Copy for (DO-US) 36

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

Authorized officer
Nissen Diana
e-mail diana.nissen@wipo.int
Telephone No. +4122 338 8054

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 (REV 10-96) — U.S. Department of Commerce Patent and Trademark Office

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

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

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 15. 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	6	- 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 PAT053889

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.

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	09169458.8		☒ 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 PAT053669

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 01/03/2010 (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.

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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-			
		US-			
		US-			
		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.

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,

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

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

Date: January 5, 2012

INVENTOR INFORMATION

Inventor One Given Name:: Juergen
Family Name:: Sigg
Postal Address Line One:: Karl-Arzet-Weg 25
City:: Loerrach
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

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($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1990**

Electronic Acknowledgement Receipt

EFS ID:	11767027
Application Number:	13382380
International Application Number:	PCT/EP10/60011
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:	
Receipt Date:	05-JAN-2012
Filing Date:	
Time Stamp:	14:56:16
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	$1990
RAM confirmation Number	1209
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. 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:

Information:

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:					
Information:					
			Total Files Size (in bytes):	11247090	

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 January 2011 (20.01.2011)

PCT

(10) International Publication Number
WO 2011/006877 A1

(51) **International Patent Classification**:
A61L 2/00 (2006.01) ***A61L 2/08*** (2006.01)
A61L 2/20 (2006.01) ***B65B 55/08*** (2006.01)
B65B 55/10 (2006.01)

(21) **International Application Number**:
PCT/EP2010/060011

(22) **International Filing Date**:
13 July 2010 (13.07.2010)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
09165456.6 14 July 2009 (14.07.2009) EP

(71) **Applicant** *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

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

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

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

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

Published:

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

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

WO 2011/006877 A1

(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. 120º C — 132º 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.

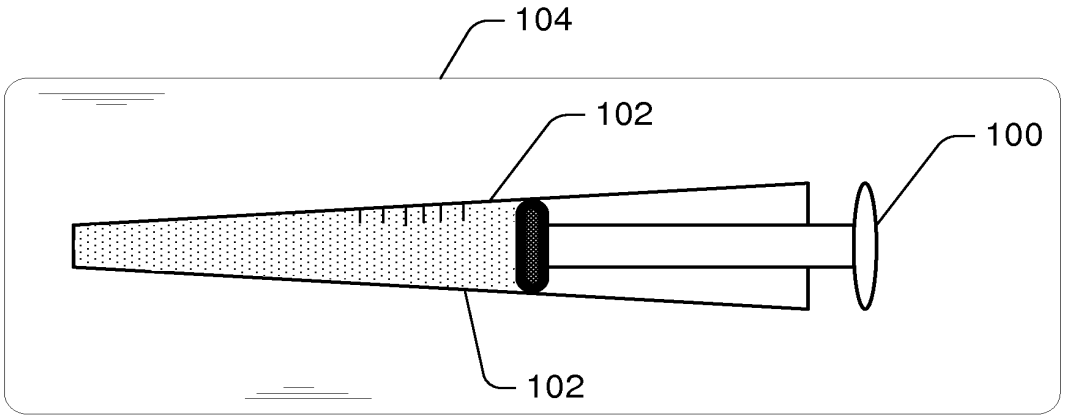

Fig. 1

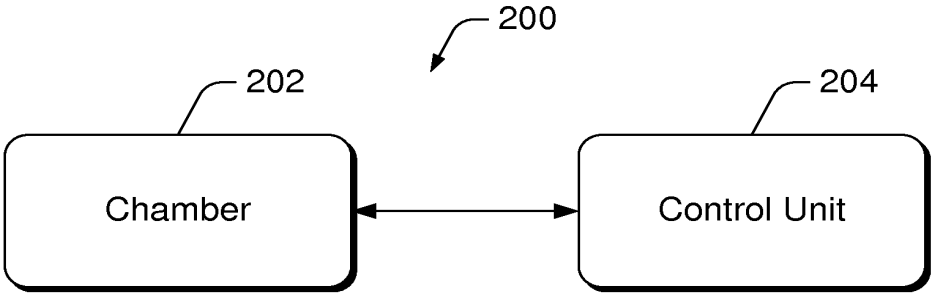

Fig. 2

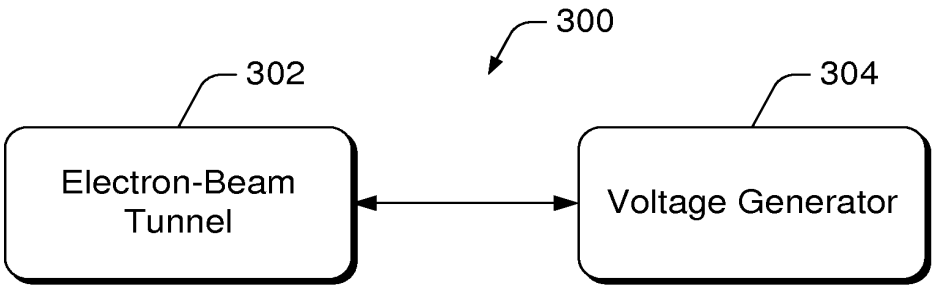

Fig. 3

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
Filing date: 14 July 2009 (14.07.2009)

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

Europäisches Patentamt
European Patent Office
Office européen des brevets

Bescheinigung	Certificate	Attestation
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

ME51241

EPA/EPO/OEB Form 1014 12.08

Anmeldung Nr:
Application no.: 09165456.6
Demande no :

Anmeldetag:
Date of filing: 14.07.09
Date de dépôt :

Anmelder / Applicant(s) / Demandeur(s):

Novartis AG
Lichtstrasse 35
4056 Basel/CH

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:

Internationale Patentklassifikation / International Patent Classification / Classification internationale de brevets:

A61L2/00

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.

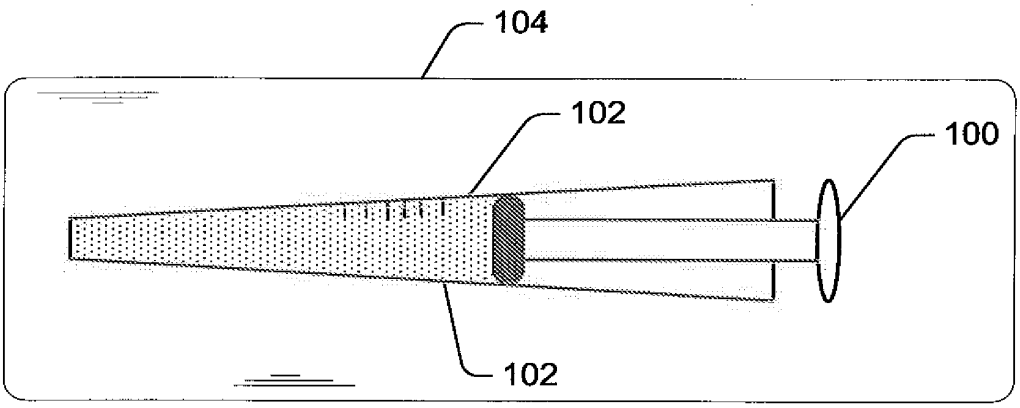

Fig. 1

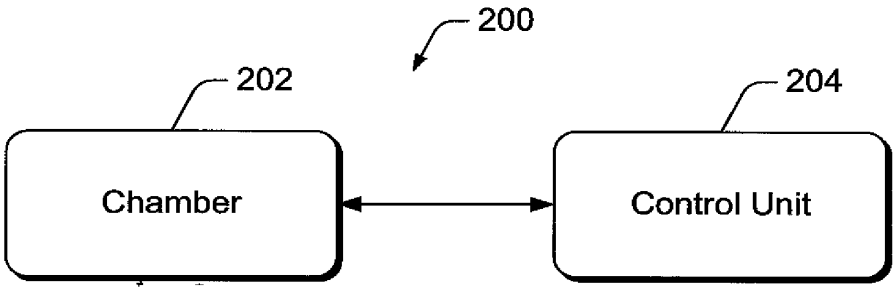

Fig. 2

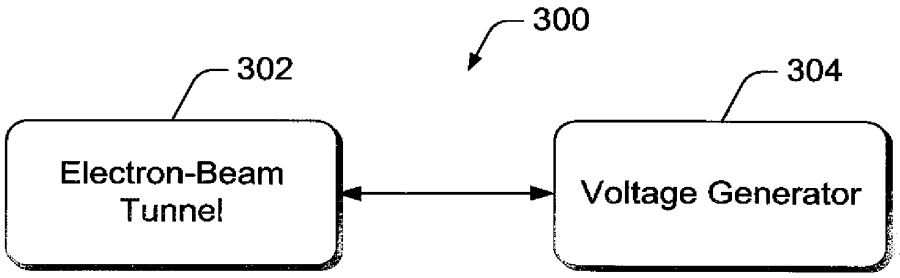

Fig. 3

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.

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

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	

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)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	01/05/2012	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		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)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	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/

Europäisches Patentamt
European Patent Office
Office européen des brevets

Bescheinigung	Certificate	Attestation
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

ME51241

EPA/EPO/OEB Form 1014 12.08

Anmeldung Nr:
Application no.: 09165456.6
Demande no :

Anmeldetag:
Date of filing: 14.07.09
Date de dépôt :

Anmelder / Applicant(s) / Demandeur(s):

Novartis AG
Lichtstrasse 35
4056 Basel/CH

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:

Internationale Patentklassifikation / International Patent Classification / Classification internationale de brevets:

A61L2/00

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.

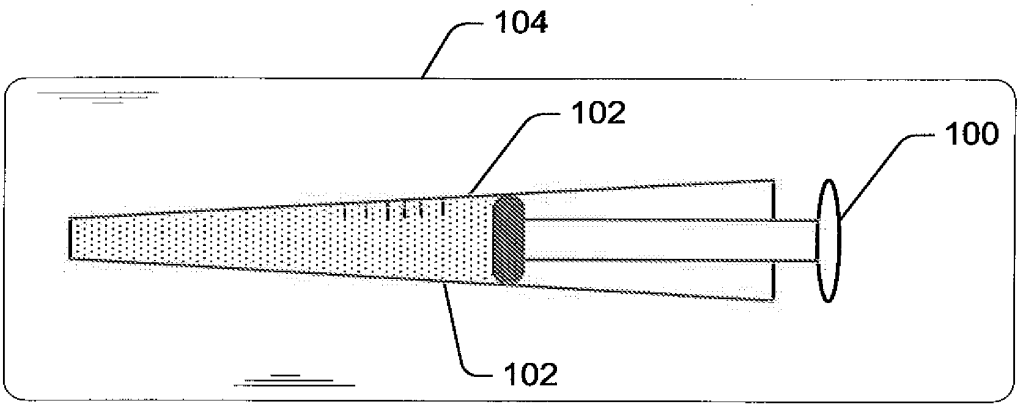

Fig. 1

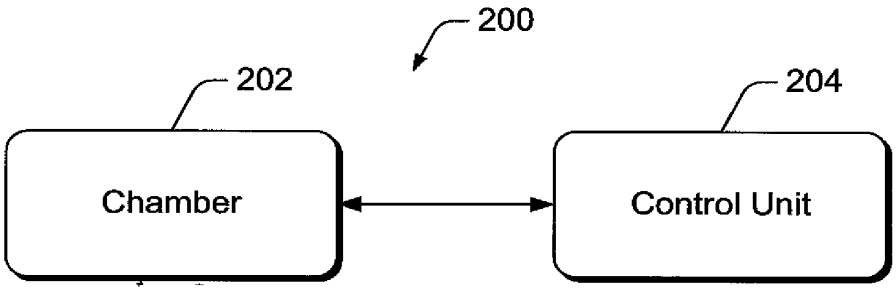

Fig. 2

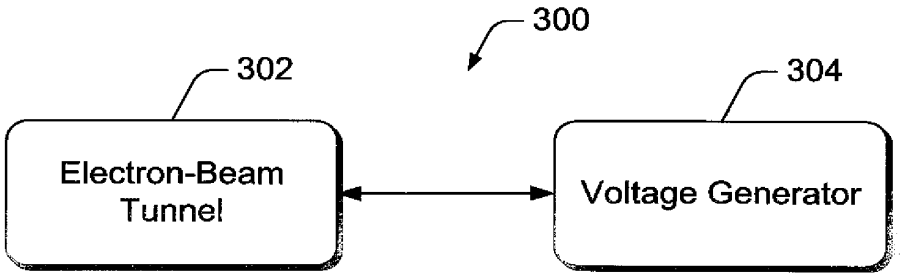

Fig. 3

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
Filing date: 14 July 2009 (14.07.2009)

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

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

Authorized officer
Nissen Diana
e-mail diana.nissen@wipo.int
Telephone No. +4122 338 8054

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

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)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2010/060011

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.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 January 2011 (20.01.2011)

PCT

(10) International Publication Number
WO 2011/006877 A1

(51) **International Patent Classification**:
A61L 2/00 (2006.01) ***A61L 2/08*** (2006.01)
A61L 2/20 (2006.01) ***B65B 55/08*** (2006.01)
B65B 55/10 (2006.01)

(21) **International Application Number**:
PCT/EP2010/060011

(22) **International Filing Date**:
13 July 2010 (13.07.2010)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
09165456.6 14 July 2009 (14.07.2009) EP

(71) **Applicant** *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

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

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

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

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

Published:

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

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

WO 2011/006877 A1

(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. 120º C — 132º 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.

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 /

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

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

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
Filing Date:	05-JAN-2012
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
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	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
FOR	NUMBER FILED	NUMBER EXTRA					
☐ 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 ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
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/

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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 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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

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	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☑ Yes ☐ No	/DONALD R SPAMER/ Examiner's Signature	☐ Initials	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	
1990	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 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.	
		US-			
		US-			
		US-			
		US-			
		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	/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.

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.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

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
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

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

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
Reg. No. 51,813

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

Date: December 12, 2012

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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-			
		US-			
		US-			
		US-			
		US-			
		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]
						☐
						☐
						☐
						☐
						☐
						☐

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.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

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:
Mail Stop RCE
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 ROBER
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	

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 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/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 2005/0226784 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/

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

Novartis Pharmaceuticals Corporation One Health Plaza, Bldg. 101 East Hanover, NJ 07936
+1 8627785816

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 3-6). 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: 27 Aug 2013

Juergen Sigg, Ph.D.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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 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 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.

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

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/

Novartis Pharmaceuticals Corporation One Health Plaza, Bldg. 101 East Hanover, NJ 07936
+1 8627783423

Jim Lynch
Agent for Applicant
Reg. No. 54,763

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
Filer Authorized By:	James L Lynch
Attorney Docket Number:	PAT053689-US-PCT
Receipt Date:	12-SEP-2013
Filing Date:	05-JAN-2012
Time Stamp:	12:10:36
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	Amendment/Req. Reconsideration-After Non-Final Reject	PAT053689-US-PCT-ResponseOA-Sep2013.pdf	170959 d4c05f3713c76ef3033aaf8484bd4189ea00bd43	no	9

Warnings:	
Information:	

Total Files Size (in bytes):	170959

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/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2008014166	WO	A2	2008-01-31	JOHNSON DIVERSEY, INC		☐
	2	0761238	EP	A2	1997-03-12	CIBA-GEIGY AG		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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

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		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*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.

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

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.**

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 the Freedom of Information Act requires disclosure of these record s.

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 inspections 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
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

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/

Jim Lynch
Agent for Applicant
Reg. No. 54,763

Novartis Pharmaceuticals Corporation One Health Plaza, Bldg. 101 East Hanover, NJ 07936
+1 8627783423

Date: September 13, 2012

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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 10/23/2013

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
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-			
	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.

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

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2008014166	WO	A2	2008-01-31	JOHNSON DIVERSEY, INC		☐
	2	0761238	EP	A2	1997-03-12	CIBA-GEIGY AG		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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	Filing Date	2012-01-05
	First Named Inventor	Sigg, Juergen
	Art Unit	1775
	Examiner Name	SPAMER, DONALD ROBERT
	Attorney Docket Number	PAT053689-US-PCT

(Not for submission under 37 CFR 1.99)

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		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

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.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.S./

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 the Freedom of Information Act requires disclosure of these record s.

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 inspections 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.

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
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

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: 13/382380
35 USC §371 DATE: January 05, 2012
FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Art Unit: 1775
Examiner: SPAMER, DONALD R

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/

Novartis Pharmaceuticals Corporation One Health Plaza, Bldg. 101 East Hanover, NJ 07936
+1 8627783423

Jim Lynch
Agent for Applicant
Reg. No. 54,763

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
Attorney Docket Number:	PAT053689-US-PCT
Receipt Date:	14-JAN-2014
Filing Date:	05-JAN-2012
Time Stamp:	11:09:42
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	Response After Final Action	PAT053689-US-PCT-ResponseOA-14Jan2014.pdf	235384 09e1b71217908664fa0cb7730ed559dcde69a226	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

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	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

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT	01/14/2014	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	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**

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	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/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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 02/07/2014

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
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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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 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

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

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/382,380	SIGG, JUERGEN	
	Examiner	Art Unit	
	DONALD SPAMER	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.

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: 13/382,380
35 USC §371 DATE: January 05, 2012
FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Art Unit: 1775
Examiner: SPAMER, DONALD R

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/

Jim Lynch
Agent for Applicant
Reg. No. 54,763

Novartis Pharmaceuticals Corporation One Health Plaza, Bldg. 101 East Hanover, NJ 07936
+1 8627783423

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 61342bc249f32ce478bf29ef1d43d3ac001dc8a8	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/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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 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 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.

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

3/24/2014 5:33:52 PM
C:\Users\dspamer\Documents\EAST\Workspaces\13382380.wsp

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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 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.