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Clarke, Modet & Cº
COLOMBIA

ESCOBAR - URIBE ASOCIADOS
Intellectual Property

As. 2961/P.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

SUPERINTENDENCIA Y COMERCIO
-00002-0000
2020 NUEVAS CREACIONES
RECIBIDO

Ref.: Expediente No. **06-031.931**
Solicitud de Patente a nombre de
Ethicon, Inc.

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **Ethicon, Inc.,** con domicilio en Somerville, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 07 - 100,434 de 10 de diciembre de 2007, por la suma de $404.000.oo, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,

JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P. 68.228

218 218

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 07 - 100,434
FECHA : DICIEMBRE 10 DE 2007

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	72394969	10/12/2007	32,420,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	404.000.00
			TOTAL : $	404,000.00

SON: CUATROCIENTOS CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06 031931

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **577** DE

FECHA **29 DE JUNIO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **27 DE SEPTIEMBRE DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO X

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogada
Jimena Escobar U.
(Apoderada)

ASUNTO	Radicación	06 - 31 931
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	[illegible] 3139
	Folios	058

Patente de Invención ✓ Patente de Modelo de Utilidad ___

Vía Nacional ___

Vía PCT (fase nacional) ___ Cap. I ___ Cap. II ___

Solicitud Internacional n.° _____
Fecha de Presentación Intrnl. _____

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción:	Folios 7 a 75 como se radicó inicialmente
Reivindicaciones:	Folios 76 a 78 como se radicó inicialmente
Dibujos:	Folios 79 a 99 como se radicó inicialmente con copia en los folios 172 a 192
Prioridad	Folios 110 a 214 2005-03-31, US 11/096 050

2. Objeto de la invención

Título de la solicitud *Monitoreo de procedimiento de limpieza*, folio 1.

entre los dos, en donde se introduce una suciedad; y, un sujetador para fijar el conjunto.

El problema planteado en esta solicitud es satisfacer la necesidad de monitorear la suciedad remanente en un elemento de uso médico, después de que ha sido limpiado, con el objetivo de pasarlo a esterilización.

Para solucionar este problema técnico la solicitud en estudio proporciona un dispositvo de soporte como el definido arriba.

Clasificación Internacional de Patentes (IPC). G01N 1/28

3. De la solicitud de Patente

Descripción *(artículo 28 D. 486)*

Durante el análisis del texto de la descripción y de las ilustraciones anexadas, se observaron los siguientes defectos:

1) El título o nombre de la invención no coincide con lo que se reclama en el capítulo reivindicatorio.

2) Gran parte de la descripción y las figuras se ocupan de divulgar cuestiones ajenas a lo que se reclama en el capitulo reivindicatorio. De hecho, en el texto, la descripción del objeto de la solicitud prácticamente sólo se inicia en la página 66, folio 72 y en la figura 16a, folio 97. Lo peor es que no se establece una relación clara entre dicho objeto y toda la información que lo precede. Esto afecta negativamente la claridad de la solicitud

3) En la página 1 folio 7, se afirma que el campo de la invención es el de los estándares de suciedad para el monitoreo de un procedimiento de limpieza pero, esto, por una parte, no coincide con el título o nombre de la invención y, por otra parte, tampoco coincide con lo que se reclama en las reivindicaciones.

4) En la página 2, folio 8, aparece por primera vez un número (*3,640,295*) en el cual se emplea mal la coma. En Colombia, para ser usada junto con los números, la coma es el signo de separación decimal.

5) En la página 3, folio 9 aparece por primera vez la expresión *la patente... no dirige estándares...* que carece de sentido. Se sugiere sustituir el término *dirige* por *señala* o *indica* o *insinúa* o *sugiere* u otra expresión que se ajuste mejor a lo que el solicitante quiere decir.

6) En la página 5, folio 11, aparece por primera vez la expresión *de nueva cuenta* que no es corriente en nuestro país.

7) En la página 7, folio 13, aparece la expresión *0.05 mm* en la cual, por primera vez en la solicitud, se utiliza el punto como separador decimal y se omite emplear la coma decimal.

8) En la página 8, folio 14, aparece por primera vez la expresión *aspas de acero inoxidable inoculadas con...* que carece de sentido porque el verbo *inocular* no es aplicable a este caso. Lo similar es aplicable a la expresión *tiras de politetrafluoroetileno inoculadas con...* que aparece en la página 9, folio 15. Un defecto similar ocurre en la expresión *la inoculación de... en aspas de acero inoxidable* que se encuentra en la página 11, folio 17.

9) En la misma pagina 8, aparece por primera vez una sigla (*RPMI*) que no está acompañada por su correspondiente significado. Otras siglas que

unidades (*EC*). En todo caso, el solicitante debe emplear las unidades del Sistema Internacional.

11) En la página 10 folio 16, aparece la expresión *las figuras 15a-15d* en la cual se deben sustituir las minúsculas por mayúsculas porque es así como se encuentran designadas en las ilustraciones de los folios 93 a 96.

12) En la página 11 folio 17 aparece la expresión *6 mg/litros* en la cual se mezclan un símbolo de unidad con un nombre de unidad -lo que no es correcto-: si se escribe un número se debe acompañarlo por los símbolos y si se escribe la palabra, se debe acompañarla por el nombre, así: *6 mg/L seis miligramos por litro*

13) En la tabla denominada *Cuadro 1* página 12 folio 18 aparecen, en primer lugar, varias cifras en donde se omiten el cero de las unidades y la coma decimal; y, en segundo lugar, aparecen varias fracciones que deben ser sustituidas por números decimales o, alternativamente, por una nueva configuración de las columnas. Un defecto similar ocurre en el *Cuadro 2*, página 13, folio 19.

14) En la página 14, folio 20, aparece la expresión *Sin embargo agua de la llave que contiene múltiples sales a una concentración relativamente baja presenta menos que un desafío ya que cristales uniformes no son propensos a formarse*, que carece de sentido.

15) En la misma página 14 aparece la expresión *el médium de cultivo* que carece de sentido, según el contexto.

16) En la página 15, folio 21, aparece la expresión *oscilaron de 0-60 segundos* en la cual, en primer lugar se debe reemplazar el término *de* por *entre*; y, en segundo lugar se deben incluir las unidades, mejor, el símbolo de las unidades, acompañando a cada número, entonces la expresión debe quedar: *oscilaron entre 0 s y 60 s*, o mejor, *oscilaron entre cero segundos y sesenta segundos.*

17) En la página 17 folio 23 aparece la expresión *sangre... citrada* cuyo significado se desconoce.

18) En la página 21, folio 27, aparece por primera vez la expresión *y/o*. Al respecto, el *Diccionario panhispánico de dudas* de la Real Academia Española y de la Asociación de Academias de la Lengua Española, primera edición, octubre de 2005, página 681, dice:

> *y/o: Hoy es frecuente el empleo conjunto de las conjunciones copulativa y disyuntiva separadas por una barra oblicua, calco del inglés «and/or», con la intención de hacer explícita la posibilidad de elegir entre la suma o la alternativa de dos opciones: «Se necesitan traductores de inglés y/o francés».* ***Se olvida que la conjunción 'o' puede expresar en español ambos valores conjuntamente.***

El examinador ha subrayado la última frase porque es particularmente aplicable a este caso.

19) En la página 24, folio 30, aparece por primera vez la expresión *cloruro de plata/sulfuro de plata* que puede tener los siguientes significados: *(cloruro de plata) o (sulfuro de plata)*; o, también, *(cloruro de plata) sobre (sulfuro de plata)* entre otras interpretaciones posibles. Para resolver la ambigüedad, el solicitante debe expresar en palabras el significado aplicable, omitiendo el uso de la barra (/).

20) En la misma página 24 aparece la expresión *pH/mV/ion* cuyo significado se desconoce. Se le sugiere al solicitante que consulte el apartado BARRA en el *Diccionario panhispánico de dudas* de la Real Academia Española

22) En la página 42, folio 48, aparece por primera vez el término *lumen*. Según el Diccionario de la Real Academia Española (DRAE), el *lumen* es una unidad de medida, por lo que no concuerda su uso con el contexto.
23) En la figura 7, folio 85, aparece la sigla *RPM* cuyo significado no ha sido definido dentro del texto de la descripción. En caso de referirse a *rpm*, el solicitante debe hacer la conversión a unidades del Sistema Internacional. Además, en la misma figura aparece la expresión *1400 RPM + 45 C* cuyo significado se desconoce (se le recuerda al solicitante que C es el símbolo de coulomb o el del carbono, según sea el contexto); en la figura 8, folio 86, aparece un defecto similar al último objetado.

- La descripción no cumple con los requisitos de claridad y divulgación completa, lo que dificulta o impide su comprensión y ejecución de acuerdo al Art. 28 de la Decisión 486

Reivindicaciones *(artículo 30 D 486)*
Durante el análisis del texto de las reivindicaciones se observaron los siguientes defectos:

1) En la reivindicación 1, folio 76, se reclama un *indicador...* pero los componentes definidos allí no permiten indicar nada, en cambio sí corresponden a *una estructura de soporte* que eventualmente podría ser usada para monitorear la limpieza resultante de un procedimiento de limpieza -la estructura no monitorea el procedimiento en sí-. Entonces, el solicitante debe hacer los ajustes necesarios en la redacción de las reivindicaciones y en el título o nombre de la invención.
2) En la misma reivindicación 1 el solicitante, al definir el dispositivo reclamado, dice que está caracterizado porque comprende: ... *suciedad en la brecha*... lo cual debe ser aclarado, porque si siempre debe tener suciedad, ¿cómo puede contribuir a monitorear la limpieza?
3) La reivindicación 3, folio 76, resulta redundante porque ya se había dicho en la reivindicación 1 que la suciedad estaba en la *brecha*, esto es, *entre los dos separadores*. Esto afecta negativamente la concisión.
4) En la reivindicación 10, folio 77, aparece la expresión *0.05 mm* en la cual se omite la coma decimal
5) En la reivindicación 16, folio 78, aparece la expresión *los substratos se pueden separar manualmente para examinar...* que, por una parte incluye una ambigüedad: *se pueden* que lleva tácita la otra posibilidad: *no se pueden*; y, por otra parte, no está explícitamente soportada por el texto de la descripción.

- Debe entenderse que las reivindicaciones dependientes de las reivindicaciones objetadas son asimismo objetadas por razones análogas
- Las reivindicaciones no cumplen con los requisitos de definición, claridad, concisión y sustento por la descripción de acuerdo al Art. 30 de la Decisión 486.

Se deben presentar, entonces, nuevos capítulos descriptivo y reivindicatorio, ambos completos, junto con un nuevo juego de dibujos, donde se hayan corregido todas las objeciones que se han hecho arriba. Esto con el fin de evitar -cuando solo se presentan algunas páginas sueltas corregidas- que el lector tenga que desplazarse desde un sitio a otro de la solicitud y luego regresar, dificultando

Se le advierte al solicitante que las modificaciones sugeridas arriba podrían resultar inconducentes si se mantienen las objeciones a la patentabilidad que se insinúan adelante.

4. Determinación del Estado de la Técnica

- La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es la

Fecha de presentación de la solicitud prioritaria 2005-03-31

- Se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud teniendo en cuenta la fecha indicada y durante la búsqueda de anterioridades se encontraron los siguientes documentos que afectan a la solicitud US 11/096 050 sobre la cual se reclama la prioridad: nuevo capitulo reivindicatorio (de fecha 09-03-11) y el rechazo final de la solicitud por parte de la USPTO (fechado 09-06-24). Se anexan las copias de las páginas pertinentes de estos documentos. También se encontraron los siguientes documentos que forman parte del estado de la técnica más cercano al objeto de la solicitud:

n.°	Documento	Título	Fecha de publicación
D1	Patente US 4 777 020, cuyo inventor es David J. Brigati, quien le cedió sus derechos a la Fisher Scientific Company	«Sheetlike object such as microscope slide»(Un objeto en forma de hoja, como por ejemplo una lámina para microscopio)	1988-10-11
D2	Patente US 6 193 931 B1, cuyos inventores son Szu-Min Lin y Paul Taylor Jacobs, quienes le cedieron sus derechos a la Ethicon, Inc.	«Container monitoring system»(Un sistema para monitorear un recipiente)	2001-02-27
D3	Patente US 6 394 111, cuyos inventores son Szu-Min Lin, Jenn-Han Wang y Paul Taylor Jacobs, quienes le cedieron sus derechos a la Ethicon, Inc.	«Detection of cleanliness of a medical device during a washing process»(Detección de falta de limpieza de un dispositivo de uso médico durante el proceso de lavado)	2002-05-28
D4	Patente US 6 454 874 B1, cuyos inventores son Szu-Min Lin, Jenn-Han Wang y Paul Taylor Jacobs, quienes le cedieron sus derechos a la Ethicon, Inc.	«Method of detecting the cleanliness of a medical device»(Un método para detectar la falta de limpieza en un dispositivo de uso médico)	2002-09-24
D5	Patente US 6 494 964 B1 cuyos inventores son Szu-Min Lin, Jenn-Han Wang y Paul Taylor Jacobs, quienes le cedieron sus derechos a la Ethicon, Inc.	«Monitoring of cleaning process»(Monitoreo de procedimiento de limpieza)	2002-12-17
D6	Patente US 6 516 817 B2, cuyos inventores son Szu-Min Lin, Jenn-Han Wang y Paul T. Jacobs	«Monitoring of cleaning process»(Monitoreo de procedimiento de limpieza)	2003-02-11
	Patente US 6 516 818 B2,	«Monitoring of cleaning	

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n.°	Documento	Título	Fecha de publicación
D8	Publicación US 2003/0164182 A1, cuyos inventores son Szu-Min Lin Jenn-Hann Wang y Paul T. Jacobs	«Monitoring of cleaning process» (Monitoreo de procedimiento de limpieza)	2003-09-04
D9	Publicación US 2004/0101439 A1, cuyos inventores son Adam J. Fusco Cheng-Chung Li y Po K. Yuen	«Biological and chemical reaction devices and methods of manufacture for use as sensors» (Dispositivos para reacción biológica y química y sus métodos de fabricación)	2004-05-27
*	Patente US 7 246 627 B2 cuyos inventores son Szu-Min Lin, Jenn-Han Wang y Paul Taylor Jacobs, quienes le cedieron sus derechos a la Ethicon, Inc.	«Monitoring of cleaning process» (Monitoreo de procedimiento de limpieza)	*2007-07-24*

(*) Este documento corresponde a la concesión del documento D8.
Se anexa la copia de las páginas pertinentes de estos documentos

NOTAS: No se realizaron las evaluaciones de los demás requisitos de patentabilidad, porque se hicieron algunas objeciones respecto a la definición, la claridad y el sustento por la descripción de las reivindicaciones; esto es, no se pudo practicar un análisis comparativo por ausencia de materia.

A pesar de lo anterior, con base en las enseñanzas de los documentos encontrados hasta ahora, en especial los documentos D1 y D9, y tomando en cuenta los argumentos establecidos en el rechazo final de la USPTO sobre la solicitud US 11/096 050, que sirvió de base para reclamar la prioridad de la solicitud en estudio, los cuales se acogen en general, lógicamente haciendo las transcripciones de legislación, se prevén objeciones respecto al nivel inventivo de la solicitud en estudio

5. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados

sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el número 5.2, letra e), del capitulo quinto del titulo primero de la Circular Única n.° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO n.° 2657

EXAMINADOR TÉCNICO
Código n. 202009

CLAIMS

The Listing of Claims replaces all prior versions of claims in the subject application.

1. (Currently amended) A cleaning indicator for monitoring and assuring adequate cleaning of a ~~cleaning process for~~ a medical instrument, the cleaning indicator comprising:

two substantially parallel substrates separated by two substantially equal thickness spacers, wherein a gap is formed between the two substrates;

a soil positioned in the gap; and

at least one holder configured to secure the two substrates and the two spacers together;

wherein a removal of the soil from between the two substrates is monitored to ensure adequate cleaning.

2. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the soil is dried in the gap.

3. (Canceled)

4. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the soil is selected from the group consisting of organic soil, inorganic soil, and mixtures thereof.

5. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the substrates are formed of a metal.

6. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the substrates are formed of a polymer.

7. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the substrates are transparent.

8. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the soil is disposed on a sheet, the sheet being disposed between the substrates.

9. (Currently amended) [[A]] The cleaning indicator according to claim 8 wherein the sheet is flexible.

10. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the spacers have a thickness of about 0.05mm.

11. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the spacers are formed integrally with the substrates.

12. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the holder comprises interlocking portions formed on the substrates.

13. (Currently amended) [[A]] The cleaning indicator according to claim 12 ~~wherein the comprise~~ further comprising a projection on one of the substrates and an opening on the other of the substrates for receiving the projection.

14. (Currently amended) [[A]] The cleaning indicator according to claim 12 wherein the interlocking portions snap together.

15. (Currently amended) [[A]] The cleaning indicator according to claim 12 wherein one of the substrates, one of the spacers and one of the interlocking portions are formed as one integral piece.

16. (Currently amended) [[A]] The cleaning indicator according to claim 1 wherein the substrates can be separated manually to examine the soil between substrates.

17. (New) The cleaning indicator according to claim 1, wherein the holder is selected from a group consisting of a clamp, clip, tape, screw, rubber band, snap-on cap, glue and adhesive.

18. (New) A cleaning indicator for monitoring and assuring adequate cleaning of a medical device, the cleaning indicator comprising:

a soil positioned between two substrates wherein the two substrates are separated by at least two spacers; and

at least one holder to secure the two substrates and the at least two spacers together;

wherein a removal of the soil from between the two substrates is monitored to ensure adequate cleaning.

19. (New) The cleaning indicator according to claim 18, wherein the holders are selected from a group consisting of a clamp, clip, tape, screw, rubber band, snap-on cap, glue and adhesive.

20. (New) A cleaning indicator for monitoring and assuring adequate cleaning of a medical device, the cleaning indicator comprising:

a soil positioned between a first and second substrate wherein the first and second substrate are separated by at least two spacers; and

at least one holder comprising an interlocking portion from one of the first and second substrate to secure the first and second substrate and the at least two spacers together, the interlocking portion comprising at least one projection on at least one of the first and second substrates and at least one corresponding opening positioned opposite the projection for interlocking engagement therewith;

wherein a removal of the soil from between the two substrates is monitored to ensure adequate cleaning.

21. (New) The cleaning indicator according to claim 20, wherein the holder is selected from a group consisting of a clamp, clip, tape, screw, rubber band, snap-on cap, glue and adhesive.

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Notice of References Cited	Application/Control No. 11/096,050	Applicant(s)/Patent Under Reexamination LIN ET AL.	
	Examiner DENNIS M. WHITE	Art Unit 1797	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number (Kind Code if known)	Date (MM-YYYY)	Name	Classification
	A	US-4,777,220	10-1988	Brigati, David J	422/99
*	B	US-2004/0101439	05-2004	Fusco et al.	422/057
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
		US-			
	I	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)
	J	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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Office Action Summary	Application No.	Applicant(s)	
	11/096,050	LIN ET AL.	
	Examiner	Art Unit	
	DENNIS M. WHITE	1797	

-- *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 *11 March 2009*

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final

3)☐ 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

4)☒ Claim(s) *1,2 and 4-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ 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

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08)

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____

5) ☐ Notice of Informal Patent Application

9DETAILED ACTION

1. Amendments filed on 3/11/2009 have been noted. Claims 12, 4-16 are amended. Claim 3 is cancelled. Claims 17-21 are new. Currently claims 1-2, 4-21 are pending.

Claim Rejections - 35 USC § 102

2. 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
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent
>
> (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
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-2, 4, 6-12, 14-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brigati (USP 4,777,020)

Regarding claims 1, 18, and 20, Brigati teach a slide pair assembly comprising:

two identical slides 110 and 130 ("two substantially parallel substrates") separated by top coating 122 and top coating 142 ("two substantially equal thickness spacers"), wherein a gap 40 is formed between the two substrates; a

specimen 20 ("soil") positioned in the gap; and a holder 150 ("at least one holder") configured to secure the two substrates and the two spacers together.

Regarding the limitations, "A cleaning indicator", "for monitoring and assuring adequate cleaning of a cleaning process for a medical instrument" and "wherein a removal of the soil from between the two substrates is monitored to ensure adequate cleaning", the limitations are considered process or intended use limitations, which do not further delineate the structure of the claimed apparatus from that of the prior art. Since these claims are drawn to an apparatus statutory class of invention, it is the structural limitations of the apparatus, as recited in the claims, which are considered in determining the patentability of the apparatus itself. These recited process or intended use limitations are accorded no patentable weight to an apparatus. Process limitations do not add patentablility to a structure, which is not distinguished from the prior art. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See In re Casey, 152 USPQ 235 (CCPA 1967); and In re Otto, 136 USPQ 458, 459 (CCPA 1963). The Courts have held that it is well settled that the recitation of a new intended use, for an old product, does not make a claim to that old product patentable. See In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). The Courts have held that the manner of operating an apparatus does not differentiate an apparatus claim from the prior art, if the prior

art apparatus teaches all of the structural limitations of the claim. See Ex Parte Masham, 2 USPQ2d 1647 (BPAI 1987) (see MPEP § 2114).

Regarding claim 2, Brigati teach the sample can be dried to the slide (col. 8 line 41)

Regarding claim 4, Brigati teach the sample are cells ("organic soil) (col. 8 38).

Regarding claims 6-7, Brigati teach the slide pair is made of glass ("transparent") (col. 5 line 50) with a coating with polymer ("wherein the substrates are formed of a polymer") (col. 11 lines 20-21).

Regarding claims 8-9, Brigati teach the slide assembly further comprises a nitrocellulose strip 643 between slides 610 and 630 where the specimen 620a-d are placed ("wherein the soil is disposed on a sheet, the sheet being disposed between the substrates" "wherein the sheet is flexible") (col. 8 lines 55-59).

Regarding claims 10, Brigati teach the raised portion such as the shim cover slip or a coating are from 50 to 500 micrometers ("wherein the spacers have a thickness of about 0.05mm")

Regarding claim 11, Brigati teach the raised patterns can be coatings ("spacers are formed integrally with the substrates") (col. 6 lines 1-7).

Regarding claim 12, 14-15, and 20, Brigati teach the slide 130 comprises protuberances 146 and 148 that are engaged within a vertically extending, downwardly-opening slot 152 within the back wall of the recess formed in holder 150, so as to force the upper portion of facing element 130 and all of shim 122 against the upper portion of first slide 10. This combination of engagement

means causes the first slide 10 and facing slide 130 to be aligned in parallel ("wherein the holder comprises interlocking portions formed on the substrates" "wherein the interlocking portions snap together" "wherein one of the substrates, one of the spacers and one of the interlocking portions are formed as one integral piece" "at least one holder comprising an interlocking portion from one of the first and second substrate to secure the first and second substrate and the at least two spacers together, the interlocking portion comprising at least one projection on at least one of the first and second substrates and at least one corresponding opening positioned opposite the projection for interlocking engagement therewith") (col. 3 line 62-col. 4 line 3)

Regarding claim 16, the slide assembly is fully capable of being separated manually to examine the specimen ("soil") between substrates.

Regarding claim 17, 19, and 21, Brigati teach the holder further comprises clips 161 and 162 ("group consisting of a clamp, clip, tape, screw, rubber band, snap-on cap, glue and adhesive").

4. Claims 1-4, 7, 10-21 are rejected under 35 U.S.C. 102(a/e) as being anticipated by Fusco et al (US 2004/0101439).

Regarding claims 1, 4, 18, and 20, Fusco et al teach a biological reaction device comprising:

A base substrate and a cover substrate ("two substantially parallel substrates")

Spacer elements 18 ("separated by two substantially equal thickness spacers"), wherein a reaction chamber ("gap") is formed between the two substrates;

A specimen area 16 for specimens such as cells or tissue ("a soil positioned in the gap" "soil is selected from the group consisting of organic soil, inorganic soil, and mixtures thereof") (Para. 0008)

and a flexible gripping element 28 ("at least one holder configured to secure the two substrates and the two spacers together") (Para. 0022).

Regarding the limitations, "A cleaning indicator", "for monitoring and assuring adequate cleaning of a cleaning process for a medical instrument" and "wherein a removal of the soil from between the two substrates is monitored to ensure adequate cleaning", the limitations are considered process or intended use limitations, which do not further delineate the structure of the claimed apparatus from that of the prior art. Since these claims are drawn to an apparatus statutory class of invention, it is the structural limitations of the apparatus, as recited in the claims, which are considered in determining the patentability of the apparatus itself. These recited process or intended use limitations are accorded no patentable weight to an apparatus. Process limitations do not add patentability to a structure, which is not distinguished from the prior art. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See

In re Casey, 152 USPQ 235 (CCPA 1967); and In re Otto, 136 USPQ 458, 459 (CCPA 1963). The Courts have held that it is well settled that the recitation of a new intended use, for an old product, does not make a claim to that old product patentable. See In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). The Courts have held that the manner of operating an apparatus does not differentiate an apparatus claim from the prior art, if the prior art apparatus teaches all of the structural limitations of the claim. See Ex Parte Masham, 2 USPQ2d 1647 (BPAI 1987) (see MPEP § 2114).

Regarding claim 5-7, Fusco et al teach the substrates are typically made from glass, however, other materials such as polymers, polystyrene, fused silica, polypropylene, metal and combinations thereof can be used ("the substrates are formed of a metal" "the substrates are formed of a polymer" "wherein the substrates are transparent") (Para. 0021).

Regarding claim 10, Fusco et al teach the height of the spacer element is less than 100 microns, and in other embodiments the height of the spacer element is less than 50 microns ("wherein the spacers have a thickness of about 0.05mm")

Regarding claim 11, Fusco et al teach the spacers are formed integrally with the substrates.

Regarding claims 12-15, 17, 19-21, Fusco et al teach the walls 31 are adapted to receive the cover substrate 22 by snap-fitting ("interlocking portions snap together") the cover substrate 22 such that the inner surface 26 ("a projection on one of the substrates") of the cover substrate 22 is in contact with

the spacer element 18, and the gripping element 28 ("clamp") has a sloped inner surface 33 that defines a space for receiving the surface of the substrate 22 ("an opening on the other of the substrates for receiving the projection" "one of the substrates, one of the spacers and one of the interlocking portions are formed as one integral piece") (Fig. 5).

Regarding claim 16. The substrates are fully capable of being separated manually to examine the soil between substrates.

Response to Arguments

5. Rejections of claims 1-9, 11-16 and claim 13 under 35 U.S.C. 112 paragraph have been withdrawn in view of claim amendments.

6. Applicant's arguments with respect to claims 1-2, 4-21 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

7. No claims are allowed.

8. 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

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D1

United States Patent [19]

Brigati

[11] Patent Number: 4,777,020

[45] Date of Patent: Oct. 11, 1988

[54] SHEETLIKE OBJECT SUCH AS MICROSCOPE SLIDE

[75] Inventor: David J. Brigati, Hummelstown, Pa.

[73] Assignee: Fisher Scientific Company, Pittsburgh, Pa.

[21] Appl. No.: 33,073

[22] Filed: Mar. 31, 1987

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 775,864, Sep. 13, 1985, Pat. No. 4,731,335.

[51] **Int. Cl.**[4] **G02B 21/34**; B01L 1/00

[52] **U.S. Cl.** **422/99**; 350/354; 428/210

[58] **Field of Search** 422/70, 100, 99, 102, 422/101; 73/864, 72; 350/534-536; 428/210

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4,624,882	11/1986	Melisz et al.	
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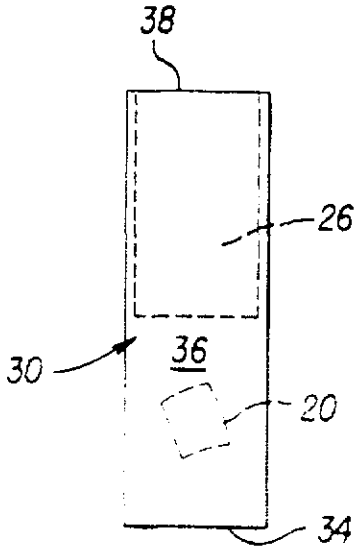
Primary Examiner—Michael S. Marcus

Attorney, Agent, or Firm—Alan M. Doernberg

[57] **ABSTRACT**

A sheetlike object with a planar front face, a linear lower edge, a thickness about 0.5–5 mm and a raised pattern on a portion of the front face about 50–500 micrometers forwardly of the front face. For example, a rectangular microscope slide 25 mm wide, 75 mm high and 1 mm thick coated on one side by an adherent coating 50–500 micrometers thick. Two such slides with abutting coating portions of 50–125 micrometer thickness form a capillary gap between the remainder of the planar surfaces of 100–250 micrometer thickness. One such slide with a coating of 100–250 micrometer thickness forms a corresponding gap when placed against a flat uncoated slide. A similar raised portion is created by affixing a thin object (e.g., a 150 micrometer thick cover slip) to a portion of a microscope slide. Liquid is drawn into and out of the capillary gap by contacting the edge of the gap with liquids and then by absorbent.

8 Claims, 5 Drawing Sheets



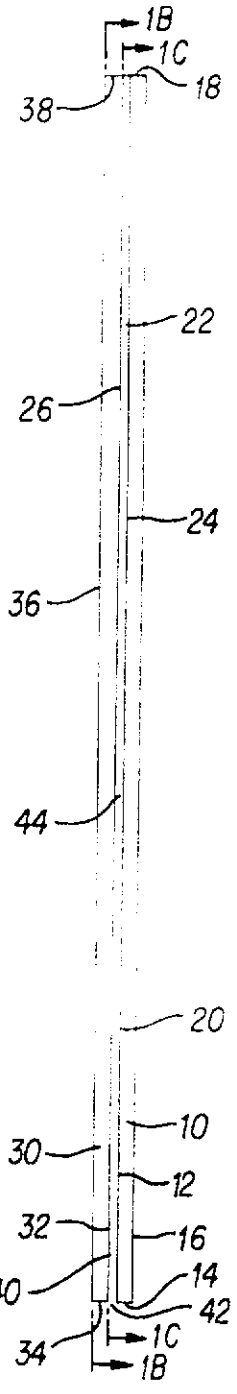


FIG. 1A

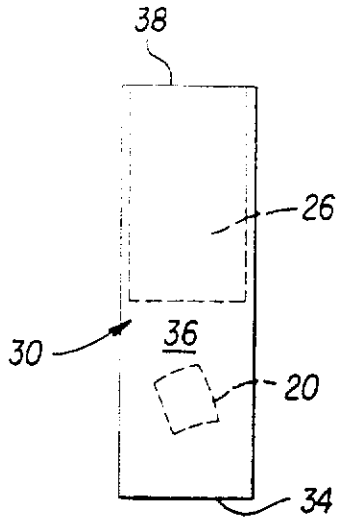


FIG. 1B

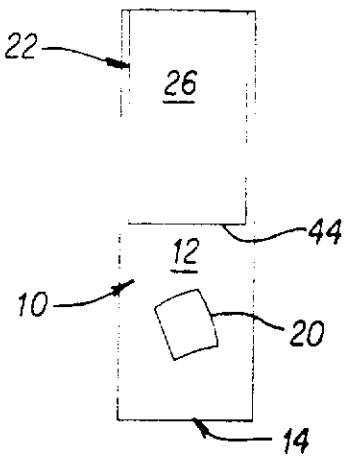


FIG. 1C

242 242

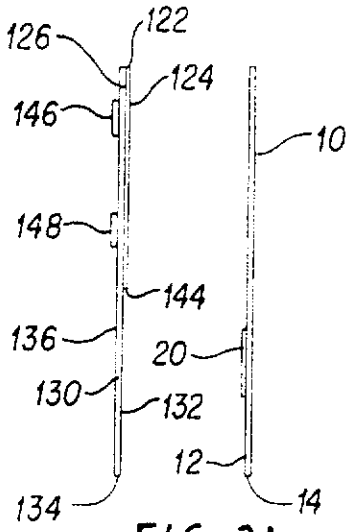


FIG. 2A

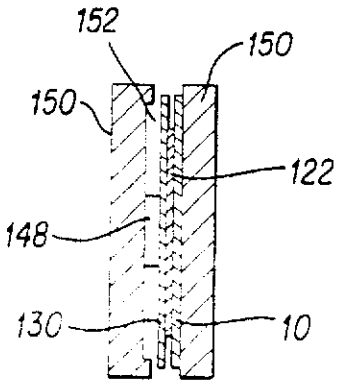


FIG. 2C

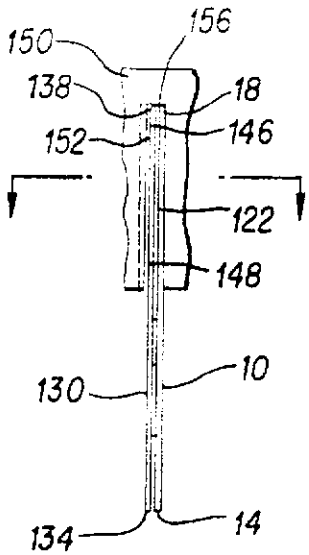


FIG. 2B

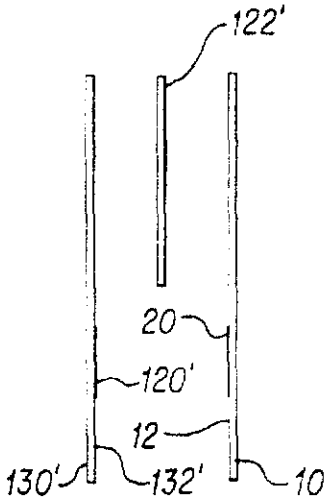


FIG. 2D

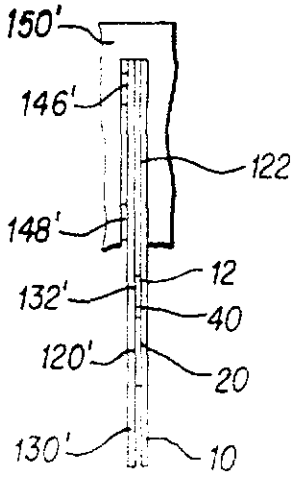


FIG. 2E

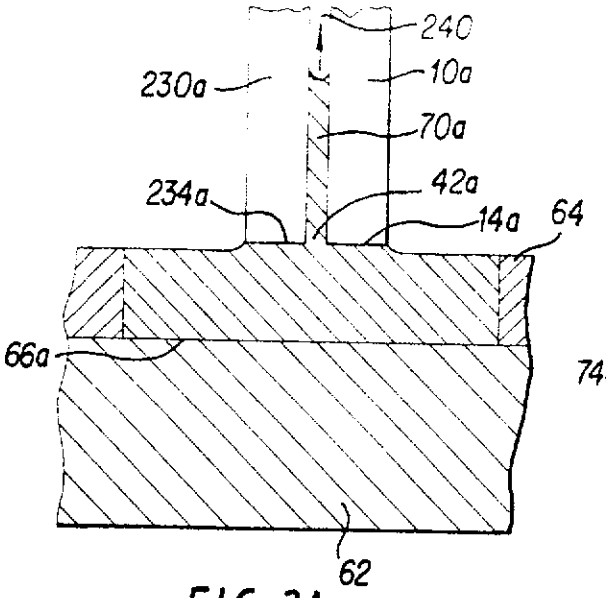


FIG. 3A

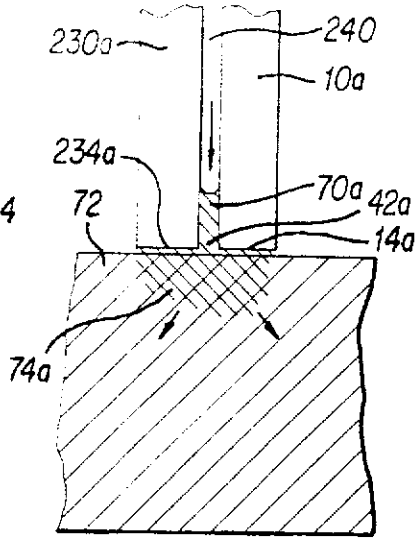


FIG. 3B

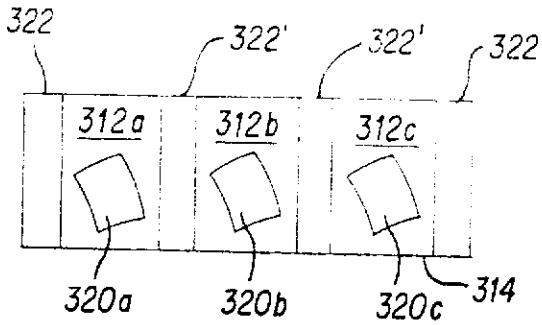


FIG. 4

245

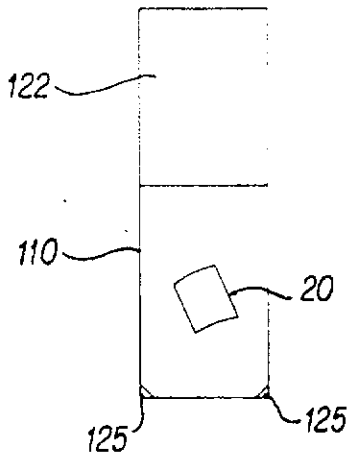


FIG. 5A

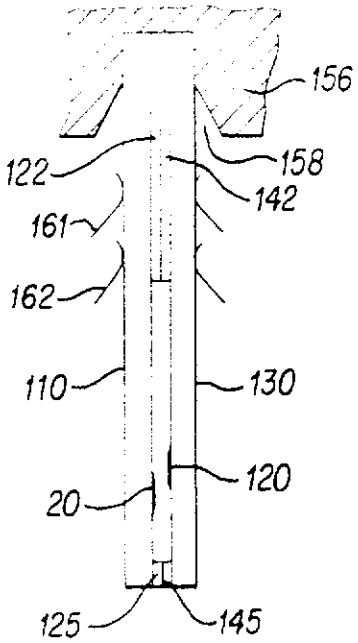


FIG. 5B

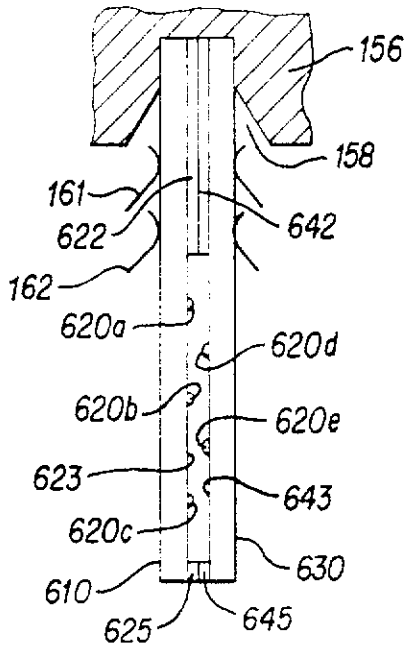


FIG. 6A

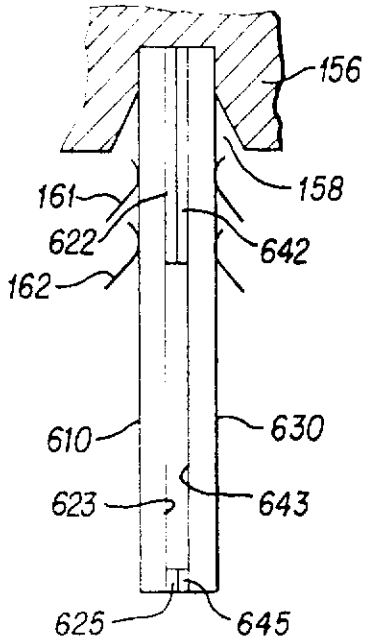


FIG. 6B

SHEETLIKE OBJECT SUCH AS MICROSCOPE SLIDE

This is a continuation-in-part of U.S. Ser. No. 775,864 of Brigati, filed Sept. 13, 1985 now U.S. Pat. No. 4,731,335.

The present invention relates to sheetlike objects such as microscope slides and especially to such objects having a planar front face and a raised pattern on a portion of the front face.

Microscope slides normally have a length of either 75 mm or 3 inches (76.4 mm) a width of 25 mm or 1 inch (25.4 mm) and a thickness of approximately 1 mm. While most of the front face is generally smooth, a portion (generally on top) is often glazed in order to provide a marking surface. A product of Erie Scientific Company, SUPERFROST ® slides (described in U.S. Pat. No. 4,481,246), has a thin coating on the upper portion of the front face to form a marking surface. Such thin coating is of a substantially uniform thickness less than 30 micrometers and covers less than 25 mm of the 75 mm or 76.4 mm height.

SUMMARY OF THE INVENTION

The present invention provides a sheetlike object having a planar front face, a linear lower edge, a thickness of about 0.5 to about 5 mm and a raised pattern on a portion of the front face measuring from 50 to about 500 micrometers forwardly of the planar front face.

In many embodiments, the sheetlike object is a microscope slide and the raised pattern is either a shim, cover slip or a coating. In many such embodiments, the lower edge is one of the shorter sides (e.g., 25 mm or 25.4 mm) of the slide and the raised portion is near the top edge which is the parallel side. In such cases, the top 25–40 mm of the slide is covered by the shim, cover slip or coating.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1A is a side elevational view of a pair of microscope slides in accordance with a first embodiment of the present invention.

FIG. 1B is a front elevational view taken along line 1B—1B in FIG. 1A.

FIG. 1C is a front elevational view, in section, taken along line 1C—1C in FIG. 1A.

FIG. 2A is a side elevational view of a disassembled slide pair according to a second embodiment of the present invention.

FIG. 2B is a view similar to FIG. 2A of the same slide pair assembled within a holder portion into a slide assembly.

FIG. 2C is a top view of the slide assembly in a holder taken in section along line 2C—2C in FIG. 2B.

FIG. 2D is a view similar to FIG. 2A of a disassembled slide assembly according to a third embodiment of the invention.

FIG. 2E is a view similar to FIG. 2B of the slide assembly of FIG. 2D in a holder.

FIG. 3A is a magnified side elevational view of the bottom of the slide assembly of FIG. 2B or 2E contacting a droplet of treating liquid, showing liquid being drawn vertically into the thin gap by capillary flow.

FIG. 3B is a view, similar to FIG. 3A, of liquid being drawn vertically out of the thin gap by capillary flow

FIG. 4 is a front elevational view in section, similar to that of FIG. 1C, of a slide assembly according to a fourth embodiment of the present invention.

FIG. 5A is a front elevational view of a partially-coated slide according to a fifth embodiment of the present invention.

FIG. 5B is a side elevational view of two of the slides shown in FIG. 5A inserted together into a holder of a different design, similar in view to FIGS. 2B and 2E.

FIG. 6A is a side elevational view similar to FIG. 5B, of two slides according to a sixth embodiment of the present invention inserted together into the same slide holder as is shown in FIG. 5B.

FIG. 6B is a side elevational view, similar to FIGS. 5B and 6A, of two slides according to a seventh embodiment of the present invention inserted together into the same slide holder as is shown in FIGS. 5B and 6A.

DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of slide pair assembly is shown in FIGS. 1A, 1B and 1C. Referring to FIG. 1A, the sample-bearing microscopic slide 10 has a sample-bearing front surface 12, a first lower edge 14, a back surface 16 and a top edge 18. A thin sample 20, such as a 5–10 micrometer thick histology specimen, is provided on a lower portion of the front surface 12. Assuming that the slide is 75 mm high, 25 mm wide and 1 mm thick (standard dimensions for a microscope slide), the sample can be a 20 mm × 20 square located at least 1.0 mm (e.g., 10 mm) above the first lower edge 14.

Attached to the upper portion of the front surface 12 of the first slide 10 is a shim 22, shown in this first embodiment as two-sided adhesive tape of thickness 0.2 mm (200 micrometer). One sticky side 24 of the shim 22 adheres to the top portion of front surface 12 of first slide 10. The opposite sticky side 26 of shim 22 adheres to a facing surface 32 of facing element or slide 30. In this embodiment, facing slide 30 is also a 75 mm × 25 mm × 1 mm microscope slide. The shim 22 holds facing slide 30 in alignment with first slide 10 such that: facing planar face 32 of facing slide is parallel to front surface 12 and spaced therefrom by the thickness of shim 22 (200 micrometers), second lower edge 34 of facing slide 30 is coplanar with first lower edge 14 of first slide 10, back surface 36 of facing slide 30 is parallel to surfaces 32, 12 and 16 and top edge 38 of facing slide 30 is coplanar with top edge 18 of first slide 10.

The spacing of 200 micrometers is substantially constant from between the inner edges of top edges 18 and 38, along the vertical lengths of front surface 12 and facing surface 32, and to the inner edges of first and second lower edges 14 and 34. Assuming that the tape is 25 mm high (its width can be the full 25 mm width of slides 10 and 30, or can be less, e.g., 22 mm as shown), then a gap 40 is formed between the front surface 12 and the facing surface 32. This gap 40, which is 50 mm high, 25 mm wide and 0.2 mm (200 micrometers) thick, is the capillary gap terminating in lower end 42. The sample 20, being only 5–10 micrometers thick, has no significant impact upon the thickness of the gap 40, even at the height of the sample 20. Similarly, other imperfections, entrapped particles, angling of the two slides toward or away from parallel, or other factors that affect the gaps 40 by less than 20% (i.e., cause the 200 micrometer thick gap to remain between 160 and 240 micrometers in thickness) have no adverse impact, and even slightly

impact. Furthermore, while the basic or average thickness of the gap in this first embodiment is 0.2 mm (200 micrometers), gaps as small as 0.05 mm (50 micrometers) or as large as 0.5 mm (500 micrometers) are permissable, with other dimensions (such as height) adjusted as described below in relation to FIG. 4. Under appropriate circumstances, thickness of the gap still less than 50 micrometers or more than 500 micrometers may also be appropriate. As described below, however, the preferred thickness of the gap is 150–250 micrometers more preferably 150–200 micrometers.

FIG. 1B shows the same slide pair assembly from the front. The facing slide **30**, with its back surface **36** on front, completely covers the first slide **10**, from the top edge **38** to the bottom edge **34** of the facing **30**. Sticky side **26** of shim **22** can be seen under the top portion of facing slide **30**; and sample **20**, which is immobilized on sample slide **10**, can be seen centered under the lower portion of facing slide **30**. The precise vertical alignment shown in FIG. 1B, wherein neither side of first slide **10** extends beyond the corresponding side of facing slide **30**, is not critical. Misalignment in such direction of 2 mm, or even 5 mm, is of no significant adverse impact. Furthermore, as indicated above, the widths need not all be equal (e.g., 25 mm).

FIG. 1C shows the same front view as FIG. 1B, but now in section so as to look behind facing slide **30**. The front face **26** of shim **22** occupies the top 25 mm of the visible surface. The bottom 50 mm×25 mm of front surface **12** of first slide **10** (below lower end **44** of shim **22**) is now visible; it is this 50 mm×25 mm that is exposed to the capillary gap **40**. The sample **20** occupies a 10×10 mm portion centrally located within this 50 mm×25 mm portion of sample-bearing surface **12**. The height of the gap can be adjusted by using shorter or longer pieces of tape as shim: e.g., 25 mm wide and 20, 30, 40 or 50 mm long (high) tape.

FIGS. 2A, 2B and 2C illustrate a second embodiment of slide pair assembly. First slide **10** with first lower edge **14**, front surface **12** and sample **20** thereon is identical to corresponding elements in FIG. 1A. The facing slide **130** is also a 75 mm×25 mm×1 mm microscope slide, with facing surface **132** and second lower edge **134**, but now the shim **122** is a 40 mm×25 mm (or 22 mm)×0.15 mm glass cover slip having a lower end **144**. The first 40 mm×25 mm surface **124** of shim **122** faces (and, when assembled in FIG. 2B abuts against) the upper portion of front surface **12** of first slide **10**. The second 40 mm×25 mm surface **126** of shim **122** is glued to the upper portion of facing surface **132** of facing slide **130**.

Along the back surface **136** of facing slide **130** are provided upper and lower elastomeric protuberances **146** and **148**, shaped as O-rings, compressible flat springs or rollers or solid discs, which may have beveled upper portions (not shown).

In FIG. 2B, the slide of FIG. 2A is assembled by placing slides **10** and **130** together in parallel and slipping their upper ends into a recess of dimensions 30 mm high, 26 mm wide and 2.4 mm thick formed in holder **150**. The recess opens downwardly and has, on its top, a horizontally-extending aligning face **156**. Top edges **18** and **138** of first slide **10** and facing element **130** abut against aligning face **156**. Protuberances **146** and **148** are engaged within a vertically extending, downwardly-opening slot **152** within the back wall of the recess formed in holder **150**, [illegible] portion of first slide **10**. This combination of engagement means causes the first slide **10** and facing slide **130** to be aligned in parallel, with a gap the thickness of shim **122** (0.15 mm), the width of slides **10** and **130** (25 mm) and the height (35 mm) not covered by shim **122**. Lower edges **14** and **134** are at the same height and are spaced from each other by substantially the same distance as the thickness of shim **122**, i.e., 0.15 mm.

FIG. 2C is a top view of FIG. 2B taken along line 2C—2C in FIG. 2B. In this sectional view, protuberance **148** is seen inside its slot **152** which is cut into the back holder **150** as a downwardly open slot in the recess. Protuberance **148** presses against slot **152** and compresses shim **122** which is glued to the opposite side of facing element **130**. This in turn exerts pressure on the upper portion of the first slide **10** which is held in place by holder **150**. In this manner the upper portion of the facing slide **130** and the first slide **10** are kept in contact and suspended vertically below. Since slot **152** is downwardly open, the facing slide **130** and the first slide **10** may be easily inserted into and removed from the recess in the holder **150** by the guiding action of slot **152** on protuberances **146** and **148**.

FIGS. 2D and 2E illustrate a third embodiment differing from that of FIG. 2A in that the protuberances **146'** and **148'** are now located on the interior of the recess within the holder **150'** rather than on the back surface **136** of facing element **130**.

Referring to FIG. 2D, the sample-bearing microscope slide **10** has its sample bearing front surface **12** facing a second sample bearing microscope slide **130'** and its sample-bearing **132'**. Thin sample **20** on sample bearing microscope slide **10** is present opposite sample **120'** on the opposite sample-bearing slide **130'**.

Referring to FIG. 2E, sample-bearing slides **10** and **130'** are held in place in the recess in holder **150'** by the pressure of the elastomeric protuberances **146'** and **148'** pressing against their upper portions. Shim **122'** is sandwiched in between their upper portions. Sample **120'** immobilized on sample bearing surface **132'** of the second sample bearing slide **130'** is held in the gap **40** produced by the close apposition of the sample-bearing surfaces held in place across and on the opposite side of the gap **40** from sample **20** by the pressure of protuberances **146'** and **148'** and the holder **150'** on the upper portions of the two sample bearing slides **10** and **130'** against shim **122'**.

A plurality of such slide pairs can be held in a parallel array as described in relation to FIGS. 3A and 5 in U.S. Ser. No. 775,864. Furthermore, such an array of slide pairs can be lowered onto an array of droplets of treating liquid as described in relation to FIGS. 3B and 7 of U.S. Ser. No. 775,864. Finally, such a step can be part of a multi-step process of treating samples on the slides with a series of treating liquids, some of which are provided on droplet holders and others as sheets or baths of liquid as described in relation to FIG. 6 of U.S. Ser. No. 775,864. Such descriptions are incorporated herein by reference.

FIG. 3A hereof (corresponding to FIG. 3C of U.S. Ser. No. 775,864) shows liquid being drawn by capillary action from a hole **66a** through an elastomeric member **64** on a rigid base **62**. Prior to contact by the slide pair, liquid stood up in hole **66a** above the top surface of elastomeric member **64**. Upon lowering the slide pair consisting of slide **10a** (corresponding to slide **10** in

between lower edges **14***a* and **234***a* contacts the droplet. A capillary column of liquid **70***a* rises in capillary gap **240** between slides **10***a* and **230***a* by capillary action. This effect is enhanced by the relative incompatibility of the liquid with the surface of elastomeric member **64**, e.g., because the aqueous droplet is repelled by the hydrophobic surface of elastomeric member **64**. Such incompatibility (evidenced by beading of the treatment liquid if it were placed on a flat surface of elastomeric material used for member **64**) also causes the droplets to stand above the top surface of member **64**.

After the capillary column **70***a* has risen as far as capillary action will take it (typically about 30 to 40 mm in the indicated gap of 0.15 mm), the slide assembly can be lifted by its holder away from elastomeric member **64**. Each slide pair (e.g., **10***a*/**230***a*) will hold, by capillary action, the treating liquid received from one or more droplets with which its lower space (e.g., **42***a*) has been contacted. After the liquid has remained in the gap for a desired time period, the slide assembly is now lowered onto an absorbent material **72** as shown in FIG. **3B**. Since the liquid is more compatible with the absorbent material **72** than with the surfaces of slides **10***a* and **230***a*, now the capillary column **70***a* will descend, with the treating liquid spreading downward and outwardly as a liquid front **74***a* within absorbent material **72**. Within a matter of seconds, the gap **240** between the slide pair will be evacuated essentially completely of liquid by such capillary action, except perhaps for minute amounts that may adhere to the sample or to other hygroscopic surfaces along the slide gap **240** or lower edges **14***a* and **234***a*. Once the liquid is evacuated from the slide gap **240**, the slide pair may now be moved to another droplet holder, or to a sheet or bath of treating liquid for the next step of a multi-step treating process such as is described in U.S. Ser. No. 775,864. FIG. **3B** hereof corresponds to FIG. 3D of U.S. Ser. No. 775,864.

FIG. **4** illustrates, in a view similar to that of FIG. 1C, an embodiment of the invention wherein three vertically-extending sample-bearing surfaces are formed on one 75 mm×25 mm slide. The slide extends horizontally with its 75 mm lower edge **314**. Two outer shims **322** of 25 mm height, 2 mm width and 0.25 mm thickness extend vertically on the front (75 mm×25 mm) face. Two inner shims **322'** have similar 25 mm×2 mm×0.25 mm dimensions, and are equally spaced from and parallel to end shims **322**. Such shims **322** and **322'** can be formed by applying a thermosetting material (e.g., epoxy or silicone or paint) to the face of a glass slide. The uncovered and isolated faces are therefore **312***a*, **312***b* and **312***c*, each extending upwardly 25 mm from lower edge **314**, and each approximately 22.33 mm in width. A facing slide can be placed over this first slide, so that gaps of 0.25 mm thickness, 25 mm height and 22.33 mm width will form over faces **312***a*, **312***b* and **312***c*. By contacting the lower space of each such face which is adjacent to lower edge **314** by a treating liquid and then by an absorbent material, liquid reagent can be drawn into and out of each gap as described above. Such a slide pair can be applied to droplets or to a bath or sheet of treating liquid manually.

Although shims **322** and **322'** of FIG. **4** are indicated as being 0.25 mm (250 micrometers) thickness, a thinner coating (e.g., 150 or 200 micrometers) can be used even with a flat glass slide forming the other half of the slide pair. It is also suitable, however, to employ pairs of thicknesses (e.g., 50, 75, 100 or 125 micrometers) which will press against each other in the slide pair so as to have a spacing between glass surfaces of 100, 150, 200 or 250 micrometers, respectively. It is also suitable, in such cases, to have other regions of the slide (e.g., portions of the top 20% of each of faces **312***a*, **312***b* and **312***c*) covered with a coating of similar thickness.

Alternatively, a series of such horizontally-extending slide pairs, each with three vertically-extending capillary gaps, can be held within a holder using, for example, the slide rack shown in FIG. 1 of U.S. Pat. No. 4,199,613 of Johnson, with such modification as is required to leave lower edges **314** of each sample-bearing slide available for contact by droplets or sheets of treating liquid. The "shims" of Johnson in this embodiment would not necessarily be attached to the slide rack, nor would they be positioned between a sample slide and its companion facing slide to help form the capillary gap between them, but would rather be located at both lateral ends and pressing on the outer surface of the facing and sample bearing slides, forcing them together by compressing the facing slide and the sample bearing slide against shims **322** described above. In this embodiment, shims **322** and **322'** in FIG. **4** would be the only parts defining the first distance of the capillary gap between the facing and sample bearing slide.

The thickness of the side walls of the recess in the holder would then define a second distance separating parallel pairs of facing and sample bearing slides. This second distance is not designed for capillary action and separates sets of slide pairs so that liquid reagents can be drawn up into them through the capillary gap from discrete droplets as in FIGS. 3A and 3B. This second distance can be any thickness greater than 1 mm, which is significantly thicker than the 200 microns of Johnson's shims or the shims described in this patent. The preferable length of this second distance and, therefore, the preferable thickness of the side walls forming the borders of any downwardly open slide recess in the slide holder, ranges from 5–7 mm. Using this range, the greatest number of slides can be engaged into a slide holder for the purpose of drawing up, incubating and removing liquid reagents from the capillary gaps between adjacent slide pairs.

This second distance range allows adjacent capillary gaps to be maintained from 7–9 mm apart. At this distance, individual droplets in the droplet holder can be maintained apart without contaminating each other by inadvertently overcoming the incompatibility of the surface of elastomeric member **64** and the individual droplets in the droplet holder. Such advantage would not be possible with the slide rack of Johnson where 200 microns is too close to stably separate adjacent reagent droplets on the hydrophobic droplet holder. Therefore, the slide rack of Johnson would have to be completely and substantively modified from its original description to achieve the advantages of the present invention.

To cause the liquid to rise 15–20 mm above lower edge **314**, the gap (thickness of shims **322** and **322'**) may be thicker than the 0.15–0.20 mm thickness most preferred in the earlier embodiments, where liquid was intended to rise 25–45 mm above lower edge **14**. Through routine experimentation, the gap can be adjusted (by varying shim thickness) to achieve the desired vertical rise of liquid for any sample-bearing slide surface.

FIGS. 5A and 5B show an embodiment of the inven-

holder which is described in more detail in an application of Brigati and Cuomo U.S. Ser. No. 032,874, filed Mar. 31, 1987 and commonly-assigned, which is also a continuation-in-part of U.S. Ser. No. 775,864.

In FIG. 5A, one of the slides **110** is shown. A top coating **122** covers the top portion of the slide (e.g., the top 31.8 mm out of a total height of 76.2 mm). Small triangular coating portions **125** cover the bottom left and right corners of slide **110**. Each of these coatings are one-half the thickness of the desired gap (e.g., each 80 micrometers thick to form a 160 micrometer thick gap). A sample **20** of tissue is placed on slide **110** below coating **122**.

FIG. **5B** is a side view of two identical slides **110** and **130** in a slide holder. Top coating **122** abuts against identical top coating **142** on slide **130**. Bottom corner coating **125** abuts against bottom corner coating **145** in slide **130**. Slides **110** and **130** are pressed together by clips **161** and **162** which are, respectively, above and below the midpoint of coatings **122** and **142**. The tops of slides **110** and **130** are received within a slot **158** of alignment strip **156** of the slide holder. The horizontally-extending surface of the slot **158** maintains precise vertical alignment between slides **110** and **130**. For the holder described in U.S. application Ser. No. 032,874, slots are provided near each two top corners of slides **110** and **130** and side walls are provided to maintain horizontal alignment between slides **110** and **130** in a direction into the page in the view of FIG. **5B**. In such slide holder, each alignment strip has multiple slots (illustrated as ten) so that multiple (ten) slide pairs can be held in a fixed array.

As shown in FIG. **5A**, two lower corners of slide **110** (slide **130** is similar) are coated with an 80 micrometer thick coating which is triangular in shape, so as to extend 4 mm up and 4 mm in from each corner along the side and bottom edges of the first slide **110**. The triangular coating on first slide **110** is labeled **125**; the triangular coating on second slide **130** is labeled **145**. Accordingly, the 160 micrometer thick gap is maintained, but flares out at a 45 degree angle from a width of 17.4 mm at the lower edge to a width of 25.4 mm at a height of 4 mm above such lower edge.

In use, up to thirty slide pairs (with samples on one or both slide of each pair) are inserted into the holder. The holder is then lowered onto a series of liquids, typically liquid reagents. Each liquid may be in the form of a bath or sheet, in the form of individual round droplets supported on a droplet holder (see FIG. 7 of U.S. Ser. No. 775,884) or in the form of laterally-extending aliquots on a modified droplet holder (see FIGS. 3A, 3B and 3C of an application of Brigati, U.S. Ser. No. 032,875, filed Mar. 31, 1987, commonly-assigned and also a continuation-in-part of U.S. Ser. No. 775,884). Liquid rises by capillary action into the gap between each first slide **110** and the adjacent second or facing slide **130**. See FIG. **3A** hereof. After the appropriate time of liquid contacting sample on one or both slides, the slide assembly is then lowered on a flat blotter. Liquid is then drawn by capillary action into the blotter so as to evacuate each capillary gap, as shown in FIG. **3B** hereof. If a droplet holder is used for the particular step, then the process can be individualized so as to treat different slide pairs with different liquids (e.g., different primary antibodies, nucleic acid probes, enzymes or chromogens). After evacuation, the slide assembly can then be contacted by proper reagent in the form of droplets, laterally

FIG. **6A** is a view similar to FIG. **5B**, but enlarged, of two slides **610** and **630** adapted for either a dotting or a blotting assay. In blotting (unlike dotting), the sample is subjected to a geometric separation before transfer to the filter material. Slides **610** and **630** are fitted into the same slide holder. Upper coatings **622** on slide **610** and **642** on slide **630** abut against each other under the compression of clips **161** and **162**. Slides **610** and **630** fit at their upper ends into slot **158** in alignment strip **156** of the holder. A thin strip of nitrocellulose material or other membrane filter material **623** covers the inner surface of slide **610** below coating **622**. A thin strip of nitrocellulose or other filter material **643** covers the inner surface of slide **630** below coating **642**. Slides **610** and **630** need not be glass, and preferably are of a thermoplastic or thermosetting material to which thin strips **623** and **643**, respectively, can tightly bind.

The gap between facing surfaces of thin strips **623** and **643** has the thickness of the first distance of U.S. Ser. No. 775,864 (generally 50 to 500 micrometers, preferably 150 to 250 micrometers, more preferably 150 to 200 micrometers). If each of thin strips **623** and **643** is 50 micrometers thick, then a gap of 150 micrometers can be created by making each of coatings **622** and **642** a thickness of 125 micrometers. Furthermore, slide **610** can be formed (especially if plastic) as a unitary structure with a top portion extending 125 micrometers further forward than the bottom portion either by molding, by removing material from the lower portion or otherwise. Thin strip **623** can be attached chemically, with adhesive or by heat setting (analogous to ironing on) if slide **610** is of an appropriate material. The entire structure represented by slide **610**, coating **622** and layer **623** can also be formed as a laminant, by analogy to FIGS. 17–20 of U.S. Pat. No. 4,308,028 to Elkins.

In use in a dotting assay, slide **610** is spotted directly with samples (such as cells or cellular extracts of protein or DNA) using a manual or automatic pipetting device. The samples are bound to the membrane of filter material on slide **610** by heating, drying or chemical linkage. The thin strips of slides **610** and **630** are then apposed, and their upper ends are placed in slot **158** in alignment strip **156** of the holder to form the capillary action gap depicted in FIGS. 6A and 6B.

In use for blotting, slide **610** (and separately slide 630) is blotted against an electrophoretic gel or other separating device so as to transfer previously separated species (e.g., antigens or polynucleotides) onto strip **623** in a defined spatial relationship (e.g., short polynucleotides migrate further into a gel than longer ones). The slide is then removed from the gel or vice versa. The blotted material can then be more firmly attached to the nitrocellulose by drying or heating or by using chemically linking reagents (e.g., glutaraldehyde) if desired. In FIG. 6A, three specimen spots **620***a*, **620***b* and **620***c* are shown on nitrocellulose strip **623**. Three other specimen spots **620***d* and **620***e* are shown on nitrocellulose strip **643**. These specimen spots, irrespective of whether they were spotted or blotted onto the membrane, can then be exposed to a series of probing, analyzing, washing, treating and developing reagents in a manner analogous to the multi-step process described for tissue specimens in U.S. Ser. No. 775,864. At the conclusion of the process, a chromphore would be deposited at the locus of each spot for which the reagents are specific. Thus, for example, a restriction enzyme digest of a DNA

250 250

see what lengths of restriction fragments have the sequence probed for.

FIG. 6B shows a corresponding slide pair on which the nitrocellulose strips **623** and **643** have reactive groups (such as carboxy or amino) which can be spotted with binding pair members (e.g., antigens, antibody or nucleic acid sequences). Chemical attachment of such binding pair members can be performed in advance by conventional linking chemistry (e.g., carbodiimide chemistry). Alternatively, loci on the membrane can be spotted to have defined pre-bound chemically reactive groups (e.g., N-hydroxysuccinimide, azido, or aldehyde groups) which directly bind to reactive moieties of sample materials (e.g., amine, carboxyl, sulfhydryl, purine, pyrimidine or hydroxyl groups) when the sample comes in contact with the loci in the course of filling the capillary action gap with sample. In these cases (unlike those described previously), the slide assembly of slides **610** and **630** is formed without a sample pre-bound on either slide. Either as the initial step or after one or more preparative washing steps (by capillary drawing and evacuation as in FIGS. 3A and 3B), a sample material such as a drop of serum is drawn up into the gap between strips **623** and **643** by capillary action (in a fashion analogous to that shown in FIG. 3A). The assembly is then incubated at an appropriate temperature or temperature profile. If binding occurs, then analyte material in the sample would bind at the appropriate loci of strip **623** or **643**. For example, if a viral antigen is bound at one locus on nitrocellulose strip **623**, any antibody to that antigen in the serum sample would bind at that locus. Other antibodies in the serum sample would not. The gap could then be evacuated and subjected to various washing steps corresponding to steps 18A–19B of the staining procedure on pages 23–29 of U.S. Ser. No. 775,864. Next, a labeled antibody could be brought in which is specific for any human antibody (e.g., rabbit anti-human Ig) or is specific for certain human antibodies (e.g., goat anti-human IgG). The label can be directly readable (e.g., a fluorescent tag), a site for further attachment of readable label (e.g., biotin serving as a site for avidin-enzyme, avidin-fluor or ABC reagents) or an enzyme (e.g., horseradish peroxidase or alkaline phosphatase). If enzyme is then present where serum antibody had originally bound, then (after further washing) chromogen can be brought in (by analogy to steps **23A** to **25B** of such staining procedure). At the conclusion of such process, slide **610** can be examined by the naked eye, by a microscope or by an electronic visualization device to determine if color is present at that spot as an indication if (and semiquantitatively how much of) the looked for antibody was present in the serum sample.

The advantage of this strategy is that the loci can be compared to the surrounding membrane as a control, or to other spots to provide a simple reference system for quantitation. For example, such other spots could have pre-bound known amounts of analyte, in either a single or multiple amounts. Alternatively, another spot could have pre-bound negative controls, or a pre-bound binding partner for a binding pair member with which the sample is spiked to serve as a calibrator or internal control for the read-out.

It should be appreciated that a single sample can be simultaneously assayed for antibodies against different antigens, if these antigens are pre-bound as spots in a known pattern on strips **623** and **643**. Alternatively, identical spots can be formed on strips **623** and **643** to be slides can then be removed from the holder and rearranged in different slide pairs so that, for example, slide **623** is exposed to anti-human Ig antibody and then developing reagents while slide **643** is exposed to anti-human IgG antibody and then developing reagents. In a third format, a single sample can be analyzed for many antigens if antibodies to these antigens are pre-bound as spots in a known pattern on strips **623** and **643**. In a fourth format, specific nucleic acid sequences are spotted at defined loci on the strips **623** and **643** for hybridization assays with prepared samples, such as those wherein sample nucleic acid has been exposed, labeled and placed in suitable hybridization media for denaturation and hybridization. Such fourth format can also be used for nucleic acid sandwich assays.

The present invention thus provides in some forms an array of slide pairs, each extending vertically and terminating at lower edges in a common horizontal plane. The surface of each slide which is designed to bear a sample (either or both of each slide pair) is separated from a facing surface of the other slide of the slide pair by a first distance which is sufficiently small to promote capillary action, as described below. Such first distance is typically about 50–500 micrometers and more preferably about 150–200 micrometers. As indicated in U.S. Ser. No. 775,864, each of the two facing surfaces may bear one or more samples, or sample may be present on only one surface.

In the present array, adjacent pairs of slide pairs are separated by a second distance sufficiently large for the adjacent capillary gaps to be separated by about 7–9 mm or more. Thus, if the slides are each 1 mm thick, a second distance of 5–7 mm will yield a 7–9 mm spacing between capillary gaps (see FIG. 3A of U.S. Ser. No. 775,864).

The first distance can be established by various shims or materials between or on the facing slides. Thus, as illustrated in FIG. **1A**, a two-sided adhesive tape of 200 micrometer thickness between the upper portions of facing slides will establish a 200 micrometer thick gap between the middle and lower portions of the two slides. Alternatively, as illustrated in FIG. **2A**, a 0.15 mm (150 micrometer) thick cover slip fastened to the top portion of one of the two slides will establish a 150 micrometer thick gap between the middle and lower portions of the two slides. Alternatively, as illustrated in FIG. **2D**, the cover slip can be sandwiched between the top portions of the two slides without being affixed to either. Finally, the gap distance can be established by building up a portion of the surface on one of the two slides, as illustrated by FIG. **4**. There, four shims of 250 micrometer thickness are formed on a microscope slide by applying a thermosetting material (e.g., epoxy or silicone or paint). A similar effect could be achieved by building up facing surfaces of both slides (e.g., 125 micrometer thick polymeric coatings on each). A preferred range for built-up areas on both facing slides is 50–150 micrometers, especially 75–100 micrometers.

In considering each slide alone, a coating, preferably on the top portion of one surface, extends above the plane of the glass surface by about 50 to about 500 micrometers. This relatively broad range encompasses slides to be matched with flat slides, in which case the built up surface is preferably about 100–500 micrometers and more preferably 150–250 micrometers. The broad range also encompasses slides to be matched with

surface is preferably about 50–250 micrometers, more preferably 75–125 micrometers.

The second distance can also be established in a variety of ways. As illustrated in FIGS. 3A and 5 of U.S. Ser. No. 775,864, each pair of slides can be fitted (with a shim or the like between them in many cases) into a slot in a holder. Each slot in the holder can then be separated from the next slot by the second distance. Alternatively, as illustrated by the description at page 16, line 32 through page 18, line 5 of U.S. Ser. No. 775,864, a relatively thick shim (e.g., 5–7 mm thick) can separate each slide pair from the next slide pair. Such an array can be used whether the vertically extending face of each slide is the longest dimension of the slide (as in the 75 mm height of FIG. 1A) or is a shorter dimension of the slide (as in the 40 mm height of FIG. 4).

The present invention further includes modified microscope slides adapted to form such slide arrays. For modified slides to be used in a slide pair with a flat slide, a portion should be built up (e.g., by affixing a cover slip or coating with polymer) to the full thickness of the desired gap (e.g., 50–500 micrometers, typically 150–200 micrometers). For modified slides to be used with other modified slides, a lesser thickness is permissable, e.g., 25–250 micrometers, typically 75–100 micrometers. Thus, in one preferred pattern, two facing slides with matching built up areas of 100 micrometer thickness will form a 200 micrometer thick capillary gap.

The built up areas of one or both slides can cover most or all of the width of the slide from the top end partially downward (e.g., the top 25–40 millimeter of a 75 mm long slide). FIGS. 1A, 1B, 1C and 2A illustrate such a pattern. Alternatively, the built up areas may be otherwise arranged on the slide surface, such as in FIG. 4, where two outer shims of 25 mm height, 2 mm width and 0.25 mm thickness cover the sides of a surface. Two inner shims of identical size in that embodiment also separate the slide pair and have the further effect of dividing the slide surface into three isolated faces 25 mm high and approximately 22 mm in width.

The built up areas of the present modified slides differ from conventional frosted slides wherein the modified portion is in or slightly behind the plane of the unmodified portion (because the frosting process removes rather than adds material). Products are also commercially available from Erie Scientific Company under the "SUPERFROST" and "COLORFROST" trademarks wherein a white, opaque coating is placed on the top portion (e.g., the top 15 mm out of 75 mm) of a slide surface. Such coating is designed to establish a writing surface and not to create a gap, and is furthermore typically no greater than 20 micrometers in thickness. Thus, U.S. Pat. No. 4,481,246 speaks of typical thickness of coating being 0.0003 to 0.0008 inch, corresponding to 7–18 micrometers. Even if one were to form a gap with two such SUPERFROST slides facing each other (a combination not disclosed in the art), the gap thickness of 40 microns or less would be undesirably small relative to the 5–10 micrometer thickness of many samples and the up to 50 micrometer thickness of some samples that one may expect to encounter. With the gap so close in thickness to the sample thickness, drainage of trapped liquids with significant surface tension such as water, buffers and other commonly-encountered liquids and especially aqueous liquids becomes impossible or at least incomplete. Such trapped liquids cause contamination of subsequently applied reagents or even prevent the entrance of the next reagent in the sequence. Therefore, variability in results might be expected of identical treatments of samples of thicknesses which differ. Such difficulties are avoided in the present invention by using thicker coatings, at least 50 micrometers in thickness, to yield capillary gaps of adequate width for filling and evacuating.

What is claimed is:

1. A sheetlike object consisting essentially of a substrate having a planar front face, a plurality of edges including a linear lower edge, a thickness of about 0.5 to about 5 mm and a raised pattern coated on a substantial width portion of the front face, the raised pattern extending about 50 to about 500 micrometers forwardly of the planar front face.

2. The sheetlike object of claim 1 being a microscope slide with a planar front face, the linear lower edge being a side of the microscope slide.

3. The sheetlike object of claim 2 wherein the microscope slide has two parallel long sides and two parallel short sides and wherein the linear lower edge is one of the two long edges.

4. The sheetlike object of claim 2 wherein the microscope slide has two parallel long sides and two parallel short sides, where the linear lower edge is one of the two parallel short sides, and wherein the raised portion is primarily adjacent to the other of the two parallel short sides, which is the top edge.

5. The sheetlike object of claim 4 wherein the raised portion covers the microscope slide from the top edge to a line from 33% to 60% of the distance from the top edge to the bottom edge.

6. The sheetlike object of claim 5 wherein the raised portion is of a substantially uniform thickness which is about 100 to about 250 micrometers.

7. The sheetlike object of claim 5 wherein the raised portion is of a substantially uniform thickness which is about 50 to about 125 micrometers.

8. The sheetlike object of claim 7 wherein the substantially uniform thickness is about 75 to about 100 micrometers.

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(12) **United States Patent**
Lin et al.

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(45) Date of Patent: ***Feb. 27, 2001**

(54) **CONTAINER MONITORING SYSTEM**

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(52) U.S. Cl. **422/28**; 422/33; 422/36; 422/37; 422/300; 436/1; 436/126; 436/128; 435/31; 435/287.4

(58) Field of Search 436/1, 126, 127, 436/128; 422/26, 28, 34, 61, 86, 87, 292, 300; 435/31, 287.4

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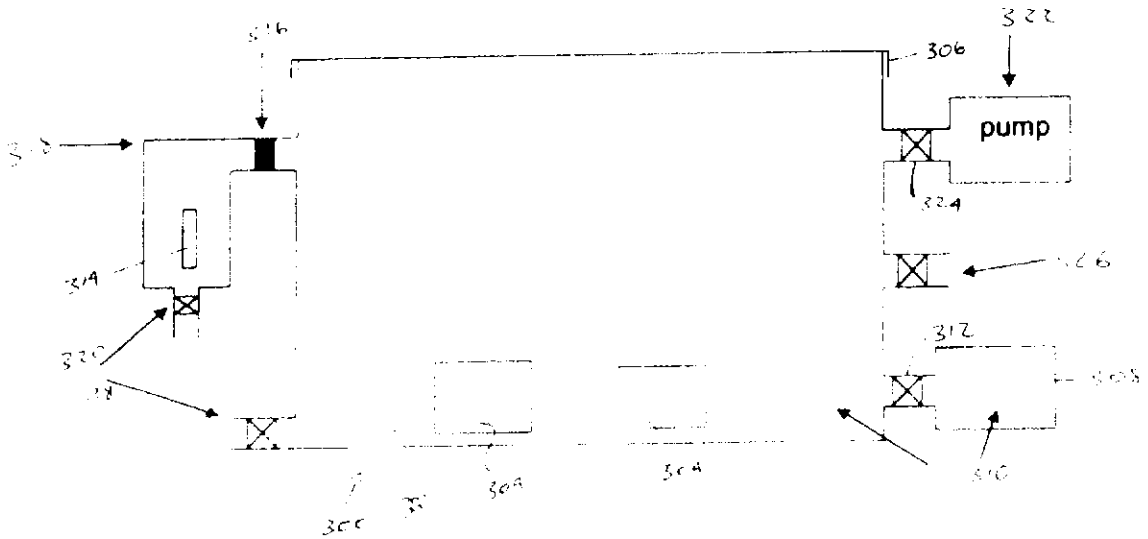
Primary Examiner—Randy Gulakowski
Assistant Examiner—LaToya I. Cross

(57) **ABSTRACT**

A [illegible] system using a sterilization process monitor [illegible] which is capable of indicating the efficacy of the [illegible] process in an enclosed sterilization container [illegible] the sealed state of the sterilization [illegible] device comprises [illegible] which [illegible] a sterilization chamber [illegible] a biological indicator [illegible] a chemical indicator [illegible] a biological or chemical indicator [illegible] the sterilization process. The removal of the [illegible] indicator does not disturb the sterile state of the articles inside the sterilization container.

20 Claims, 13 Drawing Sheets



What is claimed is:

1. A system for monitoring a sterilization or disinfection process comprising:

a container impermeable to microorganisms and having an interior space to receive articles to be sterilized or disinfected;

an antimicrobial source for providing an antimicrobial agent to said interior space;

at least one indicator for [illegible] to said sterilization/disinfection process [illegible] detachable from said container; and

an isolation means between said [illegible] interior space [illegible] said interior space [illegible] disinfection process [illegible] microorganisms [illegible] at least after said indicator has been detached from said container, whereby said indicator can be detached from said container without potentially exposing said interior space to microorganisms.

2. The system of claim 1 wherein said antimicrobial source comprises an ingress means for allowing the antimicrobial agent ingress to said container during a sterilization process.

3. The system of claim 2 wherein said ingress means comprises a valve.

4. The system of claim 2 wherein said ingress means comprises a vapor permeable, microorganism impermeable material.

5. The system of claim 1 wherein said antimicrobial source comprises a supply of said antimicrobial agent within said interior space.

6. The system of claim 1 wherein said isolation means comprises a valve.

7. The system of claim 1 wherein said isolation means comprises a vapor permeable, microorganism impermeable material.

8. The system of claim 1 [illegible] biological indicator.

9. The system of claim 1 [illegible] chemical indicator.

10. The system of claim 1 [illegible] antimicrobial agent.

11. A method of monitoring a disinfection or sterilization procedure comprising the steps of:

placing an article to be disinfected or sterilized into an interior space of a container impermeable to microorganisms;

placing at least one indicator into fluid communication with said interior space while performing said disinfection or sterilization procedure by providing an antimicrobial agent in said interior space;

[illegible] said indicator from said container while keeping said interior space isolated from microorganisms; and

[illegible] parameter relevant to said disinfection or sterilization procedure.

12. A method according to claim 11 comprising the step of introducing said antimicrobial agent into said interior space by ingress means.

13. A method according to claim 12 wherein said ingress means comprises a valve.

14. A method according to claim 12 wherein said ingress means comprises a vapor permeable, microorganism impermeable material.

15. A method of claim 11 wherein said antimicrobial agent is liberated inside of said interior space.

16. A method according to claim 15 wherein said antimicrobial agent is vaporized into said interior space.

17. A method according to claim 11 wherein said indicator is a biological indicator and said biological indicator indicates efficacy of said sterilization or disinfection procedure.

18. A method according to claim 11 wherein said antimicrobial agent is selected from the group consisting of: steam, hydrogen peroxide, peracetic acid, chlorine dioxide, glutaraldehyde and ethylene oxide.

19. A method according to claim 11 wherein said indicator is placed into fluid communication with said interior space through a vapor permeable, microorganism impermeable [illegible].

20. A method according to claim 11 wherein said [illegible] is placed in fluid communication with said interior space through a valve and said valve is closed prior to detachment [illegible] of container.

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US006394111B1

United States Patent

Jacobs et al.

(10) Patent No.: US 6,394,111 B1

(45) Date of Patent: May 28, 2002

(54) **DETECTION OF CLEANLINESS OF A MEDICAL DEVICE DURING A WASHING PROCESS**

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(73) Assignee: **Ethicon, Inc.**, Somerville, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/075,714

(22) Filed: May 11, 1998

Related U.S. Application Data

(60) Provisional application No. [illegible] filed on Mar. [illegible], 1997.

(51) **Int. Cl.**[7] **B08B 3/04**

(52) **U.S. Cl.** ..... 134/113; 134/58 R; 134/166 R; 134/166 C

(58) **Field of Search** ..... 134/116 R, 113, 134/56 R, 58 R, 200, 166 C, 68, 22.02; 435/287.3, 122.28

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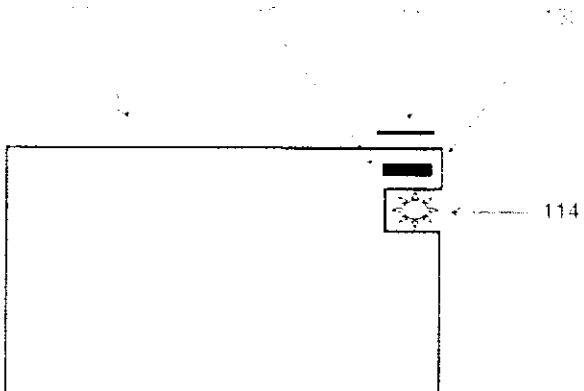
Primary Examiner—Frankie L. Stinson

(74) *Attorney, Agent, or Firm*—Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

An apparatus and method for monitoring a cleaning process for a medical device. The apparatus comprises a soil detector. The soil detector is capable of detecting inorganic and or organic soil on a medical device or in a liquid utilized in a cleaning or cleaning monitoring process or on a soil-covered standard which can serve as a surrogate indicator of cleanliness for the medical device. The method of the invention for monitoring a cleaning process for a medical device comprises the step of measuring the soil removed from a medical device with the apparatus of the invention comprising a soil detector. Preferably, the method further comprises the step of determining when the device is sufficiently clean so that it can be sterilized.

8 Claims, 18 Drawing Sheets



14. In one embodiment, valve **104** is opened at a predetermined level during a cleaning process, and the soil level in the washing solution in the enclosure **102** is monitored with detector **122**.

In another embodiment, an apparatus similar to that shown in FIG. **14** is used, the only difference is that a soil covered standard **120** is placed in enclosure **102**. Standard **120** is made of material transparent to predetermined wave length range. Preferably, standard **120** has a flat surface covered with soil which contains soil contained in the chemical source **108** (see FIG. **14**) containing certain compound that absorbs light in certain range of wave length. It is also possible to use light source **114** and spectrophotometer **112** alone without a chemical source.

FIG. **15***b* shows another embodiment, in which standard **120** is not placed in an enclosure, instead it is placed in an indentation. As shown in this figure, standard **120** is removably coupled to a support **122**. Preferably, standard **120** is a flat plate with its surface covered with soil on one side or both sides. Support **122** is mounted on the wall of the indentation **130**. Preferably, support **122** is movable, or standard can be coupled to support **122** at several positions, so that the position of standard **120** in the indentation **130** can be adjusted. Indentation **130** may have different shapes. For example, it can be an inclined gap with its two side walls **132** divergent from the wall of chamber **20** as shown in FIG. **15***b*. The two side walls **132** can also be made parallel to each other. If desired, indentation **130** may also have a surrounded side wall with only one end open to chamber **20**. Because of the limited space, the cleaning efficiency in indentation **130** is lower than the area where the items **22** and **24** are placed, and the deeper and narrower the indentation **130**, the less the cleaning efficiency is. Thus, the relative cleaning efficiency of standard **120** can be adjusted by placing it in different positions in the indentation **130**. Agitation level in chamber **20** can also be used to adjust the cleaning efficiency.

Light source **114** and detector **112** are placed on opposite sides of indentation **130**. Side walls **132** are made of material transparent to light from light source **114**. Standard **120** is also placed in the light path between light source **114**. Thus, light beam from light source **114** passes the side walls **132** and the standard **120**. FIGS. **15***c*-**15***d* illustrate two other configurations of the indentation **130**. In the arrangement shown in FIG. **15***c*, indentation **130** is located at a corner of the chamber **20**. Light source **114** is placed outside chamber **20** in a space next to indentation **130**. In the arrangement shown in FIG. **15***d*, indentation **130** is also located at a corner of the chamber **20**, but extruding outwardly. Light source **114** and detector **112** are placed outside chamber **20** in a space next to indentation **130**. If the standard **120** to be used has a flat surface, the surface can be placed in any proper orientation, vertical, horizontal, or with an angle. The light beam from the light source **114** can be vertical, horizontal, or any other angle.

The apparatus illustrated in FIGS. **15***a*-**15***d* can be easily adapted to further include one or more other detectors of proper type, a vacuum pump or vacuum source for vacuum drying the items after cleaning, a sterilization system.

Generally, the embodiments of the apparatus of the invention illustrated in FIGS. **9**-**15***d* can employ one or more additional soil detectors. Soil detectors suitable for detecting protein are particularly useful additions. In such embodiments, it is preferable to use one or more detectors for detecting inorganic soil in combination with a ultraviolet visible spectroscopy detector suitable for detecting protein or other organic species. Many of the protein soil detectors are soil detectors which detect wavelengths common to all proteins and many organic molecules found in the body. Many other wavelengths are also suitable, including 260, 265, and 280 nm. Another preferred soil detector combination employs one or more detectors along with a colorimetric autotitrator for detecting protein. Another preferred detector combination employs an [illegible] detector and a turbidimetry detector. Other soil detectors other than those listed may also be used. As the apparatus illustrated in FIGS. **9**-**15***d* [illegible] **20** which also serves as a [illegible] standard can be [illegible] Various sterilization systems [illegible] vapor phase sterilization can be employed with the apparatus of the present invention illustrated in FIGS. **9**-**15***d*. When a long and narrow lumen device is to be cleaned and or sterilized, chamber **20** can be further divided into two sub-chambers separated by a sealable interface with two open ends of the lumen positioned in the two sub-chambers separately. A pressure difference can be generated between the two sub-chambers, so that cleaning or sterilant fluid flows through the lumen. Thus, the lumen can be cleaned and sterilized more efficiently.

The foregoing examples are provided by way of illustration only and are not intended as a limitation of the present invention, many variations of which are possible without departing from the spirit and scope thereof.

What is claimed is

1. An apparatus for monitoring a cleaning process for a precision instrument, comprising:

a chamber for receiving and cleaning the instrument with a cleaning liquid;

a standard containing a predetermined amount of soil positioned in the chamber or in controllable fluid communication with the chamber, wherein said standard is in fluid communication with the liquid in said chamber; and

[illegible] to provide an indication of the amount [illegible] standard without removing the [illegible] and a sterilizer coupled to [illegible] the apparatus.

2. [illegible] claim **1**, wherein the indication is a signal selected from the group consisting of concentration of the soil, electrical potential, conductivity, transparency, [illegible] wave length, or color of a cleaning rinsing liquid used for the cleaning.

3. The apparatus of claim **2**, additionally comprising a light source which generates a light beam of a predetermined wave length which travels through said standard and reaches said detector.

4. The apparatus of claim **2**, wherein the standard is placed in an enclosure in controllable fluid communication with the chamber.

5. The apparatus of claim **4**, wherein the detector comprises an electrode located in the enclosure.

6. The apparatus according to claim **1**, wherein the detector is selected from the group consisting of ion-selective electrodes, conductivity, spectrophotometry, ion chromatography, capillary electrophoresis, high performance liquid chromatography, liquid chromatography, radioactivity, gravimetry, infra-red spectroscopy, [illegible] and turbidimetry.

7. The apparatus according to claim **1**, further comprising a vacuum pump connected to said chamber, wherein said chamber [illegible] functions as a vacuum chamber.

8. The apparatus according to claim **1**, further comprising [illegible]

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US006454874B1

(12) **United States Patent**
Jacobs et al.

(10) **Patent No.: US 6,454,874 B1**
(45) **Date of Patent: Sep. 24, 2002**

(54) METHOD FOR DETECTING THE CLEANLINESS OF A MEDICAL DEVICE

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/417,648**

(22) Filed: **Oct. 14, 1999**

Related U.S. Application Data

(62) Division of application No. [illegible], filed on May 1, 1998.

(60) Provisional application No. 60/049,381, filed on Jun. 11, 1997.

(51) **Int. Cl.**[7] **B08B 3/00**

(52) **U.S. Cl.** ..... **134/18**; [illegible] 134/22.1; 422/3

(58) **Field of Search** ..... [illegible] 134/18, 22.1, 22.18, 26, 27, 28, 29, 30

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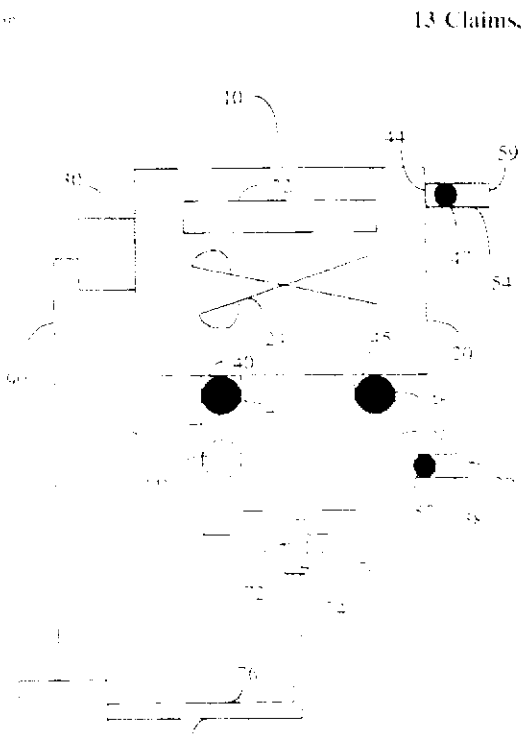
Primary Examiner—Alexander Markoff
(74) *Attorney, Agent, or Firm*—Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

A method for monitoring a cleaning process for a soiled medical device. The method involves cleaning the soiled device with a cleaning liquid in a cleaning chamber, exposing a detector to the cleaning liquid to measure the amount of soil removed, determining whether a sufficient amount of soil has been removed from the soiled device so that the [illegible] sterilized, and sterilizing the soiled device. One method of determining the amount of soil removed from the soiled device comprises [illegible] soiled standard. Another method is provided for [illegible] to the amount of soil removed from the soiled standard to determine whether enough soil has been removed from the soiled standard so that the soiled device can be sterilized. Another method involves measuring the amount of soil removed from the soiled device with at least two detectors.

13 Claims, 18 Drawing Sheets



level, the items **22** and **24** will be cleaned completely. This will allow the use of less sensitive detectors. The standard **120** can be covered with any proper soils such as those mentioned previously, or their combinations. Preferably, standard **120** is covered with the same soils as those contained in the items **22** and **24** to be cleaned. However, if desirable, the standard **120** can be covered with soil different from that of the items **22** and **24** to be cleaned. This will allow the use of certain soil on the standard and a preferred type of detection technology particularly suitable for that type of soil. Many other options are available as long as a proper correlation between the cleaning of the standard **120** and the cleaning of the items to be cleaned is established through experiments associated with particular apparatus configurations.

FIG. **15***a* illustrates an apparatus **16** with a soil covered standard **120** and a soil detector **122** positioned in an enclosure **102**. Standard **120** can be any suitable surface covered with soil. For example, standard **120** can be a plate or a piece of suitable material preferably removably coupled to a support. Preferably, the connection between the standard **120** and the support **124** is made in such a way that the [illegible] of the standard is not soiled. There are several ways for controlling the cleaning efficiency of the standard **120** relative to that of the items **22** and **24**. For example, valve **104** can be adjusted at different levels to control the fluid communication between chamber **20** and enclosure **102**. A larger valve **104** will provide a better fluid communication, thus, the cleaning efficiency in chamber **20** and enclosure **102** will be closer to each other. Another option is to provide an adjustable agitation system in enclosure **102**, or chamber **20**, or both. By adjusting the agitation level, the cleaning efficiency in enclosure **102** or chamber **20** can be adjusted to a predetermined level. Detector **122** can be any suitable type, for example, it can be an electrode. Other parts of the apparatus **16** are similar to those of FIG. **14**. In one embodiment, valve **104** is opened at a predetermined level during a cleaning process, and the soil level in the washing solution in the enclosure **102** is monitored with detector **122**.

In another embodiment, an apparatus similar to that shown in FIG. **14** is used, the only difference is that a soil covered standard **120** is placed in enclosure **102**. The [illegible] standard **120** is made of [illegible] material transparent to a predetermined wave length range. Preferably, standard **120** is a flat surface covered with soil which [illegible] contained in the chemical source **108** (see FIG. **14**) [illegible] ing certain components that [illegible] wave length. It is also possible [illegible] light source **114** and spectrophotometer **112** [illegible] detectors.

FIG. **15***b* shows another embodiment in which standard **120** is not placed in an enclosure, instead it is placed in an indentation. As shown in this figure, standard **120** is removably coupled to a support **122**. Preferably, standard **120** is a flat plate with its surface covered with soil on one side or both sides. Support **122** is mounted on the wall of the indentation **130**. Preferably, support **122** is movable, or standard can be coupled to support **122** at several positions, so that the position of standard **120** in the indentation **130** can be adjusted. Indentation **130** may have different shapes. For example, it can be an arc-shaped gap with its two side walls **132** divergent from the wall of chamber **20** as shown in FIG. **15***b*. The two side walls **132** can also be made parallel to each other. If desired, indentation **130** may also have a surrounded side wall with only one end open to chamber **20**. Because of the limited space, the cleaning efficiency in indentation **130** is lower than the area where the items **22** and **24** are placed, and the deeper and narrower the indentation **130**, the less the cleaning efficiency is. Thus, the Agitation level in chamber **20** can also be used to adjust the cleaning efficiency.

A light source **114** and a detector **112** are provided at two opposite sides of indentation **130**. Side walls **132** are made of material transparent to the light from light source **114**. Standard **120** is also made of material transparent to the light from light source **114**. Thus, quartz is a suitable material for both the side walls **132** and the standard **120**. FIGS. **15***c* and **15***d* illustrate two other configurations of the indentation **130**. In the arrangement shown in FIG. **15***c*, indentation **130** is located at a corner of the chamber **20**. Light source **114** is placed outside chamber **20** in a space next to indentation **130**. In the arrangement shown in FIG. **15***d*, indentation **130** is also located at a corner of the chamber **20**, but extending [illegible]. Light source **114** and detector **112** are placed [illegible] chamber **20** in a space next to indentation **130**. If the standard **120** [illegible] is a flat surface, the surface can be [illegible] horizontal, [illegible] angle. The light from the light source **114** can be [illegible] any other angle.

The apparatus illustrated in FIGS. **15***a*–**15***d* can be easily adapted to further include one or more other detectors of [illegible] vacuum pump or vacuum source for vacuum drying the items after cleaning, a sterilization system.

Generally, the embodiments of the apparatus of the invention illustrated in FIGS. **9**–**15***d* can employ one or more additional soil detectors. Soil detectors suitable for detecting proteins are particularly useful additions. In such embodiments, it is preferable to use one more detectors for detecting inorganic soil in combination with an ultraviolet-visible spectroscopy detector suitable for detecting protein and other organic species. An example of the latter type of detector is a spectrophotometer employing a detection wavelength of 220 nm, one of the principle ultraviolet absorption wavelengths common to all proteins and many organic molecules found in the body. Many other wavelengths are also suitable, including 260, 265, and 280 nm. Another preferred soil detector combination employs one or more detectors along with a colorimetric autotitrator for detecting protein. Another preferred detector combination employs an ion-selective electrode detector and a turbidimetry detector. Combinations of detectors other than those listed may also [illegible]. All the apparatus illustrated in FIGS. **9**–**15***d* [illegible] chamber **20** which also serves as a vacuum [illegible] drying can be conducted in the [illegible]. Various sterilization [illegible] vapor phase sterilization [illegible] the present invention [illegible] FIGS. **9**–**15**. When a long and narrow [illegible] is sterilized, chamber **20** can be further divided into two sub-chambers separated by a sealable interface with two open ends of the lumen positioned in the two sub-chambers separately. A pressure difference can be generated between the two sub-chambers, so that cleaning or sterilant fluid flows through the lumen. Thus, the lumen can be cleaned and sterilized more efficiently.

The foregoing examples are provided by way of illustration only and are not intended as a limitation of the present invention, many variations of which are possible without departing from the spirit and scope thereof.

What is claimed is:

1. A method for cleaning and sterilizing a soiled medical device comprising the steps of:

a) providing a cleaning chamber for receiving the soiled device;

b) providing a soil detector comprising a soiled standard coupled with the cleaning chamber;

c) introducing a cleaning liquid into the cleaning cham-

c) monitoring the amount of soil presented in the soiled standard with said detector to determine that a sufficient amount of the soil has been removed from the soiled device so that the soiled device can be sterilized; and

f) sterilizing the soiled device.

2. The method of claim 1, wherein the cleaning step comprises exposing the standard to a cleaning environment as effective or less effective than that in which the soiled device is exposed, and the determining step comprises determining that the soiled standard has been cleaned to a predetermined level.

3. The method of claim 1, wherein the soiled standard is more heavily soiled or more difficult to clean than the soiled device.

4. A method for cleaning and sterilizing a soiled medical device comprising the steps of:

a) providing a cleaning chamber for receiving the soiled device;

b) providing a chemical source coupled to an enclosure in controllable fluid communication with said cleaning chamber, said source containing a chemical capable of reacting with the soil on said device to generate a detectable signal, wherein the detectable signal is different from a signal from the soil or the chemical;

c) introducing a cleaning liquid into the cleaning chamber;

d) cleaning the soiled device in the cleaning chamber;

e) releasing the chemical from the source into said enclosure;

f) detecting the signal generated by reaction between the chemical and soil on said device to determine that a sufficient amount of the soil has been removed from the soiled device; and

g) sterilizing the device.

5. The method of claim 4, wherein a portion of the cleaning fluid is introduced into the enclosure prior to the chemical is released into the enclosure, and before the introduction of said portion of the cleaning liquid, the enclosure is separated from the cleaning chamber so that substantially there is no fluid communication therebetween.

6. The method of claim 4, wherein said chemical is selected from the group consisting of $HgSCN_2$, OPA (o-pathatic dialdehyde+Triton), Bromeresol purple ($C_{21}H_{16}Br_2O_5S_1$), biuret reagent and Micropractin-PR.

7. A method for cleaning and sterilizing a soiled medical device comprising the steps of:

a) providing a cleaning chamber for receiving the soiled device;

b) introducing a cleaning liquid into the cleaning chamber;

c) cleaning the soiled device in the cleaning chamber;

d) measuring the amount of soil removed from the soiled device with at least two detectors of different types;

e) determining that a sufficient amount of the soil has been removed from the soiled device so that the soiled device can be sterilized; and

f) sterilizing the device.

8. The method according to any one of claims 1, 4, and 7, wherein the sterilizing step is conducted by a sterilizing procedure.

9. The method according to any one of claims 1, 4, and 7, wherein the cleaning liquid comprises a liquid sterilization agent, such that the cleaning step and the sterilizing step are combined as a process.

10. The method according to any one of claims 1, 4, and 7, further comprising a vacuum drying step.

11. The method of claim 7, wherein step d) comprises measuring with a first detector an organic soil selected from the group consisting of inorganic electrolytes, silicates and silicate containing soils, inorganic metal-containing compounds and other inorganic compounds present in the human body, which may come in contact with a medical device, and measuring with a second detector, an organic soil selected from the group consisting of proteins, glycoproteins, lipoproteins, mucous, amino acids, polysaccharides, sugars, lipids, glycolipids, other organic compounds present in the human body which may come in contact with a medical device, microorganisms and viruses.

12. A method for cleaning and sterilizing a soiled medical device comprising the steps of:

a) providing a cleaning chamber for receiving the soiled device;

b) introducing a cleaning liquid into the cleaning chamber;

c) cleaning the soiled device in the cleaning chamber;

d) measuring the amount of soil removed from the soiled device with at least two detectors, which comprises measuring soil level of the cleaning liquid with a first detector before the cleaning step, and measuring the soil level of the cleaning liquid with a second detector [illegible] the cleaning;

[illegible] sufficient amount of the soil has been [illegible] soiled device so that the soiled [illegible] by comparing the soil level [illegible] detected by the first detector to the [illegible] cleaning liquid detected by the second detector is selected if the difference between the two soil levels is within a predetermined range, said sufficient amount of soil has been removed from the soiled device and

f) sterilizing the device.

13. A method for cleaning and sterilizing a soiled medical device comprising the steps of:

a) providing a cleaning chamber for receiving the soiled device;

b) providing a soil detector coupled with the cleaning chamber;

c) introducing a cleaning liquid into the cleaning chamber;

d) cleaning the soiled device in the cleaning chamber while the detector is not continuously in fluid communication with said soiled device;

e) contacting the detector with the cleaning liquid;

f) determining that a sufficient amount of the soil has been removed from the soiled device so the soiled device can be sterilized; and

g) sterilizing the device.

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US006494964B1

(12) **United States Patent**
Jacobs et al.

(10) **Patent No.: US 6,494,964 B1**
(45) **Date of Patent: Dec. 17, 2002**

(54) **MONITORING OF CLEANING PROCESS**

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(73) Assignee: **Ethicon, Inc.**, Somerville, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(22) Filed: **Apr. 25, 2002**

Related U.S. Application Data

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(60) Provisional application No. [illegible], filed on Jun. 1, [illegible].

(51) **Int. Cl.**[7] **B08B 3/04**

(52) **U.S. Cl.** ..... **134/18**; 134/25.1; 134/113; 134/56 R; 134/169 R

(58) **Field of Search** ..... 134/18, 25.1, 25.4, 134/115 R, 113, 56 R, 58 R, 169 R; 435/287.4; 422/28

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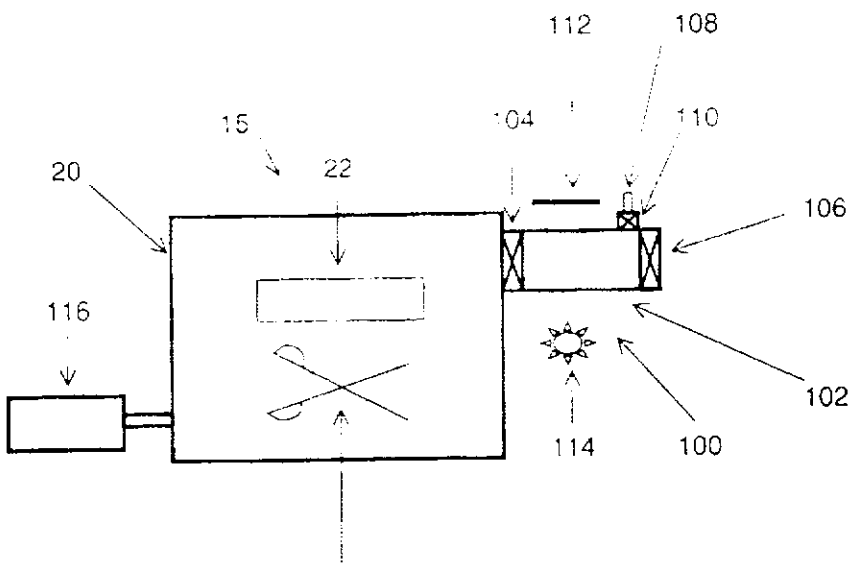
Primary Examiner—Frankie L. Stinson
(74) *Attorney, Agent, or Firm*—Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

An apparatus and method for monitoring a cleaning process for a medical device. The apparatus comprises a soil detector. The soil detector is capable of detecting inorganic and/or organic soil on a medical device or in a liquid utilized in a cleaning or cleaning monitoring process or on a soil-covered standard which can serve as a surrogate indicator of cleanliness for the medical device. The method of the invention for monitoring a cleaning process for a medical device comprises the step of measuring the soil removed from a medical device with the apparatus of the invention comprising a soil detector. Preferably, the method further comprises the step of determining when the device is sufficiently cleaned so that it can be sterilized.

11 Claims, 18 Drawing Sheets



can be adjusted. Indentation **130** may have different shapes. For example, it can be an inclined gap with its two side walls **132** divergent from the wall of chamber **20**, as shown in FIG. **15***b*. The two side walls **132** can also be made parallel to each other. If desired, indentation **130** may also have a surrounded side wall with only one end open to chamber **20**. Because of the limited space, the cleaning efficiency in indentation **130** is lower than the area where the items **22** and **24** are placed, and the deeper and narrower the indentation **130**, the less the cleaning efficiency is. Thus, the relative cleaning efficiency of standard **120** can be adjusted by placing it in different positions in the indentation **130**. Agitation level in chamber **20** can also be used to adjust the cleaning efficiency.

A light source **114** and a detector **112** are placed in two opposite sides of indentation **130**. Side walls **132** are made of material transparent to the light from light source **114**. Standard **120** is placed in the light path of light source **114**. The standard is preferably in contact with the side walls **132** and the standard **120**. FIGS. **15***c* and **15***d* illustrate two other configurations of the indentation **130**. In the arrangement shown in FIG. **15***c*, indentation **130** is located at a corner of the chamber **20**. Light source **114** is placed outside chamber **20** in a space next to indentation **130**. In the arrangement shown in FIG. **15***d*, indentation **130** is also located at a corner of the chamber **20**, but extruding outwardly. Light source **114** and detector **112** are placed outside chamber **20** in a space next to indentation **130**. If the standard **120** to be used has a flat surface, the surface can be put in any proper orientation, vertical, horizontal or with an angle. The light beam from the light source **114** can be vertical, horizontal, or any other angle.

The apparatus illustrated in FIGS. **15***a*-**15***d* can be easily adapted to further include one or more other detectors of proper type, a vacuum pump or vacuum source for vacuum drying the items after cleaning, a sterilization system.

Generally, the embodiments of the apparatus of the invention illustrated in FIGS. **9**-**15***d* can employ one or more additional soil detectors. Soil detectors suitable for detecting protein are particularly useful additions. In such embodiments, it is preferable to use one or more detectors for detecting inorganic soil in combination with a UV-visible visible spectroscopy detector suitable for detecting protein and other organic species. An example of the latter type of detector is a spectrophotometer operating at wavelengths of 220 nm and/or 280 nm, which measure absorption wavelengths common to most proteins and many organic molecules found in the body. Many other wavelengths are also suitable, including 200, 205, and 280 nm. Another preferred soil detector combination employs one or more detectors along with a colorimetric autotitrator for detecting protein. Another preferred detector combination employs an ion-selective electrode detector and a turbidimetry detector. Combinations of detectors other than those listed may also be employed. All the apparatus illustrated in FIGS. **9**-**15***d* can employ a chamber **20** which also serves as a vacuum chamber, so that vacuum drying can be conducted in the chamber with a vacuum source. Various sterilization systems for liquid phase or vapor phase sterilization can be combined into the apparatus of the present invention illustrated in FIGS. **9**-**15***d*. When a long and narrow lumen device is to be cleaned and/or sterilized, chamber **20** can be further divided into two sub-chambers separated by a sealable interface with two open ends. The lumen is positioned in the two sub-chambers separately. Various sealable interfaces can be employed. One example is a sealable interface with two open ends, each of which is sealed to the lumen of the device. Another example is a sealable interface with two open ends, each of which is sealed to the outer surface of the device. Another example is a sealable interface with two open ends, each of which is sealed to the lumen of the device. Another example is a sealable interface with two open ends, each of which is sealed to the outer surface of the device.

The foregoing examples are provided by way of illustration only and are not intended as a limitation of the present invention. Many variations of which are possible without departing from the spirit and scope thereof.

What is claimed is:

1. An apparatus for monitoring a cleaning process for a soiled medical instrument, comprising:

a chamber for receiving and cleaning the instrument;

an enclosure in controllable fluid communication with the chamber;

a chemical source coupled to the enclosure for providing a chemical capable of reacting with the soil of the instrument to generate a detectable signal in the enclosure;

a detector for detecting the signal.

2. The apparatus of claim **1**, wherein said chemical is selected from the group consisting of $Hg(SCN)_2$, OPA/o-phthaldialdehyde (OPA), Bromecresol purple (BCP), a Biuret reagent, and Microprotein-PR.

3. The apparatus of claim **1**, further comprising a light source for sending a light beam through a cleaning liquid in the enclosure to the detector.

4. The apparatus according to claim **1**, wherein the detector is selected from the group consisting of ion-selective electrodes, conductivity, spectrophotometry, ion chromatography, capillary electrophoresis, high performance liquid chromatography, liquid chromatography, radioactivity, gravimetry, infra-red spectroscopy, potentiometry and turbidimetry.

5. The apparatus according to claim **1**, further comprising a vacuum pump connected to said chamber, wherein said chamber also functions as a vacuum chamber.

6. The apparatus according to claim **1**, further comprising a sterilization system.

7. A method for cleaning a soiled medical device comprising the steps of:

providing a cleaning chamber for receiving the soiled device;

providing a chemical source coupled to an enclosure [illegible] with the cleaning chamber [illegible] said device [illegible] with the chemical [illegible] said device [illegible] a detectable signal [illegible];

introducing a cleaning liquid into the cleaning chamber;

placing the soiled device in the cleaning chamber;

releasing the chemical from the source into said enclosure; and

detecting the signal generated through reaction between the chemical and soil in said cleaning fluid to determine if a sufficient amount of soil has been removed from the device.

8. The method of claim **7**, wherein a portion of the cleaning fluid is introduced into the enclosure before the chemical is released into the enclosure, and before the introduction of said portion of the cleaning liquid, the enclosure is separated from the cleaning chamber so that substantially there is no fluid communication therebetween.

9. The method according to claim **7**, wherein the sterilizing step is conducted by a vapor phase sterilizing procedure.

10. The method according to claim **7**, wherein the cleaning liquid comprises a liquid sterilization agent, such that the cleaning step and the sterilizing step are conducted simultaneously.

11. The method according to claim **7**, further comprising

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(12) **United States Patent**
Jacobs et al.

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(45) **Date of Patent: Feb. 11, 2003**

(54) **MONITORING OF CLEANING PROCESS**

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(60) Provisional application No. 60/049,351, filed on Jun. 12, 1997.

(51) **Int. Cl.**[7] **B08B 3/04**
(52) **U.S. Cl.** ..... **134/113**; 134/58 R, 134/166 R, 134/166 C; 134/200
(58) **Field of Search** ..... 134/116 R, 113, 134/56 R, 58 R, 200, 166 C; 68/12.02, 435/287.4; 422/28

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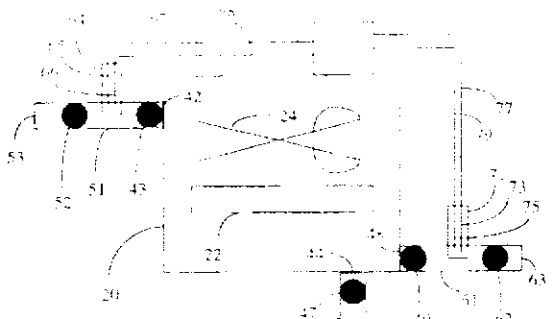
WO	[illegible]	A	7/1997

Primary Examiner—Frankie L. Stinson
(74) *Attorney, Agent, or Firm*—Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

A method for monitoring a cleaning process for a soiled medical device. The method involves cleaning the soiled device with a cleaning liquid in a cleaning chamber, exposing a detector to the cleaning liquid to measure the amount of soil removed, determining whether a sufficient amount of the soil has been removed from the soiled device so that the soiled device can be sterilized, and sterilizing the soiled device. One method of determining the amount of soil is by detecting the signal generated from the reaction between a chemical and the soil. Another method is to provide a soiled standard and measure the amount of soil removed from the soiled standard to determine whether enough soil has been removed from the soiled standard so that the soiled device can be sterilized. Another method involves measuring the amount of soil removed from the soiled device with at least [illegible]

16 Claims, 18 Drawing Sheets



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can be adjusted. Indentation **130** may have different shapes. For example, it can be an inclined gap with its two side walls **132** divergent from the wall of chamber **20** as shown in FIG. **15b**. The two side walls **132** can also be made parallel to each other. If desired, indentation **130** may also have a surrounded side wall with only one end open to chamber **20**. Because of the limited space, the cleaning efficiency in indentation **130** is lower than the area where the items **22** and **24** are placed, and the deeper and narrower the indentation **130**, the less the cleaning efficiency is. Thus, the relative cleaning efficiency of standard **120** can be adjusted by placing it in different positions in the indentation **130**. Agitation level in chamber **20** can also be used to adjust the cleaning efficiency.

A light source **114** and a detector **112** are provided at two opposite sides of indentation **130**. Side walls **132** are made of material transparent to the light from light source **114**. Standard **120** is also made of material transparent to the light from light source **114**. Thus, quartz is a suitable material for both the side walls **132** and the standard **120**. FIGS. **15c** and **15d** illustrate two other configurations of the indentation **130**. In the arrangement shown in FIG. **15c**, indentation **130** is located at a corner of the chamber **20**. Light source **114** is placed outside chamber **20** in a space next to indentation **130**. In the arrangement shown in FIG. **15d**, indentation **130** is also located at a corner of the chamber **20**, but extruding outwardly. Light source **114** and detector **112** are placed outside chamber **20** in a space next to indentation **130**. If the standard **120** to be used has a flat surface, the surface can be put in any proper orientation, vertical, horizontal, or with an angle. The light beam from the light source **114** can be vertical, horizontal, or any other angle.

The apparatus illustrated in FIGS. **15a**-**15d** can be easily adapted to further include one or more other detectors of proper type, a vacuum pump or vacuum source for vacuum drying the items after cleaning, a sterilization system.

Generally, the embodiments of the apparatus of the invention illustrated in FIGS. **9**-**15d** can employ one or more additional soil detectors. Soil detectors suitable for detecting [illegible] are particularly useful [illegible] such [illegible]. It is [illegible] detectors for detecting inorganic soil [illegible] with [illegible] visible spectroscopy detector suitable for detecting protein and other organic species. An example of the latter type of detector is a spectrophotometer employing a detection wavelength of 220 nm, one of the principle ultraviolet absorption wavelengths common to all proteins and many organic molecules found in the body. Many other wavelengths are also suitable, including 260, 265, and 280 nm. Another preferred soil detector combination employs one or more electrodes along with a colorimetric autotitrator for detecting protein. Another preferred detector combination employs an ion-selective electrode detector and a turbidimetry detector. Combinations of detectors other than those listed may also be employed. All the apparatus illustrated in FIGS. **9**-**15d** can employ a chamber **20** which also serves as a vacuum chamber, so that vacuum drying can be conducted in the chamber with a vacuum source. Various sterilization systems for liquid phase or vapor phase sterilization can be combined into the apparatus of the present invention illustrated in FIGS. **9**-**15d**. When a long and narrow lumen device is to be cleaned and/or sterilized, chamber **20** can be further divided into two sub-chambers separated by a sealable interface with two open ends of the lumen positioned in the two sub-chambers separately. A pressure [illegible] can be generated between [illegible]

The foregoing examples are provided by way of illustration only and are not intended as a limitation of the present invention, many variations of which are possible without departing from the spirit and scope thereof.

What is claimed is:

1. An apparatus for monitoring a cleaning process for a medical instrument, comprising:

a cleaning chamber for receiving and cleaning the instrument with a cleaning liquid;

a soil detector coupled to the cleaning chamber and adapted to provide an indication of the amount of the soil on the instrument;

wherein the soil detector is at least partially contained in or is closed from liquid in the chamber so that access to the detector by the cleaning liquid in the chamber is controllable during the cleaning process.

2. The apparatus of claim **1**, wherein said soil detector is moveable and by moving the detector it can be made in or out of fluid communication with the chamber.

3. The apparatus of claim **1**, wherein said soil detector comprises an electrode located in an enclosure, the enclosure is so coupled to the chamber that the cleaning liquid has controllable access to said enclosure.

4. An apparatus for monitoring a cleaning process for a medical instrument, comprising:

a cleaning chamber for receiving and cleaning the instrument, and

at least a first soil detector and a second soil detector adapted to provide an indication of the amount of soil removed from or remained on the instrument, the first and second soil detector being placeable in fluid communication with the cleaning chamber, wherein the first soil detector and the second soil detector are not identical.

5. The apparatus of claim **4**, wherein the first detector is located adjacent to an inlet of the cleaning chamber, the second detector is located adjacent to an outlet of the cleaning chamber.

6. The apparatus of claim **4**, further comprising a second chamber [illegible] in fluid communication with the cleaning chamber, and the first detector is located in the second chamber.

7. The apparatus of claim **4**, wherein the first soil detector and the second soil detector detect different types of soil.

8. The apparatus according to any one of claims **1**, and **4**, wherein the detector is selected from the group consisting of ion-selective electrodes, conductivity, spectrophotometry, ion chromatography, capillary electrophoresis, high performance liquid chromatography, liquid chromatography, radioactivity, gravimetry, infra-red spectroscopy, potentiometry and turbidimetry.

9. The apparatus according to any one of claims **1**, and **4**, further comprising a vacuum pump connected to said chamber, wherein said chamber also functions as a vacuum chamber.

10. The Apparatus according to any one of claims **1**, and **4**, further comprising a sterilization system.

11. An apparatus for monitoring a cleaning process for a medical instrument, comprising:

a cleaning chamber for receiving and cleaning the instrument, and

at least a first soil detector and a second soil detector adapted to provide an indication of the amount of soil removed from or remained on the instrument, the first and second soil detector being placeable in fluid communication with the cleaning chamber,

[illegible] the first soil detector is adapted to detect an organic [illegible]

12. An apparatus for monitoring a cleaning process for a medical instrument, comprising:

a cleaning chamber for receiving and cleaning the instrument; and

at least a first soil detector and a second soil detector adapted to provide an indication of the amount of soil removed from or remained on the instrument, the first and second soil detector being placeable in fluid communication with the cleaning chamber; and

a vacuum pump connected to said chamber, wherein said chamber also functions as a vacuum chamber.

13. An apparatus for monitoring a cleaning process for a medical instrument, comprising:

a cleaning chamber for receiving and cleaning the instrument;

at least a first soil detector and a second soil detector adapted to provide an indication of the amount of soil removed from or remained on the instrument, the first and second soil detector being placeable in fluid communication with the cleaning chamber; and

a second chamber in fluid communication with the cleaning chamber, and the first detector is located in the second chamber.

14. An apparatus for monitoring a cleaning process for a medical instrument, comprising:

a cleaning chamber for receiving and cleaning the instrument with a cleaning liquid;

a soil detector coupled to the cleaning chamber and adapted to provide an indication of the amount of the soil on the instrument;

wherein the soil detector is movable and by moving the [illegible] out of fluid communication [illegible]

15. [illegible] monitoring a cleaning process for a [illegible] comprising:

[illegible] receiving and cleaning the soil [illegible] cleaning liquid;

a soil detector coupled to the cleaning chamber and adapted to provide an indication of the amount of the soil on the instrument;

wherein the soil detector comprises an electrode located in an enclosure, the enclosure is so coupled to the chamber that the cleaning liquid has controllable access to said enclosure.

16. An apparatus for monitoring a cleaning process for a medical instrument, comprising:

a cleaning chamber for receiving and cleaning the instrument; and

at least a first soil detector and a second soil detector coupled to provide an indication of the amount of soil removed from or remained on the instrument, the first and second soil detector being placeable in fluid communication with the cleaning chamber, wherein the first soil detector and the second soil detector detect different types of soil.

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(12) **United States Patent**
Jacobs et al.

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(54) **MONITORING OF CLEANING PROCESS**

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( ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(60) Provisional application No. 60/034,352, filed on Jan. 11, 1997.

(51) **Int. Cl.**[7] **B08B 3/04**
(52) **U.S. Cl.** ..... **134/113**; 134/58 R; 134/166 R; 134/166 C; 134/200
(58) **Field of Search** ..... 134/18, 113, 134/56 R, 58 R, 200, 166 C; 435/287.4; 422/28

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Primary Examiner—Frankie L. Stinson
(74) *Attorney, Agent, or Firm*—Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

An apparatus and method for monitoring a cleaning process for a medical device. The apparatus comprises a soil detector for use in detecting soil removable by cleaning from a medical device or in a liquid utilized in a cleaning process or on a soil-covered surface, wherein the soil is an indicator of a contaminant on the medical device. The method of the invention for monitoring a cleaning process for a medical device comprises the step of measuring the soil removed from a medical device. In the apparatus of the invention comprises a soil detector. Preferably, the method further comprises the step of determining when the device is sufficiently clean so that it can be sterilized.

9 Claims, 18 Drawing Sheets

surface covered with soil which reacts with the electrical [illegible] used in the chemical source **108** (see FIG. **14**) or absorbing certain compound that absorbs light in a certain range of wave length. It is also possible to use light source **114** and spectrophotometer **112** alone without a chemical source.

FIG. **15***b* shows another embodiment, in which standard **120** is not placed in an enclosure, instead it is placed in an indentation. As shown in this figure, standard **120** is removably coupled to a support **122**. Preferably, standard **120** is a flat plate with its surface covered with soil on one side or both sides. Support **122** is mounted on the wall of the indentation **130**. Preferably, support **122** is movable, or standard can be coupled to support **122** at several positions, so that the position of standard **120** in the indentation **130** can be adjusted. Indentation **130** may have different shapes. For example, it can be an inclined gap with its two side walls **132** divergent from the wall of chamber **20** as shown in FIG. **15***b*. The two side walls **132** can also be made parallel to each other. If desired, indentation **130** may also have a surrounded side wall with only one end open to chamber **20**. Because of the limited space, the cleaning efficiency in indentation **130** is lower than the area where the items **22** and **24** are placed, and the deeper and narrower the indentation **130**, the less the cleaning efficiency is. Thus, the relative cleaning efficiency of standard **120** can be adjusted by placing it in different positions of the indentation **130**. Again, even [illegible] **20**, [illegible] efficiency.

Light source **114** and detector **112** are placed at two opposite sides [illegible] **130**. Side walls **132** are made of material transparent to the light from light source **114**. Standard **120** is also made of material transparent to the light from light source **114**. Thus, quartz is a suitable material for both the side walls **132** and the standard **120**. FIGS. **15***c* and **15***d* illustrate two other configurations of the indentation **130**. In the arrangement shown in FIG. **15***c*, indentation **130** is located at a corner of the chamber **20**. Light source **114** is placed outside chamber **20** in a space next to indentation **130**. In the arrangement shown in FIG. **15***d*, indentation **130** is also located at a corner of the chamber **20**, but extruding outwardly. Light source **114** and detector **112** are placed outside chamber **20** in a space next to indentation **130**. If the standard **120** to be used has a flat surface, the surface can be put in any proper orientation, vertical, horizontal, or with an angle. The light beam from the light source **114** can be vertical, horizontal, or any other angle.

The apparatus illustrated in FIGS. **15***a*–**15***d* can be easily adapted to further include one or more other detectors of proper type, a vacuum pump or vacuum source for vacuum drying the items after cleaning, a sterilization system [illegible].

Generally, the embodiments of the apparatus of the invention illustrated in FIGS. **9**–**15***d* can employ one or more additional soil detectors. Soil detection is useful in cleaning protein and particulate residue. [illegible] for such environments, it is preferable to use soil detectors for detecting [illegible] soil, such as [illegible] specific spectroscopy detection methods for cleaning protein and other organic species. An exemplary type of detector is a spectrophotometer measuring absorption at wavelength of 220 nm, one of the most prominent absorption wavelengths common to all proteins and many organic molecules found in the body. Many other wavelengths are also suitable, including 260, 265, and 280 nm. Another preferred soil detector combination employs one or more detectors along with a colorimetric autotitrator for detecting [illegible] detectors other than those listed may also be employed. The apparatus illustrated in FIGS. **9**–**15***d* can employ a chamber **20** which also serves as a vacuum chamber so that vacuum drying can be conducted in the chamber with a vacuum source. Various sterilization systems for liquid phase or vapor phase sterilization can be combined into the apparatus of the present invention illustrated in FIGS. **9**–**15***d*. When a long and narrow lumen device is to be cleaned and or sterilized, chamber **20** can be further divided into two sub-chambers separated by a sealable interface with two open ends of the lumen positioned in the two sub-chambers separately. A pressure difference can be generated between the two sub-chambers, so that cleaning or sterilant fluid flows through the lumen. Thus, the lumen can be cleaned and sterilized more efficiently.

The foregoing examples are provided by way of illustration only and are not intended as a limitation of the present invention, many variations of which are possible without departing from the spirit and scope thereof.

What is claimed is:

1. An apparatus for monitoring a cleaning process for a medical instrument, comprising:

a chamber for receiving and cleaning the instrument with a cleaning fluid;

a soil-covered standard positioned in the chamber or in such a way fluid communication with the chamber, wherein said standard is in fluid communication with the interior of said chamber; and

a detector adapted to provide an indication of the amount of the soil on the standard without removing the standard from said chamber.

2. The apparatus of claim **1**, wherein the indication is a signal selected from the group consisting of concentration of the soil, electrical potential, conductivity, transparency to certain wave length, or color of a cleaning rinsing liquid used for the cleaning.

3. The apparatus of claim **1**, additionally comprising a light source which generates a light beam of a predetermined wave length which travels through said standard and reaches said detector.

4. The apparatus of claim **1**, wherein the standard is placed [illegible] in controllable fluid communication with the chamber.

5. The apparatus of claim **4**, wherein the detector comprises an electrode [illegible] in the enclosure.

6. The apparatus according to claim **1**, wherein the detector is selected from the group consisting of [illegible] spectrophotometer, [illegible] capillary zone electrophoresis, liquid phase [illegible] and gel chromatography, liquid enzymatic reagent, radiometric assay, turbidity, infrared spectroscopy, potentiometric [illegible].

7. The apparatus according to claim **1**, further comprising a vacuum pump connected to said chamber, wherein said chamber also functions as a vacuum chamber.

8. The apparatus according to claim **1**, further comprising a sterilization system.

9. The apparatus according to claim **1**, wherein the soil-covered standard comprises a standard containing a predetermined amount of soil.

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(54) MONITORING OF CLEANING PROCESS

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(21) Appl. No.: **10/326,041**

(22) Filed: **Dec. 20, 2002**

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(63) Continuation-in-part of application No. 10/132,811, filed on Apr. 25, 2002, now Pat. No. 6,516,818, which is a continuation of application No. 09/075,714, filed on May 11, 1998, now Pat. No. 6,394,111.

(60) Provisional application No. 60/049,351, filed on Jun. 11, 1997.

Publication Classification

(51) **Int. Cl.**[7] **B08B 3/00**

(52) **U.S. Cl.** ..... **134/113**; 134/18; 134/26; 134/56 R; 134/95.1

(57) **ABSTRACT**

An apparatus for monitoring a cleaning process for a medical device includes a cleaning chamber for receiving and cleaning the instrument with a cleaning liquid, a receiving well within the cleaning chamber, a removable soil standard receivable within the receiving well whereby to be exposed to the cleaning process within the cleaning chamber; and a soil detector coupled to the cleaning chamber and adapted to provide an indication of the amount of the soil on the soil standard while the soil standard is received within the receiving well.

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(12) Patent Application Publication
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(54) BIOLOGICAL AND CHEMICAL REACTION DEVICES AND METHODS OF MANUFACTURE

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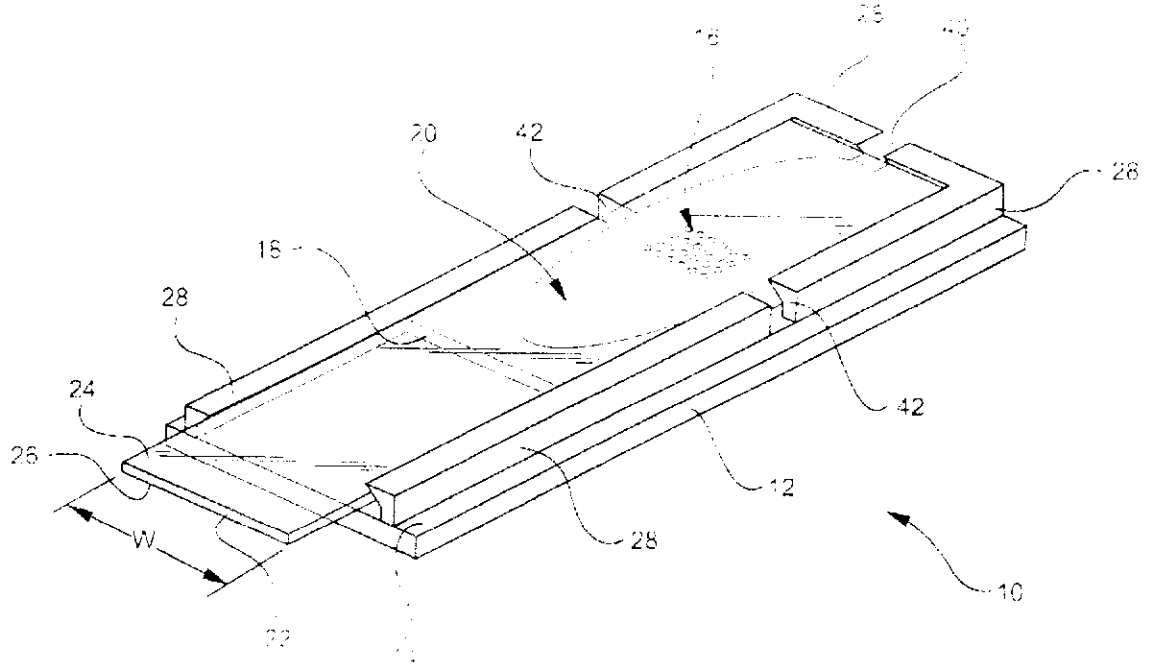
(52) U.S. Cl. 422/57

(57) ABSTRACT

Methods and devices for performing biological and chemical reactions are disclosed. The devices and methods include a reaction chamber formed on a base substrate, a spacer, and a gripping element adapted to receive a cover substrate.



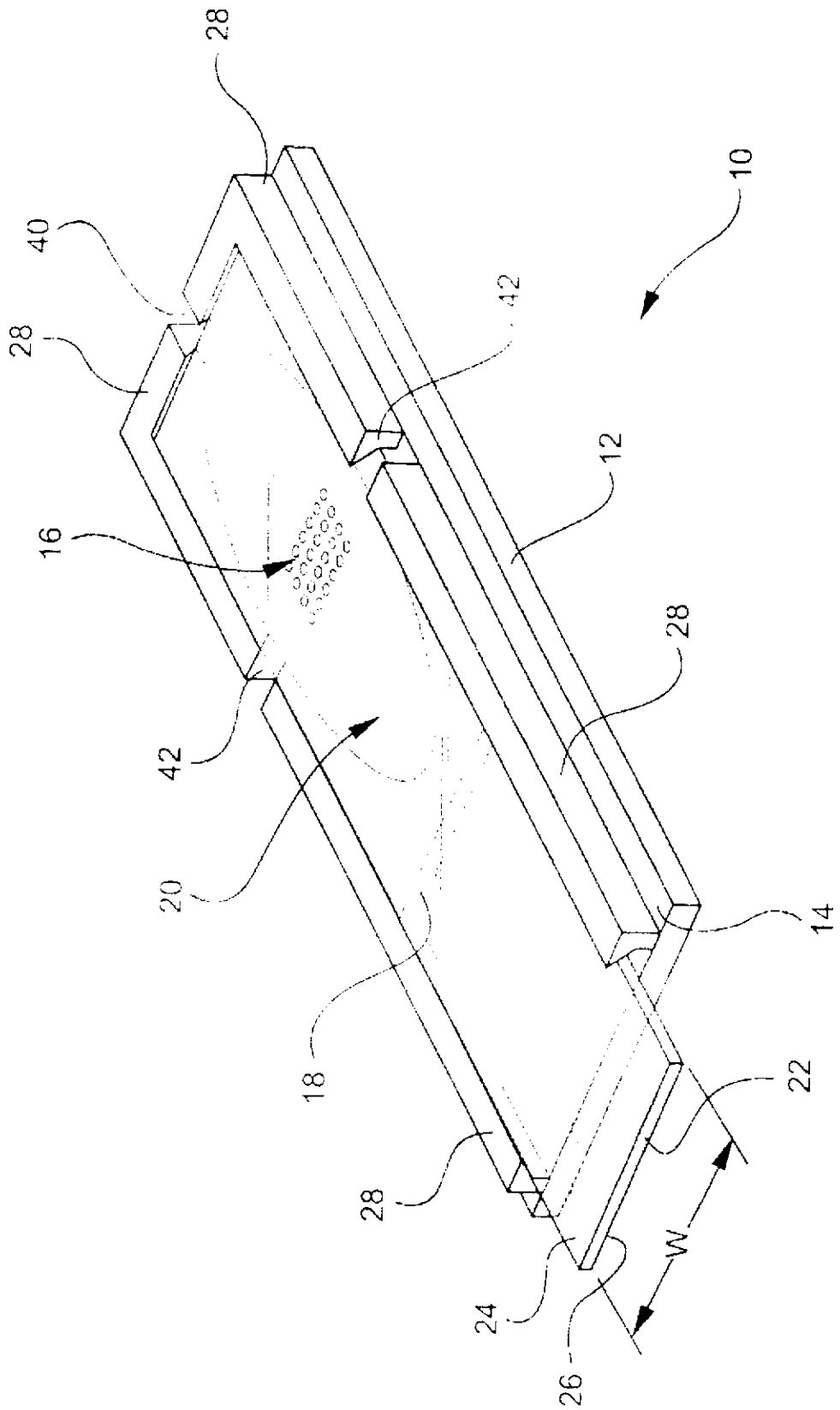


FIG. 1

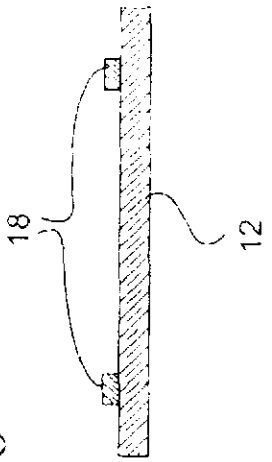


FIG. 3

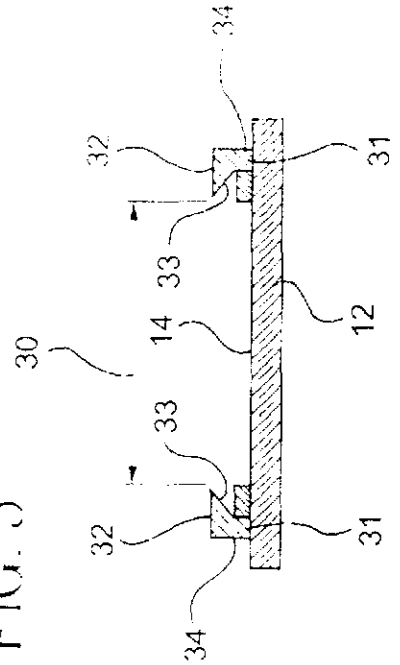


FIG. 5

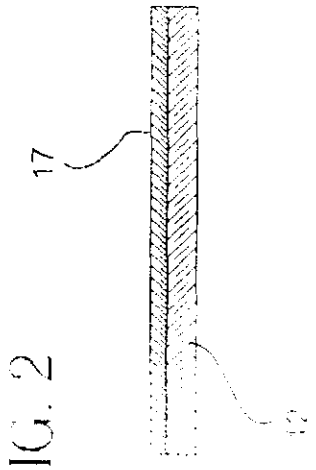


FIG. 2

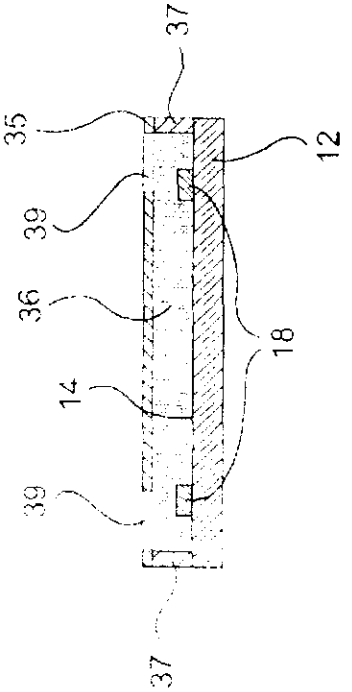


FIG. 4

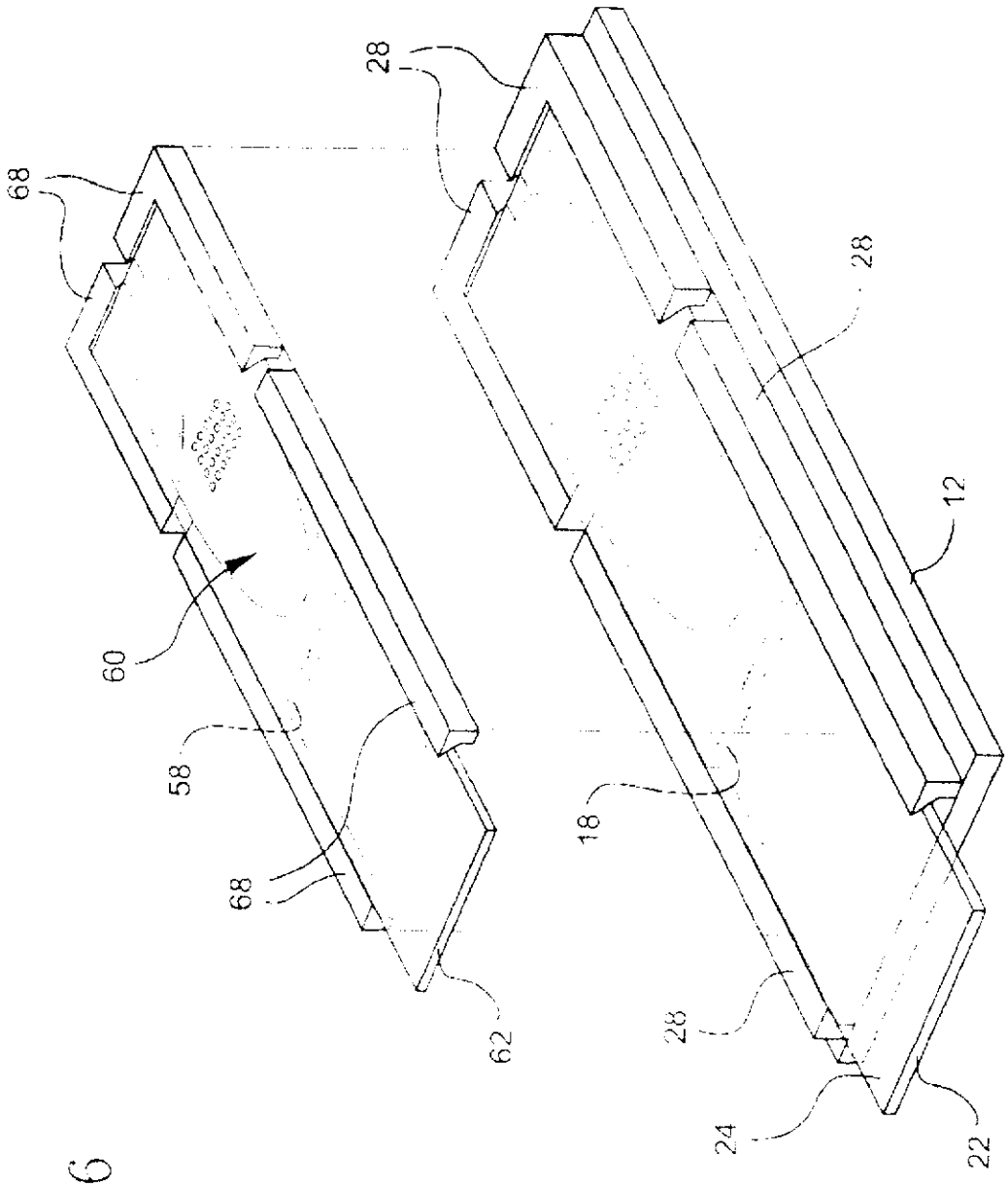


FIG. 6

FIG. 7

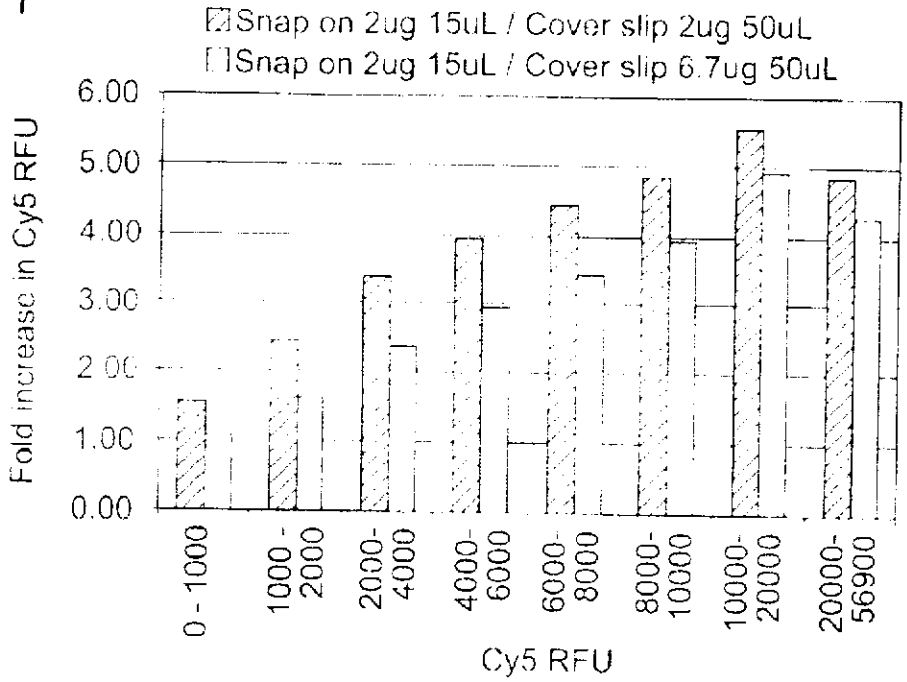
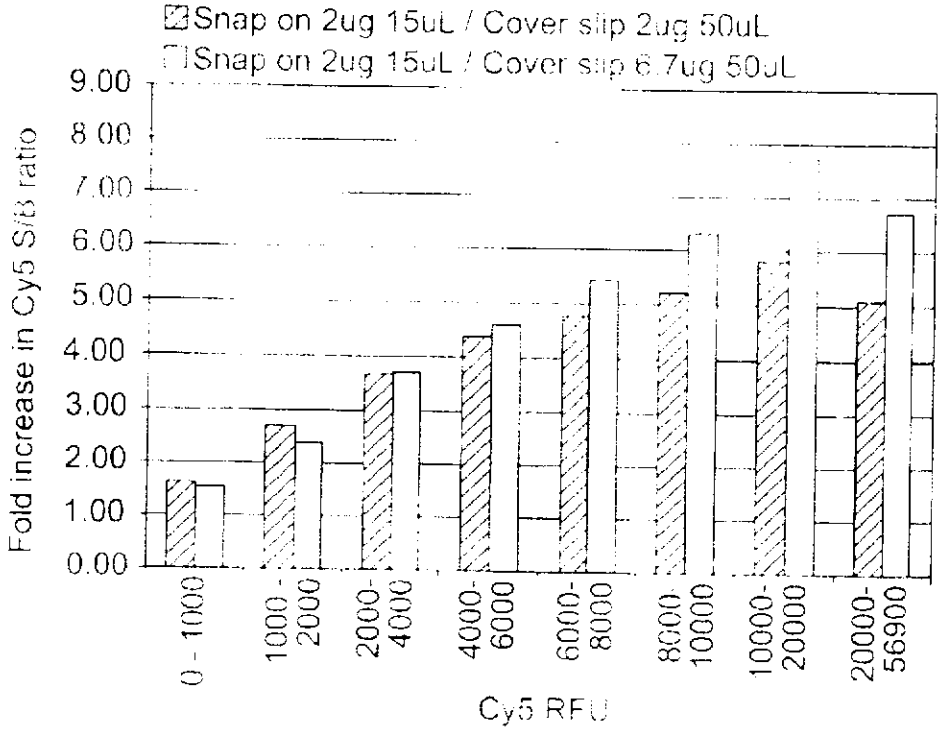

Snap on 2ug 15uL / Cover slip 2ug 50uL
Snap on 2ug 15uL / Cover slip 6.7ug 50uL
Fold increase in Cy5 RFU
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0 - 1000
1000 - 2000
2000 - 4000
4000 - 6000
6000 - 8000
8000 - 10000
10000 - 20000
20000 - 56900
Cy5 RFU

FIG. 8


Snap on 2ug 15uL / Cover slip 2ug 50uL
Snap on 2ug 15uL / Cover slip 6.7ug 50uL
Fold increase in Cy5 S/B ratio
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0 - 1000
1000 - 2000
2000 - 4000
4000 - 6000
6000 - 8000
8000 - 10000
10000 - 20000
20000 - 56900
Cy5 RFU

[0019] The present invention relates to methods and devices for performing biological or chemical reactions. Certain embodiments of the present invention provide enhanced reaction or interaction between surface bound biomolecules and analytes or biomolecules contained in solution. One type of reaction in which surface bound probes and target molecules in solution interact is called hybridization reactions. As used herein, the term hybridization refers to binding between complementary or partially complementary molecules. The term probe means a molecule adhered to a substrate. The term target means a molecule in solution.

[0020] However, the present invention is not limited to hybridization reactions or any specific type of hybridization reaction, and the chambers and methods of the various embodiments of the present invention can be used in a wide variety of biological or chemical reactions. Examples of a few of the types of reactions that the present invention can be used, include, but are not limited to fluorescent in situ hybridization (FISH), protein array reactions, immunostaining applications and general staining or histochemical reactions. In FISH reactions, the analytes in solution include DNA probes (oligomers, cDNAs, PCR fragments, or clones such as plasmids), BACs (bacterial artificial chromosomes), PACs (pinge artificial chromosomes), cosmids, or intact chromosomes, and the surface bound biomaterial (analyte, antibody or other) can include whole chromosomes or portions or regions that are typically contained on human chromosomes that are typically contained on human chromosomes spreads, wherein the affected portion of the chromosome is nucleic or even a strand of human DNA, where the DNA has been made available for hybridization to the analyte in solution. In protein arrays, the analyte in solution typically includes one or more antibodies or substrates that are labeled directly or indirectly, and the surface bound biomaterial includes one or more proteins that have affinity for one or more of the analytes in solution. In immunostaining reactions, the analyte in solution typically includes one or more antibodies that are labeled directly or indirectly, and the surface bound biomaterial includes one or more antigens of the type including DNA, RNA, protein, cell membranes, metabolites, whole cells, bacteria, fungi, viruses and the like. In other types of immunostaining reactions, the analyte in solution includes one or more antigens of the type including DNA, RNA, protein, cell membranes, metabolites, whole cells, bacteria, fungi, viruses and the like, and the surface bound biomaterial includes one or more antibodies. In general histochemical or general staining reactions, the surface bound biomaterial is any type of biomaterial and the analyte in solution includes one or more of commonly used stains, such as Eosin, Hematoxilyn, etc. Thus, it is to be understood that the devices and methods of the present invention can be used in a wide variety of biological or chemical reactions to overcome diffusion limitations imposed on the interaction between surface bound biomaterials or biomolecules and analytes contained in solution by reducing the volume of a reaction chamber which increases the effective concentration.

[0021] An exemplary embodiment of a reaction chamber device is shown in **FIG. 1** and designated generally as **10**. The device **10** includes a generally planar base substrate **12** having an inner surface **14** including a specimen area **16**. The device further includes a spacer element **18** having a height on the base substrate defining a chamber **20** surrounding the specimen area and a generally planar cover substrate **22** having a width W and including an outer surface **24**, and an inner surface **26** opposing and substantially parallel to the inner surface **14** of the base substrate **12**. A flexible gripping element **28** is located on the base substrate **12**. The flexible gripping element **28** defines a spaced apart area having a width **30** adapted to receive the cover substrate **22** and secure the cover substrate **22** to the base substrate **12**. The substrates are typically made from glass, however, other materials such as polymers, polystyrene, fused silica, polypropylene, metal and combinations thereof can be used.

[0022] According to certain embodiments, the flexible gripping element **28** forms a boundary around the spacer element **18** defined by at least two substantially parallel, the spaced apart walls **31** including an upper portion **32** and a lower portion **34** adjacent the base substrate **12**. According to certain embodiments of the invention, the spacing **30** between the substantially parallel walls is greater at the lower portion **34** adjacent the base substrate **12** than the spacing between the walls at top portion **32**. In some embodiments, the spacing **30** between the parallel walls at the top portion **34** is less than the width W of the cover substrate **22**. According to some embodiments, the walls **31** are adapted to receive the cover substrate **22** by snap fitting the cover substrate **22** such that the inner surface **26** of the cover substrate **22** is in contact with the spacer element **18**, and a portion of the element **28** provides a vertical holding force on the cover substrate. In some embodiments, the flexible gripping element **28** is defined by at least a pair of substantially parallel walls **31** including a sloped inner surface **33**. Preferably, the walls **31** have a thickness that is greater at the upper portion **32** than the thickness at the lower portion **34**.

[0023] According to certain embodiments of the invention, the device further includes at least one fluid inlet **40** and at least one fluid outlet **42**. Additional fluid inlets **40** and outlets **42** can be provided if desired. In certain embodiments, the inlet **40** and the outlet **42** extend through the spacer element **18** and flexible gripping element **28** to allow fluid to enter and exit the chamber **20**.

[0024] In certain preferred embodiments, the height of the spacer element is less than 100 microns, and in other embodiments the height of the spacer element is less than 50 microns. In some preferred embodiments, the height of the spacer element is less than 10 microns, and the height of the spacer element can be as low as 1 micron.

[0025] Certain embodiments relate to methods of forming a [illegible] reaction device. Referring to FIGS. 1-5, according to one embodiment a method of forming a biological or chemical reaction device includes providing a [illegible] base substrate **12** having an inner surface **14** [illegible] chamber **20**. A spacer element **18** is formed on the inner surface **14** of the base substrate. The spacer element **18** has a height and provides a boundary that defines a chamber **20** surrounding the specimen area **16** on the base substrate **12**.

[0026] According to certain embodiments of the invention, fabrication of chambers is accomplished by utilizing conventional photolithographic techniques that are typically used in the manufacture of optical and electronic devices. For example, the spacer element **18** can be formed using spin coating techniques to deposit a layer of photoresist **17** on the substrate **12** as shown in **FIG. 2**. Spin-coating is known in the art of electronics manufacture. Photolitho-

graphic techniques can then be used to remove portions of the photoresist to provide spacing elements **18** and form a reaction chamber in the photoresist layer **17**. It will be understood that other photo patternable materials such as polystyrene film can be used instead of photoresist. Formation of the spacer element **18** by spin coating allows the spacer element **18** to be formed to very precise dimensional tolerances, and spacer elements **18** having a height as small as 1 micron can be formed using spin coating techniques. The spacer elements could also be made using other processes such as photolithographic processes.

[0027] The method of forming a biological or chemical reaction chamber also includes forming a flexible gripping element **28** including at least a pair of flexible, substantially parallel, spaced apart walls **31** and snap fitting a generally planar cover substrate between the spaced apart walls. A flexible gripping element can be formed by first applying an adhesion promoter such as trichlorosilane to the inner surface **14** of the substrate **12**. Then, a photo definable polymer or monomer **36** can coated on top or inner surface of the substrate **12** and temporary spacers **37** can be placed between the substrate to define the height of the gripping elements. A photo mask **35** and ultraviolet light (not shown) can be used to selectively cure the polymer or monomer through apertures **39** defined in the photo mask and form at least a pair of substantially parallel walls **31**. The substantially parallel walls having inwardly sloping surfaces **33** provide a gripping element that allows a planar cover substrate to be easily snapped into the flexible substrate **12** and the reaction chamber. In preferred embodiments, the spaced apart walls **31** are formed by photolithography, for example, by curing a monomer or polymer **33** through a mask **35** having apertures **39**. The temporary spacer **37** can be used to define the overall height of the walls **31** during formation of the gripping elements.

[0028] Gripping elements or grippers are versatile structures that can be fabricated from flexible polymeric materials. Details on the construction of gripping elements are described in U.S. Pat. Nos. 6,266,472 and 5,359,687, both of which are incorporated herein by reference. In U.S. Pat. No. 5,359,687, the gripping elements, which are also called polymer microstructures, are formed on a substrate and used to grip optical fibers and position these fibers with respect to a waveguide disposed on the substrate. U.S. Pat. No. 6,266,472 describes polymer gripping elements that are used in splicing optical fibers. Applicants have discovered that flexible gripping elements can be utilized to secure cover substrates to a base substrate to form biological or chemical reaction chambers.

[0029] Gripping elements can be manufactured by depositing strips of material on the surface of the substrate. As discussed above, the strips that make up the gripping elements can be formed using well-known lithographic processes using photopolymerizable compositions and the like. For example, a photopolymerizable composition can be substantially uniformly deposited on a substrate surface. Thereafter, the photopolymerizable composition is imagewise exposed to actinic radiation using a photomask and the photomask controlled stage to expose precise areas of the composition with an ultraviolet laser beam or a controlled UV lamp together with a photomask having a pattern of substantially transparent and substantially opaque areas. The unimaged areas can then be removed with solvent, while leaving the imaged areas in the form of at least one gripping element on the substrate surface.

[0030] Alternatively, flexible strips can be formed by using a soft, flexible embossing tool to pattern the polymerizable composition in the form of at least one gripping element on the substrate surface. Such soft tooling is conveniently made with silicones. The composition is then cured and the tool is removed. The flexibility of the tool must be sufficient so that it can be removed from the cured polymer without damaging the grippers. The polymerizable composition may be cured by various means such as actinic radiation or heat, and should have the viscosity to conform to the raised features of the tool. After removing the tool from the cured composition, at least one gripping element will remain on the substrate, depending on the nature of the pattern. Suitable polymeric compositions for making the gripping elements are disclosed in commonly assigned U.S. Pat. No. 6,266,472.

[0031] However, the invention is not limited to any particular manufacturing technique. Other techniques such as injection molding can be used to form the device. For example, the micro replication methods can be used to mold a soft working tool out of a material such as silicone, and then a polymeric material can be injected into the tool to form the spaced elements, the gripping element and the substrate. The entire device can be formed in a single molding step, preferably by using UV or thermal curing. Other materials used in the fabrication of the devices of the present invention such as the flexible gripping elements could be made of elastomers, such as rubber or other suitable materials.

[0032] A wide variety of polymers can be used in the fabrication of gripping elements. Preferred for use in the fabrication of elements **14** are photopolymers formed by the photo-polymerization of a photoreactive monomer or mixtures of such monomers such as urethane acrylates and methacrylates, ester acrylates and methacrylates, epoxy acrylates and methacrylates, polyethylene glycol acrylates and methacrylates and vinyl containing organic monomers. Illustrative of such acrylate and methacrylate monomers are acryl diacrylates or methacrylates, triacrylates or methacrylates and tetra acrylates or methacrylates.

[0033] A photo mask or image mask bearing a pattern of opaque areas which allow UV light to pass through only in the areas which comprise the pattern of the flexible gripping element is positioned above monomer or polymer layer, and UV light (as shown) as for example from a mercury vapor arc lamp is directed to fall on the surface of image mask or photomask. UV light which passes through the clear areas of mask causes a photopolymerization reaction in the regions of the monomer or polymer which are directly under these image areas. No photoreaction occurs in those areas of the monomer or polymer which are shielded from the UV light by the opaque areas of image mask. After irradiation by UV light, image mask is removed and the unreacted monomer or polymer can washed away with a suitable solvent such as acetone or methanol, leaving a photopolymerized gripping on the base substrate. The gripping elements include a pair of spaced apart walls **31**. According to certain embodiments, the walls **31** have a substantially trapezoidal cross section. The unique inverted trapezoidal geometry can be achieved by the choice of

proper conditions of irradiation. The optical absorption of the unreacted monomer layer at the wavelengths of the UV light must be high enough, such that a gradient of UV light intensity is established through the film. That is, the amount of UV light available in the monomer layer to cause the initiation of the photoreaction decreases from the surface of the image mask side, towards the substrate side, due to the finite absorption of the film. This gradient of UV light causes a gradient in the rate of photopolymerization reaction that occurs from top to bottom, resulting in the unique geometry of the developed polymer structure.

[0034] In some embodiments of the invention, stacked hybridization chambers comprised of individual chambers can be snapped together to form a three dimensional integrated device for performing two or three dimensional flexible manipulation and biological or chemical reactions. As shown in **FIG. 6**, a first reaction chamber **10** including a base substrate **12**, a spacer element **18** and a cover substrate **22** having an outer surface **24** further includes a second spacer element **58** on the outer surface **24** of the cover substrate **22** defining a second specimen area **60** and a second flexible gripping element **68** defining a pair of spaced apart walls adapted to receive a second cover substrate **62**. Preferably, the second cover substrate **62** is adapted to snap fit between the spaced apart walls defined by the second flexible gripping elements **68**. In certain embodiments, instead of or in addition to providing lateral fluid inlet and outlets on each plane of the stacked device, it may be desirable to provide at least one through hole (not shown) in the cover substrate **22** that would be in fluid communication with the fluid inlets of the device. This hole would be in fluid communication, i.e., fluid flow, with the fluid inlet of at least one plane of the device. The hole would be used to introduce hybridizable analytes.

[0035] In use, the reaction chamber device can be used in biological and chemical assays. The chamber height can be as small as 1 micron to reduce the amount of hybridization solution used. The chamber is formed by snap on structures using flexible gripping elements. The cover substrate is snapped into place between the substantially parallel walls. The spacer element defines a frame that surrounds at least a portion of the specimen area, and the frame and the substrate define a well for holding a fluid such as a hybridization solution. Fluid can be introduced through the fluid inlet **40** and fluid exits the fluid outlets **42**. More specifically, hybridization solution is injected into the well through the inlet via capillary action and the hybridization chamber is left undisturbed under conditions and time sufficient to permit hybridization. The substrate can then be snapped off from the hybridization chamber and post-hybridization wash steps can be performed on the substrate. The substrate is then scanned for hybridization analysis using techniques known in the art.

[0036] Without intending to limit the invention in any manner, the invention will be more fully understood and described by the following examples, in which the claimed thin cover slip hybridization method is compared to [illegible]

EXAMPLES

[0037] Hybridization and Analysis

[0038] The prehybridization and the washing steps were performed in a conventional way. To study the hybridization kinetics, slides from the other part of the process (post-hybridization washing step), the hybridization solution was used for the hybridization step. A slide with a gasket was placed inside a humid chamber. The box was placed inside 42° C. incubator. After hybridization, the glass slides were washed, dried and scanned with the GenePix 4000A Microarray Scanner. Data were analyzed with the GenePix Pro 3.0 software (Axon Instruments, Inc., Foster City, Calif.).

[0039] Microarray hybridization assays were performed overnight at 42° C. using pre-fabricated Corning 4K Cancer arrays available from Corning, Inc and conventional hybridization processes. One group of assays was performed utilizing the embodiment shown in **FIG. 1** having a spacer element height of four microns. A second groups of assays was performed with the conventional cover slip approach method on a slide area 24 mm×50 mm. The assays performed with a device similar to the one shown in **FIG. 1** utilized 2 *ug* of total RNA, labeled with Cy3 and Cy5 fluorescent dyes, in 15 *uL* of hybridization solution. The two assays performed with the conventional cover slip approach were performed with either 2 *ug* or 6.67 *ug* of total RNA, labeled with Cy3 and Cy5 fluorescent dyes, in 50 *uL* of hybridization solution. In other words, the conventional cover slip approach either contained the same total amount of the RNA at about the same concentration but more than 3 times the amount of total RNA used compared to the present invention, or tested a hybridization mixture or assay solution in proportion using conventional protocols and [illegible] targets.

[0040] [illegible] results of the tested 4K Cancer [illegible] in FIGS. **7-10**. **FIGS. 7 and 8** respectively show the ratio of averaged net fluorescent signal for Cy 5 and the signal to background ratio (S B) of the assay using a chamber similar to the one shown in **FIG. 1** of the present invention compared to the conventional cover slip method. **FIGS. 9 and 10** respectively show the ratio of averaged net fluorescent signal for Cy 3 and the signal to background ratio (S B) of the assay using a chamber similar to the one shown in **FIG. 1** of the present invention compared to the conventional cover slip method. **FIG. 7** (Cy5) and the **FIG. 9** (Cy3) show the increase in signal achieved by using the device according to one embodiment of the present invention. The shaded bars in the Figures represent the ratio of the signal obtained from a chamber according to one embodiment of the present invention with 2 ug of total RNA in 15 *uL* of solution to the signal obtained from a chamber formed using the cover slip method with 2 *ug* of total RNA in 50 *uL* of solution. The unshaded bars in the Figures represent the ratio of the signal obtained from a chamber according to one embodiment of the present invention with 2 ug of total RNA in 15 uL of solution to the signal obtained from a chamber formed using the cover slip method with 6.67 ug of total RNA in 50 uL of solution.

[0041] **FIG. 8** (Cy5) and **FIG. 10** (Cy3) show [illegible] using a chamber according to one embodiment of the present invention compared to the

275

US007246627B2

United States Patent

Jacobs et al.

(10) Patent No.: US 7,246,627 B2

(45) Date of Patent: Jul. 24, 2007

(54) **MONITORING OF CLEANING PROCESS**

(75) Inventors: **Paul T. Jacobs**, Bicknell, UT (US); **Jenn-Hann Wang**, Northridge, CA (US); **Szu-Min Lin**, Laguna Hills, CA (US)

(73) Assignee: **Ethicon, Inc.**, Somerville, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 422 days

(21) Appl. No.: **10/326,041**

(22) Filed: **Dec. 20, 2002**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 10/132,871, filed on Apr. 25, 2002, now Pat. No. 6,595,715, which is a continuation of application No. 09/075,714, filed on May 11, 1998, now Pat. No. 6,394,111.

(60) Provisional application No. 60/049,351, filed on Jun. 11, 1997.

(51) **Int. Cl.**
B08B 3/02 (2006.01)

(52) **U.S. Cl.** ..... 134/113; 134/58 R; 134/58 R; 134/200

(58) **Field of Classification Search** ..... 134/113, 134/56 R; 135/58 R
See application file for complete search history.

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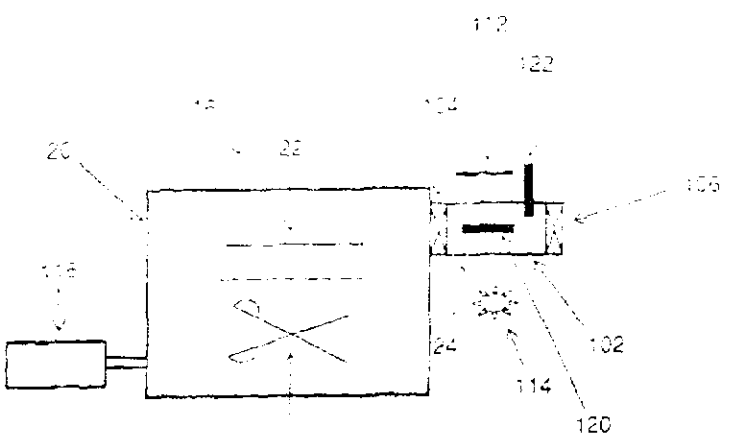
(57) **ABSTRACT**

An apparatus for monitoring a cleaning process for a medical device includes a cleaning chamber for receiving and cleaning the instrument with a cleaning liquid, a receiving well within the cleaning chamber, a removable soil standard receivable within the receiving well whereby to be exposed to the cleaning process within the cleaning chamber; and a soil detector coupled to the cleaning chamber and adapted to provide an indication of the amount of the soil on the soil standard while the soil standard is received within the receiving well.

5 Claims, 18 Drawing Sheets



from that of the items **22** and **24** to be cleaned. This will allow the use of certain soil on the standard and a preferred type of detection technology particularly suitable to that type of soil. Many other options are available as long as a proper correlation between the cleaning of the standard **120** and the cleaning of the items to be cleaned is established through experiments associated with particular apparatus configurations.

FIG. **15***a* illustrates an apparatus **16** with a soil covered standard **120** and a soil detector **122** positioned in an enclosure **102**. Standard **120** can be any suitable surface covered with soil. For example, standard **120** can be a plate or a piece of suitable material preferably removably coupled to a support. Preferably, the connection between the standard **120** and the support **124** is made in such a way that the soil covered portion of the standard is not soiled. There are several ways for controlling the cleaning efficiency of the standard **120** relative to that of the items **22** and **24**. For example, valve **104** can be adjusted at different levels to control the fluid communication between chamber **20** and enclosure **102**. A larger valve **104** will provide a better fluid communication, thus, the cleaning efficiency in chamber **20** and enclosure **102** will be closer to each other. Another option is to provide an adjustable agitation system in enclosure **102**, or chamber **20**, or both. By adjusting the agitation level, the cleaning efficiency in enclosure **102** or chamber **20** can be adjusted to a predetermined level. Detector **122** can be any suitable type, for example, it can be an electrode. Other parts of the apparatus **16** are similar to those of FIG. **14**. In one embodiment, valve **104** is opened at a predetermined level during a cleaning process, and the soil level in the washing solution in the enclosure **102** is monitored with detector **122**.

In another embodiment, an apparatus similar to that shown in FIG. **14** is used, the only difference is that a soil covered standard **120** is placed in enclosure **102**. In this case standard **120** is made of material transparent to a predetermined wave length range. Preferably, standard **120** is a flat surface covered with soil which reacts with an enzyme solution in the chemical source **108** (see FIG. **14**) producing certain compound that absorbs light at a predetermined wave length. It is also possible to use light source **114** and spectrophotometer **112** alone without chemical source.

FIG. **15***b* shows another embodiment in which standard **120** is not placed in an enclosure, instead it is positioned in chamber **20**. As shown in this figure, standard **120** is removably coupled to a support **122**. Preferably, standard **120** is a flat plate with its surface covered with soil on one side or both sides. Support **122** is mounted on the wall of the indentation **130**. Preferably, support **122** is movable, or standard can be coupled to support **122** at several positions, so that the position of standard **120** in the indentation **130** can be adjusted. Indentation **130** may have different shapes. For example, it can be an inclined gap with its two side walls **132** divergent from the wall of chamber **20** as shown in FIG. **15***b*. The two side walls **132** can also be made parallel to each other. If desired, indentation **130** may also have a surrounded side wall with only one end open to chamber **20**. Because of the limited space, the cleaning efficiency in indentation **130** is lower than the area where the items **22** and **24** are placed, and the deeper and narrower the indentation **130**, the less the cleaning efficiency is. Thus, the relative cleaning efficiency of standard **120** can be adjusted by placing it in different positions in the indentation **130**. Agitation level in chamber **20** can also be used to adjust the cleaning efficiency.

of material transparent to the light from light source **114**. Standard **120** is also made of material transparent to the light from light source **114**. Thus, quartz is a suitable material for both the side walls **132** and the standard **120**. FIGS. **15***c* and **15***d* illustrate two other configurations of the indentation **130**. In the arrangement shown in FIG. **15***c*, indentation **130** is located at a corner of the chamber **20**. Light source **114** is placed outside chamber **20** in a space next to indentation **130**. In the arrangement shown in FIG. **15***d*, indentation **130** is also located at a corner of the chamber **20**, but extending obliquely. Light source **114** and detector **112** are placed outside chamber **20** in a space adjacent to indentation **130**. If the standard **120** is soiled on its flat surface, the surface can be positioned [illegible] horizontal, or with an angle. The light beam from the light source **114** can be controlled to strike at any desired angle.

The apparatus illustrated in FIGS. **15***a*-**15***d* can be easily adapted to further include one or more other detectors of proper type, a vacuum pump or vacuum source for vacuum drying the items after cleaning, a sterilization system.

Generally, the embodiments of the apparatus of the invention illustrated in FIGS. **9**-**15***d* can employ one or more additional soil detectors. Soil detectors suitable for detecting protein are particularly useful additions in such embodiments. It is preferable to use one more detectors for detecting inorganic soil in combination with an ultraviolet-visible spectroscopy detector suitable for detecting protein and other organic species. An example of the latter type of detector is a spectrophotometer employing a detection wavelength of 220 nm, one of the principle ultraviolet absorption wavelengths common to all proteins and many organic molecules found in the body. Many other wavelengths are also suitable, including 260, 265, and 280 nm. Another preferred soil detector combination employs one or more detectors along with a colorimetric autotitrator for detecting protein. Another preferred detector combination employs an [illegible] detector and a turbidimetry detector. [illegible] detectors other than those listed may also be employed with the [illegible] illustrated in FIGS. **9**-**15***d*. [illegible] chamber **20** which also serves as a cleaning [illegible] can be connected to the chamber [illegible] sterilization. Various sterilization systems [illegible] sterilization can be employed with the apparatus of the present invention [illegible] FIGS. **9**-**15***d*. When a long and narrow lumen device is to be cleaned and/or sterilized, chamber **20** can be further divided into two sub-chambers separated by a sealable interface with two open ends of the lumen positioned in the two sub-chambers separately. A pressure difference can be generated between the two sub-chambers, so that cleaning or sterilant fluid flows through the lumen. Thus, the lumen can be cleaned and sterilized more efficiently.

The foregoing examples are provided by way of illustration only, and are not intended as a limitation of the present invention, many variations of which are possible without departing from the spirit and scope thereof.

What is claimed is:

1. An apparatus for monitoring a cleaning process for a medical instrument, comprising:

a cleaning chamber for receiving and cleaning the instrument with a cleaning fluid;

a receiving well within the cleaning chamber;

a removable soil standard comprising a body having thereon a predetermined amount of soil and which is

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a soil detector coupled to the cleaning chamber and adapted to provide an indication of the amount of the soil on the soil standard while the soil standard is received within the receiving well.

2. The apparatus of claim 1, wherein the soil detector comprises a light source which sends light through the soil standard and a light receiver which reads the amount of light shining through the soil standard.

3. An apparatus for monitoring a cleaning process in a medical instrument, comprising:

a cleaning chamber for receiving and cleaning the instrument with a cleaning liquid;

a receiving well within the cleaning chamber;

a removable soil standard comprising a body having thereon a predetermined amount of soil and which is receivable within the receiving well whereby to be exposed to the cleaning process within the cleaning chamber; and

a soil detector coupled to the cleaning chamber and adapted to provide an indication of the amount of the soil on the soil standard while the soil standard is received within the receiving well.

wherein the soil detector comprises a light source which shines light through the soil standard and a light detector which reads the amount of light shining through the soil standard; and

wherein the light source transmits light at a known wavelength and wherein the soil standard body is essentially transparent to light at this wavelength.

4. The apparatus of claim 3 wherein the soil standard body is made of quartz.

5. The apparatus of claim 4 wherein the receiving well is comprised of quartz.