an effective sterilizing method and sterilizing condition which have been neither described nor suggested in any of the prior references. More specifically, it is a purpose of the present invention to provide a method for sterilizing a sealing tool and a sealing tool sterilized using the method. As a result of serious investigations of the procedure and condition and the like, the present inventor completed the present invention.

[Means for Solving the Problems]

[0010] According to the present invention, the desired effects or intended purposes of the present invention can be accomplished by combining the following essential elements:

(1) A method for the production of a sealing tool for setting a filling rate in a sterilization bag for a sample to be sterilized to 45 % or more for a gasket for a normal type syringe and to 20 % or more for a gasket for a large-sized syringe, thereby carrying out sterilization in the case in which a rubbery sealing tool or a sealing tool made from an olefinic resin is held as an article to be processed in a sterilization unit under a high vacuum, gaseous hydrogen peroxide is then introduced into the sterilization unit, and is held for a predetermined time and is sterilized by at least one member selected from the group consisting of active oxygen and radial hydroxide, a clean gas is thereafter introduced and is held for a predetermined time to cause a sterilizing substance to penetrate into an inner side of the article to be processed, thereby setting a sterilizing condition using the gaseous hydrogen peroxide in which a sterilization treatment for the article to be processed is one sterilization pulse to a combination of 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 3 pulses and 20 pulses of an aeration. An aqueous hydrogen peroxide solution (normally a concentration of 35 % by weight) is injected in a predetermined amount [for example, 70 (g/pulse)] into a hydrogen peroxide gas generating device, and is changed into gaseous hydrogen peroxide in the generating device and is introduced into a sterilizer (or a sterilization chamber) through a supply conduit, and then comes in contact with a sample. Thus, the gaseous hydrogen peroxide fulfills the function of oxidizing and sterilizing the sample.

(2) The method for the production of a sealing tool as set forth in the foregoing item 1, wherein the filling rate of the sample to be sterilized which is accommodated in the sterilization bag is set to 50 % or more for a gasket for a normal type syringe and to 20 % or more for a gasket for a large-sized syringe under the sterilization condition, thereby carrying out the sterilization.

(3) A method for the production of a sealing tool, wherein in the case in which a sterilization condition is set to a combination of 70 (g/pulse) of an injected amount of an aqueous hydrogen peroxide solution X 4 pulses and 20 pulses of an aeration, a filling rate of a sample to be sterilized in a sterilization bag is set to 20 % or more for a gasket for a normal type syringe or a gasket for a large-sized syringe, thereby carrying out the sterilization.

(4) The method for the production of a sealing tool as set forth in any one of the foregoing items 1 to 3, wherein the number of repetitions of the aeration pulse to be carried out next to a sterilization pulse in the sterilization treatment is 30 pulses or more.

(5) The method for the production of a sealing tool as set forth in any one of the foregoing items 1 to 3, wherein the number of repetitions of the aeration pulse is 5 to 50 pulses or more.

(6) The method for the production of a sealing tool as set forth in any one of the foregoing items 1 to 4, wherein the sterilization pulses and the aeration pulses are, in advance, conducted in combination.

(7) The method for the production of a sealing tool as set forth in any one of the foregoing items 1 to 5, wherein

an outer bag further accommodating the sterilization bag having the article to be processed is mounted in a porous container for mounting with a volume rate of 12 to 55 %, thereby carrying out the sterilization treatment.

(8) The method for the production of a sealing tool as set forth in any one of the foregoing items 1 to 5, wherein the article to be processed is at least one member selected from a rubber cap, a rubber gasket, a gasket for a piston (plunger) to be inserted into an injection cylinder (syringe), a tool for preventing liquid leakage such as rubber boots, and an elastic ring for a bushing and for fitting a joint.

(9) The method for the production of a sealing member as set forth in any one of the foregoing items 1 to 7, wherein rubber is at least one member selected from the following conjugated diene rubber and non-conjugated diene rubber: the conjugated diene rubber being natural rubber, a variety of synthetic rubber materials, blends of each comprising at least two of these natural and synthetic rubber materials and copolymer rubber comprising repeating units of these rubber materials and other repeating units copolymerizable therewith, wherein the synthetic rubber comprises 1,4-cis-polyisoprene rubber obtained by 1,4-addition polymerization of isoprene, which is a repeating unit mainly constituting the natural rubber, 1,4-cis-polybutadiene rubber and isobutene-isoprene copolymer rubber; the non-conjugated diene rubber being copolymer rubber materials of at least two 1-olefins or multi-component copolymer rubber materials obtained by copolymerizing these monomers with third non-conjugated dienes, wherein the copolymer rubber materials of at least two 1-olefins is at least one member selected from the group consisting of ethylene-propylene (copolymer) rubber, ethylene-1-butene copolymer rubber and propylene-1-butene copolymer rubber, and wherein the multi-component copolymer rubber obtained by copolymerizing these monomers with a third non-conjugated diene is at least one member selected from the group consisting of ethylene-propylene-1,4-hexadiene copolymer rubber, ethylene-propylene-methylene norbornene copolymer rubber and ethylene-propylene-ethylidene norbornene copolymer rubber.

(10) The method for the production of a sealing tool as set forth in any one of items 1 to 8, wherein the thermoplastic elastomer (thermoplastic rubber) is a polymer or a kneaded composition (kneaded mixture) of at least two polymers, which simultaneously has characteristic properties of thermoplastic resin and elastomer; the polymer composition, which can be formed into a variety of shapes as set forth in the molding method applicable to the resin and can be subjected to vulcanization treatment (crosslinking treatment) applicable to the elastomer, is at least one kneaded composition selected from the group consisting of kneaded compositions of polyolefin resins and ethylene-propylene (copolymer) rubber, kneaded compositions of polyolefin resins and ethylene-propylene-non-conjugated diene copolymer rubber and kneaded compositions of propylene-1-butene copolymer resins and ethylene-propylene-non-conjugated diene copolymer rubber.

(11) The method for the production of a sealing tool as set forth in any one of items 1 to 9, wherein the thermoplastic elastomer is a thermally kneaded composition comprising at least one member selected from the group consisting of polyethylene resins, polypropylene resins, poly-1-butene resins, poly-4-methyl-1-pentene resin and poly-1-hexene resins; and at least one member selected from the group consisting of ethylene-propylene-1,4-hexadiene copolymer rubber, ethylene-propylene-methylene norbornene copolymer rubber and ethylene-propylene-ethylidene norbornene copolymer rubber.

[Brief Description of the Drawings]

[0011] Fig. 1 is a schematic circuit diagram showing a preferred embodiment of the sterilization device according to the present invention. Fig. 2 is a chart or a flow diagram showing an example of the sterilization cycle according to the present invention, in which the time is plotted as abscissa (10 min/scale) and the internal pressure of the device is plotted as ordinate, and the pressure is expressed in terms of kPa (Torr) unit. Fig. 3 shows the correlation between the storage time after the completion of the sterilization and the concentration of the residual hydrogen peroxide, in which the storage time (day) is plotted as abscissa, while the residual hydrogen peroxide concentration (μg/g) is plotted as ordinate. Fig. 4 shows the correlation between the degassing time (h) and the residual EO concentration (μg/g) observed on a sample when using ethylene oxide gas (EOG) as a conventional sterilization agent, in which the degassing treatment time (h) is plotted as abscissa and the residual EO concentration (μg/g) is plotted as ordinate. Fig. 5 shows the correlation between the degassing time (h) and the residual EG concentration (μg/g) observed when using EOG as a conventional sterilization agent, in which the degassing treatment time (h) is plotted as abscissa and the residual EG concentration (μg/g) is plotted as ordinate. Fig. 6 shows the correlation between the degassing time (h) and the residual ECH concentration (μg/g) observed when using EOG as a conventional sterilization agent, in which the degassing treatment time (h) is plotted as abscissa and the residual ECH concentration (μg/g) is plotted as ordinate.

1 Sterilization device (whole) used in the method according to the present invention;
2 Sterilization treatment unit (sterilization chamber);
4 Gaseous hydrogen peroxide supply conduit;
6 Gaseous hydrogen peroxide supply device;

8 Switching valve fitted to the gaseous hydrogen peroxide supply conduit on the side of the sterilization chamber;
10 Switching valve fitted to the gaseous hydrogen peroxide supply conduit on the side of the gaseous hydrogen peroxide supply device;
12 Vacuum pump (aspiration means);
14 Evacuation conduit;
16 Switching valve fitted to the evacuation conduit on the upstream side of the vacuum pump;
18 Switching valve fitted to the delivery conduit on the downstream side of the vacuum pump;
20 Catalyst charged in the delivery conduit;
21 Sterilization bag (sterilization basket; not shown);
22 Separate switching valve positioned between two switching valves fitted to the gaseous hydrogen peroxide supply conduit and communicated to the air-intake opening;
23 Extended conduit for connecting the separate switching valve and the air-intake opening;
24 Air-intake opening;
26 Sterilizing filter;
28 manometer for detecting the internal pressure of the sterilization chamber;
30 Thermometer for detecting the internal temperature of the sterilization chamber.

[Best Mode for Carrying out the Invention]

<As to the Gaseous hydrogen Peroxide>

[0012] The term "gaseous hydrogen peroxide" used for carrying out the method for the production of a sealing tool by sterilization according to the present invention includes hydrogen peroxide vapor, a hydrogen peroxide-containing gas or an aerosol of hydrogen peroxide prepared by, for instance, atomization of a hydrogen peroxide solution.

[0013] In this respect, the hydrogen peroxide vapor means an oxidizing gas mainly comprising a hydrogen peroxide gas volatilized from a hydrogen peroxide aqueous solution having a concentration of not less than 30% by weight, preferably, 35% by weight and the hydrogen peroxide aqueous solution generates a hydrogen peroxide gas exhibiting even higher oxidation power as the concentration of the solution increases. In other words, the higher the content of hydrogen peroxide molecules in the vapor thus generated, the higher the efficacy of the vapor as the sterilization agent. Referring to such a sterilization action, it is understood that hydrogen peroxide molecules are decomposed on the sterilization conditions and generates at least one of the group consisting of active oxygen and hydroxide radical, the active oxygen or hydroxide radical thus generated or both of them exert(s) an oxidization action on the intended bacteria cells and the like which are to be oxidized and decomposed. For example, the "concentration of 35% by weight" is not restricted to a very precise value but usually means a concentration band having a flow with the "concentration of 35% by weight (or 35 wt%).

[0014] In addition, the hydrogen peroxide-containing gas herein used also includes an oxidizing gas entrained by an inert gas stream obtained when such an inert gas, in general, a gas inert to hydrogen peroxide such as nitrogen gas and air is passed through a hydrogen peroxide aqueous solution.

[0015] Moreover, the term "an aerosol of hydrogen peroxide prepared by atomization of a hydrogen peroxide solution" used in another embodiment of the method for the present invention means a gas-liquid mixed system obtained by converting an aqueous hydrogen peroxide solution into fine droplets, using an atomizer as an atomizing device to such an extent that the resulting aerosol is almost identical to a gas. The effect thereof as an oxidizing agent is likewise substantially identical to that observed for the gaseous hydrogen peroxide.

<As to Conditions of Sterilization Treatment>

[0016] The conditions of the treatment to be used in the present invention depends on the size of a sample to be treated, a filling rate in a sterilizing device, the state of a surface of the sample, and the concentration of gaseous hydrogen peroxide to be used and the number of sterilization pulses.

[0017] According to the experiment of the present inventor, it was observed that a survival ratio (a survival ratio of bacteria cells) is rather low when a filing rate of the sample in a sterilization bag is high, and the survival ratio tends to be increased if the filling rate is reduced (second to fifth embodiments).

[0018] As a result of investigations of a sterilization bag to be used for accommodating a sample to carry out a sterilization treatment, an outer bag for further accommodating the sterilization bag having the sample, a porous container (for example, a basket) for housing the outer bag accommodating the sterilization bag having the sample and having an opening sealed in a sterilizing device (a sterilizer) by a stacking process, and a process for mounting the outer bag in the porous container (the number of the outer bags and the presence of a dummy bag), it was observed that the survival ratio also tends to be reduced (the sterilization effect is increased) with a reduction in a rate (a volume

rate) of a volume (an outer volume) of the sterilization bag to an inner volume of the porous container (sixth embodiment).

<As to Materials for Articles to be processed>

[0019] Articles (subjects to be processed) treated by the sterilization method according to the present invention are not restricted to any particular one, but favorably used herein include a variety of sealing tools since if the sterilization method for the present invention is applied thereto, the desired effects of the present invention can be ensured. As materials for these sealing tools, there may be listed, for instance, glass, ceramic wares and metals whose surface is hard and smooth, since it is very easy to achieve conspicuous effect of the present invention in case where the method is applied to these sealing tools having smooth and hard surface.

[0020] On the other hand, the results of the amount of hydrogen peroxide remaining in an article to be processed such as a sealing tool, a container, a joint, a cap or a plunger, which is formed from a resin and whose surface gives such an impression that it is apparently hard, variously vary depending on the kinds of resins used immediately after the sterilization treatment (through an aeration stage) or after several days from the treatment. In general, it has been found that the residual amount of hydrogen peroxide is substantially small if using a polyolefin resin (PO; 1-olefinic resin) such as polyethylene (PE) or polypropylene (PP) and poly(tetrafluoroethylene) (PTFE) as such a resin material and therefore, these resins can suitably be used in the present invention.

[0021] If the sealing tool is formed from a soft material such as rubber (an elastomer) or a thermoplastic elastomer (thermoplastic rubber; TPE or TPR), however, the sterilization effect is rather lower than expected. The reason of this has not yet been clearly elucidated, but it would be most probable that this is because the formation of a large number of fine unevenness on the surface (exterior).

[0022] As has been discussed above, the usual sterilization treatment with liquid hydrogen peroxide hardly kills the microorganisms penetrated into the interior of an article to be processed slightly behind the surface thereof. In this connection, it would be estimated that microorganisms may easily penetrate into the interior of a soft material such as rubber (an elastomer) or a thermoplastic elastomer (thermoplastic rubber), while hydrogen peroxide as a sterilization agent hardly penetrates into the interior thereof as compared with microorganisms and accordingly, it would be difficult that the sterilization agent is brought into contact with such microorganisms.

[0023] The foregoing rubber (or elastomer) material can roughly be divided into the conjugated diene rubber and the rubber other than the conjugated diene rubber (the non-conjugated diene rubber).

- Examples of conjugated diene rubber materials are natural rubber (NR), a variety of synthetic rubbers, blends of at least two members selected from these natural and synthetic rubber materials or copolymer rubber materials comprising repeating units of these rubber materials and other repeating units copolymerizable therewith. Specific examples of synthetic rubber materials are 1,4-cis-polyisoprene (IR) rubber obtained by 1,4-addition polymerization of isoprene, which is a repeating unit mainly constituting the natural rubber, 1,4-cis-polybutadiene rubber (BR) and isobutene- isoprene copolymer rubber (IIR; also referred to as "butyl rubber"). In this respect, halogen-substituted, in particular, chlorine-substituted derivatives of the foregoing various rubber materials have likewise widely been employed. Preferred examples thereof are chlorobutyl rubber materials.
- The non-conjugated diene rubber is a copolymer rubber material of at least two 1-olefins or a multi-component copolymer rubber material obtained by copolymerizing these monomers with a third non-conjugated diene monomer. Specific examples thereof are listed below.

[0024] The copolymer rubber material of at least two 1-olefins is, for instance, ethylene-propylene copolymer rubber (EPM), ethylene-1-butene copolymer rubber (EBM) or propylene-1-butene copolymer rubber (PBM).

[0025] The multi-component copolymer rubber (EPDM) obtained by copolymerizing at least two 1-olefins with a third non-conjugated diene is, for instance, ethylene- propylene-1,4-hexadiene copolymer rubber, ethylene-propylene-dicyclopentadien, ethylene-propylene-methylene norbornene copolymer rubber and ethylene-propylene-ethylidene norbornene copolymer rubber.

[0026] On the other hand, the thermoplastic elastomer (thermoplastic rubber) is a polymer simultaneously having characteristic properties of both the thermoplastic resin and the elastomer. More specifically, it can be formed into a variety of shapes depending on the molding processes selected and can be subjected to a vulcanization treatment (crosslinking treatment), which is usually applied to the elastomer. For this reason, the molded body obtained from the thermoplastic rubber is flexible, not so low as to the rubber material itself, but the rubber component alone is not extracted from the thermoplastic rubber material by solvent extraction thereof. This would be because the resin moiety and the elastomer moiety of the thermoplastic rubber are chemically bonded together. If it is difficult to make an elastomer material crosslinked, however, the thermoplastic rubber material also includes those obtained by kneading resins with elastomers free of such crosslinking therebetween.

[0027] In addition, if the elastomer moiety has an ability of crosslinking, but the degree of crosslinking seems to remain relatively low, however, such crosslinking is in general referred to as "partial crosslinking" or "half crosslinking".

[0028] Various kinds of thermoplastic elastomers (TPE; or TPR: thermoplastic rubber materials) can be used in the sterilization method for the present invention as the material for the article to be processed. However, suitably used herein are, from the practical standpoint, partially crosslinked (or half-crosslinked) olefinic thermoplastic elastomers prepared by kneading, at a high temperature, a composition (or a mixture) containing thermoplastic polyolefin resins (PO) and multi-component copolymer rubber (EPDM) materials or further kneading the foregoing composition at a vulcanization temperature in the coexistence of a radical initiator (a crosslinking agent or a vulcanizing agent) such as a peroxide.

[0029] Examples of these olefinic thermoplastic elastomers (TPO) include those comprising, as ingredients, a combination of a polyolefin resin (PO) such as a polyethylene resin (PE) with an ethylene-propylene-ethylidene norbornene copolymer rubber (E-P- ENB) material; a combination of a polyethylene resin (PE) with an ethylene-propylene- methylene norbornene copolymer rubber (E-P-MNB) material; and a combination of a polyethylene resin (PE) with an ethylene-propylene-1,4-hexadiene copolymer rubber (E-P-HXD) material; as well as the foregoing various combinations in which the polyethylene resin (PE) component is replaced with at least one member selected from the group consisting of polypropylene resins (PP) and propylene-1-butene copolymer resins.

[0030] The sterilization method according to the present invention, which makes use of gaseous hydrogen peroxide, permits the substantially effective sterilization of even the foregoing microorganisms penetrated into the interior of the article to be processed, whose extermination has conventionally been considered to be quite difficult.

<Kinds of Articles to be Processed>

[0031] Specific examples of the articles to be processed include wide variety of articles such as rubber stoppers (rubber gaskets), rubber caps, rubber gaskets, gaskets (also referred to as "plunger rubber") for pistons (or plungers) inserted into injection cylinders (syringes), tools for preventing liquid leakage such as rubber boots and elastic rings for bushing, sheath, sleeves and for fitting (interposition) joints, for instance, O-rings (O-rings and rings having an approximately circular cross section). The foregoing "rubber stoppers" mainly includes gaskets for syringes (injection cylinders). In this connection, the articles to be processed according to the process of the present invention may likewise include tools of glass, metals, ceramics (including ceramic wares) and plastics as well as the sealing tool. In case where these tools have porous inner surfaces (porous wall surfaces), however, the walls thereof, which come in contact with the sterilization agent, are preferably treated, in advance, so that they can block any penetration of the sterilization agent. This is because, if the walls are not pre-treated, the removal of the residue after the sterilization often requires a great deal of labor. In order to prevent hydrogen peroxide from remaining after the treatment, particularly, it is important that inner wall surfaces (to be treated) of the tools are not hydrophilic.

[0032] The term "rubber" or "rubbery" frequently used in the present invention means isobutene-isoprene copolymer rubber (abbreviated as "IIR"; common name: "butyl rubber"). This copolymer rubber (IIR) is excellent, in particular, in the gas-barrier ability and accordingly, it has widely been used in the field of goods for medical use. However, silicone rubber (SR) and fluororubber may be used in special cases since the former is excellent in self-lubricating properties and has high temperature stability and chemical stability (resistance to chemicals) as compared with the butyl rubber (IIR) and the latter surpasses the quality of the silicone rubber. The "butyl rubber" used in the present invention also includes those commonly referred to as "butyl rubber" (this is in fact chlorobutyl rubber or butyl rubber obtained by at least partially substituting a large number of hydrogen atoms bonded to the IIR molecular chain with chlorine atoms).

[0033] Preferred embodiments according to the present invention will hereunder be described in more detail with reference to the accompanying drawings and Tables given below. However, the present invention is not limited to the scope of these specific embodiments at all.

[Description of the Invention Based on the Drawings]

[0034] The present invention will hereunder be described more specifically with reference to the drawings attached hereto. However, the present invention is by no means limited by the following description and the accompanying drawings.

<Sterilization (Treatment) Unit>

[0035] A large number of rubbery sealing tools as the articles to be processed are in general accommodated in the body of a sterilization chamber (another name: "sterilization unit" : sterilizer or sterilizer device) 2. In case where the rubbery sealing tool is a stopper or plug having a tubular or columnar shape, it is sufficient that the sterilization chamber (sterilizer) 2 is a hollow body having an inner volume generally ranging from 50 to 30000 L (0.05 to 30 m^3) and preferably

1000 to 150000L (1 to 150 m^3).

[0036] Gaseous hydrogen peroxide is fed to the sterilization chamber 2, through a conduit 4 for the introduction of the gaseous hydrogen peroxide (hereunder abbreviated as "introduction conduit") fitted thereto on the upstream side. This gaseous hydrogen peroxide sterilizes the articles to be processed in the chamber and after the elapse of a desired mean retention time, it is discharged through a suction conduit (discharge conduit) 14 fitted to the sterilization chamber on its downstream side.

[0037] In the interior of the sterilization chamber 2, rubber stoppers (not shown; a tubular shape having the foregoing specifications; total number: 36000) as the articles to be processed are accommodated in sterilization bags (not shown; each containing about 500 articles) and every 50 sterilization bags are, in order, arranged within the sterilization chamber 2, so that they come close to one another and extend from the upstream side (top plate side) towards the downstream side (bottom plate side).

[0038] It is preferred to control the degree of the opening or vacant space (space ratio), which is defined to be a rate of the space within the sterilization chamber 2 (inner volume: about 8.6 m^3) other than that occupied by the articles to be processed and, in case where means for putting or suspending the articles is used, occupied by both the articles and the means, in general ranges from 10 to 85% and preferably 50 to 70%.

[0039] In the present invention, it is preferred to pass gaseous hydrogen peroxide having a hydrogen peroxide concentration ranging from 0.5 to 4.0 mg/L (Liter), preferably 1.5 to 2.5 mg/L through the sterilization chamber 2 at an average flow rate ranging from 1000 to 10000 L/min and preferably 3000 to 5000 L/min. The sterilization chamber 2 is appropriately maintained at a mean internal temperature ranging from 15 to 55°C, preferably 20 to 40°C and at an average pressure ranging from 0.002 to 0.04 atm, preferably 0.005 to 0.015 atm.

[0040] If the sterilization treatment is carried out in this sterilization chamber 2 under the foregoing treating conditions for an average treating time ranging from 30 to 240 min, preferably 45 to 120 min, the viable count of bacterial cells: Bacillus Stearothermophilus ATCC 12980 remaining on the surface of the rubber stopper can be reduced to SAL = 10EXP(-6) (= 10^{-6}).

<Volume Rate in Sterilization Unit (Sterilizer; Sterilization Chamber>

[0041] It is preferable that a sterilization bag should not be exactly mounted in a sterilization device but be mounted in a state of accommodation in an outer bag. The outer bag is further mounted in a porous container and a gaseous sterilization agent penetrates from an upper opening of the outer bag through a bottom and a side wall of the container and penetrates into the sterilization bag from a bottom surface in contact with the outside of the sterilization bag. In the sterilization bag, moreover, the sterilization agent penetrates into the bag from a bottom portion so that the sterilization agent gas can uniformly permeate into the bag easily. More specifically, the sterilization agent can fully come in contact with the surface of a sample accommodated in the sterilization bag. A box-shaped container referred to as a basket is usually used as a porous container conveniently. The box-shaped container has an advantage that it can be stacked in multistage and the limited floor area can be utilized very effectively.

[0042] The sterilization bag (inner bag) usually used is a polyolefin synthetic paper, for example, a gazette type bag formed of a polyethylene synthetic paper or a flat bag formed of a polyethylene synthetic paper, and a layer thereof is constituted by a three-layer laminated film in which a polyethylene (PE) layer and a polypropylene (PP) layer are laminated on a base layer [trade name : Tyveck 1073B (produced by Du Pont Co., Ltd.)]. The bag has three kinds of lengths and has a normal outer dimension of a width 380 mm X a thickness (upward 80 mm + downward 80 mm) X a length 350 mm, 500 mm or 800 mm. It is sufficient that the outer dimension of an outer bag formed of polyethylene having a low density further accommodating a sterilization bag having a sample to be sterilized (the sterilization bag containing the sample) can fully accommodate the sterilization bag containing the sample.

[0043] In other words, the outer dimension of the outer bag is properly selected according to the standards of the sterilization bag. For reference, an outer bag which is used most often has an outer dimension of a length 900 mm X a width 750 mm and has a mean thickness of 0.04 mm. The outer bag to be used most often is a flat polyethylene bag. As a matter of course, it can be approved that the outer dimension of the outer bag has a tolerance of approximately ±10%.

[0044] It is premised that the basket to be usually used as a porous container for mounting the outer bag having the example can stand the weight of the mounted article and a self-weight and has such a strength as to stand the loads of the basket stacked thereon and the mounted article when it is piled up. In addition, it is premised that such a reduction in the strength as to make troubles is not generated even if the basket is exposed to a hydrogen peroxide gas (gaseous hydrogen peroxide) for a long time. Accordingly, it is preferable that the material of the basket should be a synthetic resin, particularly, a synthetic resin rarely containing an unsaturated linkage, a fiber-reinforcedmaterial or a metal. While a mineral fiber such as a glass fiber, a carbon fiber or a metallic fiber is suitable for the fiber for reinforcement, a fiber made from a synthetic resin can also be used for the reinforcement depending on circumstances. In this case, the synthetic resin fiber for the reinforcement may be made from a thermosetting resin or a thermoplastic resin and it is

desirable that a crystal melting point or a softening point of the latter resin should be much higher than that of a base resin (matrix resin), for example, should be higher by 10°C or more, preferably 20°C or more.

[0045] The basket used in the present invention is classified into three types for each content, and a basket 1 (inner volume : 45 L) , a basket 2 (inner volume : 62 L) and a basket 3 (inner volume : 161 L) are employed.

[0046] Two outer filled bags are mounted in parallel in the baskets. An experiment is carried out in a sixth embodiment and the result thereof is shown in Table 8.

[0047] It is defined that a volume rate (%) = an outer volume (an occupied volume) of a filled outer bag / an inner volume of a basket is set. The interpretation of data in the Table 8 based on the definition of the volume rate is as follows:

- A survival ratio could not be always set to 0/10 for the number of times of sterilization of 1 to 5 with a volume rate to be a maximum set value of 67 %.
- However, the survival ratio could be set to 0/10 for the number of times of sterilization of 1 to 5 with a volume rate of 48 % and 16 %.

<Sample Filling Rate in Sterilization Bag>

[0048] According to the investigation of the present inventor, a ratio (a filling rate) of the sample to be sterilized in the sterilization bag is shown in Tables 4 to 7. The following is apparent from the Tables 4 to 7:

[0049] In the case in which a gasket for a normal type syringe (VF1 : outer diameter 7 mm X overall height 6 mm ; VF3 : outer diameter 9 mm X overall height 8 mm ; VF5 : outer diameter 12 mm X overall height 10 mm) is to be filled in the sterilization bag, it is desirable that a filling rate should be set to 45 % or more, preferably, 50 % or more in order to always cause a survival ratio to reach 0/10 in the sterilization treatment in which the sterilization condition is set to an injection amount of hydrogen peroxide to be a sterilization agent 70 (g/pulse) X 3 pulses + aeration 20 pulses. On the other hand, in the case in which a gasket for a large-sized syringe (outer diameter 42 mm X overall height 36 mm ; a gasket of a plunger, a piston portion of the plunger) is filled in the sterilization bag and the sterilization condition is set to an injection amount of hydrogen peroxide 70 (g/pulse) X 3 pulses + aeration 20 pulses to carry out the sterilization treatment, it is apparent from the Table 7 that the survival ratio can always reach 0/10 with a filling rate of 73 %, 53 % or 26 %.

<Final Result>

[0050] The surface and the surface layer portion in a sterilized rubber gasket thus obtained can be sterilized up to SAL = 10 EXP (-6) in bacteria cells having a name of "Bacillus Stearothermophilus ATCC 12980" to be the indicator bacteria of the hydrogen peroxide sterilization.

<Conditions and Procedures of Sterilization Treatment>

[0051] We will hereunder describe in detail the conditions for the sterilization treatment used in the present invention such as the concentration of gaseous hydrogen peroxide (including hydrogen peroxide gas and hydrogen peroxide vapor) or the content of the "hydrogen peroxide", the flow rate of the gaseous hydrogen peroxide, the treating temperature and pressure, the shape and the placed condition of the treating unit, the placed condition of the article to be processed (such as placed position, placed density and the direction of place), the treating time and the degree of agitation in the treating unit.

(1) Gaseous Hydrogen Peroxide

[0052]

(1.1) Concentration: The content of hydrogen peroxide (H_2O_2) in general ranges from 2.9 to 14.7 mol/L, preferably 8.8 to 10.3 mol/L; or 100 to 500 g/L and preferably 300 to 350 g/L.

(1.2) Flow Rate: This is in general controlled to the range of 500 to 5000 L/h (N.T.P.) and preferably 1400 to 2400 L/h (N.T.P.).

(1.3) Treating Temperature and Pressure: They are in general adjusted so as to fall within the range of 15 to 55°C and 0.2 to 50 Pa, preferably 20 to 40°C and 0.5 to 30 Pa, respectively.

(1.4) Shape and Placed Condition of Sterilization Chamber 2: A fixed hollow rectangular prism (chamber, unit or container) or a rotatable and/or rollable hollow cylinder (drum); in this connection, spherical bodies (such as steel balls) or other means for accelerating the mutual contact may be coexistent in the drum.

(1.5) Shape and Placed Condition of Article to be Processed: The article to be processed may have a variety of

shapes such as a columnar shape, a truncated cone-like shape, a tubular shape, a circular disk-like shape, a flanged columnar shape and a hollow single-ended cap. They may be treated in a box-like or bath-shaped sterilization chamber, while they are randomly accommodated in sterilization bags and the resulting bulk materials are placed or suspended in the chamber; or in a rotatable and/or rollable drum, while they are accommodated in sterilization bags, by the action of the rotation and/or rolling of the sterilization chamber in an irregularly oriented (randomly arranged) condition.

Manner of Arrangement of Articles to be Processed: There has widely been adopted a method in which a large number (several thousands of articles/sterilization bag) of articles (for instance, "syringe gasket"; another name: "syringe piston") to be processed are randomly (irregularly) accommodated in bags. In case where the articles are treated in a rotatable and/or rollable drum according to an alternative method, this irregular accommodation thereof in sterilization bags is likewise adopted in most of cases and it is sufficient for these methods to accomplish the usual purpose and to thus sufficiently achieve a desired effect.

(1.6) Manner of Contact within Treating Chamber: As an embodiment usually adopted for the sterilization of normal-sized syringe gaskets, for example, VF1 (outer diameter 7.0 mm X overall height 6 mm), VF3 (outer diameter of 9.0 mm X overall height 8 mm) and VF5 (outer diameter 12.0 mm X overall height 10 mm), about 2000, 10000 or 4000 syringe gaskets are in general accommodated in a sterilization bag and about 50 bags filled with the syringe gaskets are subjected to the sterilization treatment in one lot, in a batchwise manner.

<Preferred Embodiments>

[0053] Fig.1 is a circuit diagram showing the outline of a sterilization device according to one embodiment of the present invention. In Fig. 1, the reference numeral 2 represents a "sterilization chamber " for accommodating articles to be processed within the sterilization device and a device 6 for the supply of gaseous hydrogen peroxide is connected to the sterilization chamber 2 through a conduit 4 for the supply of gaseous hydrogen peroxide. Switching valves 8 and 10 are fitted to the gaseous hydrogen peroxide supply conduit 4 on the side of the sterilization chamber 2 and on the side of the gaseous hydrogen peroxide supply device 6, respectively.

[0054] In addition, a vacuum pump 12 for evacuating the gas present in this sterilization chamber 2 is connected to the sterilization chamber 2 through an evacuation (or aspiration) conduit 14 and a switching valve 16. The gas aspirated by the vacuum pump 12 is externally discharged from the device after coming in contact with a catalyst 20 positioned in an exhaust conduit 18 arranged on the downstream side. Moreover, an air-intake opening 24 is connected to the chamber 2 through a separate switching valve 22 and extension conduit 23 positioned between the foregoing two switching valves 8 and 10, which are arranged on the gaseous hydrogen peroxide supply conduit 4. The air is introduced into the sterilization chamber 2 through the air-intake opening 24 and a sterilization filter 26, which is connected to the gaseous hydrogen peroxide supply conduit 4. The sterilization chamber 2 is equipped with a pressure indicator 28 and a thermometer 30 for detecting the internal pressure and temperature of the chamber 2, respectively.

<<Sterilization Pulse and Aeration Pulse>>

[0055] We will hereunder explain in more detail the sterilization steps using the sterilization device having the structure described above. First of all, articles to be processed (articles to be sterilized; not shown) are introduced into the sterilization chamber 2 according to a variety of introduction methods and then the sterilization chamber 2 is sealed by closing the door thereof. At this stage, the internal pressure of the chamber 2 is approximately equal to the atmospheric pressure.

[0056] Then, the vacuum pump 12 is put into operation and the switching valve 16 fitted to the aspiration conduit 14 of the vacuum pump 12 is opened to aspirate or evacuate the sterilization chamber 2 and to thus establish a high vacuum within the chamber. The degree of the high vacuum commonly used in the sterilization pulse according to the present invention is initially about 0.13 kPa (1 Torr). Then after a desired degree of vacuum is established within the chamber, the switching valve 16 on the vacuum pump 12 side is closed, followed by opening the switching valves 8 and 10 arranged on the gaseous hydrogen peroxide supply conduit 4 to thus introduce the gaseous hydrogen peroxide accommodated in the gaseous hydrogen peroxide supply device 6 into the sterilization chamber 2 through these valves and to uniformly distribute the gaseous hydrogen peroxide within the chamber 2. The concentration (internal gas concentration) of the gaseous hydrogen peroxide usually used at this stage is about 1500 ppm.

[0057] It is important to supply gaseous hydrogen peroxide in a desired amount. More specifically, if the amount of the gaseous hydrogen peroxide supplied is too great, it is difficult to maintain the gaseous hydrogen peroxide in the sterilization chamber 2 in a gaseous state. However, the internal air pressure of the sterilization chamber 2 is extremely low as a result of the evacuation by the vacuum pump 12 and accordingly, the partial pressure of the gaseous hydrogen peroxide in the chamber is in fact increased.

<< Parameters for Operating Sterilization Cycle>>

[0058] According to an embodiment described in the following Table 1, one sterilization pulse in the sterilization step of the present invention is maintained at a high vacuum state in general for 4 minutes, then the switching valve 22 connected with the air-intake opening 24 is opened to introduce sterilized air, which has passed through the sterilization filter 26, into the sterilization chamber 2 and the chamber is maintained at this state usually for 6 minutes so that the gaseous hydrogen peroxide can enter into and/or penetrate into the whole portions of the articles to be processed. As a result, the internal pressure of the sterilization chamber 2 rises up to the usual pressure of 21.98 kPa (165 Torr) slightly higher than the vacuum state. Thereafter, the foregoing sterilization pulse is in general repeated over desired times (desired number of pulses). It is in general sufficient to repeat this sterilization pulse twice, but the pulse is preferably repeated 4 times.

Subsequent to this sterilization pulse, an aeration pulse is carried out. This aeration pulse comprises the steps of introducing sterile air into the sterilization chamber 2 to establish a desired pressure therein and maintaining the chamber 2 at that condition for a predetermined period of time to thus remove the residual hydrogen peroxide from the chamber 2. To achieve the purpose of the aeration pulse, it is sufficient to set the time required for this aeration pulse to about 7 minutes/pulse.

This aeration pulse is usually repeated over desired times. The repeated number of the aeration pulses is in general set at about 20. A series of these pulses permit the effective execution of a desired sterilization treatment. The parameters (conditions for operations) involved in the sterilization cycle of the present invention will be illustrated in the following Table 1.

Table 1:

Parameters for Sterilization Cycle		
Sterilization Step	Subject to be Established	Value Established
Dry Phase	Number of 1st Drying Pulse	1 Pulse
	Established Pressure in the 1st Drying Pulse	1.33 kPa (10 Torr)
	Number of 2nd Drying Pulse	1 Pulse
	Established Pressure in the 2nd Drying Pulse	0.13 kPa (1 Torr)
	Established Pressure at the Pressure Restoration	39.99kPa (300 Torr)
Leakage Test	Established Pressure at Pressure Reduction	0.13kPa (1 Torr)
	Retention Time in Leakage Test	5 minutes
	Established Pressure at the Pressure Restoration	6.66kPa (50 Torr)

Table 1: (continued)

Parameters for Sterilization Cycle		
Sterilization Step	Subject to be Established	Value Established
Sterilization Phase	Number of Sterilization Pulse	4 Pulses
	Established Pressure at Pressure Reduction	0.13kPa (1 Torr)
	Amt. Of Sterilization agent per Pulse	40 g (35% Aq. Soln.)
	Retention Time Immediately After Injection of the Sterilization Agent	4 minutes
	Established Pressure at the Pressure Restoration	21.98kPa (165 Torr)
	Retention Time After Pressure Restoration	6 minutes
	Rate	FAST
Aeration Phase	Number of Pulses	20 pulses
	Established Pressure at Pressure Reduction	0.67kPa (5 Torr)
	Established Pressure at the Pressure Restoration	86.66kPa (650 Torr)
Prior Conditions for the Data listed in Table 1: As a sterilization chamber (sterilization kettle), there was used a chamber having an inner volume of 8.6 m^3, and the sterilization comprises 4 sterilization pulses and 20 aeration pulses.		

<<Arrangement of These Two Kinds of Pulses>>

[0059] The foregoing steps may roughly be divided into the "sterilization pulse" and the "aeration pulse" subsequent thereto and the repetition of each of these two kinds of pulses over a plurality of times would make the effectiveness of the sterilization treatment higher. To effectively carry out the sterilization treatment according to the present invention, it is effective to combine, in order, 2 to 20 times, preferably 3 to 10 times of the sterilization pulses and 5 to 50 times, preferably 10 to 30 times of the aeration pulses. The expression "if the number of sterilization pulses is set to 3 (or 4)" in the component of the present invention is not restricted but is a prior condition (a criterion) for specifying the filling rate of bacteria cells to be sterilized which are accommodated in the sterilization bag.

[0060] After completion of the sterilization of articles to be processed according to the foregoing steps, the aeration pulses are initiated, in which the gaseous hydrogen peroxide is removed from the sterilization chamber 2.

[0061] The sterilization chamber 2 is again evacuated by the action of the vacuum pump 12 to thus establish a vacuum (a reduced pressure) of a desired pressure within the chamber 2. After the establishment of a desired vacuum, the switching valve 16 on the side of the vacuum pump 12 is closed, while the switching valve 22 to the air-intake opening 24 and the switching valve 8 of the gaseous hydrogen peroxide supply conduit 4 on the side of the sterilization chamber 2 are opened to thus introduce sterilized air into the sterilization chamber 2 and to restore the internal pressure of the chamber 2 to a pressure slightly lower than the atmospheric pressure.

[0062] At this stage wherein the sterilization and aeration pulses according to the present invention are completed, the gaseous hydrogen peroxide can be decomposed and removed within a short period of time according to a decomposition method, which makes use of a commonly used catalyst. After the removal of the gaseous hydrogen peroxide present in the sterilization chamber 2, the sterilization chamber 2 can be opened to remove the sterilized articles. This

sterilization process never suffers from a problem of environmental pollution since the decomposition products obtained after the sterilization are oxygen and water.

[0063] According to the sterilization device of the present invention, the amount of the gaseous hydrogen peroxide remaining in the sterilization chamber 2 can be reduced to a level of not more than 1 ppm because of the contribution of the aeration performed before the withdrawal of the articles after the sterilization treatment.

[0064] The sterilization method according to the present invention is suitably applied not only to the foregoing articles of resins such as syringes for injection and containers for ophthalmic medicaments, but also to a variety of articles, in particular, those having poor heat resistance and to high speed sterilization of articles having complicated shapes.

[0065] The gaseous hydrogen peroxide used as the sterilization gas in the present invention is in general supplied to the sterilization chamber 2 through the top board (or top panel) thereof, penetrates into the sterilization bag placed in the sterilization chamber 2 through a large number of through holes (meshes, stitches), comes in contact with the surface of the articles to be processed, thus a part thereof is consumed, but the hydrogen peroxide is uniformly distributed (spreaded) throughout the entire sterilization bags, since the sterilization is carried out under a high vacuum.

[0066] The foregoing sterilization bag can be prepared by, for instance, putting porous films formed from a soft resin or the like on top of each other and then fusion-bonding the peripheral edges thereof; or by knitting a fine band-like or fibrous material of, for instance, a soft resin or converting the material into (air-permeable) sheets (or films) having a large number of through holes in a span-bonding process, then putting them on top of one another and fusion-bonding the peripheral edges thereof.

<<As to the Method for Determining (Quantifying) the Concentration of the Residual Sterilization Gas (Gaseous Hydrogen Peroxide)>>

[0067] The concentration of the residual hydrogen peroxide gas was determined according to the ammonium thiocyanate method. This ammonium thiocyanate method comprises the following operations:

[0068] When a variety of articles sterilized by means of the device hereunder are container in shape, they can be directly filled with purified water prior to the determination of the concentration of a sterilizing agent. They have been sterilized by means of the foregoing high vacuum hydrogen peroxide-sterilization device (trade name VHP DV1000 available from Steris Company; hereunder referred to as "VHP Device").

[0069] While in case of, for instance, caps for ophthalmic medicaments, nozzles, rubber stoppers or sterilization bags, these samples are accommodated in a conical flask (inner volume: 200 ml; a flask with a ground-in stopper), 100 ml of purified water is added to the flask and these samples are immersed in the purified water maintained at 20°C (or room temperature) for 24 hours.

[0070] The resulting extract (5 ml each) was measured and poured into a test tube (with a ground-in stopper), 1 ml of a 1% aqueous solution of iron sulfate is added thereto, followed by sufficient stirring, addition of 5 ml of an aqueous ammonium thiocyanate solution (1.2 mol/L; M/L) for coloration and additionally stirring sufficiently.

[0071] This colored sample solution was measured for the absorbance at a wavelength of 480 nm using a spectrophotometer.

[0072] Similarly, a hydrogen peroxide reference solution (concentration: 5 ppm), purified water and an article free of any sterilization treatment were measured for the absorbance at the same wavelength.

[0073] The hydrogen peroxide concentration of each sample solution can be calculated based on the following formula (1):

$$C = (Abs - Abs0) \times N \times F \quad (1)$$

Wherein each symbol has the following meaning:

C: The concentration (ppm) of hydrogen peroxide to be determined;
Abs : The absorbance of each sample solution as determined using VHP Device after the sterilization treatment;
Abs0: The absorbance of each sample solution as determined using VHP Device prior to the sterilization treatment;
AbsH: The absorbance of the hydrogen peroxide reference solution;
AbsW: The absorbance of purified water;
N: The dilution factor of the sample solution;
S: The concentration (ppm) of the hydrogen peroxide reference solution; and
F: A coefficient calculated using the hydrogen peroxide reference solution according to the following formula (2):

$$F = S/(AbsH - AbsW) \quad (2)$$

<<As to the Precision of the Ammonium Thiocyanate (Quantification) Method>>

[0074] The ammonium thiocyanate method comprises the steps of converting bivalent iron ions (ferrous ions) added to an acidic aqueous solution as an agent into trivalent iron ions (ferric ions) while making use of the oxidation action of hydrogen peroxide in the acidic solution, forming an iron thiocyanate complex colored red through the reaction of the trivalent iron ions with thiocyanate ions and determining the absorbance of the complex to calculate the concentration of the hydrogen peroxide present in the solution. However, the degree of coloration is apt to vary with time and therefore, the determination of the coloration should be completed within one hour.

[0075] The calibration curve (represented by the following formula (3)) required in this determination was prepared on the basis of the absorbance values (X) as a function of the concentration (Y) of the hydrogen peroxide reference solution.

$$\bullet \text{ Calibration Curve: } Y = 3.480X - 0.142 \quad (3)$$

Separately, the calibration curve was inspected for the ability of quantification and the results thus obtained were statistically analyzed to obtain the correlation coefficient ® and it was found to be 0.999958. This clearly indicates that this calibration curve has a considerably high correlation (reliability). It was confirmed that the foregoing determination method (the calibration curve) permits the measurement of the concentration of an aqueous hydrogen peroxide solution within the range of 0 to 14 ppm.

<<As to the Detection Limit of the Ammonium Thiocyanate Method>>

[0076] To confirm or determine the lowest possible concentration of hydrogen peroxide capable of being detected by the ammonium thiocyanate method (detection limit of the method), hydrogenperoxide solutions having three concentrations: 5.00 ppm, 0.5 ppm and 0.05 ppm (6 samples each) were prepared, the order of measurement thereof was determined using a table of random digits as specified in JIS Z9031, and each sample solution was measured for the absorbance and coefficient (ppm/Abs) at a wavelength of 480 nm to thus investigate the relation between them. As a result, the measurement error ($\pm 2\sigma$) for each measurement thus calculated was found to be ± 0.053 ppm for the concentration of 5.00 ppm, ± 0.007 ppm for the concentration of 0.50 ppm and ± 0.009 ppm for the concentration of 0.05 ppm.

<<Tools and Materials or the like used in the Measurement>>

1. Principal Installation

1.1 Hydrogen Peroxide Vapor-Generation Device

[0077]

- Type (trade name): VHP DV1000 (available from Steris Company);
- Amt. Of Injected hydrogen Peroxide: about 4 to 400 g/pulse.

1.2 Sterilization Chamber (Sterilization Unit)

[0078]

- Internal Volume: 8.6 m^3;
- Material: SUS304
- Vacuum Pump Unit;

  Type: TRM1253+TRA1002 (available from Unozawagumi Tekkosho Co., Ltd.);

- Capacity: 760 to 1 Torr; accessible time: within 5 minutes. 1.3 Catalyst for Decomposing Hydrogen Peroxide Gas
- Specifications: Platinum-containing catalyst; Corresponding to discharge concentration of not more than 1 ppm.

1.4 Filters

[0079]

- Pre-filter: Made of PP; corresponding to 10 μm abs; one filter (three elements);
- Sterilized Filter: Made of PTFE; corresponding to 0.22μm abs; two filters (three elements each)

2. Principal Materials, Fixtures, Room Environment

2.1 Validator

[0080]

- Type: X1310CE (main body); LTR-140 (Dry Well Calibrator for low temperature);
- M2801/IRTD-400 (high precision thermometer)
- Manufacturer: KAYE; portable validator

2.2 Device for Measuring Gas Concentration in Sterilization Chamber (used after the completion of the sterilization)

[0081]

- Manufacturer: Dreager Company;
- Dreager Accuro 2000 Gas Detection Pump;
- Dreager Gas Detector Tube (hydrogen peroxide 0.1/a)

2.3 BI Used

[0082]

- Standard: 2.5×10^6 (2.5 EXP (6)) per Carrier;
- Indicator Microorganism: Apex Laboratories Co., Ltd.; Bacillus Stearothermophilus ATCC 12980.

2.4 Environment in Sterilization Chamber

[0083]

- Measured Value During Automated Operation: 1,733 cells/ft^3 (Class 10,000).

3. Outline of Sterilization Cycle

[0084] The hydrogen peroxide vapor-generation device (VHP DV1000) has been developed for the sterilization of a freeze dryer and the sterilization cycle required for the generation of hydrogen peroxide vapor is integrated (programmed) therein. The specifications thereof will be detailed below:

3.1 Drying Step (For further details, one can refer to Table 1 and Fig. 2)

[0085] In the first drying pulse, the pressure is reduced from ordinary pressure to 1.33 kPa (10 Torr) within one minute and then the pressure is restored up to 39.9 kPa (300 Torr) within one minute. In the second drying pulse, it is reduced to 0.13 kPa (1 Torr) within one minute and it is again restored up to 39.9 kPa (300 Torr) within one minute.

3.2 Leakage Test (For further details, one can refer to Table 1 and Fig. 2)

[0086] The internal pressure of the sterilization chamber is reduced from the condition after the completion of the drying step, at which the pressure has been restored up to 39.9 kPa (300 Torr) to 0.133 kPa (1 Torr) within one minute, followed by maintaining that condition for 5 minutes to confirm if any "pressure change" is observed or not and then the pressure is restored up to 6.66 kPa (50 Torr) within one minute. 3.3 Sterilization Step (For further details, one can refer to Table 1 and Fig. 2)

[0087] After reducing the internal pressure of the sterilization chamber from 6.66 kPa (50 Torr) at the completion of

the leakage test to 0.13 kPa (1 Torr) within one minute, a predetermined amount (40 to 50 g) of an aqueous hydrogen peroxide solution (concentration: about 35% by weight) is poured into the chamber, followed by maintaining the condition wherein the internal gas concentration is about 1500 ppm for about 4 minutes, restoration of the pressure to 21.98 kPa (165 Torr) by the injection of clean air into the chamber and maintaining the interior of the chamber at this pressure for 6 minutes.

[0088] The foregoing operations extending "from the establishment of a high vacuum to the internal pressure-maintenance by the injection of clean air" are defined to be one pulse and the steps for the injection of sterilizing gas and clean air are repeated over the required pulse number. The time required for the sterilization step is in general about 16 min/pulse.

3.4 Aeration Step (For further details, one can refer to Table 1 and Fig. 2)

[0089] The internal pressure of the sterilization chamber is restored from 0.67 kPa (5 Torr) observed at the completion of the sterilization step to 86.66 kPa (650 Torr) by the injection of clean air in the chamber 2 within one minute. The foregoing operations extending from the establishment of a high vacuum to the restoration of the internal pressure to about ordinary pressure is defined to be one aeration pulse and this aeration step is repeated over a desired pulse number. The time required for the aeration pulse is about 7 min/pulse.

Example 1

[0090] Three kinds of large-sized rubber stoppers for vials (they are made of chlorinated butyl rubber; comprise a cone-like head having an obtuse vertical angle and a cylindrical barrel subsequent thereto and the cylindrical barrel has a size of 42 mm (diameter)×15 mm (height) and the overall height of the stopper is 36 mm) were referred to as a rubber stopper A, a rubber stopper B and a rubber stopper C, respectively.

[0091] Each kind of rubber stoppers (150 stoppers each) were accommodated in a sterilization basket, followed by subjecting them to a sterilization step comprising 6 pulses of sterilization treatments with 70 g/pulse of a hydrogen peroxide aqueous solution (concentration: 35% by weight) and 20 pulses of aeration treatments, using the foregoing high vacuum hydrogen peroxide-sterilization device (abbreviated as "VHP Device"), storing the resulting rubber stoppers A, B and C at room temperature (23 to 25°C), and quantitatively determining the amount of the hydrogen peroxide remaining on the stoppers according to the ammonium thiocyanate method after the elapse of a predetermined period of time (immediately after the sterilization step, and 24 and 72 hours thereafter). The results thus obtained are listed in Table 2 given below and will be discussed in detail in the column entitled "Effects of the Invention" given later.

[0092] The data listed in Table 2 clearly indicates that the effects of the present invention as will be described below can be achieved in the early stage and that even if residual substances are present after the sterilization with gaseous hydrogen peroxide, the amount thereof is considerably small as compared with the remaining harmful substances observed after the EOG sterilization as will be proved in Comparative Example. In addition to the foregoing advantages, regarding the carcinogenicity of the residual substances, the difference between the hydrogen peroxide sterilization and the EOG sterilization is quite conspicuous or there is a considerable difference between the carcinogenicity of the residual substances formed after the hydrogen peroxide sterilization and that of the residual substances formed after the EOG sterilization.

Table 2:

Results conceming the determination of the amount of hydrogen peroxide remaining on large-sized rubber stoppers			
	Condition: Residual Hydrogen Peroxide Conc. (μg/g)		
Sample	Immediately After Sterilization	24 Hours After Sterilization	72 Hours After Sterilization
Rubber Stopper A	0.24	0.14	N.D.
B	0.19	0.14	N.D.
C	0.28	0.19	N.D.

Materials for rubber stoppers: chlorinated butyl rubber

[0093] N.D.: Not detected.

[0094] The amount of the H_2O_2 Solution (conc.: 35% by weight) used: 70 g.

[0095] Sterilization Conditions: VHP Device was used (6 pulses of sterilization treatments + 20 pulses of aeration treatments).

Fig. 3 shows the relation between the storage time after the completion of the sterilization step and the concentration of the remaining hydrogen peroxide.

Comparative Example 1

[0096] The amount of the residual remaining on the articles after the EOG sterilization as a conventional sterilization method was determined. The results thus obtained are summarized in the following Table 3, more specifically Table 3-1, Table 3-2 and Table 3-3 (in this respect, Table 3-2 and Table 3-3 are hereunder also denoted as "Table 4") and plotted on Fig. 4, Fig. 5 and Fig. 6. In Fig. 4 and Fig. 5, the degassing treatment time (h) is plotted as abscissa and the concentration of residual sterilization agent (μg/g) is plotted as ordinate.

[0097] In this respect, the sterilization step in Table 3 comprised a sterilization treatment at 50°C for 8 hours and 4 pulses of aeration treatments; and the degassing treatment was carried out by storing in a degassing treatment chamber at 50°C and the residual gas analysis method adopted herein was GC/FID (gas chromatography/flame ionization detector) method. In addition, Table 3-1 shows the results of the determination of residual EO concentrations, and Table 3-2 shows the results of the determination of residual ECH concentrations and Table 3-3 shows those of the determination of residual EG concentrations respectively.

Table 3-1:

Results of the determination of EO conc. remaining on rubber stoppers for syringes						
Sample Name	Measuring Conditions: Time (h) After Degassing Treatment and Residual EO Conc. (μg/g)					
	0	36	60	132	180	300
1. Top Cap	917	186	14	3.6	3.0	1.8
2. Gasket	1075	248	43	3.5	2.2	1.2
3. Top Gasket	1095	132	12	5.5	3.5	2.4

Materials for rubber stoppers: chlorinated butyl rubber.

Sterilization agent: Ethylene oxide (EO)

[0098] Sterilization Conditions: Sterilization, 50°Cx8h + 4 Pulses of Aeration

Assembled State of Glass Syringe

[0099] Degassing Conditions: Storage within a degassing chamber (at 50°C) Method for Analyzing Residual Gas: GC/FID (Gas Chromatography/Flame Ionization Detector) Method
Top Cap: Syringe Outlet End-Sealing Tool
Gasket: Gasket for Plunger
Top Gasket (Top Packing): Gasket (packing) for sealing the joint between a resin part constituting the tip of the syringe and the syringe

Table 3-2:

Results of the determination of ECH conc. remaining on rubber stoppers for syringes						
Sample Name	Measuring Conditions: Time (h) After Degassing Treatment and Residual ECH Conc. (μg/g)					
	0	36	60	132	180	300
1. Top Cap	52	43	41	31	23	10
2. Gasket	52	35	26	11	8.3	4.7
3. Top Gasket	164	176	118	53	48	30

Other items are identical to those specified in Table 4.

[0100]

Table 3-3:

Results of the determination of EG conc. remaining on rubber stoppers for syringes						
Sample Name	Measuring Conditions: Time (h) After Degassing Treatment and Residual EG Conc. (μg/g)					
	0	36	60	132	180	300
1. Top Cap	3.6	3.5	2.7	2.5	2.6	N.D.
2. Gasket	3.4	3.0	2.8	2.5	2.6	N.D.
3. Top Gasket	6.1	6.2	N.D.	N.D.	N.D.	N.D.

Other items are identical to those specified in Tables 3-2 and 3-3.

Example 2

[0101] In the case in which experiment conditions (sterilization conditions) 2-1 : 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 2 pulses and 20 pulses of an aeration were set, a sample I per sterilization bag : 20000 VFI gaskets for a syringe [formed of chlorinated butyl rubber (outer diameter 7.00 mm X overall height 6 mm)] was filled with a filling rate of 73 %, a filling rate of 53 % and a filling rate of 26 % respectively, and the sterilization bag and the basket (formed of polyethylene ; a capacity of 62 L ; an outer dimension of 622 mm X 462 mm X 268 mm) were further accommodated in parallel and experiments were variously carried out first to five times. The results of the experiments are shown in the Table 4.

[0102] The sterilization bag used herein is of a gazette type and is prepared by using a polyolefin film layer (a composition containing 50 % by weight of polyethylene and 30 % by weight of polypropylene) laminated on a polyethylene synthetic paper [trade name : Tyveck 1073B].

[0103] According to the experiment under the experimental condition 2-1, the sterilization condition was set to 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 2 pulses and 20 pulses of an aeration with a sample filling rate of 73 % in a sterilization bag 1, a sample filling rate of 53 % in a sterilization bag 2 and a sample filling rate of 26 % in a sterilization bag 3 and the treatment was carried out 1 to 5 times. As a result, a tendency of an increase in a survival ratio (a reduction in a sterilization effect) was observed with a reduction in the filling rate.

[0104] According to the experiment condition 2-1, furthermore, a survival ratio of 0/10 could not be realized in any of three kinds of filling rates. The result is shown in the Table 4.

Experiment condition 2-2 : Next, the number of pulses for the hydrogen peroxide treatment in the sterilization condition was increased from 2 to 3 under the experiment condition.

[0105] According to the experiment condition 2-2, the sterilization condition was set to 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 3 pulses and 20 pulses of an aeration with a sample filling rate of 73 % in the sterilization bag 1, a sample filling rate of 53 % in the sterilization bag 2 and a sample filling rate of 26 % in the sterilization bag 3 and the treatment was carried out 1 to 5 times. As a result, a tendency of an increase in the survival ratio (a reduction in the sterilization effect) was observed with a reduction in the filling rate.

[0106] According to the experiment condition 2-2, furthermore, it was found that the survival ratio of 0/10 can be realized for all the first to fifth treatments in the case of the filling rates of 73 % and 53 %, while the survival ratio of 0/10 cannot always be realized with the filling rate of 26 %. The result is shown in the Table 4 together.

Table 4 Sample : Result of Sterilization Treatment of VF1 rubber gasket

Number of accommodated samples 20000	Sterilization bag	1	2	3	Result of treatment and Remarks
	Filling rate %	73	53	26	
Sterilization condition	Number of treatments	Survival Ratio			
70 (g/pulse) x 2 pulses + aeration x 20 pulses	1	0/10	3/10	2/10	Under this treatment condition, a survival ratio of 0/10 cannot be realized irrespective of a filling rate.
	2	3/10	2/10	5/10	
	3	2/10	0/10	3/10	
	4	1/10	2/10	1/10	
	5	1/10	4/10	3/10	
70 (g/pulse) x 3 pulses + aeration x 20 pulses	1	0/10	0/10	0/10	Under this treatment condition, a survival ratio of 0/10 can be always realized with a filling rate of 73 %.
	2	0/10	1/10	0/10	
	3	0/10	0/10	2/10	
	4	0/10	1/10	1/10	
	5	0/10	0/10	0/10	

70 (g/pulse) : an aqueous hydrogen peroxide solution (concentration of 35 wt%) injection amount

Example 3

[0107] In the case in which experiment conditions (sterilization conditions) 3-1 : 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 2 pulses and 20 pulses of an aeration were set, a sample II per sterilization bag : 10000 VF3 gaskets for a syringe [formed of chlorinated butyl rubber (outer diameter 9.0 mm X overall height 8 mm)] was filled with a filling rate of 76 %, a filling rate of 53 % and a filling rate of 26 % respectively. Experiments were variously-carried out first to five times. The result of the experiments is shown in Table 5.

[0108] According to the experiment under the experiment condition 3-1, the sterilization condition was set to 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 2 pulses and 20 pulses of an aeration with a sample filling rate of 76 % in a sterilization bag 1, a sample filling rate of 53 % in a sterilization bag 2 and a sample filling rate of 26 % in a sterilization bag 3 and the treatment was carried out 1 to 5 times. As a result, a tendency of an increase in a survival ratio (a reduction in a sterilization effect) was observed with a reduction in the filling rate.

[0109] According to the experiment condition 3-1, furthermore, it was found that a survival ratio of 0/10 cannot be always realized in any of three kinds of filling rates. The result is shown in the Table 5. Experiment condition 3-2 : Next, the number of pulses for the hydrogen peroxide treatment in the sterilization condition was increased from 2 to 3 under the experiment condition.

[0110] According to the experiment condition 3-2, the sterilization condition was set to 70 (g/pulse) of an aqueous

hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 3 pulses and 20 pulses of an aeration with a sample filling rate of 76 % in the sterilization bag 1, a sample filling rate of 53 % in the sterilization bag 2 and a sample filling rate of 26 % in the sterilization bag 3 and the treatment was carried out 1 to 5 times. As a result, a tendency of an increase in the survival ratio (a reduction in the sterilization effect) was observed with a reduction-in the filling rate.

[0111] According to the experiment under the experiment condition 3-2, furthermore, it was found that the survival ratio of 0/10 can be realized for all the first to fifth treatments only with the filling rate of 76 %, while the survival ratio of 0/10 cannot always be realized with the filling rates of 53 % and 26 % which are lower. The result is shown in the Table 5 together.

Table 5 Sample : Result of Sterilization Treatment of VF3 rubber gasket

Number of accommodated samples 10000	Sterilization bag	1	2	3	
	Filling rate %	76	53	26	
Sterilization condition	Number of treatments	Survival Ratio			Result of treatment and Remarks
70 (g/pulse) x 2 pulses + aeration x 20 pulses	1	2/10	1/10	3/10	Under this treatment condition, a survival ratio of 0/10 cannot be realized irrespective of a filling rate.
	2	0/10	2/10	4/10	
	3	1/10	0/10	1/10	
	4	0/10	1/10	3/10	
	5	1/10	1/10	0/10	
70 (g/pulse) x 3 pulses + aeration x 20 pulses	1	0/10	0/10	0/10	Under this treatment condition, a survival ratio of 0/10 can be always realized with a filling rate of 76 %.
	2	0/10	0/10	0/10	
	3	0/10	0/10	1/10	
	4	0/10	1/10	1/10	
	5	0/10	0/10	0/10	

70 (g/pulse) : an aqueous hydrogen peroxide solution (concentration of 35 wt%) injection amount

Example 4

[0112] In the case in which experimental conditions (sterilization conditions) 4-1 : 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 2 pulses and 20 pulses of an aeration were set, a sample III per sterilization bag : 4000 VF5 gaskets for a syringe [formed of chlorinated butyl rubber (diameter

12.0 mm X overall height 10 mm)] was filled with a filling rate of 73 %, a filling rate of 53 % and a filling rate of 26 % respectively. Experiments were variously carried out first to five times. The result of the experiments is shown in Table 6.

[0113] According to the experiment condition 4-1, the sterilization condition was set to 70 (g/pulse) of an aqueous hydrogen peroxide solution injection amount X 2 pulses and 20 pulses of an aeration 20 with a sample filling rate of 73 % in a sterilization bag 1, a sample filling rate of 53 % in a sterilization bag 2 and a sample filling rate of 26 % in a sterilization bag 3 and the treatment was carried out 1 to 5 times. As a result, a tendency of an increase in a survival ratio (a reduction in a sterilization effect) was observed with a reduction in the filling rate.

[0114] According to the experiment under the experiment condition 4-1, furthermore, it was found that a survival ratio of 0/10 cannot be always realized in any of three kinds of filling rates. The result is shown in the Table 6.

Experiment condition 4-2 : Next, the number of pulses for the hydrogen peroxide treatment in the sterilization condition was increased from 2 to 3 under the experiment condition.

[0115] According to the experiment under the experiment condition 4-2, the sterilization condition was set to 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 3 pulses and 20 pulses of an aeration with a sample filling rate of 73 % in the sterilization bag 1, a sample filling rate of 53 % in the sterilization bag 2 and a sample filling rate of 26 % in the sterilization bag 3 and the treatment was carried out 1 to 5 times. As a result, a tendency of an increase in the survival ratio (a reduction in the sterilization effect) was observed with a reduction in the filling rate.

[0116] According to the experiment under the experiment condition 4-2, furthermore, it was found that the survival ratio of 0/10 can be realized for all the first to fifth treatments with the filling rates of 73 % and 53 %, while the survival ratio of 0/10 cannot always be realized with the filling rate of 26 % which is much lower. The result is shown in the Table 6 together.

Table 6 Result of Sterilization Treatment of VF5 gasket

Number of accommodated samples 4000	Sterilization bag	1	2	3	
	Filling rate %	73	53	26	
Sterilization condition	Number of treatments	Survival Ratio			Result of treatment and Remarks
70 (g/pulse) x 2 pulses + aeration x 20 pulses	1	1/10	1/10	2/10	Under this treatment condition, a survival ratio of 0/10 cannot be realized irrespective of a filling rate.
	2	0/10	1/10	1/10	
	3	2/10	0/10	3/10	
	4	0/10	1/10	0/10	
	5	0/10	2/10	1/10	
70 (g/pulse) x 3 pulses + aeration x 20 pulses	1	0/10	0/10	0/10	Under this treatment condition, a survival ratio of 0/10 can be always realized with a filling rate of 73 %.
	2	0/10	0/10	0/10	
	3	0/10	0/10	0/10	
	4	0/10	0/10	0/10	
	5	0/10	0/10	1/10	

70 (g/pulse) : an aqueous hydrogen (concentration of 35 wt%) injection amount

Example 5

[0117] In the case in which experiment conditions (sterilization conditions) 5-1 : 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 2 pulses and 20 pulses of an aeration were set, a sample IV per sterilization bag : 150 rubber gaskets for a large-sized syringe [formed of chlorinated butyl rubber (diameter 42.0 mm X overall height 36 mm)] was filled with a filling rate of 73 %, a filling rate of 51 % and a filling rate of 23 % respectively. Experiments were variously carried out first to five times.

[0118] According to the experiment under the experiment condition 5-1, the sterilization condition was set to 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 2 pulses and 20 pulses of an aeration with a sample filling rate of 73 % in a sterilization bag 1, a sample filling rate of 51 % in a sterilization bag 2 and a sample filling rate of 23 % in a sterilization bag 3 and the treatment was carried out 1 to 5 times. As a result, a survival ratio of 0/10 was observed with any filling rate any number of times. The result of the experiment is shown in Table 7.

Experiment condition 5-2 : Next, the number of pulses for the hydrogen peroxide treatment in the sterilization condition was increased from 2 to 3 under the experiment condition.

[0119] According to the experiment under the experiment condition 5-2, the sterilization condition was set to 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 3 pulses and 20 pulses of an aeration with a sample filling rate of 73 % in the sterilization bag 1, a sample filling rate of 51 % in the sterilization bag 2 and a sample filling rate of 23 % in the sterilization bag 3 and the treatment was carried out 1 to 5

times. As a result, a survival ratio 0/10 could be realized with any filling rate any number of times. The result of the experiment is shown in the table 7 together.

Table 7 Sample : Result of Sterilization Treatment of rubber gasket for large-sized syringe

Number of accommodated samples 150	Sterilization bag	1	2	3	
	Filling rate %	73	51	23	
Sterilization condition	Number of treatments	Survival Ratio			Result of treatment and Remarks
70 (g/pulse) x 2 pulses + aeration x 20 pulses	1	0/10	0/10	0/10	Under this treatment condition, a survival ratio of 0/10 can be always realized irrespective of a filling rate.
	2	0/10	0/10	0/10	
	3	0/10	0/10	0/10	
	4	0/10	0/10	0/10	
	5	0/10	0/10	0/10	
70 (g/pulse) x 3 pulses + aeration x 20 pulses	1	0/10	0/10	0/10	Under this treatment condition, a survival ratio of 0/10 can be always realized irrespective of a filling rate.
	2	0/10	0/10	0/10	
	3	0/10	0/10	0/10	
	4	0/10	0/10	0/10	
	5	0/10	0/10	0/10	

70 (g/pulse) : an aqueous hydrogen peroxide solution (concentration of 35 wt%) injection amount

Example 6

[0120] There was investigated the influence, on a sterilization efficiency, of a ratio of a capacity of a sterilization bag to a capacity of a porous container (basket) accommodating the sterilization bag (former / latter = volume rate) in sterilization using gaseous hydrogen peroxide. A material, an outer dimension and an inner volume of a basket :

- Basket 1 : formed of PE ; outer dimension 622 mm X 462 mm X 196 mm ; inner volume 45 L ;
- Basket 2 : formed of PE ; outer dimension 622 mm X 462 mm X 268 mm ; inner volume 62 L ;
- Basket 3 : formed of PE ; outer dimension 820 mm X 570 mm X 428 mm ; inner volume 161 L .

[0121] In the case in which treatment conditions (sterilization conditions) : 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 3 pulses and 20 pulses of an aeration were set, a sample IV per sterilization bag : 5000 VF5 gaskets for a syringe [formed of chlorinated butyl rubber (diameter 12.0 mm X overall height 10 mm)] was filled with a filling rate of 67 %, a filling rate of 48 % and a filling rate of 16 %

respectively. Experiments were variously carried out first to five times. The result of the experiments is shown in Table 8.

[0122] According to the experiment of the sixth embodiment, a survival ratio of 0/10 could not be always realized with a maximum volume rate of 67 %, while a survival ratio of 0/10 could be realized with the volume rates of 48 % and 16 % which are lower at first to fifth times of the treatment.

Table 8

Result of sterilization treatment for basket selection					
Basket number to be used together	Capacity (L)	Volume rate %	Number of treatments	Survival Ratio %	Remarks
1	45	67	1	1/10	
Ditto	Ditto	Ditto	2	0/10	
Ditto	Ditto	Ditto	3	0/10	
Ditto	Ditto	Ditto	4	1/10	
Ditto	Ditto	Ditto	5	0/10	
2	62	48	1	0/10	
Ditto	Ditto	Ditto	2	0/10	
Ditto	Ditto	Ditto	3	0/10	
Ditto	Ditto	Ditto	4	0/10	
Ditto	Ditto	Ditto	5	0/10	
3	161	16	1	0/10	A sterilization bag is broken due to rapid expansion.
Ditto	Ditto	Ditto	2	0/10	
Ditto	Ditto	Ditto	3	0/10	
Ditto	Ditto	Ditto	4	0/10	
Ditto	Ditto	Ditto	5	0/10	

Effects of the Invention

[0123] The sterilization method according to the present invention and a variety of sealing tools obtained using the method show various effects detailed below:

(1) Immediately after the completion of the sterilization step, the residual amounts of hydrogen peroxide were found to be 0.24μg/g for the rubber stopper A, 0.19μg/g for the rubber stopper B and 0.28 μg/g for the rubber stopper C, all of which are much lower than a normal value of 0.5μg/g. These results clearly indicate that the rubber stoppers A, B and C can be used without problems.

(2) Any residual hydrogen peroxide cannot be detected in all of the rubber stoppers after 72 hours from the completion of the sterilization step (or the amount thereof is less than the detection limit). As has been described in the foregoing item (1) and (2), the residual amount of hydrogen peroxide is reduced to the level, which is out of the question or is practically acceptable after 24 hours from the completion of the sterilization step and therefore, these results simply show the time required for the reduction of the residual amount to the level of less than the detection limit.

(3) The time required for the sterilization treatment is on the order of about 1.5 hour per batch for an ophthalmic medicaments nozzle, a vial for ophthalmic medicaments or the like and this time is sufficient to ensure the degree of sterilization of SAL = 10EXP(-6).

(4) The amounts of hydrogen peroxide remaining on the containers of polyethylene (PE), polypropylene (PP) or polytetrafluoroethylene (PTFE) after the sterilization can be improved to a level of about 0.2 to 0.3 ppm immediately after the sterilization, a level of 0.1 to 0.2 ppm one day after the sterilization and a level of not more than the detection limit (0.1 ppm) one week after the sterilization.

Therefore, these containers can be used immediately after the sterilization treatment.

(5) It is not necessary to remove, for instance, moisture and/or organic solvent from the article after the sterilization treatment or the article further subjected to the aeration treatment before forwarding.

(6) If a filling rate in a sterilization bag for a sample is set to be high, a survival ratio can be reduced (a sterilization effect can be increased).

(7) If a filling rate of 53 % or more is set to be combined with a great sterilization condition of "70 (g/pulse) of an

aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 3 pulses and 20 pulses of an aeration", a survival ratio of 0/10 can be always realized in any of the second to sixth embodiments.
(8) If a ratio of the content of a basket accommodated in a sterilizer in a stacking process to an outer volume of an outer bag mounted thereon (latter / former ; volume rate) is set to be 48 % or less, a survival ratio of 0/10 can be always realized.
(9) A polyolefinic material is optimum for the sterilization bag and a second optimum material could not be found.

Claims

1. A method for the production of a sealing tool which comprises setting a filling rate in a sterilization bag for a sample to be sterilized to 45 % or more for a gasket for a normal type syringe and to 20 % or more for a gasket for a large-sized syringe, thereby carrying out sterilization in the case in which a rubbery sealing tool or a sealing tool made from an olefinic resin is held as an article to be processed in a sterilization unit under a high vacuum, gaseous hydrogen peroxide is then introduced into the sterilization unit, and is held for a predetermined time and is sterilized by at least one member selected from the group consisting of active oxygen and radical hydroxide, a clean gas is thereafter introduced and is held for a predetermined time to cause a sterilizing substance to penetrate into an inner side of the article to be processed, thereby setting a sterilizing condition using the gaseous hydrogen peroxide in which a sterilization treatment for the article to be processed is one sterilization pulse to a combination of 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 3 pulses and 20 pulses of an aeration.

2. The method for the production of a sealing tool as set forth in claim 1, which comprises setting the filling rate of the sample to be sterilized in the sterilization bag to be to 50 % or more for a gasket for a normal type syringe and to 20 % or more for a gasket for a large-sized syringe under the sterilization condition, thereby carrying out the sterilization.

3. A method for the production of a sealing tool, which comprises setting a sterilization condition to a combination of 70 (g/pulse) of an aqueous hydrogen peroxide solution (a concentration of 35 % by weight) injection amount X 4 pulses and 20 pulses of an aeration, setting a filling rate of a sample to be sterilized in a sterilization bag to be to 20 % or more for a gasket for a normal type syringe or a gasket for a large-sized syringe, thereby carrying out the sterilization.

4. The method for the production of a sealing tool as set forth in any one of claims 1 to 3, which comprises setting the number of repetitions of the aeration pulse to be carried out next to a sterilization pulse in the sterilization treatment to be 30 pulses or more.

5. The method for the production of a sealing tool as set forth in any one of claims 1 to 3, which comprises setting the number of repetitions of the aeration pulse to be 5 to 50 pulses or more.

6. The method for the production of a sealing tool as set forth in any one of claims 1 to 4, which comprises setting the sterilization pulses and the aeration pulses to be, in advance, conducted in combination.

7. The method for the production of a sealing tool as set forth in any one of claims 1 to 5, which comprises setting an outer bag further accommodating the sterilization bag having the article to be processed to be mounted in a porous container for mounting with a volume rate of 12 to 55 %, thereby carrying out the sterilization treatment.

8. The method for the production of a sealing tool as set forth in any one of claims 1 to 5, which comprises setting the article to be processed to be at least one member selected from a rubber cap, a rubber gasket, a gasket for a piston (plunger) to be inserted into an injection cylinder (syringe), a tool for preventing liquid leakage such as rubber boots, and an elastic ring for a bushing and for fitting a joint.

9. The method for the production of a sealing member as set forth in any one of claims 1 to 7, which comprises rubber being at least one member selected from the following conjugated diene rubber and non-conjugated diene rubber: the conjugated diene rubber being natural rubber, a variety of synthetic rubber materials, blends each comprising at least two of these natural and synthetic rubber materials and copolymer rubber comprising repeating units of these rubber materials and other repeating units copolymerizable therewith, wherein the synthetic rubber comprises 1,4-cis-polyisoprene rubber obtained by 1,4-addition polymerization of isoprene, which is a repeating unit

mainly constituting the natural rubber, 1,4-cis-polybutadiene rubber and isobutene-isoprene copolymer rubber; the non-conjugated diene rubber being copolymer rubber materials of at least two 1-olefins or multi-component copolymer rubber materials obtained by copolymerizing these monomers with third non-conjugated dienes, wherein the copolymer rubber materials of at least two 1-olefins is at least one member selected from the group consisting of ethylene-propylene (copolymer) rubber, ethylene-1-butene copolymer rubber and propylene-1-butene copolymer rubber, and wherein the multi-component copolymer rubber obtained by copolymerizing these monomers with a third non-conjugated diene is at least one member selected from the group consisting of ethylene-propylene-1,4-hexadiene copolymer rubber, ethylene-propylene-methylene norbornene copolymer rubber and ethylene-propylene-ethylidene norbornene copolymer rubber.

10. The method for the production of a sealing tool as set forth in any one of claims 1 to 8, which comprises the thermoplastic elastomer (thermoplastic rubber) being a polymer or a kneaded composition (kneaded mixture) of at least two polymers, which simultaneously has characteristic properties of thermoplastic resin and elastomer; the polymer composition, which can be formed into a variety of shapes as set forth in the molding method applicable to the resin and can be subjected to vulcanization treatment (crosslinking treatment) applicable to the elastomer, is at least one kneaded composition selected from the group consisting of kneaded compositions of polyolefin resins and ethylene-propylene (copolymer) rubber, kneaded compositions of polyolefin resins and ethylene-propylene-non-conjugated diene copolymer rubber and kneaded compositions of propylene-1-butene copolymer resins and ethylene-propylene-non- conjugated diene copolymer rubber.

11. The method for the production of a sealing tool as set forth in any one of claims 1 to 9, which comprises the thermoplasticelastomer being a thermally kneaded composition comprising at least one member selected from the group consisting of polyethylene resins, polypropylene resins, poly-1-butene resins, poly-4-methyl-1-pentene resins and poly-1-hexene resins; and at least one member selected from the group consisting of ethylene-propylene-1,4-hexadiene copolymer rubber, ethylene-propylene-methylene norbornene copolymer rubber and ethylene-propylene-ethylidene norbornene copolymer rubber.

Fig. 1

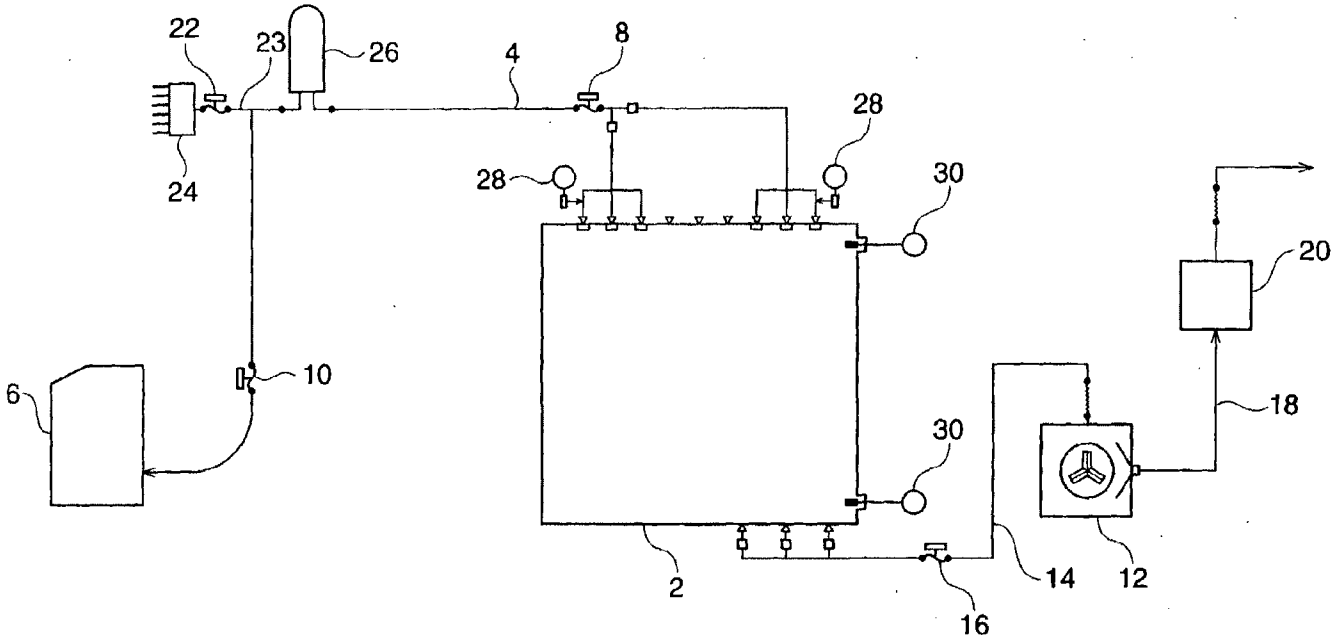
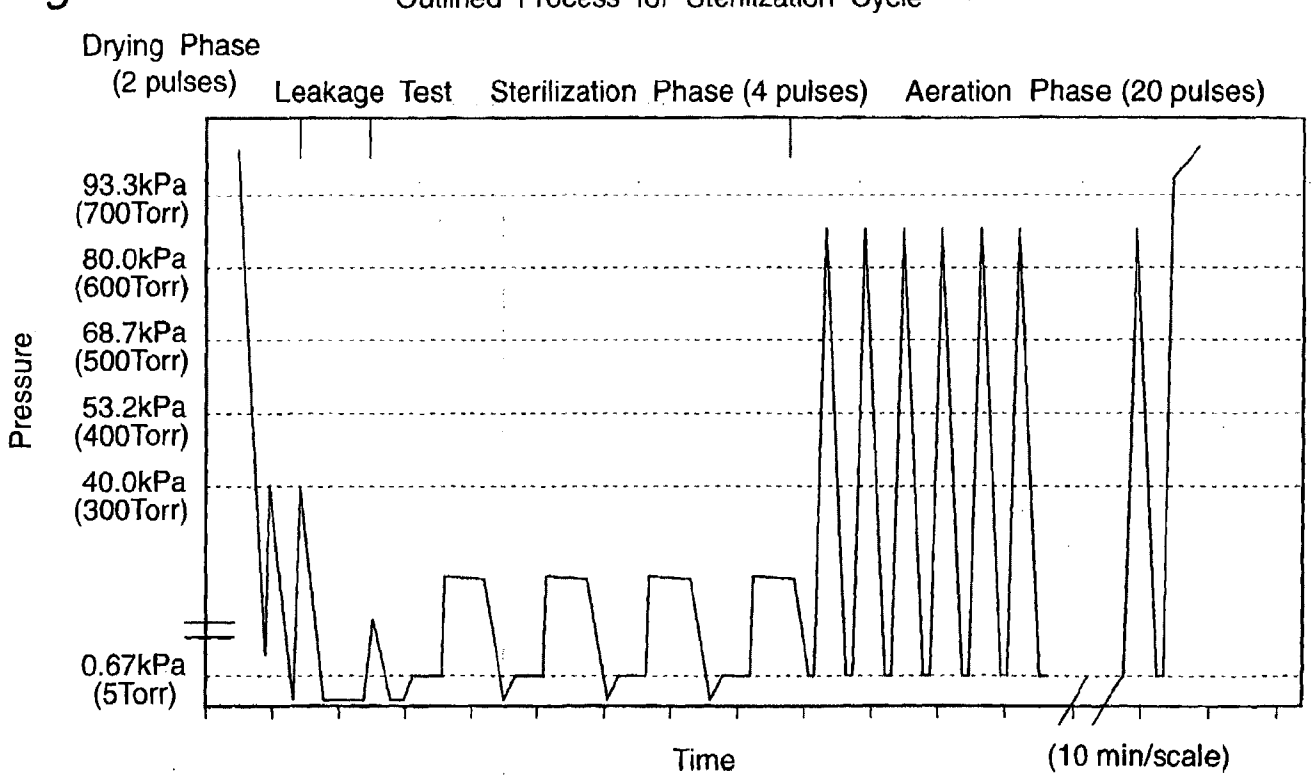


Fig. 2



In case where the sterilization cycle comprises a combination of 4 pulses of gaseous hydrogen peroxide treatment and 20 aeration pulses, the sterilization process requires about 3 hours and 20 minutes.

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Fig. 3

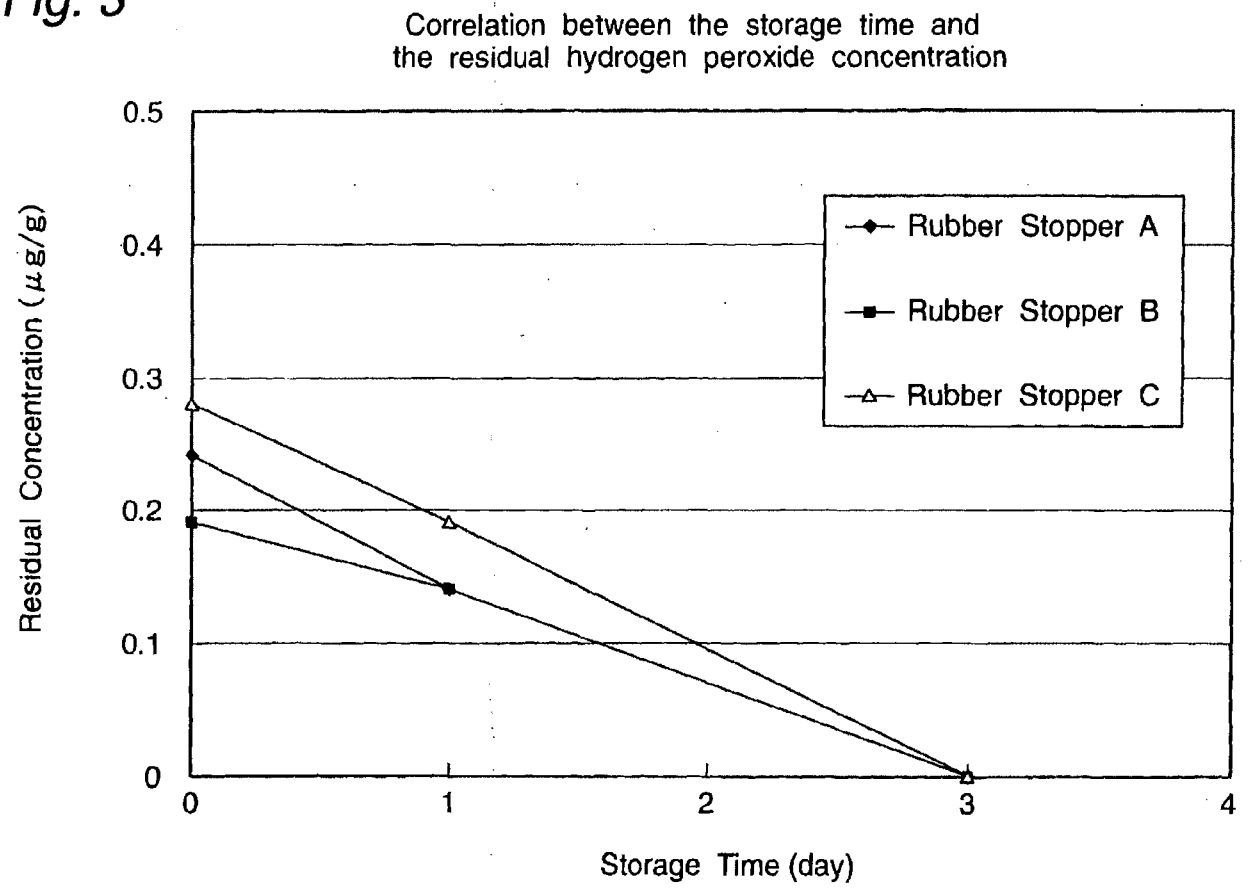

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Fig. 4

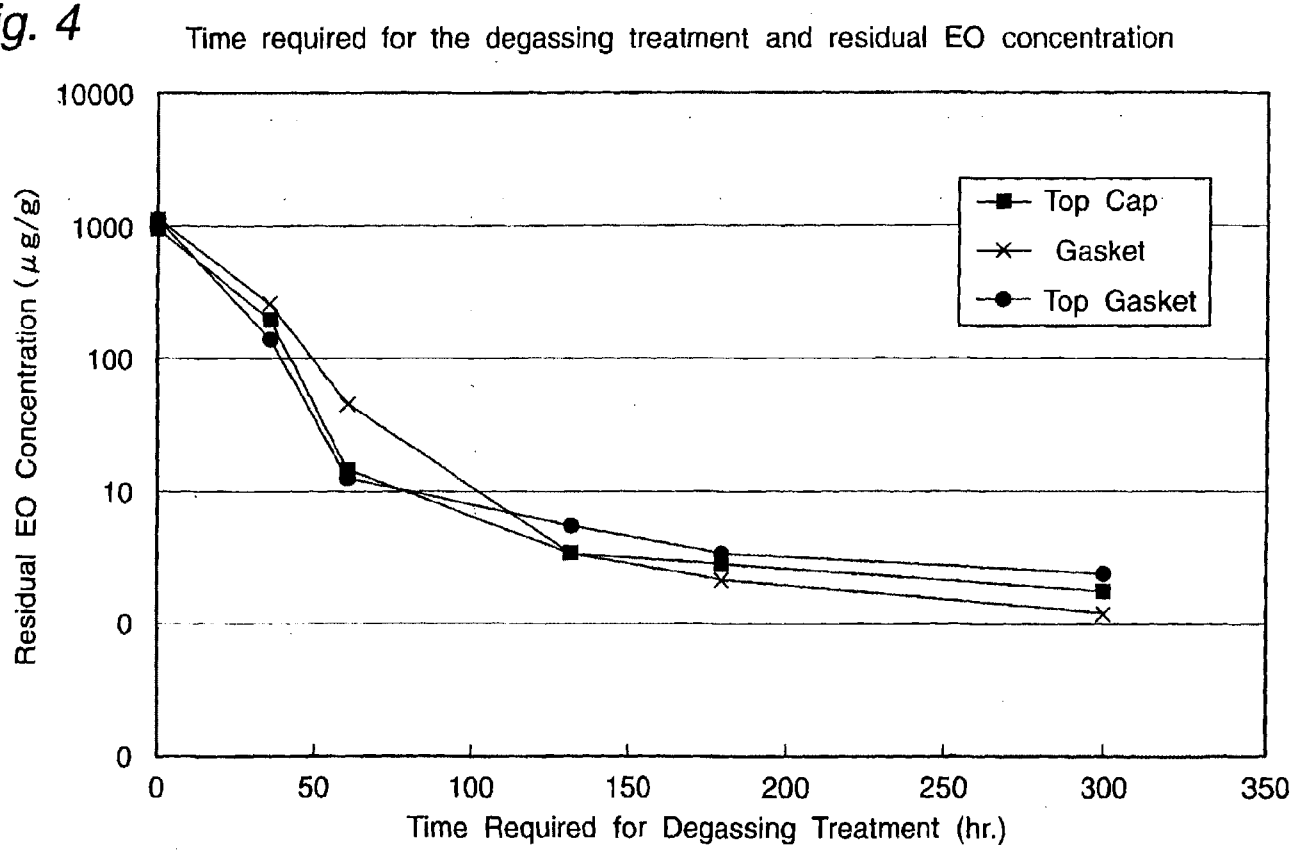

Fig. 5 Time required for the degassing treatment and residual EG concentration

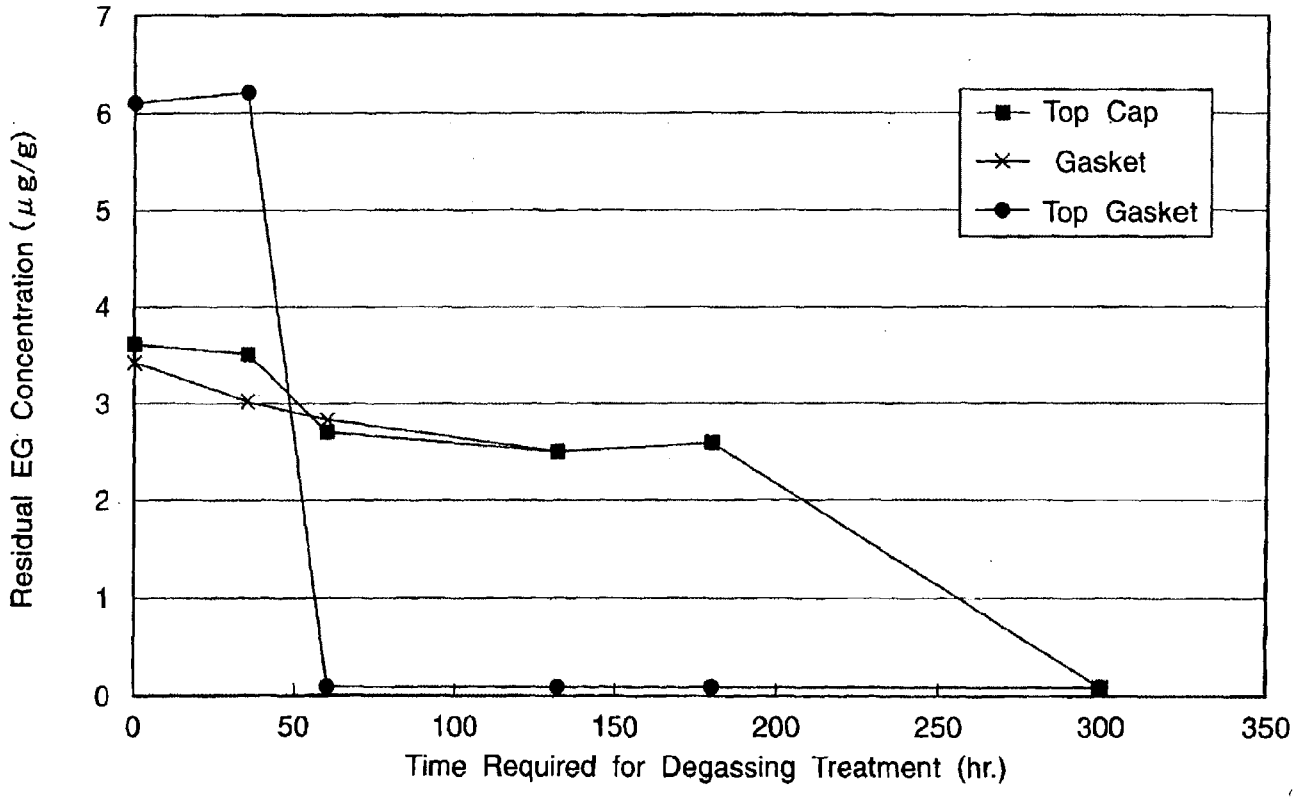

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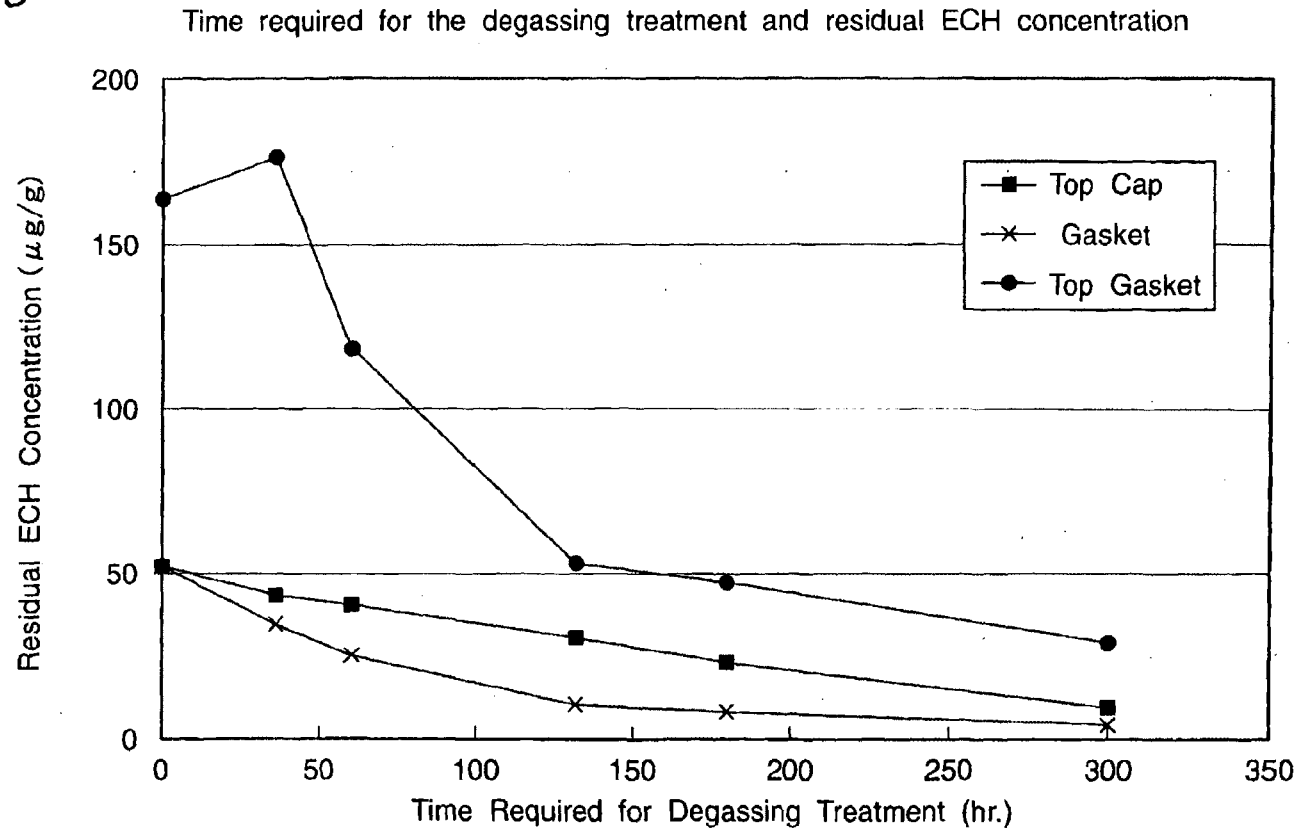
Fig. 6



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INTERNATIONAL SEARCH REPORT

International application No.
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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Int.Cl[7] A61L2/16-2/22, A61L2/26, A61L31/00, B65B55/02-55/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1926-1996 Toroku Jitsuyo Shinan Koho 1994-2001
Kokai Jitsuyo Shinan Koho 1971-2001 Jitsuyo Shinan Toroku Koho 1996-2001

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 8-505786 A (American Sterilizer Company), 25 June, 1996 (25.06.96), page 17, lines 10, 16; page 18, lines 13 to 22 & WO 94/11034 A1 & US 5837193 A & EP 668783 A	1-11
Y	JP 2-4624 A (Japan Crown Cork Co., Ltd.), 09 January, 1990 (09.01.90), page 4, upper left column, line 17 to page 5, upper left column, line 17 (Family: none)	1-11
Y	JP 11-193010 A (Seikagaku Corporation), 21 July, 1999 (21.07.99), Full text; all drawings & WO 99/27971 A2 & EP 971749 A	1-11
Y	JP 64-25865 A (Iwasaki Electric Co., Ltd.), 27 January, 1989 (27.01.89), Full text; Fig. 2 (Family: none)	7,9-11

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

* Special categories of cited documents:
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 62-176455 A (Kawasumi Lab Inc.), 03 August, 1987 (03.08.87), page 3, upper right column, line 16 to page 4, upper left column, line 1; page 5, table 1; page 6, table 2 (Family: none)	9
Y	JP 58-58057 A (Terumo Corporation), 06 April, 1983 (06.04.83), page 3, upper right column & BE 894575 A1 & GB 2108943 A & US 4444330 A & FR 2542612 A	10
Y	JP 6-327760 A (Japan Synthetic Rubber Co., Ltd.), 29 November, 1994 (29.11.94), Par. No. [0035] (Family: none)	11

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(54) Process and equipment for decontamination by radiation of a product

(57) The invention relates to a process for decontamination by radiation of a product (1), characterized in that it comprises at least one exposing step during which at least a first part (6) of said product (1) is exposed to a first radiation level, and at least a second part (5) of said product is exposed to a second radiation level.

The invention also relates to an equipment suitable for such a process.

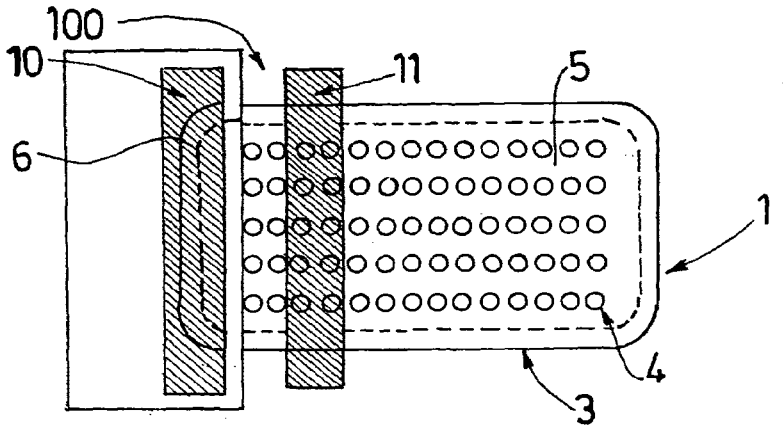

FIG.3

EP 1 944 044 A1

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Description

[0001] The present invention relates to a new process for the decontamination by radiation of a product, in particular a packaging containing medical devices.

[0002] The conditions of sterility in which certain stages of the handling or transportation of items or instruments intended for medical use are to be performed are extremely strict, particularly in the pharmaceutical industry. It is therefore extremely important to produce packaging compatible with such requirements.

[0003] In the present application, the expression "radiation screen" is to be understood as being a screen capable of reflecting or absorbing substantially all the kinetic energy of the electrons from an electron beam, and therefore of preventing these electrons from passing through the said screen.

[0004] In the present application, the expression "semi-permeable radiation screen" is to be understood as being a screen capable of partially reflecting or absorbing the kinetic energy of the electrons from an electron beam, and therefore of allowing only a restricted percentage of these electrons to pass through the said screen.

[0005] In the present application, the expression "selectively impervious material" is to be understood as meaning that the material is designed, in terms of structure, to control any exchange between the inside of the packaging and its external environment. This means, among other things, that the packaging is impervious to contamination by micro-organisms, bacteria and/or a biologically active material likely to come into contact with the packaging while it is being handled, while at the same time remaining permeable to a sterilization or decontamination gas, for example of the ETO (ethylene oxide) type.

[0006] Packagings for items that are or may be sterilized by a sterilization gas are known. In the case of medical items such as syringes, these packaging usually comprise a tub sealed with a cover sheet made of a selectively impervious material. An example of such a packaging is shown on figures 1 and 2. Figure 1 is a cross section view of a product which is a packaging 1 comprising a tub 2 and a cover sheet 3, usually made of a selectively impervious material, said cover sheet 3 being sealed to the tub 2 so as to seal said tub 2 imperviously. The tub 2 comprises a plurality of medical items under the form of syringes bodies 4. In the example shown, the syringes bodies 4 are received in holes designed on a plate placed inside the tub 2 and bearing on a rim provided on the inner wall of the tub 2.

[0007] As it appears clearly from figure 2, which is a top view of the packaging 1 of figure 1, the cover sheet 3 defines a central area 5, located more or less above the syringe bodies 4, which are shown in dashes, and a peripheral outline 6 surrounding this central area 5. The peripheral outline 6 corresponds more or less to the sealing portion of the cover sheet 3 on the tub 2.

[0008] Usually, in order to proceed with the sterilization of the items 4 contained in such a packaging 1, a sterilization gas, for example of the ethylene oxide type, enters the tub 2 through the cover sheet 3 of selectively impervious material. The tub 2 containing the sterilized items 4 is then placed in a protective bag so that the said tub 2 can be transported. In order to proceed with the subsequent handling step, for example the filling of the syringe bodies 4, the protective bag needs to be opened. The packaging 1, which may then be contaminated, needs to be decontaminated before it is taken, for example, into a sterile room.

[0009] Such decontamination can be achieved using multidirectional radiation by an electron beam developing enough energy that when it has passed through the cover sheet, it delivers a dose of radiation of, for example, 25 kGy. This means that it can be taken that the selectively impervious material has been decontaminated throughout its thickness, particularly at the sealing portion located at the peripheral outline 6 of the cover sheet 3 at the interface between the tub 2 and the said material. Indeed, it is very important that the peripheral outline 6 of the cover sheet 3, the downside 6a (see figure 1) of which is not in contact with the sealed atmosphere of the inside of the tub 2, unlike the downside 5a of the central area 5 of the cover sheet 3, be totally decontaminated. As far as the rest of the tub 2 is concerned, namely the bottom and lateral walls of said tub 2, the combination of the density and thickness of said tub 2 is such that it stops these electrons.

[0010] This type of decontamination is not, however, suitable for every type of product transported in the packaging. This is because the electron beam passing through the cover sheet 3 of selectively impervious material carries the risk, on the one hand, of altering or adversely affecting the material of which the syringe bodies 4 or items placed in the tub 2 are made of, for example glass, and on the other hand, of using the oxygen in the air contained in the said tub 2 to generate ozone which carries the risk, on the one hand, of adversely affecting the active products used to fill the syringes and/or, for example, the rubber components present in the tub 2 such as the caps on the needles mounted on the syringe bodies 4, for example, and on the other hand, of polluting the atmosphere.

[0011] There is therefore a need for a process of sterilization of a product, in particular of a packaging containing medical devices as described above, that would allow the efficient decontamination of the peripheral outline of said product while preserving the integrity of the items stored in said product or the internal part of said product, and this whatever the shape of the product.

[0012] For example, a radiation level that would not alter the content of a product such as a packaging is a radiation level of equal to or less than 8 kGy.

[0013] The present invention aims at satisfying this need by proposing a process for decontamination by radiation of a product having at least one side partially transparent to radiations, comprising at least one expos-

ing step during which at least one radiation generator is used in order to expose at least a first part of said product to a first radiation level and at least a second part of said product to a second radiation level, characterized in that said at least one side partially transparent to radiations of said product comprises a first part of said product comprising a peripheral outline, and said second part of said product comprising a central area, said first radiation level being higher than said second radiation level.

[0014] In the present application, the expression "one side opaque to radiations" is to be understood as meaning that the side is made of materials designed to stop all the radiation, ie 100% of the electron beam, it is exposed to.

[0015] In the present application, the expression "one side partially transparent to radiations" is to be understood as meaning that the side is made of materials designed to allow pass through said side a predetermined proportion of radiations, ie the electron beam, it is exposed to.

[0016] In the present application, a preferred partially transparent side is a side made of a material that, while exposed to an radiation level of 50 kGy, allows an radiation level of equal to or less than 8 kGy to pass through said side.

[0017] The process of the invention allows the efficient decontamination of a first part of a product, such as a packaging peripheral outline, and of a second part of said product such as the central area defined by said peripheral outline, without altering the integrity for example of said medical items contained in such a packaging, and regardless from the shape of said product and/or packaging. The product to be decontaminated can also be different from a packaging. It can be a product for which the inside integrity needs to be preserved by preventing electron radiation from reaching it.

[0018] In an embodiment of the invention, the product has at least one side opaque to radiations.

[0019] In an embodiment of the invention, said product having substantially the shape of a box having six sides, said product comprises five sides opaque to radiations and one side partially transparent to radiations.

[0020] In an embodiment of the process of the invention, during said exposing step, said first part and second part are successively exposed to said first and second radiation levels.

[0021] In the present application, the terms "high, low, higher and lower" used to compare the radiation levels emitted by the radiation generators or received by the product correspond to the radiation intensity respectively received and emitted.

[0022] In an embodiment of the process of the invention, during said exposing step, said first part and second part are simultaneously exposed to said first and second radiation levels.

[0023] In an embodiment of the process of the invention, said first and second radiation levels are reached by using at least a high radiation generator and a low radiation generator respectively emitting high and low radiation levels.

[0024] In an embodiment of the process of the invention, said first and second radiation levels are reached by using at least a long radiation exposition period and a short radiation exposition period respectively toward said first and second parts of said product.

[0025] In an embodiment of the process of the invention, said short and long radiation exposition periods are reached by using two different displacement speeds of said product relative to said radiation generator.

[0026] In an embodiment of the process of the invention, said first and second radiation levels are reached by using at least one variable radiation generator set in order to emit a first radiation level toward said first part of said product and a second radiation level toward said second part of said product.

[0027] In an embodiment of the process of the invention, said first and/or second radiation levels are reached by using a radiation generator having a shape roughly similar to said first and/or second part(s) of said product.

[0028] In another embodiment of the process of the invention, said first and second radiation levels are reached by using at least a high radiation generator to emit high radiation level toward said product and placing a radiation screen or semi permeable radiation screen between said high radiation generator and said second part of said product.

[0029] Said radiation screen or semi permeable radiation screen may be fixed with respect to said second part of said product.

[0030] Alternatively, said high radiation generator is mobile with respect to said product and said radiation screen or semi permeable radiation screen is removably fixed to said high radiation generator.

[0031] In another embodiment of the process of the invention, said first and second radiation levels are reached by placing at least a first and a second radiation generator at specific angle positions with respect to respectively the first and second parts of said product.

[0032] Another aspect of the invention is an equipment for radiation decontamination of a product, said product comprising at least one side partially transparent to radiations, said partially transparent side comprising a central area and a peripheral outline, said equipment comprising at least one radiation generator able to emit a predetermined quantity of radiations during a predetermined period of time toward said product, characterized in that it further comprises radiation setting means to set at least a first radiation level received by said peripheral outline of said product and a second radiation level received by said central area of said product and permitting to limit the dose of radiation received by the content of said product, said first radiation level being higher than said second radiation level.

[0033] Said radiation setting means may comprise a radiation screen or semi permeable radiation screen located between said radiation generator and said second

part of said product.

[0034] Said radiation screen or semi permeable screen may be fixed with respect to said second part of said product.

[0035] In an embodiment of the invention, the equipment comprises a high radiation generator and a low radiation generator respectively emitting said first radiation level and said second radiation level.

[0036] In an embodiment of the invention, the equipment comprises displacement means of said product relative to said generator, said displacement means being adjustable to have a low speed for the radiation of one of said first or second part and a high speed for the radiation of the other part.

[0037] In another embodiment of the invention, the equipment comprises a variable radiation generator set in order to emit a first radiation level toward said first part of said product and a second radiation level toward said second part of said product.

[0038] In another embodiment of the invention, the equipment comprises at least a radiation generator having a shape roughly similar to said first and/or second part of said product.

[0039] In another embodiment of the invention, the equipment comprises a first and a second radiation generators located at specific angle positions with respect to respectively the first and second parts of said product.

[0040] Other features and advantages will become apparent from the detailed description given hereinafter, given by way of example with reference to the appended drawings in which:

- Figure 1 is a cross section view of a packaging intended to undergo the decontamination process of the invention,
- Figure 2 is a top view of the packaging of figure 1,
- Figures 3 to 6 are top views of four steps of the process of the invention,
- Figure 7 is a top view of the radiation step of a second embodiment of the process of the invention,
- Figure 8 is a schematic side view of the radiation step of a third embodiment of the process of the invention,
- Figure 9 is a top view of the radiation step of a fourth embodiment of the process of the invention,
- Figure 10 is a top view of the radiation step of a fifth embodiment of the process of the invention.

[0041] Figures 1 and 2 are already described at the beginning of the present description. In the following description of figures 3 to 10, the product 1 to be sterilized by the different embodiments of the process of the invention is a packaging 1 according to figures 1 and 2. In consequence, the references used to designate the different elements of the packaging 1 of figures 1 and 2 are maintained in the description of figures 3 to 10. The packaging 1 has substantially the shape of a box having six sides, a top side, four lateral walls forming four lateral sides, and a bottom side. In the example shown, the cover sheet 3 of the packaging 1 is made of a selectively impervious material such as a layer of filaments of a high density polyethylene bound together by heat and pressure, such as the product sold by the Company Du Pont under the trademark "TYVEK®". The cover sheet 3 forms part of the top side of the packaging 1: the top side is partially transparent to radiations. The five other sides of the packaging, ie the four lateral walls and the bottom side, are sides which are opaque to radiations. In the example shown the syringe bodies 4 are made out of glass.

[0042] In reference to figures 3 to 6, the packaging 1 is to be sterilized according to a first embodiment of the process with an equipment 100 according to the invention. As shown on figure 3, the equipment 100 comprises a first radiation generator which is a high radiation generator 10 and a second radiation generator which is a low radiation generator 11. In particular, the high radiation generator 10 is capable to emit a high radiation level, for example a high energy electron beam, for instance ranging from 25 kGy to 50 kGy. A high radiation generator 10 suitable for the present invention is for example the generator "Kevac" supplied by the company La Calhène and ranging from 150 to 250 kVolts. The low radiation generator 11 is capable to emit a low radiation level, for example a low energy electron beam, for instance ranging from 10 kGy to 30 kGy. A low radiation generator 11 suitable for the present invention is for example a generator "Kevac" supplied by the company La Calhène and ranging from 80 to 150 kVolts.

[0043] In an embodiment of the invention, the packaging 1 is placed on a conveyor (not shown) and is moved with respect to the high and low radiation generators (10, 11) which are immobile. In an alternative embodiment of the process of the invention, the packaging 1 is fixed and the high and low generators (10, 11) move relative to the packaging 1.

[0044] On the example shown on figures 3 to 6, the high and low generators (10, 11) are fixed and the packaging 1 moves from the right of the figures to the left.

[0045] On figure 3, at the beginning of the process of the invention, the low radiation generator 11 is vis-a-vis of the central area 5 of the packaging 1, which is situated above the syringe bodies 4, which are shown in dashes and of part of the peripheral outline 6. Low radiation generator 11 emits a low radiation level towards said central area 5 and part of the peripheral outline 6 in order for them to receive, for example, a radiation level of 25 kGy. Such a low level of radiation does not alter the integrity of the syringe bodies 4 contained in the packaging 1. At the same time, the high radiation generator 10, which is spaced away from the low radiation generator 11, is vis-a-vis of part of the peripheral outline 6 of the cover sheet 3, where a high radiation level is needed in order to decontaminate the top, the inner and the downside (not visible) of the peripheral outline 6 of the cover sheet 3, at the sealing zone with the tub 2. At this stage of the

process of the invention, the high radiation generator 10 emits a high radiation level in order for the part of the peripheral outline 6 to receive, for example, a radiation level of 40 kGy.

[0046] Figure 4 shows the equipment 100 of the invention and the packaging 1 once said packaging 1 has moved a little forward. At this stage of the process of the invention, the low radiation generator 11 is vis-a-vis of further part of the central area 5 and of the peripheral outline 6 and it continues to emit the low radiation level in order for the parts of the central area 5 and of the peripheral outline 6 to receive a radiation level of 25 kGy. The high radiation generator 10 is now also vis-a-vis of a part of the central area 5 of the cover sheet 3 and of a part of the peripheral outline 6. A radiation screen 12 is now provided between the high radiation generator 10 and the central area 5 to prevent the high radiation level emitted by said high radiation generator 10 to damage the syringe bodies 4 situated below the central area 5 of the cover sheet 3. The radiation screen 12 may be chosen in the group of, for example, stainless steel, aluminium, thick plastic plate. Such a radiation screen 12 reflects or absorbs substantially all the kinetic energy of the electrons from the electron beam of the high radiation level emitted by the high radiation generator 10, and therefore prevents these electrons from passing through it. In the example, the radiation screen 12 is connected to the high radiation generator 10 and collapsible in order to be placed between the high radiation generator 10 and the packaging 1 before the central area is submitted to high level radiations. In another example not shown, the radiation screen can be mobile and moves along with the packaging in regards to the high and low radiation generators. As appears clearly on figures 4 and 5, the radiation screen 12 is dimensioned so as to be in regard to the central area 5 only and so as to leave the peripheral outline 6 on the lateral side of the cover sheet 3 free of any screen, so that said peripheral outline 6 is able to receive the high radiation level emitted by the high radiation generator 10.

[0047] Figure 5 shows the equipment 100 of the invention and the packaging 1 once said packaging 1 has moved a little forward with respect to figure 4. The low radiation generator 11 is now vis-a-vis of the peripheral outline 6 of the cover sheet 3 while the high radiation generator 10 is still vis-a-vis of the central area 5 which is protected from the high radiation level emitted by the high radiation generator 10 by the radiation screen 12.

[0048] Figure 6 shows the equipment 100 of the invention and the packaging 1 once said packaging 1 has moved forward so that the high radiation generator 10 is again vis-a-vis of the peripheral outline 6 of the cover sheet 3. At this stage of the process of the invention, the radiation screen 12, which was removably fixed to the high radiation generator 10, is removed. The peripheral outline 6 is then allowed to receive the high radiation level emitted by the high radiation generator 10.

[0049] As not shown on the drawing, the lateral sides and downside of the product are also submitted to radiation level emitted by additionnal radiation generators, for example a low radiation level of 25 kGy.

[0050] With the process of the invention described in figures 3 to 6, the central area 5 of the product 1 has undergone only a low radiation level of 25 kGy. The peripheral outline 6 of the product 1 has undergone a high radiation level of 40 kGy. Therefore, the packaging 1 is decontaminated without altering the syringe bodies 4 it contains. In particular, it has been shown that the peripheral outline 6, and especially the downside 6a of such peripheral outline (see figure 1), is perfectly decontaminated.

[0051] In another embodiment of the invention, the peripheral outline 6 and the central area 5 may be submitted to a same level of radiation emission but for different periods of time, for example by varying the speed displacement of an only radiation generator related to the packaging. In this case, the speed can be chosen lower when two sides of the peripheral outline 6 are submitted to the radiations and higher when the central area 5 is submitted to the radiations. The product can be have a second passage under radiation generator after having been rotated by 90° in order to expose the two other sides of the peripheral outline to a small speed during radiation. The speed difference and the radiation intensity are chosen accordingly with a formula detailed after in order to reach, for example, a radiation level of 25 kGy received by the central area 5 a radiation level of 40 kGy received by the peripheral outline.

[0052] In an embodiment of the invention not shown, the central area 5 of the product 1 is protected by a semi permeable radiation screen. In consequence, when the high radiation generator 10 is vis-a-vis of the central area 5, a certain percentage of the electron beams is allowed to pass through the semi permeable radiation screen, realising the decontamination of the central area 5 of the cover sheet 3. For example, the semi-permeable radiation screen allows 60% of the electrons of the electron beam to pass through it. For example, for an initial electron beam emitted by the high radiation level generator 10 as above, the central area 5 will undergo only a radiation level of 25 kGy, whereas the peripheral outline 6 will still receive the initial high radiation level of 40 kGy. The semi-permeable radiation screen may be chosen in the group comprising for example, stainless steel, aluminium, thin plastic plate, titanium. In such an embodiment, the low radiation generator 11 is no more necessary and may be removed.

[0053] The process of the invention allows the total decontamination of the cover sheet 3, in its central area 5 as well as on its peripheral outline 6 where it is sealed with the tub 2 and where its downside 6a (see figure 1) is not in contact with the sealed atmosphere of the inside of the tub 2.

[0054] Figure 7 illustrates a second embodiment of the process of the invention in which the equipment 100 of the invention comprises a single radiation generator

which is a variable radiation generator. A variable radiation generator suitable for the present invention is the generator "Kevac" supplied by the company La Cahlène equipped with regulation means. In such a case, two different radiation zones, a high radiation zone 13 and a low radiation zone 14 are defined and the radiation level emitted is variable from a radiation zone to the other. The variation of the radiation level is set by varying the parameters of the electron beam from the generator, in accordance with the following formula :

$$D = k \,.\, i \,.\, E/(S \,.\, W)$$

in which:

- D is the sterilization dose in kGy,
- i is the intensity of the electric current in mA (micro Ampère),
- E is the energy of the electrons in KeV (kilo Electron volts),
- S is the speed of the rays from the radiation in m/min,
- W is the width of the rays in cm,
- k is a multiplier factor.

[0055] The decontamination dose may therefore be adjusted by varying the speed of the rays or the energy of the electrons or the intensity of the electric current.

[0056] Similar results may be achieved by using a combination not shown of high and low radiation generators. In this case, the high radiation generator is set in order to emit radiations according to the high radiation zone 13 and no radiation or very few in the low radiation zone 14. The low radiation generator is set in order to emit radiations according to at least the low radiation zone 14.

[0057] Figure 8 illustrates in a schematic way another embodiment of the process of the invention in which a first and a second radiation levels are reached by placing a first and a second radiation generators at specific angle positions with respect to the peripheral outline 6 and the central area 5. The downside 6a of the peripheral outline 6 of the cover sheet 3 is decontaminated by horizontal rays 15 coming from a first radiation generator (not shown) whereas the central area 5 is decontaminated by oblique rays 16 coming from a second radiation generator (not shown). For example, in the embodiment shown on figure 8, the oblique rays 16 may form an angle α of 1 to 45° and preferably from 1 to 10° with the surface of the central area. The lateral walls of the tub 2, which are opaque to radiations, protect the syringe bodies (not shown) contained in the tub 2 from being altered by the horizontal and oblique rays (15, 16).

[0058] Figure 9 illustrates another embodiment of the process of the invention in which the high radiation level is reached by using a first radiation generator 19 having a shape roughly similar to the peripheral outline 6 and emitting flashes of high level of radiation along the peripheral outline 6. The low radiation level is reached using a second radiation generator 18 similar to the low radiation generator 11 of figures 3 to 6. In this example shown, the use of a radiation screen 17 dimensioned to cover substantially all the central area 5 of the cover sheet 3 is optional. The radiation screen 17 may be chosen from the group comprising, for example, stainless steel, aluminium, thick plastic plate. The equipment 100 of the invention is provided with a continuous electric strand 18 which acts as a low radiation generator and creates a low radiation level such as a low energy electron beam in order to decontaminate the central area 5 of the cover sheet 3. The equipment 100 is also provided with a flash electric strand 19 which runs along the peripheral outline 6, forming a rectangle, and which acts as a high radiation generator by creating a high radiation level such as a high energy electron beam in order to decontaminate the peripheral outline 6 of the cover sheet 3. During the emission of the high radiation level by the flash electric strand 19, the central area 5 can be protected by the radiation screen 17 and the syringe bodies contained in the packaging 1 are not altered.

[0059] Figure 10 illustrates an alternative of the embodiment of the invention shown on figure 9. In this embodiment, the rectangular flash electric strand of the equipment 100 of figure 9 is replaced by linear high electric strands 21 able to emit a high radiation level and potentially combined and separated by a linear low electric strand 18 to emit low radiation level. The equipment 100 further comprises a continuous electric strand 20 which creates a low radiation level like in the embodiment of figure 9. The lateral parts of the peripheral outline 6 are then submitted to the high radiation level from the linear high electric strands 21 and the extremity parts of the outline 6 are submitted to a high radiation level reached by the addition of the low radiation level emitted by the linear low electric strand 18 and the low radiation level emitted by the continuous electric strand 20. The central area is submitted to the low radiation level emitted by the continuous electric strand 20.

[0060] The process of the invention and the equipment of the invention allow the efficient decontamination of a first part of a product, such as a packaging for medical items, and of a second part of said product, without altering the integrity of the contents of said product such as medical items, and regardless from the shape of said product and/or packaging. They also enable to efficiently decontaminate any kind of other products for which it is required to expose one of its parts to a lower radiation level than the other parts of it.

Claims

1. Process for decontamination by radiation of a product (1) having at least one side partially transparent to radiations, comprising at least one exposing step during which at least one radiation generator (10,

11; 18; 19) is used in order to expose at least a first part of said product (1) to a first radiation level and at least a second part of said product (1) to a second radiation level, **characterized in that** said at least one side partially transparent to radiations of said product (1) comprises a first part of said product (1) comprising a peripheral outline (6), and said second part of said product (1) comprising a central area (5), said first radiation level being higher than said second radiation level.

2. Process according to claim 1, **characterized in that** said product (1) has substantially the shape of a box having six sides, said product (1) comprising five sides opaque to radiations and one side partially transparent to radiations.

3. Process according to claim 1 or 2, **characterized in that** during said exposing step, said first part and second part are successively exposed to said first and second radiation levels.

4. Process according to claim 1 or 2, **characterized in that** during said exposing step, said first part and second part are simultaneously exposed to said first and second radiation levels.

5. Process according to claim 1 or 2, **characterized in that** said first and second radiation levels are reached by using at least a high radiation generator (10; 19) and a low radiation generator (11; 18) respectively emitting high and low radiation levels.

6. Process according to claim 1 or 2, **characterized in that** said first and second radiation levels are reached by using at least a long radiation exposition period and a short radiation exposition period respectively toward said first and second parts of said product (1).

7. Process according to claim 6, **characterized in that** said short and long radiation exposition periods are reached by using two different displacement speeds of said product (1) relative to said radiation generator (10; 19; 11; 18).

8. Process according to claim 1 or 2, **characterized in that** said first and second radiation levels are reached by using at least one variable radiation generator set in order to emit a first radiation level toward said first part of said product (1) and a second radiation level toward said second part of said product (1).

9. Process according to claim 1 or 2, **characterized in that** said first and/or second radiation levels are reached by using a radiation generator (19) having a shape roughly similar to said first and/or second part of said product (1).

10. Process according to claim 1 or 2, **characterized in that** said first and second radiation levels are reached by using at least a high radiation generator (10; 19) to emit high radiation level toward said product (1) and placing a radiation screen (12; 17) or semi permeable radiation screen between said high radiation generator (10; 19) and said second part of said product (1).

11. Process according to claim 10, **characterized in that** said radiation screen (17) or semi permeable radiation screen is fixed with respect to said second part of said product (1).

12. Process according to claim 10, **characterized in that** said high radiation generator (10) being mobile with respect to said product (1), said radiation screen (12; 17) or semi permeable radiation screen is removably fixed to said high radiation generator (10).

13. Process according to claim 1 or 2, **characterized in that** said first and second radiation levels are reached by placing at least a first and a second radiation generators (15, 16) at specific angle positions with respect to respectively the first and second parts of said product (1).

14. Equipment (100) for radiation decontamination of a product (1), said product (1) comprising at least one side partially transparent to radiations, said partially transparent side comprising a central area (5) and a peripheral outline (6), said equipment comprising at least one radiation generator (10, 11; 18, 19; 20, 21) able to emit a predetermined quantity of radiations during a predetermined period of time toward said product (1), **characterized in that** it further comprises radiation setting means (12; 17) to set at least a first radiation level received by said peripheral outline (6) of said product (1) and a second radiation level received by said central area (5) of said product (1) and permitting to limit the dose of radiation received by the content of said product (1), said first radiation level being higher than said second radiation level.

15. Equipment (100) according to claim 14, **characterized in that** said radiation setting means comprises a radiation screen (12; 17) or a semi permeable radiation screen located between said radiation generator (10; 19) and said central area (5) of said product (1).

16. Equipment (100) according to claim 15, **characterized in that** said radiation screen (17) or semi permeable radiation screen is fixed with respect to said central area (5) of said product (1).

17. Equipment (100) according to claim 14, **characterized in that** it comprises a high radiation generator (10; 19) and a low radiation generator (11; 18) respectively emitting said first radiation level and said second radiation level.

18. Equipment (100) according to claim 14, **characterized in that** it comprises displacement means of said product (1) relative to said generator (10, 11), said displacement means being adjustable to have a low speed for the radiation of one of said peripheral outline (6) or central area (5) and a high speed for the radiation of the other part (5, 6).

19. Equipment (100) according to claim 14, **characterized in that** it comprises a variable radiation generator set in order to emit a first radiation level toward said peripheral outline (6) of said product (1) and a second radiation level toward said central area (5) of said product (1).

20. Equipment (100) according to claim 14, **characterized in that** it comprises at least a radiation generator (19) having a shape roughly similar to said central area (5) and/or peripheral outline (6) of said product (1).

21. Equipment (100) according to claim 14, **characterized in that** it comprises a first and a second radiation generators located at specific angle positions with respect to respectively the central area (5) and peripheral outline (6) of said product (1).

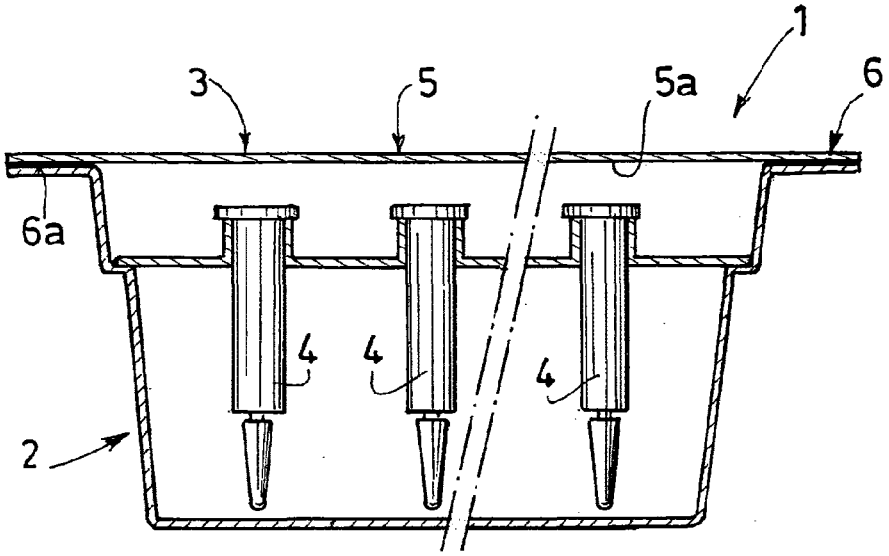

FIG.1

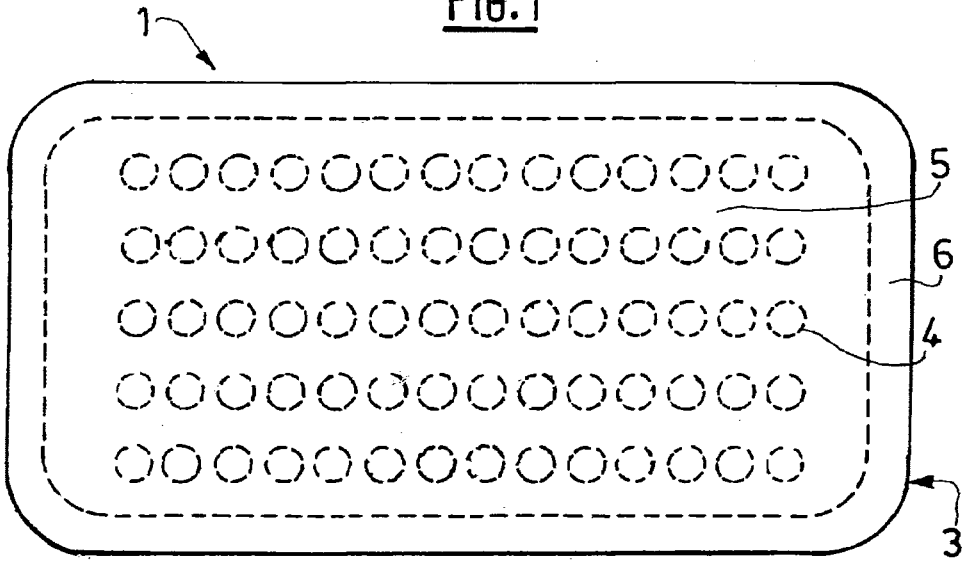

FIG.2

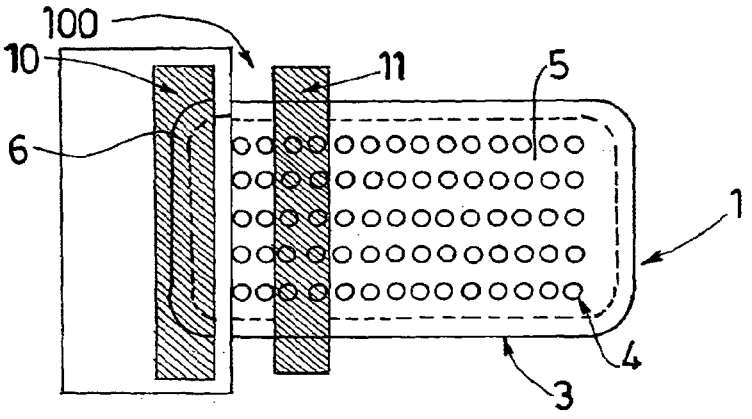

FIG.3

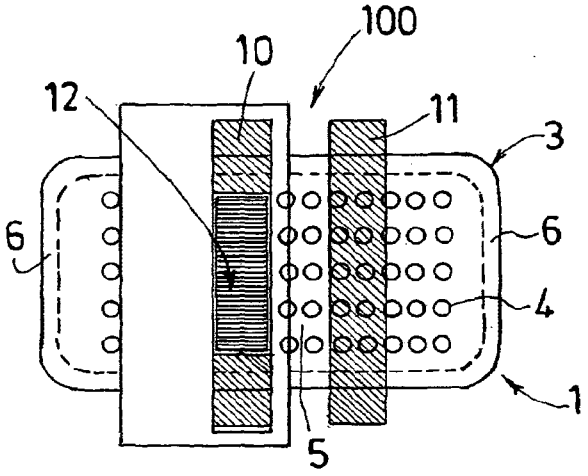

FIG.4

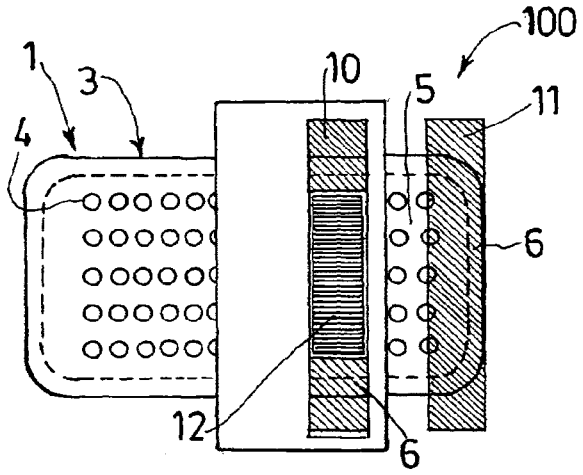

FIG.5

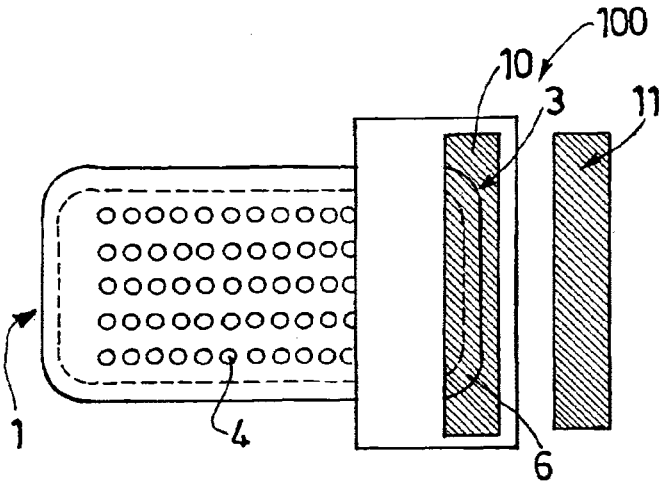

FIG.6

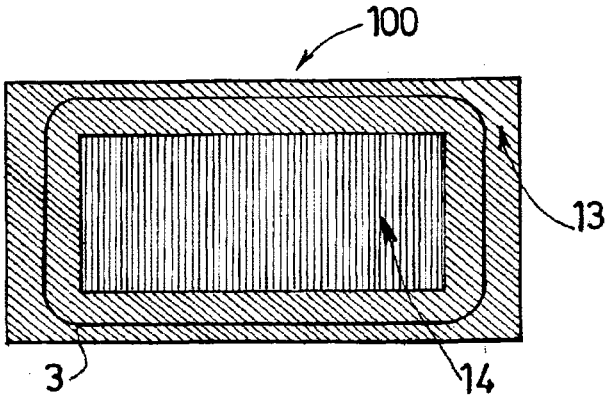

FIG.7

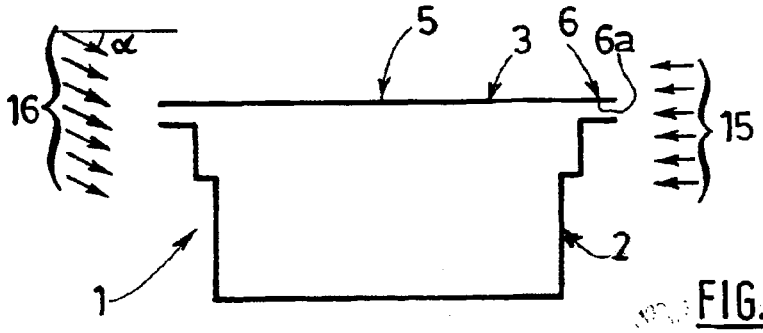

FIG.8

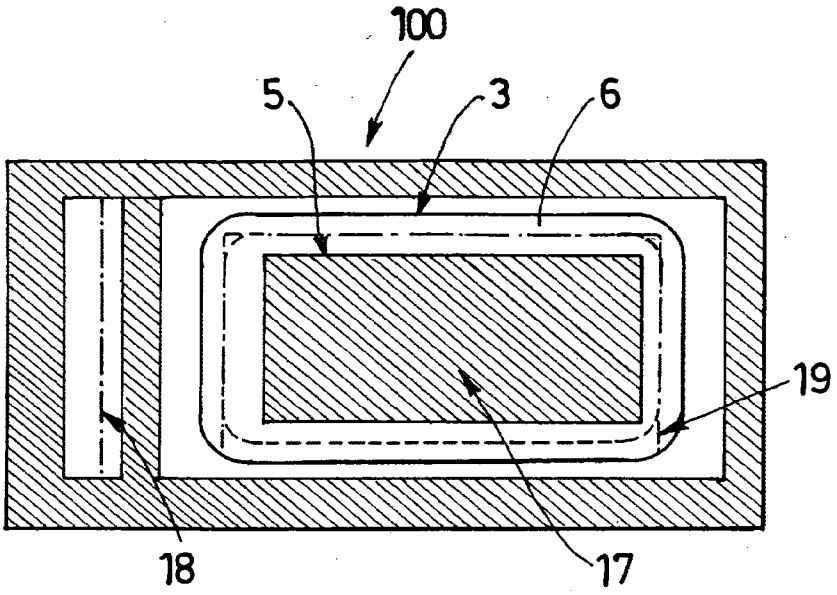

FIG.9

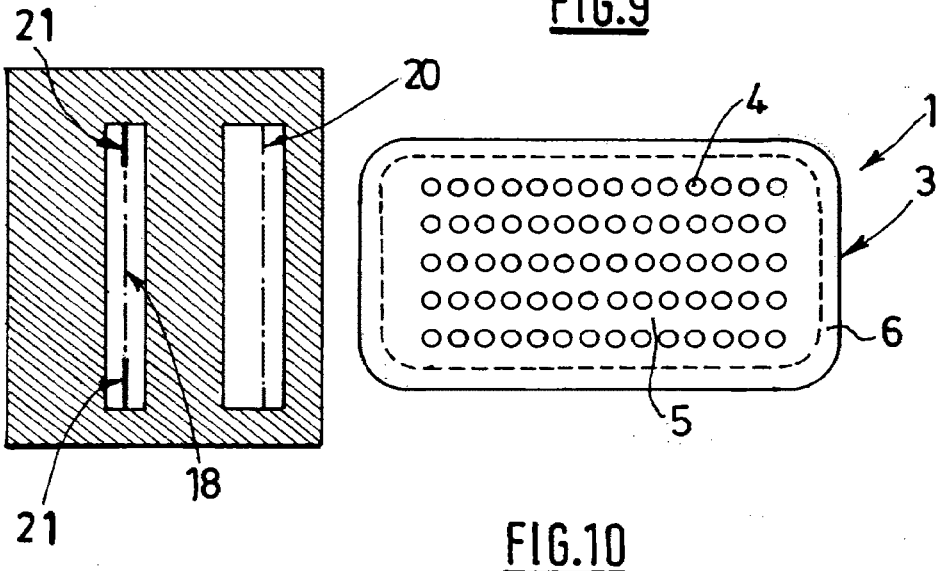

FIG.10

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 08 35 6002

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 6 203 755 B1 (ODLAND THOMAS L [US]) 20 March 2001 (2001-03-20) * column 2, line 16 - column 4, line 16 * * column 6, lines 18-28 *	1,2, 14-16, 18,19	INV. A61L2/08 B65B55/08
Y		3-13	

X	US 2005/078789 A1 (MILLER ROBERT BRUCE [US]) 14 April 2005 (2005-04-14) * paragraphs [0029] - [0036], [0044]; figures 2,5,8,9 *	14,17-21	
Y		3-9,13	

X	WO 2004/110157 A (GRITTI MASSIMO [IT]) 23 December 2004 (2004-12-23) * page 2, line 16 - page 3, line 26; figure *	14, 17-19,21	
Y		3-9,13	

X	US 5 496 302 A (MINSHALL BILLY W [US] ET AL) 5 March 1996 (1996-03-05) * column 1, lines 28-37 * * column 2, lines 28-40 * * column 3, lines 7-53 * * column 7, lines 9-39 * * column 8, lines 23-27 * * column 9, line 55 - column 10, line 55 *	14-16,19	TECHNICAL FIELDS SEARCHED (IPC) A61L B65B A23L
Y		10-12	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	29 May 2008	Maremonti, Michele

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

Application Number
EP 08 35 6002

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☒ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

☐ The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 08 35 6002

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1(part),2-5,13,14(part),17,21

   Process and equipment for decontamination by radiation of a product by using at least a first and a second radiation generator.

   ---

2. claims: 1(part),6,7,14(part),18

   Process and equipment for decontamination by radiation of a product by using a long radiation exposition period and a short radiation exposition period respectively toward a first and a second part of the product.

   ---

3. claims: 1(part),8,14(part),19

   Process and equipment for decontamination by radiation of a product by using at least one variable radiation generator.

   ---

4. claims: 1(part),9,14(part),20

   Process and equipment for decontamination by radiation of a product by using at least a radiation generator having a shape roughly similar to at leat a part of the product.

   ---

5. claims: 1(part),10-12,14(part),15,16

   Process and equipment for decontamination by radiation of a product by using at least a radiation generator and a radiation screen.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 08 35 6002

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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29-05-2008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6203755 B1	20-03-2001	AU 2096995 A	18-09-1995
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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PCT

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PCT/US2007/088728

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21 December 2007 (21.12.2007)

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(26) Publication Language: English

(30) Priority Data:
60/871,426 21 December 2006 (21.12.2006) US

(71) Applicant *(for all designated States except US)*: **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LAM, Xanthe, M.** [US/US]; 662 Orchid Drive, South San Francisco, CA 94080 (US). **NGUYEN, Tue** [US/US]; 16 Woodleaf Ave., Redwood City, CA 94061 (US).

(74) Agent: **KALINOWSKI, Grant**; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US).

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

WO 2008/077155 A1

(54) Title: STERILIZATION OF OBJECTS CONTAINING BIOLOGICAL MOLECULES

(57) Abstract: The invention relates to methods for surface-sterilizing objects containing ethylene-oxide-sensitive, temperature-sensitive compounds, including biological molecules.

STERILIZATION OF OBJECTS CONTAINING BIOLOGICAL MOLECULES

Cross-Reference to Related Applications

This application claims the benefit of U.S. Provisional Application No. 60/871,426, filed December 22, 2007, which is incorporated by reference in its entirety.

Field of Invention

The invention relates to methods for surface-sterilizing objects containing ethylene-oxide-sensitive, temperature-sensitive compounds, including biological molecules.

Background of Invention

Objects used in medical applications are generally sterilized before use. Sterilization can be accomplished by a variety of methods including, *e.g.*, steam sterilization, radiation sterilization, gas sterilization (*e.g.* with ethylene oxide), and chemical sterilization. However, these treatments cannot be used for objects containing pharmaceutical compositions because their active ingredients are typically sensitive to them. For example, steam and gas sterilization are generally performed at high temperatures (approx. 45°C to 55°C or higher) that damage certain active ingredients in pharmaceutical compositions. Similarly, the agents used for radiation or chemical sterilization generally cause chemical damage to the active ingredients. Consequently, pharmaceutical compositions are generally sterilized by an alternative method, *e.g.* by filtration, and then packaged into separately sterilized objects. Because of the complexity of this process, it is difficult to also ensure the sterility of the surfaces of the objects.

In many circumstances it would be advantageous to sterilize the surfaces of these objects in order to reduce the risk of contamination during subsequent handling. For example, there is an increased risk of endophthalmitis after intraocular injection if the surface of the syringe used for injection is not sterilized. Thus, there remains a need for efficient and cost-effective methods of surface-sterilizing objects containing ethylene-oxide-sensitive, temperature-sensitive compounds, such as biological molecules, without a significant adverse effect on their activity or integrity.

Summary of the Invention

The invention relates to methods for surface-sterilizing objects containing ethylene-oxide-sensitive, temperature-sensitive compounds, such as biological molecules. The invention is based, in part, on the surprising discovery of ethylene-oxide-based sterilization conditions that will effectively sterilize the surface of an object but which do not significantly damage ethylene-oxide-sensitive, temperature-sensitive compounds contained inside.

In one aspect, the invention provides a method for surface-sterilizing an object having an ethylene-oxide(EtO)-impermeable interior space containing a compound with a temperature-sensitive and EtO-sensitive activity by exposing the object to EtO under conditions such that the object is surface-sterilized and the compound retains at least 50% of said activity. In some embodiments, the conditions comprise: a) temperature between 25°C and 35°C; b) EtO concentration of between 300 mg/L and 800 mg/L; and c) relative humidity between 45% and 60%; for between 1 and 6 hours. In some embodiments, the conditions comprise: a) temperature between 27°C and 33°C; b) EtO concentration of between 300 mg/L and 600 mg/L; and c) relative humidity between 48% and 52%; for between 1 and 6 hours. In some embodiments, the conditions comprise: a) temperature of 30°C; b) EtO concentration of 600 mg/L; and c) relative humidity of 50%; for 1, 1.5 or 2 hours.

In some embodiments, the compound retains at least 90% of said activity. In some embodiments, the compound is a polypeptide, *e.g.* an antibody, which includes monoclonal antibodies, chimeric antibodies, humanized antibodies or human antibodies. In some embodiments where the compound is a polypeptide, the percent alkylation of the polypeptide is not statistically different from a control polypeptide not exposed to EtO. In some embodiments, the antibody is an antigen-binding fragment, *e.g.* a Fab fragment. In some embodiments, the Fab fragment binds VEGF, *e.g.* ranibizumab (LUCENTIS®).

In some embodiments, the compound is present in an aqueous pharmaceutical composition, *e.g.* a composition comprising at least one of: an amino acid, a disaccharide and a non-ionic surfactant. In some embodiments the pharmaceutical composition comprises histidine, trehalose and polysorbate 20.

In some embodiments, the object is a syringe. In some embodiments the syringe comprises glass and comprises a stopper comprising D777-7 laminated with FluroTec®; and a tip cap comprising D777-7 laminated with FluroTec® or D21-7H laminated with FluroTec®. In some embodiments, the object is contained within a package comprising an EtO-permeable material, e.g. TYVEK®.

In another aspect, the invention provides an object produced by a method of the invention.

Detailed Description of the Invention

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the relevant art. All patents and publications mentioned herein are expressly incorporated by reference in their entireties for all purposes.

Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising," indicate the inclusion of any recited integer or group of integers but not the exclusion of any other integer or group of integers.

As used herein, a "compound" is any molecule that has an activity which can be measured. Compounds according to the present invention generally have a pharmacological activity. For example, the activity of a compound may include the ability to bind to a particular molecule, to inhibit (or enhance) an enzymatic activity, induce a particular physiological response, *etc.*

As used herein, an "ethylene-oxide-impermeable" or "EtO-impermeable" object is one in which no more than 0.5 ppm EtO is present inside the object after EtO sterilization. As EtO-impermable object my comprise, e.g., glass and/or certain plastics.

As used herein, an activity is "ethylene-oxide-sensitive" or "EtO-sensitive" when the activity is reduced following exposure to ethylene oxide (EtO). In some embodiments, the exposure is to 10 ppm EtO at 30°C for 3 days. In some embodiments, the activity is reduced by at least 90% following EtO exposure. In some embodiments, the activity is reduced by less that 90%, e.g. at least 80%, 70%, 60% or 50%.

As used herein, "percent alkylation" in the context of a polypeptide is the percentage of polypeptide that is in the basic peak relative to polypeptide that is in the acidic or main peaks as measured by IEC.

As used herein, an activity is "temperature-sensitive" when the activity is reduced following exposure to a high temperature, *e.g.* above room temperature. In some embodiments, the exposure is for 2 hours. In some embodiments, the activity is reduced following exposure to temperatures of at least 30°C, *e.g.* at least 35°C, 40°C, 45°C, 50°C, 55°C or 60°C. In some embodiments, the activity is reduced by at least 90% following exposure to a high temperature. In some embodiments, the activity is reduced by less that

90%, e.g. at least 80%, 70%, 60% or 50%. In some embodiments, the activity is reduced by at least 5% or at least 1%.

As used herein, the surfact of an object is "sterilized" when the amount of at least one biological contaminant present on the surface of the object being treated according to the present invention is reduced following the treatment. Typically, the amount is reduced by at least one log (*i.e.* by at least 10-fold). In some embodiments of the invention, the amount is reduced by 2 logs, 3 logs, 4 logs, 5 logs, or 6 logs.

As used herein, a "biological contaminant" is a contaminant that, upon direct or indirect contact with a biological material, may have a deleterious effect on the biological material. Examples of biological contaminants include viruses; bacteria or bacterial spores; parasites; yeasts; molds; mycoplasmas; and prions. Further, a biological contaminant need not be naturally or accidentally present. For example, a biological contaminant may be *Bacillus subtilis* spores deliberately placed on the surface of an object to be sterilized in order to monitor the success of the sterilization.

As used herein, a "subject" is a human subject or patient.

As used herein, a "polypeptide" is broadly defined and includes both short polypeptides as well as longer polypeptides such as proteins and protein fragments. For example, the term polypeptide may include from dipeptides, tripeptides, and the like to enzymes, hormones, antibodies or any fragments of these that has an activity.

As used here, the term "antibody" is used in the broadest sense and specifically covers monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.* bispecific antibodies), and antibody fragments, so long as they exhibit the desired biological activity.

The term "monoclonal antibody" as used herein refers to an antibody from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical and/or bind the same epitope(s), except for possible variants that may arise during production of the monoclonal antibody, such variants generally being present in minor amounts. Such monoclonal antibody typically includes an antibody comprising a polypeptide sequence that binds a target, wherein the target-binding polypeptide sequence was obtained by a process that includes the selection of a single target binding polypeptide sequence from a plurality of polypeptide sequences. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones or recombinant DNA clones. It should be understood that the selected target binding sequence can be further altered, for example, to improve affinity

for the target, to humanize the target binding sequence, to improve its production in cell culture, to reduce its immunogenicity *in vivo*, to create a multispecific antibody, *etc.*, and that an antibody comprising the altered target binding sequence is also a monoclonal antibody of this invention. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. In addition to their specificity, monoclonal antibody preparations are advantageous in that they are typically uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including, for example, the hybridoma method (*e.g.*, Kohler *et al., Nature*, 256:495 (1975); Harlow *et al., Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling *et al.*, in: Monoclonal Antibodies and T-Cell Hybridomas 563-681, (Elsevier, N.Y., 1981)), recombinant DNA methods (see, *e.g.*, U.S. Patent No. 4,816,567), phage display technologies (see, *e.g.*, Clackson *et al., Nature*, 352:624-628 (1991); Marks *et al., J. Mol. Biol.*, 222:581-597 (1991); Sidhu *et al., J. Mol. Biol.* 338(2):299-310 (2004); Lee *et al., J.Mol.Biol.*340(5):1073-1093 (2004); Fellouse, *Proc. Nat. Acad. Sci. USA* 101(34):12467-12472 (2004); and Lee *et al. J. Immunol. Methods* 284(1-2):119-132 (2004), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, *e.g.,* WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits *et al., Proc. Natl. Acad. Sci. USA*, 90:2551 (1993); Jakobovits *et al., Nature*, 362:255-258 (1993); *Bruggemann et al., Year in Immuno.*, 7:33 (1993); U.S. Patent Nos. 5,545,806; 5,569,825; 5,591,669 (all of GenPharm); U.S. Patent No. 5,545,807; WO 1997/17852; U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016; Marks *et al., Bio/Technology*, 10: 779-783 (1992); Lonberg *et al., Nature*, 368: 856-859 (1994); Morrison, *Nature*, 368: 812-813 (1994); Fishwild *et al., Nature Biotechnology*, 14: 845-851 (1996); Neuberger, *Nature Biotechnology*, 14: 826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.*, 13: 65-93 (1995)).

The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding

sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; and Morrison *et al., Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (*e.g.* Old World Monkey, Ape etc) and human constant region sequences, as well as "humanized" antibodies.

"Humanized" forms of non-human (*e.g.*, rodent) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al., Nature* 321:522-525 (1986); Riechmann *et al., Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992).

"Antibody fragments" comprise a portion of an intact antibody, preferably comprising the antigen binding region thereof ("an antigen-binding fragment"). Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragment(s).

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment,

whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-binding sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and antigen-binding site. This region consists of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. It is in this configuration that the three hypervariable regions of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six hypervariable regions confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three hypervariable regions specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear at least one free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

In some embodiments, particular antibodies or molecules are used in the methods of the invention. For example, exemplary antibodies include HER2 antibodies including trastuzumab (HERCEPTIN®) (Carter *et al.*, *Proc. Natl. Acad. Sci. USA*, 89:4285-4289 (1992), U.S. Patent No. 5,725,856) and pertuzumab (OMNITARG™) (WO01/00245); CD20 antibodies (see below); IL-8 antibodies (St John *et al.*, *Chest*, 103:932 (1993), and International Publication No. WO 95/23865); VEGF or VEGF receptor antibodies including humanized and/or affinity matured VEGF antibodies such as the humanized VEGF antibody huA4.6.1 bevacizumab (AVASTIN®) and ranibizumab (LUCENTIS®) (Kim et al., *Growth Factors*, 7:53-64 (1992), International Publication Nos. WO 96/30046 and WO 98/45331); PSCA antibodies (WO01/40309); CD40 antibodies, including S2C6 and humanized variants thereof (WO00/75348) and TNX 100 (Chiron/Tanox); CD11a antibodies including efalizumab (RAPTIVA®) (US Patent No. 5,622,700, WO 98/23761, Steppe *et al.*, *Transplant Intl.* 4:3-7 (1991), and Hourmant *et al.*, *Transplantation* 58:377-380 (1994)); antibodies that bind IgE including omalizumab (XOLAIR®) (Presta *et al.*, *J. Immunol.* 151:2623-2632

(1993), and International Publication Nos. WO 93/04173, WO 95/19181, and WO 99/01556; US Patent Nos. 5,091,313 and 5,714,338); CD18 antibodies (US Patent No. 5,622,700, or as in WO 97/26912); Apo-2 receptor antibody antibodies (WO 98/51793); TNF-α antibodies including cA2 or infliximab (REMICADE®), CDP571, MAK-195, adalimumab (HUMIRA™), CDP-870 (Celltech), anti-TNF-α polyclonal antibody (e.g. PASSTNF-a™; Verigen); Tissue Factor (TF) antibodies (European Patent No. 0 420 937 B1); α4-α7 integrin antibodies (WO 98/06248); EGFR antibodies (chimerized or humanized 225 antibody, cetuximab (ERBUTIX®; ImClone; WO 96/40210) or panitumumab (VECTIBIX™; Amgen)); CD3 antibodies such as OKT3 (US Patent No. 4,515,893); CD25 or Tac antibodies such as CHI-621 (SIMULECT®) and ZENAPAX® (US Patent No. 5,693,762); CD4 antibodies such as the cM-7412 antibody (Choy *et al.*, *Arthritis Rheum* 39(1):52-56 (1996)); CD52 antibodies such as CAMPATH-1H (ILEX/Berlex) (Riechmann *et al.*, *Nature* 332:323-337 (1988)); Fc receptor antibodies such as the M22 antibody directed against FçRI as in Graziano *et al.*, *J. Immunol.* 155(10):4996-5002 (1995); an alpha 4 integrin antibody such as natalizumab (ANTEGREN®) available from Biogen Idec/Elan; carcinoembryonic antigen (CEA) antibodies such as hMN-14 (Sharkey *et al.*, *Cancer Res.* 55(23Suppl): 5935s-5945s (1995); antibodies directed against breast epithelial cells including huBrE-3, hu-Mc 3 and CHL6 (Ceriani *et al.*, *Cancer Res.* 55(23): 5852s-5856s (1995); and Richman *et al.*, *Cancer Res.* 55(23 Supp): 5916s-5920s (1995)); antibodies that bind to colon carcinoma cells such as C242 (Litton *et al.*, *Eur. J. Immunol.* 26(1):1-9 (1996)); CD38 antibodies, e.g. AT 13/5 (Ellis *et al.*, *J. Immunol.* 155(2):925-937 (1995)); CD33 antibodies such as Hu M195 (Jurcic *et al.*, *Cancer Res* 55(23 Suppl):5908s-5910s (1995) and CMA-676 or CDP771; CD22 antibodies such as LL2 or epratuzumab (LYMPHOCIDE®; Immunomedics), including epratuzumab Y-90 (Juweid *et al.*, *Cancer Res* 55(23 Suppl):5899s-5907s (1995)), CD22 antibody (Abiogen, Italy), CMC 544 (Wyeth/Celltech), combotox (UT Southwestern), BL22 (NIH), and LympoScan Tc99 (Immunomedics); EpCAM antibodies such as 17-1A (PANOREX®); GpIIb/IIIa antibodies such as abciximab or c7E3 Fab (REOPRO®); RSV antibodies such as MEDI-493 (SYNAGIS®); CMV antibodies such as PROTOVIR®; HIV antibodies such as PRO542; hepatitis antibodies such as the Hep B antibody OSTAVIR®; CA 125 antibody OvaRex; idiotypic GD3 epitope antibody BEC2; γ3 antibody (e.g. VITAXIN®; Medimmune); human renal cell carcinoma antibody such as ch-G250; ING-1; anti-human 17-1A antibody (3622W94); anti-human colorectal tumor antibody (A33); anti-human melanoma antibody R24 directed against GD3 ganglioside; anti-human squamous-cell

carcinoma (SF-25); human leukocyte antigen (HLA) antibody such as Smart ID10 and the anti-HLA DR antibody Oncolym (Lym-1); CD37 antibody such as TRU 016 (Trubion); IL-21 antibody (Zymogenetics/Novo Nordisk); anti-B cell antibody (Impheron); B cell targeting MAb (Immunogen/Aventis); 1D09C3 (Morphosys/GPC); LymphoRad 131 (HGS); Lym-1 antibody Y-90 (USC); LIF 226 (Enhanced Lifesci.); BAFF antibody (e.g., WO 03/33658); BAFF receptor antibody (e.g., WO 02/24909); BR3 antibody; Blys antibody such as belimumab; LYMPHOSTAT -B™; anti-Lym-1 Oncolym (USC/Peregrine); ISF 154 (UCSD/Roche/Tragen); gomiliximа (Idec 152; Biogen Idec); IL-6 receptor antibody such as atlizumab (ACTEMRA™; Chugai/Roche); IL-15 antibody such as HuMax-Il-15 (Genmab/Amgen); chemokine receptor antibody, such as a CCR2 antibody (e.g. MLN1202; Millennium); anti-complement antibody, such as C5 antibody (e.g. eculizumab, 5G1.1; Alexion); oral formulation of human immunoglobulin (e.g. IgPO; Protein Therapeutics); IL-12 antibody such as ABT-874 (CAT/Abbott); and Teneliximab (BMS-224818). In some embodiments, the antibody herein is ranibizumab.

Examples of CD20 antibodies include: "C2B8," which is now called "rituximab" ("RITUXAN®") (US Patent No. 5,736,137); the yttrium-[90]-labelled 2B8 murine antibody designated "Y2B8" or "Ibritumomab Tiuxetan" (ZEVALIN®) commercially available from IDEC Pharmaceuticals, Inc. (US Patent No. 5,736,137; 2B8 deposited with ATCC under accession no. HB11388 on June 22, 1993); murine IgG2a "B1," also called "Tositumomab," optionally labelled with ^{131}I to generate the "^{131}I-B1" or "iodine I^{131} tositumomab" antibody (BEXXAR™) commercially available from Corixa (see, also, US Patent No. 5,595,721); murine monoclonal antibody "1F5" (Press *et al.*, *Blood* 69(2):584-591 (1987) and variants thereof including "framework patched" or humanized 1F5 (WO 2003/002607, Leung, S.; ATCC deposit HB-96450); murine 2H7 and chimeric 2H7 antibody (US Patent No. 5,677,180); humanized 2H7 (WO 2004/056312, Lowman *et al.*, and as set forth below); 2F2 (HuMax-CD20), a fully human, high-affinity antibody targeted at the CD20 molecule in the cell membrane of B-cells (Genmab, Denmark; see, for example, Glennie and van de Winkel, *Drug Discovery Today* 8: 503-510 (2003) and Cragg *et al.*, *Blood* 101: 1045-1052 (2003); WO 2004/035607; US2004/0167319); the human monoclonal antibodies set forth in WO 2004/035607 and US2004/0167319 (Teeling *et al.*); the antibodies having complex N-glycoside-linked sugar chains bound to the Fc region described in US 2004/0093621 (Shitara *et al.*); monoclonal antibodies and antigen-binding fragments binding to CD20 (WO 2005/000901, Tedder *et al.*) such as HB20-3, HB20-4, HB20-25, and MB20-11; CD20

binding molecules such as the AME series of antibodies, e.g., AME 33 antibodies as set forth in WO 2004/103404 and US2005/0025764 (Watkins *et al.*, Eli Lilly/Applied Molecular Evolution, AME); CD20 binding molecules such as those described in US 2005/0025764 (Watkins *et al.*); A20 antibody or variants thereof such as chimeric or humanized A20 antibody (cA20, hA20, respectively) or IMMU-106 (US 2003/0219433, Immunomedics); CD20-binding antibodies, including epitope-depleted Leu-16, 1H4, or 2B8, optionally conjugated with IL-2, as in US 2005/0069545A1 and WO 2005/16969 (Carr *et al.*); bispecific antibody that binds CD22 and CD20, for example, hLL2xhA20 (WO2005/14618, Chang *et al.*); monoclonal antibodies L27, G28-2, 93-1B3, B-C1 or NU-B2 available from the International Leukocyte Typing Workshop (Valentine *et al.*, In: Leukocyte Typing III (McMichael, Ed., p. 440, Oxford University Press (1987)); 1H4 (Haisma *et al.*, *Blood* 92:184 (1998)); anti-CD20 auristatin E conjugate (Seattle Genetics); anti-CD20-IL2 (EMD/Biovation/City of Hope); anti-CD20 MAb therapy (EpiCyte); anti-CD20 antibody TRU 015 (Trubion). The preferred CD20 antibodies herein are chimeric, humanized, or human CD20 antibodies, more preferably rituximab, humanized 2H7, 2F2 (Hu-Max-CD20) human CD20 antibody (Genmab), and humanized A20 antibody (Immunomedics).

In some embodiments, a "hormone" is used in the methods of the invention. This generally refers to polypeptide hormones, which are generally secreted by glandular organs with ducts. Included among the hormones are, for example, growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; estradiol; hormone-replacement therapy; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, or testolactone; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); prolactin, placental lactogen, mouse gonadotropin-associated peptide, gonadotropin-releasing hormone; inhibin; activin; mullerian-inhibiting substance; and thrombopoietin. As used herein, the term hormone includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native-sequence hormone, including synthetically produced small-molecule entities and pharmaceutically acceptable derivatives and salts thereof.

In some embodiments, a "growth factor" is used in the methods of the invention. This generally refers to proteins that promote growth, and include, for example, hepatic growth factor; fibroblast growth factor; vascular endothelial growth factor; nerve growth factors such

as NGF-β; platelet-derived growth factor; transforming growth factors (TGFs) such as TGF-α and TGF-β; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon-α, -β, and -γ; and colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF). As used herein, the term growth factor includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native-sequence growth factor, including synthetically produced small-molecule entities and pharmaceutically acceptable derivatives and salts thereof.

In some embodiments, non-polypeptide compounds are used in the methods of the invention. These include, e.g., pegaptanib (MACUGEN®; Eyetech Pharmaceuticals), steroids, and compounds used for RNA-interference mediated therapy.

As used herein, a "pharmaceutical composition" is a solution comprising a compound which is suitable for administration to a subject. Pharmaceutical compositions according to the invention may be obtained by mixing the compound with optional physiologically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of aqueous solutions, lyophilized or other dried formulations. Acceptable carriers, excipients, or stabilizers are nontoxic to subjects at the dosages and concentrations employed, and may include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.,* Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™, polyethylene glycol (PEG), or a polysorbate (e.g. polysorbate 20). In some embodiments, the pharmaceutical composition is designed for intraocular injection.

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that

do not adversely affect each other. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

Generally, the formulations placed inside the object are also sterile. This is readily accomplished, *e.g.* by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the fusion polypeptide, which matrices are in the form of shaped articles, *e.g.,* films, or microcapsule. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

The methods of the invention are typically used to sterilize objects containing pharmaceutical formulations. For example, the methods of the invention may be used with syringes, vials or cartridges (such as are used in devices designed for multiple injections). In

addition, the method of the invention may be used with a syringe with or without a needle. In the latter case, some sort of cap or needle shield is generally positioned where the needle will subsequently be attached.

The following example is intended merely to illustrate the practice of the present invention and is not provided by way of limitation. The disclosures of all patent and scientific literatures cited herein are expressly incorporated in their entirety by reference.

EXAMPLE

Identification of EtO sterilization conditions for surface sterilization of objects containing ethylene-oxide-sensitive, temperature-sensitive compounds.

We performed experiments to identify whether there were parameters for EtO sterilization that would effectively sterilize the surface of an object but which do not damage an ethylene-oxide-sensitive, temperature-sensitive compound contained inside. We performed EtO sterilization runs on syringes containing a ranibizumab solution (at a protein concentration indicated in Table 2 in a solution with 10 mM histidine HCl, 10% α, α - trehalose dehydrate, 0.01% polysorbate 20, pH 5.5) where each run had the following standard EtO sterilization steps: (1) set temperature; (2) evacuate chamber to about 5.0" HgA; (3) leak test; (4) wash twice with nitrogen; (5) humidify chamber and incubate about 30 min; (6) inject EtO gas and incubate for dwell time; (7) evacuate chamber to about 5.0" HgA; and (8) wash four times with nitrogen (each wash cycle is about 15-20 min). In addition to the syringe, each run also included a paper strip with approximately 1.9 x 10^6 *Bacillus subtilis* spores, which was used to monitor the sterilization as follows: the strip was soaked in media, vortexed vigorously and then serial dilutions were plated and grown for one week. We then varied the following sterilization-critical factors as indicated in Table 1: temperature, relative humidity, time of exposure (gas dwell), and EtO concentration.

Table 1. Test runs for EtO Sterilization

Parameters	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run 10
Temp (°C)	37	37	40	37	37	30	30	30	30	30
Gas dwell (h)	1	2	1	2	2	2	2	6	6	2
EtO (mg/l)	600	600	600	600	400	600	400	600	600	600
Relative humidity	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%

Sterility (log reduction)	3.2	5.5	4.2	>6	6.3	3.4	2.1	NT (not tested)	NT	5.2

After each run, the ranibizumab in the syringe was tested in a variety of ways to measure its activity. First, the physical integrity of the molecule was analyzed by size-exclusion chromatography (SEC), ion-exchange chromatography (IEC), reverse-phase high-performance liquid chromatography (rp-HPLC) and capillary electrophoresis-SDS (CE-SDS). As shown below in Table 2, the ranibizumab in the syringe remained largely intact following each of the runs.

In addition, we tested the functionality of the ranibizumab in the treated syringes for function by testing both its ability to bind VEGF by ELISA and its ability to antagonize VEGF induction of human umbilical vein endothelial cell (HUVEC) growth. As shown in Table 2, in all runs tested ranibizumab retained both its ability to bind to VEGF and its ability to antagonize VEGF-mediated induction of HUVEC cell growth.

Table 2. Protein is intact and active after EtO sterilization.

	Protein conc. (mg/ml)	pH	SEC % monomer	IEC % main peak	rp-HPLC % main peak	CE-SDS % main peak	ELISA % activity	HUVEC % potency
Control	5.9	5.4	99.8	97.7	98.5	96.4	101	97
Run 1	5.9	5.5	99.7	98.1	99.2	95.8	109	91
Run 2	5.9	5.6	99.6	98.1	99.2	95.7	100	91
Run 3	6.1	5.6	99.6	98.2	99.3	95.8	102	93
Control	9.8	5.6	99.7	98.2	99.3	96.8	100	NT
Run 4	9.9	5.7	99.7	98.6	99.3	96.6	103	NT
Run 5	9.8	5.7	99.7	98.1	99.3	96.6	106	NT
Run 6	9.8	5.7	99.7	98.2	99.3	96.6	109	NT
Run 7	9.9	5.7	99.6	98.1	99.3	96.4	105	NT
Control	9.8	5.6	99.7	98.2	99.3	96.8	100	NT
Run 8	9.8	5.7	99.7	98.2	99.3	96.6	109	NT
Run 9	10.1	5.6	99.6	98.0	99.1	96.4	98	NT
Run 10	10.0	5.6	99.6	97.9	98.9	96.4	112	NT

We next tested additional conditions with different dwell times during the EtO cycle, different numbers of washes and different container components. We performed EtO sterilization runs on syringes containing a ranibizumab solution (at 10.0 mg/ml in a solution with 10 mM histidine HCl, 10% α, α -trehalose dehydrate, 0.01% polysorbate 20, pH 5.6) where each run had the following standard EtO sterilization steps: (1) set temperature to 30°C; (2) evacuate chamber to about 5.0" HgA; (3) leak test; (4) wash twice with nitrogen; (5) humidify chamber and incubate about 30 min; (6) inject EtO gas and incubate for dwell time indicated in Table 3; (7) evacuate chamber to about 5.0" HgA; and (8) wash with with nitrogen the number of time indicated in Table 3. In addition to the syringe, each run also included a paper strip with approximately 1.9 x 10^6 *Bacillus subtilis* spores, which was used to monitor the sterilization as follows: the strip was soaked in media, vortexed vigorously and then serial dilutions were plated and grown for one week. We also tested several different syringe components: where the stopper on the plunger comprised D777-7 laminated with a 125 μm coating of FluroTec® barrier film and where the tip cap comprised either D777-7 or D21-7H laminated on both the surface in contact with the tip of the syringe and the exterior surface with a 125 μm coating of FluroTec® barrier film (all components from West Pharmaceutical Services / Daikyo Seiko). We measured the residual EtO in the syringe and the stability of ranibizumab by IEC the same day as the treatment and at various monthly time points thereafter. For IEC, we measured the percentage of protein in the main peak and in the acidic and basic peaks, with the protein in the basic peak representative of alkylation which may have been caused by the EtO treatment. As shown in Table 3, under all conditions tested the percentage of protein in the basic peaks was at most approximately 1% over control. Further, when the FluroTec® barrier film was used on the syringe components, the percentage of protein in the basic peak was not statistically different from control.

Table 3.

	Tip cap	Stopper	EtO cycle	Time (months)	Resid. EtO (ppm)	% acidic peaks	% main peak	% basic peaks	% basic minus control
A	As above	As above	None (control)	0	NT	0.65	97.70	1.66	(control)
				1	NT	0.59	98.12	1.29	
				2	NT	1.22	97.00	1.78	
B	As above	As above	Cycle 10 Table 2	1	2.4	0.54	98.03	1.43	-0.01
				4	9.4	0.64	97.15	2.21	0.79
				6	4.3	0.87	96.87	2.26	0.66
				9	NT	1.09	96.13	2.78	1.00
C	D777-7 + FluroTec®	D777-7 + FluroTec®	2 h dwell + 4 washes	0	<0.5	0.67	97.57	1.76	0.10
				1	0.46	0.78	97.83	1.39	0.10
				2	1.64	1.24	96.96	1.80	0.02
D	D777-7 + FluroTec®	D777-7 + FluroTec®	1.5 h dwell + 8 washes	0	<0.5	0.66	97.66	1.69	0.03
				1	0.27	0.57	98.17	1.26	-0.03
				2	0.65	1.23	96.98	1.78	0.00
E	D21-7H + FluroTec®	D777-7 + FluroTec®	2 h dwell + 4 washes	0	<0.9	0.67	97.57	1.75	0.09
				1	0.36	0.70	97.92	1.38	0.09
				2	0.68	1.24	96.95	1.80	0.02
F	D21-7H + FluroTec®	D777-7 + FluroTec®	1.5 h dwell + 8 washes	0	0.9	0.65	97.74	1.61	-0.05
				1	0.32	0.75	98.01	1.24	-0.05
				2	0.57	1.25	96.99	1.76	-0.02

The above specification, example and data provide a complete description of the manufacture and use of the composition of the invention. Since many embodiments of the invention can be made without departing from the spirit and scope of the invention, the invention includes all such embodiments.

This specification contains numerous citations to literature and patents. Each is hereby incorporated by reference for all purposes, as if fully set forth.

WE CLAIM:

1. A method for sterilizing the surface of an object having an ethylene-oxide(EtO)-impermeable interior space, wherein said interior space contains a compound having an activity that is temperature-sensitive and EtO-sensitive, the method comprising exposing said object to EtO under conditions such that the surface of said object is sterilized and said compound retains at least 50% of said activity.

2. The method of claim 1, wherein said conditions comprise:
a) temperature between 25°C and 35°C;
b) EtO concentration of between 300 mg/L and 800 mg/L; and
c) relative humidity between 45% and 60%;
for between 1 and 6 hours.

3. The method of claim 2, wherein said conditions comprise:
a) temperature between 27°C and 33°C;
b) EtO concentration of between 300 mg/L and 600 mg/L; and
c) relative humidity between 48% and 52%;
for between 1 and 6 hours.

4. The method of claim 3, wherein said conditions comprise:
a) temperature of 30°C;
b) EtO concentration of 600 mg/L; and
c) relative humidity of 50%;
for 2 hours.

5. The method of claim 4, wherein said conditions comprise:
a) temperature of 30°C;
b) EtO concentration of 600 mg/L; and
c) relative humidity of 50%;
for 1.5 hours.

6. The method of claim 1, wherein said compound retains at least 90% of said activity.

7. The method of claim 1, wherein said compound is a polypeptide.

8. The method of claim 7, wherein the percent alkylation of said polypeptide is not statistically different from a control polypeptide not exposed to EtO.

9. The method of claim 7 or 8, wherein said polypeptide is an antibody.

10. The method of claim 9, wherein said antibody is a monoclonal antibody.

11. The method of claim 9 or 10, wherein said antibody is a chimeric antibody, a humanized antibody, or a human antibody.

12. The method of any one of claims 9 to 11, wherein said antibody is an antigen-binding fragment.

13. The method of claim 12, wherein said antigen-binding fragment is a Fab fragment.

14. The method of claim 13, wherein said Fab fragment binds to VEGF.

15. The method of claim 14, wherein said Fab fragment is ranibizumab.

16. The method of claim 15, wherein said compound is present in an aqueous pharmaceutical composition.

17. The method of claim 16, wherein said pharmaceutical composition comprises at least one of the following ingredients: an amino acid, a disaccharide and a non-ionic surfactant.

18. The method of claim 17, wherein said pharmaceutical composition comprises an amino acid, a disaccharide and a non-ionic surfactant.

19. The method of claim 18, wherein said pharmaceutical composition comprises histidine, trehalose and polysorbate 20.

20. The method of claim 1, wherein said object is a syringe.

21. The method of claim 20, wherein said syringe comprises glass and comprises:

(a) a stopper comprising D777-7 laminated with FluroTec®; and

(b) a tip cap comprising (i) D777-7 laminated with FluroTec® or (ii) D21-7H laminated with FluroTec®.

22. The method of claim 1, wherein said object is contained within a package comprising an EtO-permeable material.

23. The method of claim 22, wherein said EtO-permeable material is TYVEK®.

24. An object produced by the method of any one of claims 1-23.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/088728

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L2/00 A61L2/20

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

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 5 472 702 A (MUTH ROSS R [US] ET AL) 5 December 1995 (1995-12-05) examples 1-3 abstract column 2, lines 1-3,12-19,64-67 column 3, lines 1,2 column 5, lines 1-10 column 6, lines 5-9,21-39	1-19, 22-24 20,21
Y	WO 2005/065705 A (TAIYO YAKUHIN CO LTD [JP]; TAKEYAMA KEISUKE [JP]; AKITA ERIKO [JP]; HI) 21 July 2005 (2005-07-21) abstract page 5	20,21

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[X] Further documents are listed in the continuation of Box C.

[X] 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 May 2008	14/05/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Varga, Viktoria

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/088728

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/281861 A1 (HUGHES PATRICK M [US] ET AL) 22 December 2005 (2005-12-22) abstract paragraphs [0109], [0110]	1-24
A	US 2006/099273 A1 (LOTAN TAMAR [IL]) 11 May 2006 (2006-05-11) paragraphs [0006], [0062], [0065], [0080]	1-24
A	WO 02/26271 A (CORDIS CORP [US]) 4 April 2002 (2002-04-04) pages 60-61 page 68, line 33	1-24

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/088728

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5472702 A	05-12-1995	NONE	
WO 2005065705 A	21-07-2005	AU 2003292649 A1	12-08-2005
US 2005281861 A1	22-12-2005	NONE	
US 2006099273 A1	11-05-2006	NONE	
WO 0226271 A	04-04-2002	US 2002133183 A1 US 2002051730 A1	19-09-2002 02-05-2002

Form PCT/ISA/210 (patent family annex) (April 2005)

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Filer:	Andrew K. Holmes/Andrea Jacquin
Attorney Docket Number:	
Filed as Large Entity	

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
National Stage Fee	1631	1	380	380
Natl Stage Search Fee - Report provided	1642	1	490	490
National Stage Exam - all other cases	1633	1	250	250
Pages:				
Claims:				
Claims in excess of 20	1615	2	60	120
Independent claims in excess of 3	1614	3	250	750
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
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First Named Inventor/Applicant Name:	Juergen Sigg
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Filer:	Andrew K. Holmes/Andrea Jacquin
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		53689_US_PCT_FilingPaperwork_2012Dec5.pdf	2982460 b21bbf83fada3b0d6819cfd677cf0ceef6687aa9	yes	17

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal of New Application	1	2
Oath or Declaration filed	3	5
Transmittal Letter	6	7
Information Disclosure Statement (IDS) Form (SB08)	8	8
Preliminary Amendment	9	9
Specification	10	10
Abstract	11	11
Claims	12	15
Applicant Arguments/Remarks Made in an Amendment	16	16
Application Data Sheet	17	17

Warnings:					
Information:					
2	Foreign Reference	1_EP1433486A1.pdf	1153643 dcb1469a395f8589445a2e5641bfdf3adb745971	no	15
Warnings:					
Information:					
3	Foreign Reference	2_WO0520847A2.pdf	2134336 c6370472ce45ad456f2be69e80c3c4d3c54c0231	no	41
Warnings:					
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4	Foreign Reference	3_WO9744068A1.pdf	1068300 2c9753707b668e9a674aede6422b6db1012e9e11	no	27

Warnings:					
Information:					
5	Foreign Reference	4_EP1283061A1.pdf	1909877 9e086f85f9d4bf0640bcc2d28dfe2e5766c5cf2a	no	34
Warnings:					
Information:					
6	Foreign Reference	5_EP1944044A1.pdf	873344 6a6fe0d40c5f6fe665da5ee7ddd1683982008758	no	16
Warnings:					
Information:					
7	Foreign Reference	6_WO0877155A1.pdf	1087219 2b4b8615abc20ea9682bc20888d192d9e70eca1b	no	23
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	37911 4bdc6df49a7dde6e3c0ee7d09d3ca8fb06649f59	no	2
Warnings:					
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			Total Files Size (in bytes):	11247090	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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

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— *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))*

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

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

Surface Decontamination of Prefilled Containers in Secondary Packaging

FIELD OF THE INVENTION

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

BACKGROUND

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

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

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

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

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

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

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

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

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

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

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.

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

DETAILED DESCRIPTION

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.

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 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.

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 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 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, 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.

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 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 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 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 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 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 80ºC until sterility is achieved. The lowest temperature disclosed in either the Moore or Forstrom patents is 20ºC.

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 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 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.

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 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.

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.

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

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 H_2O_2 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) [µMol/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:

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 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.

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.

3. The method of claim 1 or claim 2, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

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.

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.

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.

8. A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

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.

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.

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.

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.

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.

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.

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

a sealed chamber; and

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.

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 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 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 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-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, 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

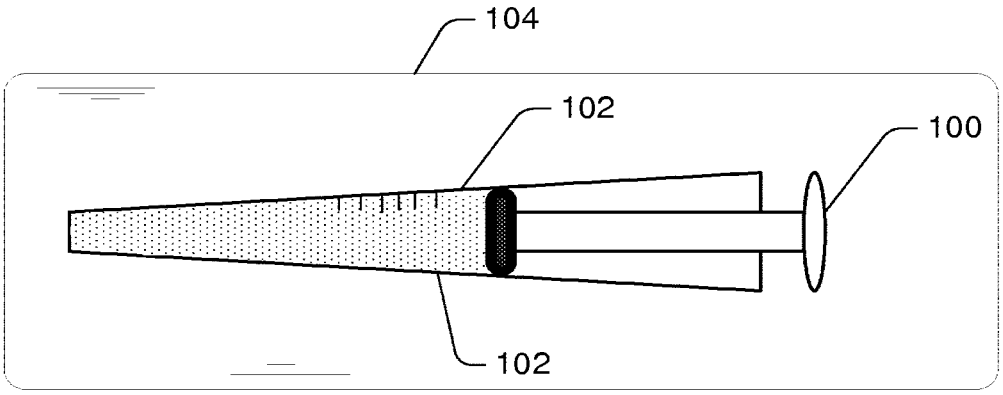

Fig. 1

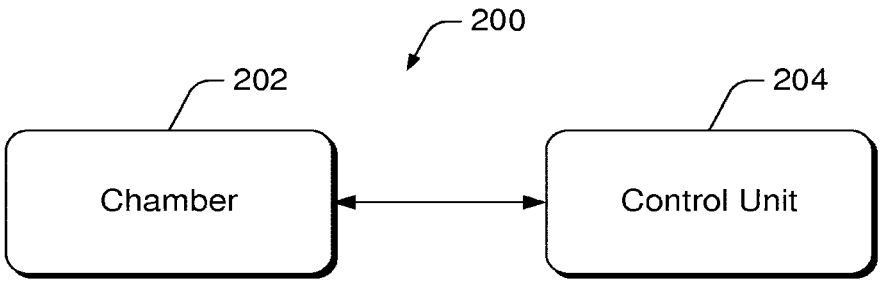

Fig. 2

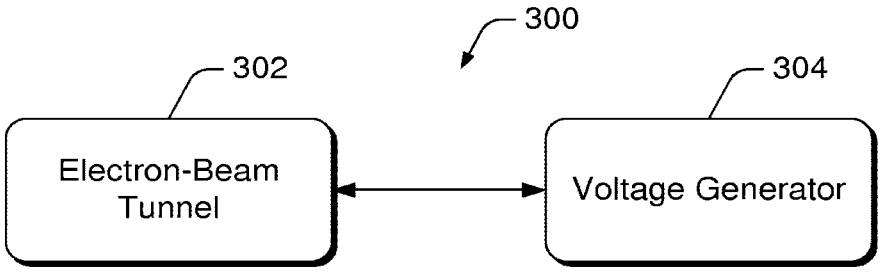

Fig. 3

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Patentanmeldung Nr.	**Patent application No.**	**Demande de brevet n°**

09165456.6 / EP09165456

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP09165456.

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le President de l'Office européen des brevets
p.o.

R.C. van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Surface decontamination of prefilled containers in secondary packaging

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Surface Decontamination of Prefilled Containers in Secondary Packaging

FIELD OF THE INVENTION

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

BACKGROUND

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

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

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

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

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

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 top increased stickiness of the components thus impairing the functionality of the system. Thus radiation is not an appropriate means for sterilizing prefilled containers, such as syringes, containing a biotech drug product.

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

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

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

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

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. 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.

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

In one embodiment, the use of low penetration depth radiation from a low-energy electron beam generator for a new application to sterilize the surface of secondary

packaged drug product containers avoids aseptic packaging. In another embodiment, the penetration depth of electron beam radiation is tunable by adjustment of the accelerator voltage of the irradiation generator.

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

DETAILED DESCRIPTION

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.

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.

Instructional Material

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 SAL

for a given product is based on regulatory requirements. For example, 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 and terminally processed 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.

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 constitution in 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.

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 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 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, 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 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 thickness.

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 thickness of the container 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.

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 treatment by VHP and post-treatment measures to reduce or prevent VHP from entering into prefilled containers.

In one embodiment, hydrogen peroxide vapor is introduced into the chamber, either generated within or released within the chamber for a sufficient time to 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 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 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 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.

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, 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 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 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.

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 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.

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.

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 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
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 H_2O_2 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 Polyethylene bag	Dosimeter in aluminum bag	Dosimeter shielded by 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) [µMol/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:

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 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.

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.

3. The method of Claim 1, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

4. The method of Claim 1, wherein sufficient time to decontaminate the surface of the prefilled container is determined by validation of treatment times and compared to a control standard.

5. The method of Claim 1, 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.

6. The method of Claim 1, 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. A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

8. The method of claim 7, 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.

9. The method of Claim 7, 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.

10. The method of Claim 7, 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.

11. The method of Claim 7, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

12. The method of Claim 7, wherein the penetration depth is measured by dosimetry.

13. The method of Claim 7, 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.

14. The method of Claim 7, 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.

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

a sealed chamber; and

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.

16. 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 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 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

17. 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 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-hydrogen peroxide in the chamber, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container.

18. A kit for surface-decontaminating a prefilled container in secondary packaging, 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.

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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.

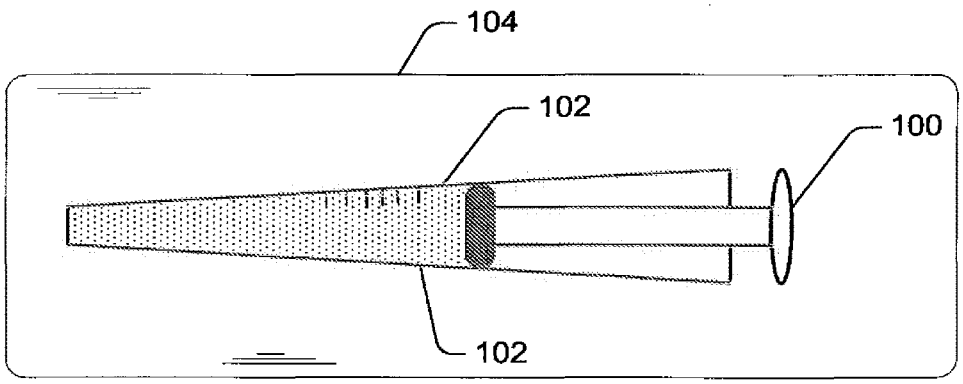

Fig. 1

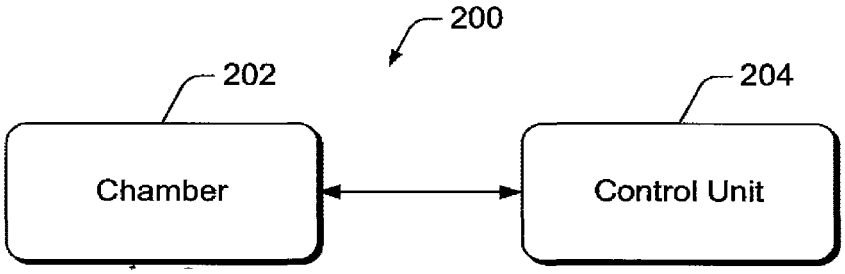

Fig. 2

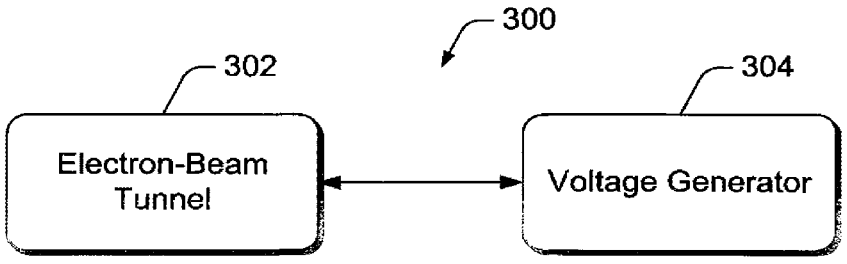

Fig. 3

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(iv)		an assignment from SIGG, Jürgen to NOVARTIS AG, dated 07 May 2010 (07.05.2010)

Amendments to the Specification:

Please insert the following as the first paragraph beneath the title on page1:

-- This application is a 371 of PCT/EP2010/060011 filed on July 13, 2010 which claims benefit of EP Application No. 09165456.6 filed on July 14, 2009, which in their entirety are herein incorporated by reference.--

A copy of the abstract is herein provided on the following separate sheet.

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.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Amended) 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 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, wherein the prefilled container contains 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.

2. (Original) 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.

3. (Amended) The method of claim 1 ~~or claim 2~~, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

4. (Amended) The method of ~~any previous~~ claim 1, wherein sufficient time to decontaminate the surface of the prefilled container is determined by validation of treatment times and compared to a control standard.

5. (Amended) The method of ~~any previous~~ claim 1, 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.

6. (Amended) The method of ~~any of~~ claim~~s 1-4~~ 1, 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. (Amended) The method of ~~any of~~ claim~~s 1-4~~ 1, wherein the post-decontamination measure includes gas plasma treatment.

8. (Original) A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

9. (Original) 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.

10. (Amended) 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.

11. (Amended) The method of ~~any one of claims 8-10~~ claim 8, 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.

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

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

14. (Amended) The method of ~~any one of claims 8-13~~ claim 8, 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.

15. (Amended) The method of ~~any one of claims 8-14~~ claim 8, 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.

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

a sealed chamber; and

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, wherein the prefilled container contains 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.

17. (Original) 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 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 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

18. (Original) 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 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-hydrogen peroxide in the chamber, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container.

19. (Original) A kit for surface-decontaminating a prefilled container in secondary packaging, 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. (Amended) A system according to claim 16 ~~or a kit according to claim 19~~, wherein post-decontamination measure includes gas plasma treatment.

21. (New) A kit according to claim 19, wherein post-decontamination measure includes gas plasma treatment.

22. (New) The method of claim 1, wherein the drug product is a protein solution.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/382,380	Filing Date 01/05/2012	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/05/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 22	Minus	** 22	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/LAWRENCE BRITT JR/

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Die angehefteten Unterlagen stimmen mit der als ursprünglich eingereicht geltenden Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.	The attached documents are exact copies of the text in which the European patent application described on the following page is deemed to have been filed.	Les documents joints à la présente attestation sont conformes au texte, considéré comme initialement déposé, de la demande de brevet européen qui est spécifiée à la page suivante.

Patentanmeldung Nr.	**Patent application No.**	**Demande de brevet n°**

09165456.6 / EP09165456

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP09165456.

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le President de l'Office européen des brevets
p.o.

R.C. van Dijk

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Anmeldung Nr:
Application no.: 09165456.6
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Anmelder / Applicant(s) / Demandeur(s):

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Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Surface decontamination of prefilled containers in secondary packaging

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

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Am Anmeldetag benannte Vertragstaaten / Contracting States designated at date of filing / Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR

Surface Decontamination of Prefilled Containers in Secondary Packaging

FIELD OF THE INVENTION

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

BACKGROUND

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

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

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

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

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

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 top increased stickiness of the components thus impairing the functionality of the system. Thus radiation is not an appropriate means for sterilizing prefilled containers, such as syringes, containing a biotech drug product.

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

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

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

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

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. 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.

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

In one embodiment, the use of low penetration depth radiation from a low-energy electron beam generator for a new application to sterilize the surface of secondary

packaged drug product containers avoids aseptic packaging. In another embodiment, the penetration depth of electron beam radiation is tunable by adjustment of the accelerator voltage of the irradiation generator.

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

DETAILED DESCRIPTION

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.

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.

Instructional Material

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 SAL

for a given product is based on regulatory requirements. For example, 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 and terminally processed 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.

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 constitution in 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.

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 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 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, 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 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 thickness.

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 thickness of the container 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.

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 treatment by VHP and post-treatment measures to reduce or prevent VHP from entering into prefilled containers.

In one embodiment, hydrogen peroxide vapor is introduced into the chamber, either generated within or released within the chamber for a sufficient time to 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 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 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 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.

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, 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 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 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.

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 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.

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.

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 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
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 H_2O_2 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 Polyethylene bag	Dosimeter in aluminum bag	Dosimeter shielded by 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) [µMol/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:

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 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.

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.

3. The method of Claim 1, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

4. The method of Claim 1, wherein sufficient time to decontaminate the surface of the prefilled container is determined by validation of treatment times and compared to a control standard.

5. The method of Claim 1, 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.

6. The method of Claim 1, 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. A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

8. The method of claim 7, 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.

9. The method of Claim 7, 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.

10. The method of Claim 7, 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.

11. The method of Claim 7, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

12. The method of Claim 7, wherein the penetration depth is measured by dosimetry.

13. The method of Claim 7, 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.

14. The method of Claim 7, 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.

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

a sealed chamber; and

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.

16. 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 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 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

17. 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 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-hydrogen peroxide in the chamber, thereby preventing vaporized-hydrogen peroxide from diffusing into the prefilled container.

18. A kit for surface-decontaminating a prefilled container in secondary packaging, 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.

5

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.

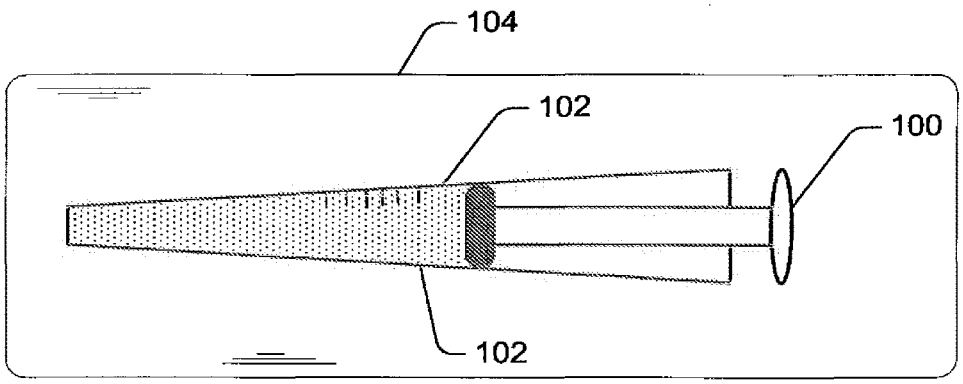

Fig. 1

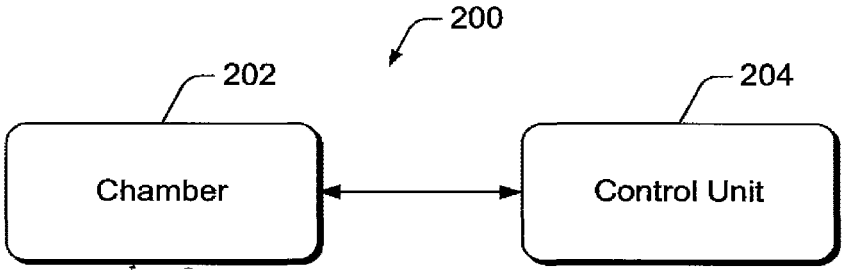

Fig. 2

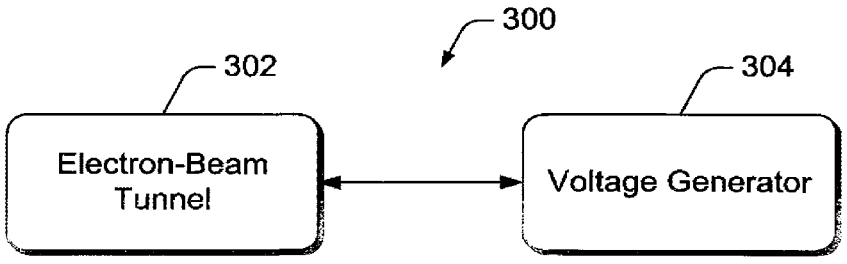

Fig. 3

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP2010/060011

International filing date: 13 July 2010 (13.07.2010)

Document type: Certified copy of priority document

Document details: Country/Office: EP
Number: 09165456.6
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Date of receipt at the International Bureau: 19 August 2010 (19.08.2010)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

NOVARTIS PHARMACEUTICALS CORPORATION
Patent Department
One Health Plaza
Building 101
East Hanover, NJ 07936
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
20 September 2011 (20.09.2011)

Applicant's or agent's file reference
53689-WO-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2010/060011

International filing date *(day/month/year)*
13 July 2010 (13.07.2010)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

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NOVARTIS PHARMACEUTICALS CORPORATION
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☒ Notifications by e-mail authorized

3. Further observations, if necessary:
All future correspondence should be sent to the address for correspondence indicated in Box 2. Advance copies of future notifications will also be sent in electronic form via e-mail to the e-mail address indicated above.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
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☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 53689-WO-PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2010/060011	International filing date *(day/month/year)* 13 July 2010 (13.07.2010)	Priority date *(day/month/year)* 14 July 2009 (14.07.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NOVARTIS AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 17 January 2012 (17.01.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yolaine Cussac e-mail: pt05.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2010/060011	13.07.2010	14.07.2009

International Patent Classification (IPC) or both national classification and IPC
INV. A61L2/00 A61L2/20 B65B55/10 A61L2/08 B65B55/08

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Katsoulas, K Telephone No. +49 89 2399-8613

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 19

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 19 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. 1-7, 16, 18, 20

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-4, 6-15, 17, 18, 20
	No:	Claims	1, 5, 16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18, 20
Industrial applicability (IA)	Yes:	Claims	1-18, 20
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Ad Sections III-V, VII and VIII

D1: US-A-5779973; D2: WO 2008/77155 D3: EP-A-1433486;
D4: WO 2005/020847; D5: EP-A-1283061; D6: US-A-4652763
D7: EP-A-1944044

Lack of Unity (Rule 13.1 PCT)

1. 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. 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 accelerator 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.

3. The common features of claims 1 and 8 purely reside in a method for surface decontamination of a prefilled container in a secondary packaging, which is known as acknowledged in the description and apparent from the cited documents. Given that the additional features of the independent claims are neither similar nor corresponding no single inventive concept is present. Therefore the requirements of unity of invention are not fulfilled.

(I) First Invention (Claims 1-7, 16, 18, 20)

A. Lack of novelty (Art. 33(2) PCT)

1. D1 discloses (c.f... passages cited in the SR) a method of decontaminating the surfaces (24) of a prefilled container in a secondary packaging (22) by introducing VHP in the interstitial space of the packages for a suitable period for sterilising the internal space of the bag assembly. Afterwards an applied vacuum introduces a sterile

air stream within the interstices to displace residual VHP, which is either vented or degraded. It follows that claims 1 and 5 are directly known from D1. This applies also to independent apparatus claim 16, whose features are directly or implicitly disclosed.

B: Lack of inventive step (Art. 33(3) PCT)

1. The additional features of claims 2, 4 and 18 are known from D3, wherein both the application to a syringe/drug system and the appropriate validation steps are disclosed. Thus, no inventive step can be acknowledged for said claims.

2. The additional feature of claim 3 is known from D2, wherein the sterilisation of syringes containing ranibizumab is disclosed.

3. The additional feature of claim 6 is known from D4, wherein the use of UV radiation to decompose residual VHP is disclosed (cf. page 23, lines 25-30).

4. The use of gas plasma as post treatment, after hydrogen peroxide sterilisation, is generally known to the skilled person, as illustrated in D5 (cf. §7).

(II) Second Invention (Claims 8-15, 17 and 19)

1. D6 discloses (cf. passages cited in the search report) a method for sterilising a prefilled container in a secondary packaging using a low-energy e-beam (beta radiation) tunnel in a tunable electron beam generator. The operating conditions are chosen so that adequate radiation of the surface of the primary package is received (e.g. 2.5 megarads / 25KGy), essentially without penetrating the primary package and reaching its contents. Method claim 8 difres from the above disclosure only in that the beam generator used is also capable of oscillating the electron beams produced. This is however a standard option of the more recent generators. In fact, D7 employs a similar low radiation "Kevac" generator as in the present application (§47). It follows that claim 1 is anticipated by the combined teaching of D6 and D7 (Art. 33(3) PCT). This applies equally to device claim 17, as well as to dependent claims 9-15.
2. Independent claim 19 essentially defines a kit comprising only an "instruction" with suitable information for operating a decontamination system. No further kit components have been defined (Art. 6 PCT). It is noted that claim 19 is equivalent to an instruction manual for such a system, which is normally supplied therewith.
3. In claim 9 said "primary packaging material" has no proper andecedent basis (Art. 6 PCT).

4. On page 9 lines 10-14 it is indicated that a secondary package can be optional (Art. 6 support).

5. To meet the requirements of Rule 5.1 (a) (ii) PCT, the documents D1-D3 and D6, D7 should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

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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))*

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

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

Surface Decontamination of Prefilled Containers in Secondary Packaging

FIELD OF THE INVENTION

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

BACKGROUND

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

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

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

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

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

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

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

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

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

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

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.

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

DETAILED DESCRIPTION

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.

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 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.

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 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 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, 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.

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 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 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 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 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 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 80ºC until sterility is achieved. The lowest temperature disclosed in either the Moore or Forstrom patents is 20ºC.

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 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 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.

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 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.

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.

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

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 H_2O_2 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) [µMol/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:

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 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.

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.

3. The method of claim 1 or claim 2, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

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.

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.

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.

8. A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

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.

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.

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.

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.

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.

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.

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

a sealed chamber; and

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.

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 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 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 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-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, 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

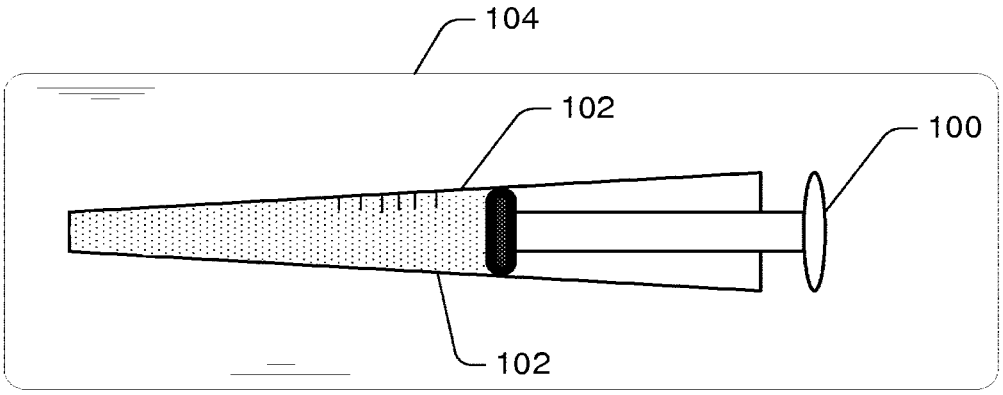

Fig. 1

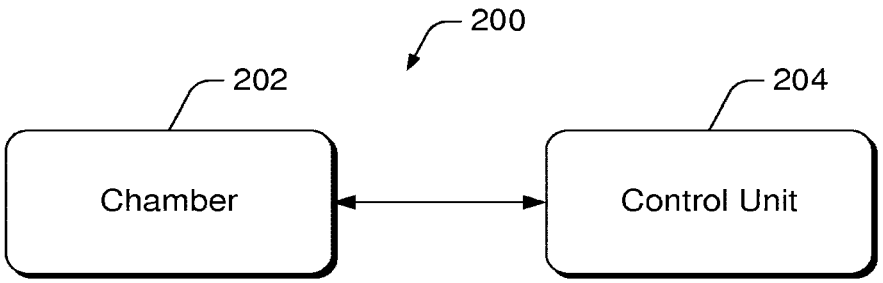

Fig. 2

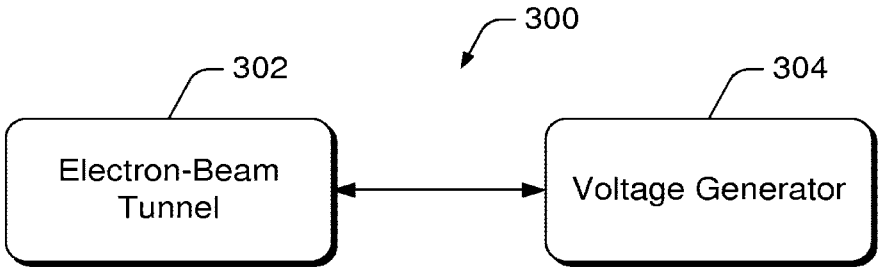

Fig. 3

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371 ACCEPTANCE LETTER

OC000000052182679

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NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

01/05/2012	01/05/2012
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 01/05/2012
- Copy of the International Search Report filed on 01/05/2012
- Preliminary Amendments filed on 01/05/2012
- Information Disclosure Statements filed on 01/05/2012
- Oath or Declaration filed on 01/05/2012
- Request for Immediate Examination filed on 01/05/2012
- U.S. Basic National Fees filed on 01/05/2012
- Priority Documents filed on 01/05/2012
- Power of Attorney filed on 01/05/2012
- Specification filed on 01/05/2012
- Claims filed on 01/05/2012
- Abstracts filed on 01/05/2012
- Drawings filed on 01/05/2012

FORM PCT/DO/EO/903 (371 Acceptance Notice)

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

PAULETTE R KIDWELL

Telephone: (571) 272-0398

FORM PCT/DO/EO/903 (371 Acceptance Notice)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE RECD	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/382,380	01/05/2012		1990	53689-US-PCT	22	5

CONFIRMATION NO. 9960

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

FILING RECEIPT

OC000000052182678

Date Mailed: 01/27/2012

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Juergen Sigg, Loerrach, GERMANY;

Power of Attorney:
Andrew Holmes--51813

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP10/60011 07/13/2010

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) 09165456.6 07/14/2009

If Required, Foreign Filing License Granted: 01/24/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/382,380**

Projected Publication Date: 05/10/2012

Non-Publication Request: No

Early Publication Request: No

Title

Surface Decontamination of Prefilled Containers in Secondary Packaging

Preliminary Class

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier

license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/382,380

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	490
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	22 minus 20 =	* 2			OR	x 60 =	120
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 minus 3 =	* 2				x 250 =	500
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1740

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)	Application Number 13382380	Filing Date
	Applicant(s) Juergen Sigg	
	* May be used for additional claims or amendments	

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1		1			
2		1		1		
3		2		1		
4		(1)		1		
5		(1)		1		
6		(1)		1		
7		(1)		1		
8	1			1		
9		1		1		
10		2		1		
11		(1)		1		
12		(1)		1		
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Total Indep	6		5		0	
Total Depend	17	↵	17	↵	0	↵
Total Claims	23		22		0	

CLAIMS	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/382,380	01/05/2012	Juergen Sigg	53689-US-PCT

CONFIRMATION NO. 9960

1095
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

PUBLICATION NOTICE

Title: Surface Decontamination of Prefilled Containers in Secondary Packaging

Publication No.US-2012-0114524-A1
Publication Date:05/10/2012

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/382,380	01/05/2012	Juergen Sigg	PAT053689-US-PCT	9960

1095 7590 07/02/2012

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
SPAMER, DONALD ROBERT	
ART UNIT	**PAPER NUMBER**
4142	

NOTIFICATION DATE	DELIVERY MODE
07/02/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Office Action Summary	Application No.	Applicant(s)	
	13/382,380	SIGG, JUERGEN	
	Examiner	Art Unit	
	DONALD SPAMER	4142	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-22* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-22* are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-7 and 22, drawn to a method of surface decontamination using hydrogen peroxide.
Group II, claim(s) 8-15, drawn to a method of surface decontamination using electron beams.
Group III, claim(s) 16 and 20, drawn to a system for surface decontamination with hydrogen peroxide as the sterilizing agent.
Group IV, claim(s) 17, drawn to a system for surface decontamination with electron beams as the sterilizing agent.
Group V, claim(s) 18, drawn to a kit for decontaminating a surface with hydrogen peroxide.
Group VI, claim(s) 19 and 21, drawn to a kit for decontaminating a surface with electron beams.

2. The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

3. Groups I, III, and V contain the special technical feature of surface decontamination with hydrogen peroxide. Groups II, IV, VI contain the special technical feature of surface decontamination using electron beam generation. These are different technologies and thus lack unity.

4. If the applicant elects groups I, III, and V then there is a further restriction between these groups which share the special technical feature of surface decontamination with hydrogen peroxide. This cannot be a special technical feature as described by PCT Rule 13.1 as it has been shown to be known in

the prior art. US Patent Application Publication No. 2006/0106349, Kito et al., teaches the concept of using hydrogen peroxide to sterilize or decontaminate a surface (paragraph 205).

5. If the applicant elects groups II, IV, and VI then there is a further restriction between these groups which share the special technical feature of surface decontamination using electron beams. This cannot be a special technical feature as described by PCT Rule 13.1 as it has been shown to be known in the prior art. US Patent Application Publication No. 2006/0106349, Kito et al., teaches the concept of using radioactive rays from electron beams to sterilize or decontaminate a surface (paragraph 205).

6. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention or species.

Should applicant traverse on the ground that the inventions have unity of invention (37 CFR 1.475(a)), applicant must provide reasons in support thereof. Applicant may submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. Where such evidence or admission is provided by applicant, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

7. The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process

invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DONALD SPAMER whose telephone number is (571)272-3197. The examiner can normally be reached on Monday through Friday, 9 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on 571-272-1374. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DONALD SPAMER/
Examiner, Art Unit 4142

/SEAN E CONLEY/
Primary Examiner, Art Unit 1775

Notice of References Cited	Application/Control No. 13/382,380	Applicant(s)/Patent Under Reexamination SIGG, JUERGEN	
	Examiner DONALD SPAMER	Art Unit 4142	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2006/0106349	05-2006	Kito et al.	604/187
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

CASE PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 4142
Examiner: SPAMER, DONALD ROBER

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: 13/382380

35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

Sir:

This is in response to the Restriction Requirement mailed 2 July 2012.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Remarks/Arguments

I. Claims

Claims 1-22 are presently pending in this patent application. Claims 16, 18, 20 and 21 (withdrawn as being drawn to non-elected subject matter) are amended without prejudice herein.

Claims 16, 18, 20 and 21 are amended without prejudice herein to ultimately depend from claim 1. No new matter has been added.

Applicants reserve the right to pursue subject matter that remains after the prosecution of the present application in a future continuing patent application, for example, a division.

II. Restriction Requirement

The Examiner has required restriction between the following groups:

Group I: having claims 1-7 and 22, drawn to a method of surface decontamination using hydrogen peroxide;

Group II: having claims 8-15, drawn to a method of surface decontamination using electron beams;

Group III: having claims 16 and 20, drawn to a system for surface decontamination with hydrogen peroxide as the sterilizing agent;

Group IV: having claim 17, drawn to a system for surface decontamination with electron beams as the sterilizing agent;

Group V: having claim 18, drawn to a kit for surface decontamination with hydrogen peroxide as the sterilizing agent; and

Group VI: having claims 19 and 21, drawn to a kit for surface decontamination with electron beams as the sterilizing agent.

Applicants elect Group I encompassing claims 1-7 and 22. Applicants acknowledge the possibility of rejoinder of claims 16, 18, 20 and 21, all amended to ultimately depend from claim 1, if the method claims are found to be allowable because claims 16, 18, 20 and 21 incorporate all the limitations of claim 1.

Respectfully submitted,

/ Andrew Holmes /

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Date: August 2, 2012

Electronic Acknowledgement Receipt	
EFS ID:	13403696
Application Number:	13382380
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Customer Number:	1095
Filer:	Andrew K. Holmes/Andrea Jacquin
Filer Authorized By:	Andrew K. Holmes
Attorney Docket Number:	PAT053689-US-PCT
Receipt Date:	02-AUG-2012
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Time Stamp:	14:34:37
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		53689-US-PCT_ResptoRR_2012Aug2.pdf	1161125 7014ff050f953a428bbb760483c824065e53a9eb	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6
Warnings:			
Information:			
	Total Files Size (in bytes):	1161125	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/382,380	Filing Date 01/05/2012	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/02/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 22	Minus	** 22	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/AMANDA FORD/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Amended) 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 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, wherein the prefilled container contains 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.

2. (Original) 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.

3. (Previously submitted) The method of 1, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

4. (Previously submitted) The method of 1, wherein sufficient time to decontaminate the surface of the prefilled container is determined by validation of treatment times and compared to a control standard.

5. (Previously submitted) The method of 1, 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.

6. (Previously submitted) The method of 1, 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. (Previously submitted) The method of 1, wherein the post-decontamination measure includes gas plasma treatment.

8. (Withdrawn) A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

9. (Withdrawn) 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.

10. (Withdrawn) The method of claim 8, 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.

11. (Withdrawn) The method of claim 8, 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.

12. (Withdrawn) The method of claim 8, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

13. (Withdrawn) The method of claim 8, wherein the penetration depth is measured by dosimetry.

14. (Withdrawn) The method of claim 8, 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.

15. (Withdrawn) The method of claim 8, 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.

16. (Withdrawn; currently amended) A system for decontaminating a surface of a prefilled container in secondary packaging, the system comprising:

a sealed chamber; and

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, wherein the prefilled container contains 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~~ perform the method according to claim 1.

17. (Withdrawn) 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 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 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

18. (Withdrawn; currently amended) 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 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 hydrogen peroxide in the chamber, thereby preventing vaporized hydrogen peroxide from diffusing into the prefilled container~~ perform the method according to claim 1.

19. (Withdrawn) A kit for surface-decontaminating a prefilled container in secondary packaging, 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. (Withdrawn) A system according to claim 16, wherein post-decontamination measure includes gas plasma treatment.

21. (Withdrawn; currently amended) A kit according to claim ~~19~~ 18, wherein post-decontamination measure includes gas plasma treatment.

22. (Previously submitted) The method of claim 1, wherein the drug product is a protein solution.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/382,380	01/05/2012	Juergen Sigg	PAT053689-US-PCT	9960

1095 7590 09/14/2012

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
SPAMER, DONALD R	
ART UNIT	**PAPER NUMBER**
1775	

NOTIFICATION DATE	DELIVERY MODE
09/14/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Office Action Summary	Application No.	Applicant(s)	
	13/382,380	SIGG, JUERGEN	
	Examiner	Art Unit	
	DONALD SPAMER	4142	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-22* is/are pending in the application.

5a) Of the above claim(s) *8-21* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-7 and 22* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *05 January 2012* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of claims 1-7 and 22 in the reply filed on 08/02/2012 is acknowledged.

2. Claims 8- 21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/02/2012.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. **37 CFR 1.98(b)** requires a list of all patents, publications, applications, or other information submitted for consideration by the Office, and MPEP § **609.04(a)**, subsection I. states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

4. The following US Patents were found referenced in the specifications but were not on the IDS: 7,060,269 Baca et al.; 4,512,951 Koubek; 4,169,123 Moore; and 4,169,124 Forstrom.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 4, 5, 7, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent Application Publication Number 2003/0003014 Metzner et al. as evidenced by US Patent 6,228,324 Hasegawa et al.

7. With regards to claim 1, Metzner et al. teaches a method for surface decontamination of a prefilled container in secondary packaging (para [0010-0011]). Metzner et al. teaches the use of vaporized hydrogen peroxide in order to sterilize the surfaces of the packaging (para [0019]). Metzner et al. also teaches that the hydrogen peroxide is left in contact with the surfaces for a sufficient amount of

time to achieve decontamination (para [0032-0033]) and gives an example of about 17 min in each half cycle in example 3 (para [0071]). Metzner et al. also teaches the use of post-decontamination measures of applying a vacuum (para [0034 - 0035]). The vacuum post decontamination treatment taught by Metzner et al. would remove the hydrogen peroxide as evidenced by Hasegawa et al. Hasegawa et al. states that the application of a vacuum removes the hydrogen peroxide from inside the packaging (column 8 lines 63-67 and column 9 lines 32-38).

8. In the background of the invention, Metzner et al. teaches that this method can be done on temperature sensitive pharmaceutical products (para [0002]). It expands to say that such products are sensitive to sterilization with gamma radiation (para [0005]), autoclaving (para [0003]) (exposure to steam), and ethylene oxide (since ethylene oxide residue can render the drug product toxic or carcinogenic) (gas) (para [0004]).

9. With regards to claim 2, in the background of the invention, Metzner et al. teaches that this method can be done on temperature sensitive pharmaceutical products (para [0002]). It expands to say that such products are sensitive to sterilization with gamma radiation (para [0005]), autoclaving (para [0003]) (exposure to steam), and ethylene oxide (since ethylene oxide residue can render the drug product toxic or carcinogenic) (gas) (para [0004]). In example 3, Metzner et al. teaches that the protein drug product is in a carpule (para [0061]). A carpule is the same as a syringe. A carpule is an integral part of a syringe and would not be useable to administer a drug without the rest of the syringe.

10. With regards to claim 4, Metzner et al. teaches determining if the sterilization method is effective (para [0037]). This is considered to include testing whether the treatment times are sufficient since treatment times are part of the method. Metzner et al. teaches that sterilization effectiveness is determined by comparing the reduction factor of colony forming units (CFU) and comparing this value to a control standard (para [0037]). The control standard taught by Metzner et al. is that sterilization is achieved if $\log_{10}$(CFU) is greater than or equal to 6 (para [0037]).

11. With regards to claim 5, Metzner et al. teaches a post decontamination measure of applying a vacuum following treatment with vaporized hydrogen peroxide (para [0034]). While Metzner et al. does not specifically state the intended use of “reversing the direction of diffusion of vaporized hydrogen

peroxide and preventing intrusion of vaporized hydrogen peroxide into the prefilled container," the method of using a vacuum after effective treatment inherently achieves this. This is affirmatively shown by the teaching Hasegawa et al.

12. Hasegawa et al. states that the application of a vacuum (taught by Metzner et al.) removes the hydrogen peroxide from inside the packaging (column 8 lines 63-67 and column 9 lines 32-38).

13. The prevention of hydrogen peroxide intrusion can be further confirmed when Metzner et al. measures the amount of proteins undamaged by the sterilization method and finds that the method damaged very little to none of the protein products (para [0076]).

14. With regards to claim 7, teaches a post decontamination measure that includes a plasma treatment (para [0035]). This is considered to be a gas plasma.

15. With regards to claim 22, Metzner et al. teaches that the hydrogen peroxide vapor sterilization method can be used for sterilizing prefilled containers in secondary packaging where the prefilled drug product is various proteins (para [0061]).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claim 2 rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication Number 2003/0003014 Metzner et al. as applied to claim 1 above, and further in view of US Patent 6,228,324 Hasegawa et al.

18. Metzner et al. remains as applied to claim 1 above. Metzner et al. teaches this method can be done on temperature sensitive pharmaceutical products (para [0002]). It expands to say that such products are sensitive to sterilization with gamma radiation (para [0005]), autoclaving (para [0003]) (exposure to steam), and ethylene oxide (since ethylene oxide residue can render the drug product toxic or carcinogenic) (gas) (para [0004]). In example 3, Metzner et al. teaches that the protein drug product is

in a carpule (para [0061]). A carpule is a container for medicine that is administered to the patient with a syringe. Metzner thus does not expressly state the use of the method on a syringe in secondary packaging. Hasegawa et al. teaches a method for sterilizing a syringe in secondary packaging using hydrogen peroxide vapor (abstract and figure 4). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. to sterilize a syringe in secondary packaging as shown in Hasegawa et al. in order to provide a sterile drug product by using hydrogen peroxide vapor (abstract and figure 4).

19. Claim 3 rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication Number 2003/0003014 Metzner et al. as applied to claim 1 above, and further in view of US Patent Application Publication 2007/0190058 Shams.

20. Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. teaches a method of using hydrogen peroxide vapor for sterilizing different proteins in secondary packaging (para [0061]) at 30°C (para [0063]) and teaches that the treatment did not destroy the protein products (para [0076]). Metzner et al. does not specifically mention the use of the method for treating a medical product where the prefilled drug is ranibizumab, a protein. The claim recites "therapeutically effective" (implying non degraded protein when administered into a body for treatment). A person having ordinary skill in the art at the time of the invention would understand that if this method is capable of sterilizing prefilled protein drug products in secondary packaging without causing degradation of the proteins that the method is capable of treating the specific protein ranibizumab.

21. Additionally the concept of using ranibizumab delivered by a syringe is also known in the prior art. Shams teaches the administration of ranibizumab by syringe injection (para [0128]). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. with the addition of ranibizumab being the drug in the syringe, as taught by Shams, in order to administer a dose of ranibizumab as a therapuetic drug (abstract and para [0028]) in a sterile manner which is desired by Shams who states that the treatment should be formulated, dosed, and administered in a fashion consistent with good medical practice (para [0092]) which would include using a sterile syringe.

22. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication Number 2003/0003014 Metzner et al. as applied to claim 1 above, and further in view of US Patent Application Publication 2005/0226764 Moirandat et al.

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. also teaches the use of a post decontamination measure using a vacuum (para [0034]) and a plasma treatment (para [0035]).

23. Metzner et al. does not teach the use of ultraviolet rays in a post decontamination measure.

24. Moirandat et al. teaches a method of decontaminating a clean room with hydrogen peroxide followed by post decontamination measures (para [0008], summary of invention). Moirandat et al. teaches that hydrogen peroxide remaining after decontamination can be photochemically broken down by UV radiation (ultraviolet rays) into oxygen and water (para [0031]). A person having ordinary skill in the art at the time of the invention would have been able to modify the method of Metzner et al. with the addition of ultraviolet rays to deactivate hydrogen peroxide vapors rapidly and in the least costly manner (Moirandat et al. para [0008]).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DONALD SPAMER whose telephone number is (571)272-3197. The examiner can normally be reached on Monday through Friday, 9 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on 571-272-1374. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DONALD SPAMER/
Examiner, Art Unit 4142

/GORDON R BALDWIN/
Supervisory Patent Examiner, Art Unit 4161

Notice of References Cited	Application/Control No. 13/382,380	Applicant(s)/Patent Under Reexamination SIGG, JUERGEN	
	Examiner DONALD SPAMER	Art Unit 4142	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2005/0226764	10-2005	Moirandat et al.	422/030
*	B	US-2003/0003014	01-2003	Metzner et al.	422/29
*	C	US-2007/0190058	08-2007	Shams, Naveed	424/145.1
*	D	US-6,228,324	05-2001	Hasegawa et al.	422/30
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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CONFIRMATION NO. 9960

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/382,380	01/05/2012 RULE	422	4142	PAT053689-US-PCT

APPLICANTS
Juergen Sigg, Loerrach, GERMANY;

**** CONTINUING DATA ***************************
This application is a 371 of PCT/EP10/60011 07/13/2010

**** FOREIGN APPLICATIONS ***************************
EUROPEAN PATENT OFFICE (EPO) 09165456.6 07/14/2009

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
01/24/2012

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /DONALD R SPAMER/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		GERMANY	1	22	5

ADDRESS

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080
UNITED STATES

TITLE

Surface Decontamination of Prefilled Containers in Secondary Packaging

FILING FEE RECEIVED	FEES: Authority has been given in Paper	☐ All Fees
1990	No._____ to charge/credit DEPOSIT ACCOUNT	☐ 1.16 Fees (Filing)
	No._____ for following:	☐ 1.17 Fees (Processing Ext. of time)
		☐ 1.18 Fees (Issue)
		☐ Other _____
		☐ Credit

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	Not yet Known
Filing Date	Herewith
First Named Inventor	Sigg, Juergen
Art unit	
Examiner Name	
Attorney Docket Number	PAT053689-US-PCT

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-5,779,973	07-14-1998	Edwards et al.	
		US-4,652,736	03-24-1987	Nablo, Samuel	
		US-6,189,292 B1	02-20-2001	Odell et al.	
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
		EP 1 433 486 A1	06-30-2004	Closure Medical Corp		☐
		WO 2005/020847 A2	03-10-2005	Cook Biotech Inc.		☐
		DE 196 22 283 A1 (Equivalent to WO 97/44068)	11-27-1997	Schering AG		☐
		WO 97/44068 (English Abstract)	11-27-1997	Schering AG		
		EP 1 283 061 A1	02-12-2003	Taisei Kako Co., Ltd		☐
		EP 1 944 044 A1	07-16-2008	Becton Dickinson France		☐
		WO 2008/077155 A	06-26-2008	Genetech Inc.		☐

Examiner Signature	/Donald Spamer/	Date Considered	08/16/2012

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.S./

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	2	(decontaminating or sterliz$3) same (prefilled)	US-PGPUB; USPAT	ADJ	ON	2012/06/27 07:45
S2	351	(decontaminating or steriliz$3) same (prefilled)	US-PGPUB; USPAT	ADJ	ON	2012/06/27 07:49
S3	41	(decontaminating or steriliz$3) same (prefilled) and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2012/06/27 08:42
S4	11	("6027482" | "4452473" | "4266815" | "5184742" | "5609584" | "5855568" | "6632199" | "6004295" | "5047021" | "5702374" | "5755696").PN.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 10:02
S5	1	"5779973".pn.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 10:08
S6	212	604/199.ccls.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:06
S7	1451	terminal steriliz$	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:46
S8	116	terminal steriliz$ and ((pre-filled or prefilled) syringe)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:47
S9	22	terminal steriliz$ same ((pre-filled or prefilled) syringe)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:48
S10	4	("2006/0106349").URPN.	USPAT	ADJ	ON	2012/08/08 11:59
S11	21	(decontaminating or steriliz$3) same (pre-filled) and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2012/08/08 12:02
S12	14	("4230663" | "4878903" | "5407070" | "5615772" | "5792422" | "5817065").PN. OR ("6228324").URPN.	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 12:20
S13	86	"422".clas. and ((pre-filled or prefilled) (syringe or container))	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 13:26
S14	24	("4226410" | "4236731" | "4947620" | "4962856" | "5033252" | "5052558" | "5178267" | "5178277" | "5217772" | "5220769" | "5536356" | "5571361" | "5590778" | "5715943" | "5830547" | "5868244" | "5949032" | "5976299" | "6034008" | "6117505" | "6228324" |	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 15:39

		"6419392" | "6449925").PN. OR ("6986730").URPN.				
S15	34	("4878903").URPN.	USPAT	ADJ	ON	2012/08/08 16:16
S16	376	206/364.ccls.	USPAT	ADJ	ON	2012/08/08 16:35
S17	7	206/364.ccls. and (hydrogen peroxide)	USPAT	ADJ	ON	2012/08/08 16:36
S18	1119	ranibizumab	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:42
S19	527	ranibizumab and syringe	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:43
S20	122	ranibizumab and syringe and (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:43
S21	15	206/364.ccls. and (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 17:06
S22	195	syringe and (hydrogen peroxide)	EPO; JPO; DERWENT	ADJ	ON	2012/08/08 17:22
S23	0	(nishimura and onishi and saiki).pn.	US-PGPUB; USPAT	ADJ	ON	2012/08/09 11:16
S24	17	protein same syringe same (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/09 11:28
S25	1408	(filter or selective$3) same (UV or ultraviolet) same (sterili$3 or saniti$3 or decontaminate)	US-PGPUB; USPAT	ADJ	ON	2012/08/13 16:39
S26	70	(filter or selective$3) same (UV or ultraviolet) same (package or item) and "422".clas.	US-PGPUB; USPAT	ADJ	ON	2012/08/13 16:46
S27	0	2003/0003014	US-PGPUB; USPAT	ADJ	ON	2012/08/13 17:51
S28	399	metzner.in.	US-PGPUB; USPAT	ADJ	ON	2012/08/13 17:52
S29	49330	hydrogen peroxide and (uv or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2012/08/16 12:54
S30	21	hydrogen peroxide with (uv or ultraviolet) with (inactivat$3)	US-PGPUB; USPAT	ADJ	ON	2012/08/16 12:55
S31	19	hydrogen peroxide and (uv or ultraviolet) and 422/30.ccls.	US-PGPUB; USPAT	ADJ	ON	2012/08/16 13:47

8/16/2012 3:29:18 PM
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13382380	SIGG, JUERGEN
	Examiner	Art Unit
	DONALD SPAMER	4142

SEARCHED			
Class	Subclass	Date	Examiner
422	(text limitated)	08/13/2012	Donald Spamer
422	30 (text limited)	08/16/2012	Donald Spamer
206	364 (text limited)	08/08/2012	Donald Spamer
604	199	08/08/2012	Donald Spamer

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search in eDAN	08/16/2012	Donald Spamer
East search history attached	08/16/2012	Donald Spamer

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

CASE PAT053689-US-PCT

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 4142
Examiner: SPAMER, DONALD ROBER
Conf. No.: 9960

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: 13/382380

35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

This Reply is submitted in response to the Office Action mailed September 14, 2012. Reconsideration of the present rejections and withdrawal of the present rejections are respectfully requested.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method for surface decontamination of a prefilled ~~container~~ syringe in secondary packaging, comprising:

   applying vaporized-hydrogen peroxide to the surface of the prefilled container in secondary packaging at ambient pressure;

   allowing vaporized-hydrogen peroxide to remain in contact with the prefilled container surface for a sufficient time to decontaminate the prefilled container surface at ambient pressure; 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, wherein the prefilled container contains 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.

2. (Currently amended) The method of claim 1, wherein the ~~prefilled container is a~~ syringe ~~containing~~ contains 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.

3. (Currently amended) The method of claim 1, wherein the ~~prefilled container is a~~ syringe ~~containing~~ contains a therapeutically effective amount of ranibizumab.

4. (Previously presented) The method of claim 1, wherein sufficient time to decontaminate the surface of the prefilled ~~container~~ syringe is determined by validation of treatment times and compared to a control standard.

5. (Currently amended) The method of claim 1, 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~~ syringe.

6. (Previously presented) The method of claim 1, 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. (Previously presented) The method of claim 1, wherein the post-decontamination measure includes gas plasma treatment.

8. (Withdrawn) A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

9. (Withdrawn) 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.

10. (Withdrawn) The method of claim 8, 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.

11. (Withdrawn) The method of claim 8, 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.

12. (Withdrawn) The method of claim 8, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

13. (Withdrawn) The method of claim 8, wherein the penetration depth is measured by dosimetry.

14. (Withdrawn) The method of claim 8, 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.

15. (Withdrawn) The method of claim 8, 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.

16. (Withdrawn; previously presented) A system for decontaminating a surface of a prefilled container in secondary packaging, the system comprising:

a sealed chamber; and

a control unit coupled to the chamber, the control unit configured to automatically perform the method according to claim 1.

17. (Withdrawn) 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 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 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

18. (Withdrawn; previously presented) 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 sealed chamber to perform the method according to claim 1.

19. (Withdrawn) A kit for surface-decontaminating a prefilled container in secondary packaging, 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. (Withdrawn) A system according to claim 16, wherein post-decontamination measure includes gas plasma treatment.

21. (Withdrawn; previously presented) A kit according to claim 18, wherein post-decontamination measure includes gas plasma treatment.

22. (Previously presented) The method of claim 1, wherein the drug product is a protein solution.

Remarks/Arguments

I. Claims

Claims 1-22 are presently pending in this patent application. Claims 8- 21 have been withdrawn as being drawn to non-elected subject matter.

Claims 1-3 and 5 are amended without prejudice to specify that the claimed prefilled container is a syringe. Support for these amendments can be found throughout the specification as filed, e.g., original claims 2, 3, 11 and 12, Figure 1, and Paragraphs [0027], [0028], [0043] and [0044] of the original specification as published (US 2012/0014524). Thus, no new matter has been added. Claim 1 is further amended to clarify that the application of H_2O_2 and subsequent step of decontamination of the prefilled syringe by H_2O_2 is done at ambient pressure, i.e., in the absence of a vacuum or low pressure system. Support for this amendment can be found throughout the specification as filed, which nowhere contains disclosure of a requirement that the application of H_2O_2 and subsequent step of decontamination of the prefilled syringe by H_2O_2 be performed under vacuum. Thus, this amendment adds no new matter.

Claims 3-7 have also been amended to correct a typographical error. The Applicants have discovered that the preamble for claims 3-7 on record reads "[t]he method of 1", so these claims have been corrected so that the preamble reads "[t]he method of claim 1." These amendments add no new matter.

Applicants reserve the right to pursue subject matter that remains after the prosecution of the present application in a future continuing patent application, for example, a division.

II. Rejection under 35 U.S.C. § 102 - Anticipation

Claims 1, 4, 5, 7 and 22 have been rejected under 35 U.S.C. § 102 as anticipated by published US Patent Application 2003/0003014 to Metzner ("Metzner"). According to the Examiner, Metzner teaches each and every element of the rejected claims.

With conceding the validity of the Examiner's rejection, the Applicants have amended claim 1 (and thereby claims 4, 5, 7 and 22, which all depend from claim 1) to specify that the claimed prefilled container is a syringe. The Examiner concedes that Metzner does not teach sterilization of a syringe in secondary packaging (see Office Action, p. 5, paragraph 18). Moreover, claim 1 as amended also carifies that the application of H_2O_2 and the subsequent step of decontamination of the prefilled syringe by H_2O_2 occur at ambient pressure. All of the methods disclosed (and claimed) in Metzner require that the secondary packaging be under vacuum to achieve pressure to about 400-500 mtorr prior to injection of H_2O_2 (see Metzer at claim 1, Comparative Example 1 (paragraph [0044]), Example 2 (paragraph [0056], Example 3 (paragraph [0070]), Example 4 (paragraph [0083]), Example 5 (paragraph [0093]), and Example 6 (paragraph [0103]). Indeed, nowhere in Metzger is there any teaching or suggestion that the

aforementioned steps can be performed in the absence of a vacuum to achieve a low pressure environment.

Therefore, for at least the aforementioned reasons, claim 1 as amended is not anticipated by Metzner. Moreover, because claims 4, 5, 7 and 22 depend from claim 1, these claims are not anticipated by Metzner, either. Accordingly, the Applicants respectfully request withdrawal of this rejection.

III. Rejections under 35 U.S.C. § 103 - Obviousness

Claim 2 is rejected under 35 U.S.C. § 103 for obviousness over Metzner in view of US Patent 6,228,324 to Hasegawa ("Hasegawa"). As stated above, the Examiner concedes that Metzner does not teach sterilization of a syringe in secondary packaging. The Examiner relies on Hasegawa to cure this deficiency of Metzner.

As stated above, claim 1 as amended specifies that the prefilled container is a syringe, and also clarifies that the application of H_2O_2 and the subsequent step of decontamination of the prefilled syringe by H_2O_2 occur at ambient pressure. The Applicants concede that the Examiner's reliance on Hasegawa for its disclosure that the prefilled container can be a syringe is well placed. However, the surface sterilization methods of Hasegawa also require that a vacuum environment is established prior to supplying the system with H_2O_2 (see Hasegawa at Fig. 1, and column 8, lines 30-37 ("Successively, **after** the operation of the vacuum pump (52) on the pressure-reducing line (B) is stopped or changed-over to idling and the sluice valves (62) and (63) are closed, the hydrogen peroxide gas is fed through the supply line (A) for hydrogen peroxide gas")). Thus, Hasegawa cannot be relied upon to cure the second deficiency of Metzner, namely that the methods according to Metzner require establishment of a vacuum environment prior to supplying the system with H_2O_2, while the claimed method is performed at ambient pressure.

Therefore, for at least the aforementioned reasons, claim 1 as amended is not obvious over Metzner in view of Hasegawa. And, because claim 2 depends from claim 1, claim 2 cannot be obvious over Metzner in view of Hasegawa, either. Accordingly, the Applicants respectfully request withdrawal of this rejection.

Claim 3 is rejected under 35 U.S.C. § 103 for obviousness over Metzner in view of published US Patent Application 2007/0190058 to Shams ("Shams"). The Examiner concedes that Metzner does not teach sterilization of a syringe containing ranibizumab. The Examiner relies on Shams to cure this deficiency of Metzner. On the basis of the amendment to claim 1 clarifying that the application of H_2O_2 and the subsequent step of decontamination of the prefilled syringe by H_2O_2 occur at ambient pressure, the Applicants traverse.

More specifically, because Shams does not disclose any method for surface sterilization of prefilled syringes, it cannot cure this deficiency of Metzner.

Therefore, for at least the aforementioned reasons, claim 1 as amended is not obvious over Metzner in view of Shams. And, because claim 3 depends from claim 1, claim 3 cannot be obvious over Metzner in view of Shams, either. Accordingly, the Applicants respectfully request withdrawal of this rejection.

Claim 6 is rejected under 35 U.S.C. § 103 for obviousness over Metzner in view of published US Patent Application 2005/0226764 to Moirandat ("Moirandat"). The Examiner concedes that Metzner does not teach a post-decontamination step using ultraviolet radiation. The Examiner relies on Moirandat to cure this deficiency of Metzner. On the basis of the amendment to claim 1 clarifying that the application of H_2O_2 and the subsequent step of decontamination of the prefilled syringe by H_2O_2 occur at ambient pressure, the Applicants traverse.

More specifically, because Moirandat does not disclose any method for surface sterilization of prefilled syringes, it cannot cure this deficiency of Metzner.

Therefore, for at least the aforementioned reasons, claim 1 as amended is not obvious over Metzner in view of Moirandat. And, because claim 3 depends from claim 1, claim 3 cannot be obvious over Metzner in view of Moirandat, either. Accordingly, the Applicants respectfully request withdrawal of this rejection.

IV. Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Action of record. If there are any issues that can be resolved by a telephone conference, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

/ Andrew Holmes /

Andrew Holmes
Agent for Applicant
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Date: December 12, 2012

Case PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 4142
Examiner: SPAMER, DONALD ROBER

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: 13/382380

35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:
This paper is being filed:

☒ supplemental to the Information Disclosure Statement filed January 5, 2012.

If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134 in the name of Novartis.

☒ A letter for payment of fee set forth in 37 C.F.R. §1.17(p) is enclosed.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO/SB/08A/B.

☒ Copies of the references are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO/SB/08A/B form(s).

Respectfully submitted,

/ Andrew Holmes /

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Andrew Holmes
Agent for Applicant
Reg. No. 51,813

Date: December 12, 2012

CASE PAT053689-US-PCT

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Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 4142
Examiner: SPAMER, DONALD ROBER

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: 13/382380

35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

FEE LETTER FOR INFORMATION DISCLOSURE STATEMENT

Sir:

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $180 for payment of the fee pursuant to 37 CFR §1.17(p) for the submission of an Information Disclosure Statement under 37 CFR §1.97(c).

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

/ Andrew Holmes /

Andrew Holmes
Agent for Applicant
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Date: December 12, 2012

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/382380
Filing Date	July 13, 2010
First Named Inventor	Sigg, Juergen
Art unit	4142
Examiner Name	SPAMER, DONALD ROBER
Attorney Docket Number	PAT053689-US-PCT

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US 7,060,269	06-13-2006	Baca et al	
		US 4,512,951	04-23-1985	Koubek	
		US 4,169,123	09-25-1979	Moore et al	
		US 4,169,124	09-25-1979	Forstrom et al	
		US-			
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
						☐
						☐
						☐
						☐
						☐
						☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal	
Application Number:	13382380
Filing Date:	05-Jan-2012
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Filer:	Andrew K. Holmes/Andrea Jacquin
Attorney Docket Number:	PAT053689-US-PCT
Filed as Large Entity	

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	14447610
Application Number:	13382380
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Customer Number:	1095
Filer:	Andrew K. Holmes/Andrea Jacquin
Filer Authorized By:	Andrew K. Holmes
Attorney Docket Number:	PAT053689-US-PCT
Receipt Date:	12-DEC-2012
Filing Date:	05-JAN-2012
Time Stamp:	14:07:35
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	397
Deposit Account	190134
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		53689-US-PCT_Amendment_SuppIDS_2012Dec12.pdf	1854899 6d35834ad9c089d0c4bb10c92257ee4ff1075f00b	yes	11

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	8
Transmittal Letter	9	9
Miscellaneous Incoming Letter	10	10
Information Disclosure Statement (IDS) Form (SB08)	11	11

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30087 71f86e79263a3754a599182fa88267b2d569212b	no	2

Warnings:

Information:

Total Files Size (in bytes):	1884986

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/382,380	Filing Date 01/05/2012	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT	12/12/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 22	Minus	** 22	= 0	X $ =		OR	X $62 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 5	= 0	X $ =		OR	X $250 =	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/C. Dessau/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/382,380	01/05/2012	Juergen Sigg	PAT053689-US-PCT	9960

1095 7590 01/03/2013

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
SPAMER, DONALD R	
ART UNIT	**PAPER NUMBER**
1775	

NOTIFICATION DATE	DELIVERY MODE
01/03/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Office Action Summary	Application No.	Applicant(s)	
	13/382,380	SIGG, JUERGEN	
	Examiner	Art Unit	
	DONALD SPAMER	1775	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-22* is/are pending in the application.

5a) Of the above claim(s) *8-21* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-7 and 22* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☒ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/12/2012*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed 12/12/2012 has been received and considered for examination.

Response to Arguments

2. Applicant's arguments with respect to claims 1-7 and 22 have been considered but are moot in view of the new grounds of rejection. Applicant's amendment necessitated the new grounds of rejection. The newly relied upon prior art of Dalmasso et al. (US Patent 5,788,941) teaches the newly claimed limitation regarding "ambient pressure". See rejection below.

3. The Applicant remarks that the addition of requiring the application of hydrogen peroxide and subsequent decontamination to be carried out at ambient pressure is not new matter since there is no teaching of a requirement that it be carried out at a reduced pressure. This argument is not persuasive because the specification does not disclose or teach that the pressure is ambient during the application and decontamination.

Specification

4. The amendment filed 12/12/2012 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the limitation that the vaporized hydrogen peroxide is applied to the prefilled container in secondary packaging and that the hydrogen peroxide remains long enough to decontaminate the surface occurs at ambient pressure.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of 35 U.S.C. 112(a):
(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), first paragraph:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. The following is a quotation of 35 U.S.C. 112(d):
(d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

8. Claims 1-7 and 22 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment to claim 1 adds the limitation that the vaporized hydrogen peroxide is applied to the prefilled container in secondary packaging and that the hydrogen peroxide remains long enough to decontaminate the surface occurs at ambient pressure. There is no teaching in the specification that this occurs at ambient pressure. Since claims 2-7 and 22 all depend on claim 1, they also contain all the limitations of claim 1 and thus are also rejected for containing new matter.

9. Claims 1-7 and 22 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

10. Claim 1 recites the limitation "the prefilled container" in lines 3, 5, 6, and 10. There is insufficient antecedent basis for this limitation in the claim.

Claims 2-7 and 22 are rejected for being dependent on claim 1 and thus containing the limitation "the prefilled container" as well.

11. Claim 2 is rejected under 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Since claim 1 has been amended to include the limitation of a syringe (instead of a prefilled container) the limitations of the dependent claim 2 are now already claimed in the independent claim 1. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1, 4, 5, 7, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Metzner et al. (US Patent Application Publication Number 2003/0003014) as evidenced by Hasegawa et al. (US Patent 6,228,324) and in view of Hasegawa et al. (US Patent 6,228,324) and Dalmasso et al. (US Patent 5,788,941).

With regards to claim 1, Metzner et al. teaches a method for surface decontamination of a prefilled container in secondary packaging (para [0010-0011]). Metzner et al. teaches the use of vaporized hydrogen peroxide in order to sterilize the surfaces of the packaging (para [0019]). Metzner et al. also teaches that the hydrogen peroxide is left in contact with the surfaces for a sufficient amount of time to achieve decontamination (para [0032-0033]) and gives an example of about 17 min in each half cycle in example 3 (para [0071]). Metzner et al. also teaches the use of post-decontamination measures of applying a vacuum (para [0034 - 0035]). The vacuum post decontamination treatment taught by

Metzner et al. would remove the hydrogen peroxide as evidenced by Hasegawa et al. Hasegawa et al. states that the application of a vacuum removes the hydrogen peroxide from inside the packaging (column 8, lines 63-67 and column 9, lines 32-38).

Metzner et al. teaches this method can be done on temperature sensitive pharmaceutical products (para [0002]). It expands to say that such products are sensitive to sterilization with gamma radiation (para [0005]), autoclaving (para [0003]) (exposure to steam), and ethylene oxide (since ethylene oxide residue can render the drug product toxic or carcinogenic) (gas) (para [0004]). In example 3, Metzner et al. teaches that the protein drug product is in a carpule (para [0061]). A carpule is a container for medicine that is administered to the patient with a syringe. Metzner thus does not expressly state the use of the method on a syringe in secondary packaging. Hasegawa et al. teaches a method for sterilizing a syringe in secondary packaging using hydrogen peroxide vapor (abstract and figure 4). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. to sterilize a syringe in secondary packaging as shown in Hasegawa et al. in order to provide a sterile drug product by using hydrogen peroxide vapor (abstract and figure 4).

The method taught by Metzner includes a step of lowering the pressure in the treatment chamber below ambient atmospheric pressure prior to the application of hydrogen peroxide and subsequent decontamination. Dalmasso et al. teaches a method for sterilizing a biological medical product that is sensitive to traditional heat, gamma ray, and ethylene oxide sterilization methods (the proteins in bone can be denatured by heat, gamma ray, and ethylene oxide methods) by applying hydrogen peroxide vapor (abstract and column 1, lines 31-60). Delmasso et al. teaches that effective sterilization can be achieved at atmospheric (ambient) pressure and room temperature (column 7, lines 40-53). A person having ordinary skill in the art at the time of the invention would have found it obvious to simplify the method taught by Metzner by applying the hydrogen peroxide vapor causing subsequent decontamination at ambient (atmospheric) pressure (removing a step of evacuating the chamber to near vacuum prior to the application and decontamination) motivated by simplifying the method taught by Metzner (saving energy by having to run the vacuum less) with a reasonable expectation of success as taught by Delmasso et al.

With regards to claim 4, Metzner et al. teaches determining if the sterilization method is effective (para [0037]). This is considered to include testing whether the treatment times are sufficient since treatment times are part of the method. Metzner et al. teaches that sterilization effectiveness is determined by comparing the reduction factor of colony forming units (CFU) and comparing this value to a control standard (para [0037]). The control standard taught by Metzner et al. is that sterilization is achieved if $\log_{10}$(CFU) is greater than or equal to 6 (para [0037]).

With regards to claim 5, Metzner et al. teaches a post decontamination measure of applying a vacuum following treatment with vaporized hydrogen peroxide (para [0034]). While Metzner et al. does not specifically state the intended use of "reversing the direction of diffusion of vaporized hydrogen peroxide and preventing intrusion of vaporized hydrogen peroxide into the prefilled container," the method of using a vacuum after effective treatment inherently achieves this. This is affirmatively shown by the teaching Hasegawa et al.

Hasegawa et al. states that the application of a vacuum (taught by Metzner et al.) removes the hydrogen peroxide from inside the packaging (column 8, lines 63-67 and column 9, lines 32-38).

The prevention of hydrogen peroxide intrusion can be further confirmed when Metzner et al. measures the amount of proteins undamaged by the sterilization method and finds that the method damaged very little to none of the protein products (para [0076]).

With regards to claim 7, teaches a post decontamination measure that includes a plasma treatment (para [0035]). This is considered to be a gas plasma.

With regards to claim 22, the combination of Metzner et al. and Hasegawa et al. teaches that the hydrogen peroxide vapor sterilization method can be used for sterilizing prefilled syringes in secondary packaging where the prefilled drug product is various proteins (Metzner et al. para [0061]).

14. Claim 3 rejected under 35 U.S.C. 103(a) as being unpatentable over Metzner et al. (US Patent Application Publication Number 2003/0003014), Hasegawa et al. (US Patent 6,228,324), and Dalmasso et al. (US Patent 5,788,941) as applied to claim 1 above, and further in view of Shams (US Patent Application Publication 2007/0190058).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. teaches a method of using hydrogen peroxide vapor for sterilizing different proteins in secondary packaging (para [0061]) at 30°C (para [0063]) and teaches that the treatment did not destroy the protein products (para [0076]). Metzner et al. does not specifically mention the use of the method for treating a medical product where the prefilled drug is ranibizumab, a protein. The claim recites "therapeutically effective" (implying non degraded protein when administered into a body for treatment). A person having ordinary skill in the art at the time of the invention would understand that if this method is capable of sterilizing prefilled protein drug products in secondary packaging without causing degradation of the proteins that the method is capable of treating the specific protein ranibizumab.

Additionally the concept of using ranibizumab delivered by a syringe is also known in the prior art. Shams teaches the administration of ranibizumab by syringe injection (para [0128]). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. with the addition of ranibizumab being the drug in the syringe, as taught by Shams, in order to administer a dose of ranibizumab as a therapuetic drug (abstract and para [0028]) in a sterile manner which is desired by Shams who states that the treatment should be formulated, dosed, and administered in a fashion consistent with good medical practice (para [0092]) which would include using a sterile syringe.

15. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable Metzner et al. over (US Patent Application Publication Number 2003/0003014), Hasegawa et al. (US Patent 6,228,324), and Dalmasso et al. (US Patent 5,788,941. as applied to claim 1 above, and further in view of Moirandat et al. (US Patent Application Publication 2005/0226764).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. also teaches the use of a post decontamination measure using a vacuum (para [0034]) and a plasma treatment (para [0035]).

Metzner et al. does not teach the use of ultraviolet rays in a post decontamination measure.

Moirandat et al. teaches a method of decontaminating a clean room with hydrogen peroxide followed by post decontamination measures (para [0008], summary of invention). Moirandat et al.

teaches that hydrogen peroxide remaining after decontamination can be photochemically broken down by UV radiation (ultraviolet rays) into oxygen and water (para [0031]). A person having ordinary skill in the art at the time of the invention would have been able to modify the method of Metzner et al. with the addition of ultraviolet rays to deactivate hydrogen peroxide vapors rapidly and in the least costly manner (Moirandat et al. para [0008]).

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DONALD SPAMER whose telephone number is (571)272-3197. The examiner can normally be reached on Monday through Friday, 9 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on 571-272-1374. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

a. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DONALD SPAMER/
Examiner, Art Unit 1775

/SEAN E CONLEY/
Primary Examiner, Art Unit 1775

Notice of References Cited	Application/Control No. 13/382,380	Applicant(s)/Patent Under Reexamination SIGG, JUERGEN	
	Examiner DONALD SPAMER	Art Unit 1775	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,788,941	08-1998	Dalmasso et al.	422/33
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	2	(decontaminating or sterliz$3) same (prefilled)	US-PGPUB; USPAT	ADJ	ON	2012/06/27 07:45
S2	351	(decontaminating or steriliz$3) same (prefilled)	US-PGPUB; USPAT	ADJ	ON	2012/06/27 07:49
S3	41	(decontaminating or steriliz$3) same (prefilled) and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2012/06/27 08:42
S4	11	("6027482" | "4452473" | "4266815" | "5184742" | "5609584" | "5855568" | "6632199" | "6004295" | "5047021" | "5702374" | "5755696").PN.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 10:02
S5	1	"5779973".pn.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 10:08
S6	212	604/199.ccls.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:06
S7	1451	terminal steriliz$	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:46
S8	116	terminal steriliz$ and ((pre-filled or prefilled) syringe)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:47
S9	22	terminal steriliz$ same ((pre-filled or prefilled) syringe)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:48
S10	4	("2006/0106349").URPN.	USPAT	ADJ	ON	2012/08/08 11:59
S11	21	(decontaminating or steriliz$3) same (pre-filled) and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2012/08/08 12:02
S12	14	("4230663" | "4878903" | "5407070" | "5615772" | "5792422" | "5817065").PN. OR ("6228324").URPN.	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 12:20
S13	86	"422".clas. and ((pre-filled or prefilled) (syringe or container))	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 13:26
S14	24	("4226410" | "4236731" | "4947620" | "4962856" | "5033252" | "5052558" | "5178267" | "5178277" | "5217772" | "5220769" | "5536356" | "5571361" | "5590778" | "5715943" | "5830547" | "5868244" | "5949032" | "5976299" | "6034008" | "6117505" | "6228324" |	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 15:39

		"6419392" | "6449925").PN. OR ("6986730").URPN.				
S15	34	("4878903").URPN.	USPAT	ADJ	ON	2012/08/08 16:16
S16	376	206/364.ccls.	USPAT	ADJ	ON	2012/08/08 16:35
S17	7	206/364.ccls. and (hydrogen peroxide)	USPAT	ADJ	ON	2012/08/08 16:36
S18	1119	ranibizumab	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:42
S19	527	ranibizumab and syringe	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:43
S20	122	ranibizumab and syringe and (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:43
S21	15	206/364.ccls. and (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 17:06
S22	195	syringe and (hydrogen peroxide)	EPO; JPO; DERWENT	ADJ	ON	2012/08/08 17:22
S23	0	(nishimura and onishi and saiki).pn.	US-PGPUB; USPAT	ADJ	ON	2012/08/09 11:16
S24	17	protein same syringe same (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/09 11:28
S25	1408	(filter or selective$3) same (UV or ultraviolet) same (sterili$3 or saniti$3 or decontaminate)	US-PGPUB; USPAT	ADJ	ON	2012/08/13 16:39
S26	70	(filter or selective$3) same (UV or ultraviolet) same (package or item) and "422".clas.	US-PGPUB; USPAT	ADJ	ON	2012/08/13 16:46
S27	0	2003/0003014	US-PGPUB; USPAT	ADJ	ON	2012/08/13 17:51
S28	399	metzner.in.	US-PGPUB; USPAT	ADJ	ON	2012/08/13 17:52
S29	49330	hydrogen peroxide and (uv or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2012/08/16 12:54
S30	21	hydrogen peroxide with (uv or ultraviolet) with (inactivat$3)	US-PGPUB; USPAT	ADJ	ON	2012/08/16 12:55
S31	19	hydrogen peroxide and (uv or ultraviolet) and 422/30.ccls.	US-PGPUB; USPAT	ADJ	ON	2012/08/16 13:47
S32	0	2007/0190058	US-PGPUB; USPAT	ADJ	ON	2012/08/20 08:54
S33	1	"20070190058"	US-PGPUB; USPAT	ADJ	ON	2012/08/20 08:54
S34	4	("4169123" | "4169124" | "4512951" |	US-	ADJ	ON	2012/12/17

		"7060269").PN.	PGPUB; USPAT			08:22
S35	0	(sterili$ or disinfect or decontaminat$ or saniti$) same (pre-filled or prefilled) same (hydrogen peroxide) same ((atmosphere or ambient) pressure)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 17:56
S36	31	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same ((atmosphere or ambient) pressure)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 17:56
S37	204	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same (atmospheric pressure)	US-PGPUB; USPAT	ADJ	ON	2012/12/18 10:33
S38	1	"6228324".pn.	US-PGPUB; USPAT	ADJ	ON	2012/12/18 11:00
S39	58	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same (atmospheric pressure) same (below and above)	US-PGPUB; USPAT	ADJ	ON	2012/12/18 11:04
S40	17	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same ((atmospheric pressure) with (below and above))	US-PGPUB; USPAT	ADJ	ON	2012/12/18 11:05

12/18/2012 1:09:52 PM
C:\Users\dspamer\Documents\EAST\Workspaces\13382380.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13382380	SIGG, JUERGEN
	Examiner	Art Unit
	DONALD SPAMER	4142

SEARCHED			
Class	Subclass	Date	Examiner
422	(text limitated)	08/13/2012	Donald Spamer
422	30 (text limited)	08/16/2012	Donald Spamer
206	364 (text limited)	08/08/2012	Donald Spamer
604	199	08/08/2012	Donald Spamer

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search in eDAN	08/16/2012	Donald Spamer
East search history attached	08/16/2012	Donald Spamer
Updated East search history attached	12/18/2012	DS

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

Receipt date: 12/12/2012

PTO/SB/08a (07-09)
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13382380 GAU 1775

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/382380
Filing Date	July 13, 2010
First Named Inventor	Sigg, Juergen
Art unit	4142
Examiner Name	SPAMER, DONALD ROBER
Attorney Docket Number	PAT053689-US-PCT

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US 7,060,269	06-13-2006	Baca et al	
		US 4,512,951	04-23-1985	Koubek	
		US 4,169,123	09-25-1979	Moore et al	
		US 4,169,124	09-25-1979	Forstrom et al	
		US-			
		US-			
		US-			
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		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
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Examiner Signature	/Donald Spamer/	Date Considered	12/18/2012

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.S./

PTO/SB/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Request for Continued Examination (RCE) Transmittal

Address to:
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	13/382380
Filing Date	January 05, 2012
First Named Inventor	Sigg, Juergen
Art unit	4142
Examiner Name	SPAMER, DONALD ROGER
Attorney Docket Number	PAT053689-US-PCT

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant must request non-entry of such amendment(s).
   - a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. ☐ Other _____
   - b. ☒ Enclosed
     - i. ☒ Amendment/Reply
     - ii. ☒ Affidavit(s)/Declaration(s)
     - iii. ☐ Information Disclosure Statement (IDS)
     - iv. ☐ Other _____

2. Miscellaneous
   - a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   - a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 19-0134 in the name of Novartis.
     - i. ☒ RCE fee required under 37 CFR 1.17(e)
     - ii. ☒ Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. ☐ Other _____
   - b. ☐ Check in the amount of $_____ enclosed
   - c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit Card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Andrew Holmes /	Date	May 3, 2013
Name (Print/Type)	Andrew Holmes	Registration No.	51,813

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print/Type)		Date	

CASE PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 41424142
Examiner: SPAMER, DONALD ROBERT

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011
FILED: July 13, 2010
U.S. APPLICATION NO: 13/382380
35 USC §371 DATE: January 05, 2012
FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER FINAL REJECTION

Sir:

This Reply is submitted in response to the Final Office Action mailed January 3, 2013. A one-month extension of time petition is included herewith. Reconsideration of the present rejections and withdrawal of the present rejections are respectfully requested.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method for surface decontamination of a prefilled syringe in secondary packaging, comprising:

applying vaporized-hydrogen peroxide to the surface of the prefilled ~~container~~ syringe in secondary packaging ~~at ambient pressure~~;

allowing vaporized-hydrogen peroxide to remain in contact with the prefilled ~~container~~ syringe surface for a sufficient time to decontaminate the prefilled ~~container~~ syringe surface ~~at ambient pressure~~; 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~~ syringe, wherein the prefilled ~~container~~ syringe contains 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.

2. (Cancelled)

3. (Previously presented) The method of claim 1, wherein the syringe contains a therapeutically effective amount of ranibizumab.

4. (Previously presented) The method of claim 1, wherein sufficient time to decontaminate the surface of the prefilled syringe is determined by validation of treatment times and compared to a control standard.

5. (Previously presented) The method of claim 1, 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 syringe.

6. (Previously presented) The method of claim 1, 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. (Previously presented) The method of claim 1, wherein the post-decontamination measure includes gas plasma treatment.

8. (Withdrawn) A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

9. (Withdrawn) 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.

10. (Withdrawn) The method of claim 8, 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.

11. (Withdrawn) The method of claim 8, 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.

12. (Withdrawn) The method of claim 8, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

13. (Withdrawn) The method of claim 8, wherein the penetration depth is measured by dosimetry.

14. (Withdrawn) The method of claim 8, 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.

15. (Withdrawn) The method of claim 8, 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.

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

a sealed chamber; and

a control unit coupled to the chamber, the control unit configured to automatically perform the method according to claim 1.

17. (Withdrawn) 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 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 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

18. (Withdrawn) 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 sealed chamber to perform the method according to claim 1.

19. (Withdrawn) A kit for surface-decontaminating a prefilled container in secondary packaging, 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. (Withdrawn) A system according to claim 18, wherein post-decontamination measure includes gas plasma treatment.

21. (Withdrawn) A kit according to claim 18, wherein post-decontamination measure includes gas plasma treatment.

22. (Previously presented) The method of claim 1, wherein the drug product is a protein solution.

Remarks/Arguments

I. Claims

Claims 1-22 are presently pending in this patent application. Claims 8- 21 have been withdrawn as being drawn to non-elected subject matter. Claim 2 is cancelled with this Amendment.

Claim 1 has been amended to delete the limitation added in Applicants' December 14, 2012 Amendment, i.e., the amendment adding a limitation to clarify that the application of H_2O_2 and subsequent step of decontamination of the prefilled syringe by H_2O_2 is done at ambient pressure, i.e., in the absence of a vacuum or low pressure system. Claim 1 has been further amended to specify that claim recites a prefilled syringe rather than a container. No new matter is added by these amendments.

Therefore, upon entry of this Amendment, claims 1, 3-7 and 22 are under examination.

Applicants reserve the right to pursue subject matter that remains after the prosecution of the present application in a future continuing patent application, for example, a division.

II. Rejections under 35 U.S.C. § 112

Claims 1-7 and 22 stand rejected for failing to comply with the written description requirement. More specifically, the Examiner contends that the limitations in claim 1 relating to the performance of steps of the claimed method "at ambient pressure" constitute new matter. In response, without conceding the validity of the Examiner's rejections, the Applicants have amended claim 1 to delete the limitation "at ambient pressure," obviating the Examiner's rejection. Accordingly, the Applicants request withdrawal of this rejection.

Claims 1-7 and 22 stand rejected for indefiniteness. More specifically, the Examiner contends that the limitation in claim 1 reciting "the prefilled container" does not have antecedent basis in the claim. In response, claim 1 has been amended to specify that claim recites a prefilled syringe rather than a container, thereby obviating the Examiner's rejection. Accordingly, the Applicants request withdrawal of this rejection.

Claim 2 stands rejected because it recites a "syringe" and thus fails to further limit claim 1, from which it depends. In response, claim 2 has been cancelled, thereby obviating the Examiner's rejection.

III. Rejections under 35 U.S.C. § 103 - Obviousness

Claim 2 is rejected under 35 U.S.C. § 103 for obviousness over published U.S. Patent Application 2003/0003014 to Metzner et al. ("Metzner") as evidenced by U.S. Patent 6,228,324 to Hasegawa ("Hasegawa"), and further in view of Hasegawa and U.S. Patent 5,788,941 to Dalmasso ate al. ("Dalmasso"). The Examiner relies on Metzner for its teaching of a method for surface decontamination of a prefilled container in secondary packaging (citing Metzner at ¶¶ [0001-0011]). The Examiner concedes that Metzner does not teach sterilization of a syringe in

secondary packaging. The Examiner relies on Hasegawa to cure this deficiency. The Examiner also concedes that the method according to Metzner includes the steps of (i) applying a vacuum prior to injection of H_2O_2 vapor, (ii) maintaining the system under vacuum during the sterilization process, and (iii) removing the vacuum after sterilization is complete (see, e.g., Metzner Example 2, at ¶¶ [0052]-[0060]). In response to a September 4, 2012 rejection of the pending claims over Metzner, the Applicants responded in part by asserting that the claimed method does not involve a step of pressure reduction before application of the H_2O_2 – instead, in the claimed method, the decontamination steps are performed at ambient pressure. The Examiner responded in the current Office Action by citing Dalmasso for teaching surface decontamination at ambient pressure, and stated that "a person of ordinary skill in the art would have found it obvious to simplify the method taught by Metzner by applying the hydrogen peroxide vapor causing subsequent decontamination at ambient (atmospheric) pressure …." (See January 3, 2013 Office Action, p. 5). The Examiner contends that skilled artisan would have been motivated to this because it simplified the method of Metzner by removing a step in the Metzner method and saving the energy required to perform that step. The Examiner concludes that this could be done "with a reasonable expectation of success as taught by Dalmasso." (*Id.*).

The Applicants respectfully traverse this rejection, on the basis that the Examiner's contentions regarding the teachings of Metzner and Dalmasso and the ability to combine these teaching to arrive at the claimed method are incorrect. More specifically, one of ordinary skill in the art at the critical time (i.e., the time of filing of the current application) would have concluded that (i) the method taught in Metzner would not have worked if applied to the prefilled syringe to be decontaminated in the claimed method; (ii) the method of Metzner could not have been performed at ambient pressure (according to the teachings of Dalmasso) with any expectation of success; and (iii) in any instance, one of ordinary skill in the art (at the critical time) would not have looked to the teachings of Dalmasso for guidance at arriving at the claimed method. In support their position, the Applicants submit the Declaration of Dr. Juergen Sigg, the sole inventor of the method claimed in the patent application under examination ("Sigg Declaration").

There are two potential problems associated with using the Metzner method to sterilize a syringe filled with a substance that would become denatured if contacted by H_2O_2, e.g., a protein. The first application of the vacuum to prior to adding H_2O_2 vapor would likely cause a breach in the syringe seal, which in turn could cause entry of the H_2O_2 into the syringe, resulting in denaturation of the protein in the syringe. The second problem is that, even if the seal is not breached, the plunger stopper would move upon application of the vacuum pump, and move again when the vacuum is released. The first time the plunger stopper moved, it would cover of parts of the syringe barrel, preventing these parts from exposure to the H_2O_2 and thus from sterilization. Then, after the vacuum is released and the plunger stopper migrates back to its original position, these non-sterile parts of the syringe barrel would now be exposed. Even Metzner notes the existence of this second problem, stating that "[] care must be taken that

movable closures such as stoppers, plunger seals or caps are fixed so that no opening and no leak occurs in the primary packaging under vacuum. This can be prevented, for example, by appropriate devices, whether by directly fixing the closures or by ensuring by an appropriate secondary packaging that no leak or displacement of stoppers or plunger seals can occur." (See Metzner, ¶ [0024]; see also Sigg Declaration at ¶ 6.). For the sake of completeness, the Applicants note that the claimed method does not require any such devices to prevent stopper movement. Accordingly, the vacuum method taught by Metzner may not result in a sterile product and, indeed, may result in denaturation of the protein in the syringe.

The Examiner cannot rely on Hasegawa to cure this deficiency of Metzner, because the surface sterilization methods of Hasegawa also require that a vacuum environment is established prior to supplying the system with H_2O_2 (see Hasegawa at Fig. 1, and column 8, lines 30-37 ("Successively, after the operation of the vacuum pump (52) on the pressure-reducing line (B) is stopped or changed-over to idling and the sluice valves (62) and (63) are closed, the hydrogen peroxide gas is fed through the supply line (A) for hydrogen peroxide gas")).

Therefore, the Examiner now relies on Dalmasso to cure this deficiency of Metzner. This reliance, however, is also misplaced. As a first matter, one of ordinary skill in the art at the critical time would not look to the teachings of Dalmasso for guidance if they were seeking a method of sterilizing a primary container, e.g., a syringe, containing a protein sensitive to H_2O_2-facilitated degradation, wherein the syringe was itself packaged in a secondary container prior to sterilizing. The Dalmasso method represents non-analogous art – the Dalmasso method is used to sterilize bone tissue prior to transplantation, which is very different from sterilizing a syringe in secondary packaging and containing a protein that would be degraded if it was contacted by H_2O_2, not least because the bone tissue to be sterilized by the method according to Dalmasso (i) is not sensitive to H_2O_2-facilitated degradation (see Dalmasso at column 4, line 42); and (ii) is not packaged in secondary packaging. Moreover, even if one of ordinary skill in the art at the critical time was aware of the teachings of Dalmasso, and sought to combine them with the teachings of Metzner and/or Hasegawa, he would not arrive at the claimed invention. This is because Dalmasso teaches that in the absence of a vacuum, penetration of bone tissue by H_2O_2 vapor is very limited even when the bone tissue is not in a secondary package. (See Dalmasso at column 4, lines 3-5). Therefore, the skilled artisan at the critical time, upon reviewing the teachings of Metzner, Hasegawa and Dalmasso, taken alone or in any combination, would understand that they could not be combined with any expectation of success.

Therefore, for at least the aforementioned reasons, claim 1 as amended is not obvious over Metzner in view of Hasegawa and Dalmasso. And, because claims 4, 5, 7 and 22 depend from claim 1, these claims cannot be obvious over Metzner in view of Hasegawa and Dalmasso, either. Accordingly, the Applicants respectfully request withdrawal of this rejection.

Claim 3 is rejected under 35 U.S.C. § 103 for obviousness over Metzner in view of Hasegawa and Dalmasso, and in further view of published US Patent Application 2007/0190058 to Shams ("Shams"). The Examiner concedes that Metzner does not teach sterilization of a syringe containing ranibizumab. The Examiner relies on Shams to cure this deficiency of Metzner. However, this teaching of Shams is of no matter, because Shams cannot cure the primary deficiency of Metzner any more than can Hasegawa or Dalmasso. Therefore, for at least the aforementioned reasons, claim 3 is not obvious over Metzner in view of Hasegawa and Dalmasso and Shams. Accordingly, the Applicants respectfully request withdrawal of this rejection.

Claim 6 is rejected under 35 U.S.C. § 103 for obviousness over Metzner in view of Hasegawa and Dalmasso, and in further view of published US Patent Application 2005/0226764 to Moirandat ("Moirandat"). The Examiner concedes that Metzner does not teach a post-decontamination step using ultraviolet radiation. The Examiner relies on Moirandat to cure this deficiency of Metzner. However, as with Shams, this teaching of Moirandat is of no matter, because Moirandat cannot cure the primary deficiency of Metzner any more than can Hasegawa or Dalmasso. Therefore, for at least the aforementioned reasons, claim 6 is not obvious over Metzner in view of Moirandat. Accordingly, the Applicants respectfully request withdrawal of this rejection.

IV. Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Action of record. If there are any issues that can be resolved by a telephone conference, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

/Andrew Holmes/

Novartis Pharmaceuticals Corporation One Health Plaza, Bldg. 101 East Hanover, NJ 07936
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Andrew Holmes
Agent for Applicant
Reg. No. 51,813

Date: May 3, 2013

APPENDIX A

CASE PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 41424142
Examiner: SPAMER, DONALD ROBERT

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: 13/382380

35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JUERGEN SIGG, Ph.D.

I, Juergen Sigg, declare and say that:

1. I reside at Karl-Arzet-Weg 25, Loerrach, Germany.

2. I am employed by Novartis Pharma AG ("Novartis"), located at Fabrikstrasse, Basel, Switzerland. I have been so employed since 1992. My title is Principal Fellow. In this position, which I have held since 2006, I am responsible for development, transfer and validation of pharmaceutical formulations and manufacturing processes of biotechnically derived pharmaceutical drug products.

3. I received a Ph.D. degree in Pharmaceutical Technology from University of Regensburg in Regensburg (Germany) in 1991.

4. I am the sole inventor of the invention claimed in pending patent application, U.S. Serial No. 13/382380, with claims 1-7 and 22 directed to a method for surface decontamination of a pre-filled container.

5. I understand that the PTO Patent Examiner has rejected claims 1, 4, 5, 7, and 22 as obvious over Metzner *et al.*, published U.S. Patent Application No. 2003/0003014 ("Metzner"), as evidenced by and in view of Hasegawa et al., U.S. Patent No. 6,228,324 ("Hasegawa") and further in view of Dalmasso et al., U.S. Patent No. 5,788,941 ("Dalmasso"). I have read and understand Metzner, Hasegawa and Dalmasso. The Examiner asserts that Metzner teaches the claimed method, but that the "method taught by Metzner includes a step of lowering the pressure in the treatment chamber below ambient atmospheric pressure prior to the application of hydrogen peroxide and subsequent decontamination." (January 3, 2013 Office Action, page 5). In response to the Applicants' assertion that the claimed method does not include the step of lowering the pressure prior to application of H_2O_2, the Examiner cited Dalmasso for its teaching that "effective sterilization can be achieved at atmospheric (ambient) pressure and room temperature." (*Id.*). The Examiner concludes that a "person having ordinary skill in the art at the time of the invention would have found it obvious to simplify the method taught by Metzner by applying the hydrogen peroxide vapor causing subsequent decontamination at ambient (atmospheric) pressure ... with a reasonable expectation of success as taught by Dalmasso et al." (*Id.*).

6. I believe that the Examiner's conclusion with regard to Metzner is incorrect. The method taught by Metzner would likely result in denaturation of the protein in the syringe, or a non-sterile pre-filled syringe, or both. More specifically, if the method of Metzner were used, i.e., carrying out the sterilization under vacuum, this would likely cause a breach in the syringe seal, which in turn could cause entry of the H_2O_2 into the syringe. This would cause denaturation of the protein in the syringe, which is sensitive to H_2O_2-facilitated degradation. In addition, in the vacuum method taught by Metzner, if the syringe in question contained an air bubble (even a very small air bubble), the plunger stopper in the syringe would be pulled back by a certain distance upon application of the vacuum, and would thus cover parts of the inside of the syringe barrel, preventing these parts from exposure to the H_2O_2 and thus from sterilization. And, subsequent to the sterilization step, when the vacuum is released, the plunger would move back into its original position and expose this non-sterile surface to the environment. Thus the vacuum method taught by Metzner may not result in a sterile product. Metzner does not teach any steps that can be taken to avoid breach of the syringe seal or movement of the syringe as the vacuum is applied and then removed. One possible solution to

these problems resulting from using the method of Metzner would be to use a method such as the claimed method, in which there is no pressure change during the sterilization process.

7. The Examiner contends that one such method is that taught by Dalmasso. I believe that the Examiner's conclusion with respect to Dalmasso is incorrect, for the reasons stated below. As a first matter, I would not look to the teachings of Dalmasso for guidance if I were seeking a method of sterilizing a primary container, e.g., a syringe, containing a protein sensitive to H_2O_2-facilitated degradation, wherein the syringe was itself packaged in a secondary container prior to sterilizing. And, even if I was already aware of the teachings of Dalmasso, I do not believe that the teachings of Dalmosso, taken alone or combined with those of Metzner (or any of the other references cited by the Examiner in this case), could help a person of ordinary skill in the art to arrive at the claimed invention with any expectation of success. The method taught by Dalmasso relates to a completely different technical problem than the one addressed by the claimed invention, i.e., sterilization of bone tissue prior to transplantation. Dalmasso states that the bone tissue can even be pre-treated with liquid hydrogen peroxide solution, which gives evidence that bone tissue is not sensitive to H_2O_2 (column 4, line 42), unlike the protein in the syringe in the claimed invention. In addition, the method taught by Dalmasso does not use secondary packaging for the bone tissue to be sterilized. In fact, Dalmasso teaches that if penetration of the bone beyond its cortical surface is needed, sterilization under vacuum may be desired, and even then, fat and marrow that fill spaces within the bone should be removed to allow the H_2O_2 vapors to enter these spaces. (See Dalmasso at column 4, lines 3-5). Thus, Dalmasso indicates that in the absence of a vacuum, only limited penetration into the surface of the bone is achieved, and even then, that is when there is no packaging around the bone. In short, contrary to what the Examiner contends, it is not a simple, trivial matter to merely perform the Metzner method at ambient (atmospheric) pressure based upon the teachings of Dalmasso. Put another way, the Metzner and Dalmasso methods could not be combined with any expectation of success.

8. A person of ordinary skill in the art when seeking a method of sterilizing a syringe, containing a protein, wherein the syringe is itself packaged in a secondary container, would not look to the Dalmasso reference for guidance, and certainly would not look to combine non-analogous methods, i.e., Metzner and Dalmasso, with any expectation of success.

9. With the claimed invention, the syringe, the surface of which is to be sterilized, is sealed in secondary packaging. Conventional thinking, at the time of filing the current patent application, was that in order to get the sterilizing agent to penetrate the packaging, a vacuum would have to be applied. However, as I state above, that carries with it the risk that (i) the seal of the syringe is compromised, leading to degradation of the protein product, or (ii) that the plunger is moved during application and removal of the vacuum, leading to incomplete sterilization. The present application disclosed for the first time, and contrary to conventional thinking, that it is possible to obtain sufficient sterilization of the outer surface of a syringe in secondary packaging at ambient pressure.

All statements made herein based on knowledge are true and all statements made herein based on knowledge and belief are believed to be true. All statements made herein were made with the knowledge that willful false statements and the like may jeopardize the patentability of the above patent application and the validity of any patent that issues from it, and may subject me to penalties, including fines and imprisonment, under Section 1001, Title 18 of the United States Code.

Respectfully submitted,

Date: 25 May 2023

Juergen Sigg, Ph.D.

CASE PAT053689-US-PCT

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number | Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 4142
Examiner: SPAMER, DONALD ROBER

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: 13/382380

35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of January 3, 2013 has a shortened statutory time set to expire on April 3, 2013. A one-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $200 for payment of the extension fee. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

/Andrew Holmes/

Novartis Pharmaceuticals Corporation One Health Plaza, Bldg. 101 East Hanover, NJ 07936
+1 8627785816

Andrew Holmes
Agent for Applicant
Reg. No. 51,813

Date: May 3, 2013

Electronic Patent Application Fee Transmittal	
Application Number:	13382380
Filing Date:	05-Jan-2012
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Filer:	Andrew K. Holmes/Andrea Jacquin
Attorney Docket Number:	PAT053689-US-PCT
Filed as Large Entity	

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	200	200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**1400**

Electronic Acknowledgement Receipt	
EFS ID:	15684892
Application Number:	13382380
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Customer Number:	1095
Filer:	Andrew K. Holmes/Andrea Jacquin
Filer Authorized By:	Andrew K. Holmes
Attorney Docket Number:	PAT053689-US-PCT
Receipt Date:	03-MAY-2013
Filing Date:	05-JAN-2012
Time Stamp:	13:40:09
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1400
RAM confirmation Number	10285
Deposit Account	190134
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		53689-US-PCT_RCE_AmendAfterFinal_JS Declaration_TimeExt_2013May 3.pdf	2211799 fbc92e2379bf63940d1f0ef772396f41c9efacf	yes	16

Multipart Description/PDF files in .zip description

Document Description	Start	End
Request for Continued Examination (RCE)	1	1
Amendment After Final	2	2
Claims	3	6
Applicant Arguments/Remarks Made in an Amendment	7	10
Miscellaneous Incoming Letter	11	15
Extension of Time	16	16

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	31952 9338c7aead8f907175cfdae91b0dcbf600bfbc42	no	2

Warnings:

Information:

Total Files Size (in bytes):	2243751

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number	Filing Date	To be Mailed
13/382,380	01/05/2012	☐

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	380
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☒ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	630

APPLICATION AS AMENDED – PART II

AMENDMENT **05/03/2013**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 21	Minus	** 22	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***5	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/ANGELA JONES/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/382,380	01/05/2012	Juergen Sigg	PAT053689-US-PCT	9960

1095 7590 06/14/2013

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
SPAMER, DONALD R	
ART UNIT	**PAPER NUMBER**
1775	

NOTIFICATION DATE	DELIVERY MODE
06/14/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Office Action Summary	Application No. 13/382,380	Applicant(s) SIGG, JUERGEN	
	Examiner DONALD SPAMER	Art Unit 1775	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3 May 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1 and 3-22* is/are pending in the application.

5a) Of the above claim(s) *8-21* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 3-7, and 22* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPH-feedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/3/2013 has been entered.

Claim 2 has been cancelled and claims 8-21 remain withdrawn. Claims 1, 3-7, and 22 remain presented for examination.

Response to Amendment

2. The affidavit under 37 CFR 1.132 filed 5/3/2013 is insufficient to overcome the rejection of claims 1, 3-7, and 22 based upon the combination of Metzner et al. (US Patent Application 2003/003014), Hasegawa (US 6,228,324), and Dalmasso et al. (US Patent 5,788,941) as set forth in the last Office action.

The claim amendments filed 5/3/2013 remove the limitations that Dalmasso et al. was relied upon to teach (ambient pressure). Thus statements regarding modifying the method taught by Metzner et al. with the teachings of Dalmasso et al. are no longer commensurate in scope with the claims.

With regards to the modification of the method taught by Metzner et al. with the teachings of Hasegawa, the Affiant merely makes conjectures that the combination of Metzner and Hasegawa (using the method of Metzner to sterilize a drug filled syringe in secondary packaging) would be deleterious through statements such as “would likely result in denaturation" and “may not result in a sterile product". The Affiant has not provided any factual evidence or proof of these conjectures. Further the Affiant states that Metzner does not teach any means of preventing seal breech or movement of the syringe. Metzner does in fact recognize these possibilities and teaches that if movement of a plunger or leaking seel is a concern to ensure appropriate packaging or using a device to prevent displacement of the stoppers or plunger seals (para [0024]).

Response to Arguments

3. The amendment of claim 1 and the cancellation of claim 2 have overcome the previously presented rejection under 35 USC 112. The rejections under 35 USC 112 are consequently withdrawn.

4. Applicant's arguments regarding the rejection under 35 USC 103 are not persuasive.

The claim amendments filed 5/3/2013 remove the limitations that Dalmasso et al. was relied upon to teach (ambient pressure). Thus arguments regarding modifying the method taught by Metzner et al. with the teachings of Dalmasso et al. are no longer commensurate in scope with the claims.

In regards to the combination of Metzner and Hasegawa, Metzner does recognize that issues such as seal leaking and plunger movement can occur when treating a sealed carpule/syringe. Metzner does, however, teach that this issues can be overcome by insuring appropriate packaging and using a device to prevent plunger motion (para [0024]) and thus that the method of Metzner can be used on prefilled syringes in secondary packaging. The Applicant argues that the claimed method does not use such extra devices to treat prefilled syringes in secondary packaging. This is not commensurate in scope with the claims since the claims have open or comprising language meaning that other steps or elements can occur along with the claimed steps such as a step of preventing the plunger from moving with the use of a motion stopping device. The claims do not preclude such an extra step from occurring.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 4, 5, 7, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Metzner et al. (US Patent Application Publication Number 2003/0003014) as evidenced by Hasegawa et al. (US Patent 6,228,324) and in view of Hasegawa et al. (US Patent 6,228,324).

With regards to claim 1, Metzner et al. teaches a method for surface decontamination of a prefilled container in secondary packaging (para [0010-0011]). Metzner et al. teaches the use of

vaporized hydrogen peroxide in order to sterilize the surfaces of the packaging (para [0019]). Metzner et al. also teaches that the hydrogen peroxide is left in contact with the surfaces for a sufficient amount of time to achieve decontamination (para [0032-0033]) and gives an example of about 17 min in each half cycle in example 3 (para [0071]). Metzner et al. also teaches the use of post-decontamination measures of applying a vacuum (para [0034 - 0035]). The vacuum post decontamination treatment taught by Metzner et al. would remove the hydrogen peroxide as evidenced by Hasegawa et al. Hasegawa et al. states that the application of a vacuum removes the hydrogen peroxide from inside the packaging (column 8, lines 63-67 and column 9, lines 32-38).

Metzner et al. teaches this method can be done on temperature sensitive pharmaceutical products (para [0002]). It expands to say that such products are sensitive to sterilization with gamma radiation (para [0005]), autoclaving (para [0003]) (exposure to steam), and ethylene oxide (since ethylene oxide residue can render the drug product toxic or carcinogenic) (gas) (para [0004]). In example 3, Metzner et al. teaches that the protein drug product is in a carpule (para [0061]). A carpule is a container for medicine that is administered to the patient with a syringe. Metzner thus does not expressly state the use of the method on a syringe in secondary packaging. Hasegawa et al. teaches a method for sterilizing a syringe in secondary packaging using hydrogen peroxide vapor (abstract and figure 4). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. to sterilize a syringe in secondary packaging as shown in Hasegawa et al. in order to provide a sterile drug product by using hydrogen peroxide vapor (abstract and figure 4).

With regards to claim 4, Metzner et al. teaches determining if the sterilization method is effective (para [0037]). This is considered to include testing whether the treatment times are sufficient since treatment times are part of the method. Metzner et al. teaches that sterilization effectiveness is determined by comparing the reduction factor of colony forming units (CFU) and comparing this value to a control standard (para [0037]). The control standard taught by Metzner et al. is that sterilization is achieved if $\log_{10}$(CFU) is greater than or equal to 6 (para [0037]).

With regards to claim 5, Metzner et al. teaches a post decontamination measure of applying a vacuum following treatment with vaporized hydrogen peroxide (para [0034]). While Metzner et al. does

not specifically state the intended use of "reversing the direction of diffusion of vaporized hydrogen peroxide and preventing intrusion of vaporized hydrogen peroxide into the prefilled container," the method of using a vacuum after effective treatment is capable of achieving this. This is affirmatively shown by the teaching Hasegawa et al.

Hasegawa et al. states that the application of a vacuum (taught by Metzner et al.) removes the hydrogen peroxide from inside the packaging (column 8, lines 63-67 and column 9, lines 32-38).

The prevention of hydrogen peroxide intrusion can be further confirmed when Metzner et al. measures the amount of proteins undamaged by the sterilization method and finds that the method damaged very little to none of the protein products (para [0076]).

With regards to claim 7, teaches a post decontamination measure that includes a plasma treatment (para [0035]). This is considered to be a gas plasma.

With regards to claim 22, the combination of Metzner et al. and Hasegawa et al. teaches that the hydrogen peroxide vapor sterilization method can be used for sterilizing prefilled syringes in secondary packaging where the prefilled drug product is various proteins (Metzner et al. para [0061]).

7. Claim 3 rejected under 35 U.S.C. 103(a) as being unpatentable over Metzner et al. (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above, and further in view of Shams (US Patent Application Publication 2007/0190058).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. teaches a method of using hydrogen peroxide vapor for sterilizing different proteins in secondary packaging (para [0061]) at 30°C (para [0063]) and teaches that the treatment did not destroy the protein products (para [0076]). Metzner et al. does not specifically mention the use of the method for treating a medical product where the prefilled drug is ranibizumab, a protein. The claim recites "therapeutically effective" (implying non degraded protein when administered into a body for treatment). A person having ordinary skill in the art at the time of the invention would understand that if this method is capable of sterilizing prefilled protein drug products in secondary packaging without causing degradation of the proteins that the method is capable of treating the specific protein ranibizumab.

Additionally the concept of using ranibizumab delivered by a syringe is also known in the prior art. Shams teaches the administration of ranibizumab by syringe injection (para [0128]). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. with the addition of ranibizumab being the drug in the syringe, as taught by Shams, in order to administer a dose of ranibizumab as a therapuetic drug (abstract and para [0028]) in a sterile manner which is desired by Shams who states that the treatment should be formulated, dosed, and administered in a fashion consistent with good medical practice (para [0092]) which would include using a sterile syringe.

8. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable Metzner et al. over (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above, and further in view of Moirandat et al. (US Patent Application Publication 2005/0226764).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. also teaches the use of a post decontamination measure using a vacuum (para [0034]) and a plasma treatment (para [0035]).

Metzner et al. does not teach the use of ultraviolet rays in a post decontamination measure.

Moirandat et al. teaches a method of decontaminating a clean room with hydrogen peroxide followed by post decontamination measures (para [0008], summary of invention). Moirandat et al. teaches that hydrogen peroxide remaining after decontamination can be photochemically broken down by UV radiation (ultraviolet rays) into oxygen and water (para [0031]). A person having ordinary skill in the art at the time of the invention would have been able to modify the method of Metzner et al. with the addition of ultraviolet rays to deactivate hydrogen peroxide vapors rapidly and in the least costly manner (Moirandat et al. para [0008]).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DONALD SPAMER whose telephone number is (571)272-3197. The examiner can normally be reached on Monday through Friday, 9 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on 571-272-1374. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DONALD SPAMER/
Examiner, Art Unit 1775

/SEAN E CONLEY/
Primary Examiner, Art Unit 1775

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13382380	SIGG, JUERGEN
	Examiner	Art Unit
	DONALD SPAMER	4142

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
422	(text limitated)	08/13/2012	Donald Spamer
422	30 (text limited)	08/16/2012	Donald Spamer
206	364 (text limited)	08/08/2012	Donald Spamer
604	199	08/08/2012	Donald Spamer

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search in eDAN	08/16/2012	Donald Spamer
East search history attached	08/16/2012	Donald Spamer
Updated East search history attached	12/18/2012	DS
Updated inventor search in eDAN	5/16/2013	DS

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

CASE PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 1775
Examiner: SPAMER, DONALD ROBERT

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: 13/382380

35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICE ACTION

Sir:

This Reply is submitted in response to the Office Action mailed June 14, 2013. Reconsideration of the present rejections and withdrawal of the present rejections are respectfully requested.

Listing of Claims is reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Previously presented) A method for surface decontamination of a prefilled syringe in secondary packaging, comprising:

   applying vaporized-hydrogen peroxide to the surface of the prefilled syringe in secondary packaging;

   allowing vaporized-hydrogen peroxide to remain in contact with the prefilled syringe surface for a sufficient time to decontaminate the prefilled syringe 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 syringe, wherein the prefilled syringe contains 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.

2. (Cancelled)

3. (Previously presented) The method of claim 1, wherein the syringe contains a therapeutically effective amount of ranibizumab.

4. (Previously presented) The method of claim 1, wherein sufficient time to decontaminate the surface of the prefilled syringe is determined by validation of treatment times and compared to a control standard.

5. (Previously presented) The method of claim 1, 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 syringe.

6. (Previously presented) The method of claim 1, 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. (Previously presented) The method of claim 1, wherein the post-decontamination measure includes gas plasma treatment.

8-21. (Withdrawn)

22. (Previously presented) The method of claim 1, wherein the drug product is a protein solution.

Remarks

I. Claims

Claims 1 and 3-22 are presently pending in this patent application. Claims 8- 21 have been withdrawn as being drawn to non-elected subject matter and Claim 2 has been cancelled.

Applicants reserve the right to pursue subject matter that remains after the prosecution of the present application in a future continuing patent application, for example, a division.

II. Rejections under 35 U.S.C. § 103 - Obviousness

Claims 1, 4, 5 7 and 22 are rejected under 35 U.S.C. § 103 for obviousness over published U.S. Patent Application 2003/0003014 to Metzner et al. ("Metzner") as evidenced by, and in view of, U.S. Patent 6,228,324 to Hasegawa ("Hasegawa"). The Examiner relies on Metzner for its teaching of a method for surface decontamination of a prefilled container in secondary packaging (citing Metzner at paragraphs [0010-0011]). The Examiner contends that Metzner teaches the use of vaporized hydrogen peroxide to sterilize the surfaces of the packaging (citing Metzner at paragraph [0019]). The Examiner also contends that Metzner teaches the use of a vacuum as a post-contamination treatment (citing Metzner at paragraphs [0034-0035]). In the Examiner's opinion, this post-contamination treatment would remove hydrogen peroxide as evidenced by Hasegawa, as it teaches that the application of a vacuum removes peroxide from inside the packaging (citing column 8, lines 63-67 and column 9, lines 32-28).

The Examiner concedes that Metzner does not teach sterilization of a syringe in secondary packaging. However, the Examiner relies on Hasegawa to cure this deficiency.

Regarding Claim 5, the Examiner admits that the intended use of "reversing the direction of diffusion of vaporized hydrogen peroxide and preventing intrusion of vaporized peroxide into the pre-filled container" is not disclosed in Metzner; however it is "capable" of achieving this. As support, the Examiner relies on Hasegawa, and contends that the application of a vacuum removes the hydrogen peroxide from the vacuum removes peroxide from inside the packaging (citing column 8, lines 63-67 and column 9, lines 32-28) and as evidenced by Metzner paragraph [0076].

With regards to claim 7, the Examiner contends that the post-decontamination measure includes plasma treatment as shown in paragraph [0035] of Metzner.

Claim 3 was rejected under 35 U.S.C. § 103 as obvious in view of a combination of Metzner, Hasegawa and US Pat. Pub. No. US2007/0190058 to Shams ("Shams"). The Examiner cited Shams to teach the administration of ranibizumab via syringe injection.

Finally, the Examiner rejected Claim 6 under 35 U.S.C. § 103 as obvious in view of a combination of Metzner, Hasegawa and US Pat. Pub. No. US2005/0226764 to Moirandat et al. ("Moirandat"). In the Examiner's view Moirandat teaches that UV radiation can be used to photochemically break down hydrogen peroxide vapor into oxygen and water and that it could

be combined with Metzner to “deactivate hydrogen peroxide vapors rapidly and in the least costly manner”, citing Moirandat at paragraph [0008].

III. Response/Arguments

A. The references do not teach every element of Claim 1

Initially, the Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness. With regards to Claim 1, the Examiner asserts, *inter alia*, that Metzner teaches the use of vaporized hydrogen peroxide in order to sterilize the surfaces of the packaging as taught in paragraph [0019]. In addition, the Examiner asserts that Metzner teaches the use of post-decontamination measures of applying a vacuum as shown in paragraphs [0034-0035]. However, the Examiner has failed to consider the teachings of Metzner (and the prior art) as a whole and as a result his reliance on these paragraphs is misplaced.

Metzner is directed to a method of using hydrogen peroxide plasma at low temperatures for the sterilization of various products. The properties and use of plasma is well known in the art and described, for example in EP0707186 (hereinafter “the ‘186 patent”, attached hereto), cited in Metzner.

More specifically, as taught in the ‘186 patent, hydrogen peroxide plasma is a completely different state of matter than the hydrogen peroxide vapor from which it is derived. Hydrogen peroxide plasma is created by applying a magnetic field or other external forces under a vacuum to hydrogen peroxide vapor (see paragraph 2 of the ‘186 patent). Thus, hydrogen peroxide vapor is merely a precursor to hydrogen peroxide plasma.

As described in greater detail in the ‘186 patent, to create plasma, a vapor gas is injected into a chamber under near vacuum conditions; RF is then applied to create plasma. The plasma is responsible for the decontamination of the products and is maintained for a period of time to ensure that the components in the chamber are sterilized. Once the process is completed, the plasma loses its energy and dissociates into water, oxygen and other nontoxic byproducts. After the completion of the process, the RF is turned off, the vacuum is released and the water, oxygen and byproducts are ventilated out of the chamber (see paragraph 2). Further evidence of this process is shown in U.S. Pat. No. 4,643,876 (hereinafter “the ‘876 patent”) which is attached hereto.

Metzner is an extension of the process taught in both the ‘876 patent and the ‘186 patent in that it first utilizes a “pre-plasma” process as described in paragraphs [0026-29] to remove moisture or to further adapt the product temperature to the chamber temperature (see Metzner, paragraph [0017]). Following the preplasma procedure, Metzner teaches utilizing a standard hydrogen peroxide plasma sterilization procedure as taught in paragraphs [0031 to 0036], albeit at a lower temperature than was previously known.

Paragraph [0019] merely teaches that multiple injections of hydrogen peroxide can be used to create more plasma, which is then utilized to disinfect the product of interest. It does not

teach or suggest, in light of the prior art or Metzner as a whole, that vaporized hydrogen peroxide is used to sterilize anything. Instead, as taught in the '186 patent and the '876 patent, it is the plasma, as opposed to the vapor, which is responsible for the sterilization.

This is in marked contrast to the present claims, which recite the use of vaporized hydrogen peroxide as the sterilizing agent. Accordingly, Metzner does not teach each and every element of Claim 1 or its dependent claims.

Although other references teach the use of hydrogen peroxide vapor such as Hasegawa and Moirandat, neither reference is cited for such a combination. Nor would such a combination be proper. The whole point of Metzner is to use hydrogen peroxide plasma, which is generated from vapor, at lower temperatures than were previously known. Substituting the final product for sterilization (i.e., plasma) with the precursor it is generated from (i.e., vapor) would render Metzner completely unsuitable for its intended purpose. This is impermissible under MPEP § 2143.01 and as such any combination would be improper.

In addition, the Examiner's assertion that Metzner teaches using a vacuum as a post decontamination measure as taught in paragraphs [0034-35] is incorrect. Paragraphs [0031-0036] of Metzner teach the standard hydrogen peroxide plasma sterilization procedure shown in the '186 patent and the '876 patent. Initially, pressure is lowered and hydrogen peroxide vapor is introduced into a chamber (paragraphs [0031-0032]). The hydrogen peroxide vapor is allowed to diffuse for several minutes (paragraph [0033]), and the pressure is then lowered to ensure an adequate vacuum is in the chamber (paragraph [0034]) so that the plasma can be generated (paragraph [0035]). After the plasma is generated, as taught by both the '186 and '876 patents, it sterilizes any product placed in the chamber. After sterilization, the plasma dissociates into water, oxygen and other by-products as taught by the '186 patent. The water, oxygen, and other by-products are then ventilated out of the chamber (paragraph [0036]) so that the product can be removed.

Accordingly, the vacuum step relied on by the Examiner occurs *before* the plasma is generated and ensure that the vapor is *converted into a plasma* so that the product in the chamber can *then* be sterilized. As a result, the vacuum step cannot be considered as a *post*-decontamination measure to reduce hydrogen peroxide as recited in Claim 1.

Even assuming, *arguendo*, that this vacuum procedure *could* reduce hydrogen peroxide vapor, there is no evidence that it actually does so. In order to prove this assertion, the Examiner relies on Hasegawa. Specifically, the Examiner asserts that the vacuum process used by Metzner would remove hydrogen peroxide because Hasegawa teaches that a vacuum removes hydrogen peroxide vapor from the packaging, citing Hasegawa at column 8, lines 63-67 and column 9, lines 32-38.

The Examiner's reliance on Hasegawa is misplaced. Column 8, lines 63-67 explicitly state that the process is used to "ensure the penetration of hydrogen peroxide gas into delicate portions of the medicine filled injector" and that the hydrogen peroxide gas is closed "thereby

discharging hydrogen peroxide gas from the chamber" (emphasis added). Thus, the first passage relied on by the Examiner shows that hydrogen peroxide in fact does enter into a syringe ("delicate portions" include the space between an injector cylinder and the piston rod, see Hasegawa, Col. 8, lines 50-54; Fig. 4) and that hydrogen peroxide is merely removed from the *chamber* as opposed to the *packaging*.

Indeed, Hasegawa is very clear that hydrogen peroxide remains after any such vacuum procedure at column 9, lines 19-20 when it unambiguously states that "the hydrogen peroxide gas *remaining in the injection pack* is removed". Lines 21-32 go on to describe that the gas is removed by heating the package in the chamber. Lines 32-38 describe that the hydrogen peroxide is removed from the package only after this step. As a result, the Examiner's reliance on this passage is misplaced as it does not bear any relation to a vacuum. Thus, the assertion that Hasegawa shows vacuum treating as removing hydrogen peroxide from packaging is simply incorrect. Accordingly, there is no evidence that the vacuum shown in Metzner actually removes hydrogen peroxide from the primary packaging of a product.

Even if the Examiner considers the heat treatment of Hasegawa a post-decontamination procedure, one of skill in the art would not modify Metzner to include such a step. First, Metzner uses hydrogen peroxide plasma, and as is known in the art (see e.g., EP0707186), the plasma *decomposes on its own* into water, oxygen and byproducts. As a result, there is simply no need to post-decontaminate hydrogen peroxide plasma; it dissociates on its own into non-toxic materials which are simply vented out of the chamber as taught by Metzner at paragraph [0036]. Secondly, Metzner is directed to low temperature sterilization to reduce protein denaturation. Hasegawa teaches removing hydrogen peroxide vapor via additional heat. In short, the references teach away from each other. As such, the skilled artisan would not modify Metzner with Hasegawa because it is not necessary and not appropriate.

Nor does Moirandat cure this deficiency. Moirandat simply shows that hydrogen peroxide can be broken down photochemically by UV radiation. A skilled artisan would not modify Metzner with Moirandat for the same reason as stated above with regard to Hasegawa. That is, there is simply no need to break down hydrogen peroxide plasma in Metzner because the plasma dissociates on its own into water, oxygen and byproducts.

In conclusion, none of the references, alone or when properly combined, teach or suggest a method for surface decontamination which utilizes hydrogen peroxide vapor and a post-decontamination measure to reduce the presence of vaporized-hydrogen peroxide, thereby preventing vaporized hydrogen peroxide from diffusing into a pre-filled syringe as recited in independent Claim 1. As such, the references fail to teach or suggest all of the elements of Claim 1. As it is axiomatic that a *prima facie* case of obviousness requires a teaching of each and every claim limitation (see MPEP §§2141-2143), the Examiner has failed to establish a *prima facie* case of obviousness, and the Applicant respectfully submits that the rejection of Claim 1, and its dependent claims 3-7 and 22 should be withdrawn.

B. The Examiner's rejection of Claim 5 is flawed

The Examiner, as with Claim 1, contends that Claim 5 is obvious because Metzner teaches the use of a vacuum following treatment, and that such use is "capable" of reversing the direction of diffusion of vaporized hydrogen as shown by Hasegawa. However, as stated above, Metzner does not show a vacuum as a post-decontamination treatment. In addition, Hasegawa unambiguously shows that vapor is not removed from the packaging via vacuum but from the *chamber*. A separate heating step is required to remove the hydrogen peroxide vapor from the *packaging*. As such the Examiner cannot rely on Hasegawa for such a showing.

The Examiner also cites as evidence of the "capability" of the vacuum for reducing the direction of diffusion the fact that Metzner measures the amount of undamaged protein and finds that the method damaged little to no protein product. This statement, however, is a mischaracterization of the findings disclosed in Metzner. Metzner did not determine whether there was any damage to the protein or whether any hydrogen peroxide entered the syringe. Instead, it measured whether the protein was thermally denatured (see paragraph [0051]). This is a completely different process than determining whether a protein was chemically altered by intrusion of hydrogen peroxide vapor and thus has no bearing on the matter. Accordingly, the rejection of Claim 5 is improper and should be withdrawn.

C. The rejection of Claim 7 is improper

The Examiner also contends that Metzner teaches a post-decontamination measure comprised of gas plasma. However, this rejection completely misses the mark. The plasma generated in Metzner is hydrogen peroxide plasma which is used to sterilize a product. As such, it cannot act as a post decontamination measure because it is the plasma that actually decontaminates the packaging. Thus, the rejection is improper and should be withdrawn.

D. The Examiner's rationale to combine Metzner and Moirandat is flawed

With regards to Claim 6, the Examiner admits that Metzner does not teach the use of UV rays in a post decontamination procedure. However, the Examiner asserts that Moirandat teaches such a procedure, and that the skilled artisan would be motivated to combine the references because the addition of UV rays would "deactivate hydrogen peroxide vapors rapidly and in the least costly manner."

However, as stated above and as known in the prior art, the hydrogen peroxide plasma process simply does not leave any hydrogen peroxide vapors after the process is complete. Instead, the hydrogen peroxide plasma breaks down into water, oxygen and other byproducts. As such, there is simply no need to apply a post-decontamination procedure, and adding UV radiation would therefore surely not be the least costly manner. Instead, the least costly manner is to do exactly what Metzner teaches. That is, simply let the plasma degrade and then vent the chamber of impurities.

IV. Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Action of record and that Claims 1, 3-7 and 22 are now in condition for allowance. Applicant respectfully requests that the Office withdraw all grounds for rejection and issue a Notice of Allowance at its earliest convenience. If there are any issues that can be resolved by a telephone conference, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

/Jim Lynch/

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Agent for Applicant
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Date: September 13, 2012

Electronic Acknowledgement Receipt	
EFS ID:	16833483
Application Number:	13382380
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Customer Number:	1095
Filer:	James L Lynch/Denise Cooper
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13382380
	Filing Date	2012-01-05
	First Named Inventor	Sigg, Juergen
	Art Unit	1775
	Examiner Name	SPAMER, DONALD ROBERT
	Attorney Docket Number	PAT053689-US-PCT

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Signature	/jim lynch/	Date (YYYY-MM-DD)	2013-09-12
Name/Print	Jim Lynch	Registration Number	54763

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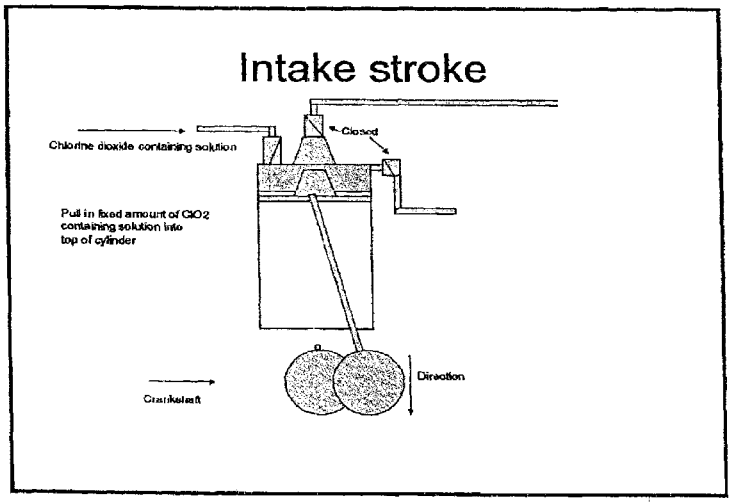
(54) Title: METHOD AND APPARATUS FOR TREATING ITEMS



(57) Abstract: One aspect of the present invention relates to separating a gas, such as chlorine dioxide, from a solution. In another aspect of the invention, the separated gas is then used for the sterilization or sanitation of items, such as food, food storage containers, other food contact surfaces, medical devices, and the like. In yet another aspect of the invention, that gas is then decomposed or otherwise neutralized after contacting the item. In yet another aspect of the invention, the separated gas is dissolved or otherwise introduced into a pure solution, such as water, to form highly pure solution containing the gas.

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METHOD AND APPARATUS FOR TREATING ITEMS

BACKGROUND OF THE INVENTION

[0001] Chlorine dioxide (ClO_2) is a strong oxidizing and antimicrobial agent. It has been reported to effectively inactivate bacteria, including pathogens, viruses, bacterial spores, and algae. In the food industry, chlorine dioxide has been used to sanitize food contact surfaces and food surfaces in the form of chlorine dioxide gas or a chlorine dioxide aqueous solution. For example, aqueous chlorine dioxide solutions have been approved for use in washing fruits and vegetables in a manner that residual chlorine dioxide does not exceed 3 ppm. Gaseous chlorine dioxide is also known as a disinfectant especially related to use in the medical sciences.

[0002] Prevention of foods from spoilage or contamination with microorganisms, including spoilage bacteria, yeast, molds, and pathogenic bacteria, has been a large challenge for the food industry. Currently, steam or aqueous sanitizers are widely used to sanitize food storage containers in the food industry. For example, some current methods of sanitizing containers on a filling line introduce peracetic acid (1000-2500 ppm), peracetic acid in steam (up to 2000 ppm stock solution), or hydrogen peroxide in steam (up to 200 ppm) in containers. After sterilization of containers, a large volume of waste solution must be stored or disposed of in appropriate manner. Further, the containers may also need to be rinsed (creating more waste solution) and subsequently dried. Also, in some applications, by-products of the sanitizing solution can be of concern.

SUMMARY OF THE INVENTION

[0003] One embodiment of the present invention provides method and apparatus for treating, sanitizing, and/or sterilizing an item, such as a container for food, a medical device, and the like. In one embodiment of the invention, a water soluble gas, such as chlorine dioxide gas, is removed from a solution containing the water soluble gas and is circulated about the item for a time. The water soluble gas can be removed from the solution many ways. For example, it can be heated, shaken or otherwise agitated, sprayed, and the like to cause the water soluble gas to disassociate from the solution. In one particular embodiment, a vacuum is applied to the solution to remove the gas from the solution. Once the gas has contacted the item for a sufficient time, it can then be eliminated from contact with the item.

In one particular embodiment, an ultraviolet light is utilized to decompose or deactivate the chlorine dioxide gas.

[0004] Another embodiment of the present invention is directed toward a process of producing a highly pure water soluble gas solution, such as chlorine dioxide gas solution. In such embodiments, the water soluble gas is removed from an impure solution and then dissolved in a pure solution. In one particular embodiment, a vacuum is used to extract chlorine dioxide gas from a solution having impurities, such as by-products from the production of the chlorine dioxide. Then, the chlorine dioxide gas is dissolved in a purified water solution.

[0005] One particular embodiment is directed toward a method for treating a food container. The method includes providing a chlorine dioxide containing solution; extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum; removing the chlorine dioxide gas from the vacuum; and injecting the chlorine dioxide gas from the vacuum into the food container. Some embodiments further provide eliminating the chlorine dioxide gas from the container, such as by exposing the chlorine dioxide gas to an ultraviolet light to deactivate the chlorine dioxide gas. Also, some embodiments indicate that the step of extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum comprises: providing a sample of the chlorine dioxide containing solution into a chamber; and applying a vacuum to the sample. The step of applying a vacuum can include sealing the chamber and actuating a piston within the chamber to generate a vacuum within the chamber.

[0006] Another particular embodiment is directed toward an apparatus for treating a food container. The apparatus comprises a reservoir containing a chlorine dioxide solution; a vacuum coupled to the reservoir to remove chlorine dioxide gas from the chlorine dioxide solution; and a conduit coupled to the vacuum and positioned to inject the chlorine dioxide gas into the container. Some embodiments further provide a device positioned adjacent the container to eliminate the chlorine dioxide gas in the container once the container has been effectively treated by the chlorine dioxide gas. That device can be an ultraviolet light adapted to be selectively illuminated to deactivate the chlorine dioxide gas in the container. The vacuum described above can include a selectively sealable chamber adapted to receive a sample of the chlorine dioxide solution and a piston selectively moveable within the chamber, wherein movement of the piston in a first direction generates a vacuum within the chamber to separate chlorine dioxide gas from the solution.

[0007] Yet another particular embodiment is directed toward a method for treating a food container. The method includes providing a food container; injecting chlorine dioxide gas into the food container to treat the food container; allowing the chlorine dioxide gas to contact the container for a sufficient time to treat the container; and deactivating the chlorine dioxide gas within the containers via an illuminated ultraviolet light positioned adjacent the container. This method can include providing a chlorine dioxide containing solution; and extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum. The step of extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum can include providing a sample of the chlorine dioxide containing solution into a chamber and applying a vacuum to the sample. The step of applying a vacuum can include sealing the chamber and actuating a piston within the chamber to generate a vacuum within the chamber.

[0008] One particular embodiment is directed toward an apparatus for treating a food container. The apparatus includes a source of chlorine dioxide gas, a conduit coupled to the source of chlorine dioxide gas and positioned to inject the chlorine dioxide gas into the container, and an ultraviolet light positioned adjacent to the container and adapted to be selectively illuminated to deactivate the chlorine dioxide gas in the container. The source of chlorine dioxide gas can include a reservoir containing a chlorine dioxide solution and a vacuum coupled to the reservoir to remove chlorine dioxide gas from the chlorine dioxide solution. The vacuum of this embodiment can include a selectively sealable chamber adapted to receive a sample of the chlorine dioxide solution and a piston selectively moveable within the chamber, wherein movement of the piston in a first direction generates a vacuum within the chamber to separate chlorine dioxide gas from the solution.

[0009] Another particular embodiment is directed toward a method of separating chlorine dioxide gas from a solution containing chlorine dioxide. The method includes providing a chlorine dioxide containing solution; providing a sample of the chlorine dioxide containing solution into a chamber; sealing the chamber; actuating a piston within the chamber to generate a vacuum within the chamber; and extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum.

[0010] Yet another particular embodiment is directed toward an apparatus for separating chlorine dioxide gas from a solution containing chlorine dioxide. The apparatus includes a reservoir containing a chlorine dioxide solution, a selectively sealable chamber adapted to receive a sample of the chlorine dioxide solution from the reservoir, and a piston selectively

moveable within the chamber. Movement of the piston in a first direction generates a vacuum within the chamber to separate chlorine dioxide gas from the solution and movement of the piston in the opposite direction forces the chlorine dioxide gas from the chamber.

[0011] One other particular embodiment is directed toward a method for disinfecting an item. The method comprises providing a solution containing a water soluble gas having disinfecting properties; extracting the water soluble gas from the solution with a vacuum; removing the water soluble gas from the vacuum; injecting the water soluble gas from the vacuum toward the item; and disinfecting the item with the water soluble gas. The step of extracting the water soluble gas from the solution with a vacuum can include providing a sample of the solution into a chamber and applying a vacuum to the sample. The step of applying a vacuum can include sealing the chamber and actuating a piston within the chamber to generate a vacuum within the chamber. The step of removing the water soluble gas from the chamber can include actuating the piston within the chamber to expel the gas via an outlet in the chamber.

[0012] Another particular embodiment is directed toward an apparatus for disinfecting an item. The apparatus includes a reservoir containing a solution containing a water soluble gas having disinfecting properties, a vacuum coupled to the reservoir to remove the water soluble gas from the solution, and a conduit coupled to the vacuum and positioned to inject the water soluble gas into contact with the item to disinfect the item.

[0013] Yet another particular embodiment is directed toward a method for disinfecting an item. The method includes providing a solution containing a water soluble gas having disinfecting properties; extracting the water soluble gas from the solution with a vacuum; removing the water soluble gas from the vacuum; dissolving the extracted water soluble gas into purified water to create a highly pure solution; contacting the item with the highly pure solution; and disinfecting the item with the highly pure solution.

[0014] One particular embodiment is directed toward a method for creating a purified chlorine dioxide solution. The method comprises providing a solution containing chlorine dioxide gas and other impurities; extracting the chlorine dioxide gas from the solution with a vacuum; and dissolving the extracted chlorine dioxide gas into purified water to create a highly pure chlorine dioxide solution.

[0015] Further aspects of the present invention, together with the organization and operation thereof, will become apparent from the following detailed description of the invention when taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1A is a schematic view of a vacuum device embodying aspects of the present invention, wherein the vacuum device is shown actuating a piston through an intake stroke.

[0017] Figure 1B is a schematic view of the vacuum device shown in Figure 1A, wherein the vacuum device is shown actuating the piston through a vacuum stroke.

[0018] Figure 1C is a schematic view of the vacuum device shown in Figure 1A, wherein the vacuum device is shown actuating the piston through a discharge stroke.

[0019] Figure 1D is a schematic view of the vacuum device shown in Figure 1A, wherein the vacuum device is shown actuating the piston through a purge stroke.

DETAILED DESCRIPTION

[0020] Before any embodiments of the invention are explained in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the following drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, it is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limited. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items. The terms "mounted," "connected," and "coupled" are used broadly and encompass both direct and indirect mounting, connecting and coupling. Further, "connected" and "coupled" are not restricted to physical or mechanical connections or couplings, and can include electrical connections or couplings, whether direct or indirect. Finally, as described in subsequent paragraphs, the specific mechanical configurations illustrated in the drawings are intended to exemplify embodiments of the invention. Accordingly, other alternative

mechanical configurations are possible, and fall within the spirit and scope of the present invention.

[0021] The present invention includes multiple aspects that can be implemented or used independently or in combination. One aspect of the present invention relates to separating a water soluble gas, such as chlorine dioxide, from a solution. In another aspect of the invention, that gas is then used for the sterilization or sanitation of items, such as food, food storage containers, food processing equipment, other food contact surfaces, medical devices, and the like. In yet another aspect of the invention, that gas is then decomposed, deactivated, or otherwise neutralized after contacting the item.

[0022] The present invention has particular utility for treating, cleaning, disinfecting, sanitizing, and/or sterilizing an item, such as a container for food, a medical device, and the like. One particular embodiment of the invention provides a method and apparatus for the sterilization or sanitation of an item, such as an empty food container, other food contact surfaces, food items, medical devices, and the like. The invention can be practiced with relatively small food containers such as bottles, cans, cartons, and other food storage containers on a filling line that demand a sterilized, sanitary or aseptic condition or reduced microbial concentration. For instance, aseptic packaging may be desirable in some food applications for extended shelf life. However, this invention is not limited to aseptic requirements. Rather, containers or other surfaces can be treated for other reasons as well. Additionally, the invention can be adapted for use to sanitize or sterilize food processing equipment, such as pipes and large tanks or containers used for storing and transporting bulk quantities of food items or used for fermentation in any biotechnology industry, such as alcohol, beer, or pharmaceutical production.

[0023] In some particular embodiments, chlorine dioxide gas is the preferred gas for use in the sterilization or sanitation process. Although chlorine dioxide gas is the preferred gas for use with the methods and apparatuses described herein, other gases having known sterilization and/or sanitation capabilities can be used.

[0024] For embodiments utilizing chlorine dioxide, the chlorine dioxide gas can be initially produced as part of a chlorine dioxide solution and then removed from the solution. For example, in one particular embodiment, the chlorine dioxide solution can be produced according to the process taught in U.S. Patent Application Publication No. 2003/0064018,

which is hereby incorporated by reference. In summary, this patent application teaches one particular process in which sodium chlorite is fed through an ion exchanger and a catalyst to quickly and efficiently generate a chlorine dioxide solution. However, as indicated above, other processes can be utilized to generate a chlorine dioxide solution. Such processes fall within the spirit and scope of the present invention.

[0025] Once a solution containing chlorine dioxide (or other gas) is generated, the chlorine dioxide can be removed from the solution containing chlorine dioxide. The chlorine dioxide can be removed from the solution many ways. For example, it can be heated, shaken or otherwise agitated, sprayed or atomized, and the like to cause the chlorine dioxide gas to disassociate from the solution. In one particular preferred embodiment, a vacuum is applied to the solution to remove the chlorine dioxide gas from the solution.

[0026] Putting a vacuum on a solution containing chlorine dioxide has been shown to reduce the amount of chlorine dioxide in the solution. Specifically, the vacuum causes the gas to be released from the solution into the atmosphere of the vacuum. By repeatedly exposing a chlorine dioxide solution to a vacuum, the levels of chlorine dioxide generally continue to reduce. Accordingly, in some embodiments, an intermittent or timed vacuum can be applied to a solution to maximize the extraction of chlorine dioxide gas from the solution.

[0027] Although many different vacuum devices can be used to extract chlorine dioxide from a solution, Figure 1 illustrates one particular vacuum device that can be utilized to generate a vacuum on a sample of chlorine dioxide solution. As shown in this figure, the vacuum device includes a chamber or cylinder having a piston that can reciprocate within the cylinder. The cylinder also includes an inlet and two outlets, with a valve located at each location to control the flow through each inlet and outlet. The inlet allows the solution containing chlorine dioxide into the cylinder. One of the outlets allows chlorine dioxide gas (that has been separated from the solution) to exit the cylinder. The other outlet allows the solution to exit the cylinder.

[0028] In operation, the vacuum has four phases of operation, as illustrated in Figures 1A-1D. Figure 1A illustrates an intake stroke, wherein the piston is drawn away from the end of the cylinder adjacent the inlet and the outlets to allow the solution containing chlorine dioxide into the cylinder. As the piston is drawn back, the solution enters the cylinder via the inlet. Specifically, the valve adjacent the inlet opens to allow the solution into the cylinder.

The solution can be drawn into the cylinder via the vacuum created during the back stroke or the solution can be injected with a properly timed pump. Similarly, the valve can be opened via the vacuum generated during the back stroke or the valve can be controlled via other means, such as mechanical or electrical actuators. As shown in this figure, only a small quantity (relative to the volume of the cylinder) of chlorine dioxide solution is drawn into the cylinder.

[0029] Once the chlorine dioxide solution is drawn into the cylinder via the intake stroke, the vacuum stroke illustrated in Figure 1B begins. During the vacuum stroke, the inlet valve is closed and the piston continues to be drawn away from the end of the cylinder. Since the cylinder is sealed, this creates a vacuum within the cylinder. As this vacuum is applied to the solution, the amount of chlorine dioxide in the solution is reduced as it is released into the atmosphere within the cylinder.

[0030] Once the piston reaches the opposite end (i.e., opposite the inlet and outlets) of the cylinder, the vacuum stroke is complete and the chlorine dioxide gas discharge stroke begins. During this discharge stroke, the piston is driven toward the gas outlet and the valve located in the outlet is opened to allow the extracted chlorine dioxide gas to exit the cylinder. Once substantially all of the gas is forced out of the cylinder during this stroke, the outlet valve for the gas is closed and the outlet valve for the solution is opened (as shown in Figure 1D). The piston continues moving toward the end of the cylinder to purge the solution from the cylinder. Once all of the solution has been purged from the cylinder, the process described in Figure 1A can begin again.

[0031] During operation of an entire system, one or more vacuum devices can be used in series, in parallel, or in a combination of series and parallel. The number and size of vacuum devices included in an entire gas extraction system will depend upon the amount of gas needed at peak demand. Smaller operations will need fewer and/or smaller vacuum devices than larger operations, such as a larger international bottling plant.

[0032] Although the vacuum device is described specifically with reference to a chlorine dioxide solution and chlorine dioxide gas, this vacuum device can be utilized to remove other water soluble gases from a solution. For example, this may also have utility removing ozone, oxygen, ammonia, peracetic acid, and the like, from a solution.

[0033] Once the chlorine dioxide gas is extracted from the solution, the gas can be immediately used to clean, sanitize, sterilize, and/or disinfect various items or surfaces. For example, in one particular use, the chlorine dioxide gas can be injected into individual food containers, such as bottles, jars, cartons, cups, and the like. In other uses, the chlorine dioxide is injected into piping, vessels, tanks, and other food processing equipment. In yet other uses, the chlorine dioxide gas in pumped into a chamber, housing, or the like containing various items, such as food, medical equipment, and the like. In yet other embodiments, as will be described in greater detail below, the chlorine dioxide gas can be reintroduced into a pure or purified water stream to provide a highly pure chlorine dioxide solution.

[0034] Once the chlorine dioxide has contacted the item for a sufficient time to clean, disinfect, sanitize, and/or sterilize the item, the chlorine dioxide can then be eliminated from contact with the item. For example, in one particular embodiment, an ultraviolet light is utilized to decompose or deactivate the chlorine dioxide gas. In other embodiments, the gas can be evacuated by flushing the container with sterile (filtered) nitrogen, air or other suitable pressurized gas. The evacuated chlorine dioxide can then be reused, reintroduced into solution, or neutralized.

[0035] As indicated above, the chlorine dioxide gas contacts the item for a sufficient time to clean, disinfect, sanitize, and/or sterilize the item. The exact amount of contact time needed will depend upon many factors, such as the concentration of chlorine dioxide gas in the carrier gas, relative humidity adjacent the item, temperature adjacent the item or in the container, the types of target microorganisms, container surface properties (coated or uncoated), and size of the target container or item.

[0036] In one specific use, the various aspects of the present invention can be utilized in combination in a sterilization or sanitation process for relatively small food containers, such as bottles on a filling line. The vacuum device described above is used to extract chlorine dioxide gas from a reservoir or sample of chlorine dioxide solution. The chlorine dioxide gas is then injected into each individual container to disinfect the container prior to filling the container. Once the gas has contacted the surfaces for a sufficiently long time to sterilize the container, the gas can be eliminated from the container. In one specific embodiment, the gas is inactivated by an ultraviolet light. Specifically, the chlorine dioxide gas is exposed to an ultraviolet light of sufficient frequency and wave length for a sufficient period of time to deactivate or decompose the gas. In some embodiments, the gas is exposed to the ultraviolet

light long enough such that the residual chlorine dioxide levels fall below the levels allowed in potable water. Some embodiments can utilize a rinse with sterile water to further remove the chlorine dioxide gas from the containers if desired or needed.

[0037] In another specific use, the various aspects of the present invention can be utilized while processing food, such as fruit, vegetables, poultry, etc. The vacuum device described above is used to extract chlorine dioxide gas from a chlorine dioxide solution. The chlorine dioxide gas is then injected into a chamber containing the food. The gas can be injected directly onto the food or indirectly onto the food via the surrounding environment. Once the gas has contacted the surfaces for a sufficiently long time, the gas can be eliminated from the chamber or the food can be removed from the chamber. In one specific embodiment, the gas is eliminated or inactivated by an ultraviolet light as described above. Subsequently, the food is removed from the chamber. Alternatively, the food can be removed from the chamber via a conveyor system and any escaping gas can be eliminated via an ultraviolet light located adjacent the exit of the chamber.

[0038] In yet other uses, the extracted water soluble gas, such as chlorine dioxide, can be injected in a room (or chamber, container, etc.) to disinfect the room or objects within the room. For example, the chlorine dioxide gas can be used to treat library books or rare art. Additionally, the gas can be used to decontaminate an entire room, such as a room with suspected anthrax and/or mold contamination.

[0039] As indicated above, the present invention can be used to create a highly pure chlorine dioxide (or other soluble gas) solution. Particularly, once the gas is extracted from the original solution, the gas can be dissolved into a pure or purified solution, such as purified water. The gas can be dissolved into the pure solution many ways known in the art. For example, in one embodiment, the gas can be dissolved in the solution by bubbling the gas into the solution.

[0040] This process of extracting a water soluble gas from one solution and dissolving it in another solution can enable one to make a highly purified solution containing the gas. For example, many chlorine dioxide solutions can contain some impurities that may be undesirable in some applications. For example, some by-products from reactions that produce chlorine dioxide solutions can include chlorate, chloride, chlorite, hypochlorite, and the like. These by-products may be a concern in some applications. Accordingly, the

gas can be extracted from the solution and dissolved into purified water to create a highly pure chlorine dioxide solution.

[0041] The embodiments described above and illustrated in the figures are presented by way of example only and are not intended as a limitation upon the concepts and principles of the present invention. As such, it will be appreciated by one having ordinary skill in the art that various changes in the elements and their configuration and arrangement are possible without departing from the spirit and scope of the present invention. For example, the examples described above can be modified to apply to food processing equipment, medical devices, etc. Further, various alternatives to the certain features and elements of the present invention may be described with reference to specific embodiments of the present invention. With the exception of features, elements, and manners of operation that are mutually exclusive of or are inconsistent with each embodiment described above, it should be noted that the alternative features, elements, and manners of operation described with reference to one particular embodiment may be applicable to the other embodiments.

[0042] Various features of the invention are set forth in the following claims.

What is claimed is:

1. A method for treating a food container, the method comprising:
providing a chlorine dioxide containing solution;
extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum;
removing the chlorine dioxide gas from the vacuum; and
injecting the chlorine dioxide gas from the vacuum into the food container.

2. The method of claim 1 further comprising eliminating the chlorine dioxide gas from the container.

3. The method of claim 2 wherein the step of eliminating the chlorine dioxide gas from the container comprises exposing the chlorine dioxide gas to an ultraviolet light to deactivate the chlorine dioxide gas.

4. The method of claim 1 wherein the step of extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum comprises:
providing a sample of the chlorine dioxide containing solution into a chamber; and
applying a vacuum to the sample.

5. The method of claim 4 wherein the step of applying a vacuum comprises:
sealing the chamber; and
actuating a piston within the chamber to generate a vacuum within the chamber.

6. The method of claim 5 wherein the step of removing the chlorine dioxide gas from the chamber comprises actuating the piston within the chamber to expel the gas via an outlet in the chamber.

7. An apparatus for treating a food container, the apparatus comprising:

a reservoir containing a chlorine dioxide solution;

a vacuum coupled to the reservoir to remove chlorine dioxide gas from the chlorine dioxide solution; and

a conduit coupled to the vacuum and positioned to inject the chlorine dioxide gas into the container.

8. The apparatus of claim 7, further comprising a device positioned adjacent the container to eliminate the chlorine dioxide gas in the container once the container has been effectively treated by the chlorine dioxide gas.

9. The apparatus of claim 8, wherein the device that eliminates the chlorine dioxide gas comprises an ultraviolet light adapted to be selectively illuminated to deactivate the chlorine dioxide gas in the container.

10. The apparatus of claim 7, wherein the vacuum comprises:

a selectively sealable chamber adapted to receive a sample of the chlorine dioxide solution; and

a piston selectively moveable within the chamber, wherein movement of the piston in a first direction generates a vacuum within the chamber to separate chlorine dioxide gas from the solution and movement of the piston in the opposite direction forces the chlorine dioxide gas from the chamber.

11. A method for treating a food container, the method comprising:

providing a food container;

injecting chlorine dioxide gas into the food container to treat the food container;

allowing the chlorine dioxide gas to contact the container for a sufficient time to treat the container; and

deactivating the chlorine dioxide gas within the containers via an illuminated ultraviolet light positioned adjacent the container.

12. The method of claim 11, further comprising:

providing a chlorine dioxide containing solution; and

extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum.

13. The method of claim 11, wherein the step of extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum comprises:

providing a sample of the chlorine dioxide containing solution into a chamber; and

applying a vacuum to the sample.

14. The method of claim 13, wherein the step of applying a vacuum comprises:

sealing the chamber; and

actuating a piston within the chamber to generate a vacuum within the chamber.

15. An apparatus for treating a food container, the apparatus comprising:

a source of chlorine dioxide gas;

a conduit coupled to the source of chlorine dioxide gas and positioned to inject the chlorine dioxide gas into the container; and

an ultraviolet light positioned adjacent to the container and adapted to be selectively illuminated to deactivate the chlorine dioxide gas in the container.

16. The apparatus of claim 15, wherein the source of chlorine dioxide gas comprises:

a reservoir containing a chlorine dioxide solution; and

a vacuum coupled to the reservoir to remove chlorine dioxide gas from the chlorine dioxide solution.

17. The apparatus of claim 16, wherein the vacuum comprises:

a selectively sealable chamber adapted to receive a sample of the chlorine dioxide solution; and

a piston selectively moveable within the chamber, wherein movement of the piston in a first direction generates a vacuum within the chamber to separate chlorine dioxide gas from the solution and movement of the piston in the opposite direction forces the chlorine dioxide gas from the chamber.

18. A method of separating chlorine dioxide gas from a solution containing chlorine dioxide, the method comprising:

providing a chlorine dioxide containing solution;

providing a sample of the chlorine dioxide containing solution into a chamber;

sealing the chamber;

actuating a piston within the chamber to generate a vacuum within the chamber; and

extracting chlorine dioxide gas from the chlorine dioxide solution with a vacuum.

19. An apparatus for separating chlorine dioxide gas from a solution containing chlorine dioxide, the apparatus comprising:

a reservoir containing a chlorine dioxide solution;

a selectively sealable chamber adapted to receive a sample of the chlorine dioxide solution from the reservoir; and

a piston selectively moveable within the chamber, wherein movement of the piston in a first direction generates a vacuum within the chamber to separate chlorine dioxide gas from the solution and movement of the piston in the opposite direction forces the chlorine dioxide gas from the chamber.

20. A method for disinfecting an item, the method comprising:
providing a solution containing a water soluble gas having disinfecting properties;
extracting the water soluble gas from the solution with a vacuum;
removing the water soluble gas from the vacuum;
injecting the water soluble gas from the vacuum toward the item; and
disinfecting the item with the water soluble gas.

21. The method of claim 20 wherein the step of extracting the water soluble gas from the solution with a vacuum comprises:
providing a sample of the solution into a chamber; and
applying a vacuum to the sample.

22. The method of claim 21 wherein the step of applying a vacuum comprises:
sealing the chamber; and
actuating a piston within the chamber to generate a vacuum within the chamber.

23. The method of claim 22 wherein the step of removing the water soluble gas from the chamber comprises actuating the piston within the chamber to expel the gas via an outlet in the chamber.

24. An apparatus for disinfecting an item, the apparatus comprising:

a reservoir containing a solution containing a water soluble gas having disinfecting properties;

a vacuum coupled to the reservoir to remove the water soluble gas from the solution; and

a conduit coupled to the vacuum and positioned to inject the water soluble gas into contact with the item to disinfect the item.

25. The apparatus of claim 24, further comprising a device positioned adjacent the item to eliminate the water soluble gas once the item has been effectively treated by the water soluble gas.

26. The apparatus of claim 25, wherein the water soluble gas is chlorine dioxide and the device that eliminates the chlorine dioxide gas comprises an ultraviolet light adapted to be selectively illuminated to deactivate the chlorine dioxide gas in the container.

27. The apparatus of claim 24, wherein the vacuum comprises:

a selectively sealable chamber adapted to receive a sample of the solution; and

a piston selectively moveable within the chamber, wherein movement of the piston in a first direction generates a vacuum within the chamber to separate water soluble gas from the solution and movement of the piston in the opposite direction forces the water soluble gas from the chamber.

28. A method for disinfecting an item, the method comprising:

providing a solution containing a water soluble gas having disinfecting properties;

extracting the water soluble gas from the solution with a vacuum;

removing the water soluble gas from the vacuum;

dissolving the extracted water soluble gas into purified water to create a highly pure solution;

contacting the item with the highly pure solution; and

disinfecting the item with the highly pure solution.

29. The method of claim 28 wherein the step of extracting the water soluble gas from the solution with a vacuum comprises:

providing a sample of the solution into a chamber; and
applying a vacuum to the sample.

30. The method of claim 29 wherein the step of applying a vacuum comprises:
sealing the chamber; and
actuating a piston within the chamber to generate a vacuum within the chamber.

31. The method of claim 30 wherein the step of removing the water soluble gas from the chamber comprises actuating the piston within the chamber to expel the gas via an outlet in the chamber.

32. A method for creating a purified chlorine dioxide solution, the method comprising:
providing a solution containing chlorine dioxide gas and other impurities;
extracting the chlorine dioxide gas from the solution with a vacuum; and
dissolving the extracted chlorine dioxide gas into purified water to create a highly pure chlorine dioxide solution.

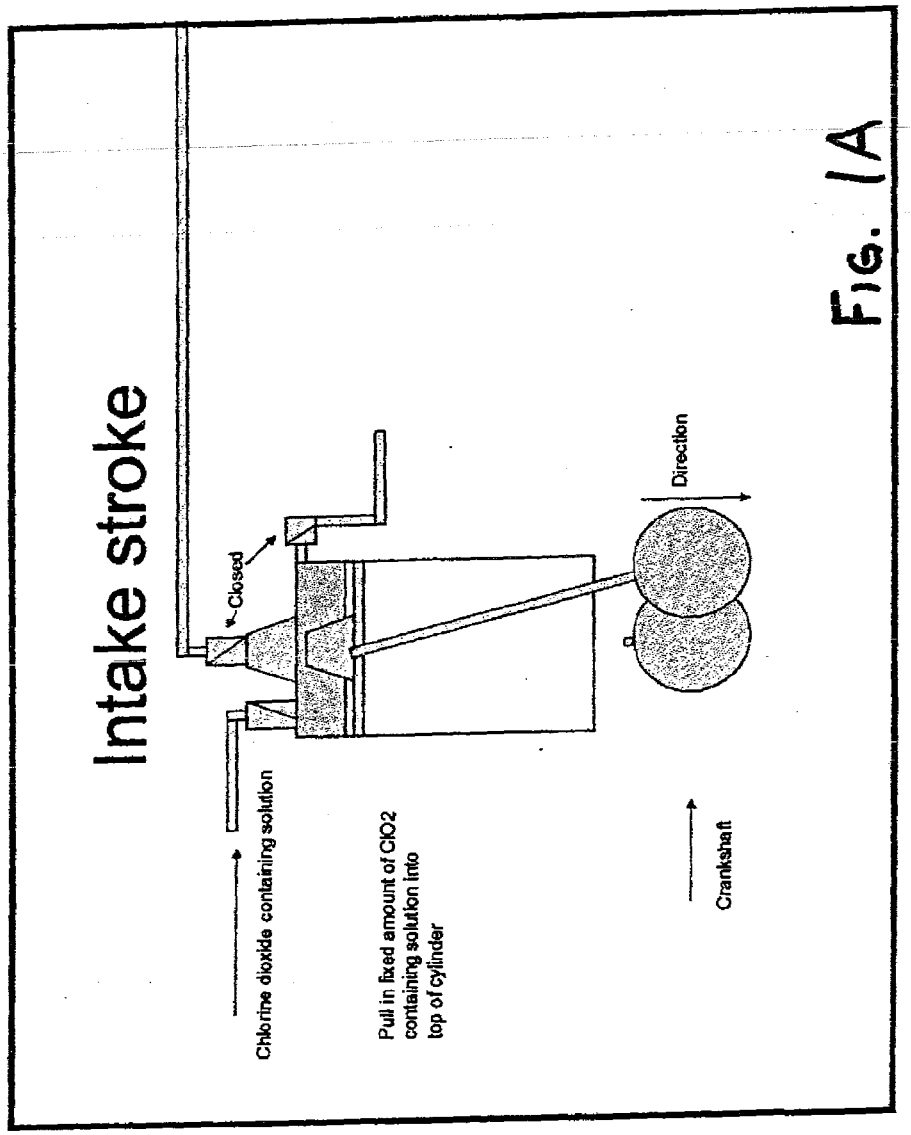

FIG. 1A

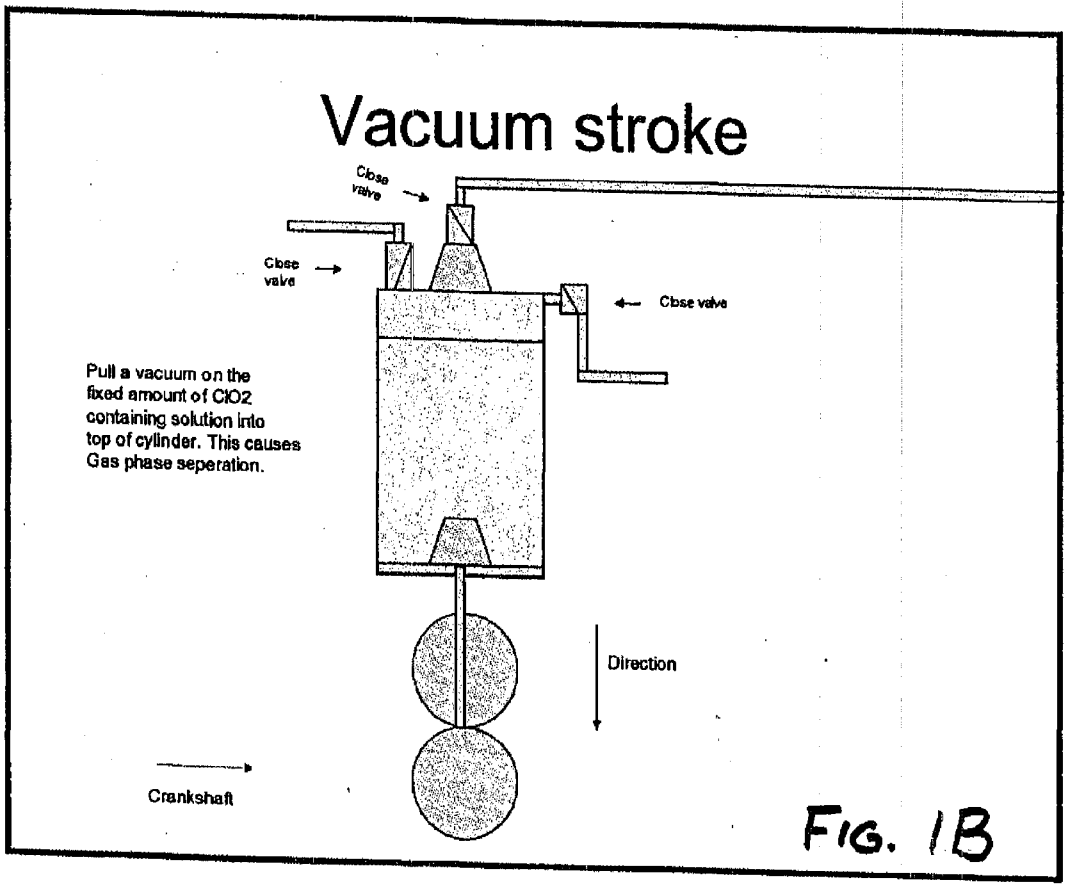

FIG. 1B

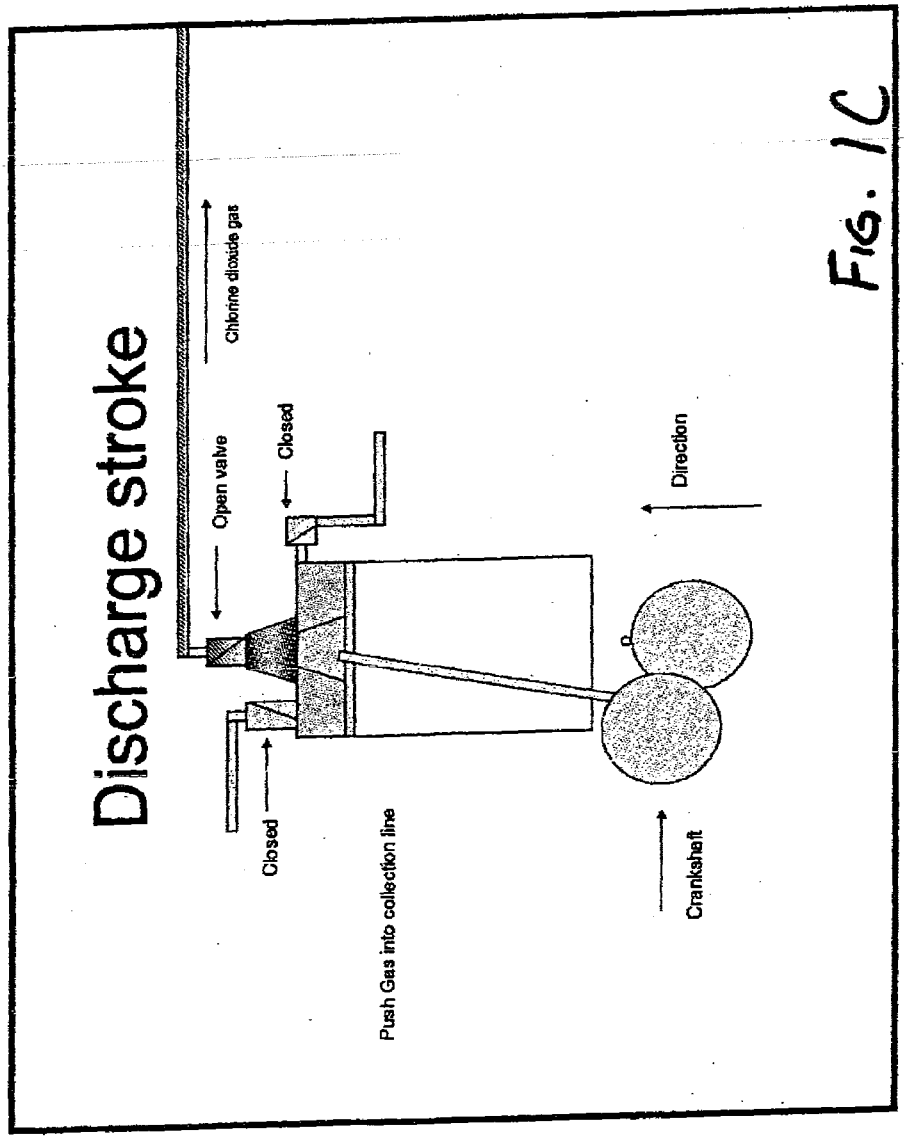

Fig. 1C

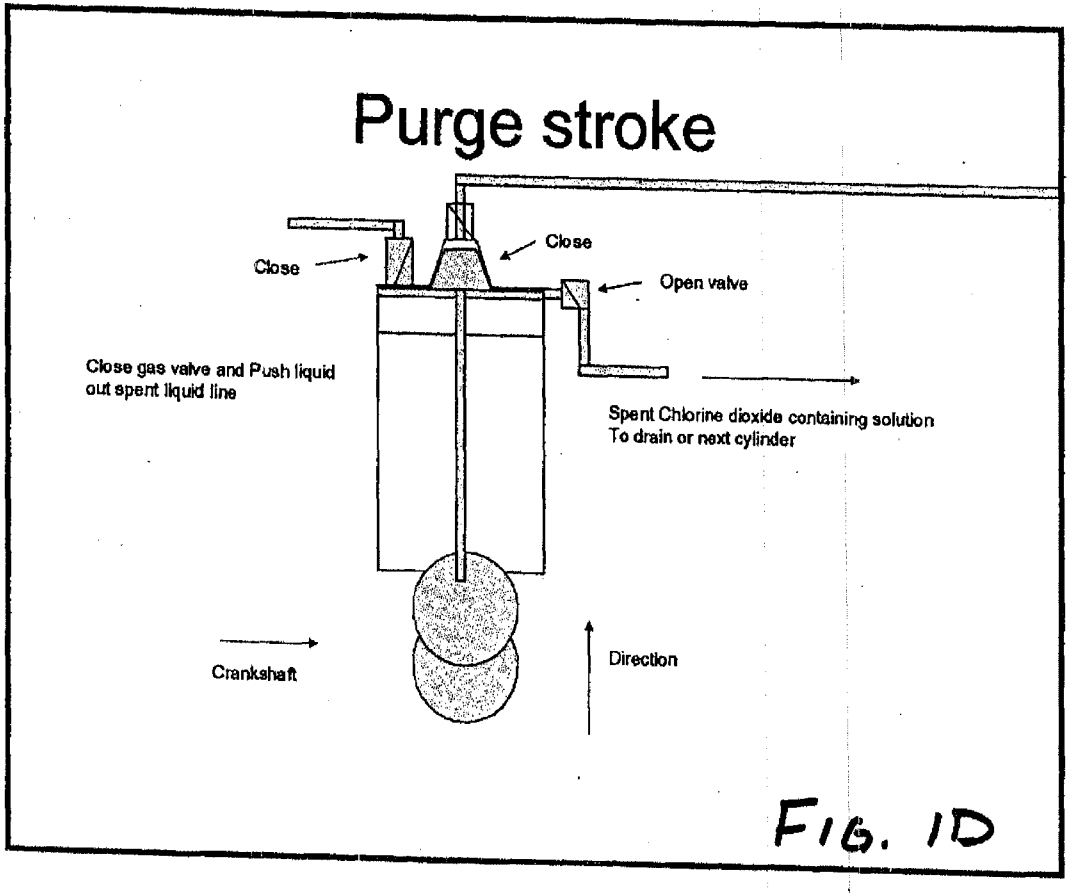

FIG. 1D

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(54) Disinfection apparatus

(57) A disinfection apparatus including a container; a cap having an article-retaining means, a sealing means and a catalytic element-retaining means affixed thereto; and a catalytic element. The disinfection apparatus has particular utility in the disinfection of contact lenses with hydrogen peroxide solutions. Also disclosed are venting and sealing components, catalytic elements, molded article-retaining assemblies, and catalytic element formation methods.

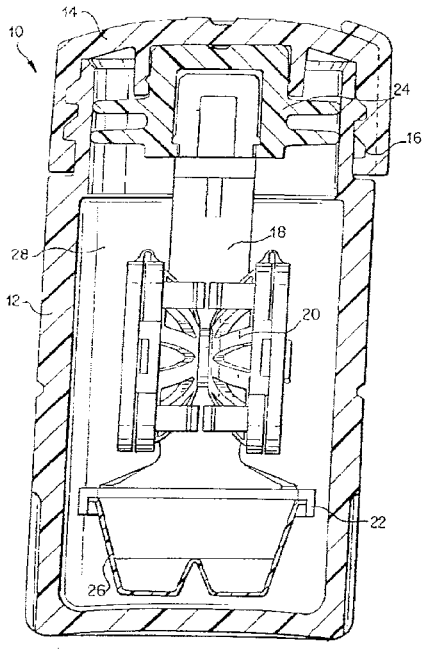

FIG. 1

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EP 0 761 238 A2

Description

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

This invention relates broadly to devices for disinfection. In a preferred embodiment, the invention relates to devices for disinfection of contact lenses.

2. DESCRIPTION OF THE RELATED ART

Contact lenses provide the consumer with an exceptionally convenient and comfortable alternative to conventional eyeglasses. However, proper maintenance of contact lenses involves periodic lens sterilization or disinfection to eliminate harmful bacteria and fungi, and cleaning to remove deposits such as proteins or lipids which adhere to the lens. In order to clean and disinfect contact lenses, a wide variety of devices have been developed.

A particularly efficacious method of disinfecting contact lenses is by a chemical treatment of the lenses with a hydrogen peroxide solution, as described in U.S. Patent No. 3,912,451, issued to Gaglia, Jr., Oct. 14, 1975. In a typical lens disinfecting apparatus, contact lenses are placed in hydrogen peroxide solution inside a container. The container is sealed (e.g., by threads on the container mating with threads on a cap) for a predetermined period of time to sufficiently disinfect the lenses, with the seal preventing liquid spillage resulting from container movement.

Although hydrogen peroxide is highly effective in disinfecting contact lenses, hydrogen peroxide must be removed from lenses prior to placing the lenses in a patient's eye in order to avoid patient discomfort. One method of removing hydrogen peroxide involves contacting the hydrogen peroxide with a platinum catalyst, thereby rapidly decomposing the hydrogen peroxide into water and gaseous oxygen. Liberated gaseous oxygen resulting from the peroxide decomposition generates internal pressure in the disinfecting container which must be vented. In order to alleviate this pressure, a variety of venting means have been developed. Also, a number of catalytic elements and lens retaining assemblies have been developed. The catalytic elements disclosed in the art have primarily been some form of platinum-coated disk-shaped elements.

For example, U.S. Patent No. 4,011,941, issued to Parsons on Mar. 15, 1977, discloses a contact lens sterilization container which includes a hollow cylindrical chamber having two opposing openings which are sealed by two caps. One cap includes a convoluted catalytic reactor which is friction-retained on the cap. The catalyst is essentially a disc-shaped element with protuberances extending therefrom. The other cap includes a stem with contact lens holders and a resealable venting means. The venting means is an O-ring positioned in an annular groove passageway from the interior of the container to the exterior surroundings. The O-ring acts as a pressure release valve when oxygen is produced by the decomposition of peroxide in the presence of the catalyst.

U.S. Patent No. 4,637,919, issued to Ryder, et al., Jan. 20, 1987, discloses a contact lens cleaning container and mating cap, where the cap includes a filter assembly positioned in a vent passageway. The filter assembly includes a hydrophobic membrane which continuously vents the gas generated within the container during the decomposition of peroxide. The pores in the hydrophobic membrane are sufficiently small to inhibit liquid leakage from the container. The catalyst used is the same or analogous to the catalyst disclosed in U.S. Patent No. 4,011,941.

U.S. Patent No. 4,750,610, issued to Ryder, Jun. 14, 1988, discloses a disinfecting container which is affixed to a cap via loose threading. The cap includes a resiliently deflectable flange which acts as a check valve in conjunction with the container. In operation, the cap flange is typically in a closed position, i.e., the flange is positioned immediately adjacent a portion of the container, thereby preventing liquid leakage. When excess internal pressure develops, the cap flange deflects, allowing gas to pass through the loosely threaded container-cap connection to the outside of the container. The catalyst used is the same or analogous to the catalyst disclosed in U.S. Patent No. 4,011,941.

U.S. Patent No. 4,956,156, issued to Kanner, et al., Sep. 11, 1990, discloses a disinfecting system which includes a cap having a bore. A post is positioned in the bore with a resiliently-deflectable diaphragm positioned around the post. The diaphragm-post seal prevents liquid leakage, while allowing gas to pass upon deflection of the diaphragm when sufficient internal pressure develops.

U.S. Patent No. 4,996,027, issued to Kanner, Feb. 26, 1991, discloses a disinfecting system which includes a container and cap connected by threading. A self-reseating unitary gasket is positioned between the cap and container to provide a liquid-tight seal. Increased internal pressure causes the gasket to unseat, at least partially, allowing gas to pass between the cap and container connection to the environment.

U.S. Patent No. 5,196,174, issued to Cerola, et al., on Mar. 23, 1993, discloses a structure for removably mounting a catalyst between the contact lenses holders. The catalyst is a disc which is defined as a generally flat, disc-like member with a pattern of recesses and ridges formed on either face or surface thereof. The advantage of the design is that the catalyst may be removed and replaced by a user as the catalytic agent becomes exhausted from use.

U.S. Patent No. 5,250,266, issued to Kanner, Oct. 5, 1993, discloses a lens disinfecting apparatus, including a container and a cap, in which gas is vented through a type of check valve in the cap. The check valve in-

cludes a disc having a linear slit therethrough. The slit generally provides a liquid-impermeable barrier, but when internal pressure is generated, the slit opens to allow gas to pass to the environment.

Although various disinfection apparatusses have been proposed in the past, there is a need to provide a less complicated system, both from a manufacturing perspective and from an operational perspective. In addition, there is a need for catalyst elements which are less expensive to manufacture and which provide improved fluid flow profiles during peroxide decomposition. Further, there is a need for improved means for allowing internally generated gas to vent from the disinfection device. There is also a need to improve the cap and lens retaining assembly.

SUMMARY OF THE INVENTION

An object of the invention is to provide a disinfection device which may be manufactured with less complexity than prior art devices.

Another object of the invention is to provide a catalytic element which has improved fluid flow profiles.

A further object of the invention is to provide a catalytic element which is less complex and less costly to manufacture than prior art catalytic elements.

Yet another object of the invention is to provide an improved vent means for a disinfection device which generates gas during operation.

An additional object of the present invention is to provide a contact lens disinfection system having improved venting means, an improved catalytic element, and improved ease of manufacturing.

One embodiment of the present invention is a catalytic element for a disinfection device. The catalytic element includes a catalyst substrate having a base portion, a side wall portion extending from the peripheral edge of the base portion, with the portions defining an inner concave surface and an outer convex surface, and a means for affixing the catalytic element to a catalytic element supporting member. The catalytic element further includes a coating of catalytic material deposited on at least a portion of a surface of the catalyst substrate, which catalytic material catalyzes the decomposition of a disinfectant species in solution. A preferred catalytic material is platinum and a preferred disinfectant is hydrogen peroxide.

Another embodiment of the present invention is a sealing and venting component for a device which generates internal gas pressure during operation. The sealing and venting component provides a substantially liquid impermeable seal which vents internally generated gas at a certain pressure differential. The sealing and venting component includes a housing having an internal and an external surface, and at least two elongated rims extending outwardly from the external surface a distance which is sufficient for the rims to contact the internal surfaces of the cylindrical container to establish a sealed chamber with said container. The rims are sufficiently flexible to at least partially deform to allow gas to vent from said chamber. The rims are sufficiently resilient to return to a position of contact with the container after venting, thereby reestablishing said sealed chamber.

A further embodiment of the present invention is an assembly for use in a disinfection container. The assembly is inexpensive and simple to manufacture and assemble, and may be easily recycled. The assembly includes (a) a cap including a means for affixing the cap to the container, (b) an elongated support member affixed to the cap, (c) sealing means affixed to the elongated support member, with the sealing means being capable of forming a substantially liquid impermeable chamber with said container, (d) lens-retaining means affixed to the elongated support member, (e) catalytic element-retaining means affixed to said elongated support member; and a catalytic element retained within the catalytic element-retaining means.

Yet another embodiment of the present invention is a disinfection device, which is particularly useful in the disinfection of contact lenses. The disinfection device includes (a) a container adapted to receive a disinfecting solution; (b) a cap adapted to be releasably affixed to the container at the open end; (c) an elongated support member extending into the container and being affixed to the cap; (d) an article-retaining means affixed to the elongated member; (e) a sealing mens affixed to said elongated member; and (f) a catalytic element affixed to the elongated member. The sealing means is at least partially deformable, such that internal gas generated within said container will vent to a point outside said container.

Still another embodiment of the invention is a process for making a catalytic element. The process includes the steps of (a) feeding a continous sheet of substrate material into a vacuum forming chamber, (b) vacuum forming a desired cataltyic element shape in the substrate material, (c) feeding the continuous sheet into a coating chamber, (d) coating at least one surface of the shaped catalytic element substrate to form a catalytic element, and (e) removing a catalytic element from the sheet.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side sectional view of one embodiment of a contact lens disinfection apparatus of the present invention.

FIGS. 2a and 2b are side sectional views of one embodiment of an unassembled, molded member of the present invention which includes article- and catalyst-retaining means.

FIG. 3 is a side sectional view of an alternative embodiment of the molded member of the present invention which includes article- and catalyst-retaining means.

FIGS. 4a and 4b are bottom views of the molded member of FIG 3.

FIGS. 5a, 5b, 5c, and 5d are side, top, bottom and side sectional views, respectively, of one embodiment of the cap.

FIGS. 6a, 6b, and 6c are side sectional, top and side views, respectively, of one embodiment of the sealing means of the present invention.

FIGS. 7a and 7b are bottom and side sectional views of one embodiment of the catalytic element of the present invention.

FIG. 8 is a bottom view of a molded sheet of catalytic elements of FIGS. 7a and 7b.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention has utility in the disinfection of articles, such as ophthalmic lenses, which require routine disinfection procedures to be peformed by consumers. "Disinfection", as used herein, refers broadly to deactivativating, killing, or removing microorganisms from an article, and is sometimes referred to as sterilization or cleaning. The disinfection processes which are useful in accordance with the present invention are those in which a gas is liberated during or after the disinfection process, for example, by decomposition of the disinfectant. The invention finds particular utility in the disinfection of contact lenses with peroxide, concurrently with or followed by catalytic decomposition of the peroxide into water and gaseous oxygen.

The invention may be easily understood with reference to the drawings. FIG. 1 is a side sectional view of one embodiment of a disinfection apparatus of the present invention. Disinfection apparatus 10 includes container 12 which is adapted to receive a disinfecting solution. Container 12 has an end which includes a substantially circular periphery defining an opening which is adapted to receive a lens retaining means. Cap 14 is releasably affixed to the open end of container 12 via mating threading 16 on the cap and container.

Cap 14 has elongated member 18 affixed thereto. Elongated member 18 supports article-retaining means 20, catalytic element-retaining means 22, and deformable sealing means 24. The catalyst element-retaining means holds catalytic element 26 beneath article-retaining means 20. Elongated member 18 extends into cavity 26 defined by container 12 when cap 14 is affixed to the container. The deformable sealing means is positioned between cap 14 and article-retaining means 20 to seal cavity 28 from the surroundings, and prevent liquid held within the cavity from leaking from the disinfection apparatus when the apparatus is tilted or turned upside down.

The deformable sealing means provides a normally closed, substantially liquid-impermeable seal for liquid held within the container. However, the sealing means is at least partially deformable, such that internal gas generated within the container will vent to a point outside the container by at least partially deforming a portion of the sealing means, thereby forming a passageway between a point inside said container to a point outside said container. The passageway may include a path through a loosely threaded cup-container connection or openings, such as circular holes, directly through the cap.

FIGS. 2a and 2b are side sectional views of one embodiment of an unassembled, molded member which includes article-retaining means 20, catalytic element-retaining means 22, and elongated member 18. In order to assemble molded member 30, first a catalytic element (not shown in FIGS. 2a and 2b) is inserted into catalytic element-retaining means. Then, elongated member 18 is folded at flexible joints 32 so that end 34 is positioned immediately adjacent end 36. Ends 34 and 36 are permanently affixed to one another by any means known in the art, including without limitation thereto, use of adhesives, use of pressure affixation methods, use of interference fit designs of the ends, or use of heat sealing methods.

FIG. 3 is a side sectional view of an alternative molded member to the embodiment shown in FIGS. 2a and 2b. While the embodiment of FIGS. 2a and 2b requires a step of affixing end 34 to end 36 subsequent to molding, the FIG. 3 embodiment is a molded member which does not require a subsequent affixation step to form end 43. In this embodiment, article-retaining means 20 includes two holders which are shaped to hold ophthalmic lenses, especially contact lenses. Lens holder 38 includes a concave portion 40 and a convex portion 42 connected by a flexible joint 44. In use, a contact lens may be placed in concave portion 40, while convex portion 42 is rotated to a position immediately adjacent concave portion 40. The concave and convex portions are releasably affixed to one another, e.g., by interference fit or some form of snap fitting, to retain the lens during the disinfection cycle. Concave portion 40 and convex portion 42 include openings 46 and 48, respectively, to allow disinfecting solution to pass through to the lens retained therein.

A catalytic element is inserted into opening 45 of the FIG. 3 embodiment and dropped onto catalytic element-retaining means 41. The peripheral rim of the catalytic element-retaining means (See FIG. 7b) rests on the peripheral support of catalytic element-retaining means 41. Once the catalytic element is inserted into its resting position, the two article-retaining members are moved into position as shown in FIG. 4a and 4b, with the article-retaining means trapping the cataltic element from the side opposite the catalytic element retaining means 41.

FIGS. 4a and 4b are bottom views of the molded member of FIG 3. FIG. 4a illustrates the molded member with the contact lens holders in an open position, ready to receive contact lenses. FIG. 4b illustrates the molded member with contact lens holders releasably affixed to

the molded member in a position which minimizes the cross-sectional area, so that the molded member and contact lenses may be easily inserted into the disinfection container. The contact lens holders are affixed to one another by an interference between male affixation member 47 on one contact lens holder and female affixation member 49 on the other contact lens holder. The interference fit is preferably sufficiently secure to prevent the consumer from manually separating the contact lens holders, so that the consumer is encouraged to recycle the entire assembly, i.e., molded member and catalytic element, at one time.

FIGS. 5a and 5b are side and top views of one embodiment of the cap, respectively. Cap 50 preferably includes grasping means such as ribs 52, as shown in FIG. 5a, which are raised from the surface of the cap an amound which promotes consumer convenience in grasping the cap. In the FIG. 5b embodiment, the cap also includes venting passageways which are openings extending through the cap. Cap 50 includes two substantially circular holes 54 extending through the cap, providing a passageway from a point inside the container to a point outside the container when the cap is affixed to the container.

FIGS. 5c and 5d are bottom and side sectional views, respectively, of cap 50. Cap 50 includes a cylindrical-shaped affixation means 56 which extends substantially perpendicularly from the inside surface of cap 50. Affixation means 56 includes a peripheral lip 58 which extends inwardly from the end of the affixation means which is opposite the surface of cap 50. The sealing means is connected to the cap by affixation means 56.

FIGS. 6a, 6b, and 6c are side sectional, top and side views of one embodiment of the sealing means of the present invention. Sealing means 60 includes cup-shaped housing 62 having a concave and a convex surface. The convex surface includes a substantially flat surface 63 which is adapted to mate with cap 50 and a substantially cylindrical wall 65. Two elongated rims 64 and 66 extend peripherally outward and substantially perpendicularly from the cylindrical wall of the convex surface of sealing means 60. Sealing means 60 further includes a lip 68 which extends peripherally outward from the cylindrical wall of the convex surface of sealing means 60, at a position between the flat surface 63 and rims 64 and 66. When the device is assembled, sealing means 60 is retained on cap 50 by an interference fit between sealing means lip 68 and cap lip 58.

Sealing means 60 is formed from a resiliently flexible material so that rims 64 and 66 may be deformed by internal pressure to provide a vent passageway between the sealing means and the container wall for venting. Thus, the seal is not formed within the cap, but is formed by intimate contact between sealing rims 64 and 66 and the container walls. While sealing means 60 may be formed from a wide variety of materials, preferred materials include polypropylene and polyethylene.

The sealing means of the present invention provides a substantially liquid impermeable seal with the interior of the container walls to form a sealed chamber for liquid retention. When gas in the sealed chamber causes the internal pressure to reach a predetermined value in excess of the external ambient pressure, the sealing means rims flex or deform, at least partially, to allow gas to pass. The gas may then vent outside the apparatus through openings in the cap or through the mating threads of the cap-container connection.

The sealing means of the present invention presents clear advantages over the prior art. One advantage is that the sealing means includes at least two rims, both of which provide protection from solution leakage or spills. If one of the rims becomes damaged (e.g., torn) or inadvertently held open (e.g., by debris on the container walls), the other rim still provides completely independent sealing and venting functions. Another advantage of the present sealing means is that the double rim design prevents any leakage from any solution which inadvertently passes the first rim. For example, if the apparatus is placed in a travel container and shaken during travel, increased disinfectant decomposition rates and foaming may result. Alternatively, if the apparatus is placed upside down during the disinfectant decomposition process, solution may conceivably be forced past the first rim. In either of these instances, the second sealing rim provides additional protection to keep the solution from leaking out of the disinfection apparatus.

The catalytic element includes a thin molded substrate and a catalytic coating deposited on the substrate. The substrate is preferably an inexpensive plastic material, such as poly(ethylene terephthalate), also known as PET. The preferred catalytic coating is platinum or a platinum-containing alloy, because platinum catalyzes the decomposition of hydrogen peroxide into water and oxygen. The coating may be deposited by a number of methods known in the art, including dip coating and ion beam deposition methods. A preferred method of coating the substrate material is by ion beam-assisted deposition. Thus, a preferred catalytic element has a PET substrate which is coated or impregnated with platinum metal.

The catalytic element is preferably of a shape which lends itself to inexpensive and efficient mass production by vacuum forming. Thus, the catalytic element preferably has a convex surface and a concave surface. The catalytic element should have a base portion and a side wall portion which extends from the peripheral edge of the base portion, with the side walls having either a cylindrical or conical shape. In addition, the catalytic element preferably has protrusions or extensions which increase surface area without either substantially increasing the volume the element must occupy or substantially increasing the difficulty of manufacture.

The catalytic element should also be shaped to promote good fluid flow and minimize "dead space" (i.e.,

areas of little or no flow) during the disinfectant decomposition process. Therefore, the catalytic element preferably includes a plurality of holes therethrough, with the holes being located to facilitate improved flow regimes. Finally, the catalytic element should have a means for affixing the catalytic element to the disinfection apparatus.

In a preferred embodiment, the catalytic element has a truncated cone shape. Thus, the catalytic element has a circular flat surface with a conical wall extending outwardly from the edge of the circular flat surface. The angle which the conical wall extends from the flat surface has an impact on both the flow during the decomposition of the disinfectant and the catalytic metal deposition process. If the angle of the wall is too steep, deposition of metal (e.g., platinum) on the wall is very difficult. On the other hand, angles which are too large (i.e., approaching a flat sheet) tend to cause gas bubbles to remain adhered to the wall during the disinfection process. The adhered bubbles prevent disinfectant from efficiently contacting the catalyst, thereby slowing the decomposition process. Therefore, the angle between the conical portion and flat bottom portion of the catalyst is preferably about 30 to 60 degrees.

Also, the catalytic coating is preferably only deposited on the inner walls of the catalyst substrate material. Coating only the inner walls of the catalyst substrate ensures that gas from disinfectant decomposition is generated only on the concave interior portion of the catalytic element. A current is then generated as the gas bubbles are released from the interior of the catalytic element and move towards the top of the disinfectant container. Solution from beneath the catalytic element passes through the openings in the bottom of the catalytic element to replace the gas bubbles which are released from the inside. Thus, gas bubbles moving upward in the interior of the container cause an interior upward solution flow and a downward solution flow near the container walls. In contrast, if catalytic material were deposited on the exterior of the catalytic element, decomposition gas bubbles would form on, and be released from, the exterior of the catalytic element, thereby opposing the previously-described current. Therefore, the catalytic element is preferably coated only on the interior surfaces in order to promote good mixing and minimize the time required to decompose the disinfectant.

FIGS. 7a and 7b are bottom and side sectional views of one embodiment of the catalytic element of the present invention. Catalytic element 80 has a interior concave surface 82 and an exterior which includes a base portion 84 and walls 86 extending in a conical fashion from bottom 84. Catalytic element 80 also includes a plurality of holes 88 through bottom surface 84. Bottom surface 84 includes raised portions 90 which add surface area to the catalytic element without adding substantially to the difficulty of manufacturing the catalytic element or to the volume required by the catalytic element when placed in the container.

Catalytic element 80 also includes rim 92 which extends outwardly along the peripheral edge of the catalytic element. The catalytic element is retained within the assembled elongated member when rim 92 rests within catalytic element-retaining means 22 (See FIG.1).

The substrate of the catalytic element is a flexible material which has sufficient rigidity to give the catalytic element a definite shape. Preferably, the substrate is formed in an efficient, inexpensive vacuum forming process. FIG. 8 is a bottom view of a molded sheet of catalytic element substrates having the shape of the catalytic elements of FIGS. 7a and 7b. A plurality of catalytic element 100 are vacuum formed in a sheet of substrate material 102. The catalytic element substrates may then be punched out or cut out of the sheet 102.

Coating of the catalytic elements may occur prior to or subsequent to the removal of the shaped catalytic element substrates from the material sheet. In a preferred embodiment, the catalytic elements are vacuum formed and coated with catalyst in a semi-batch or continuous process. For example, the catalytic element formation process may include the steps of (a) feeding a continous sheet of substrate material into a vacuum forming chamber, (b) vacuum forming a desired cataltyic element shape in the substrate material, (c) feeding the continuous sheet into a coating chamber, (d) coating at least one surface of the shaped catalytic element substrate to form a catalytic element, and (e) removing a catalytic element from the sheet. While all surfaces of the catalytic element may be coated, it is preferably to have only the interior surface of the shaped catalytic element substrate coated with catalyst material.

It should be noted that the methods of affixing components of the disinfecting apparatus to one another may be selected from a wide variety of affixation methods known in the art and described generally herein. However, "releasably affixing" one component to another refers to the affixing of components in a manner that allows the components to be separated from, and reaffixed to, one another many times without substantially damaging the components or the affixation means. "Permanently affixing" one component to another refers to methods of affixing components such that separation of the components results in substantial damage to one or more of the components, likely to render the components or affixation means inoperable.

The invention has been described in detail, with reference to certain preferred embodiments, in order to enable the reader to practice the invention without undue experimentation. However, a person having ordinary skill in the art will readily recognize that many of the components and parameters may be varied or modified to a certain extent without departing from the scope and spirit of the invention. Furthermore, titles, headings, or the like are provided to enhance the reader's comprehension of this document, and should not be read as limiting the scope of the present invention. Accordingly,

the intellectual property rights to this invention are defined only by the following claims and reasonable extensions and equivalents thereof.

Claims

1. A disinfection device, comprising:

(a) a container adapted to receive a disinfecting solution, said container having at least one end which includes a substantially circular periphery defining an opening which is adapted to receive a lens retaining means;
(b) a cap adapted to be releasably affixed to said container at said open end;
(c) an elongated member affixed to said cap, wherein said elongated member extends into said container when said cap is affixed to said container;
(d) means for retaining articles to be disinfected, said article-retaining means being affixed to said elongated member, whereby said article-retaining means extends into said container when said cap is affixed to said container;
(e) means for releasably sealing said container, thereby providing a normally liquid-impermeable seal, wherein said sealing means is affixed to said elongated member interposed between said article-retaining means and said cap,

whereby said sealing means is at least partially deformable, such that internal gas generated within said container will vent to a point outside said container, when the internal pressure reaches a predetermined pressure in excess of the external pressure, by at least partially deforming a portion of said sealing means, thereby forming a passageway between a point inside said container to a point outside said container; and

(f) a catalytic element affixed to said elongated member, wherein said catalytic element is positioned inside said sealed container when said cap is affixed to said container.

2. A device of claim 1, wherein said cap includes at least one hole therethrough, such that when internal gas pressure exceeds a predetermined pressure beyond the external atmospheric pressure, gas will vent by at least partially deforming said sealing means, passing between said sealing means and said container wall, and passing through said hole in said cap.

3. A device of claim 1, wherein said cap is affixed to said container by mating threads on said cap and said container, wherein said mating threads provide sufficient space therebetween to allow gas to vent through the space between said mating threads when the pressure inside said sealed container exceeds said predetermined pressure.

4. A device of claim 1, wherein said catalytic element has a concave surface and a convex surface.

5. A device of claim 4, wherein said concave surface of said catalytic element faces said article-retaining means.

6. A device of claim 1, wherein said catalytic element is permanently affixed to said elongated member, such that removal of said catalytic element will damage said catalytic element-retaining means and render said catalytic element-retaining means inoperable.

7. A device of claim 1, wherein said article is an ophthalmic lens.

8. A device of claim 7, wherein said ophthalmic lens is a contact lens.

9. A device of claim 1, wherein said catalytic element comprises:

(a) a catalyst substrate, including:

(1) a base portion,
(2) a side wall portion extending from the peripheral edge of the base portion, wherein said portions define an inner concave surface and an outer convex surface, and
(3) a means for affixing said catalytic element to a catalytic element supporting member; and

(b) a coating of catalytic material deposited on at least a portion of at least one of said surfaces, which catalytic material catalyzes the decomposition of a said species in solution.

10. A device of claim 1, wherein said sealing means comprises:

(a) a housing having an internal and an external surface;
(b) at least two elongated rims extending outwardly from said external surface a distance which is sufficient for said rims to contact the internal surfaces of said container to establish a sealed chamber with said container, which sealed chamber is substantially liquid impermeable,

wherein said rims are sufficiently flexible to at least partially deform to allow gas to vent from said

chamber when the internal pressure of the chamber exceeds a predetermined amount beyond the pressure outside said rims, and

wherein said rims are sufficiently resilient to return to contact said internal surfaces of said container after venting, thereby reestablishing said sealed chamber.

11. A catalytic element for increasing the reaction rate of a chemical species in solution, said catalytic element comprising:

(a) a catalyst substrate, including:

(1) a base portion,
(2) a side wall portion extending from the peripheral edge of the base portion, wherein said portions define an inner concave surface and an outer convex surface, and
(3) a means for affixing said catalytic element to a catalytic element supporting member; and

(b) a coating of catalytic material deposited on at least a portion of at least one of said surfaces, which catalytic material catalyzes the decomposition of a said species in solution.

12. A catalytic element of claim 11, wherein said catalyst material is platinum.

13. A catalytic element of claim 11, wherein both said convex and concave surfaces are coated with a catalyst material.

14. A catalytic element of claim 11, wherein said base portion has a plurality of holes extending therethrough.

15. A catalytic element of claim 11, wherein said base portion includes raised portions extending therefrom, thereby providing said catalytic element with a surface area greater than a catalytic element with a base portion which is substantially flat.

16. A catalytic element of claim 11, wherein said side walls extend conically outward from the peripheral edge of said base portion.

17. A catalytic element of claim 11, wherein said side walls extend cylindrically outward from the peripheral edge of said base portion.

18. A catalytic element of claim 11, wherein said chemical species in solution is hydrogen peroxide.

19. A catalytic element of claim 11, wherein said affixation means is a rim extending outwardly from the edge defined by the side walls.

20. A catalytic element of claim 11, wherein said catalyst substrate is vacuum formed.

21. A catalytic element of claim 11, wherein said catalyst material is deposited on said substrate by ion beam assisted deposition.

22. A catalytic element of claim 11, wherein said catalytic element has an internal surface which includes a substantially flat bottom wall and conical side walls extending outwardly from the peripheral edge of said bottom wall.

23. A catalytic element of claim 22, wherein the angle between said conical side walls and said bottom wall is about 30 to 60 degrees.

24. A catalytic element of claim 11, wherein said catalytic material is deposited only on the interior portion of said catalyst substrate.

25. A sealing and venting component for an apparatus including a substantially cylindrical container which retains solution, which apparatus is exposed to internally generated gas which must be vented during apparatus use or storage, said sealing and venting component comprising:

(a) a housing having an internal and an external surface;
(b) at least two elongated rims extending outwardly from said external surface a distance which is sufficient for said rims to contact the internal surfaces of said cylindrical container to establish a sealed chamber with said container, which sealed chamber is substantially liquid impermeable,

wherein said rims are sufficiently flexible to at least partially deform to allow gas to vent from said chamber when the internal pressure of the chamber exceeds a predetermined amount beyond the pressure outside said rims, and

wherein said rims are sufficiently resilient to return to contact said internal surfaces of said container after venting, thereby reestablishing said sealed chamber.

26. A sealing and venting component of claim 2, wherein said external component surface includes a substantially flat base portion and a substantially cylindrical side wall portion extending from the edge of said base portion, and wherein said rims extend outwardly from said side wall portion.

27. A sealing and venting component of claim 26, fur-

ther comprising a means for affixing said component to said container.

28. A sealing and venting component of claim 27, wherein said affixation means includes a lip extending outwardly from said side wall portion at a point between said rims and said base portion.

29. A sealing and venting component of claim 25, wherein said component is composed of polypropylene.

30. An assembly for retaining ophthalmic lenses, sealing a container, and retaining a catalytic element, said assembly comprising:

(a) a cap including a means for affixing said cap to a container to be used with said assembly;
(b) an elongated support member affixed to said cap;
(c) means for sealing said container, said sealing means being affixed to said elongated support member, said means being capable of forming a substantially liquid impermeable, gas permeable chamber with said container;
(d) means for retaining contact lenses affixed to said elongated support member;
(e) a means for retaining a catalytic element, said catalytic element-retaining means being affixed to said elongated support member; and
(f) a catalytic element retained within said catalytic element-retaining means.

31. An assembly of claim 30, wherein said sealing means is capable of forming a seal with the interior walls of said container.

32. An assembly of claim 30, whererin said sealing means is positioned between said lens-retaining means and said cap.

33. An assembly of claim 32, wherein said lens-retaining means is positioned between said sealing means and said catalytic element-retaining means.

34. An assembly of claim 32, wherein said lens-retaining means is positioned between said sealing means and said catalytic element-retaining means.

35. A method of forming a catalytic element, comprising the steps of:

(a) feeding a continous sheet of substrate material into a vacuum forming chamber;
(b) vacuum forming a desired cataltyic element shape in said substrate material;
(c) feeding said continuous sheet into a coating chamber;
(d) coating at least one surface of the shaped catalytic element substrate to form a catalytic element; and
(e) removing said catalytic element from said sheet.

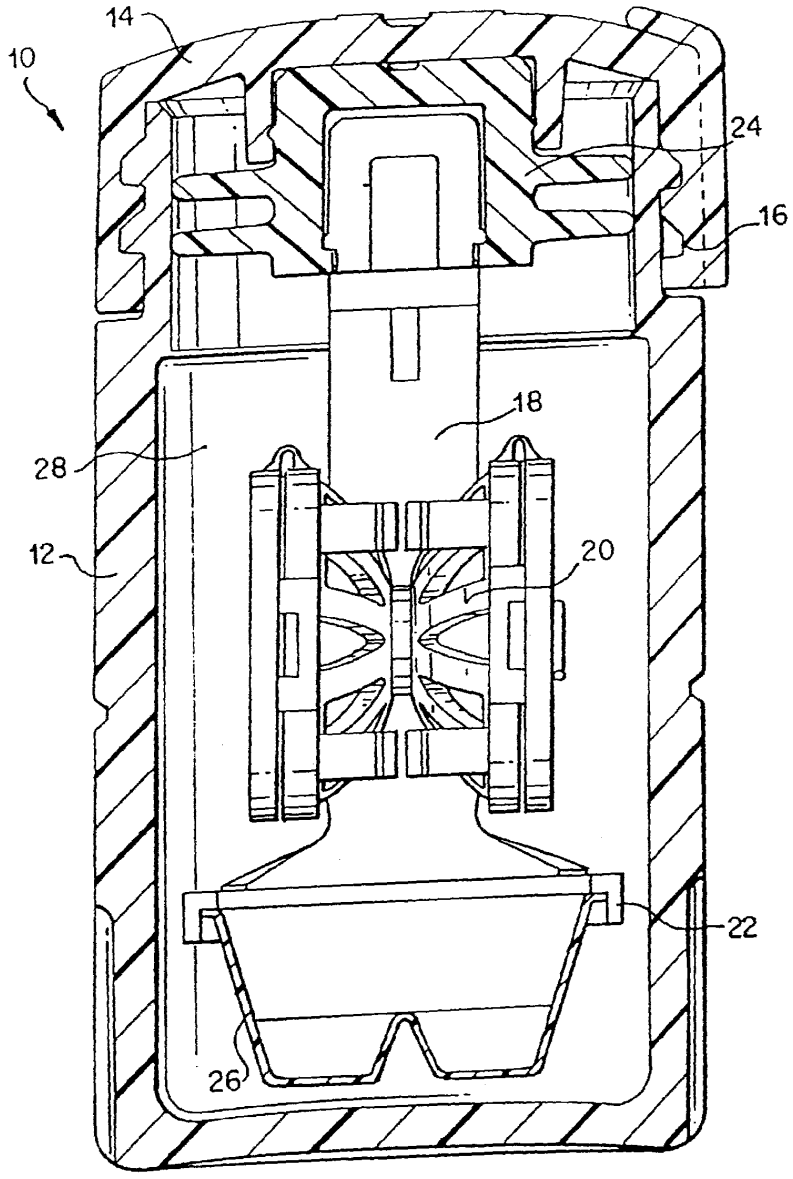

FIG. 1

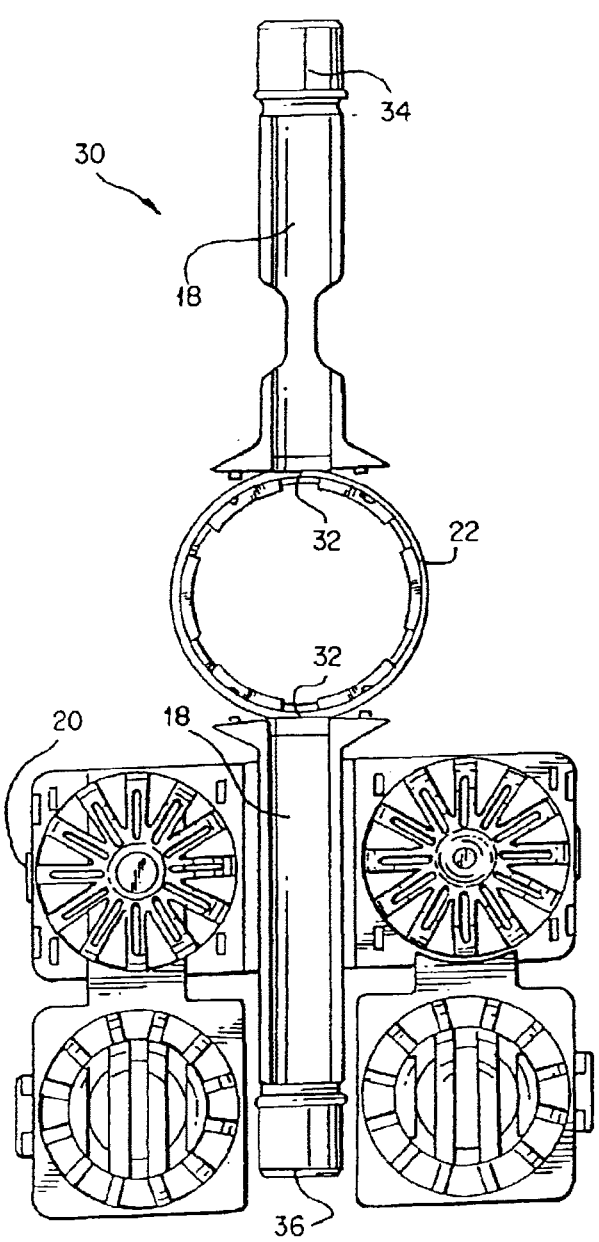

FIG. 2a

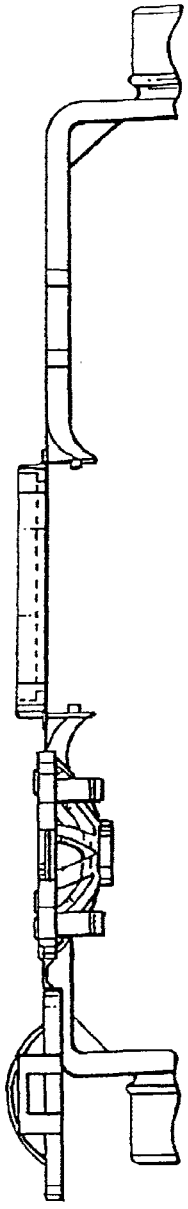

FIG. 2b

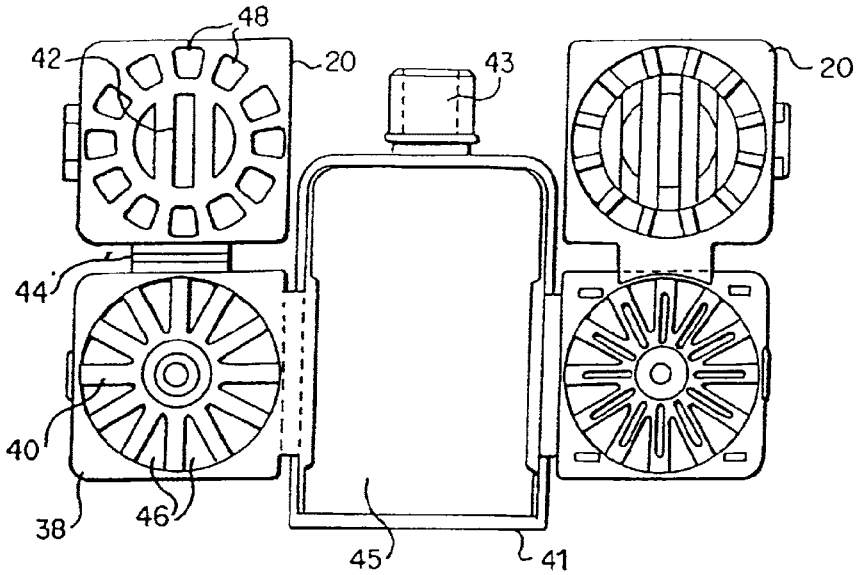

FIG. 3

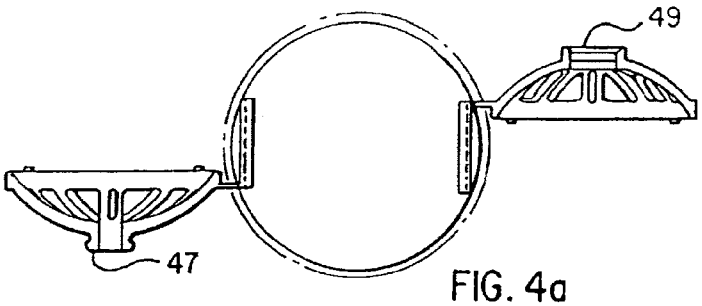

FIG. 4a

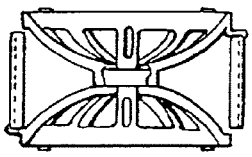

FIG. 4b

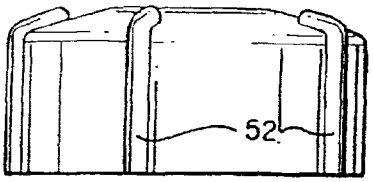

FIG. 5a

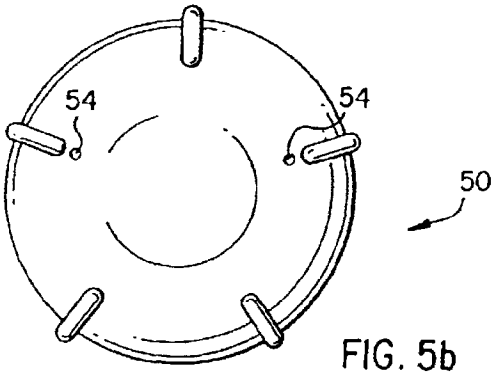

FIG. 5b

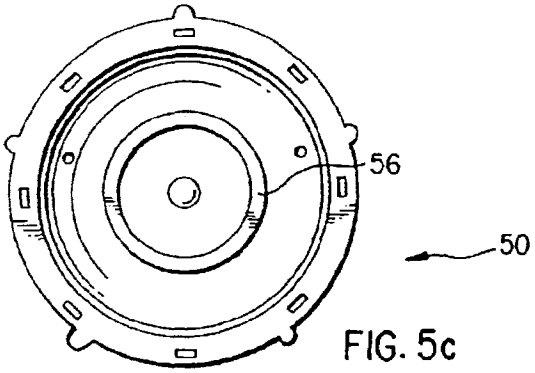

FIG. 5c

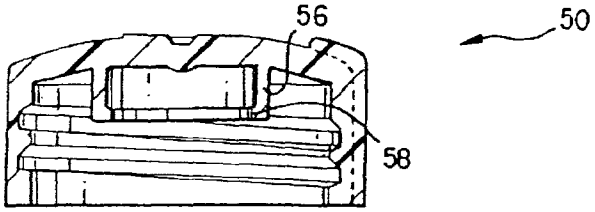

FIG. 5d

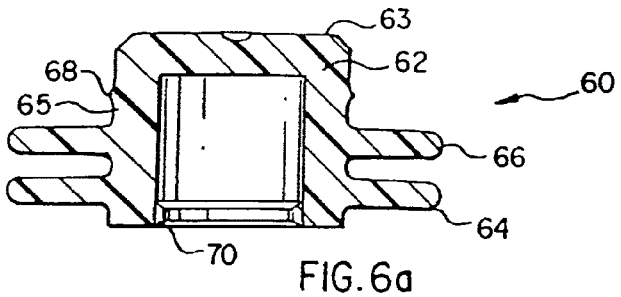

FIG. 6a

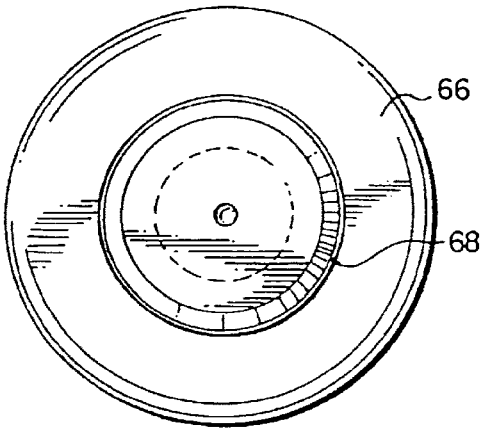

FIG. 6b

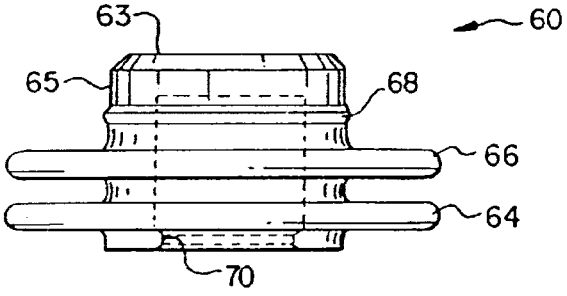

FIG. 6c

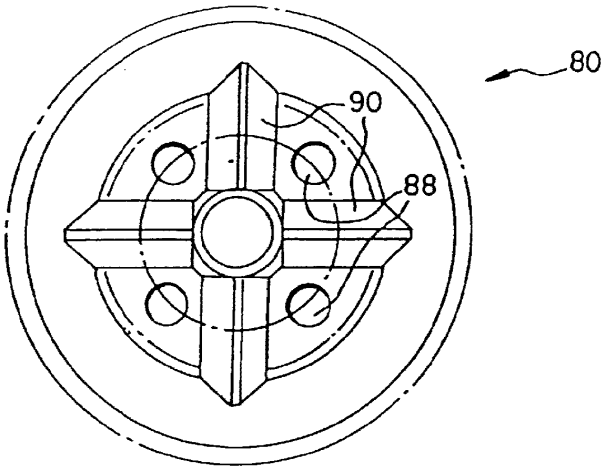

FIG. 7a

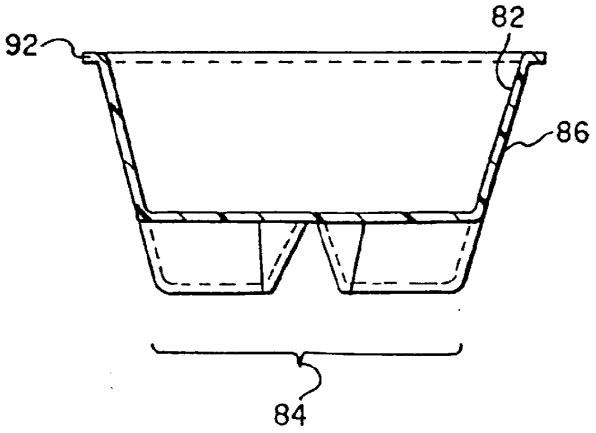

FIG. 7b

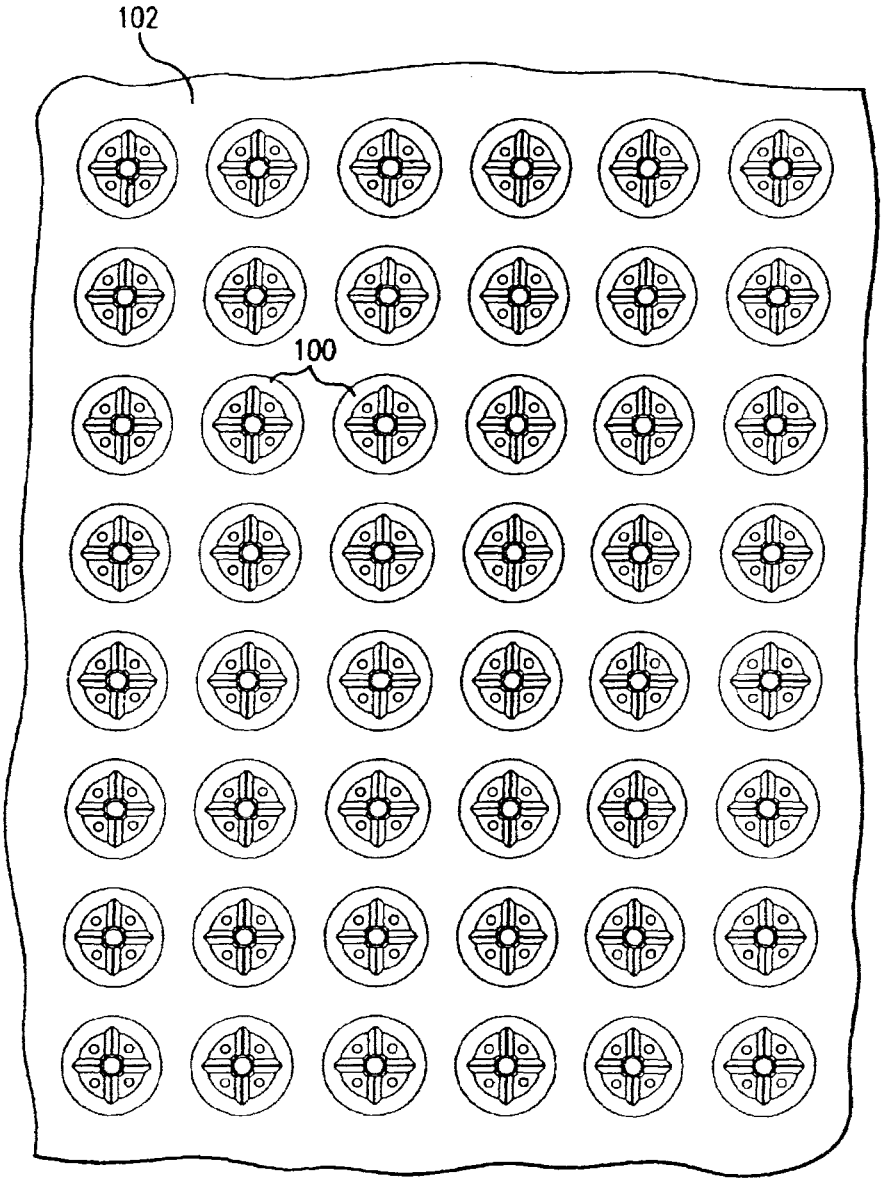

FIG.8

Electronic Patent Application Fee Transmittal	
Application Number:	13382380
Filing Date:	05-Jan-2012
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Filer:	James L Lynch/Denise Cooper
Attorney Docket Number:	PAT053689-US-PCT
Filed as Large Entity	

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	16844692
Application Number:	13382380
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Customer Number:	1095
Filer:	James L Lynch/Denise Cooper
Filer Authorized By:	James L Lynch
Attorney Docket Number:	PAT053689-US-PCT
Receipt Date:	13-SEP-2013
Filing Date:	05-JAN-2012
Time Stamp:	10:47:19
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	9424
Deposit Account	190134
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	PAT053689-US-PCT-IDS.pdf	642528 916525b4021e13656e6d6db708ea534fcd8781ce	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
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Warnings:					
Information:					
3	Foreign Reference	EP0761238A2.pdf	852104 38cef5e9d89be9921b725ebd3be6d110045de216	no	16
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4	Fee Worksheet (SB06)	fee-info.pdf	29920 689606bb86aca829e4b926e55570391b9be1e9df	no	2
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CASE PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 1775
Examiner: SPAMER, DONALD ROBERT

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

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35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL RESPONSE TO OFFICE ACTION

Sir:

In response to the Office Action mailed June 14, 2013, Applicants enclose herewith copies of EP0707186 (hereinafter "the '186 patent") and U.S. Pat. No. 4,643,876 (hereinafter "the '876 patent") mentioned in Applicants' Response to Office Action electronically filed on September 12, 2013.

If there are any issues that can be resolved by a telephone conference, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

/Jim Lynch/

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(54) **Plasma-enhanced vacuum drying**

Plasmaunterstützte Vakuumtrocknung

Séchage sous vide à l'aide d'un plasma

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US-A- 3 238 632
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Description

Field of the Invention

[0001] The invention relates generally to methods of drying by evacuation. In particular, the invention pertains to enhanced vacuum drying using plasma excitation.

Background of the Invention

[0002] Some new commercial systems for sterilizing medical instruments and the like utilize low-temperature reactive gas plasma to achieve rapid, low-temperature, low-moisture sterilization of medical items. Low-temperature gas plasma is sometimes described as a reactive cloud which may contain ions, electrons, and/or neutral atomic particles. This state of matter can be produced through the action of electric or magnetic fields, or through other external forces such as high-energy particle flux. In general, an electric field can be in any frequency range (An example of a naturally occurring plasma is the aurora borealis or the northern lights). One commercial embodiment of plasma sterilization is the STERRAD® Sterilization Process practiced by the assignee of the present application. The STERRAD® process is performed in the following manner. The items to be sterilized are placed in the sterilization chamber, the chamber is closed, and a vacuum is drawn. An aqueous solution of hydrogen peroxide is injected and vaporized into the chamber so that it surrounds the items to be sterilized. After reduction of the pressure in the sterilization chamber, a low-temperature gas plasma is initiated by applying radio frequency energy to create an electrical field. In the plasma, the hydrogen peroxide vapor is dissociated into reactive species that collide/react with and kill microorganisms. After the activated components react with the organisms or with each other, they lose their high energy and recombine to form oxygen, water, and other nontoxic byproducts. The plasma is maintained for a sufficient time to achieve sterilization and remove residuals. At the completion of the process, the RF energy is turned off, the vacuum is released, and the chamber is returned to atmospheric pressure by the introduction of High Efficiency Particulate - filtered Air (HEPA).

[0003] The above-described sterilization system can safely process medical items currently sterilized by ethylene oxide and steam, with the exception of linens, other cellulosic materials, powders, and liquids. Sterilized items are ready to be used in a little over an hour after starting the sterilizer. The process requires no aeration, and there are no toxic residues or emissions. Preparation of instruments for sterilization is similar to current practices: cleaning the instruments, reassembly, and wrapping. The system typically uses non-woven polypropylene wraps, which are commercially available, and a special tray and container system. A special adaptor placed on long, narrow lumen instruments allows rapid sterilization of their channels. A chemical indicator specifically formulated for this process is used, as well as a specifically designed biological indicator test pack.

[0004] The efficacy of the STERRAD plasma sterilization system has been demonstrated by: (1) killing a broad spectrum of microorganisms; (2) killing highly resistant bacterial spores in less than one-half of the full sterilization exposure cycle; (3) killing highly resistant bacterial spores on 16 different substrates commonly used in medical items. Depending upon the particular design plasma sterilization systems can therefore provide efficient, safe methods for sterilizing medical instruments and other hospital products.

[0005] For optimum operation, a plasma sterilization system such as that described above requires the loads that are to be sterilized to be quite dry. However, normal hospital practice in the preparation of instruments for sterilization often results in levels of water that may be excessive. The excess water makes it difficult to achieve the low-pressure thresholds required to initiate the sterilization process. To initiate the sterilization process, the chamber pressure is preferrably reduced to relatively low levels, for example approximately 200-700 mTorr. Since the equilibrium vapor pressure of water is significantly higher than 700 mTorr at room temperature, any water in the chamber or load will begin to vaporize during the vacuum phase. The heat of vaporization required for the water to vaporize causes the load and any remaining water to chill. When enough water has vaporized, the remaining liquid begins to freeze. Eventually, the remaining liquid will completely freeze, which slows the rate of vapor generation and retards the attainment of the pressure levels required for optimum operation of the sterilizer. These conditions can cause undesirably long sterilization cycles or even cancellation of the sterilization cycle. To avoid this problem, a method is needed for preventing or removing any solid water in the vacuum chamber so that the desired pressure may be quickly achieved for sterilization.

[0006] Gaseous ion bombardment of surfaces in vacuo, commonly known as sputtering, is often used to remove adsorbed molecular species from surfaces and even to remove surface layers of the material itself. Although it is known that noble gas plasma sputtering may enhance outgassing in high and ultra high vacuum systems, the energy and momentum exchange mechanisms between the plasma and surface can also lead to material damage of the surface as well as emission of the adsorbed species. Clearly, sputtering with the attendant material damage is unacceptable for a sterilization process.

Summary of the Invention

[0007] According to the present invention there is provided a method which comprises evacuating ambient air from a volume surrounding a substrate to a first prede-

termined vacuum pressure; generating a residual gas plasma within the evacuated volume; and further evacuating the volume surrounding the substrate to a second predetermined pressure which is lower than the first predetermined vacuum pressure.

[0008] The present method can be used for sterilizing an object in which the item to be sterilized is first placed in a sealed chamber. A vacuum is then applied to the chamber. At a first predetermined vacuum pressure, a plasma is generated in the chamber. This first plasma enhances the drying of the item to be sterilized by transferring energy to any ice or water which may be present inside the sterilizer, thereby promoting vaporization with evacuation. Preferably, the plasma generated at the first pressure is terminated after a period of time which is proportional to the quantity of wetting agent present. The vacuum is further applied to reach a second predetermined vacuum pressure which is lower than the first pressure. Finally, a sterilizing gas can be injected into the chamber and radio frequency or other energy may be applied to generate a plasma with the sterilizing gas. After a sufficient time has elapsed for the item to be completely sterilized, the chamber is vented to atmospheric pressure and the article is removed.

[0009] The first predetermined vacuum pressure is preferably approximately 700 mTorr, and the second predetermined level is suitably approximately 300 mTorr. While the plasma is being generated, the vacuum can continue to be drawn until a pressure of approximately 300 mTorr has been reached. Alternatively, the RF generator may be engaged for a predetermined period of time, after which the RF generator is switched off while continuing to evacuate the chamber. When the second predetermined level has been reached, a reactive fluid such as hydrogen peroxide can be introduced into the sterilizer. The fluid is allowed to diffuse throughout the sterilizer for a number of minutes and then a further vacuum is drawn inside the sterilizer. When a vacuum of approximately 500 mTorr has been reached, the RF generator is then energized for a second time. In the plasma sterilization apparatus, the RF energy initiates a plasma of the remaining air molecules and molecules of the sterilizing gas transforming them into a number of highly reactive species. These reactive species attack any micro organism present in the chamber, inactivating them. After the RF generator has been engaged for a sufficient time and the sterilization process is complete, the RF generator is turned off and the vacuum is vented to atmospheric pressure through a suitable filter.

[0010] By aiding in the removal of water from the sterilizer, the plasma drying technique of the present invention advantageously reduces the time required to draw the required vacuum inside the sterilizer during the initial phase of the sterilization process. Indeed, if large amounts of water are present in the material to be sterilized, it may not be possible to draw the required vacuum within a reasonable time without using the plasma vacuum drying technique of the present invention. Consequently, the sterilization operation can be conducted in a much shorter time than otherwise possible by use of the method of the present invention.

[0011] The present method can also be employed as a plasma enhanced drying process which is of course useful in itself as a low-temperature evacuation dryer independent of the sterilization process. In accordance with this aspect of the present invention, ambient air in the volume surrounding a quantity of condensed material is evacuated to promote vaporization. The volume is evacuated to a first predetermined vacuum pressure which is substantially at or less than the equilibrium vapor pressure of the condensed material. Such a condensed material may for example be water or ice but may also be other volatile wetting agents. A residual gas plasma is excited in the evacuated volume to advantageously promote vaporization during evacuation or intermittently with evacuation. The method of plasma enhanced drying according to the present invention is particularly suited for removing quantities of water that would otherwise freeze to form ice, substantially slowing conventional evacuation drying methods.

Brief Description of the Figures

[0012] Figure 1 is a simplified diagram of a plasma sterilization apparatus.

[0013] Figure 2 is a block diagram of a plasma sterilization process.

[0014] Figure 3 is a vacuum profile of a plasma sterilization process.

[0015] Figure 4 is a plot of evacuation characteristics for various process loads.

[0016] Figure 5 is a block diagram of a plasma-enhanced vacuum drying process.

[0017] Figure 6 is a vacuum profile of a plasma-enhanced drying process.

[0018] Figure 7 is a vacuum profile of a plasma sterilization process using plasma-enhanced vacuum drying.

[0019] Figure 8 is a plot of evacuation performance for vacuum drying with and without plasma enhancement.

Detailed Description of the Preferred Embodiments

[0020] Referring to the drawings, Figure 1 depicts a plasma sterilizer in block diagram form generally at 10. The sterilizer 10 and its components and methods of use are described more fully in U.S. Patent 4,756,882, issued July 12, 1988 and assigned to the assignee of the present application. The sterilizer includes a vacuum and plasma chamber 11; a vacuum pump 12 connected to the electrode 11 by a valve 17; and a source of suitable reactive agent 13 such as hydrogen peroxide and connected to the vacuum chamber 11 by a line having a valve 19 therein. The sterilizer 10 also includes an RF generator 14 electrically connected to the plasma gen-

erator inside the vacuum chamber 11 by a suitable coupling 18, as well as a HEPA vent 15 connected to the vacuum chamber via a line and a valve 41. A process control logic 16, preferably a programmable computer, is connected to each of the components which are connected to the vacuum chamber 11. The process control logic 16 directs the operation of each of the components connected to the vacuum chamber at the appropriate time to effectuate the sterilization operation.

[0021] The vacuum chamber 11 contains the objects to be sterilized and is sufficiently gas-tight to support a vacuum of less than 300 mTorr (1 Torr = 133,3 N/m^2). Inside the chamber 11 is an RF antenna, or electrode array 27 to which the RF energy is supplied. In a preferred embodiment the electrode is arranged such that it is tubuler and equidistant from the chamber 11 wall to produce a symmetric RF electric field distribution. The electrode excites a plasma when an RF potential is applied by the RF generator 14 through the RF coupling 18. The RF coupling 18 may be a coaxial cable or other such waveguide capable of transmitting high power RF energy without significant impedance loss connected to an impedance matching device for the electrode.

[0022] The vacuum pump 12 and connecting valve 17 comprise a conventional arrangement well known in the art. The vacuum pump is typically a mechanical vacuum pump such as the rotary vane variety, capable of drawing a vacuum in the dry vacuum chamber 11 of approximately 300 mTorr or less within approximately 5 minutes of pumping. The valves 17 should have sufficient integrity to seal a vacuum of less than 300 mTorr without significant leakage. This requirement also applies to the other valves 19 and 41 present in the sterilizer.

[0023] The RF generator 14 is a conventional RF oscillator well known in the art, such as for example a solid-state or a vacuum tube oscillator with RF power amplification. The combination may generate RF energy in a frequency range of .1 MHz to 30 MHz and powers ranging from 50 W to 1500 W, and preferably a frequency of 13.56 MHz and power greater than 100 W.

[0024] Operation of the plasma sterilizer 10 without the plasma-enhanced drying technique of the present invention is described in schematic form in Figures 2 and 3, which respectively illustrate the sequence of operations employed by the sterilizer 10 and the corresponding pressure in chamber 11 as a function of time.

[0025] After the objects to be sterilized have been placed in the vacuum chamber and the chamber has been sealed, the process control logic 16 engages the vacuum pump 12 and valve 17 to evacuate the chamber to a pressure substantially at or below the equilibrium vapor pressure of the wetting agent, in this case water, as indicated by step 20. The pressure inside the vacuum chamber is tracked by the curve 21 in Figure 3. The pressure drop generally follows a non-linear path, often accurately described by first-order differential behavior. Under such circumstances, water or other such condensed solvent can act as a reservoir for residual vapor, limiting evacuation rate and possibly even base-pressure. Hence, the time required to attain a desired pressure is strongly dependent on the amount of water present on the objects to be sterilized, as indicated by the evacuation performance curves of Figure 4. Curve 52 shows the evacuation time for an empty chamber 11, while curves 58, 60 and 62 shows the evacuation performance for water bearing loads of 500 µl, 600 µl and 2500 µl respectively. In the present exemplary sterilization process, it is preferable to attain a chamber pressure of 300 mTorr within a 20 minute evacuation time span. Clearly the evacuation and drying time can become unacceptably long for even typical quantities of residual water, as would be encountered in hospital cleaning processes.

[0026] The process of vacuum vaporization causes heat transfer between the load, including the condensed water, and the portion of water undergoing vaporization (i.e. heat of vaporization). Since the load and condensed water are thermally isolated (e.g. in a vacuum) they cool as vaporization occurs during evacuation step 20. Cooling can cause the remaining water to transition the triple point and freeze, thus further slowing the evacuation step 20. This frozen water may be removed from the chamber only by the much slower process of sublimation, which significantly increases the time required to dry the load and evacuate the chamber to the required pressure. Consequently, a considerable length of time may be required to evacuate chamber 11 during the initial step 20.

[0027] When a desired vacuum threshold has been reached, the reactive sterilization agent 13 is injected during step 22. The injection of the sterilization agent during step 22 causes the pressure inside the vacuum chamber to rapidly rise; in the preferred embodiment, the pressure may rise to a level of approximately 5000 mTorr or more, as indicated by the curve 23 in Figure 3. The injection phase may take approximately 6 minutes. After the sterilization agent is injected into the chamber, it is allowed to diffuse completely and evenly throughout the vacuum chamber during step 24. This step typically lasts approximately 45 minutes, at which time the sterilization agent should be substantially in equilibrium inside the vacuum chamber 11.

[0028] At the end of the diffusion period, the process control logic 16 again engages the vacuum pump 12 and opens the valve 17 to pump down the chamber 11 to a vacuum of approximately 500 mTorr during step 26. The pressure inside the vacuum chamber rapidly drops to a value of 500 mTorr, as indicated by the curve 25 in Figure 3. When the pressure inside the chamber 11 has reached 500 mTorr, the process control logic 16 commands the RF generator 14 to generate an RF signal which is transmitted to the plasma generator. This action causes a gas plasma to be created inside the vacuum chamber during step 28. The components of the plasma are dissociation species of the reactive agent as well as molecules of residual gas remaining in the chamber 11.

[0029] Generating the plasma induces a brief rise in pressure, as indicated by the pressure immediately after step 28. The plasma generator remains energized for approximately 15 minutes during the sterilization step 30, and the plasma it creates can effectively destroy any pathogens present in the vacuum chamber 11. The sterilization process is conducted at an approximately constant pressure of 500 mTorr, as indicated by curve 31 in Figure 3.

[0030] After the sterilization process is complete, the chamber 11 is vented through the HEPA vent 15 during the venting step 32. This venting step is indicated by the curve 33 in Figure 3. A final vacuum application is undertaken to flush any remaining sterilizing agent which may be present in the chamber. A vacuum of approximately 1 Torr is quickly drawn, as indicated by curve 35 in Figure 3. Following this step, the vacuum chamber is again vented to atmospheric pressure through the HEPA vent 15, as indicated by the curve 37, and the sterilized articles are removed from the chamber.

[0031] A preferred method of plasma-enhanced drying according to the present invention is disclosed in the context of the aforementioned sterilization method, and described with respect to Figures 5 and 6. It is understood that in all other respects, the operation of the sterilizer 10 described above is the same. It is also understood that the plasma enhanced drying can be applied to a wide variety of vacuum applications in addition to the plasma sterilization described.

[0032] After the articles to be sterilized are introduced into the chamber 11 and the chamber 11 is sealed, the vacuum pump 12 and valve 17 are energized to evacuate the chamber 11 to a predetermined pressure, in this case a pressure of about 700 mTorr, as indicated by step 40 in Figure 5. The chamber pressure generally behaves as shown by curve 50 of Figure 6. When the desired pressure has been reached, the process control logic 16 transmits a command to the RF generator 14 to energize the electrode within the chamber 11, as indicated by step 42. This action causes a gas plasma to be created inside the chamber 11 comprised of residual gas species. It will be appreciated that other chamber and electrode configurations as well as RF generators may render appreciable variation in the pressure range over which a plasma may be supported. Moreover, various other conditions such as solvent content, process time, temperature and equilibrium vapor pressure will determine the conditions under which plasma enhancement is most desirable. In the present embodiments herein disclosed the plasma tranfers energy to the condensed water thereby aiding the vaporization process. While such energy transfer serves to increase the water temperature, it is preferred that the plasma does not chemically or physically alter the load surfaces as is commonly encountered in a sputtering or plasma chemical process. Thus, the plasma should preferably have average energy and momentum characteristics sufficient to impart heat energy to the condensed water, while leaving the load surface molecules and molecular bonds intact. In the present embodiment, the plasma is usually generated when the chamber pressure is approximately 700 mTorr, whereas at higher pressures such generation may be limited due to the impedance between the chamber 11 and the RF generator 14. Furthermore, plasma generation at about 700 mTorr substantially minimizes the total process time required to reach a pre-sterilization pressure of 300 mTorr.

[0033] The creation of the residual gas plasma causes the pressure to rise inside the chamber, indicating enhanced vapor generation, as shown by the cusp 52 of curve section 51 in figure 6. While plasma is being generated, the vacuum pump 12 remains engaged to further evacuate the chamber concurrent with this period of enhanced vapor generation as indicated by step 44. After a period of time, in this case approximately 5-15 minutes of operation, the plasma generator is turned off, step 46, and the evacuation continues during step 48. In this exemplary embodiment, evacuation continues until a pressure of approximately 300 mTorr is attained. As indicated by a second cusp 53 in curve 51 of Figure 6, evacuation proceeds at a higher rate upon quenching the residual gas plasma, indicating a reduced rate of vaporization. In the present preferred embodiment the period over which the plasma enhanced evacuation 44 operates is determined by a maximum desirable evacuation time of 20 minutes to reach a desired pressure of 300 mTorr. It will be appreciated that there are many variations in the manner in which the plasma-enhanced evacuation 44 is implemented in a drying or sterilization process. In the present exemplary embodiment, the plasma enhanced evacuation 44 is initiated at a predetermined pressure and may be terminated after a period of time or upon reaching a second predetermined pressure. A vacuum profile of an entire sterilization process utilizing plasma-enhanced drying is shown in Figure 7, where process step 20 is replaced by process steps 40-48. After the evacuation and drying process steps 40-48, the remainder of the sterilization process is substantially similar to the aforementioned sterilization process steps. As indicated in Figure 7, plasma-enhanced drying is conveniently incorporated into the initial evacuation phase, requiring no additional material or construction

[0034] As shown in Figure 4, the plasma-enhanced drying technique of the present invention substantially decreases the time required for the vacuum pump 12 to reduce the chamber pressure required for the operation of the sterilizer 10. Performance curves 54 and 56 represent the chamber pressure as a function of time during evacuation for representative loads with and without a plasma-enhanced vacuum drying process respectively. Figure 8 is a plot of evacuation performance for evacuation after plasma-enhancement 82 and without plasma enhancement 80 as the chamber pressure approaches a nominal final pressure of about 300 mTorr. Indeed, as shown in Figure 8, the evacuation rate after plasma ex-

citation, curve 82, is considerably higher than by vacuum evacuation alone, curve 80. A comparison of these data indicates that the performance gain realized through use of plasma-enhanced drying is substantial. The present invention achieves this result because the plasma generated during step 42 transfers energy from the RF generator to the liquid present in the chamber. The energy transferred to the liquid promotes vaporization and hence speeds the drying process.

[0035] This gain in performance represents an increase in the effective pump efficiency during the initial evacuation/drying stages 40-48, and results in faster, more consistent operation of the sterilizer 10. It has been found that plasma-enhanced drying is most useful when the time taken by the vacuum pump 12 to reach a pressure of 1 Torr during stage 40 is between 5 and 9 minutes. If this time is less than 5 minutes, the items in the chamber are already reasonably dry and plasma-enhanced drying may not greatly speed up the drying process. If, on the other hand, this time is greater than 9 minutes, the items in the chamber may be too wet to process by the sterilizer as presently constituted. The values disclosed herein are valid for the particular configuration of the current embodiment. However, these values may differ substantially to maximize the benefit of the invention for other configurations. It has been determined in practice that application of the plasma for a duration of time proportional to the wetness of the objects in the chamber results in optimum drying of the materials placed therein. However, durations longer than 15 minutes have been found to decrease the chance of reaching the desired pre-sterilization pressure of 300 mTorr inside the chamber 11 within the desired 20 minute duration (the maximum time presently allowed in a commercial embodiment of the sterilizer 10) of initiation of the vacuum pumping step 40.

[0036] An additional advantage of the present invention is that plasma enhanced drying may be applied to the full complement of load material types compatible with the plasma sterilizing process without perceptible physical or chemical damage. Finally, a residual gas or other such plasma intended for enhancing vaporization can be energetically tailored by varying gas species and applied RF power to render an efficient energy transfer to a variety of wetting agents. It is particularly advantageous for applications requiring low temperature vacuum drying, and furthermore is not limited to aqueous wetting agents.

[0037] While the present invention has been described with respect to use in a sterilization system, it should, of course, be understood that plasma-enhanced vacuum drying can be applied to other systems in which it is desirable to improve drying efficiency for objects in vacuum. In this regard the invention may be useful as simply a dryer if the load to be dried includes at least one milliliter of water.

Claims

1. A method which comprises:

   evacuating ambient air from a volume surrounding a substrate to a first predetermined vacuum pressure;
   generating a residual gas plasma within the evacuated volume; and
   further evacuating the volume surrounding the substrate to a second predetermined pressure which is lower than the first predetermined vacuum pressure.

2. The method of claim 1 wherein the first predetermined pressure in the evacuated volume is approximately 700 mTorr.

3. The method of claim 1 or claim 2, wherein the plasma is excited at or below approximately the equilibrium vapour pressure of a vapourisable component of the substrate.

4. The method of any one of claims 1 to 3, wherein the duration of plasma generation is shorter than 15 minutes.

5. The method of any one of claims 1 to 4, wherein the substrate is a condensed material and the generation of the plasma promotes vaporisation of the material.

6. The method of claim 5, wherein the duration of plasma generation is proportional to the quantity of the condensed material to be vapourised.

7. The method of any one of claims 1 to 4, wherein the substrate is a wet article and wherein the article is removed from the volume without introducing any fluid into the volume other than the fluid which relieves the vacuum.

8. The method of claim 7, wherein the plasma is quenched when the pressure in the volume is about 600 mTorr.

9. The method of any one of claims 1 to 4, wherein the substrate is an article which includes at least one milliliter of water and wherein plasma generation and evacuation are continued until a desired quantity of water is removed from the article.

10. The method of any one of claims 7 to 9, wherein the generation of the plasma is continued until the evacuation rate increases, as an indication that the article is substantially dry.

11. The method of any one of claims 1 to 4, wherein the

substrate is an article to be sterilised and a sterilising gas is introduced into said volume at said second predetermined vacuum pressure.

12. The method of claim 11, wherein generation of the plasma is terminated after a period of time which is proportional to the wetness of the article.

13. The method of claim 11 or claim 12, wherein said second pressure is about 300 mTorr.

14. The method of any one of claims 11 to 13, including generating a second gas plasma containing the sterilizing gas.

15. The method of claim 14, wherein the second gas plasma is generated after the gas has permeated throughout the volume and the article being sterilized.

16. The method of claim 14 or claim 15, wherein the second gas plasma is generated at a third pressure at a level, preferably of about 500 mTorr, between the first and second pressures.

Patentansprüche

1. Verfahren, welches die folgenden Schritte umfaßt:

- Evakuieren von Umgebungsluft aus einem Volumen, das ein Substrat umgibt, bis zu einem ersten vorbestimmten Vakuumdruck,
- Erzeugen eines Restgasplasmas in dem evakuierten Volumen und
- weiteres Evakuieren des Volumens, welches das Substrat umgibt, bis zu einem zweiten vorbestimmten Druck, welcher geringer als der erste vorbestimmte Vakuumdruck ist.

2. Verfahren nach Anspruch 1, bei dem der erste vorbestimmte Druck in dem evakuierten Volumen ungefähr 700 mTorr beträgt.

3. Verfahren nach Anspruch 1 oder 2, bei dem das Plasma ungefähr bei dem Gleichgewichtsdampfdruck einer verdampfbaren Komponente des Substrats oder darunter erregt wird.

4. Verfahren nach einem der Ansprüche 1 bis 3, bei dem die Dauer der Plasmaerzeugung kürzer als 15 Minuten ist.

5. Verfahren nach einem der Ansprüche 1 bis 4, bei dem das Substrat eine kondensierte Substanz ist und das Erzeugen des Plasmas das Verdampfen der Substanz fördert.

6. Verfahren nach Anspruch 5, bei dem die Dauer der Plasmaerzeugung proportional zu der Menge der zu verdampfenden kondensierten Substanz ist.

7. Verfahren nach einem der Ansprüche 1 bis 4, bei dem das Substrat ein nasser Artikel ist und bei dem der Artikel aus dem Volumen entfernt wird, ohne außer dem Fluid, welches das Vakuum verringert, ein anderes Fluid in das Volumen einzuleiten.

8. Verfahren nach Anspruch 7, bei dem das Plasma gelöscht wird, wenn der Druck in dem Volumen ungefähr 600 mTorr beträgt.

9. Verfahren nach einem der Ansprüche 1 bis 4, bei dem das Substrat ein Artikel ist, der zumindest 1 ml Wasser enthält, und bei dem die Plasmaerzeugung und Evakuierung fortgesetzt werden, bis eine gewünschte Menge an Wasser von dem Artikel entfernt ist.

10. Verfahren nach einem der Ansprüche 7 bis 9, bei dem die Erzeugung des Plasmas fortgesetzt wird, bis die Evakuierungsrate als Indiz dafür, daß der Artikel im wesentlichen trokken ist, wächst.

11. Verfahren nach einem der Ansprüche 1 bis 4, bei dem das Substrat ein zu sterilisierender Artikel ist und ein sterilisierendes Gas in das Volumen bei dem zweiten vorbestimmten Vakuumdruck eingeleitet wird.

12. Verfahren nach Anspruch 11, bei dem das Erzeugen des Plasmas nach einer Zeitdauer beendet wird, welche proportional zu der Nässe des Artikels ist.

13. Verfahren nach Anspruch 11 oder Anspruch 12, bei dem der zweite Druck ungefähr 300 mTorr beträgt.

14. Verfahren nach einem der Ansprüche 11 bis 13, welches das Erzeugen eines zweiten Gasplasmas, das sterilisierendes Gas enthält, umfaßt.

15. Verfahren nach Anspruch 14, bei dem das zweite Gasplasma erzeugt wird, nachdem das Gas sich über das Volumen und den Artikel, der sterilisiert wird, verteilt hat.

16. Verfahren nach Anspruch 14 oder Anspruch 15, bei dem das zweite Gasplasma bei einem dritten Druck auf einem Niveau zwischen dem ersten und dem zweiten Druck erzeugt wird, vorzugsweise bei ungefähr 500 mTorr.

Revendications

1. Procédé qui comprend :

   - l'évacuation d'air ambiant d'un volume entourant un substrat à une première pression sous vide prédéterminée ;
   - la production d'un plasma de gaz résiduel à l'intérieur du volume évacué ; et
   - l'évacuation en outre du volume entourant le substrat à une deuxième pression prédéterminée qui est inférieure à la première pression sous vide prédéterminée.

2. Procédé selon la revendication 1, dans lequel la première pression prédéterminée dans le volume évacué est approximativement de 700 mTorr.

3. Procédé selon la revendication 1 ou 2, dans lequel le plasma est excité à ou en dessous approximativement de la pression de vapeur d'équilibre d'un composant vaporisable du substrat.

4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel la durée de production de plasma est inférieure à 15 minutes.

5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le substrat est un élément condensé et où la production du plasma favorise la vaporisation de l'élément.

6. Procédé selon la revendication 5, dans lequel la durée de la production de plasma est proportionnelle à la quantité de l'élément condensé à vaporiser.

7. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le substrat est un article humide et dans lequel l'article est retiré du volume sans introduire dans le volume d'autre fluide que le fluide qui libère le vide.

8. Procédé selon la revendication 7, dans lequel le plasma est refroidi rapidement lorsque la pression dans le volume est de 600 mTorr environ.

9. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le substrat est un article qui comprend au moins un millilitre d'eau et dans lequel la production de plasma et l'évacuation continuent jusqu'à ce qu'une quantité souhaitée d'eau soit enlevée de l'article.

10. Procédé selon l'une quelconque des revendications 7 à 9, dans lequel la production du plasma continue jusqu'à l'augmentation de la vitesse d'évacuation servant d'indication au fait que l'article est pratiquement sec.

11. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le substrat est un article à stériliser et où un gaz stérilisant est introduit dans ledit volume à ladite deuxième pression sous vide prédéterminée.

12. Procédé selon la revendication 11, dans lequel la production du plasma est terminée après une période de temps qui est proportionnelle à l'humidité de l'article.

13. Procédé selon la revendication 11 ou 12, dans lequel ladite deuxième pression est de 300 mTorr environ.

14. Procédé selon l'une quelconque des revendications 11 à 13, comprenant la production d'un second plasma de gaz contenant le gaz stérilisant.

15. Procédé selon la revendication 14, dans lequel le second plasma de gaz est produit une fois que le gaz a traversé la totalité du volume, et que l'article est stérilisé.

16. Procédé selon la revendication 14 ou 15, dans lequel le second plasma de gaz est produit à un troisième niveau de pression, de préférence de 500 mTorr environ, compris entre les première et deuxième pressions.

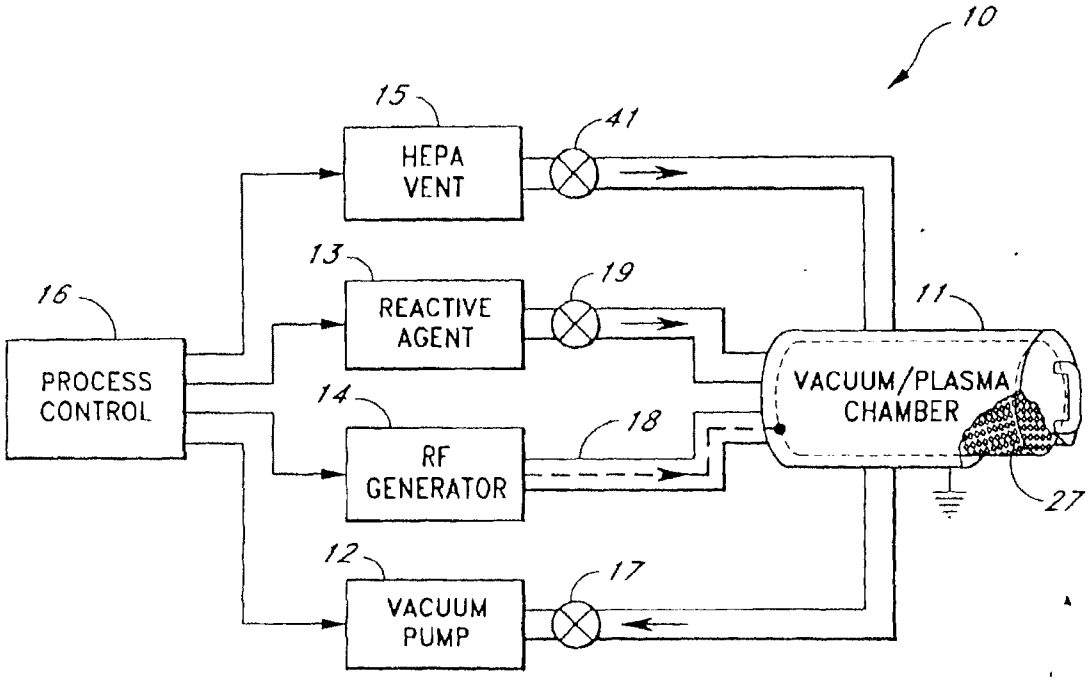

FIG. 1

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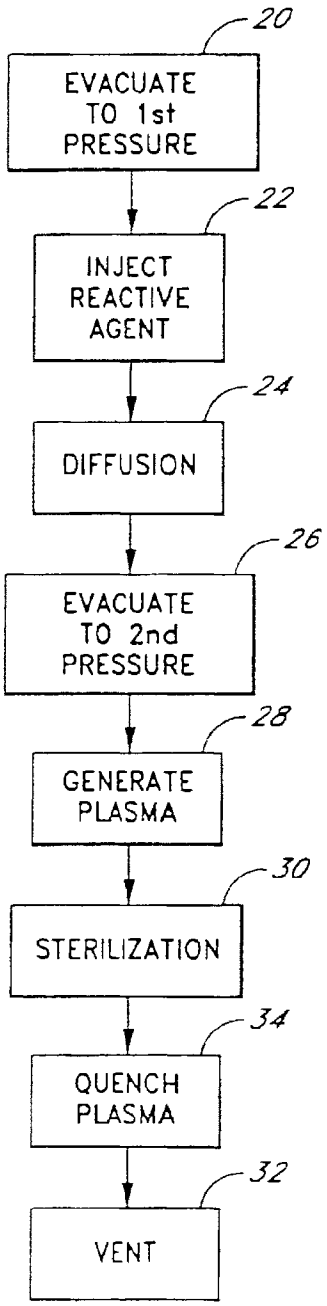

FIG. 2

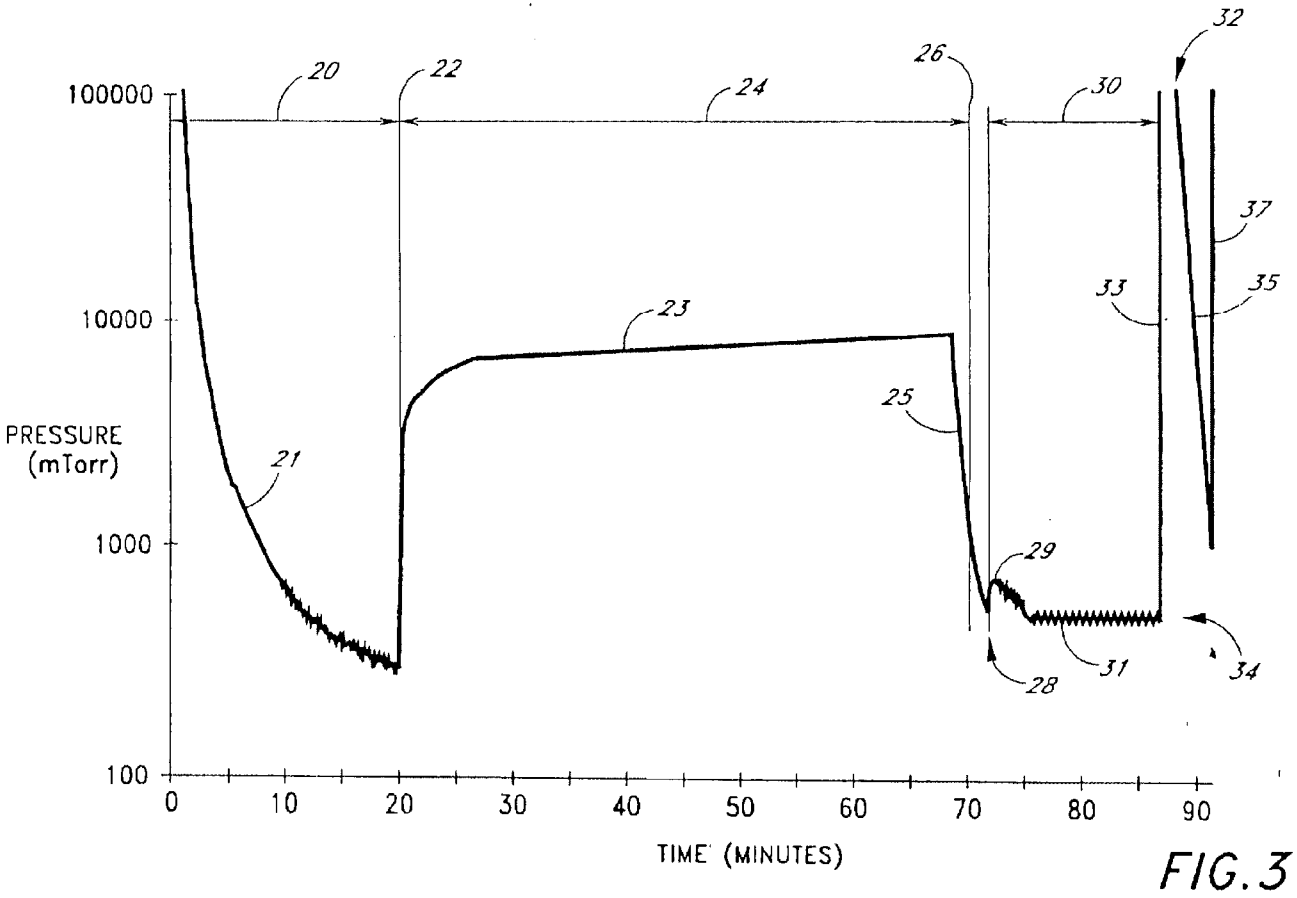

FIG. 3

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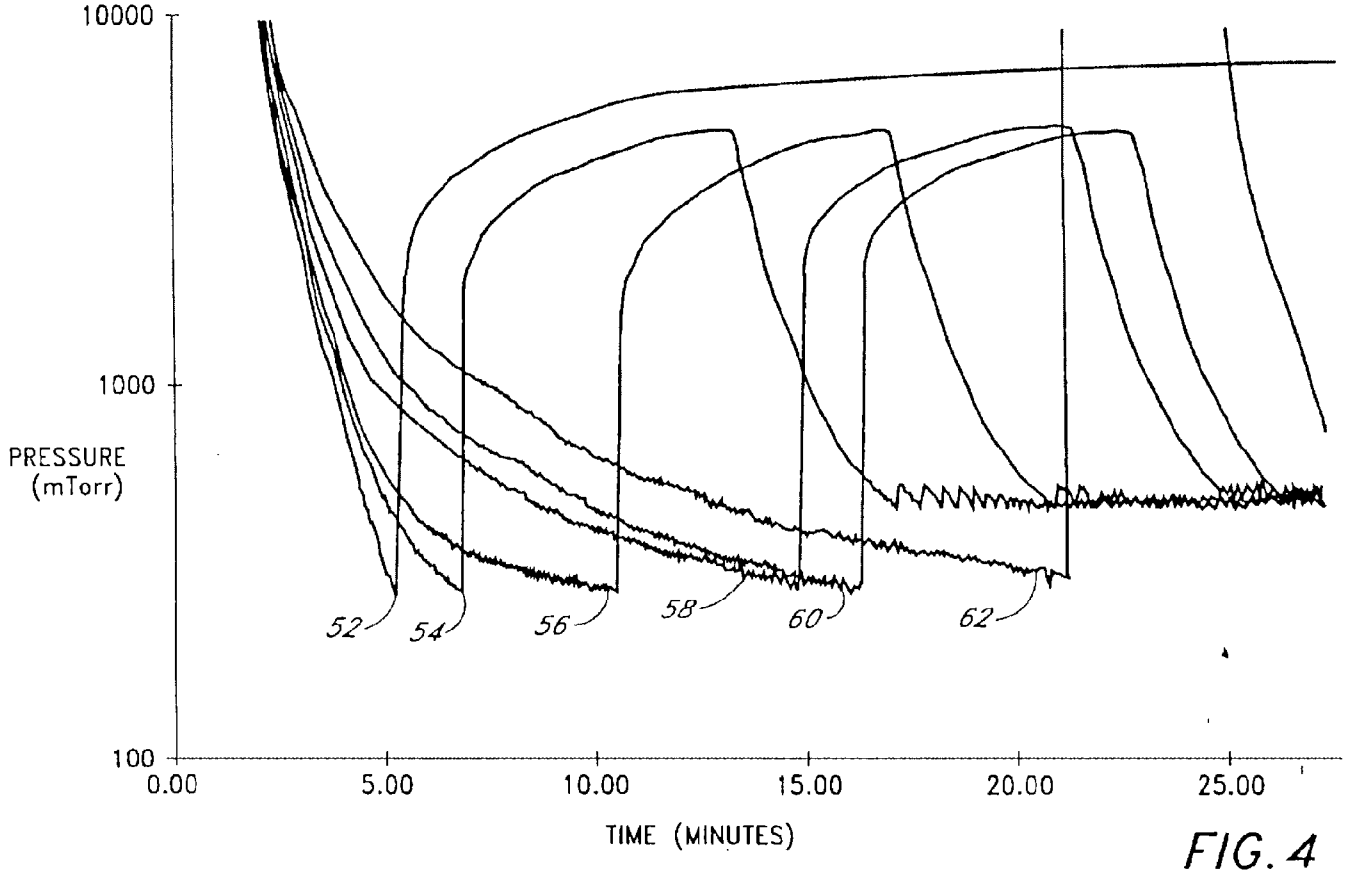

FIG. 4

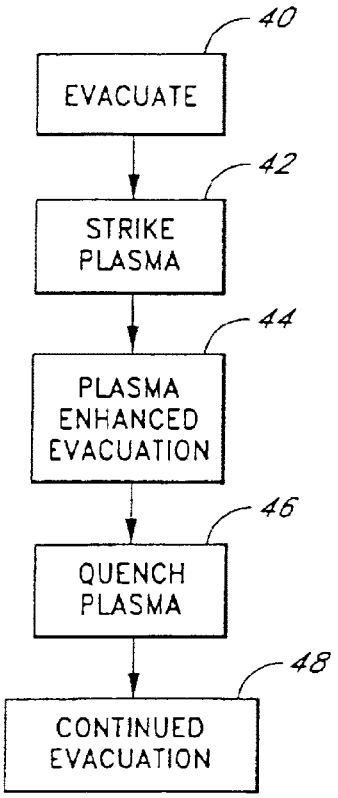

FIG. 5

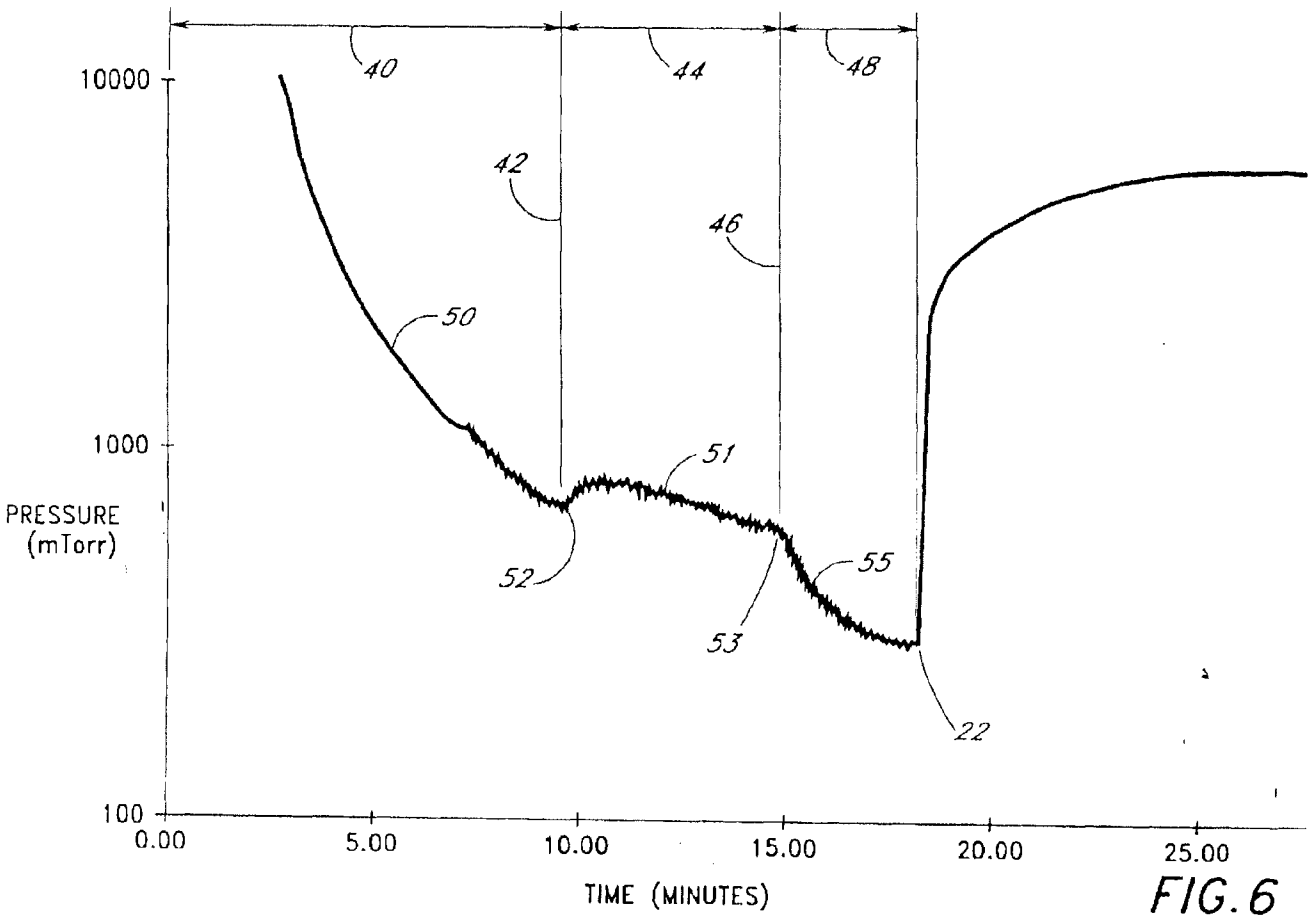

FIG. 6

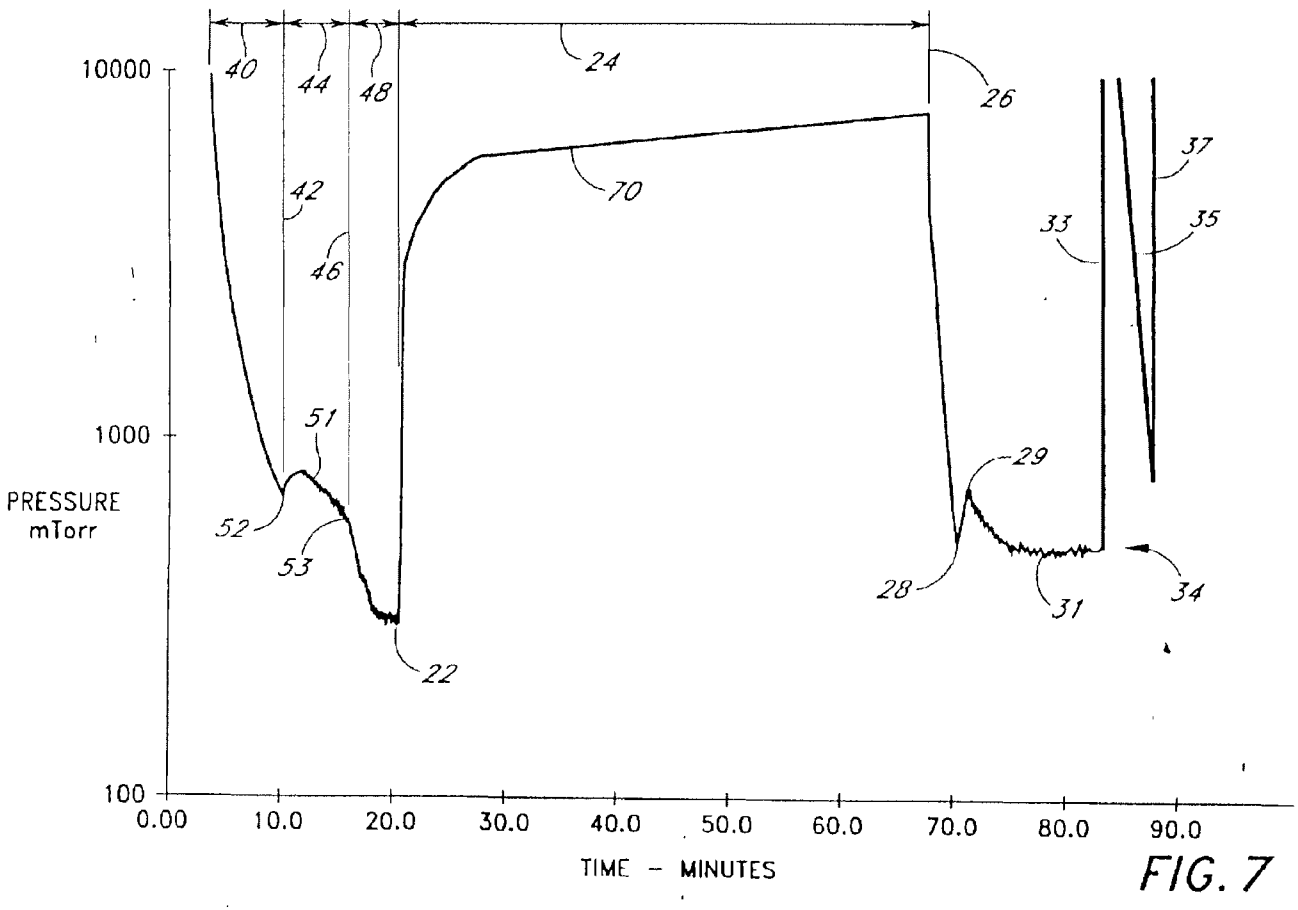

FIG. 7

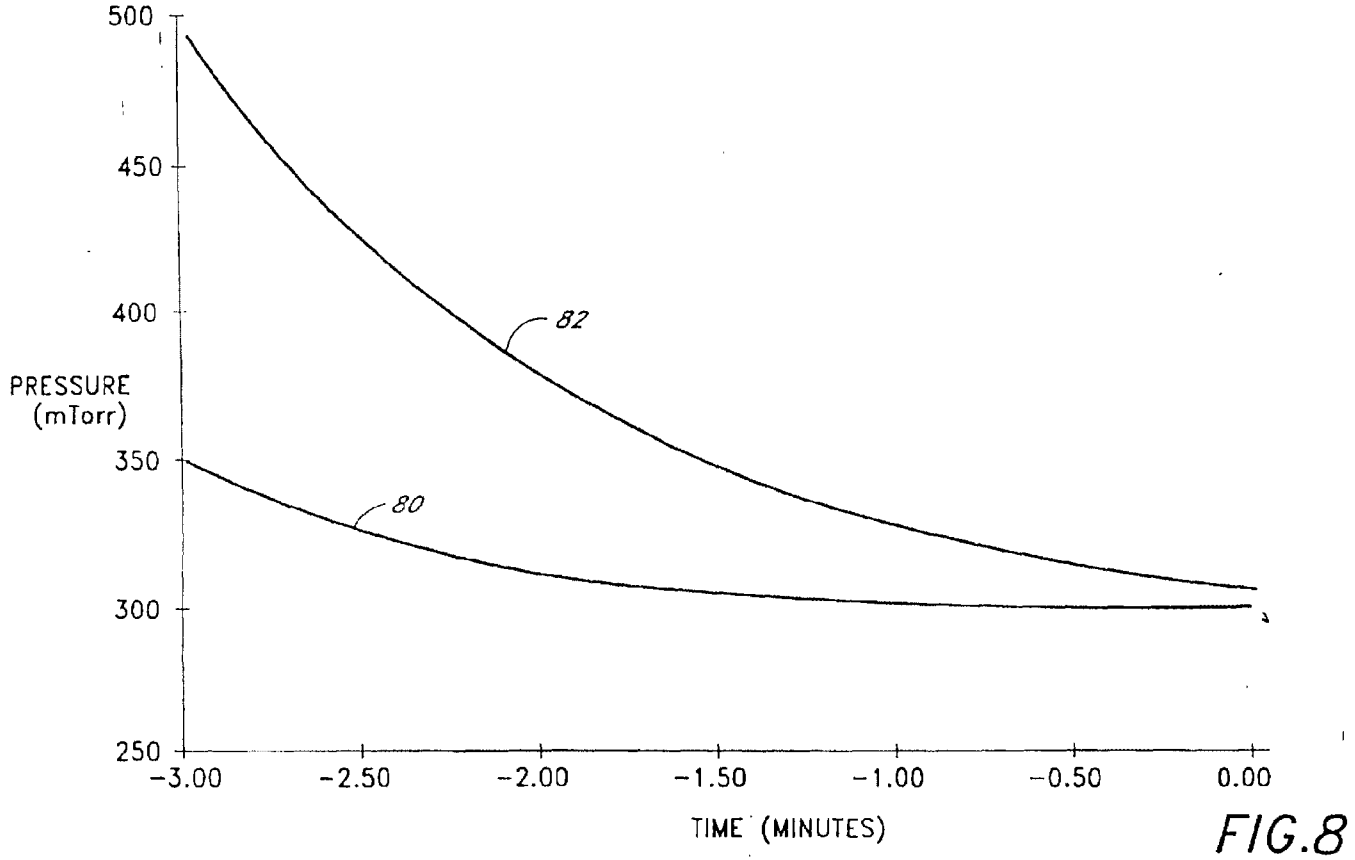

FIG.8

United States Patent [19]

Jacobs et al.

[11] **Patent Number: 4,643,876**

[45] **Date of Patent: Feb. 17, 1987**

[54] **HYDROGEN PEROXIDE PLASMA STERILIZATION SYSTEM**

[75] Inventors: **Paul T. Jacobs; Szu-Min Lin,** both of Arlington, Tex.

[73] Assignee: **Surgikos, Inc.,** Arlington, Tex.

[21] Appl. No.: **747,209**

[22] Filed: **Jun. 21, 1985**

[51] **Int. Cl.**[4] **A61L 2/14;** A61L 2/18

[52] **U.S. Cl.** **422/23;** 422/28

[58] **Field of Search** 422/22, 28, 33, 23, 422/32; 424/130; 361/230; 250/455.1

[56] **References Cited**

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3,701,628	10/1972	Ashman	422/23
3,851,436	12/1974	Fraser et al.	422/22 X
4,169,123	9/1979	Moore et al.	422/28 X
4,169,124	9/1979	Forstrom et al.	422/28 X
4,207,286	6/1980	Gut Boucher	422/28 X
4,230,663	10/1980	Forstrom et al.	422/28 X
4,289,728	9/1981	Peel et al.	422/24
4,321,232	3/1982	Bithell	422/22 X
4,348,357	9/1982	Bithell	422/22
4,366,125	12/1982	Kodera et al.	422/24 X

FOREIGN PATENT DOCUMENTS

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Venugopalan, M. & A. Shih, *Plasma Chemistry and Plasma Processing,* vol. 1, (2), pp. 191–199 (1981).

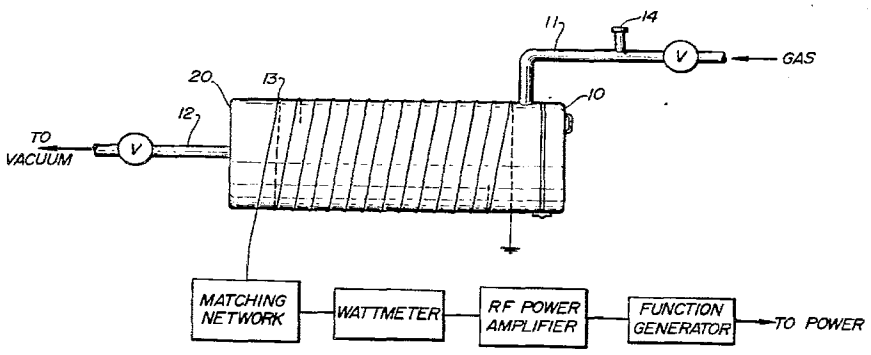
Boucher, R. M. G., "State of the Art in Gas Plasma Sterilization, *MD & DI,* Feb. 1985, pp. 51–56.

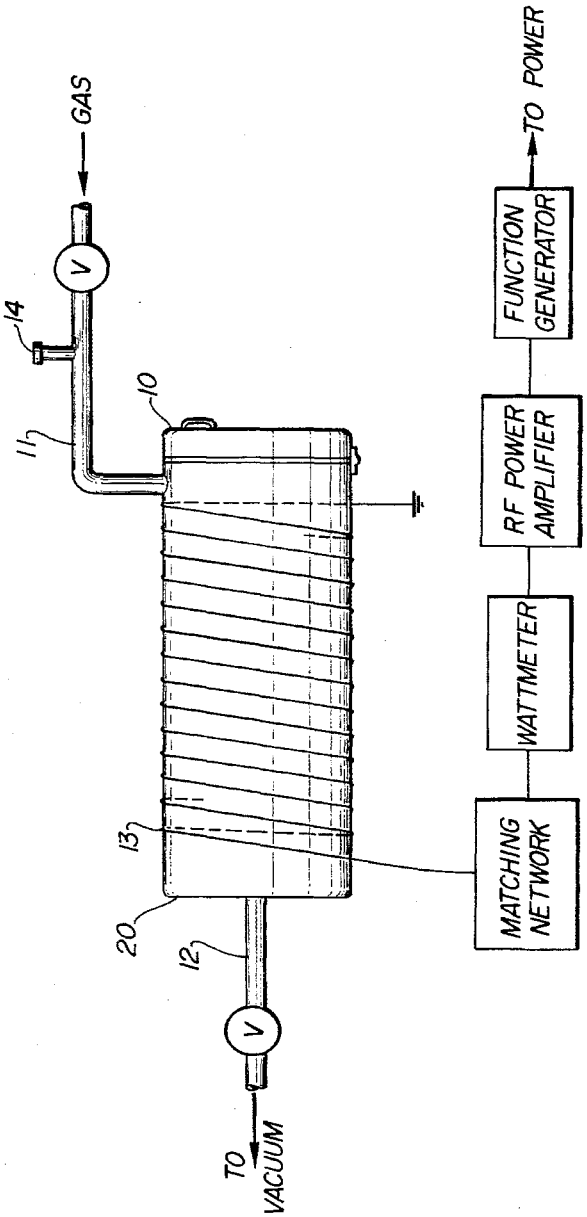
Primary Examiner—David L. Lacey
Assistant Examiner—Jill Johnston
Attorney, Agent, or Firm—Michael Q. Tatlow

[57] **ABSTRACT**

A plasma sterilization process which employs hydrogen peroxide vapor as the precursor for the active species generated during the plasma generation cycle and employs a pre-treatment cycle prior to the plasma generation cycle.

9 Claims, 1 Drawing Figure





HYDROGEN PEROXIDE PLASMA STERILIZATION SYSTEM

FIELD OF THE INVENTION

The present invention relates to the sterilization of articles in gaseous plasmas and, more particularly, to the use of hydrogen peroxide in the plasma to kill microorganisms on surfaces and objects such as medical instruments.

BACKGROUND OF THE INVENTION

Various methods of sterilization have been used in the past for the sterilization of different types of articles including disposable and reusable medical equipment, foods and food containers. Sterilization by steam or by dry heat has been extensively used in the past. Sterilization by heat, either wet or dry, is not useful to sterilize materials that are adversely effected by such heat or steam. Ethylene oxide gas has also been used but suffers from the drawback that it may leave toxic residues on the articles to be sterilized, which may have adverse effects, particularly on patients who come into contact with such articles. The extended aeration cycles required to remove residual ethylene oxide from some sterilized items also makes ethylene oxide sterilization excessively long.

The use of plasma to sterilize containers was suggested in U.S. Pat. No. 3,383,163. Plasma is an ionized body of gas which may be generated by the application of power from different sources. The ionized gas will contact microorganisms on the surfaces of the items to be sterilized and effectively destroy the microorganisms.

U.S. Pat. No. 3,851,436 discloses the use of radio frequency generators to produce such plasmas from inert gases such as argon, helium or xenon. U.S. Pat. No. 3,948,601 also discloses the use of a radio frequency generated plasma which ionizes argon, nitrogen, oxygen, helium or xenon. The processes set forth in the above-mentioned patent require the direct contact of the plasma on the surface of the product to be sterilized, which product is not packaged at the time of sterilization. The commercial sterilization procedures used to sterilize disposable medical goods generally require that the medical goods be packaged prior to sterilization because of the possibility of contamination by microorganisms if the products are packaged subsequent to sterilization.

U.S. Pat. No. 4,207,286 discloses a gas plasma sterilization system which uses glutaraldehyde as the gas which is used in a plasma sterilization system. The item to be sterilized is placed in an unsealed container or package and then subjected to the sterilization cycle. When the sterilization cycle is completed, the containers are sealed. The container must be opened during the sterilization cycle to allow the gas to flow into the interior of the package or container to allow contact of the gas with any microorganisms which may be on the surface of the item to be sterilized.

U.S. Pat. No. 4,321,232 discloses a plasma sterilization system in which the item to be sterilized is placed in a package made from a porous material. The gas used in the process is oxygen, and it is indicated that sterilization can be accomplished through the porous packaging within 60 minutes.

U.S. Pat. No. 4,348,357 discloses a plasma sterilization procedure using oxygen, nitrogen, helium, argon or freon as the gas. The pressure is pulsed, that is, the pressure within the container is alternately increased or decreased in a cyclic fashion. In addition, the plasma may be de-energized during the pressure fall portion of the pressure cycle to reduce the heating effect on the article to be sterilized.

Japanese Application Disclosure No. 103460-1983 discloses a plasma sterilization process in which the gas consists of nitrous oxide or a mixture of nitrous oxide with another gas such as oxygen, helium or argon. It is stated that the process can be used to sterilize through packaging and, particularly, packaging which is made from polyethylenetrifluoride or polyethylenetetrafluoride resins or paper coated with these materials.

Japanese Application Disclosure No. 162276-1983 discloses the sterilization of foods using nitrogen oxide gas or mixtures of nitrogen oxide gas and ozone in a plasma.

All of these prior plasma sterilization systems have not been put into wide commercial use because of the limitations on the time required to effect sterilization, the temperature obtained in the sterilization process or the particular requirements of some of the processes that would require post-sterilization packaging.

Hydrogen peroxide has been known to have bactericidal properties and has been used in solutions to kill bacteria on various surfaces. U.S. Pat. No. 4,437,567 discloses the use of aqueous hydrogen peroxide solutions at low concentrations, i.e., 0.01% to 0.10% by weight, to sterilize packaged products for medical or surgical use. At room temperature sterilization requires at least 15 days. At higher temperatures sterilization can be accomplished in approximately one day.

U.S. Pat. Nos. 4,169,123; 4,169,124 and 4,230,663 disclose the use of hydrogen peroxide in the gas phase at temperatures below 80° C. and concentrations of 0.10 to 75 mg H_2O_2 vapor/L for sterilization and disinfection. Depending upon concentration and temperature, sterilization times are reported to vary from 30 minutes to four hours.

The use of ultraviolet radiation with hydrogen peroxide for improved antimicrobial activity has been disclosed in U.S. Pat. Nos. 4,366,125 and 4,289,728. The lack of penetration by UV radiation below the surface of the object to be sterilized limits the application of this effect to clear solutions or surfaces that can be directly exposed to the radiation. Objects in an opaque package, or objects in a clear package that absorbs UV light could not be sterilized.

Food packaging materials sterilized with hydrogen peroxide contain hydrogen peroxide residuals that must be removed from the materials prior to use. U.S. Pat. No. 4,368,081 discloses the use of antioxidants or reducing agents such as L-ascorbic acid to remove residual hydrogen peroxide from a sterilized food package.

The combination of hydrogen peroxide and plasma has heretofore not been used for sterilization.

SUMMARY OF THE INVENTION

The present invention employs the use of hydrogen peroxide as a precursor of the active species in a low temperature plasma sterilization system. The sterilization process provides an initial contact of the material to be sterilized with the hydrogen peroxide before the generation of plasma at a power level sufficient to achieve sterilization. It has been found that the use of an initial contact period with hydrogen peroxide signifi-

cantly decreases the total time and power required to accomplish sterilization with low temperature plasma. In addition, the use of the pre-treatment with hydrogen peroxide also allows sterilization to occur within many different types of packaging material.

Since the decomposition products of H_2O_2 in plasma include water, oxygen and hydrogen, no toxic residues remain on the sterilized items after plasma treatment.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** shows a schematic drawing of the plasma reactor used in the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The process of the present invention differs from prior art gas plasma sterilization processes in two important aspects. The first is the use of hydrogen peroxide vapor as a precursor of the reactive species rather than an inert gas such as oxygen, nitrogen, etc. The second major difference is the use of a pre-treatment time where the hydrogen peroxide vapor is allowed to contact the article to be sterilized prior to the application of the power at levels required to effect sterilization. In the present process, the article to be sterilized is placed in the plasma chamber, the chamber is closed and vacuum is drawn on the chamber to remove the gas that is in the chamber. An aqueous solution of hydrogen peroxide is then injected into the chamber raising the pressure in the chamber to a level of approximately 0.1 to 10 Torr. The hydrogen peroxide remains in the chamber for a period of sufficient duration to allow the hydrogen peroxide to come in intimate contact with the item to be sterilized, normally five to 30 minutes, before the plasma is generated at a power level sufficient to achieve sterilization. The power then remains on for up to 50 minutes to allow complete sterilization, although sterilization can be effective in periods as short as 5 minutes from initial plasma generation, depending on the concentration of the hydrogen peroxide in the chamber and the power that is applied to the chamber. It is also possible to carry out the pre-treatment step outside of the plasma chamber. The object to be sterilized could be placed in a vacuum chamber in which plasma could not be generated. The chamber would be evacuated and the hydrogen peroxide injected into the vacuum chamber. The object to be sterilized would be kept in the vacuum chamber for the desired pre-treatment time and then placed in a plasma chamber and the plasma generated.

The materials or objects to be sterilized by the present process may be packaged in various commonly employed packaging materials used for sterilized products. The preferred materials are spunbonded polyethylene packaging material commonly available under the trademark "TYVEK" or composites of "TYVEK" with a polyethylene terephthalate packaging material commonly available under the trademark "MYLAR". Other similar packaging materials may also be employed. Paper packaging materials may also be used. With paper packaging, longer processing times may be required to achieve sterilization because of possible interactions of hydrogen peroxide and other reactive species with paper.

Plasmas are normally generated by electrical discharges in gases. Plasmas generated at atmospheric pressure or at higher pressures are called "arcs" or high temperature plasma and may involve temperatures in excess of 1000° C. Plasmas generated at reduced pressures, i.e., 10^{-3} to 10^{2} Torr, are called "glow discharge" or low temperature plasma and involve temperatures of a few tenths to a few hundred degrees Centigrade. The low temperature plasma of the present invention is preferably generated at pressures of less than 10 Torr and generally involves temperatures of less than 100° C.

When used in the present application, the term "plasma" is intended to include any portion of the gas or vapors which contains electrons, ions, free radicals, dissociated and/or excited atoms or molecules produced as a result of the applied electrical field including any accompanying radiation which might be produced. The applied field may cover a broad frequency range, however, a radio frequency is commonly used.

Plasma sterilization is usually carried out in a chamber **20** as illustrated in FIG. **1**. The chamber includes a door or opening **10** through which articles to be sterilized can be introduced. The chamber also includes an inlet **11** to inject gas into the chamber and a line **12** connected to a vacuum pump to enable the chamber to be evacuated. There is a port **14** in the gas inlet line **11** to introduce the aqueous solution of hydrogen peroxide into the chamber **20**. The chamber includes radio frequency electrodes **13** which can be wound around the entire chamber or placed on the sides of the chamber and a radio frequency generator to generate the requisite radio frequency signal. Coupling of RF power from the output of the matching network to the discharge is accomplished by means of either a coil or a set of capacitor plates. These two forms of coupling are referred to as inductive and capacitive coupling, respectively. Various control devices which control the generation of the radio frequency signal including function generators, RF power amplifers, wattmeter and matching network are also employed and are illustrated in FIG. **1**. The matching network matches the input of the amplified RF signal into the coil. The plasma is generated by evacuating the chamber, introducing a gas or vaporized liquid and turning on the power to the electrodes. The plasma is generated in the present process in the same manner as in the previously-mentioned prior art plasma sterilization system.

The plasma used in the present process may be continuous or pulsed, that is, the power may be applied continuously to the plasma or the plasma may be pulsed by activating the power in a cyclic manner while maintaining the pressure of the plasma constant. The use of a pulsed plasma prevents the overheating of the gas within the chamber as well as preventing the overheating of objects that may be desired to be sterilized. The pulsed sequence may vary over a fairly wide range without the danger of overheating any object. Generally, the pulsing sequence is the ratio of power on to power off. For example with a 1:2 pulsed plasma, power would be applied for 0.5 milliseconds and then turned off and applied again 1.0 milliseconds later. The particular pulsing sequence is not critical. The power may be applied for periods measured in minutes rather than seconds. The purpose of pulsing is to avoid overheating of the objects to be sterilized, and any pulsing sequence that avoids overheating and sterilizes in a reasonable time period may be employed. Continuous plasma may be employed if there is little danger of overheating the item to be sterilized.

As previously indicated, in the present process the hydrogen peroxide is injected into the plasma chamber prior to the application of the power necessary to steril-

ize. The hydrogen peroxide is injected in the form of an aqueous solution of hydrogen peroxide containing from about 3% to 20% by weight of hydrogen peroxide. The concentration of hydrogen peroxide vapor in the chamber may range from 0.05 to 10 mg of hydrogen peroxide per liter of chamber volume. The higher concentrations of hydrogen peroxide will result in shorter sterilization times. A concentration of 0.125 mg per liter is the minimum preferred concentration of hydrogen peroxide. Air or an inert gas such as argon, helium, nitrogen, neon or xenon may be added to the chamber with the hydrogen peroxide to maintain the pressure in the chamber at the desired level. The hydrogen peroxide solution may be injected in one or more separate injections. For example, at time "zero" one-half of the total amount of hydrogen peroxide solution to be used could be injected into the chamber, and five minutes later the remainder of the hydrogen peroxide solution can be injected. The hydrogen peroxide would then remain in the chamber before power was applied for an additional five to ten minutes. Apparently, the pre-treatment time allows the hydrogen peroxide to diffuse through the packaging material and come into close proximity, if not contact, with the surface of the item to be sterilized. Upon the application of power to the radio frequency generator, sporicidally active species are generated by the combination of hydrogen peroxide and plasma, and, therefore, the time required to effect sterilization is shorter than in prior art processes. It is possible to generate plasma at low power levels during the pre-treatment cycle, but there is no particular advantage in applying power during the pre-treatment cycle.

Although the exact mechanism of the sporicidal activity is not known with certainty, in an electrical discharge hydrogen peroxide can be dissociated into free radicals, i.e., OH, O_2H, H (M. Venugopalan and A. Shih, *Plasma Chemistry and Plasma Processing*, Vol. 1, No. 2, pages 191–199, 1981). These free radicals, either alone or in combination with hydrogen peroxide, are probably the primary source of sporicidal activity. Ultraviolet radiation is also produced in a low temperature plasma and may play a role in sporicidal activity, especially in the presence of hydrogen peroxide.

The general operation of the present process is as follows:

(1) The object or article to be sterilized is placed in a vacuum chamber or into the plasma chamber.

(2) The chamber is evacuated to a pressure of approximately 0.05 Torr.

(3) An aqueous solution of hydrogen peroxide is injected into the chamber to a pressure of vaporized water and hydrogen peroxide of from 0.5 to 10 Torr. The preferred pressure is from 1 to 2 Torr. The concentration of the hydrogen peroxide injected into the chamber may be from about 0.05 to 10 mg/liter of chamber volume. The preferred concentration is 0.208 mg/liter.

(4) The object to be sterilized is held in the chamber before plasma with sufficient power to sterilize is generated for a period of from about 5 to 30 minutes. This period is referred to herein as the pre-treatment time. Pre-treatment times longer than 30 minutes may be employed. The duration of the pre-treatment time may depend on the type of package used, the number of items to be sterilized, and the placement of the items in the chamber.

(5) The object to be sterilized is subjected to a plasma either in the pre-treatment chamber or in a separate plasma chamber.

(6) The RF energy used to generate the plasma may be continuous or it may be pulsed. The object remains in the plasma for a period of from 5 to 60 minutes to effect complete sterilization.

Since the hydrogen peroxide is decomposed into non-toxic products during the plasma treatment, no additional steps are required to remove residual hydrogen peroxide from the sterilized object or its packaging prior to use of the object.

In the following examples, the effectiveness of the sterilization cycle is expressed as the ratio of the number of organisms surviving the test (S) to the initial number of organisms which were placed on the specimen prior to the test (SO). In all of these examples, the organism tested was *Bacillus subtilis* (var. Globigii) spores which were placed on paper discs and packaged in a spunbonded polyethylene package. All examples were conducted in a 5.5 liter plasma chamber operating at a frequency of 2.49 MHz, except for Example V which was conducted at a frequency of 3.89 MHz.

EXAMPLE I

Table I contains a comparison of the sporicidal activity of the present hydrogen peroxide/plasma system to other prior art gases in the present plasma cycle. All tests were run under the same reaction conditions, i.e., 150 watts of pulsed plasma in a cycle of 0.5 milliseconds plasma on, 1.0 milliseconds plasma off for 15 minutes. All tests employed a 10 minute pre-treatment cycle with the gas listed in the Table. All pre-treatments and plasma treatments occurred at 1.5 Torr pressure. The glutaraldehyde and hydrogen peroxide pre-treatment cycle contained 0.208 mg/liter of glutaraldehyde and hydrogen peroxide, respectively. The results are expressed as S/SO in which S is the number of surviving organisms and SO is the initial number of organisms.

TABLE I

SPORICIDAL ACTIVITY OF H_2O_2/PLASMA SYSTEM COMPARED TO OTHER GAS/PLASMA SYSTEMS

Gas	Sporicidal Activity S/SO
O_2	$9.1 \times 10^5/1.3 \times 10^6 = 0.72$
N_2O	$4.9 \times 10^4/1.6 \times 10^5 = 0.31$
Glutaraldehyde	$5.7 \times 10^4/1.1 \times 10^5 = 0.52$
H_2O_2	$0/3.4 \times 10^5 = 0$

Only the hydrogen peroxide/plasma system exhibited good sporicidal activity and sterilized the treated item.

EXAMPLE II

The effect of hydrogen peroxide concentration in the plasma chamber on sporocidal activity was determined by pre-treating test samples with hydrogen peroxide vapor of different concentrations at 1.0 Torr pressure for ten-minutes. The treated samples were then exposed to 200 watts of pulsed plasma in a cycle of 0.5 milliseconds plasma on and 1.0 milliseconds plasma off for 15 minutes. Two controls, one using only hydrogen peroxide and one using only water plasma, were also run. The results are shown in Table II.

TABLE II

EFFECT OF H_2O_2 CONCENTRATION ON SPORICIDAL ACTIVITY

Conc. H_2O_2 (mg H_2O_2/liter)	SPORICIDAL ACTIVITY H_2O_2 Alone (S/SO)	SPORICIDAL ACTIVITY H_2O_2 + Plasma (S/SO)
0*	1.0	1.0
.125	1.0	7.3×10^{-2}
.208	1.0	1.4×10^{-2}
.416	1.0	0**
.625	9.1×10^{-2}	0**

*A plasma containing 4.16 mg H_2O/liter was used in this test.
**Total kill of 2.4×10^5 organisms.

No significant sporicidal activity was obtained with the water plasma treatment alone, or with H_2O_2 alone at concentrations below 0.625 mg/liter. However, a significant enhancement in sporicidal activity was obtained with the H_2O_2/plasma combination at all H_2O_2 concentration evaluated.

EXAMPLE III

The effect of pressure on sporicidal activity was determined using a hydrogen peroxide concentration of 0.208 mg/liter and the same pre-treatment and plasma cycle as in Example II. The activity was determined at pressures of 0.5, 1.0, 1.5 and 2.0 torr. The activity of air plasma only and hydrogen peroxide only were also determined. The results of these experiments are reported in Table III.

TABLE III

EFFECT OF PRESSURE ON SPORICIDAL ACTIVITY OF H_2O_2 PLASMA

Pressure (Torr)	SPORICIDAL ACTIVITY Plasma Only (S/SO)	SPORICIDAL ACTIVITY H_2O_2 Only (S/SO)	SPORICIDAL ACTIVITY H_2O_2 + Plasma (S/SO)
0.5	6.0×10^{-1}	9.6×10^{-1}	4.1×10^{-1}
1.0	6.7×10^{-1}	1.0	1.4×10^{-2}
1.5	2.8×10^{-1}	3.9×10^{-1}	0*
2.0	2.4×10^{-1}	6.6×10^{-1}	1.9×10^{-4}

*Total kill of 3.4×10^5 organisms.

A low level of activity was obtained with either plasma only or H_2O_2 only at all pressures. The optimum activity with the H_2O_2 plus plasma system was obtained at 1.5 Torr pressure.

EXAMPLE IV

The effect of plasma power on sporicidal activity was determined using a hydrogen peroxide concentration of 0.208 mg H_2O_2/liter at a pressure of 1.5 Torr. The power levels were 50, 100, 150 and 200 watts. The plasma was pulsed as in Example II, and the samples were pre-treated for 10 minutes with the procedure used in Example II. Air plasma only and hydrogen peroxide only tests were also run. The results are shown in Table IV.

TABLE IV

EFFECT OF RF POWER LEVEL ON SPORICIDAL ACTIVITY OF AIR PLASMA AND H_2O_2 PLUS PLASMA

Power (Watts)	SPORICIDAL ACTIVITY Plasma Only (S/SO)	SPORICIDAL ACTIVITY H_2O_2 + Plasma (S/SO)
0	1.0	4.0×10^{-1}
50	4.0×10^{-1}	8.1×10^{-1}
100	6.7×10^{-1}	2.5×10^{-3}
150	2.4×10^{-1}	0*
200	3.9×10^{-1}	0*

*Total kill of 1.8×10^5 organisms.

A low level of sporicidal activity was obtained with air plasma alone at all power loads evaluated. Significant sporicidal acitvity was obtained with the H_2O_2 plus plasma system at 100 watts power, and sterilization was achieved at 150 and 200 watts power.

EXAMPLE V

The-effect of plasma generation during the hydrogen peroxide pre-treatment time on sporicidal activity was determined using a hydrogen peroxide concentration of 0.208 mg H_2O_2/liter at a pressure of 1.5 Torr. During the 10 minute hydrogen peroxide pre-treatment time 50, 75, 100, 125 and 150 watts of power were applied at 3.89 MHz. The plasma was pulsed in a cycle of 0.5 milliseconds power on to 1.0 milliseconds power off. After the 10 minute pre-treatment time, all samples were exposed to 150 watts of power pulsed 0.5 milliseconds on to 1.0 milliseconds off for 15 minutes. The results of this test are shown in Table V.

TABLE V

EFFECT OF RF POWER LEVEL DURING PRE-TREATMENT ON SPORICIDAL ACTIVITY OF H_2O_2 PLUS PLASMA

Power Level During Pretreatment (Watts)	Sporicidal Activity (S/SO)
50	9.4×10^{-5}
75	1.2×10^{-4}
100	1.0
125	0.83
150	0.94

Significant sporicidal activity was obtained when low power levels, i.e., 50 and 75 watts, were applied during the hydrogen peroxide pre-treatment time. At higher power levels, which would dissociate more of the hydrogen peroxide before it could diffuse to the sample, very limited sporicidal activity was observed.

EXAMPLE VI

The effect of pulsing the plasma power on the sporicidal acitivty was determined using a hydrogen peroxide concentration of 0.208 mg H_2O_2/liter and a pressure of 1.5 Torr. Samples were pre-treated with hydrogen peroxide for 10 minutes as in Example II. Air plasma only and hydrogen peroxide only tests were also run. As in previous tests, the hydrogen peroxide only test gave an S/SO value of approximately 4.0×10^{-1}. The results of the tests with 100 watts of continuous plasma for 5 minutes, and 150 watts of plasma pulsed in a cycle of 0.5 milliseconds plasma on, and 1.0 milliseconds plasma off for 15 minutes are presented in Table VI.

TABLE VI

EFFECT OF PLASMA PULSING ON SPORICIDAL ACTIVITY

Plasma Condition	Plasma Only (S/SO)	H_2O_2 + Plasma (S/SO)
5 minute 100 watts Continuous Plasma	3.4×10^{-1}	0*
15 minute 150 watts 1:2 pulsed plasma	2.4×10^{-1}	0*

*Total kill of 2.2×10^5 organisms

The results of these tests illustrate that sterilization can be achieved within five minutes with a continuous plasma treatment.

EXAMPLE VII

The effect of repeat H_2O_2/plasma treatments on the sporicidal activity was determined using a hydrogen peroxide concentration of 0.125 mg/liter and a pressure of 1.5 Torr. Each treatment cycle consisted of a 10 minute pre-treatment time with H_2O_2 and a 15 minute exposure to 200 watts of pulsed plasma (0.5 milliseconds plasma on and 1.0 milliseconds plasma off). The effect of one and two treatment cycles are presented in Table VII.

TABLE VII

EFFECT OF NUMBER OF H_2O_2/PLASMA CYCLES ON SPORICIDAL ACTIVITY

	Sporicidal Activity		
No. Cycles	H_2O_2 Alone (S/SO)	Plasma Alone (S/SO)	H_2O_2 + Plasma (S/SO)
1	5.9×10^{-1}	6.6×10^{-1}	8.8×10^{-3}
2	8.2×10^{-1}	1.8×10^{-1}	0*

*Total kill of 2.5×10^5 organisms.

These results illustrate that sterilization can be achieved at low H_2O_2 concentrations by exposing the sample to two H_2O_2/plasma treatment cycles.

The above examples demonstrate the effectiveness of the use of hydrogen peroxide as the precursor of the reactive species in a plasma sterilization process. The operating parameters of the process, i.e., hydrogen peroxide concentration, pre-treatment cycle, power applied and time duration of plasma generation can be varied within fairly wide limits to produce an adequate sterilization cycle. The power applied or the hydrogen peroxide concentration may be reduced if the duration of plasma generation is increased, and, similarly, the duration of the plasma generation can be decreased if the concentration of hydrogen peroxide or the power applied is increased.

EXAMPLE VIII

Because items exposed to plasma increase in temperature, an experiment was conducted to compare the sporicidal activity obtained with hydrogen peroxide and heat to that obtained with hydrogen peroxide and plasma. This test was conducted by placing samples inside and outside a wire cage in the plasma chamber. Since metals effectively shield RF radiation, the sample inside the wire cage was shielded from RF radiation and plasma formation but not from exposure to hydrogen peroxide vapor or the heat generated by the plasma. The samples were treated with 0.208 mg hydrogen peroxide/liter at 1.5 Torr pressure for 10 minutes. The treated samples were then exposed to 150 watts of pulsed plasma in a cycle of 0.5 milliseconds plasma on and 1.0 milliseconds plasma off for 15 minutes. The temperature of nylon blocks located inside and outside the wire cage was monitored with a Luxtron Model 1000A, FLUOROPTIC™ Thermometer. At the end of the plasma treatment the temperature recorded inside and outside the wire cage was 52.1° C. and 56.9° C. respectively. The sporicidal test results are presented in Table VIII. A control experiment with hydrogen peroxide vapor only was also run.

TABLE VIII

A COMPARISON OF SPORICIDAL ACTIVITY WITH HYDROGEN PEROXIDE AND HEAT AND HYDROGEN PEROXIDE AND PLASMA

	Sporicidal Activity	
Conditions	Inside cage (S/SO)	Outside cage (S/SO)
H_2O_2 Vapor	4.2×10^{-1}	3.3×10^{-1}
H_2O_2 + Plasma	2.4×10^{-1}	0**

**Total kill of 3.0×10^5 spores.

These results illustrate that significantly better sporicidal activity was obtained outside than inside the wire cage with the combination of hydrogen peroxide and plasma. The reduced sporicidal activity inside the wire cage should largely be due to the absence of plasma formation since similar sporicidal activity was obtained with hydrogen peroxide alone inside and outside the cage, and after plasma treatment the temperatures inside and outside the wire cage were similar.

We claim:

1. A process of plasma sterilization using hydrogen peroxide as a precusor of the active species in the plasma comprising the steps of:
   placing an item to be sterilized in a chamber,
   contacting the item with a hydrogen peroxide vapor for a pretreatment time period which is a sufficient time period to allow the hydrogen peroxide to come in close proximity with the item;
   generating a hydrogen peroxide plasma around the item, and
   maintaining the item in said hydrogen peroxide plasma for a time period sufficient to allow an active species generated from the hydrogen peroxide plasma to effect sterilization.

2. The process of claim 1 in which the concentration of hydrogen peroxide vapor in the chamber is at least 0.05 mg per liter of chamber volume.

3. The process of claim 1 in which the hydrogen peroxide plasma is pulsed in a power-on-power-off ratio of 1:2.

4. The process of claim 1 in which the concentration of hydrogen peroxide vapor in the chamber is between 0.05 to 10 mg/liter of chamber volume.

5. The process of claim 1 in which the concentration of hydrogen peroxide vapor in the chamber is 0.208 mg/liter of chamber volume.

6. The process of claim 1 in which the pretreatment time period is between 5 and 30 minutes.

7. The process of claim 1 in which the hydrogen peroxide plasma is generated over a period of from 5 to 60 minutes.

8. The process of claim 1 in which the steps of:
   contacting the item with a hydrogen peroxide vapor for a pretreatment time period which is sufficient to

allow for the hydrogen peroxide to come in close proximity with the item,

generating a hydrogen peroxide plasma around the item, and

maintaining the item in said hydrogen peroxide for a time period sufficient to allow an active species generated from the hydrogen peroxide plasma to effect sterilization

are repeated.

9. The process of claim **1** in which the hydrogen peroxide plasma is maintained until the hydrogen peroxide is decomposed into nontoxic products.

* * * * *

Electronic Acknowledgement Receipt	
EFS ID:	16850527
Application Number:	13382380
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Customer Number:	1095
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Supplemental Response or Supplemental Amendment	PAT053689-US-PCT-SuppResponseOA-Sept2013.pdf	57729 9c7438ff14d318792dbb0539f430f352462e9d31	no	1
Warnings:					
Information:					

2	Foreign Reference	EP0707186B1.pdf	702176 8101679bd43e85c18a41c4681c9701096471f906	no	16
Warnings:					
Information:					
3	Foreign Reference	US4643876.pdf	685871 139937fdb5b53f1fa8629eef29ecf400bf79a2ea	no	8
Warnings:					
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			Total Files Size (in bytes):	1445776	

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/382,380	01/05/2012	Juergen Sigg	PAT053689-US-PCT	9960

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ONE HEALTH PLAZA 101/2
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EXAMINER	
SPAMER, DONALD R	
ART UNIT	**PAPER NUMBER**
1775	

NOTIFICATION DATE	DELIVERY MODE
10/23/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Office Action Summary	Application No. 13/382,380	Applicant(s) SIGG, JUERGEN	
	Examiner DONALD SPAMER	Art Unit 1775	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/12/2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,3-7 and 22* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3-7 and 22* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/13/2013*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Claims 1, 3-7, and 22 remain pending.

Response to Arguments

3. Applicant's arguments filed 9/12/2013 regarding 1, 3-5, 7, and 22 have been fully considered but they are not persuasive.

The applicant argues that Metzner teaches a pre-treatment with hydrogen peroxide and then does the vacuum step before the sterilization step of generating a plasma sterilant. Thus the applicant contends that Metzner does not teach applying vacuum as a post decontamination step. While the applicant correctly points out the order of events taught by Metzner, applying hydrogen peroxide, applying vacuum, and then generating a plasma, the examiner disagrees that Metzner does not teach claim 1. Hydrogen peroxide vapor is in itself a decontaminant. Thus the application of hydrogen peroxide is a decontamination step. This is followed by a post decontamination (occurring after a decontamination step) application of a vacuum.

The applicant argues that Hasegawa does not teach that the application of a vacuum prevents hydrogen peroxide from diffusing into the syringe. The examiner disagrees. The applicant states that Hasegawa teaches that the hydrogen peroxide enters the space between the piston and the cylinder. While correct in that statement, this is not inside the syringe where the prefiled product is. Hasegawa states that the hydrogen peroxide is inside the injection pack which is the primary packaging about the syringe and not inside the body chamber of the syringe in which the product is held. Further applying vacuum removes hydrogen peroxide from the chamber and reverses the pressure gradient and concentration gradient such that hydrogen peroxide vapor is reversed and drawn away from the syringe. Thus since the gradients are reversed, hydrogen peroxide is prevented from diffusing into the syringe.

The applicant argues that there is no evidence in Metzner that the hydrogen peroxide did not damage the protein and that Metzner only tested for thermal denaturation. While the applicant is correct that Metzner was most concerned with thermal denaturation the tests showing undamaged protein

indicate that the protein was not damaged or denatured regardless of whether or not it was by chemical or thermal means.

4. Applicant's arguments, see part D regarding claim 6, filed 9/12/2013, with respect to the rejection(s) of claim(s) 6 under 35 USC 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Metzner et al. over (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above, and further in view of Asahara et al. et al. (US Patent Application Publication 2003/0198570) and Metzner et al. over (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above as evidenced by Jacobs et al. (US Patent 4,643,876).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 4, 5, 7, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Metzner et al. (US Patent Application Publication Number 2003/0003014) as evidenced by Hasegawa et al. (US Patent 6,228,324) and in view of Hasegawa et al. (US Patent 6,228,324).

With regards to claim 1, Metzner et al. teaches a method for surface decontamination of a prefilled container in secondary packaging (para [0010-0011]). Metzner et al. teaches the use of vaporized hydrogen peroxide in order to sterilize the surfaces of the packaging (para [0019]). Metzner et al. also teaches that the hydrogen peroxide is left in contact with the surfaces for a sufficient amount of time to achieve decontamination (para [0032-0033]) and gives an example of about 17 min in each half cycle in example 3 (para [0071]). Metzner et al. also teaches the use of post-decontamination measures of applying a vacuum (para [0034 - 0035]). The vacuum post decontamination treatment taught by

Metzner et al. would remove the hydrogen peroxide as evidenced by Hasegawa et al. Hasegawa et al. states that the application of a vacuum removes the hydrogen peroxide from inside the packaging (column 8, lines 63-67 and column 9, lines 32-38).

Metzner et al. teaches this method can be done on temperature sensitive pharmaceutical products (para [0002]). It expands to say that such products are sensitive to sterilization with gamma radiation (para [0005]), autoclaving (para [0003]) (exposure to steam), and ethylene oxide (since ethylene oxide residue can render the drug product toxic or carcinogenic) (gas) (para [0004]). In example 3, Metzner et al. teaches that the protein drug product is in a carpule (para [0061]). A carpule is a container for medicine that is administered to the patient with a syringe. Metzner thus does not expressly state the use of the method on a syringe in secondary packaging. Hasegawa et al. teaches a method for sterilizing a syringe in secondary packaging using hydrogen peroxide vapor (abstract and figure 4). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. to sterilize a syringe in secondary packaging as shown in Hasegawa et al. in order to provide a sterile drug product by using hydrogen peroxide vapor (abstract and figure 4).

With regards to claim 4, Metzner et al. teaches determining if the sterilization method is effective (para [0037]). This is considered to include testing whether the treatment times are sufficient since treatment times are part of the method. Metzner et al. teaches that sterilization effectiveness is determined by comparing the reduction factor of colony forming units (CFU) and comparing this value to a control standard (para [0037]). The control standard taught by Metzner et al. is that sterilization is achieved if $\log_{10}$(CFU) is greater than or equal to 6 (para [0037]).

With regards to claim 5, Metzner et al. teaches a post decontamination measure of applying a vacuum following treatment with vaporized hydrogen peroxide (para [0034]). While Metzner et al. does not specifically state the intended use of “reversing the direction of diffusion of vaporized hydrogen peroxide and preventing intrusion of vaporized hydrogen peroxide into the prefilled container,” the method of using a vacuum after effective treatment is capable of achieving this. This is affirmatively shown by the teaching Hasegawa et al.

Hasegawa et al. states that the application of a vacuum (taught by Metzner et al.) removes the hydrogen peroxide from inside the packaging (column 8, lines 63-67 and column 9, lines 32-38).

The prevention of hydrogen peroxide intrusion can be further confirmed when Metzner et al. measures the amount of proteins undamaged by the sterilization method and finds that the method damaged very little to none of the protein products (para [0076]).

With regards to claim 7, teaches a post decontamination measure that includes a plasma treatment (para [0035]). This is considered to be a gas plasma.

With regards to claim 22, the combination of Metzner et al. and Hasegawa et al. teaches that the hydrogen peroxide vapor sterilization method can be used for sterilizing prefilled syringes in secondary packaging where the prefilled drug product is various proteins (Metzner et al. para [0061]).

7. Claim 3 rejected under 35 U.S.C. 103(a) as being unpatentable over Metzner et al. (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above, and further in view of Shams (US Patent Application Publication 2007/0190058).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. teaches a method of using hydrogen peroxide vapor for sterilizing different proteins in secondary packaging (para [0061]) at 30°C (para [0063]) and teaches that the treatment did not destroy the protein products (para [0076]). Metzner et al. does not specifically mention the use of the method for treating a medical product where the prefilled drug is ranibizumab, a protein. The claim recites “therapeutically effective” (implying non degraded protein when administered into a body for treatment). A person having ordinary skill in the art at the time of the invention would understand that if this method is capable of sterilizing prefilled protein drug products in secondary packaging without causing degradation of the proteins that the method is capable of treating the specific protein ranibizumab.

Additionally the concept of using ranibizumab delivered by a syringe is also known in the prior art. Shams teaches the administration of ranibizumab by syringe injection (para [0128]). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. with the addition of ranibizumab being the drug in the syringe, as taught by Shams, in order to administer a dose of ranibizumab as a therapuetic drug (abstract and para [0028]) in a sterile manner

which is desired by Shams who states that the treatment should be formulated, dosed, and administered in a fashion consistent with good medical practice (para [0092]) which would include using a sterile syringe.

8. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable Metzner et al. over (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above, and as evidenced by Jacobs et al. (US Patent 4,643,876).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. also teaches the use of a post decontamination measure using a vacuum (para [0034]) and a plasma treatment (para [0035]). The post decontamination (after a decontamination using hydrogen peroxide) applies a plasma. This causes an application of ultraviolet light following the duration of hydrogen peroxide vapor treatment and breaks down the hydrogen peroxide vapor inactivating the vapors oxidative action. Jacobs et al. provides and evidentiary teaching of the breakdown of hydrogen peroxide vapors upon the generation of plasma. Jacobs et al. teaches that forming a plasma from hydrogen peroxide vapor causes a breakdown of hydrogen peroxide that gives off UV light (column 5, lines 34-45).

9. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable Metzner et al. over (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above, and further in view of Asahara et al. (US Patent Application Publication 2003/0198570).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. also teaches the use of a post decontamination measure using a vacuum (para [0034]) and a plasma treatment (para [0035]).

Metzner et al. is silent on how to generate the plasma. It is necessary and therefore obvious to look to the prior art for a known method of generating a plasma from hydrogen peroxide vapor. Asahara et al. provides a teaching that it is known to generate plasma from hydrogen peroxide vapor using ultraviolet light (para [0040], [0049], and [0052]). A person having ordinary skill in the art at the time of the invention would have found it obvious to have used ultraviolet light as taught by Asahara et al. to generate the plasma motivated by the expectation of practicing the invention of Metzner et al. Further it would have been obvious to a person having ordinary skill in the art to substitute one known means to

generate plasma from hydrogen peroxide for another known means of generating plasma from hydrogen peroxide with an expectation of successfully generating plasma from hydrogen peroxide.

The combination teaches a post decontamination including the application of ultraviolet light following the duration of treatment with hydrogen peroxide vapor and thereby inactivating the oxidative action of the hydrogen peroxide vapors.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DONALD SPAMER whose telephone number is (571)272-3197. The examiner can normally be reached on Monday through Friday, 9 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on 571-272-1374. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DONALD SPAMER/
Examiner, Art Unit 1775

/SEAN E CONLEY/
Primary Examiner, Art Unit 1775

Notice of References Cited	Application/Control No. 13/382,380	Applicant(s)/Patent Under Reexamination SIGG, JUERGEN	
	Examiner DONALD SPAMER	Art Unit 1775	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2003/0198570	10-2003	Asahara et al.	422/22
*	B	US-4,643,876	02-1987	Jacobs et al.	422/23
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
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FOREIGN PATENT DOCUMENTS

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Doc description: Information Disclosure Statement (IDS) Filed

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13382380
	Filing Date	2012-01-05
	First Named Inventor	Sigg, Juergen
	Art Unit	1775
	Examiner Name	SPAMER, DONALD ROBERT
	Attorney Docket Number	PAT053689-US-PCT

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	1	2008014166	WO	A2	2008-01-31	JOHNSON DIVERSEY, INC		☐
	2	0761238	EP	A2	1997-03-12	CIBA-GEIGY AG		☐

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Receipt date: 09/13/2013	Application Number	13382380 13382380 - GAU: 1775
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2012-01-05
(Not for submission under 37 CFR 1.99)	First Named Inventor	Sigg, Juergen
	Art Unit	1775
	Examiner Name	SPAMER, DONALD ROBERT
	Attorney Docket Number	PAT053689-US-PCT

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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EXAMINER SIGNATURE

Examiner Signature	/Donald Spamer/	Date Considered	09/30/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.S./

Receipt date: 09/13/2013	Application Number	13382380	13382380 - GAU: 1775
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2012-01-05	
	First Named Inventor	Sigg, Juergen	
	Art Unit	1775	
	Examiner Name	SPAMER, DONALD ROBERT	
	Attorney Docket Number	PAT053689-US-PCT	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/jim lynch/	Date (YYYY-MM-DD)	2013-09-12
Name/Print	Jim Lynch	Registration Number	54763

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	2	(decontaminating or sterliz$3) same (prefilled)	US-PGPUB; USPAT	ADJ	ON	2012/06/27 07:45
S2	351	(decontaminating or steriliz$3) same (prefilled)	US-PGPUB; USPAT	ADJ	ON	2012/06/27 07:49
S3	41	(decontaminating or steriliz$3) same (prefilled) and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2012/06/27 08:42
S4	11	("6027482" | "4452473" | "4266815" | "5184742" | "5609584" | "5855568" | "6632199" | "6004295" | "5047021" | "5702374" | "5755696").PN.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 10:02
S5	1	"5779973".pn.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 10:08
S6	212	604/199.ccls.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:06
S7	1451	terminal steriliz$	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:46
S8	116	terminal steriliz$ and ((pre-filled or prefilled) syringe)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:47
S9	22	terminal steriliz$ same ((pre-filled or prefilled) syringe)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:48
S10	4	("2006/0106349").URPN.	USPAT	ADJ	ON	2012/08/08 11:59
S11	21	(decontaminating or steriliz$3) same (pre-filled) and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2012/08/08 12:02
S12	14	("4230663" | "4878903" | "5407070" | "5615772" | "5792422" | "5817065").PN. OR ("6228324").URPN.	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 12:20
S13	86	"422".clas. and ((pre-filled or prefilled) (syringe or container))	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 13:26
S14	24	("4226410" | "4236731" | "4947620" | "4962856" | "5033252" | "5052558" | "5178267" | "5178277" | "5217772" | "5220769" | "5536356" | "5571361" | "5590778" | "5715943" | "5830547" | "5868244" | "5949032" | "5976299" | "6034008" | "6117505" | "6228324" |	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 15:39

		"6419392" | "6449925").PN. OR ("6986730").URPN.				
S15	34	("4878903").URPN.	USPAT	ADJ	ON	2012/08/08 16:16
S16	376	206/364.ccls.	USPAT	ADJ	ON	2012/08/08 16:35
S17	7	206/364.ccls. and (hydrogen peroxide)	USPAT	ADJ	ON	2012/08/08 16:36
S18	1119	ranibizumab	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:42
S19	527	ranibizumab and syringe	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:43
S20	122	ranibizumab and syringe and (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:43
S21	15	206/364.ccls. and (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 17:06
S22	195	syringe and (hydrogen peroxide)	EPO; JPO; DERWENT	ADJ	ON	2012/08/08 17:22
S23	0	(nishimura and onishi and saiki).pn.	US-PGPUB; USPAT	ADJ	ON	2012/08/09 11:16
S24	17	protein same syringe same (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/09 11:28
S25	1408	(filter or selective$3) same (UV or ultraviolet) same (sterili$3 or saniti$3 or decontaminate)	US-PGPUB; USPAT	ADJ	ON	2012/08/13 16:39
S26	70	(filter or selective$3) same (UV or ultraviolet) same (package or item) and "422".clas.	US-PGPUB; USPAT	ADJ	ON	2012/08/13 16:46
S27	0	2003/0003014	US-PGPUB; USPAT	ADJ	ON	2012/08/13 17:51
S28	399	metzner.in.	US-PGPUB; USPAT	ADJ	ON	2012/08/13 17:52
S29	49330	hydrogen peroxide and (uv or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2012/08/16 12:54
S30	21	hydrogen peroxide with (uv or ultraviolet) with (inactivat$3)	US-PGPUB; USPAT	ADJ	ON	2012/08/16 12:55
S31	19	hydrogen peroxide and (uv or ultraviolet) and 422/30.ccls.	US-PGPUB; USPAT	ADJ	ON	2012/08/16 13:47
S32	0	2007/0190058	US-PGPUB; USPAT	ADJ	ON	2012/08/20 08:54
S33	1	"20070190058"	US-PGPUB; USPAT	ADJ	ON	2012/08/20 08:54
S34	4	("4169123" | "4169124" | "4512951" |	US-	ADJ	ON	2012/12/17

		"7060269").PN.	PGPUB; USPAT			08:22
S35	0	(sterili$ or disinfect or decontaminat$ or saniti$) same (pre-filled or prefilled) same (hydrogen peroxide) same ((atmosphere or ambient) pressure)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 17:56
S36	31	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same ((atmosphere or ambient) pressure)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 17:56
S37	204	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same (atmospheric pressure)	US-PGPUB; USPAT	ADJ	ON	2012/12/18 10:33
S38	1	"6228324".pn.	US-PGPUB; USPAT	ADJ	ON	2012/12/18 11:00
S39	58	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same (atmospheric pressure) same (below and above)	US-PGPUB; USPAT	ADJ	ON	2012/12/18 11:04
S40	17	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same ((atmospheric pressure) with (below and above))	US-PGPUB; USPAT	ADJ	ON	2012/12/18 11:05
S41	155	hydrogen peroxide with plasma with (UV or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2013/10/02 12:32
S42	1	"20050158206".pn.	US-PGPUB; USPAT	ADJ	ON	2013/10/02 12:58
S43	4	(make or generate or generation) with hydrogen peroxide with plasma with (UV or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2013/10/02 13:22
S44	4	(make or generate or generation) with hydrogen peroxide with plasma same (UV or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2013/10/02 13:24
S45	41	(make or generate or generation) with hydrogen peroxide with plasma and (UV or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2013/10/02 13:25

10/12/2013 2:49:14 PM
C:\Users\dspamer\Documents\EAST\Workspaces\13382380.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13382380	SIGG, JUERGEN
	Examiner	Art Unit
	DONALD SPAMER	4142

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
422	(text limitated)	08/13/2012	Donald Spamer
422	30 (text limited)	08/16/2012	Donald Spamer
206	364 (text limited)	08/08/2012	Donald Spamer
604	199	08/08/2012	Donald Spamer

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search in eDAN	08/16/2012	Donald Spamer
East search history attached	08/16/2012	Donald Spamer
Updated East search history attached	12/18/2012	DS
Updated inventor search in eDAN	5/16/2013	DS
Updated EAST search history	10/02/2013	DS
Updated inventor search in eDAN	10/02/2013	DS

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

CASE PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF Art Unit: 1775

Sigg, Juergen Examiner: SPAMER, DONALD R

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: 13/382380

35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICE ACTION

Sir:

This Reply is submitted in response to the Final Office Action mailed October 23, 2013. Reconsideration of the present rejections and withdrawal of the present rejections are respectfully requested.

Amendments to the Claims is reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A method for surface decontamination of a prefilled syringe in secondary packaging, comprising:

   applying vaporized-hydrogen peroxide to the surface of the prefilled syringe in secondary packaging;

   allowing vaporized-hydrogen peroxide to remain in contact with the prefilled syringe surface for a sufficient time to decontaminate the prefilled syringe 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 syringe, wherein the prefilled syringe ~~contains~~ comprises 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.

2. (Cancelled)

3. (Previously presented) The method of claim 1, wherein the syringe contains a therapeutically effective amount of ranibizumab.

4. (Previously presented) The method of claim 1, wherein sufficient time to decontaminate the surface of the prefilled syringe is determined by validation of treatment times and compared to a control standard.

5. (Previously presented) The method of claim 1, 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 syringe.

6. (Previously presented) The method of claim 1, 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. (Previously presented) The method of claim 1, wherein the post-decontamination measure includes gas plasma treatment.

8. (Withdrawn) A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

9. (Withdrawn) 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.

10. (Withdrawn) The method of claim 8, 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.

11. (Withdrawn) The method of claim 8, 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.

12. (Withdrawn) The method of claim 8, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

13. (Withdrawn) The method of claim 8, wherein the penetration depth is measured by dosimetry.

14. (Withdrawn) The method of claim 8, 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.

15. (Withdrawn) The method of claim 8, 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.

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

a sealed chamber; and

a control unit coupled to the chamber, the control unit configured to automatically perform the method according to claim 1.

17. (Withdrawn) 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 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 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

18. (Withdrawn) 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 sealed chamber to perform the method according to claim 1.

19. (Withdrawn) A kit for surface-decontaminating a prefilled container in secondary packaging, 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. (Withdrawn) A system according to claim 16, wherein post-decontamination measure includes gas plasma treatment.

21. (Withdrawn) A kit according to claim 18, wherein post-decontamination measure includes gas plasma treatment.

22. (Previously presented) The method of claim 1, wherein the drug product is a protein solution.

Remarks

I. Claims

Claims 1 and 3-22 are presently pending in this patent application. Claims 8- 21 have been withdrawn as being drawn to non-elected subject matter and Claim 2 has been cancelled. Claim 1 has been amended for clarification purposes only.

Applicants reserve the right to pursue subject matter that remains after the prosecution of the present application in a future continuing patent application, for example, a division.

II. Rejections under 35 U.S.C. § 103 - Obviousness

After careful consideration of the Applicant's arguments, the Examiner maintained his rejection of Claims 1, 4, 5, 7 and 22 under 35 U.S.C. § 103 for obviousness over published U.S. Patent Application 2003/0003014 to Metzner et al. ("Metzner") as evidenced by, and in view of, U.S. Patent 6,228,324 to Hasegawa ("Hasegawa"). The Examiner relies on Metzner for its teaching of a method for surface decontamination of a prefilled container in secondary packaging (citing Metzner at paragraphs [0010-0011]). The Examiner contends that Metzner teaches the use of vaporized hydrogen peroxide to sterilize the surfaces of the packaging (citing Metzner at paragraph [0019]). The Examiner also contends that Metzner teaches the use of a vacuum as a post-contamination treatment (citing Metzner at paragraphs [0034-0035]). In the Examiner's opinion, this post-contamination treatment would remove hydrogen peroxide as evidenced by Hasegawa, as it teaches that the application of a vacuum removes peroxide from inside the packaging (citing column 8, lines 63-67 and column 9, lines 32-28).

The Examiner concedes that Metzner does not teach sterilization of a syringe in secondary packaging. However, the Examiner relies on Hasegawa to cure this deficiency.

With regards to claim 4, the Examiner contends that Metzner teaches a means for determining whether the sterilization is effective, and that this equates to determining whether the treatment times are sufficient.

Regarding Claim 5, the Examiner admits that the intended use of "reversing the direction of diffusion of vaporized hydrogen peroxide and preventing intrusion of vaporized peroxide into the pre-filled container" is not disclosed in Metzner; however it is "capable" of achieving this. As support, the Examiner relies on Hasegawa, and contends that the application of a vacuum removes the hydrogen peroxide from inside the packaging (citing column 8, lines 63-67 and column 9, lines 32-28) and as evidenced by Metzner paragraph [0076].

With regards to claim 7, the Examiner contends that the post-decontamination measure includes plasma treatment as shown in paragraph [0035] of Metzner.

With regards to claim 22, the Examiner asserts that the combination of Hasegawa and Metzner teaches that the prefilled syringes can be filled with various proteins.

Claim 3 was rejected under 35 U.S.C. § 103 as obvious in view of a combination of Metzner, Hasegawa and US Pat. Pub. No. US2007/0190058 to Shams ("Shams"). The Examiner cited Shams to teach the administration of ranibizumab via syringe injection.

The Examiner rejected Claim 6 under 35 U.S.C. § 103 as obvious in view of a combination of Metzner, Hasegawa and Jacobs et al., US Pat, No. 4,643,786 ("Jacobs"). In the Examiner's view Jacobs teaches that the breakdown of hydrogen peroxide vapor causes a breakdown of hydrogen peroxide that gives off UV light.

The Examiner withdrew his previous rejection of claim 6, but added new grounds of rejection. Specifically, claim 6 was also rejected under 35 U.S.C. § 103 as obvious in view of a combination of Metzner, Hasegawa, and further in view of Asahara et al., US Pat. Pub. No. 2003/0198570 ("Asahara"). According to the Examiner, Asahara teaches the use of UV light to generate plasma from vapor, and as a result, the combination teaches the use of UV light as a post-decontamination measure.

III. Response/Arguments

A. The Examiner's inherency argument is flawed

Initially, the Applicant thanks the Examiner for withdrawing his previous rejection for claim 6. However, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness.

The Examiner has admitted that the events taught by Metzner are applying hydrogen peroxide vapor, applying a vacuum, and then generating plasma. The Examiner has repeatedly stated that Metzner teaches present claim 1 because hydrogen peroxide vapor itself is a decontaminant, and that the application of hydrogen peroxide vapor is a decontamination step. However, nowhere in Metzner is this mentioned or explicitly stated. Nor does any other reference explicitly state this. As such, the Examiner must be relying on the implicit, inherent teachings of the cited references. However, it is well settled that "to establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' MPEP §2112 (quoting *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). Applicants submit that the Examiner has fallen far short of this burden in the present case.

As admitted by the Examiner, the process of Metzner comprises an optional pre-plasma step, followed by insertion of a container into a chamber. The pressure in the chamber is then lowered to create a vacuum, upon which hydrogen peroxide solution is injected. The pressure is then re-lowered and plasma is then generated. Finally, the chamber is ventilated. See Metzner, claim 1 and paragraph 0038 ("the method to which the invention relates is essentially described in the claims.") Metzner refers to such a cycle as a "half-cycle". Metzner repeatedly and

consistently refers to the hydrogen plasma which is generated as the decontaminant. No mention is ever made of hydrogen peroxide as the decontaminant.

Applicant concedes that hydrogen peroxide can be used as a decontaminant. Indeed, that is the basic premise of Applicant's invention! However, numerous variables are required to ensure that hydrogen peroxide vapor acts as a decontaminant. These include, inter alia, the time for which the hydrogen peroxide contacts the surface to be decontaminated, the pressure and temperature at which it is applied, and the concentration of hydrogen peroxide vapor which is used. Metzner is silent on several of these variables.

At best then, Metzner teaches that hydrogen peroxide is injected into a chamber. Such a use **could be** considered a decontaminant, but without all of the required variables, one cannot simply state that is **necessarily discloses** that hydrogen peroxide is used as a decontaminant.

This argument is bolstered by the teachings of Metzner. Metzner refers to the invention as a "method for hydrogen peroxide *plasma* sterilization (emphasis added)." Indeed, every reference to sterilization in Metzner refers to plasma, as opposed to vapor. Further, the method of determining whether the sterilization occurs is after each half step. That is, determining whether a particular item is sterilized is only done after application of the plasma. If the hydrogen peroxide vapor was to be used as the decontaminant, there would be no need to generate plasma and the testing could be performed after the injection step (as opposed to the plasma step).

As a result, there is nothing in Metzner that teaches that the injection of hydrogen peroxide solution necessarily is a decontamination step. None of the other references relied upon by the Examiner cure this deficiency. As such, the Examiner's assertion that the Accordingly, the Examiner's inherency argument is improper under the MPEP. Thus, the rejection is improper and should be withdrawn.

B. The Examiner's application of Hasegawa to the claims is incorrect

The Examiner has admitted that Hasegawa teaches that hydrogen peroxide enters the space between the cylinder and the piston (see page 2 of the Office Action), but nevertheless asserts that it is not inside the syringe where the prefilled product is. Indeed, Hasegawa, at column 8, lines 63-67 explicitly state that the process is used to "ensure the penetration of hydrogen peroxide gas into delicate portions of the medicine filled injector (emphasis added). Claim 1 of the current application recites that vaporized-hydrogen peroxide is prevented from diffusing into the prefilled syringe. Hasegawa explicitly teaches that the hydrogen peroxide is applied to the packaging to ensure that it enters into the syringe. Claim 1 of the instant application merely recites that the hydrogen peroxide is prevented from entering the syringe, not that it is prevented from entering the syringe where the prefilled product is found. As a result, the Examiner has misapplied the teachings of Hasegawa to the current claims. Since the Examiner admits that Hasegawa teaches that hydrogen peroxide vapor enters delicate portions

of the syringe, and the claims recite that hydrogen peroxide is prevented from entering the syringe the Examiner's rejection is improper and should be withdrawn.

IV. Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Action of record and that Claims 1, 3-7 and 22 are now in condition for allowance. Applicant respectfully requests that the Office withdraw all grounds for rejection and issue a Notice of Allowance at its earliest convenience. If there are any issues that can be resolved by a telephone conference, the Examiner is invited to call the undersigned attorney at his convenience.

Respectfully submitted,

/Jim Lynch/

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Date: January 14, 2014

Electronic Acknowledgement Receipt	
EFS ID:	17904542
Application Number:	13382380
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Customer Number:	1095
Filer:	James L Lynch/Denise Cooper
Filer Authorized By:	James L Lynch
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Application Type:	U.S. National Stage under 35 USC 371

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response After Final Action	PAT053689-US-PCT-ResponseOA-14Jan2014.pdf	235384 09e1b7121708664fa0cb7730ed559dcde69a226	no	9
Warnings:					
Information:					

Total Files Size (in bytes):	235384

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/382,380	Filing Date 01/05/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 = *		X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 = *		X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 01/14/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 21	Minus	** 22	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***5	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/CRYSTAL QUEEN/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/382,380	01/05/2012	Juergen Sigg	PAT053689-US-PCT	9960

1095 7590 02/07/2014

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
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EXAMINER	
SPAMER, DONALD R	
ART UNIT	PAPER NUMBER
1775	

NOTIFICATION DATE	DELIVERY MODE
02/07/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Office Action Summary	Application No. 13/382,380	Applicant(s) SIGG, JUERGEN	
	Examiner DONALD SPAMER	Art Unit 1775	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/14/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1 and 3-22* is/are pending in the application.

5a) Of the above claim(s) *8-21* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 3-7, and 22* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

Response to Arguments

2. Applicant's arguments filed 1/14/2014 have been fully considered but they are not persuasive.

The applicant argues that it is incorrect to consider the application of hydrogen peroxide vapor taught by Metzner as a decontamination step since Metzner refers to the generation of hydrogen peroxide plasma from the vapor as the decontamination step. The examiner disagrees. In order to decontaminate an object some microorganism, bacteria, virus, etc. must be destroyed or killed. It does not require all or a majority by killed. The introduction of hydrogen peroxide vapor as taught by Metzner would result in at least some destruction of microorganisms present on the syringe. Whether or not Metzner calls it the decontamination step or continues with another decontamination step (generating plasma out of the vapor) does not negate that at least some microorganisms would be destroyed thus constituting decontamination. Further the claim language does not exclude the addition of more steps.

The applicant argues that Hasegawa is not appropriately applied since Hasegawa teaches hydrogen peroxide entering the space between the cylinder and the piston and thus does not constitute preventing hydrogen peroxide from diffusing into the syringe. The examiner disagrees. The space between the piston and cylinder is an exterior of the syringe and not an interior of the syringe. Thus hydrogen peroxide entering the space does not constitute "diffusing into the syringe" but constitutes hydrogen peroxide entering a space that is exterior (ie not in) the syringe. Further, under the assumption that hydrogen peroxide entering the space between the piston and cylinder does constitute a diffusion into the syringe, the claim language does not require a certain amount of hydrogen peroxide or all of the hydrogen peroxide must be prevented from diffusing into the syringe. The application of a vacuum as explained in the previous office action would prevent at least some hydrogen peroxide from diffusing into the space between the piston and cylinder (ie the hydrogen peroxide in the surrounding atmosphere and packaging).

For at least the reasons above the previously presented rejection is maintained.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 4, 5, 7, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Metzner et al. (US Patent Application Publication Number 2003/0003014) as evidenced by Hasegawa et al. (US Patent 6,228,324) and in view of Hasegawa et al. (US Patent 6,228,324).

With regards to claim 1, Metzner et al. teaches a method for surface decontamination of a prefilled container in secondary packaging (para [0010-0011]). Metzner et al. teaches the use of vaporized hydrogen peroxide in order to sterilize the surfaces of the packaging (para [0019]). Metzner et al. also teaches that the hydrogen peroxide is left in contact with the surfaces for a sufficient amount of time to achieve decontamination (para [0032-0033]) and gives an example of about 17 min in each half cycle in example 3 (para [0071]). Metzner et al. also teaches the use of post-decontamination measures of applying a vacuum (para [0034 - 0035]). The vacuum post decontamination treatment taught by Metzner et al. would remove the hydrogen peroxide as evidenced by Hasegawa et al. Hasegawa et al. states that the application of a vacuum removes the hydrogen peroxide from inside the packaging (column 8, lines 63-67 and column 9, lines 32-38).

Metzner et al. teaches this method can be done on temperature sensitive pharmaceutical products (para [0002]). It expands to say that such products are sensitive to sterilization with gamma radiation (para [0005]), autoclaving (para [0003]) (exposure to steam), and ethylene oxide (since ethylene oxide residue can render the drug product toxic or carcinogenic) (gas) (para [0004]). In example 3, Metzner et al. teaches that the protein drug product is in a carpule (para [0061]). A carpule is a container for medicine that is administered to the patient with a syringe. Metzner thus does not expressly state the use of the method on a syringe in secondary packaging. Hasegawa et al. teaches a method for sterilizing

a syringe in secondary packaging using hydrogen peroxide vapor (abstract and figure 4). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. to sterilize a syringe in secondary packaging as shown in Hasegawa et al. in order to provide a sterile drug product by using hydrogen peroxide vapor (abstract and figure 4).

With regards to claim 4, Metzner et al. teaches determining if the sterilization method is effective (para [0037]). This is considered to include testing whether the treatment times are sufficient since treatment times are part of the method. Metzner et al. teaches that sterilization effectiveness is determined by comparing the reduction factor of colony forming units (CFU) and comparing this value to a control standard (para [0037]). The control standard taught by Metzner et al. is that sterilization is achieved if $\log_{10}$(CFU) is greater than or equal to 6 (para [0037]).

With regards to claim 5, Metzner et al. teaches a post decontamination measure of applying a vacuum following treatment with vaporized hydrogen peroxide (para [0034]). While Metzner et al. does not specifically state the intended use of "reversing the direction of diffusion of vaporized hydrogen peroxide and preventing intrusion of vaporized hydrogen peroxide into the prefilled container," the method of using a vacuum after effective treatment is capable of achieving this. This is affirmatively shown by the teaching Hasegawa et al.

Hasegawa et al. states that the application of a vacuum (taught by Metzner et al.) removes the hydrogen peroxide from inside the packaging (column 8, lines 63-67 and column 9, lines 32-38).

The prevention of hydrogen peroxide intrusion can be further confirmed when Metzner et al. measures the amount of proteins undamaged by the sterilization method and finds that the method damaged very little to none of the protein products (para [0076]).

With regards to claim 7, teaches a post decontamination measure that includes a plasma treatment (para [0035]). This is considered to be a gas plasma.

With regards to claim 22, the combination of Metzner et al. and Hasegawa et al. teaches that the hydrogen peroxide vapor sterilization method can be used for sterilizing prefilled syringes in secondary packaging where the prefilled drug product is various proteins (Metzner et al. para [0061]).

5. Claim 3 rejected under 35 U.S.C. 103(a) as being unpatentable over Metzner et al. (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above, and further in view of Shams (US Patent Application Publication 2007/0190058).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. teaches a method of using hydrogen peroxide vapor for sterilizing different proteins in secondary packaging (para [0061]) at 30°C (para [0063]) and teaches that the treatment did not destroy the protein products (para [0076]). Metzner et al. does not specifically mention the use of the method for treating a medical product where the prefilled drug is ranibizumab, a protein. The claim recites "therapeutically effective" (implying non degraded protein when administered into a body for treatment). A person having ordinary skill in the art at the time of the invention would understand that if this method is capable of sterilizing prefilled protein drug products in secondary packaging without causing degradation of the proteins that the method is capable of treating the specific protein ranibizumab.

Additionally the concept of using ranibizumab delivered by a syringe is also known in the prior art. Shams teaches the administration of ranibizumab by syringe injection (para [0128]). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. with the addition of ranibizumab being the drug in the syringe, as taught by Shams, in order to administer a dose of ranibizumab as a therapuetic drug (abstract and para [0028]) in a sterile manner which is desired by Shams who states that the treatment should be formulated, dosed, and administered in a fashion consistent with good medical practice (para [0092]) which would include using a sterile syringe.

6. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable Metzner et al. over (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above, and as evidenced by Jacobs et al. (US Patent 4,643,876).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. also teaches the use of a post decontamination measure using a vacuum (para [0034]) and a plasma treatment (para [0035]). The post decontamination (after a decontamination using hydrogen peroxide) applies a plasma. This causes an application of ultraviolet light following the duration of hydrogen peroxide vapor treatment

and breaks down the hydrogen peroxide vapor inactivating the vapors oxidative action. Jacobs et al. provides and evidentiary teaching of the breakdown of hydrogen peroxide vapors upon the generation of plasma. Jacobs et al. teaches that forming a plasma from hydrogen peroxide vapor causes a breakdown of hydrogen peroxide that gives off UV light (column 5, lines 34-45).

7. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable Metzner et al. over (US Patent Application Publication Number 2003/0003014) and Hasegawa et al. (US Patent 6,228,324) as applied to claim 1 above, and further in view of Asahara et al. (US Patent Application Publication 2003/0198570).

Metzner et al. teaches the limitations of claim 1 as discussed above. Metzner et al. also teaches the use of a post decontamination measure using a vacuum (para [0034]) and a plasma treatment (para [0035]).

Metzner et al. is silent on how to generate the plasma. It is necessary and therefore obvious to look to the prior art for a known method of generating a plasma from hydrogen peroxide vapor. Asahara et al. provides a teaching that it is known to generate plasma from hydrogen peroxide vapor using ultraviolet light (para [0040], [0049], and [0052]). A person having ordinary skill in the art at the time of the invention would have found it obvious to have used ultraviolet light as taught by Asahara et al. to generate the plasma motivated by the expectation of practicing the invention of Metzner et al. Further it would have been obvious to a person having ordinary skill in the art to substitute one known means to generate plasma from hydrogen peroxide for another known means of generating plasma from hydrogen peroxide with an expectation of successfully generating plasma from hydrogen peroxide.

The combination teaches a post decontamination including the application of ultraviolet light following the duration of treatment with hydrogen peroxide vapor and thereby inactivating the oxidative action of the hydrogen peroxide vapors.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DONALD SPAMER whose telephone number is (571)272-3197. The examiner can normally be reached on Monday through Friday, 9 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on 571-272-1374. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DONALD SPAMER/
Examiner, Art Unit 1775

/SEAN E CONLEY/
Primary Examiner, Art Unit 1775

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13382380	SIGG, JUERGEN
	Examiner	Art Unit
	DONALD SPAMER	4142

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
422	(text limitated)	08/13/2012	Donald Spamer
422	30 (text limited)	08/16/2012	Donald Spamer
206	364 (text limited)	08/08/2012	Donald Spamer
604	199	08/08/2012	Donald Spamer

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search in eDAN	08/16/2012	Donald Spamer
East search history attached	08/16/2012	Donald Spamer
Updated East search history attached	12/18/2012	DS
Updated inventor search in eDAN	5/16/2013	DS
Updated EAST search history	10/02/2013	DS
Updated inventor search in eDAN	10/02/2013	DS
Updated inventor search in eDAN	1/24/2014	DS

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/382,380	01/05/2012	Juergen Sigg	PAT053689-US-PCT	9960

1095 7590 03/12/2014

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
SPAMER, DONALD R	
ART UNIT	**PAPER NUMBER**
1775	

NOTIFICATION DATE	DELIVERY MODE
03/12/2014	ELECTRONIC

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Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Applicant-Initiated Interview Summary	**Application No.** 13/382,380	**Applicant(s)** SIGG, JUERGEN	
	Examiner DONALD SPAMER	**Art Unit** 1775	

All participants (applicant, applicant's representative, PTO personnel):

(1) *DONALD SPAMER*. (3) *Jim Lynch*.

(2) _____. (4)_____.

Date of Interview: *04 March 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: *Metzner (US 2003/0003014) and Hasegawa et al. (US 6,228,324)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed how the specification provided a definition for sterility and stated that the terms "sterilization", "decontamination", "sanitization", and "antimicrobial treatment" are used interchangeably by the specification.

The examiner agreed that adding a clause to the claims specifying the level of decontamination/sterility achieved by the hydrogen peroxide vapor would further prosecution.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/DONALD SPAMER/ Examiner, Art Unit 1775	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
PAT053689-US-PCT	13/382,380	January 5, 2012
First Named Inventor:	**Title:**	
Juergen Sigg	Surface Decontamination of Prefilled Containers in Secondary Packaging	

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:
    - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
    - The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
        - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
        - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
            - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
            - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	Date
/Jim Lynch/	March 13, 2014
Name (Print/Typed) Jim Lynch	Practitioner Registration No. 54,763

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

[✓] * Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

CASE PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF Art Unit: 1775

Sigg, Juergen Examiner: SPAMER, DONALD R

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011

FILED: July 13, 2010

U.S. APPLICATION NO: 13/382,380

35 USC §371 DATE: January 05, 2012

FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CONSIDERATION UNDER AFCP 2.0 AND AMENDMENT

Sir:

This Request for consideration under AFCP 2.0 is being submitted in response to the Final Office Action ("Office Action") in the above application that was mailed to Applicant's attorney on February 7, 2014. Submitted herewith is a request for consideration form (PTO/SB/434) and a response under 37 CFR § 1.116 containing an amendment to at least one independent claim that does not broaden its scope.

Amendments to the Claims is reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A method for surface decontamination of a prefilled syringe in secondary packaging, comprising:

   applying vaporized-hydrogen peroxide to the surface of the prefilled syringe in secondary packaging;

   allowing vaporized-hydrogen peroxide to remain in contact with the prefilled syringe surface for a sufficient time to decontaminate the prefilled syringe surface to a sterility assurance level of at least 10^{-6}; 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 syringe, wherein the prefilled syringe comprises 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.

2. (Canceled)

3. (Previously presented) The method of claim 1, wherein the syringe contains a therapeutically effective amount of ranibizumab.

4. (Previously presented) The method of claim 1, wherein sufficient time to decontaminate the surface of the prefilled syringe is determined by validation of treatment times and compared to a control standard.

5. (Previously presented) The method of claim 1, 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 syringe.

6. (Previously presented) The method of claim 1, 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. (Previously presented) The method of claim 1, wherein the post-decontamination measure includes gas plasma treatment.

8. (Withdrawn) A method for surface decontamination of a prefilled container in secondary packaging, comprising:

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

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.

9. (Withdrawn) 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.

10. (Withdrawn) The method of claim 8, 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.

11. (Withdrawn) The method of claim 8, 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.

12. (Withdrawn) The method of claim 8, wherein the prefilled container is a syringe containing a therapeutically effective amount of ranibizumab.

13. (Withdrawn) The method of claim 8, wherein the penetration depth is measured by dosimetry.

14. (Withdrawn) The method of claim 8, 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.

15. (Withdrawn) The method of claim 8, 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.

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

a sealed chamber; and

a control unit coupled to the chamber, the control unit configured to automatically perform the method according to claim 1.

17. (Withdrawn) 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 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 radiation is allowed to penetrate the secondary package while the thickness of the prefilled container shields the contents therein from beta radiation.

18. (Withdrawn) 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 sealed chamber to perform the method according to claim 1.

19. (Withdrawn) A kit for surface-decontaminating a prefilled container in secondary packaging, 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. (Withdrawn) A system according to claim 16, wherein post-decontamination measure includes gas plasma treatment.

21. (Withdrawn) A kit according to claim 18, wherein post-decontamination measure includes gas plasma treatment.

22. (Previously presented) The method of claim 1, wherein the drug product is a protein solution.

Remarks

I. Claims

Claims 1, 3-7 and 22 are presently pending in this patent application. Independent claim 1 has been amended to recite the level of decontamination.

II. Rejections under 35 U.S.C. § 103 - Obviousness

Initially, the Examiner found that the Applicant's arguments were unpersuasive. Specifically, the Examiner alleges that the initial application of hydrogen peroxide vapor in Metzner is a decontamination step because introduction of such a vapor would "result in at least some destruction of microorganisms."

After careful consideration of the Applicant's other arguments, the Examiner maintained his rejection of Claims 1, 3-7 and 22 under 35 U.S.C. § 103 for obviousness over published U.S. Patent Application 2003/0003014 to Metzner et al. ("Metzner") as evidenced by, and in view of, U.S. Patent 6,228,324 to Hasegawa ("Hasegawa"). The Examiner relies on Metzner for its teaching of a method for surface decontamination of a prefilled container in secondary packaging (citing Metzner at paragraphs [0010-0011]). The Examiner contends that Metzner teaches the use of vaporized hydrogen peroxide to sterilize the surfaces of the packaging (citing Metzner at paragraph [0019]). The Examiner also contends that Metzner teaches the use of a vacuum as a post-contamination treatment (citing Metzner at paragraphs [0034-0035]). In the Examiner's opinion, this post-contamination treatments would remove hydrogen peroxide as evidenced by Hasegawa, as it teaches that the application of a vacuum removes peroxide from inside the packaging (citing column 8, lines 63-67 and column 9, lines 32-28).

The Examiner concedes that Metzner does not teach sterilization of a syringe in secondary packaging. However, the Examiner relies on Hasegawa to cure this deficiency.

With regards to claim 4, the Examiner contends that Metzner teaches a means for determining whether the sterilization is effective, and that this equates to determining whether the treatment times are sufficient.

Regarding Claim 5, the Examiner admits that the intended use of "reversing the direction of diffusion of vaporized hydrogen peroxide and preventing intrusion of vaporized peroxide into the pre-filled container" is not disclosed in Metzner; however it is "capable" of achieving this. As support, the Examiner relies on Hasegawa, and contends that the application of a vacuum removes the hydrogen peroxide from inside the packaging (citing column 8, lines 63-67 and column 9, lines 32-28) and as evidenced by Metzner paragraph [0076].

With regards to claim 7, the Examiner contends that the post-decontamination measure includes plasma treatment as shown in paragraph [0035] of Metzner.

With regards to claim 22, the Examiner asserts that the combination of Hasegawa and Metzner teaches that the prefilled syringes can be filled with various proteins.

Claim 3 was rejected under 35 U.S.C. § 103 as obvious in view of a combination of Metzner, Hasegawa and US Pat. Pub. No. US2007/0190058 to Shams ("Shams"). The Examiner cited Shams to teach the administration of ranibizumab via syringe injection.

The Examiner rejected Claim 6 under 35 U.S.C. § 103 as obvious in view of a combination of Metzner, Hasegawa and Jacobs et al., US Pat, No. 4,643,786 ("Jacobs"). In the Examiner's view Jacobs teaches that the breakdown of hydrogen peroxide vapor causes a breakdown of hydrogen peroxide that gives off UV light.

Claim 6 was also rejected under 35 U.S.C. § 103 as obvious in view of a combination of Metzner, Hasegawa, and further in veiew of Asahara et al., US Pat. Pub. No. 2003/0198570 ("Asahara"). According to the Examiner, Asahara teaches the use of UV light to generate plasma from vapor, and as a result, the combination teaches the use of UV light as a post-decontamination measure.

III. Response/Arguments

The term "decontamination" has been misconstrued by the Examiner

At the heart of the rejection of the claims is the construction of the term "decontaminate". In the Examiner's view, as long as some microorganisms are destroyed from the surface of a syringe, the surface is decontaminated. Applicant's do not dispute this general definition of the term "decontaminate". However, the specification of the present application is very clear as to the meaning of the term "decontaminate". According to paragraph 0036, the terms "sterilization" and "decontamination" are used interchangeably. Paragraph 0037 defines "sterility" to refer to the complete absence of microbial like as defined by a probability of non-sterility as measured by the sterility assurance level (SAL). The SAL for health care products, such as a pre-filled syringe, is defined to be at least 10^{-6}.

While it is black letter law that a patentee can be his own lexicographer, *see In re Paulsen*, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994), in order to expedite prosecution and to clarify the claims Applicant has amended claim 1 to recite that the decontamination step results in a SAL of at least 10^{-6}. In light of this clarification, the Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness. With regards to Claim 1, the Examiner alleges, *inter alia*, that Metzner teaches that the use of vaporized hydrogen peroxide to decontaminate the surfaces of packaging as taught in paragraph [0019].

However, as stated in previous responses, Metzner is directed to a method of using hydrogen peroxide plasma at low temperatures for the sterilization of various products. Paragraph [0019] merely teaches that multiple injections of hydrogen peroxide can be used to create more plasma, which is then utilized to disinfect the product of interest. It does not teach or suggest that vaporized hydrogen peroxide decontaminates surfaces to the degree recited in the instantly present claims. Instead, as repeatedly stated in Metzner, it is the plasma, as

opposed to the vapor, which is responsible for the sterilization (i.e., the decontamination). This is in marked contrast to the present claims, which recite the use of vaporized hydrogen peroxide as the sterilizing agent.

Nor do any of the other references relied upon by the Examiner cure this deficiency. While some references disclose the use of hydrogen peroxide, as stated in previous replies, they operate under different temperatures, pressures and the like and are not suitably combined. As a result, no combination of references teaches the present invention. As such, the rejection under 35 USC §103 is improper and accordingly Applicant respectfully requests that the rejections be withdrawn.

IV. Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Action of record and that Claims 1, 3-7 and 22 are now in condition for allowance. Applicant respectfully requests that the Office withdraw all grounds for rejection and issue a Notice of Allowance at its earliest convenience. If there are any issues that can be resolved by a telephone conference, the Examiner is invited to call the undersigned attorney at his convenience.

Respectfully submitted,

/Jim Lynch/

Novartis Pharmaceuticals Corporation One Health Plaza, Bldg. 101 East Hanover, NJ 07936
+1 8627783423

Jim Lynch
Agent for Applicant
Reg. No. 54,763

Date: March 13, 2014

Electronic Acknowledgement Receipt	
EFS ID:	18460464
Application Number:	13382380
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Surface Decontamination of Prefilled Containers in Secondary Packaging
First Named Inventor/Applicant Name:	Juergen Sigg
Customer Number:	1095
Filer:	James L Lynch/Denise Cooper
Filer Authorized By:	James L Lynch
Attorney Docket Number:	PAT053689-US-PCT
Receipt Date:	13-MAR-2014
Filing Date:	05-JAN-2012
Time Stamp:	14:39:42
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	After Final Consideration Program Request	PAT053689-US-PCT-sb0434.pdf	226717 61342bc249f32ce4788bf29ef1d43d3ac001dc8a8	no	2
Warnings:					
Information:					

2	Response After Final Action	PAT053689-US-PCT-ResponseOA-2013-03-13.pdf	232707 82b34a21b58f5e276c4fc37de09f5e0307df6e63	no	8

Warnings:	
Information:	
Total Files Size (in bytes):	459424

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/382,380	Filing Date 01/05/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 = *		X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 = *		X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	03/13/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 22	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***5	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/BRENDA MURPHY/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/382,380	01/05/2012	Juergen Sigg	PAT053689-US-PCT	9960

1095 7590 04/02/2014

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
SPAMER, DONALD R	
ART UNIT	**PAPER NUMBER**
1775	

NOTIFICATION DATE	DELIVERY MODE
04/02/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Office Action Summary	Application No. 13/382,380	Applicant(s) SIGG, JUERGEN	
	Examiner DONALD SPAMER	Art Unit 1775	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/13/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1 and 3-22* is/are pending in the application.

5a) Of the above claim(s) *8-21* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 3-7, and 22* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPH-feedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Arguments and Amendments filed 3/13/2014 have been entered and considered. Claims 1 and 3-22 remain pending with claims 8-21 withdrawn. Claims 1, 3-7, and 22 are presented for examination.

Response to Arguments

3. Applicant's arguments, see part III, filed 3/13/2014, with respect to the rejection(s) of claim(s) 1, 3-7, and 22 under 35 U.S.C.103 have been fully considered and are persuasive. The applicant correctly points out that decontamination is defined by the specification to be the same as sterilization. The specification continues to define sterility as the complete absence of microbial life as defined by a sterility assurance level of 10^{-6}. The application of vapor hydrogen peroxide taught by Metzner et al., relied upon as the decontamination step, occurs so that Metzner et al. can generate a plasma from the hydrogen peroxide vapor (consequently destroying the hydrogen peroxide vapor). The plasma is used as the sterilization step by Metzner et al. Thus it is clear in Metzner et al. that the hydrogen peroxide vapor is not in contact with the prefilled syringe long enough to cause a sterility assurance level of 10^{-6} (a common standard for sterility) since Metzner et al. follows the application of hydrogen peroxide vapor with the plasma sterilization step. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is presented below.

4. The finality of the rejection mailed 2/7/2014 is withdrawn. Claim amendments filed 3/13/2014 have been entered.

Claim Rejections - 35 USC § 112

5. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3-7, and 22 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 1 recites the limitation "the surface" in 3. There is insufficient antecedent basis for this limitation in the claim. Claims 3-7 and 22 depend from claim 1 and are thus rejected for the same reason.

Claim Rejections - 35 USC § 103

7. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 4, 5, and 22 are are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Hasegawa et al. (US Patent 6,228,324) and further in view of Metzner et al. (US Patent Application Publication 2003/0003014) and Schneider et al. (US Patent 5,037,623).

With regards to claim 1, Hasegawa et al. teaches a method of sterilizing a prefilled syringe (medicine filled injector 4) in secondary packaging (packaging container 1) (fig 4 and column 2, lines 20-28). Hasegawa et al. teaches applying vaporized hydrogen peroxide to the surface of the prefilled syringe in secondary packaging and allowing the hydrogen peroxide vapor to remain in contact with the prefilled syringe surface for a sufficient time to sterilize the syringe surface (abstract, column 8, lines 38-47, and column 12, lines 13-19). Hasegawa et al. teaches a post decontamination measure (vacuum and degassing treatment) to occur to reduce the presence of vaporized hydrogen peroxide thereby preventing

vaporized hydrogen peroxide from diffusing into the prefilled syringe (column 8, line 63 through column 10, line 39).

Hasegawa et al. does not teach a specific degree of sterilization such as the claimed sterility assurance level of at least 10^{-6}. Schneider et al. teaches that sterilization connotes the absence of all life forms including endospores and that a sterility assurance level of a one in one million chance of having a contaminated item after the sterilization (SAL of 10^{-6}) is the minimum acceptable level for medical devices (column 1, line 55 through column 2, line 14). A person having ordinary skill in the art at the time of the invention would have found it obvious to have achieved a sterility assurance level of at least 10^{-6} in order to have a properly and effectively sterilized medical device (prefilled syringe).

Hasegawa et al. does not teach that the medicine in the syringe is a drug that is otherwise sensitive to sterilization treatments using gamma radiation, steam, and other vapors and gases. Metzner et al. teaches a sterilization method for a prefilled container in secondary packaging that includes a step of exposing the prefilled container in secondary packaging to hydrogen peroxide vapors (para [0010], [0011], [0032], [0033]). Metzner et al. teaches that the container can be prefilled with temperature sensitive pharmaceuticals (para [0002]) which are sensitive to sterilization with gamma radiation (para [0005]), autoclaving (para [0003]) (exposure to steam), and ethylene oxide (since ethylene oxide residue can render the drug product toxic or carcinogenic) (gas) (para [0004]) and gives the example of a protein drug product (para [0061]). A person having ordinary skill in the art at the time of the invention would have found it obvious to have used the sterilization method on a syringe that is prefilled with a drug product that is sensitive to sterilization treatments using gamma radiation, steam, and ethylene oxide such as a protein drug product motivated by the expectation that the method taught by Hasegawa et al. would be safe for use with a protein drug product as taught by Metzner et al. (Metzner et al. exposes a prefilled container of protein drug product in secondary packaging to hydrogen peroxide vapor).

With regards to claim 4, Hasegawa et al. is silent as to how sufficient time to decontaminate the surface is determined. It is therefore necessary and thus obvious to look to the prior art for a known way of determining sterilization treatment times. Schneider et al. teaches establishing the time to achieve sterility by exposing a given quantity of endospores known to be resistant to the sterilant, obtaining a D

value, and then using the D value to find the exposure time necessary to achieve a SAL of 10^{-6} (column 1, line 55 through column 2, line 14). A person having ordinary skill in the art at the time of the invention would have found it obvious to have used the treatment time determination method taught by Schneider et al. in order to insure proper and effective sterilization of the medical device (prefilled syringe) thus successfully practicing the invention of Hasegawa et al. The combination results in determining the sufficient time for decontamination by validation of treatment times compared to a control standard.

With regards to claim 5, the post decontamination measure taught by Hasegawa et al. 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 syringe (column 8, line 63 through column 10, line 39).

With regards to claim 22, the combination of Metzner et al. and Hasegawa et al. teaches that the hydrogen peroxide vapor sterilization method can be used for sterilizing prefilled syringes in secondary packaging where the prefilled drug product is various protein solutions (Metzner et al. para [0061]).

9. Claim 3 rejected under 35 U.S.C. 103(a) as being unpatentable over Hasegawa et al. (US Patent 6,228,324), Metzner et al. (US Patent Application Publication 2003/0003014), and Schneider et al. (US Patent 5,037,623) as applied to claim 1 above, and further in view of Shams (US Patent Application Publication 2007/0190058).

The combination of Hasegawa et al. and Metzner et al. as described above teaches a method of using hydrogen peroxide vapor for sterilizing different proteins in secondary packaging (para [0061]) at 30°C (para [0063]) and teaches that the treatment did not destroy the protein products (para [0076]). Metzner et al. does not specifically mention the use of the method for treating a medical product where the prefilled drug is ranibizumab, a protein. The claim recites “therapeutically effective” (implying non degraded protein when administered into a body for treatment). A person having ordinary skill in the art at the time of the invention would understand that if this method is capable of sterilizing prefilled protein drug products in secondary packaging without causing degradation of the proteins that the method is capable of treating the specific protein ranibizumab.

Additionally the concept of using ranibizumab delivered by a syringe is also known in the prior art. Shams teaches the administration of ranibizumab by syringe injection (para [0128]). A person having ordinary skill in the art at the time of the invention would be capable of modifying the method taught by Metzner et al. with the addition of ranibizumab being the drug in the syringe, as taught by Shams, in order to administer a dose of ranibizumab as a therapuetic drug (abstract and para [0028]) in a sterile manner which is desired by Shams who states that the treatment should be formulated, dosed, and administered in a fashion consistent with good medical practice (para [0092]) which would include using a sterile syringe.

10. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hasegawa et al. (US Patent 6,228,324), Metzner et al. (US Patent Application Publication 2003/0003014), and Schneider et al. (US Patent 5,037,623) as applied to claim 1 above, and further in view of Bates et al. (US Patent Application Publication 2008/018195).

Hasegawa et al. does not teach that the post decontamination measure includes applying UV rays following the duration of treatment with the vaporized hydrogen peroxide thereby inactivating the hydrogen peroxide vapors. Hasegawa et al. instead teaches that the post decontamination measure includes degassing the chamber and sending the hydrogen peroxide vapors to a catalytic reactor to breakdown and remove the hydrogen peroxide vapor from the air (column 9, lines 39-48). Bates et al. teaches that another known way to break down hydrogen peroxide after a disinfecting treatment is to expose the hydrogen peroxide to UV light (para [0129]). A person having ordinary skill in the art at the time of the invention would have found it obvious to substitute one known way of breaking down hydrogen peroxide (UV light exposure) for another (catalyst) with the expectation of successfully breaking down the hydrogen peroxide. The combination would result in applying UV rays following the duration of treatment with the vaporized hydrogen peroxide thereby inactivating the hydrogen peroxide vapors

11. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hasegawa et al. (US Patent 6,228,324), Metzner et al. (US Patent Application Publication 2003/0003014), and Schneider et

al. (US Patent 5,037,623) as applied to claim 1 above, and further in view of Rohatgi et al. (Development of Vapor Phase Hydrogen Peroxide Sterilization Process for Spacecraft Applications).

Hasegawa et al. does not teach that the post decontamination measure includes gas plasma treatment. Hasegawa et al. instead teaches that the post decontamination measure includes degassing the chamber and sending the hydrogen peroxide vapors to a catalytic reactor to breakdown and remove the hydrogen peroxide vapor from the air (column 9, lines 39-48). Rohatgi et al. teaches that another known way to break down hydrogen peroxide after a disinfecting treatment is to generate a plasma to break down the hydrogen peroxide into nontoxic products (step 4 on page 225, see whole document). A person having ordinary skill in the art at the time of the invention would have found it obvious to substitute one known way of breaking down hydrogen peroxide (gas plasma treatment) for another (catalyst) with the expectation of successfully breaking down the hydrogen peroxide. The combination would result in the post decontamination measure including gas plasma treatment.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DONALD SPAMER whose telephone number is (571)272-3197. The examiner can normally be reached on Monday through Friday, 9 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on 571-272-1374. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DONALD SPAMER/
Examiner, Art Unit 1775

/SEAN E CONLEY/
Primary Examiner, Art Unit 1775

Notice of References Cited	Application/Control No. 13/382,380	Applicant(s)/Patent Under Reexamination SIGG, JUERGEN	
	Examiner DONALD SPAMER	Art Unit 1775	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2008/0181950	07-2008	Bates et al.	424/484
*	B	US-5,037,623	08-1991	Schneider et al.	422/292
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Rohatgi et al. Development of Vapor Phase Hydrogen Peroxide Sterilization Process for Spacecraft Applications. Society of Automotive Engineers, Inc. 2001.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13382380	SIGG, JUERGEN
	Examiner	Art Unit
	DONALD SPAMER	4142

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
422	(text limitated)	08/13/2012	Donald Spamer
422	30 (text limited)	08/16/2012	Donald Spamer
206	364 (text limited)	08/08/2012	Donald Spamer
604	199	08/08/2012	Donald Spamer

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search in eDAN	08/16/2012	Donald Spamer
East search history attached	08/16/2012	Donald Spamer
Updated East search history attached	12/18/2012	DS
Updated inventor search in eDAN	5/16/2013	DS
Updated EAST search history	10/02/2013	DS
Updated inventor search in eDAN	10/02/2013	DS
Updated inventor search in eDAN	1/24/2014	DS
Updated inventor search in eDAN	3/24/2014	DS
Updated EAST search history attached	3/24/2014	DS

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9	((break down) or breakdown or (broken down) or decompos$ or destroy$) with hydrogen peroxide with (UV or ultraviolet) same plasma	US-PGPUB; USPAT	ADJ	ON	2014/03/24 15:47
L2	3	(dissociation) with hydrogen peroxide with (UV or ultraviolet) same plasma	US-PGPUB; USPAT	ADJ	ON	2014/03/24 15:58
L3	122	((break down) or breakdown or (broken down) or decompos$ or destroy$) with hydrogen peroxide with plasma	US-PGPUB; USPAT	ADJ	ON	2014/03/24 16:02
L4	410	((break down) or breakdown or (broken down) or decompos$ or destroy$) with hydrogen peroxide with (UV or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2014/03/24 16:51
S1	2	(decontaminating or sterliz$3) same (prefilled)	US-PGPUB; USPAT	ADJ	ON	2012/06/27 07:45
S2	351	(decontaminating or steriliz$3) same (prefilled)	US-PGPUB; USPAT	ADJ	ON	2012/06/27 07:49
S3	41	(decontaminating or steriliz$3) same (prefilled) and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2012/06/27 08:42
S4	11	("6027482" | "4452473" | "4266815" | "5184742" | "5609584" | "5855568" | "6632199" | "6004295" | "5047021" | "5702374" | "5755696").PN.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 10:02
S5	1	"5779973".pn.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 10:08
S6	212	604/199.ccls.	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:06
S7	1451	terminal steriliz$	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:46
S8	116	terminal steriliz$ and ((pre-filled or prefilled) syringe)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:47
S9	22	terminal steriliz$ same ((pre-filled or prefilled) syringe)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 11:48
S10	4	("2006/0106349").URPN.	USPAT	ADJ	ON	2012/08/08 11:59
S11	21	(decontaminating or steriliz$3) same (pre-filled) and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2012/08/08 12:02

S12	14	("4230663" | "4878903" | "5407070" | "5615772" | "5792422" | "5817065").PN. OR ("6228324").URPN.	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 12:20
S13	86	"422".clas. and ((pre-filled or prefilled) (syringe or container))	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 13:26
S14	24	("4226410" | "4236731" | "4947620" | "4962856" | "5033252" | "5052558" | "5178267" | "5178277" | "5217772" | "5220769" | "5536356" | "5571361" | "5590778" | "5715943" | "5830547" | "5868244" | "5949032" | "5976299" | "6034008" | "6117505" | "6228324" | "6419392" | "6449925").PN. OR ("6986730").URPN.	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/08/08 15:39
S15	34	("4878903").URPN.	USPAT	ADJ	ON	2012/08/08 16:16
S16	376	206/364.ccls.	USPAT	ADJ	ON	2012/08/08 16:35
S17	7	206/364.ccls. and (hydrogen peroxide)	USPAT	ADJ	ON	2012/08/08 16:36
S18	1119	ranibizumab	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:42
S19	527	ranibizumab and syringe	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:43
S20	122	ranibizumab and syringe and (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 16:43
S21	15	206/364.ccls. and (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/08 17:06
S22	195	syringe and (hydrogen peroxide)	EPO; JPO; DERWENT	ADJ	ON	2012/08/08 17:22
S23	0	(nishimura and onishi and saiki).pn.	US-PGPUB; USPAT	ADJ	ON	2012/08/09 11:16
S24	17	protein same syringe same (hydrogen peroxide)	US-PGPUB; USPAT	ADJ	ON	2012/08/09 11:28
S25	1408	(filter or selective$3) same (UV or ultraviolet) same (sterili$3 or saniti$3 or decontaminate)	US-PGPUB; USPAT	ADJ	ON	2012/08/13 16:39
S26	70	(filter or selective$3) same (UV or ultraviolet) same (package or item) and "422".clas.	US-PGPUB; USPAT	ADJ	ON	2012/08/13 16:46
S27	0	2003/0003014	US-PGPUB; USPAT	ADJ	ON	2012/08/13 17:51
S28	399	metzner.in.	US-PGPUB; USPAT	ADJ	ON	2012/08/13 17:52
S29	49330	hydrogen peroxide and (uv or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2012/08/16 12:54

S30	21	hydrogen peroxide with (uv or ultraviolet) with (inactivat$3)	US-PGPUB; USPAT	ADJ	ON	2012/08/16 12:55
S31	19	hydrogen peroxide and (uv or ultraviolet) and 422/30.ccls.	US-PGPUB; USPAT	ADJ	ON	2012/08/16 13:47
S32	0	2007/0190058	US-PGPUB; USPAT	ADJ	ON	2012/08/20 08:54
S33	1	"20070190058"	US-PGPUB; USPAT	ADJ	ON	2012/08/20 08:54
S34	4	("4169123" | "4169124" | "4512951" | "7060269").PN.	US-PGPUB; USPAT	ADJ	ON	2012/12/17 08:22
S35	0	(sterili$ or disinfect or decontaminat$ or saniti$) same (pre-filled or prefilled) same (hydrogen peroxide) same ((atmosphere or ambient) pressure)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 17:56
S36	31	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same ((atmosphere or ambient) pressure)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 17:56
S37	204	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same (atmospheric pressure)	US-PGPUB; USPAT	ADJ	ON	2012/12/18 10:33
S38	1	"6228324".pn.	US-PGPUB; USPAT	ADJ	ON	2012/12/18 11:00
S39	58	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same (atmospheric pressure) same (below and above)	US-PGPUB; USPAT	ADJ	ON	2012/12/18 11:04
S40	17	(sterili$ or disinfect or decontaminat$ or saniti$) same (hydrogen peroxide) same ((atmospheric pressure) with (below and above))	US-PGPUB; USPAT	ADJ	ON	2012/12/18 11:05
S41	155	hydrogen peroxide with plasma with (UV or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2013/10/02 12:32
S42	1	"20050158206".pn.	US-PGPUB; USPAT	ADJ	ON	2013/10/02 12:58
S43	4	(make or generate or generation) with hydrogen peroxide with plasma with (UV or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2013/10/02 13:22
S44	4	(make or generate or generation) with hydrogen peroxide with plasma same (UV or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2013/10/02 13:24
S45	41	(make or generate or generation) with hydrogen peroxide with plasma and (UV or ultraviolet)	US-PGPUB; USPAT	ADJ	ON	2013/10/02 13:25
S46	55	(sterili$ or disinfect$ or decontamin$ or saniti$) with syringe same hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2014/03/20 09:20
S47	190	(sterili$ or disinfect$ or decontamin$ or saniti$) with secondary with packag$	US-PGPUB; USPAT	ADJ	ON	2014/03/20 09:26

S48	27	(sterili$ or disinfect$ or decontamin$ or saniti$) with secondary with packag$ and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2014/03/20 09:26
S49	78	sterili$ with sterility assurance level and hydrogen peroxide and (terminal or secondary)	US-PGPUB; USPAT	ADJ	ON	2014/03/24 12:37
S50	26	sterili$ with sterility assurance level with (syringe or medical) and hydrogen peroxide	US-PGPUB; USPAT	ADJ	ON	2014/03/24 12:38

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/382,380	01/05/2012	Juergen Sigg	PAT053689-US-PCT	9960

1095 7590 11/06/2014

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
SPAMER, DONALD R	
ART UNIT	**PAPER NUMBER**
1775	

NOTIFICATION DATE	DELIVERY MODE
11/06/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Notice of Abandonment	Application No.	Applicant(s)
	13/382,380	SIGG, JUERGEN
	Examiner	Art Unit
	DONALD SPAMER	1775

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *02 April 2014*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection. (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33(b). See 37 CFR 1.138(b).

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

/SEAN E CONLEY/
Primary Examiner, Art Unit 1775

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.