Espacio reservado para el adhesivo de radicación

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-094674- -00003-0000

Fecha: 2012-06-15 12:50:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 32

Industria y Comercio
SUPERINTENDENCIA

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

X Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: 11 094.674

Solicitante: REVANCE THERAPEUTICS, INC

Apoderado: LUZ CLEMENCIA DE PAEZ

Título de la Nueva Creación: FORMULACIONES INYECTABLES DE TOXINA BOTULÍNICA.

Gaceta: 640

2. Datos del Opositor

☐ Persona Natural ☒ Persona Jurídica

SYNTHESIS S.A.S

Nombre o denominación /Razón social completa

LUIS PALACIOS ARAGON

Nombre del representante legal

Documento de identificación: C.C. ☐ C.E ☐ NIT ☒ Otro ☐ Cuál _____

Número 860000760-1

Dirección: CRA 44 20C 73 Ciudad BOGOTA D.C.

Teléfono 3692222 Fax: _____ Correo electrónico _____

☐ **Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico**

3. Datos del representante o apoderado:

MORENO BOHORQUEZ ELIANA ISAURA	51.975.664	83823
Apellidos y Nombre	**Documento de identificación**	**Tarjeta profesional**

Dirección del representante		
CRA 13 119-95 OFICINA 104		
Dirección electrónica negocios@optimum-t.com	No. Fax (571)6121979	Número telefónico (571)2131213

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general:

4. Fundamentos de la oposición

Causal: Art14, 16, 18,20 y 30 de la decisión 486 de la CAN no cumple con los requisitos De patentabilidad.

Justificación: La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "fundamento de hecho".

Prórroga: **SI** ☐ **NO** ☐

5. Anexos

- ☒ Comprobante de pago de la tasa.
- ☒ Poder, si fuera el caso.
- ☒ Fundamentos de la oposición. Se anexan ___ folios (obligatorios indicar cuántos).
- ☒ Anexo de fundamentos de la oposición. Se anexan ____folios (obligatorios indicar cuántos)
- ☒ Copias para traslado.
- ☐ Copia de la solicitud y sus anexos en formato magnético.

6. Firma	
Nombre del Firmante ELIANA ISAURA MORENO BOHORQUEZ	Firma
CC. 51.975.664	Tarjeta Profesional: 83823

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0053630

Bogotá D.C., Mayo 29 de 2012 - 10:34:26

RECIBIDO DE : LABORATORIOS SYNTHESIS S.A.S. NI 860.000.760

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	468325955	28/05/2012	1.890.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 MARCAS Y LEMAS COMERCIALES	315.000.00	315.000.00
				$315.000.00

SON: **TRESCIENTOSQUINCE MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-094674- -00003-0000
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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señor Director,

DIRECCIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 11 94674
Asunto	: Oposición a la solicitud de patente de Invención titulada *"FORMULACIONES INYECTABLES DE TOXINA BOTULÍNICA"*
Solicitante	: REVANCE THERAPEUTICS, INC
Opositora	: LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 640 del 15 de marzo de 2012

Yo, *ELIANA ISAURA MORENO BOHORQUEZ,* abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Bogotá, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada *"FORMULACIONES INYECTABLES DE TOXINA BOTULÍNICA",* cuyo titular es **REVANCE THERAPEUTICS, INC ,** y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legitimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **TOXINA BOTULÍNICA**. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 28 de julio de 2011, reivindicando prioridad bajo la solicitud US20080142063 del 2008-12-31; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **N° 640 del 15 de marzo de 2012**, cuya publicación internacional corresponde a la WO2010078242 del 2010-07-08.

2.2. La solicitud colombiana **11 94674** objeto de la presente oposición, se refiere a composiciones inyectables novedosas con contenido de toxina botulínica, que pueden administrarse a un sujeto para varios propósitos terapéuticos, estéticos y/o

cosméticos. Composiciones inyectables que según el documento exhiben una o más ventajas sobre las formulaciones convencionales de toxina botulínica, incluyendo antigenicidad reducida, una menor tendencia a experimentar difusión localizada indeseada luego de la inyección, una mayor duración de la eficacia clínica o potencia mejorada relativa, manifestación más rápida de la eficacia clínica, y/o estabilidad mejorada.

2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: US2008107690 publicada el 08 de mayo de 2008.

2.4. El documento D1, particularmente en la descripción revela una composición para la aplicación tópica de una toxina botulínica (incluyendo los derivados de la toxina botulinum) que comprende una toxina botulínica y un vehículo o portador que comprende un esqueleto polimérico que comprende un polipéptido de cadena larga o un polímero no peptídico que tiene unidos grupos eficientes o ramificaciones cargadas positivamente. El documento D1 también se refiere a métodos para reducir la parálisis muscular y otras condiciones que pueden tratarse con una toxina botulínica, particularmente parálisis subcutánea, y más

particularmente, faciales, músculos, por aplicación tópica de una cantidad eficaz de la toxina botulínica y el portador, en conjunción, a la piel del sujeto o epitelio. Los kits para la administración también se describen en dicho documento D1. De manera mas explicita, el mismo documento D1 revela un método de administración de una toxina botulínica para lograr un efecto cosmético o terapéutico en un individuo que lo necesite, donde el método consiste en inyectar una cantidad efectiva de la composición al individuo, para lograr el efecto terapéutico o cosmético, donde la composición comprende un portador de carga positiva que comprende un esqueleto cargado positivamente con una pluralidad de grupos de eficiencia unido al mismo y una toxina botulínica, y en donde el portador cargado positivamente no está asociado de manera covalente con la toxina botulínica. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.5. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **11 94674** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con el mas importante de los tres requisitos necesarios para su protección, la novedad.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. <u>CARECE DE NOVEDAD</u>: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está*

comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.". A la fecha de prioridad, 31 de diciembre de 2008 ya era conocido, pues como se demostró, eran parte del arte anterior con base en el documento D1, composiciones inyectables con contenido de toxina botulínica, que pueden administrarse a un sujeto para varios propósitos terapéuticos, estéticos y/o cosméticos; sobre el cual busca protección en el capítulo reivindicatorio.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.".* La solicitud pretendida no cumple con en mas importante de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada ***"FORMULACIONES INYECTABLES DE TOXINA BOTULÍNICA",*** cuyo titular es **REVANCE THERAPEUTICS, INC ,** solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial **N° 640 del 15 de marzo de 2012.**

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US2008107690 publicada el 08 de mayo de 2008.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **LABORATORIOS SYNTHESIS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: US2008107690 publicada el 08 de mayo de 2008.

Carrera 13 Nº 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

ANEXO 1

US 20080107690A1

(19) United States

(12) Patent Application Publication

Dake et al.

(10) Pub. No.: US 2008/0107690 A1

(43) Pub. Date: May 8, 2008

(54) COMPOSITIONS AND METHODS FOR TOPICAL APPLICATION AND TRANSDERMAL DELIVERY OF BOTULINUM TOXINS

(76) Inventors: Michael D. Dake, Stanford, CA (US); Jacob M. Waugh, Mountain View, CA (US)

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MORGAN & FINNEGAN, L.L.P.
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NEW YORK, NY 10281-2101

(21) Appl. No.: 10/591,732

(22) PCT Filed: Mar. 3, 2005

(86) PCT No.: PCT/US05/07524

§ 371 (c)(1),
(2), (4) Date: Sep. 26, 2007

Related U.S. Application Data

(60) Provisional application No. 60/550,015, filed on Mar. 3, 2004.

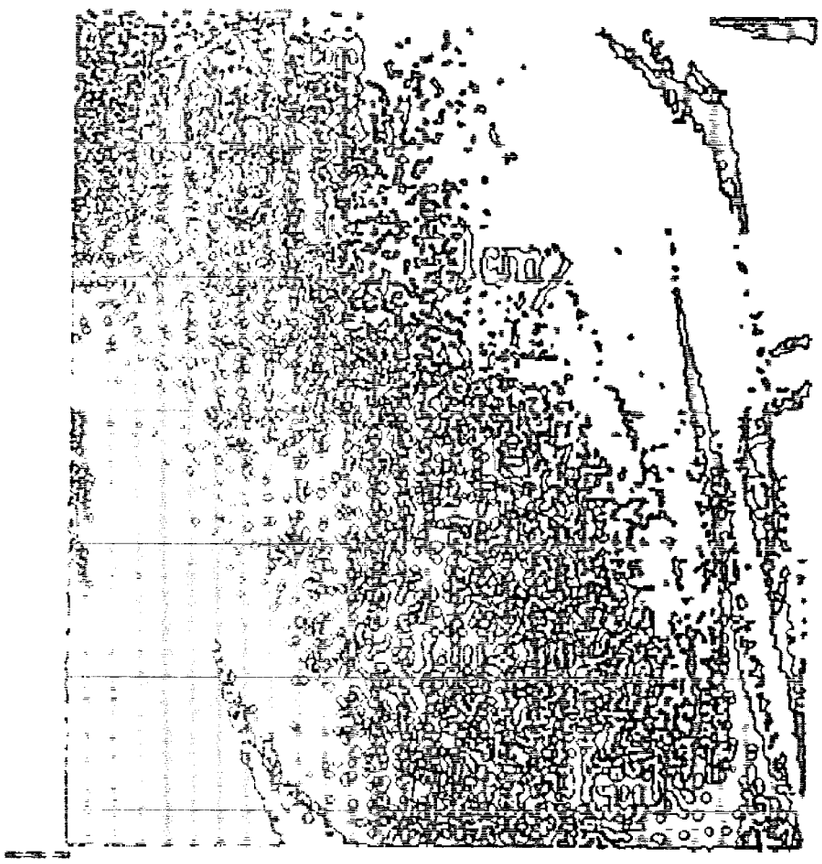
Publication Classification

(51) Int. Cl.
A61K 51/00 (2006.01)
A61K 39/40 (2006.01)
A61K 39/42 (2006.01)

(52) U.S. Cl. 424/236.1

(57) ABSTRACT

A composition for topical application of a botulinum toxin (including botulinum toxin derivatives) comprises a botulinum toxin and a carrier comprising a polymeric backbone comprising a long-chain polypeptide or nonpeptidyl polymer having attached positively charged branching or "efficiency" groups. The invention also relates to methods for reducing muscle paralysis and other conditions that may be treated with a botulinum toxin, particularly paralysis of subcutaneous, and most particularly, facial, muscles, by topically applying an effective amount of the botulinum toxin and carrier, in conjunction, to the subject's skin or epithelium. Kits for administration are also described.



COMPOSITIONS AND METHODS FOR TOPICAL APPLICATION AND TRANSDERMAL DELIVERY OF BOTULINUM TOXINS

[0001] This application claim the benefit of priority to U.S. Provisional Patent Application No. 60/550,015, filed on Mar. 3, 2004. U.S. Provisional Patent Application No. 60/550,015 is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Skin protects the body's organs from external environmental threats and acts as a thermostat to maintain body temperature. It consists of several different layers, each with specialized functions. The major layers include the epidermis, the dermis and the hypodermis. The epidermis is a stratifying layer of epithelial cells that overlies the dermis, which consists of connective tissue. Both the epidermis and the dermis are further supported by the hypodermis, an internal layer of adipose tissue.

[0003] The epidermis, the topmost layer of skin, is only 0.1 to 1.5 millimeters thick (Inlander, Skin, New York, N.Y.: People's Medical Society, 1-7 (1998)). It consists of keratinocytes and is divided into several layers based on their state of differentiation. The epidermis can be further classified into the stratum corneum and the viable epidermis, which consists of the granular malpighian and basal cells. The stratum corneum is hygroscopic and requires at least 10% moisture by weight to maintain its flexibility and softness. The hygroscopicity is attributable in part to the water-holding capacity of keratin. When the horny layer loses its softness and flexibility it becomes rough and brittle, resulting in dry skin.

[0004] The dermis, which lies just beneath the epidermis, is 1.5 to 4 millimeters thick. It is the thickest of the three layers of the skin. In addition, the dermis is also home to most of the skin's structures, including sweat and oil glands (which secrete substances through openings in the skin called pores, or comedos), hair follicles, nerve endings, and blood and lymph vessels (Inlander, Skin, New York, N.Y.: People's Medical Society, 1-7 (1998)). However, the main components of the dermis are collagen and elastin.

[0005] The hypodermis is the deepest layer of the skin. It acts both as an insulator for body heat conservation and as a shock absorber for organ protection (Inlander, Skin, New York, N.Y.: People's Medical Society, 1-7 (1998)). In addition, the hypodermis also stores fat for energy reserves. The pH of skin is normally between 5 and 6. This acidity is due to the presence of amphoteric amino acids, lactic acid, and fatty acids from the secretions of the sebaceous glands. The term "acid mantle" refers to the presence of the water-soluble substances on most regions of the skin. The buffering capacity of the skin is due in part to these secretions stored in the skin's horny layer.

[0006] Wrinkles, one of the telltale signs of aging, can be caused by biochemical, histological, and physiologic changes that accumulate from environmental damage (Bencdetto, International Journal of Dermatology, 38:641-655 (1999)). In addition, there are other secondary factors that can cause characteristic folds, furrows, and creases of facial wrinkles (Stegman et al., The Skin of the Aging Face Cosmetic Dermatological Surgery, 2nd ed., St. Louis, Mo.: Mosby Year Book: 5-15 (1990)). These secondary factors include the constant pull of gravity, frequent and constant positional pressure on the skin (i.e., during sleep), and repeated facial movements caused by the contraction of facial muscles (Stegman et al., The Skin of the Aging Face Cosmetic Dermatological Surgery, 2nd ed., St. Louis, Mo.: Mosby Year Book: 5-15 (1990)). Different techniques have been utilized in order potentially to mollify some of the signs of aging. These techniques range from facial moisturizers containing alpha hydroxy acids and retinol to surgical procedures and injections of neurotoxins.

[0007] One of the principal functions of skin is to provide a barrier to the transportation of water and substances potentially harmful to normal homeostasis. The body would rapidly dehydrate without a tough, semi-permeable skin. The skin helps to prevent the entry of harmful substances into the body. Although most substances cannot penetrate the barrier, a number of strategies have been developed to selectively increase the permeability of skin with variable success.

[0008] Botulinum toxins (also known as **botulin** toxins or botulinum neurotoxins) are neurotoxins produced by the gram-positive bacteria *Clostridium botulinum*. They act to produce paralysis of muscles by preventing synaptic transmission or release of acetylcholine across the neuromuscular junction, and are thought to act in other ways as well. Their action essentially blocks signals that normally would cause muscle spasms or contractions, resulting in paralysis.

[0009] Botulinum toxin is classified into eight neurotoxins that are serologically related, but distinct. Of these, seven can cause paralysis, namely botulinum neurotoxin serotypes A, B, C, D, E, F and G. Each of these is distinguished by neutralization with type-specific antibodies. Nonetheless, the molecular weight of the botulinum toxin protein molecule, for all seven of these active botulinum toxin serotypes, is about 150 kD. As released by the bacterium, the botulinum toxins are complexes comprising the 150 kD botulinum toxin protein molecule in question along with associated non-toxin proteins. The botulinum toxin type A complex can be produced by Clostridia bacterium as 900 kD, 500 kD and 300 kD forms. Botulinum toxin types B and C are apparently produced as only a 700 kD or 500 kD complex. Botulinum toxin type D is produced as both 300 kD and 500 kD complexes. Botulinum toxin types E and F are produced as only approximately 300 kD complexes. The complexes (i.e. molecular weight greater than about 150 kD) are believed to contain a *non-toxin hemaglutinin protein and a non-toxin and non-toxic nonhemaglutinin protein*. These two non-toxin proteins (which along with the botulinum toxin molecule comprise the relevant neurotoxin complex) may act to provide stability against denaturation to the botulinum toxin molecule and protection against digestive acids when toxin is ingested. Additionally, it is possible that the larger (greater than about 150 kD molecular weight) botulinum toxin complexes may result in a slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection of a botulinum toxin complex.

[0010] The different serotypes of botulinum toxin vary in the animal species that they affect and in the severity and duration of the paralysis they evoke. For example, it has been determined that botulinum toxin type A is 500 times more potent, as measured by the rate of paralysis produced in the rat, than is botulinum toxin type B. Additionally, botulinum toxin type B has been determined to be non-toxic in primates at a dose of 480 U/kg, about 12 times the primate LD_{50} for type A. Due to the molecule size and molecular structure of botulinum toxin, it cannot cross stratum corneum and the multiple layers of the underlying skin architecture.

[0011] Botulism, the characteristic symptom complex from systemic botulinum toxin exposure, has existed in Europe since antiquity. In 1895, Emile P. van Ermengem first isolated the anaerobic spore-forming *bacillus* from raw salted pork meat obtained from post-mortem tissue of victims who died of botulism in Belgium. Van Ermengem found the disease to be caused by an extracellular toxin that was produced by what he called *Bacillus* botulinus (Van Ermengem, Z Hyyg Infektionskr, 26:1-56; Rev Infect (1897)). The name was changed in 1922 to *Clostridium botulinum*. The name *Clostridium* was used to reflect the anaerobic nature of the microorganism and also its morphologic characteristics (Carruthers and Carruthers, Can J Opthalmol, 31:389-400 (1996)). In the 1920's, a crude form of Botulinum toxin type A was isolated after additional outbreaks of food poisoning. Dr. Herman Sommer at the University of California, San Francisco made the first attempts to purify the neurotoxin (Borodic et al., Opthalmic Plast Reconst Surg, 7:54-60 (1991)). In 1946, Dr. Edward J. Schantz and his colleagues isolated the neurotoxin in crystalline form (Schantz et al., In: Jankovi J, Hallet M (Eds) Therapy with Botulinum Toxin. New York, N.Y.: Marcel Dekker, 41-49 (1994)). By 1949, Burgen and his associates were able to demonstrate that the Botulinum toxin blocks impulses across the neuromuscular junction (Burgen et al., J Physiol, 109:10-24 (1949)). Allan B. Scott first used botulinum toxin A (BTX-A) in monkeys in 1973. Scott demonstrated reversible ocular muscle paralysis lasting 3 months (Lamanna, Science, 130:763-772 (1959)). Soon afterwards, BTX-A was reported to be a successful treatment in humans for strabismus, blepharospasm, and spasmodic torticollis (Baron et al., In: Baron E J, Peterson L R, Finegold S M (Eds), Bailey & Scotts Diagnostic Microbiology, St. Louis, Mo.: Mosby Year Book, 504-523 (1994); Carruthers and Carruthers, Adv Dermatol, 12:325-348 (1997); Markowitz, In: Strickland G T (Eds) Hunters Tropical Medicine, 7th ed. Philadelphia: W.B. Saunders, 441-444 (1991)). In 1986, Jean and Alastair Carruthers, a husband and wife team consisting of an oculoplastic surgeon and a dermatologist, began to evolve the cosmetic use of BTX-A for treatment of movement-associated wrinkles in the glabella area (Schantz and Scott, In Lewis G E (Ed) Biomedical Aspects of Botulinum. New York: Academic Press, 143-150 (1981)). The Carruthers' use of BTX-A for the treatment of wrinkles led to their seminal publication of this approach in 1992 (Schantz and Scott, In Lewis G E (Ed) Biomedical Aspects of Botulinum. New York: Academic Press, 143-150 (1981)). By 1994, the same team reported experiences with other movement-associated wrinkles on the face (Scott, Opthalmol, 87:1044-1049 (1980)). This in turn led to the birth of the era of cosmetic BTX-A treatment.

[0012] Botulinum toxin type A is said to be the most lethal natural biological agent known to man. Spores of *C. botulinum* are found in soil and can grow in improperly sterilized and sealed food containers. Ingestion of the bacteria can cause botulism, which can be fatal. At the same time, the muscle-paralyzing effects of botulinum toxin have been used for therapeutic effects. Controlled administration of botulinum toxin has been used to provide muscle paralysis to treat conditions, for example, neuromuscular disorders characterized by hyperactive skeletal muscles. Conditions that have been treated with botulinum toxin include hemifacial spasm, adult onset spasmodic torticollis, anal fissure, blepharospasm, cerebral palsy, cervical dystonia, migraine headaches, strabismus, temperomandibular joint disorder, and various types of muscle cramping and spasms. More recently the muscle-paralyzing effects of botulinum toxin have been taken advantage of in therapeutic and cosmetic facial applications such as treatment of wrinkles, frown lines, and other results of spasms or contractions of facial muscles.

[0013] Topical application of botulinum toxin would provide for a safer and more desirable treatment alternative due to the painless nature of application, the larger treatment surface area that can be covered, the ability to formulate a pure toxin with higher specific activity, the reduced training necessary for applying the botulinum therapeutic, the smaller doses that would be necessary to produce the desired effect, and the lack of a requirement for large wells of toxin to reach a therapeutic clinical result. An effective means for transdermal delivery of botulinum toxin, as well as an effective means for administering botulinum toxin to treat or prevent a number of conditions that does not require injection is thus highly desirable.

SUMMARY OF THE INVENTION

[0014] This invention relates to new compositions comprising a botulinum toxin, more specifically to such compositions that enable the transport or delivery of a botulinum toxin through the skin or epithelium (also referred to as "transdermal delivery"), and that therefore may be used as topical applications for providing a botulinum toxin to a subject, for various therapeutic, aesthetic and/or cosmetic purposes, as described herein.

[0015] One aspect of this invention is to provide a composition containing a botulinum toxin and a carrier. The carrier has a polymeric backbone with attached positively charged branching groups. The association between the carrier and the botulinum toxin is non-covalent.

[0016] Another aspect of this invention is to provide a kit for administration of a botulinum toxin to a subject. The kit includes a botulinum toxin present in an effective amount for transdermal delivery thereof, and a carrier that has a polymeric backbone with attached positively charged branching groups. The association between the carrier and the botulinum toxin is non-covalent.

[0017] Yet another aspect of this invention is to provide a kit for administration of a botulinum toxin to a subject. The kit includes a device for delivering the botulinum toxin to the skin and a composition containing a carrier having a polymeric backbone with attached positively charged branching groups selected from $-(gly)_{n1}-(arg)_{n2}$, HIV-TAT and fragments thereof, and Antennapedia PTD, in which the subscript n1 is an integer of from 0 to about 20, and the subscript n2 is independently an odd integer of from about 5 to about 25.

[0018] This invention also provides a method of administering a botulinum toxin to a subject involving topically applying to the skin or epithelium of the subject the botulinum toxin in conjunction with an effective amount of a carrier. The carrier has a polymeric backbone with attached positively charged branching groups, and associates non-covalently with the botulinum toxin.

[0019] In one aspect, this invention relates to a composition comprising a botulinum toxin (as defined herein) and a carrier comprising a positively charged "backbone" having positively charged branching or "efficiency" groups, as described herein. Most preferably the positively charged carrier is a long-chain positively charged polypeptide or a positively charged nonpeptidyl polymer, for example, a polyalkyleneimine. The invention further relates to a method for producing

a biologic effect such as muscle paralysis, reducing hypersecretion or sweating, treating neurologic pain or migraine headache, reducing muscle spasms, preventing or reducing acne, or reducing or enhancing an immune response, by topically applying an effective amount of such a composition, preferably to the skin, of a subject or patient in need of such treatment. The invention also relates to a method for producing an aesthetic or cosmetic effect, for example by topical application of botulinum toxin to the face instead of by injection into facial muscles.

[0020] This invention also provides kits for preparing or formulating a composition that comprises the carrier and the botulinum toxin, as well as such additional items that are needed to produce a usable formulation, or a premix that may in turn be used to produce such a formulation. Alternatively the kit comprises means for separately but in conjunction administering the botulinum toxin and the carrier to a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. **1** represents the results of an experiment demonstrating efficiency of transdermal delivery of botulinum toxin using a composition of the invention comprising a peptide backbone.

[0022] FIG. **2** is a photograph depicting the state of the hind limbs of a mouse in which the area of one limb was treated with a composition of the invention and the area of the other was treated with another botulinum toxin-containing composition that did not contain a carrier according to the invention.

[0023] FIG. **3** is a photograph depicting wrinkles on subject's forehead before and after treatment with "Essentia Botox lotion" topically.

[0024] FIG. **4** shows a Mikrosil cast of the forehead (A) after topical treatment of wrinkles with "Essentia Botox Lotion", and (b) before treatment. These Mikrosil casts, which are useful because they minimize artifacts that can result from photographing the actual subject, clearly show that the untreated side has deeper wrinkles.

[0025] FIG. **5** shows photographs depicting Minor's starch/iodine test performed on subject's forehead five days after application of "Essentia Botox Lotion" (A) and a control lotion (B). The control lotion contained a positively charged polylysine backbone with a molecular weight of about 21,000 and with TAT branching groups. These pictures were taken two minutes after application.

[0026] FIG. **6** is the same as FIG. **5**, but except that they were taken after four minutes had elapsed.

[0027] FIG. **7** shows the dose area used in the axillary hyperhidrosis studies. Note that the dose area extends one centimeter beyond the area of the skin covered by axillary hair.

[0028] FIG. **8***a* represents the results of an experiment demonstrating efficiency of botulinum toxin therapeutically delivered across intact skin as a topical agent using a short peptidyl carrier for the treatment of axillary hyperhidrosis on human subjects. Graph depicts significant reduction in amount of sweat (mg per 5 minutes) measured gravimetrically 4 weeks after treatment with Botox plus a short peptidyl carrier or carrier alone. Results are 4 week values as ratio to baseline value for same group, with significance determined by Wilcoxon analysis with $P<0.05$, $N=10$ patients. FIG. *8b* represents the results of an experiment demonstrating efficiency of botulinum toxin therapeutically delivered across intact skin as a topical agent using a short peptidyl carrier for the treatment of axillary hyperhidrosis on human subjects. Graph depicts significant reduction in amount of sweat (mg per 5 minutes) measured gravimetrically 4 weeks after treatment with Botox plus a short peptidyl carrier or carrier alone. Results are treatment values as ratio to control value for both timepoints, with significance determined by Wilcoxon analysis with $P<0.05$, $N=10$ patients.

[0029] FIG. **9** shows photographs depicting Minor's starch/iodine test before and after treatment with "Essentia Botox lotion" topically for the treatment of axillary hyperhidrosis. Starch/iodine test at Baseline vs. 2 week is shown where right axilla was treated with "Essentia Botox lotion" (a and c) and left axilla was applied with the control (b and d) for subject #12. These photographs illustrate typical benefits observed after treatment with carrier+botox in starch iodine. Although some crosswave is observed on the control side (consistent with 25% reduction in gravimetric data), significant reductions are afforded with treatment (consistent with 65% reduction in gravimetric data on treated side).

DETAILED DESCRIPTION OF THE INVENTION

[0030] This invention provides compositions and methods for delivery, particularly transdermal delivery, of a botulinum toxin by topical application of an appropriate formulation.

[0031] According to the present invention, a positively charged carrier molecule having efficiency groups, as described herein, has been found suitable as a transport system for a botulinum toxin, enabling that toxin to be administered transdermally to muscles and/or other skin-associated structures. The transport occurs without covalent modification of the botulinum toxin.

[0032] By "positively charged" is meant that the carrier has a positive charge under at least some solution-phase conditions, more preferably under at least some physiologically compatible conditions. More specifically, "positively charged" as used herein, means that the group in question contains functionalities that are charged under all pH conditions, for instance, a quaternary amine, or contains a functionality which can acquire positive charge under certain solution-phase conditions, such as pH changes in the case of primary amines. More preferably, "positively charged" as used herein refers to those groups that have the behavior of associating with anions over physiologically compatible conditions. Polymers with a multiplicity of positively-charged moieties need not be homopolymers, as will be apparent to one skilled in the art. Other examples of positively charged moieties are well known in the prior art and can be employed readily, as will be apparent to those skilled in the art.

[0033] Generally, the positively-charged carrier (also referred to as a "positively charged backbone") is typically a linear chain of atoms, either with groups in the chain carrying a positive charge at physiological pH, or with groups carrying a positive charge attached to side chains extending from the backbone. Preferably, the positively charged backbone itself will not have a defined enzymatic or therapeutic biologic activity. The linear backbone is a hydrocarbon backbone which is, in some embodiments, interrupted by heteroatoms selected from nitrogen, oxygen, sulfur, silicon and phosphorus. The majority of backbone chain atoms are usually carbon. Additionally, the backbone will often be a polymer of repeating units (e.g., amino acids, poly(ethyleneoxy), poly(propyleneamine), polyalkyleneimine, and the like) but can be a heteropolymer. In one group of embodiments, the positively charged backbone is a polypropyleneamine wherein a number of the amine nitrogen atoms are present as amino-

nium groups (tetra-substituted) carrying a positive charge. In another embodiment, the positively charged backbone is a nonpeptidyl polymer, which may be a hetero- or homo-polymer such as a polyalkyleneimine, for example a polyethyleneimine or polypropyleneimine, having a molecular weight of from about 10,000 to about 2,500,000, preferably from about 100,000 to about 1,800,000, and most preferably from about 500,000 to about 1,400,000. In another group of embodiments, the backbone has attached a plurality of side-chain moieties that include positively charged groups (e.g., ammonium groups, pyridinium groups, phosphonium groups, sulfonium groups, guanidinium groups, or amidinium groups). The sidechain moieties in this group of embodiments can be placed at spacings along the backbone that are consistent in separations or variable. Additionally, the length of the sidechains can be similar or dissimilar. For example, in one group of embodiments, the sidechains can be linear or branched hydrocarbon chains having from one to twenty carbon atoms and terminating at the distal end (away from the backbone) in one of the above-noted positively charged groups. In all aspects of the present invention, the association between the carrier and the biologically active agent is by non-covalent interaction, non-limiting examples of which include ionic interactions, hydrogen bonding, van der Waals forces, or combinations thereof.

[0034] In one group of embodiments the positively charged backbone is a polypeptide having multiple positively charged sidechain groups (e.g., lysine, arginine, ornithine, homoarginine, and the like). Preferably, the polypeptide has a molecular weight of from about 10,000 to about 7,500,000, more preferably from about 25,000 to about 1,200,000, most preferably from about 100,000 to about 1,000,000. One of skill in the art will appreciate that when amino acids are used in this portion of the invention, the sidechains can have either the D- or L-form (R or S configuration) at the center of attachment. Alternatively, the backbone can be an analog of a polypeptide such as a peptoid. See, for example, Kessler, *Angew. Chem. Int. Ed. Engl.* 32:543 (1993); Zuckermann et al. *Chemtracts—Macromol. Chem.* 4:80 (1992); and Simon et al. *Proc. Nat'l. Acad. Sci. USA* 89:9367 (1992). Briefly, a peptoid is a polyglycine in which the sidechain is attached to the backbone nitrogen atoms rather than the α-carbon atoms. As above, a portion of the sidechains will typically terminate in a positively charged group to provide a positively charged backbone component. Synthesis of peptoids is described in, for example, U.S. Pat. No. 5,877,278, which is hereby incorporated by reference in its entirety. As the term is used herein, positively charged backbones that have a peptoid backbone construction are considered "non-peptide" as they are not composed of amino acids having naturally occurring sidechains at the α-carbon locations.

[0035] A variety of other backbones can be used employing, for example, steric or electronic mimics of polypeptides wherein the amide linkages of the peptide are replaced with surrogates such as ester linkages, thioamides (—CSNH—), reversed thioamide (—NHCS—), aminomethylene (—CH_2NH—) or the reversed methyleneamino (—CH_2NH—) groups, keto-methylene (—$COCH_2$—) groups, phosphinate (—PO_2RCH_2—), phosphonamidate and phosphonamidate ester (—PO_2RNH—), reverse peptide (—NHCO—), trans-alkene (—CR=CH—), fluoroalkene (—CF=CH—), dimethylene (—CH_2CH_2—), thioether (—CH_2S—), hydroxyethylene (—$CH(OH)CH_2$—), methyleneoxy (—CH_2O—), tetrazole (CN_4), sulfonamido (—SO_2NH—), methylenesulfonamide (—$CHRSO_2NH$—), reversed sulfonamide (—$NHSO_2$—), and backbones with malonate and/or gem-diamino-alkyl subunits, for example, as reviewed by Fletcher et al. ((1998) *Chem. Rev.* 98:763) and detailed by references cited therein. Many of the foregoing substitutions result in approximately isosteric polymer backbones relative to backbones formed from α-amino acids.

[0036] In each of the backbones provided above, sidechain groups can be appended that carry a positively charged group. For example, the sulfonamide-linked backbones (—SO_2NH— and —$NHSO_2$—) can have sidechain groups attached to the nitrogen atoms. Similarly, the hydroxyethylene (—$CH(OH)CH_2$—) linkage can bear a sidechain group attached to the hydroxy substituent. One of skill in the art can readily adapt the other linkage chemistries to provide positively charged sidechain groups using standard synthetic methods.

[0037] In one embodiment, the positively charged backbone is a polypeptide having branching groups (also referred to as efficiency groups). As used herein, an efficiency group or branching group is any agent that has the effect of promoting the translocation of the positively charged backbone through a tissue or cell membrane. Non-limiting examples of branching or efficiency groups include -$(gly)_{n1}$-$(arg)_{n2}$-, HIV-TAT or fragments thereof, or the protein transduction domain of Antennapedia, or a fragment thereof, in which the subscript n1 is an integer of from 0 to 20, more preferably 0 to 8, still more preferably 2 to 5, and the subscript n2 is independently an odd integer of from about 5 to about 25, more preferably about 7 to about 17, most preferably about 7 to about 13. Still further preferred are those embodiments in which the HIV-TAT fragment has the formula $(gly)_p$-RGRDDRRQRRR-$(gly)_q$, $(gly)_p$-YGRKKRRQRRR-$(gly)_q$, or $(gly)_p$-RKKRRQRRR-$(gly)_q$, wherein the subscripts p and q are each independently an integer of from 0 to 20 and the fragment is attached to the backbone via either the C-terminus or the N-terminus of the fragment. Preferred HIV-TAT fragments are those in which the subscripts p and q are each independently integers of from 0 to 8, more preferably 2 to 5. In another preferred embodiment the positively charged side chain or branching group is the Antennapedia (Antp) protein transduction domain (PTD), or a fragment thereof that retains activity. Preferably the positively charged carrier includes side-chain positively charged branching groups in an amount of at least about 0.05%, as a percentage of the total carrier weight, preferably from about 0.05 to about 45 weight %, and most preferably from about 0.1 to about 30 weight %. For positively charged branching groups having the formula -$(gly)_{n1}$-$(arg)_{n2}$-, the most preferred amount is from about 0.1 to about 25%.

[0038] In another embodiment, the backbone portion is a polylysine and positively charged branching groups are attached to the lysine sidechain amine groups. The polylysine may have a molecular weight of from about 10,000 to about 1,500,000, preferably from about 25,000 to about 1,200,000, and most preferably from about 100,000 to about 1,000,000. It can be any of the commercially available (Sigma Chemical Company, St. Louis, Mo., USA) polylysines such as, for example, polylysine having MW>70,000, polylysine having MW of 70,000 to 150,000, polylysine having MW 150,000 to 300,000 and polylysine having MW>300,000. The selection of an appropriate polylysine will depend on the remaining components of the composition and will be sufficient to provide an overall net positive charge to the composition and

provide a length that is preferably from one to four times the combined length of the negatively charged components. Preferred positively charged branching groups or efficiency groups include, for example, -gly-gly-gly-arg-arg-arg-arg-arg-arg-arg (-Gly_3Arg_7) or HIV-TAT. In another preferred embodiment the positively charged backbone is a long chain polyalkyleneimine such as a polyethyleneimine, for example, one having a molecular weight of about 1,000,000.

[0039] The positively charged backbones or carrier molecules comprising polypeptides or polyalkyleneamines, having the branching groups described above, are novel compounds and form an aspect of this invention.

[0040] In one embodiment of the invention, only a positively charged carrier that has positively charged branching groups is necessary for transdermal delivery of the botulinum toxin. In certain embodiments, the positively charged carrier is a polypeptide (e.g., lysine, arginine, ornithine, homoarginine, and the like) having multiple positively charged side-chain groups, as described above. Preferably, the polypeptide has a molecular weight of at least about 10,000. In another embodiment, the positively charged carrier is a nonpeptidyl polymer such as a polyalkyleneimine having multiple positively charged side-chain groups having a molecular weight of at least about 100,000. Such polyalkyleneamines include polyethylene- and polypropyleneimines. In either instance, for use as the sole necessary agent for transdermal delivery the positively charged carrier molecule includes positively charged branching or efficiency groups, comprising $-(gly)_{n1}-(arg)_{n2}$, in which the subscript n1 is an integer of from 0 to 20 more preferably 0 to 8, still more preferably 2 to 5, and the subscript n2 is independently an odd integer of from about 5 to about 25, more preferably from about 7 to about 17, and most preferably from about 7 to about 13. HIV-TAT or fragments thereof, or Antennapedia PTD or a fragment thereof. Preferably the side-chain or branching groups have the general formula $-(gly)_{n1}-(arg)_{n2}$ as described above. Other preferred embodiments are those in which the branching or efficiency groups are HIV-TAT fragments that have the formula $(gly)_p$-RGRDDRRQRRR-$(gly)_q$, $(gly)_p$-YGKKRRQRRR-$(gly)_q$, or $(gly)_p$-RKKRRQRRR-$(gly)_q$, wherein the subscripts p and q are each independently an integer of from 0 to 20 and the fragment is attached to the carrier molecule via either the C-terminus or the N-terminus of the fragment. The side branching groups can have either the D- or L-form (R or S configuration) at the center of attachment. Preferred HIV-TAT fragments are those in which the subscripts p and q are each independently integers of from 0 to 8, more preferably 2 to 5. Other preferred embodiments are those in which the branching groups are Antennapedia PTD groups or fragments thereof that retain the group's activity. These are known in the art, for instance, from Console et al., J. Biol. Chem. 278: 35109 (2003). Preferably, the positively charged carrier includes side-chain positively charged branching groups in an amount of at least about 0.05%, as a percentage of the total carrier weight, preferably from about 0.05 to about 45 weight %, and most preferably from about 0.1 to about 30 weight %. For positively charged branching groups having the formula $-(gly)_{n1}-(arg)_{n2}$, the most preferred amount is from about 0.1 to about 25%.

[0041] In another embodiment, the carrier is a polylysine with positively charged branching groups attached to the lysine side-chain amino groups. The polylysine used in this particularly embodiment can be any of the commercially available (Sigma Chemical Company, St. Louis, Mo., USA, e.g.) polylysines such as, for example, polylysine having MW>70,000, polylysine having MW of 70,000 to 150,000, polylysine having MW 150,000 to 300,000 and polylysine having MW>300,000. However, preferably the polylysine has MW of at least about 10,000. Preferred positively charged branching groups or efficiency groups include, for example, -gly-gly-gly-arg-arg-arg-arg-arg-arg-arg (-Gly_3Arg_7), HIV-TAT or fragments of it, and Antennapedia PTD or fragments thereof.

[0042] In other embodiments of this invention, the carrier is a relatively short polylysine or polyethyleneimine (PEI) backbone (which may be linear or branched) and which has positively charged branching groups. Such carriers are useful for minimizing uncontrolled aggregation of the backbones and botulinum toxin in a therapeutic composition, which causes the transport efficiency to decrease dramatically. When the carrier is a relatively short linear polylysine or PEI backbone, the backbone will have a molecular weight of less than 75,000, more preferably less than 30,000, and most preferably, less than 25,000. When the carrier is a relatively short branched polylysine or PEI backbone, however, the backbone will have a molecular weight less than 60,000, more preferably less than 55,000, and most preferably less than 50,000. If, however, partitioning agents as described herein are included in the composition, the molecular weight of the branched polylysine and PEI backbones may be up to 75,000, while the molecular weight of the linear polylysine and PEI backbones may be up to 150,000.

[0043] The term "botulinum toxin" as used herein is meant to refer to any of the known types of botulinum toxin, whether produced by the bacterium or by recombinant techniques, as well as any such types that may be subsequently discovered including engineered variants or fusion proteins. As mentioned above, at the present time, seven immunologically distinct botulinum neurotoxins have been characterized, namely botulinum neurotoxin serotypes A, B, C, D, E, F and G, each of which is distinguished by neutralization with type-specific antibodies. The botulinum toxin serotypes are available from Sigma-Aldrich and from Metabiologics, Inc. (Madison, Wis.), as well as from other sources. The different serotypes of botulinum toxin vary in the animal species that they affect and in the severity and duration of the paralysis they evoke. At least two types of botulinum toxin, types A and B, are available commercially in formulations for treatment of certain conditions. Type A, for example, is contained in preparations of Allergan having the trademark BOTOX® and of Ipsen having the trademark DYSPORT®, and type B is contained in preparations of Elan having the trademark MYOBLOC®.

[0044] The botulinum toxin used in the compositions of this invention can alternatively be a botulinum toxin derivative, that is, a compound that has botulinum toxin activity but contains one or more chemical or functional alterations on any part or on any chain relative to naturally occurring or recombinant native botulinum toxins. For instance, the botulinum toxin may be a modified neurotoxin (e.g., a neurotoxin which has at least one of its amino acids deleted, modified or replaced, as compared to a native, or a recombinantly produced neurotoxin or a derivative or fragment thereof). For instance, the botulinum toxin may be one that has been modified in a way that, for instance, enhances its properties or decreases undesirable side effects, but that still retains the desired botulinum toxin activity. The botulinum toxin may be any of the botulinum toxin complexes produced by the bac-

terium, as described above. Alternatively, the botulinum toxin may be a toxin prepared using recombinant or synthetic chemical techniques (e.g. a recombinant peptide, a fusion protein, or a hybrid neurotoxin, as prepared from subunits or domains of different botulinum toxin serotypes (see U.S. Pat. No. 6,444,209, for instance)). The botulinum toxin may also be a portion of the overall molecule that has been shown to possess the necessary botulinum toxin activity, and in such case may be used per se or as part of a combination or conjugate molecule, for instance a fusion protein. Additionally, the botulinum toxin may be in the form of a botulinum toxin precursor, which may itself be non-toxic, for instance a nontoxic zinc protease that becomes toxic on proteolytic cleavage.

[0045] This invention also contemplates the general use of combinations and mixtures of botulinum toxins, although due to their differing nature and properties mixtures of botulinum toxin serotypes are not generally administered at this time in the health-care or cosmetic industries.

[0046] Compositions of this invention are preferably in the form of products to be applied to the skin or epithelium of subjects or patients, i.e. humans or other mammals in need of the particular treatment. The term "in need" is meant to include both pharmaceutical or health-related needs, for example, treating conditions involving undesirable facial muscle spasms, as well as cosmetic and subjective needs, for example, altering or improving the appearance of facial tissue. In general the compositions are prepared by mixing the botulinum toxin with the carrier, and usually with one or more additional pharmaceutically acceptable carriers or excipients. In their simplest form they may contain a simple aqueous pharmaceutically acceptable carrier or diluent, such as buffered saline. However, the compositions may contain other ingredients typical in topical pharmaceutical or cosmeceutical compositions, including a dermatologically or pharmaceutically acceptable carrier, vehicle or medium, (i.e. a carrier, vehicle or medium that is compatible with the tissues to which they will be applied.) The term "dermatologically or pharmaceutically acceptable," as used herein, means that the compositions or components thereof so described are suitable for use in contact with these tissues or for use in patients in general without undue toxicity, incompatibility, instability, allergic response, and the like. As appropriate, compositions of the invention may comprise any ingredient conventionally used in the fields under consideration, and particularly in cosmetics and dermatology. The compositions also may include a quantity of a small anion, preferably a polyvalent anion, for example, phosphate, aspartate, or citrate.

[0047] In terms of their form, compositions of this invention may include solutions, emulsions (including microemulsions), suspensions, creams, lotions, gels, powders, or other typical solid or liquid compositions used for application to skin and other tissues where the compositions may be used. Such compositions may contain, in addition to the botulinum toxin and carrier, other ingredients typically used in such products, such as antimicrobials, moisturizers and hydration agents, penetration agents, preservatives, emulsifiers, natural or synthetic oils, solvents, surfactants, detergents, emollients, antioxidants, fragrances, fillers, thickeners, waxes, odor absorbers, dyestuffs, coloring agents, powders, and optionally including anesthetics, anti-itch additives, botanical extracts, conditioning agents, darkening or lightening agents, glitter, humectants, mica, minerals, polyphenols, silicones or derivatives thereof, sunblocks, vitamins, and phytomedicinals.

[0048] In particularly preferred embodiments, the compositions include gelling agents and/or viscosity-modifying agents. These agents are generally added to increase the viscosity of the composition, so as to make the application of the composition easier and more accurate. Additionally, these agents help to prevent the aqueous botulinum toxin/carrier solution from drying out, which tends to cause a decrease in the activity of the botulinum toxin. Particularly preferred agents are those that are uncharged and do not interfere with the botulinum toxin activity or the efficiency of the toxin-carrier complexes in crossing skin. The gelling agents may be certain cellulose-based gelling agents, such as hydroxypropylcellulose (HPC) for example. In some embodiments, the botulinum toxin/carrier complex is formulated in a composition having 2-4% HPC. Alternatively, the viscosity of a solution containing a botulinum toxin/carrier complex may be altered by adding polyethylene glycol (PEG). In other embodiments, the botulinum toxin/carrier solution is combined with pre-mixed viscous agents, such as Cetaphil® moisturizer.

[0049] The compositions of this invention may optionally include partitioning agents. As used herein, a "partitioning agent" is any substance or additive that has the property of preventing or minimizing unwanted or uncontrolled aggregation of the botulinum toxin with the carriers of this invention. Partitioning agents may be useful, for example, when a concentrated botulinum toxin solution must be employed due to volume constraints. In these cases, the partitioning agent keeps the botulinum toxin dispersed, thereby preventing aggregation of the toxin that would otherwise occur without the partitioning agent. Generally, a partitioning agent is (1) non-irritating, (2) does not destroy the botulinum toxin, (3) does not confer any increase in permeability, (4) affords reliable and stable particle sizes, (5) is uncharged, and (6) does not interfere with complexes of the toxin and the transdermal carrier. An example of a suitable partitioning agent is ethanol (EtOH). In preferred embodiments, the EtOH is less than 20% of the composition, and most preferably, less than 5% of the composition.

[0050] By way of example, if volume constraints require reconstituting 100 U of botulinum toxin in 0.5 ml of solution, rather than 2.5 ml, one typically observes that the botulinum toxin will exhibit undesirable aggregation, and thus lowered activity. However, by adding 1% EtOH as a dispersing agent, full activity is maintained even after 24 hours at this concentration. As another example, Botox® at 1.0 ml 0.9% NaCl reconstitution has full activity, while reconstitution at 0.5 ml in 1% and 5% EtOH plus 0.9% NaCl produces solutions with full activity.

[0051] In certain embodiments of this invention, oligo- or polyanion bridges are added to the botulinum toxin compositions to improve the complexation of the toxin with a positively charged backbone carrier. As is well known in the art, botulinum toxin is actually a complex of different proteins, some of which are positively charged, and some of which are negatively charged. Because the exact distribution of the components of the toxin varies depending on the source of the toxin, it may be that botulinum toxin from certain sources has a lower propensity for complexation with the positively charged backbones described herein. However, one aspect of this invention is the discovery that by adding an oligo- or

resulting composition was mixed to homogeneity with 5.4 ml of Cetaphil and aliquoted in 200 microliter portions.

Animal Experiments to Determine Therapeutic Efficacy after Single Time Treatment with Peptidyl Carriers and Botulinum Toxin:

[0082] Animals were anesthetized via inhalation of isoflurane during application of treatments. After being anesthetized, C57 black 6 mice (n=4 per group) underwent topical application of metered 400 microliter dose of the appropriate treatment applied uniformly from the toes to the mid-thigh. Both limbs were treated, and treatments were randomized to either side. Animals did not undergo depilation. At 30 minutes after the initial treatment, mice were evaluated for digital abduction capability according to published digital abduction scores for foot mobility after botulinum toxin administration [Aoki, K R. *A comparison of the safety margins of botulinum neurotoxin serotypes A, B, and F in mice.* Toxicon. 2001 December; 39(12): 1815-20]. Mouse mobility was also subjectively assessed.

Data Handling and Statistical Analysis:

[0083] Digital abduction scores were tabulated independently by two blinded observers. Mean and standard error were subsequently determined for each group with analysis of significance at 95% confidence in one way ANOVA repeated measures using Statview software (Abacus, Berkeley, Calif.).

Results.

[0084] Mean digital abduction scores after single-time topical administration of botulinum toxin with KNR ("IMW-9"), K ("IMW-10") or diluent without polycation ("IMW-11"), are presented in table 2 and illustrated in the representative photomicrograph of FIG. 2 below. The peptidyl carrier KNR afforded statistically significant functional delivery of the botulinum toxin across skin relative to both controls, which were comparable to one another. Additional independent repetitions (total of three independent experiments all with identical conclusions in statistically significant paralysis from topical botulinum toxin with KNR but not controls) of the present experiment confirmed the present findings and revealed no significant differences between topical botulinum toxin with or without K (i.e. both controls). Interestingly, the mice consistently ambulated toward a paralyzed limb (which occurred in 100% of treated animals and 0% of controls from either control group). As shown in FIG. 2, a limb treated with botulinum toxin plus the control polycation polylysine or with botulinum toxin without polycation ("Botox alone") can mobilize digits (as a defense mechanism when picked up), but the limbs treated with botulinum toxin plus the peptidyl carrier KNR ("Essentia Botox lotion") could not be moved.

TABLE 2

Digital abduction scores 30 minutes after single-time topical application of botulinum toxin with the peptidyl carrier KNR ("IMW-9"), with a control polycation K ("IMW-10"), or a diluent ("IMW-11").

Group	Mean	Std. Error
IMW-9	3.875	0.125
IMW-10	0.375	0.375
IMW-11	0.250	0.250

P = 0.0031 (Significant at 95%)

Conclusions:

[0085] This experiment serves to demonstrate that the peptidyl transdermal carrier can transport a therapeutically effective amount of botulinum therapeutic across skin without covalent modification of the therapeutic. The experiment also confirms that botulinum toxin does not function when applied topically in controls.

Example 3

Therapeutic Efficacy of a Topical Botulinum Toxin Preparation with a Nonpeptidyl Carrier

[0086] This experiment demonstrates the performance of a non-peptidyl carrier in the invention.

Methods:

Backbone Selection.

[0087] The positively charged backbone was assembled by conjugating -Gly_2Arg_7 to polyethyleneimine (PEI) MW 1,000,000 via the carboxyl of the terminal glycine to free amines of the PEI side chains at a degree of saturation of 50% (i.e., 30 out of each 100 lysine residues is conjugated to a -Gly_2Arg_7). The modified backbone was designated "PEI" to denote the large nonpeptidyl carrier. Control polycation was unmodified PEI (designated "PEI", Sigma Chemical Co., St. Louis, Mo.) of the same size and from the same lot. The same botulinum toxin therapeutic agent was used as in example 1.

[0088] Botulinum toxin was reconstituted from the Botox product according to the manufacturer's instructions. In each case, an excess of polycation was employed to assemble a final complex that had an excess of positive charge as in delivery of highly negative large nucleotide complexes. A net neutral or positive charge prevents repulsion of the protein complex from highly negative cell surface proteoglycans and extracellular matrix. The botulinum toxin dose was standardized across all groups as was total volume and final pH of the composition to be applied topically. Samples were prepared as follows:

[0089] Group labeled "AZ": 2.0 units of botulinum toxin per aliquot (i.e. 60 U total) and the nonpeptidyl carrier PEIR in ultrapure form at a calculated MW ratio of 5:1 were mixed to homogeneity and diluted to 600 microliters with phosphate buffered saline. The resulting composition was mixed to homogeneity with 5.4 ml of Cetaphil and aliquoted in 200 microliter portions.

[0090] Group labeled "BA": 2.0 units of botulinum toxin per aliquot (i.e. 60 U total) and PEI at a charge ratio of 5:1 were mixed to homogeneity and diluted to 600 microliters with phosphate buffered saline. The resulting composition was mixed to homogeneity with 5.4 ml of Cetaphil and aliquoted in 200 microliter portions.

Animal Experiments to Determine Therapeutic Efficacy after Single Time Treatment:

[0091] Animals were anesthetized via inhalation of isoflurane during application of treatments. After being anesthetized, C57 black 6 mice (n=3 per group) underwent topical application of metered 400 microliter dose of the appropriate treatment applied uniformly from the toes to the mid-thigh. Both limbs were treated, and treatments were randomized to either side. Animals did not undergo depilation. At 30 minutes after the initial treatment, mice were evaluated for digital

abduction capability according to published digital abduction scores for foot mobility after botulinum toxin administration [Aoki, K R. *A comparison of the safety margins of botulinum neurotoxin serotypes A, B, and F in mice.* Toxicon. 2001 December; 39(12): 1815-20]. Mouse mobility was also subjectively assessed.

Data Handling and Statistical Analysis:

[0092] Digital abduction scores were tabulated independently by two blinded observers. Mean and standard error were subsequently determined for each group with analysis of significance at 95% confidence in one way ANOVA repeated measures using Statview software (Abacus, Berkeley, Calif.).

Results:

[0093] Mean digital abduction scores after single-time topical administration of botulinum toxin with ultrapure PEIR ("AZ"), or control polycation PEI ("BA"), are presented in table 3 and repetition presented as table 4 (single independent repetition for this experiment). The nonpeptidyl carrier PEIR afforded statistically significant functional delivery of botulinum toxin across skin relative to controls. As before, animals were observed to walk in circles toward the paralyzed limbs

TABLE 3

Digital abduction scores 30 min. (se after single-time topical administration of Botox with ultrapure PEIR ("AZ"), or control polycation PEI ("BA"). Mean and standard error are presented.

Group	Mean	Std. Error
BA	0.833	0.307
AZ	3.917	0.085

P = 0.0002 (Significant at 99%)

TABLE 4

Digital abduction scores 30 minutes after single-time topical administration of Botox with ultrapure PEIR ("AZ1"), or control polycation PEI ("BA1"). Mean and standard error are presented.

Group	Mean	Std. Error
BA1	0.333	0.211
AZ1	3.833	0.167

P = 0.0003 (Significant at 99%)

Conclusions:

[0094] This experiment demonstrated that the nonpeptidyl transdermal carrier can transport therapeutic doses of botulinum toxin across skin without prior covalent modification of the botulinum toxin. These findings complement those with peptidyl transfer agents. The option of using a nonpeptidyl or a peptidyl carrier to achieve the therapeutic effect will allow tailoring to specific circumstances, environments, and methods of application and add to the breadth of the transdermal delivery platform of this invention.

Example 4

Therapeutic Efficacy of a Topical Botulinum Toxin Preparation with Peptidyl Carrier for Forehead Hyperhidrosis and Wrinkles

[0095] This experiment demonstrates that botulinum toxin can be therapeutically delivered across intact skin as a topical agent using this peptidyl carrier for the treatment of forehead hyperhidrosis and wrinkles on human subjects

Experimental Procedure for Forehead Hyperhidrosis and Wrinkles Study:

[0096] Baseline and post-treatment photographs of the subject's forehead were taken on a blue background using a Nikon D70 camera with Nikon TTL Macro-speedlight SB29s flash (Nikon, Inc. USA).

[0097] Baseline and post-treatment videos of the subject's forehead were taken on a blue background using a Sony Digital Handycam camcorder.

[0098] Minor's starch/iodine test was performed to visualize sweat production using 10% topical povidone iodine solution (Walgreen Co., Deerfield, Ill.) and Kingsford's 100% corn starch (ACH Food Companies, Inc., Memphis, Tenn.). The subject's forehead was painted with an iodine solution using sterile cotton balls (Johnson & Johnson Consumer Product Company, Skillman, N.J.), and then allowed to dry completely. The area was lightly dusted with starch powder using sterile cotton balls. The sweat was induced with physical activity at ambient room temperature. Dark blue-black spots appeared as the sweat dissolved the iodine and reacted with starch powder. Baseline and post-treatment photographs of iodine-starch test were taken on a blue background using a Nikon D70 camera with Nikon TTL Macro-speedlight SB29s flash. The subject's forehead was cleansed with 70% EtOH and then deionized water.

[0099] The subject's predefined treatment area on the forehead was prepared by non-invasive tape stripping method for stratum corneum prior to treatment application. Precut tape was applied to the treatment area with firm pressure for few seconds. It was removed rapidly by pulling on one corner of the tape. The second tape was carefully applied to the same area immediately after the first tape was removed. Tape-stripping was repeated 3-5 times.

Treatment Preparation:

[0100] The Botox reconstituting solution of sterile 0.9% sodium chloride (Abbott Laboratories, North Chicago, Ill.) plus 5% EtOH plus 5% short chained polyaspartate solution labeled A-3C (Donlar BioPolymer, Inc. Bedford Park, Ill.) was prepared (i.e., for every 1.0 milliliter solution, 900 microliters of sterile 0.9% sodium chloride plus 50 microliters of 100% EtOH plus 50 microliters of short chained polyaspartate solution). Kn21T was prepared at 1 milligram/milliliter concentration with 0.9% sodium chloride plus 5% EtOH (i.e., 500 microliters of Kn21T was aliquoted and 25 microliters of 100% EtOH was added). As used herein, Kn21T refers to a positively charged polylysine backbone having a molecular weight of 21,000 and TAT branching groups. 100 units of Botox (Allergan, Irvine, Calif.) was reconstituted with 1.0 milliliters of reconstituting solution using sterile 3 ml latex free syringe with 18 G1 ½ (Becton Dickinson & Co., Franklin Lakes, N.J.). The reconstituted Botox was carefully mixed by inversion 8 times. 200 units of Botox were used for each subject. The "Essential Botox solution" was prepared with 200 units of Botox and Kn21T plus 5% EtOH (ie. 2.0 milliliters of Botox was added to 500 microliters of Kn21T plus 25 microliters of 100% EtOH) and sat at room temperature for 5 minutes for the complexes to form.

[0101] The control solution was prepared with reconstituting solution and Kn21T plus 5% EtOH (ie. 2.0 ml of recon-

stituting solution was added to 500 microliters of Kn21T plus 25 microliters of 100% EtOH) and kept at room temperature.

Treatment Application:

[0102] The subject reclined on a table with protective covering around the eyes, face, and upper body. The treatment was applied evenly to the subject's forehead using a pipette and massaged into the skin in circular motion with fingers while wearing powder-free, nitrile gloves. The treatment area was covered with a thin layer of Cetaphil® moisturizing cream (Galderma, Fort Worth, Tex.) and incubated for 60 minutes. After 60 minute incubation, the treatment was removed with sterile gauze pads. The gauze pads and gloves were discarded in a Biohazard bag.

Results:

[0103] FIG. 3 depicts significant reduction in wrinkle length depth and width after topical treatment with Peptidyl carrier and botulinum combination. This experiment confirms that topically applied botulinum toxin, when combined with transdermal carrier, can afford significant muscular paralysis to afford a cosmetic effect. FIG. 4 is a Mikrosil cast of the treated skin (A) versus untreated skin (B). Wrinkles are visible on the cast of the untreated skin.

[0104] FIGS. 5 and 6 show the results of the Minor's starch/iodine test. FIG. 5 shows photos taken two minutes after application, with panel (A) corresponding to the side treated with Essentia Botox Lotion, and panel (B) corresponding to the side treated with a control lotion containing Kn21T carrier alone. FIG. 6 is the same as FIG. 5, except that it was taken at four minutes. Note the more pronounced coloration on the control lotion side, indicating that the skin on that side is secreting more sweat. Also note that the sweating starts earlier on the untreated side.

Conclusions:

[0105] This example demonstrates that topically applied complexes of botulinum toxin can afford significant aesthetic benefit in reducing fine and coarse wrinkles. This transepithelial effect further confirms that muscle paralysis can be accomplished with appropriate carriers after topical application of botulinum toxin complexes such as those disclosed herein. This example thus indicates that topical application of botulinum toxin can lead to relief from muscle spasms such as blepharospasm or torticollis as well as relief of muscle spasm-related pain such as lower back pain.

example 5

Therapeutic Efficacy of a Topical Botulinum Toxin Preparation with Peptidyl Carrier for Axillary Hyperhidrosis

[0106] This experiment demonstrates whether botulinum toxin can be therapeutically delivered across intact skin as a topical agent using this peptidyl carrier for the treatment of axillary hyperhidrosis on human subjects (n=10 axillae per group with one axilla treated and one control per patient in a randomized double-blind fashion).

Inclusion Criteria for Axillary Hyperhidrosis Study:

[0107] Age: 18 years or older

[0108] Healthy volunteers

[0109] Informed consent given and signed by the volunteer

[0110] Subject willing to follow instruction and return for follow-up visits.

[0111] Subject has presence of pre-existing, subjective hyperhidrosis

[0112] Subject is NOT pregnant or planning on becoming pregnant within the next 3 months

[0113] Subject lives and/or work in San Francisco or near study area

[0114] Subject has NOT had treatment for underarm sweating within the past 6 months

[0115] Subject is NOT planning on having treatment for underarm sweating within the next 3 months

Gravimetric Measurement Procedures:

[0116] As a part of the gravimetric measurement procedure, the subjects were first acclimated to the testing area. Specifically, each subject sat for 15 minutes at a room temperature of 72-77° F. in the resting position.

[0117] Axillae preparation: (Powder-free, nitrile gloves were worn for the following procedures.) The subject changed into disposable cape and bra (if a woman) or took off all upper body garments (if a man) so as to expose both of the axillae fully. The dose area was predetermined to be the area covered by hair bearing skin, plus an area extending 1 cm beyond the hair bearing skin at each axilla. The dose area was cleaned with a pre-wet sterile gauze pad from a 50 ml conical tube by wiping with 5 long strokes from top to bottom in the same direction using one side of the gauze. This step was repeated three more times with a clean pre-wet gauze pad each time while being careful not to irritate or abrade the skin. The gauze pads were discarded in the trash. The same wash procedure was repeated for the other axilla. The axilla was dried with dry sterile gauze by using firm padding motion from top to bottom of the axilla while being careful not to irritate or abrade the skin. Then, the axilla was further dried by placing a filter paper under the axillary crease and allowing the filter to dwell in the test site for 5 minutes following the procedure for gravimetric assessment. The patient sat with their arms against his/her body in a resting position. The filter papers were discarded in the trash. The subject was allowed to rest for 1 minute without axilla manipulation prior to the first gravimetric assessment.

[0118] Sweat production measurement (gravimetric measurement): (A new pair of powder-free, nitrile gloves was donned prior to these measurements). The subject held his or her hands together at the back of head to expose axillae fully, while being partially reclined (about 45 degrees). A pre-weighed filter paper was removed from a conical storage tube and placed under the subject's axilla with the tip of the filter aligning with the center of axillary crease line. The filter paper held in place by using fingers while the subject relaxed arms to the side of the body. The subject sat with both arms held tightly against his/her trunk for five minutes. The timing started when the filter papers were securely placed under both of the axillae. Both axillae were measured simultaneously. After 5 minutes, the filter papers were removed from the axillae and placed back into the same respective conical tubes. The filter paper placed first was removed first. The cups of the conical tubes were screwed tightly to prevent the evapo-

ration of the sweat from the tube. The sweat production was repeated two more times at one-minute intervals.

Minor's Starch/Iodine Test:

[0119] The subject held his/her hands together at the back of head to expose the axillae fully. The iodine solution was painted onto the axilla area predetermined as before with a sterile gauze pad and allowed to air-dry. When the iodine had completely dried, a thin layer of starch was painted onto the area covered by iodine with cotton balls. The iodine was allowed to air-dry before the application of starch in order to reduce false positive and background. The subject then sat with both arms held tightly against his/her trunk. After 5 minutes, the subject raised his/her arms and held hands together at the back of head to expose axillae fully. Photographs of each axilla with left and right axilla and the date clearly labeled were taken. The axillae were cleaned with 70% EtOH and then with sterile deionized water.

Treatment Preparation:

[0120] Kn21pr was prepared at 1 milligram/milliliter concentration with saline plus 5% EtOH (i.e., 500 microliters of Kn21pr was aliquoted and 25 microliters of 100% EtOH was added). As used herein, Kn21pr refers to a positively charged polylysine backbone with a molecular weight of 21,000 and branching groups comprising protected oligoarginine. 100 units of Botox® (Allergan, Irvine, Calif.) was reconstituted with 0.75 milliliters of 0.9% sodium chloride (Abbott Laboratories, North Chicago, Ill.) using sterile 3 ml latex free syringe with 18½1/2 (Becton Dickinson and Company, Franklin Lakes, N.J.). The reconstituted Botox® was carefully mixed by inversion 8 times. 200 units of Botox® were used for each subject. The treatment solution was prepared with 200 units of Botox® and Kn21pr plus 5% EtOH (i.e., 1.5 milliliters of Botox® was added to 500 microliters of Kn21pr plus 25 microliters of 100% EtOH) and kept at room temperature for 5 minutes to allow the complexes to form. After a 5-minute incubation period, approximately 1.0 milliliters of 4% HPC (hydroxypropylcellulose) (with 1% EtOH) was added and mixed gently and thoroughly with a small metal spatula. The homogenous treatment solution was transferred into a 3 ml syringe and syringe tip cap. (Becton Dickinson and Company, Franklin Lakes, N.J.).

[0121] The control solution was prepared with 0.9% sodium chloride and Kn21pr plus 5% EtOH (i.e. 1.5 milliliters of 0.9% sodium chloride was added to 500 microliters of Kn21pr plus 25 microliters of 100% EtOH) and sat at room temperature for five minutes. After incubation, approximately 1.0 milliliters of 4% HPC (with 1% EtOH) was added and mixed gently and thoroughly with a small metal spatula. The homogenous control solution was transferred into a 3 ml syringe and syringe tip cap.

Treatment Application (Wear Powder-Free, Nitrile Gloves):

[0122] The subject held his/her hands together with interlocking fingers and placed them on the back of the head to fully exposure the subject's axillae. Then, the subject reclined in a chair to an angle of about 45 degrees. As shown in FIG. 7, the dose area was visually mapped out (i.e. 1 cm beyond the hair bearing skin) for application. The dose area were checked for dryness. The syringe tip cap was removed from the labeled syringe marked "L" for left and "R" for right, and prepared for application onto the subject's axilla. The treatment solution was spread evenly around the dose area with a syringe and massaged into the skin with fingers for 1 minute. The subject then placed his/her arms down along the side of the body and incubated for 60 minutes. After 60 minute incubation, the treatment was cleaned with sterile gauze pads. The gauze pads and gloves were discarded in a bio-hazard bag. The subject was discharged.

Results.

[0123] Essentia topical BT reduced sweating by 65% and illustrated in *FIG. 8a*. Sweat production 4 weeks after treatment (randomized by side) with Kn21pr backbone alone (control) or kn21pr backbone plus 200 U Botox (ratio to baseline). Statistical analyses by Wilcoxon signed ranks using NPSS with P as noted and significance at $P<0.05$. [n=10 subjects].

[0124] Second comparison: Baseline vs. 4 weeks (See FIG. 8*b*). Sweat production (mg per 5 minutes) 4 weeks after axillary treatment (randomized by side) with kn21pr backbone alone (control) or kn21pr backbone plus 200 U Botox (ratio of treatment to control) presented in Table 6. Statistical analyses by Wilcoxon signed ranks using NPSS with P as noted and significance at $P<0.05$. (Pr T p 0.0217) [n 10].

[0125] FIG. **9** shows photographs depicting Minor's starch/iodine test before and after treatment with "Essentia Botox lotion" topically for the treatment of axillary hyperhidrosis. Starch/iodine test at Baseline vs 2 weeks is shown where right axilla was treated with "Essentia Botox lotion" (a and c) and left axilla was applied with the control (b and d) for subject #12. These photographs illustrate typical benefits observed after treatment with carrier+botox in starch iodine. Although some crossover is observed on the control side (consistent with 25% reduction in gravimetric data), significant reductions are afforded with treatment (consistent with 65% reduction in gravimetric data on treated side).

Conclusions:

[0126] This example confirms that topical application of botulinum complexes formed according to the invention disclosed herein readily afford therapeutic benefit in reduction of sweating in a cohort of patients with hyperhidrosis—subjective or quantitative. This effect in reducing sweating has also been afforded in the forehead case presented above and in palmar/plantar application when combined with a glove to limit spread of formulation during dwell time. This transepithelial delivery of botulinum toxin complexes for therapeutic benefit confirms further that the approach can be extended to other cases where SNAP function or acetylcholine signals are crucial such as bladder dysfunction or spasm, gastrointestinal applications, or sebaceous gland secretions for smell reduction or acne prevention/treatment.

1-50. (canceled)

51. A method of administering a botulinum toxin to a subject comprising topically applying to the skin or epithelium of the subject the botulinum toxin in conjunction with an effective amount of a carrier comprising a polymeric backbone having attached positively charged branching groups, wherein the association between the carrier and the botulinum toxin is non-covalent.

52. The method according to claim **51** comprising topically applying to the skin or epithelium of the subject an effective amount of a composition according to claim **1**.

53. The method according to claim 51 in comprising separately applying the botulinum toxin and the carrier to the skin or epithelium of the subject.

54. The method according to claim 51 in which the botulinum toxin is administered to achieve a desired biologic effect.

55. The method according to claim 54 in which the botulinum toxin is administered to achieve an aesthetic or cosmetic benefit.

56. The method according to claim 54 in which the botulinum toxin is applied to reduce or prevent an immune response.

57. The method according to claim 56 in which the reduced or prevented immune response improves therapeutic response on later repeat re-administrations of the composition.

58. The method according to claim 54 in which the botulinum toxin is administered for prevention or reduction of symptoms associated with subjective or clinical hyperhidrosis.

59. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of subjective or clinical dystonic contractions or dystonia.

60. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with muscle spasm.

61. The method according to claim 60 in which the botulinum toxin is applied topically to the lower back of the subject.

62. The method according to claim 60 in which the botulinum toxin is topically applied to the neck of the subject.

63. The method according to claim 60 in which the botulinum toxin is topically applied to at least one leg of the subject.

64. The method according to claim 51 in which the botulinum toxin is applied topically to the face of the subject, or to a portion thereof.

65. The method according to claim 51 in which the botulinum toxin is applied topically to the axilla of the subject, or to a portion thereof.

66. The method according to claim 51 in which the botulinum toxin is applied topically to the palms of the hands or to the feet of the subject, or to a portion thereof.

67. The method according to claim 51 in which the botulinum toxin is applied topically to the back or neck of the subject, or to a portion thereof.

68. The method according to claim 51 in which the botulinum toxin is applied topically to the groin of the subject, or to a portion thereof.

69. The method according to claim 51 in which the composition is applied topically to the hands or feet of the subject, or to a portion thereof.

70. The method according to claim 51 in which the botulinum toxin is applied topically to the elbows, upper arms, knees, or upper legs of the subject, or to a portion thereof.

71. The method according to claim 51 in which the botulinum toxin is applied topically to the buttocks of the subject or to a portion thereof.

72. The method according to claim 51 in which the botulinum toxin is applied topically to the torso of the subject or to a portion thereof.

73. The method according to claim 51 in which the botulinum toxin is applied topically to the pelvis of the subject or to a portion thereof.

74. The method according to claim 51 in which the botulinum toxin is applied to generate or enhance an immune response.

75. The method according to claim 51 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with migraine headache.

76. The method according to claim 51 in which the botulinum toxin is applied topically for prevention or reduction of acne.

77. The method according to claim 51 in which the botulinum toxin is a botulinum toxin derivative.

78. The method according to claim 51 in which the botulinum toxin comprises a recombinant botulinum toxin.

79. The A method according to claim 51 in which the botulinum toxin comprises a modified botulinum toxin.

80. The method according to claim 51 in which the botulinum toxin is selected from botulinum toxin serotypes A, B, C, D, E, F and G.

81. The method according to claim 51 in which the botulinum toxin is botulinum toxin A.

82. The method according to claim 51 in which the botulinum toxin is botulinum toxin B.

83. The method according to claim 51 in which the botulinum toxin is botulinum toxin C.

84. The method according to claim 51 in which the botulinum toxin is botulinum toxin D.

85. The method according to claim 51 in which the botulinum toxin is botulinum toxin E.

86. The method according to claim 51 in which the carrier comprises a polymeric backbone having attached positively charged branching groups selected from $-(gly)_{n1}-(arg)_{n2}$, HIV-TAT, Antennapedia PTD, and fragments of HIV-TAT or of Antennapedia PTD, in which the subscript n1 is an integer of from 0 to about 20, and the subscript n2 is independently an odd integer of from about 5 to about 25.

87. The method according to claim 86 in which the carrier comprises a polypeptide having positively charged branching groups selected from $-(gly)_{n1}-(arg)_{n2}$ in which the subscript n1 is an integer of from about 0 to about 20 and the subscript n2 is independently an odd integer of from about 5 to about 25.

88. The method according to claim 87 in which the subscript n1 is an integer of from 0 to about 8.

89. The method according to claim 87 in which the subscript n1 is an integer of from about 2 to about 5.

90. The method according to claim 87 in which the subscript n2 is an odd integer of from about 7 to about 17.

91. The method according to claim 87 in which the subscript n2 is an odd integer from about 7 to about 13.

92. The method according to claim 86 in which the carrier comprises a polypeptide having attached positively charged branching groups selected from HIV-TAT and fragments thereof.

93. The method according to claim 92 in which the branching groups are positively charged HIV-TAT fragments that have the formula $(gly)_p$-RGRDDRRQRRR-$(gly)_q$, $(gly)_p$-YGRKKRRQRRR-$(gly)_q$, or $(gly)_p$-RKKRRQRRR-$(gly)_q$, wherein the subscripts p and q are each independently an integer of from 0 to 20.

94. The method according to claim 51 in which the positively charged branching groups comprise at least about 0.05% by weight of the total carrier weight.

95. The method according to claim 51 in which the positively charged branching groups comprise from about 0.5% to about 45% by weight of the total carrier weight.

96. The method according to claim 51 in which the positively charged branching groups comprise from about 0.1% to about 30% by weight of the total carrier weight.

97. The method according to claim 51 in which the backbone comprises a positively charged polypeptide.

98. The method according to claim 97 in which the backbone comprises a positively charged polylysine.

99. The method according to claim 98 in which the polylysine has a molecular weight of from about 10,000 to 1.5 million.

100. The method according to claim 98 in which the polylysine has a molecular weight of from about 25,000 to about 1,200,000.

101. The method according to claim 98 in which the polylysine has a molecular weight of from about 100,000 to about 1,000,000.

102. The method according to claim 51 in which the backbone comprises a positively charged nonpeptidyl carrier.

103. The method according to claim 102 in which the positively charged nonpeptidyl polymer is polyalkyleneimine.

104. The method according to claim 102 in which the polyalkyleneamine is a polyethyleneimine.

105. The method according to claim 104 in which the polyethyleneimine has a molecular weight of from about 10,000 to about 2,500,000.

106. The method according to claim 104 in which the polyethyleneimine has a molecular weight of from about 100,000 to about 1,800,000.

107. The method according to claim 104 in which the polyethyleneimine has a molecular weight of from about 500,000 to about 1,400,000.

108. The method according to claim 51 in which the botulinum toxin comprises a recombinant botulinum toxin.

109. The method according to claim 51 in which the botulinum toxin is applied in a composition having a pH of from about 4.5 to about 6.3.

110. The method according to claim 51 in which the botulinum toxin is applied in a controlled release composition.

111. The method according to claim 51 in which the botulinum toxin is contained in a liquid composition.

112. The method according to claim 51 in which the botulinum toxin is contained in a gel composition.

113. The method according to claim 51 in which the botulinum toxin is contained in a composition that is a cream, lotion or ointment.

114. The method according to claim 51 in which the botulinum toxin is contained in a composition further comprising saline.

115. The method according to claim 51 in which the botulinum toxin is contained in a composition further comprising saline and a pH buffer system.

116. The method according to claim 51 in which the botulinum toxin is contained in a device for dispensing the botulinum toxin, which device is applied topically to the skin or epithelium of the subject.

117. The method according to claim 116 in which the device is a skin patch.

118. The method according to claim 117 in which the device is a cell-encapsulating device.

119. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with mucous secretion.

120. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of obesity or symptoms thereof.

121. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of inflammation or symptoms thereof.

122. The method according to claim 121 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with psoriasis.

123. The method according to claim 122 in which the composition is applied in conjunction with other treatment modalities.

124. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of snoring.

125. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of cutaneous symptoms associated with diabetes.

126. The method according to claim 54 in which the botulinum toxin is applied topically for improvement of wound healing.

127. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with autonomic nerve dysfunction.

128. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with cerebral palsy.

129. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with Hashimoto's thyroiditis.

130. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with mammary gland disorders.

131. The method according to claim 54 in which the botulinum toxin is applied topically for alteration of hair growth.

132. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with parathyroid disorders.

133. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with movement disorders.

134. The method according to claim 133 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with parkinson's disease.

135. The method according to claim 133 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with tremors.

136. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with epilepsy.

137. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with inner ear disorders.

138. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with urologic disorders.

139. The method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of other cholinergic-controlled secretions.

140. The method according to claim **54** in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with neuropsychiatric disorders.

141. The method according to claim **54** in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with injured muscles.

142. The method according to claim **54** in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with ear disorders.

143. The method according to claim **54** in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with cancer.

144. The method according to claim **54** in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with nerve entrapment disorders.

145. The method according to claim **54** in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with hypercalcemia.

146. The method according to claim **51** in which the botulinum toxin comprises a fusion protein.

147-148. (canceled)

149. The method according to claim **51** in which the botulinum toxin is botulinum toxin F.

150. The method according to claim **51** in which the botulinum toxin is botulinum toxin G.

* * * * *

PODER ESPECIAL

Yo**LUIS ALBERTO PALACIOS ARAGÓN,,** mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Gerente de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Bogotá (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 **del C.S. de la J.**, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **11 094.674,** titulada **"FORMULACIONES INYECTABLES DE TOXINA BOTULÍNICA",** cuyo titular ***REVANCE THERAPEUTICS, INC.*** publicada en la gaceta No. 640 del 15 de marzo de 2012.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Bogotá (Colombia) a los 06 días del mes de junio de 2012.

LABORATORIOS SYNTHESIS S.A.S.

_____

Gerente General
Cédula de Extranjería: No. 319788.
NIT: 860.000.760-1

Acepto:

_____

ELIANA ISAURA MORENO BOHÓRQUEZ
C.C. 51.975.664
T.P. 83823 del C.S.J

REPUBLICA DE COLOMBIA

DILIGENCIA DE RECONOCIMIENTO

Comparació ante el Notario ... del Circulo de Bogota JUIS ALBERTO PALACIOS ARAGON quien exhibió la C E 13197 88 Expedida en ... y declaró que la ... suya que aparecen en el ... son suyas y que el ... es cierto. 06 JUN 2012

BOGOTA, D C

FIRMA

EL NOTARIO

NOTARIA DEC 30 CIRCULO DE BOGOTA D C LA HUELLA SE AUTENTICA POR ... ATRAS

REPUBLICA DE COLOMBIA

JOSE MIGUEL ... Y OTROS

NOTARIA DEL CIRCULO DE BOGOTA D.C.

01

11888693 0

Cámara de Comercio de Bogotá

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

30 DE MAYO DE 2012 HORA 09:32:55

R034891996 PAGINA: 1 de 5

* *

****
* EN JUNIO DE ESTE AÑO SE ELEGIRA JUNTA DIRECTIVA DE LA CAMARA DE *
* COMERCIO DE BOGOTA. LAS INSCRIPCIONES DE CANDIDATOS DEBEN *
* HACERSE HASTA EL ULTIMO DIA HABIL DE LA SEGUNDA QUINCENA DE ABRIL.*
* PARA INFORMACION DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL, QUINTO *
* PISO, O COMUNICARSE AL SIGUIENTE TELEFONO: 5941000 EXTENSION 2597.*
****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL

CERTIFICA:

NOMBRE : LABORATORIOS SYNTHESIS S A S
N.I.T. : 860000760-1
DOMICILIO : BOGOTA D.C.

CERTIFICA:

MATRICULA NO: 00008059 DEL 23 DE MARZO DE 1972

CERTIFICA:

RENOVACION DE LA MATRICULA :29 DE FEBRERO DE 2012
ULTIMO AÑO RENOVADO: 2012
ACTIVO TOTAL REPORTADO:$78,678,599,000

CERTIFICA:

DIRECCION DE NOTIFICACION JUDICIAL : CRA 44 NO 20C 73
MUNICIPIO : BOGOTA D.C.
EMAIL DE NOTIFICACION JUDICIAL : lmbautista@synthesis.com.co
DIRECCION COMERCIAL : CRA 44 NO 20C 73
MUNICIPIO : BOGOTA D.C.
EMAIL COMERCIAL : lmbautista@synthesis.com.co

CERTIFICA:

CONSTITUCION: ESCRITURA PUBLICA NO.2078, NOTARIA 8 BOGOTA, DEL 27 DE JULIO DE 1.950, INSCRITA EL 10 DE AGOSTO DE 1.950, BAJO EL NO. 21.766 DEL LIBRO RESPECTIVO ACLARADA POR ESCRITURA NO. 3608 DEL 8 DE OCTUBRE DE 1.956 NOTARIA 8 DE BOGOTA INSCRITA EN ESTA - CAMARA DE COMERCIO EL 19 DE OCTUBRE DE 1.956 BAJO EL NO. 35.547 DEL LIBRO RESPECTIVO, SE CONSTITUYO LA SOCIEDAD DENOMINADA: "LA-BORATORIOS BALBAG".

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 3997 OTORGADA EN LA NOTARIA 8 DE BOGOTA EL 24 DE NOVIEMBRE DE 1.952, INSCRITA EN ESTA CAMARA DE CO MERCIO EL 1 DE DICIEMBRE DE 1.952, BAJO EL NUMERO 26.158 DEL LI-- BRO RESPECTIVO, LA SOCIEDAD CAMBIO SU NOMBRE DE:"LABORATORIOS --- BALBAG" POR EL DE "LABORATORIO SYNTHESIS" E INTRODUJO OTRAS RE-- FORMAS.

CERTIFICA :

QUE POR ESCRITURA PUBLICA NUMERO 6491 OTORGADA EN LA NOTARIA 1. -

DE BOGOTA EL 24 DE DICIEMBRE DE 1.981, INSCRITA EN ESTA CAMARA DE COMERCIO EL 12 DE MARZO DE 1.982, BAJO EL NUMERO 113.297 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE "LABORATORIOS SYNTHESIS - BALAVOINE Y CIA. S.C.A" POR EL DE "LABORATORIOS SYNTHESIS LTDA. Y CIA. S.C.A" E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 8580 OTORGADA EN LA NOTARIA 3 DE BOGOTA EL 4 DE DICIEMBRE DE 1.973, INSCRITA EN ESTA CAMARA DE COMERCIO EL 7 DE ENERO DE 1.974, BAJO EL NUMERO 14.478 DEL LIBRO IX, LA SOCIEDAD SE TRASFORMO DE LIMITADA EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE LABORATORIOS SYNTHESIS BALAVOINE Y CIA. S.C.A.

CERTIFICA:

QUE POR ACTA NO. 117 DE LA ASAMBLEA DE ACCIONISTAS, DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NÚMERO 1390261 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES A SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE: LABORATORIOS SYNTHESIS S.A.S.

CERTIFICA:

QUE POR E.P. NO.5.435 DEL 17 DE SEPTIEMBRE DE 1.996, NOTARIA PRIMERA DE SANTAFE DE BOGOTA, INSCRITA EL 30 DE SEPTIEMBRE DE 1.996, BAJO EL NO.556.909 DEL LIBRO IX, ADICIONADA POR LOS REGISTROS 557 146 DEL 1 DE OCTUBRE DE 1.996, Y 557.301 DEL 2 DE OCTUBRE DE 1996 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA COMUNICO QUE SE FUSIONO, ABSORBIENDO A LA SOCIEDAD "SYNTHESIS VETERINARIA LTDA Y CIA S C A"

CERTIFICA:

QUE POR E.P. NO.1024 DEL 28 DE FEBRERO DE 1997, DE LA NOTARIA 1. DE SANTAFE DE BOGOTA, INSCRITA EL 31 DE MARZO DE 1997, BAJO EL NUMERO 579245 DEL LIBRO IX, CELEBRO ACUERDO DE FUSIÓN CON LA SOCIEDAD PRODUCTOS DIETÉTICAS DIETESYN S.A, DONDE LA SOCIEDAD DE LA REFERENCIA FUE LA ABSORBENTE.

CERTIFICA:

QUE POR ACTA NO. 120 DE LA ASAMBLEA DE ACCIONISTAS DEL 29 DE JULIO DE 2010, INSCRITA EL 19 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01429837 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA (ABSORBENTE) ABSORBE MEDIANTE FUSIÓN A LAS SOCIEDADES INMUNOSYN SAS Y GYNOPHARM SAS LAS CUALES SE DISUELVEN SIN LIQUIDARSE.

CERTIFICA:

REFORMAS:

ESCRITURAS NO.	FECHA	NOTARIA	INSCRIPCION
4471	18-XII-1.956	8 BTA.	22-XII-1.956 NO. 36.077
3322	31-XII-1.958	8 BTA.	12-I-1.959 NO. 42.034
2322	22-IX-1.961	8 BTA.	29-IX-1.961 NO. 51.161
290	2-II-1.967	6 BTA.	24-II-1.967 NO. 71.304
8545	16-XII-1.967	6 BTA.	26-I-1.968 NO. 75.041
4679	20-XII-1.967	8 BTA.	26-I-1.968 NO. 75.042
3010	14-V-1.968	6 BTA.	30-V-1.968 NO. 76.244
2931	4-V-1.970	6 BTA.	18-V-1.970 NO. 84.983
5656	13-VII-1.970	6 BTA.	13-VIII-1.970 NO. 86.126
3487	15-VII-1.971	3 BTA.	29-VII-1.971 NO. 90.980
4638	10-VII-1.984	11 BTA.	27-VIII-1.984 NO.157.001
1443	14-III-1.985	11 BTA.	26- III-1.985 NO.167.627
724	11- II-1.985	1 BTA.	21- II-1.985 NO.165.940
4836	11-VIII-1986	1 BTA.	23- IX -1.986 NO.197.784
5659	15- IX -1986	1 BTA.	23- IX -1.986 NO.197.784
6326	16- X -1987	1 BTA.	23- X -1.987 NO.221.604
5164	21-VIII-1990	1 BTA.	3- IX -1.990 NO.303.579

9244	23-XII- 1991 1 STAFE.BTA. 8-I -1.992 NO.351.255
8145	15- X - 1992 1 STAFE.BTA. 16- X-1.992 NO.382.488
1374	26- III-1993 1 STAFE.BTA. 19- III-1993 NO.399972
3120	01-VI-1.995 1A.STAFE BTA 23-VI- 1.995 NO.498.060
5435	17-IX-1.996 1A.STAFE BTA 30-IX- 1.996 NO.556.909
5435	17-IX-1.996 1A.STAFE BTA 01- X- 1.996 NO.557.146
5435	17-IX-1.996 1A.STAFE BTA 02- X- 1.996 NO.557.301
5942	7-X -1.996 1A.STAFE BTA 11- X- 1.996 NO.558.222
6305	24-X--1.996 1A.STAFE BTA 07-XI--1.996 NO.561.207
6929	25-XI-1.996 1A.STAFE BTA 12-XII-1.996 NO.565.961
787	19-II-1.997 1A.STAFE BTA 25-II -1.997 NO.575.141
1024	28-II-1.997 1A.STAFE BTA 31-III-1.997 NO.579.245

CERTIFICA:

REFORMAS:

E.P. NO.	FECHA	NOTARIA	CIUDAD	FECHA	NO.INSC.
0007110	1997/10/28	0001	BOGOTA D.C.	1997/11/06	00609204
0001896	1998/03/16	0001	BOGOTA D.C.	1998/04/01	00628368
0002924	1998/04/21	0001	BOGOTA D.C.	1998/05/18	00634309
0002377	2000/06/14	0001	BOGOTA D.C.	2000/06/20	00733626
0000SIN	2004/06/22	0000	BOGOTA D.C.	2004/06/28	00940785
117	2010/04/30	0000	BOGOTA D.C.	2010/06/10	01390261
120	2010/08/18	0000	BOGOTA D.C.	2010/08/26	01409241
120	2010/08/30	0000	BOGOTA D.C.	2010/09/13	01413659
120	2010/07/29	0000	BOGOTA D.C.	2010/11/19	01429837
139	2011/06/07	0000	BOGOTA D.C.	2011/06/20	01489422
146	2011/10/24	0000	BOGOTA D.C.	2011/11/30	01531828

CERTIFICA:

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 27 DE JULIO DE 2040

CERTIFICA:

OBJETO SOCIAL: EL OBJETO DE LA SOCIEDAD ES EL EJERCICIO DE TODAS LAS ACTIVIDADES COMERCIALES PARA: 1) LA IMPORTACIÓN, EXPORTACIÓN, FABRICACIÓN, COMERCIALIZACIÓN, DISTRIBUCIÓN Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, VETERINARIOS E IMPLEMENTOS MÉDICOS. 2) CUALQUIER OTRA ACTIVIDAD LÍCITA DE COMERCIO RELACIONADA CON SU OBJETO SOCIAL PRINCIPAL Y TODO LO QUE SE RELACIONA CON LA IMPORTACIÓN DE LOS BIENES Y EQUIPOS NECESARIOS PARA EL DESARROLLO DE SU OBJETO SOCIAL. 3) TENER LA REPRESENTACIÓN EN COLOMBIA DE EMPRESAS O SOCIEDADES ESTABLECIDAS FUERA DEL TERRITORIO COLOMBIANO, CUYO OBJETO SEA SIMILAR O COMPLEMENTARIO. EN DESARROLLO DE SU OBJETO SOCIAL PRINCIPAL, LA SOCIEDAD PODRÁ ADELANTAR Y CELEBRAR LOS SIGUIENTES ACTOS Y CONTRATOS: A) EXPORTAR E IMPORTAR, AGENCIAR, DISTRIBUIR, COMERCIALIZAR, COMPRAR O VENDER A COMISIÓN O CONSIGNACIÓN O DE CUALQUIER OTRA FORMA O MODALIDAD, TODA CLASE DE EQUIPOS, APARATOS, BIENES AL POR MAYOR O AL DETAL, Y SERVICIOS RELACIONADOS CON SU ACTIVIDAD. B) GRAVAR EN

CUALQUIER FORMA LOS BIENES DE SU PROPIEDAD MUEBLES O INMUEBLES, DAR EN PRENDA LOS PRIMEROS O HIPOTECAR LOS SEGUNDOS PARA GARANTIZAR OBLIGACIONES DE LA SOCIEDAD. C) CONSTITUIR APODERADOS QUE LE REPRESENTEN, ASOCIARSE CON OTRAS COMPAÑÍAS DE LA MISMA O PARECIDA NATURALEZA Y EN GENERAL REALIZAR TODA CLASE DE OPERACIONES COMERCIALES O CIVILES Y EJECUTAR O CELEBRAR TODA CLASE DE CONTRATOS O ACTOS DEL MISMO ORDEN, YA SEAN INDUSTRIALES, COMERCIALES O FINANCIEROS ENCAMINADOS A ALCANZAR LOS FINES QUE SE PROPONEN. D) ADQUIRIR, ENAJENAR, ADMINISTRAR, RECIBIR O DAR EN ARRENDATARIO O A CUALQUIER TÍTULO, TODA CLASE DE BIENES MUEBLES E INMUEBLES. E) INTERVENIR ANTE TERCEROS O ANTE LOS ACCIONISTAS MISMOS COMO ACREEDORA O COMO DEUDORA EN TODA CLASE DE OPERACIONES DE CRÉDITO, DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRESTAMOS. OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR Y NEGOCIAR EN GENERAL TÍTULOS VALORES RECIBIRLOS EN PAGO; G) CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES.

CERTIFICA:

CAPITAL:

** CAPITAL AUTORIZADO **

VALOR : $22,000,000,000.00
NO. DE ACCIONES : 22,000,000.00
VALOR NOMINAL : $1,000.00

** CAPITAL SUSCRITO **

VALOR : $20,877,288,000.00
NO. DE ACCIONES : 20,877,288.00
VALOR NOMINAL : $1,000.00

** CAPITAL PAGADO **

VALOR : $20,877,288,000.00
NO. DE ACCIONES : 20,877,288.00
VALOR NOMINAL : $1,000.00

CERTIFICA:

REPRESENTACION LEGAL: LA SOCIEDAD CONTARÁ CON UN GERENTE, QUIEN TENDRÁ DOS SUPLENTES DENOMINADOS SUBGERENTES, QUIENES LO REEMPLAZARÁN EN LAS FALTAS OCASIONALES, TEMPORALES O ABSOLUTAS DE AQUÉL.

CERTIFICA:

** NOMBRAMIENTOS **

QUE POR ACTA NO. 127 DE ASAMBLEA DE ACCIONISTAS DEL 12 DE NOVIEMBRE DE 2010, INSCRITA EL 23 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01430759 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE IDENTIFICACION

GERENTE

PALACIOS LUIS ALBERTO C.E. 000000000319788

QUE POR ACTA NO. 117 DE ASAMBLEA DE ACCIONISTAS DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NUMERO 01390261 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE IDENTIFICACION

SUBGERENTE

MUÑOZ MARTINEZ ORLANDO C.C. 000000008317044

QUE POR ACTA NO. 139 DE ASAMBLEA DE ACCIONISTAS DEL 7 DE JUNIO DE

2011, INSCRITA EL 20 DE JUNIO DE 2011 BAJO EL NUMERO 01489425 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
SUBGERENTE	
PICART LAURENZ FRANCISCO JAVIER	C.E. 00000000E399661

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A SU CARGO LA ADMINISTRACIÓN INMEDIATA DE LA SOCIEDAD, ASÍ COMO LA REPRESENTACIÓN LEGAL DE LA MISMA Y EN TAL VIRTUD LE ESTÁN ASIGNADAS LAS SIGUIENTES FUNCIONES Y ATRIBUCIONES: A) LLEVAR LA REPRESENTACIÓN DE LA ENTIDAD, TANTO JUDICIAL COMO EXTRAJUDICIALMENTE. B) EJECUTAR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. C) CONSTITUIR, PARA CASOS ESPECIALES, APODERADOS JUDICIALES O EXTRAJUDICIALES. D) CELEBRAR LOS ACTOS, OPERACIONES Y CONTRATOS CONDUCENTES AL BUEN LOGRO DEL OBJETO DE LA SOCIEDAD. E) CUIDAR DE LA RECAUDACIÓN E INVERSIÓN DE LOS FONDOS DE LA SOCIEDAD. F) PRESENTAR A LA REUNIÓN ORDINARIA ANUAL DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL INVENTARIO Y LOS ESTADOS FINANCIEROS DE PROPÓSITO GENERAL DE FIN DE EJERCICIO, JUNTO CON UN INFORME ESCRITO RELACIONADO CON LA SITUACIÓN Y LA MARCHA DE LA ENTIDAD. G) CREAR LOS EMPLEADOS NECESARIOS PARA LA DEBIDA MARCHA DE LA SOCIEDAD, SEÑALAR SUS FUNCIONES Y ASIGNACIONES Y HACER LOS NOMBRAMIENTOS CORRESPONDIENTES. H) CONVOCAR A LA ASAMBLEA GENERAL CUANDO PROCEDA HACERLO CONFORME A LA LEY O A ESTOS ESTATUTOS. I) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO ASÍ LO SOLICITE, ESTADOS FINANCIEROS MENSUALES DE PRUEBA E INFORMES. J) EJERCER LAS FUNCIONES QUE LE DELEGUE LA ASAMBLEA GENERAL DE ACCIONISTAS. K) CUMPLIR Y HACER QUE SE CUMPLAN EN OPORTUNIDAD Y DEBIDAMENTE TODAS LAS EXIGENCIAS DE LAS LEYES EN RELACIÓN CON EL FUNCIONAMIENTO Y LAS ACTIVIDADES DE LA INSTITUCIÓN. L) LAS DEMÁS QUE LE CORRESPONDAN CONFORME A LA LEY Y A ESTOS ESTATUTOS. EL GERENTE DE LA SOCIEDAD DEBERÁ CONTAR CON AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO PRETENDA SUSCRIBIR EN NOMBRE DE LA SOCIEDAD (I) ACTOS O CONTRATOS PARA ADQUIRIR, ENAJENAR, RECIBIR O DAR EN ARRENDAMIENTO O A CUALQUIER OTRO TÍTULO, TODA CLASE DE BIENES INMUEBLES DE LA SOCIEDAD O BIENES MUEBLES DIFERENTES A LOS PRODUCTOS COMERCIALIZADOS ORDINARIAMENTE POR LA SOCIEDAD, ASÍ COMO (II) ACTOS O CONTRATOS, INDEPENDIENTE DE SU OBJETO, QUE SUPERE EN CUANTÍA EL EQUIVALENTE A 300 SMLMV (TRESCIENTOS SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES).

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 3511 DE LA NOTARIA 18 DE BOGOTA D.C., DEL 8 DE SEPTIEMBRE DE 2010, INSCRITA EL 1 DE OCTUBRE DE 2010 BAJO EL NO. 00018604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE BOGOTA, EN SU CALIDAD DE GERENTE DE LABORATORIOS SYNTHESIS LTDA., POR

MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL A OLGA VICTORIA PRIETO ZAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.303 DE BOGOTA PARA QUE EN NOMBRE DE LA SOCIEDAD LABORATORIOS SYNTHESIS S.A.S., PROMUEVA Y DEFIENDA LOS INTERESES DE LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE, EN TODA ESPECIE DE GESTIONES Y ACTUACIONES ANTE LAS AUTORIDADES ADMINISTRATIVAS O JURISDICCIONALES Y EN ESPECIAL PARA: A. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS. B. TRANSIGIR, DESISTIR Y APELAR A DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C. ADELANTAR CUALQUIER TIPO DE TRÁMITE ANTE EL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES. D. RECIBIR NOTIFICACIÓN DE TODAS LAS PROVIDENCIAS QUE SE EXPIDAN DENTRO DE LOS DIFERENTES TRÁMITES E INTERPONER LOS RECURSOS PROPIOS DE LA VÍA GUBERNATIVA. E. REPRESENTAR Y VIGILAR ANTE LOS FUNCIONARIOS, OFICINAS Y DEPENDENCIAS DEL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES, TODAS LAS SOLICITUDES QUE CONTENGAN TRÁMITES A NOMBRE DE LABORATORIOS SYNTHESIS S.A.S. F. SOLICITAR, OBTENER, REVISAR Y MODIFICAR REGISTROS SANITARIOS. G. OBTENER ANTE LAS OFICINAS Y AUTORIDADES NACIONALES QUE CORRESPONDAN Y EN ESPECIAL DE LA DIVISIÓN DE PROPIEDAD INDUSTRIAL DE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, REGISTROS DE MARCAS, RENOVACIÓN DE REGISTROS MARCARIOS, ANOTACIÓN DE TRASPASOS Y CAMBIO DE NOMBRE, PRESENTACIÓN Y TRÁMITE DE OPOSICIONES, PRESENTACIÓN Y TRÁMITE DE RECURSOS POR LA VÍA GUBERNATIVA Y DEMÁS DILIGENCIAS RELACIONADAS, A CUYO EFECTO LA FACULTA PARA DAR ANTE DICHAS AUTORIDADES, PARA ELEVAR SOLICITUDES, FORMULAR DESCRIPCIONES, APELACIONES Y RECLAMOS, SOLICITAR TESTIMONIO, RECIBIR, DESISTIR, SUSTITUIR, CANCELAR, TRANSIGIR, RENUNCIAR, ACEPTAR NOTIFICACIONES Y NOMBRAR APODERADOS JUDICIALES Y EXTRAJUDICIALES. H. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. I. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES. J. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. K. PRESENTAR RECURSOS POR LA VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR. I. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES. M. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES. N. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA REPÚBLICA DE COLOMBIA.

CERTIFICA:

** REVISOR FISCAL **

QUE POR CERTIFICACION DE REVISOR FISCAL DEL 4 DE OCTUBRE DE 2011, INSCRITA EL 10 DE OCTUBRE DE 2011 BAJO EL NUMERO 01519171 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PRINCIPAL	
ARCILA SABOGAL DIANA YAMILE	C.C. 000000052828052

QUE POR DOCUMENTO PRIVADO DE REVISOR FISCAL DEL 6 DE FEBRERO DE 2012, INSCRITA EL 8 DE FEBRERO DE 2012 BAJO EL NUMERO 01605220 DEL LIBRO IX,

FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL SUPLENTE	
VILLATE AVENDAÑO MARIA PILAR	C.C. 000001053605913

QUE POR ACTA NO. 119 DE ASAMBLEA DE ACCIONISTAS DEL 22 DE JUNIO DE 2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397026 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PERSONA JURIDICA	
DELOITTE & TOUCHE LTDA	N.I.T. 000008600058134

CERTIFICA:

PERMISO DE FUNCIONAMIENTO:QUE POR RESOLUCION NO.05952 DEL 11 DE - JUNIO DE 1.985, INSCRITA EN ESTA CAMARA DE COMERCIO EL 8 DE JULIO DE 1.985 BAJO EL NO. 172.879 DEL LIBRO IX, LA SUPERINTENDENCIA - DE SOCIEDADES CONCEDIO PERMISO DEFINITIVO DE FUNCIONAMIENTO A LA SOCIEDAD.

CERTIFICA:

QUE POR RESOLUCION NO.09006 DEL 19 DE DICIEMBRE DE 1.986 SUPERIN-TENDENCIA DE SOCIEDADES INSCRITA EL 16 DE ENERO DE 1.987 BAJO EL NO.204.133 DEL LIBRO IX, SE AUTORIZO A LA SOCIEDAD PARA COLOCAR SETENTA Y CUATRO MIL ($74.000) ACCIONES DE LAS QUE TIENE EN RE-SERVA, A SU VALOR NOMINAL DE CIEN PESOS ($100.00) M/CTE., CADA UNA.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DE REPRESENTANTE LEGAL DEL 28 DE JUNIO DE 2011, INSCRITO EL 1 DE JULIO DE 2011 BAJO EL NUMERO 01492789 DEL LIBRO IX, SE COMUNICO QUE SE HA CONFIGURADO UNA SITUACION DE CONTROL POR PARTE DE LA SOCIEDAD MATRIZ: LABORATORIOS SYNTHESIS S A S, RESPECTO DE LAS SIGUIENTES SOCIEDADES SUBORDINADAS:

- SOCIEDAD PARA LA ENSEÑANZA DE LA HOMEOPATIA CLINICA S A S QUIEN SE IDENTIFICARA CON LA SIGLA S E C H

DOMICILIO: BOGOTA D.C.

FECHA DE CONFIGURACION DE LA SITUACION DE CONTROL : 2011-05-31

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DE REPRESENTANTE LEGAL DEL 9 DE MARZO DE 2011, INSCRITO EL 18 DE MARZO DE 2011 BAJO EL NUMERO 01462396 DEL LIBRO IX, COMUNICO LA SOCIEDAD MATRIZ:

- EUROPEAN CHEMICALS & CO

DOMICILIO: (FUERA DEL PAIS)

QUE SE HA CONFIGURADO UNA SITUACION DE CONTROL CON LA SOCIEDAD DE LA REFERENCIA.

CERTIFICA:

*** ACLARACIÓN SITUACIÓN DE CONTROL Y DE GRUPO EMPRESARIAL ***

SE ACLARA LA SITUACIÓN DE CONTROL Y GRUPO EMPRESARIAL INSCRITA CON EL NO. 01462396 DEL 9 DE MARZO DE 2011 DEL LIBRO IX EN EL SENTIDO DE

INDICAR QUE SE CONFIGURÓ DESDE EL 19 DE NOVIEMBRE DE 2010.

CERTIFICA:

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS:

NOMBRE : CARDIOPHARM
MATRICULA NO : 00537358 DE 3 DE MARZO DE 1993
RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012
ULTIMO AÑO RENOVADO : 2012

****

NOMBRE : GENERICS
MATRICULA NO : 00664623 DE 18 DE SEPTIEMBRE DE 1995
RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012
ULTIMO AÑO RENOVADO : 2012

****

NOMBRE : MASCOTT
MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995
RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012
ULTIMO AÑO RENOVADO : 2012

****

NOMBRE : ONCOPHARM
MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012
ULTIMO AÑO RENOVADO : 2012

****

NOMBRE : GASTROPHARM
MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012
ULTIMO AÑO RENOVADO : 2012

****

NOMBRE : GYNECOPHARM
MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012
ULTIMO AÑO RENOVADO : 2012

****

NOMBRE : ENTEROPHARM
MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012
ULTIMO AÑO RENOVADO : 2012

****

NOMBRE : EQUIPHARMA
MATRICULA NO : 00556630 DE 21 DE JULIO DE 1993
RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012
ULTIMO AÑO RENOVADO : 2012

****

CERTIFICA:

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

* * * EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE * * *
* * * FUNCIONAMIENTO EN NINGUN CASO * * *

SEÑOR EMPRESARIO, SI SU EMPRESA TIENE ACTIVOS INFERIORES A 30.000 SMLMV Y UNA PLANTA DE PERSONAL DE MENOS DE 200 TRABAJADORES, USTED TIENE DERECHO A RECIBIR UN DESCUENTO EN EL PAGO DE LOS PARAFISCALES DE 75% EN EL PRIMER AÑO DE CONSTITUCION DE SU EMPRESA, DE 50% EN EL

01

1188869344

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

30 DE MAYO DE 2012 HORA 09:32:55

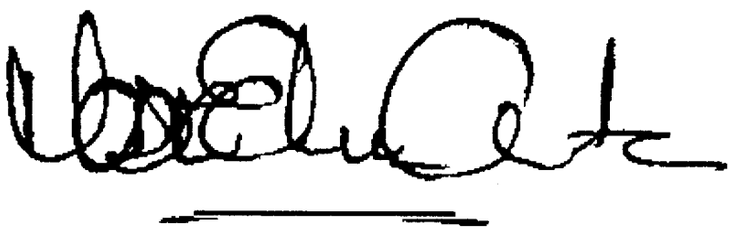
R034891996 PAGINA: 5 de 5

* *

SEGUNDO AÑO Y DE 25% EN EL TERCER AÑO. LEY 590 DE 2000 Y DECRETO 525 DE 2009.

RECUERDE INGRESAR A www.supersociedades.gov.co PARA VERIFICAR SI SU EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,
VALOR : $ 4,000
DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES



Tesa 200

Señor Director,

DIRECCIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente Nº 11 94674

Asunto : Oposición a la solicitud de patente de Invención titulada *"FORMULACIONES INYECTABLES DE TOXINA BOTULÍNICA"*

Solicitante : REVANCE THERAPEUTICS, INC

Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

Nº 640 del 15 de marzo de 2012

Yo, *ELIANA ISAURA MORENO BOHORQUEZ,* abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad LABORATORIOS SYNTHESIS S.A.S. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Bogotá, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada *"FORMULACIONES INYECTABLES DE TOXINA BOTULÍNICA",* cuyo titular es REVANCE THERAPEUTICS, INC , y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Carrera 13 Nº 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legitimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **TOXINA BOTULÍNICA**. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 28 de julio de 2011, reivindicando prioridad bajo la solicitud US20080142063 del 2008-12-31; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **Nº 640 del 15 de marzo de 2012**, cuya publicación internacional corresponde a la WO2010078242 del 2010-07-08

2.2. La solicitud colombiana **11 94674** objeto de la presente oposición, se refiere a composiciones inyectables novedosas con contenido de toxina botulínica, que pueden administrarse a un sujeto para varios propósitos terapéuticos, estéticos y/o

cosméticos. Composiciones inyectables que según el documento exhíben una o más ventajas sobre las formulaciones convencionales de toxina botulínica, incluyendo antigenicidad reducida, una menor tendencia a experimentar difusión localizada indeseada luego de la inyección, una mayor duración de la eficacia clínica o potencia mejorada relativa, manifestación más rápida de la eficacia clínica, y/o estabilidad mejorada.

2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: US2008107690 publicada el 08 de mayo de 2008.

2.4. El documento D1, particularmente en la descripción revela una composición para la aplicación tópica de una toxina botulínica (incluyendo los derivados de la toxina botulinum) que comprende una toxina botulínica y un vehículo o portador que comprende un esqueleto polimérico que comprende un polipéptido de cadena larga o un polímero no peptídico que tiene unidos grupos eficientes o ramificaciones cargadas positivamente. El documento D1 también se refiere a métodos para reducir la parálisis muscular y otras condiciones que pueden tratarse con una toxina botulínica, particularmente parálisis subcutánea, y más

particularmente, faciales, músculos, por aplicación tópica de una cantidad eficaz de la toxina botulínica y el portador, en conjunción, a la piel del sujeto o epitelio. Los kits para la administración también se describen en dicho documento D1. De manera mas explicita, el mismo documento D1 revela un método de administración de una toxina botulínica para lograr un efecto cosmético o terapéutico en un individuo que lo necesite, donde el método consiste en inyectar una cantidad efectiva de la composición al individuo, para lograr el efecto terapéutico o cosmético, donde la composición comprende un portador de carga positiva que comprende un esqueleto cargado positivamente con una pluralidad de grupos de eficiencia unido al mismo y una toxina botulínica, y en donde el portador cargado positivamente no está asociado de manera covalente con la toxina botulínica. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.5. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **11 94674** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con el mas importante de los tres requisitos necesarios para su protección, la novedad.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está*

comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.". A la fecha de prioridad, 31 de diciembre de 2008 ya era conocido, pues como se demostró, eran parte del arte anterior con base en el documento D1, composiciones inyectables con contenido de toxina botulínica, que pueden administrarse a un sujeto para varios propósitos terapéuticos, estéticos y/o cosméticos; sobre el cual busca protección en el capítulo reivindicatorio.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.*". La solicitud pretendida no cumple con en mas importante de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada "***FORMULACIONES INYECTABLES DE TOXINA BOTULÍNICA***", cuyo titular es REVANCE THERAPEUTICS, INC , solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial **Nº 640 del 15 de marzo de 2012**.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US2008107690 publicada el 08 de mayo de 2008.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

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Bogotá Colombia

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **LABORATORIOS SYNTHESIS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: US2008107690 publicada el 08 de mayo de 2008.

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6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor director,

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.