



No. 08-127744- -00002-0000

Fecha: 2009-07-31 14:47:16 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYII Eve: 378 FASENACIONAL I
Act. 400 OPOSIOBSERVTER Folios: 31

**FORMULARIO UNICO DE OPOSICION
2000-12**

1

OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

2

**SOLICITUD
PUBLICADA**

Número del expediente: 08-127744
Solicitante: SHERING PLOUGH HEALTHCARE PRODUCTS INC.
Apoderado: CARLOS R. OLARTE
Título de la nueva creación o denominación del signo:
"FORMA DE DOSIFICACIÓN FARMACEUTICA DE
LIBERACIÓN SOSTENIDA QUE CONTIENE FENILEFEDRINA"

Gaceta: 603 de 30-04-2009, Número de Publicación 41

3

OPOSICION PRESENTADA POR:

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	Domicilio: Cali - Valle		
REPRESENTANTE O APODERADO (74)	Nombre: Tito Noe Parra Murillo	IDENTIFICACION	
	Dirección: Calle 108 # 51-45	C.C. ☒	NIT ☐
	Teléfono: 7422525 Ext. 1111	C.E. ☐	Otro ☐
	E-mail:		
	Fax: 7424092	Número: 79'579.680 de Bogotá	
	Domicilio: Bogotá, D.C.	TP 71168	

4

FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000).

Justificación: VER ANEXO

TOTAL F
21
1

5

Comprobante de pago No. _____ (Oposición) Fecha _____

(Prórroga) Fecha _____

6

Anexos:

- ☒ Comprobante de pago de la tasa
- ☒ Poderes, si fuere el caso
- ☒ Pruebas de los fundamentos de la oposición
- ☒ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso
- ☒ Copia de la oposición para el traslado al solicitante.

7

NOMBRE: TITO NOE PARRA MURILLO

FIRMA: _____

C.C. No. 79.579.680 T.P. No. 71168

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-127744-00002-0000

Fecha: 2009-07-31 14:47:16 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 31

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 56,619
FECHA : JULIO 31 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAFRANCOL S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	95071443	30/07/2009	2,261,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	287,000.00
TOTAL :			\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S.D.

REF: Expediente: 08-127744

TÍTULO SOLICITADO: FORMA DE DOSIFICACIÓN FARMACÉUTICA DE
LIBERACIÓN SOSTENIDA QUE CONTIENE
FENILEFRINA.

PUBLICACIÓN: GACETA 603 del 30 de abril de 2009, N° de
publicación 41.

SOLICITANTE: SCHERING PLOUGH HEALTHCARE PRODUCTS
INC.

APODERADO: CARLOS R. OLARTE

TRÁMITE: PRESENTACIÓN DE OPOSICIÓN

TITO NOE PARRA MURILLO, mayor de edad y vecino de Bogotá, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 71168 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO COLOMBIANO S.A. LAFRANCOL S.A.**, sociedad constituida y vigente de conformidad con las leyes colombianas, con domicilio en Cali, Valle, en los términos y para los efectos del poder y del certificado de existencia y representación legal adjuntos, y estando dentro del plazo establecido por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito presentar oposición contra la solicitud de patente de invención indicada en el epígrafe.

I. PETICIÓN

Sírvase, señor Superintendente, proceder a negar el beneficio patentario a la solicitud contenida en el expediente 08-127744, por incumplir los requisitos materiales de patentabilidad establecidos en el Título II, Capítulo I de la Decisión 486 de 2000 de la Comisión de la Comunidad Andina. Lo anterior con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LABORATORIO FRANCO COLOMBIANO S.A LAFRANCOL S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría, en forma contraria al Régimen Común Andino de Propiedad Industrial, el empleo de ciertas sustancias y composiciones farmacéuticas, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud de la referencia incumple los requisitos materiales de patentabilidad establecidos en el Título II, Capítulo I de la Decisión 486 de 2000 de la Comisión de la Comunidad Andina, particularmente en materia de Novedad y Nivel Inventivo. Vale recordar que por Novedad se entiende aquella invención que no se encuentra comprendida dentro del estado de la técnica, siendo ésta última la que comprende 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 la patente. Con respecto al Nivel Inventivo, cabe señalar que dicho requisito se cumple cuando a una persona del oficio normalmente versada en la materia técnica correspondiente, no se le hubiese resultado dicha invención obvia o derivada de manera evidente del estado de la técnica.

Así, conforme con lo anterior, es imprescindible señalar que composiciones farmacéuticas de liberación sostenida de fenilefrina, las cuales pueden tener un agente activo adicional entre los que se encuentran antihistaminas como la Loratadina son totalmente comunes en la industria farmacéutica. No existe ninguna novedad sobre este precepto y mucho menos nivel inventivo. Como prueba de lo anterior, consideramos pertinente traer a colación la mención sobre la Loratadina que se hace en "The Merck Index" (Anexo), en el cual puede observarse que dicha molécula fue patentada en Estados Unidos de América en el año 1981 bajo el **No. 4, 282, 233**. Dicho así, es claro que no puede existir un beneficio patentario sobre una molécula que actualmente se encuentra bajo el conocimiento y dominio público.

Ahora bien, no sobra decir que las composiciones farmacéuticas de liberación sostenida de fenilefrina ni siquiera requieren prueba de utilización puesto que es evidente que es utilizada por innumerables empresas del sector farmacéutico. No obstante, consideramos pertinente mencionar las patentes estadounidenses **No. 4,816,264** (Marzo 28 de 1989) y **No. 4,623,664** (Noviembre 18 de 1986) (Anexos), con las cuales se puede constatar que la liberación sostenida y pulsada de fenilefrina es conocida desde hace bastantes años atrás en la industria farmacéutica. Con respecto a la primera patente, el titular WARNER-LAMBERT COMPANY accedió en el año 1989 al beneficio patentario sobre formulaciones de liberación sostenida, en las cuales se incluye en el acápite del núcleo, la fenilefrina como descongestionante. De esta forma, resulta inocuo pretender solicitar lo mencionado en el expediente de referencia, considerando que el tema es conocido públicamente y en consecuencia carente de novedad. Por otro lado, con respecto a la segunda patente, resaltamos que en el acápite de los antecedentes de la invención, se menciona la fenilefrina como sustancia conocida en el campo farmacéutico.

De esta forma, la presente solicitud no cumple con los requisitos esenciales para acceder al derecho patentario por cuanto no se encuentran presentes la novedad y el nivel inventivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho los artículos 16 y 18 de la Decisión 486 de 2000.

V. PRUEBAS

1. The Merck Index. "An encyclopedia of chemicals, drugs, and biologicals. Twelfth Edition. 1996. Página 5611. (LORATADINE)
2. United States Patent No. 4,623,664. Noviembre 18 de 1986. Titular: University of Iowa Research Foundation. Tomado de página web: <http://patft.uspto.gov>
3. United States Patent No. 4,816,264. Marzo 28 de 1989. Titular: WARNER-LAMBERT COMPANY. Tomado de página web: <http://patft.uspto.gov>

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

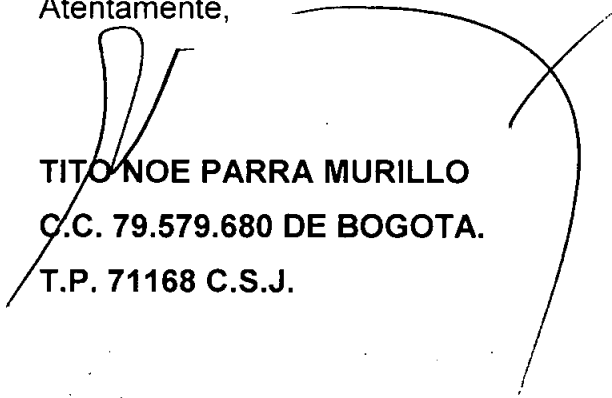
1. Poder para actuar.
2. Certificado de existencia y representación legal de LAFRANCOL S.A.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. Los mencionados en el acápite de pruebas.

VII. NOTIFICACIONES

Mi representada y el suscrito las recibiremos en la Secretaría de su Despacho, o en la sede de LAFRANCOL ubicada en la Calle 108 No. 51-45 de Bogotá D.C.

Señor Superintendente,

Atentamente,



TITO NOE PARRA MURILLO
C.C. 79.579.680 DE BOGOTA.
T.P. 71168 C.S.J.

USPTO PATENT FULL-TEXT AND IMAGE DATABASE

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(7 of 8)

United States Patent
Schoenwald , et al.

4,623,664
November 18, 1986

Oil suspended phenylephrine

Abstract

An oil suspension, preferably sesame seed oil suspension, of the base form of phenylephrine as an ophthalmic medicament. Surprisingly, the base form of phenylephrine is much quicker absorbed into the eye than the conventional acid salt form. As a result, lower dosage levels can be used to achieve the same mydriatic effect, thus reducing the risk of adverse side effects from systemic absorption.

Inventors: **Schoenwald; Ronald D.** (Iowa City, IA), **Chien; Du-Shieng** (Formosa, TW)

Assignee: **University of Iowa Research Foundation** (Iowa City, IA)

Appl. No.: **06/793,138**

Filed: **October 31, 1985**

Current U.S. Class: **514/653 ; 514/912**

Current International Class: **A61K 9/00 (20060101); A61K 31/135 (20060101); A61K 031/135 ()**

Field of Search: **514/653,912**

References Cited [Referenced By]**U.S. Patent Documents**

<u>1890860</u>	December 1932	Omohundro
<u>3149035</u>	September 1964	Riegelman
<u>3172816</u>	March 1965	Swintosky
<u>3515781</u>	June 1970	Steinberg
<u>3908017</u>	September 1975	Hussain et al.
<u>4001388</u>	November 1977	Shell
<u>4271143</u>	June 1981	Schoenwald et al.

4469706

September 1984

Nathanson

Other References

Handbook of Ocular Pharmacol., 2nd ed.--1978, p. 228, PSG Publishing Co., Inc.--Littleton, Mass. .

Ocular Pharmacol., 4th ed.--1978, pp. 236-238, The C. V. Mosby Co.--Saint Louis. .

Chem. Abst. 82: 116057(w) (1975)--Hardberger et al..

Primary Examiner: Robinson; Douglas W.

Attorney, Agent or Firm: Zarley, McKee, Thomte, Voorhees & Sease

Claims

What is claimed is:

1. An ocular dilating composition, comprising:

from about 0.5% by weight to about 5.0% by weight of the unionized base form of phenylephrine; and

a non-toxic pharmaceutically acceptable oil selected from the group consisting of mineral oil and edible vegetable oil, said composition providing unionized base form of phenylephrine to the eye for preferential absorption in comparison with acid and salt forms of phenylephrine.

2. The composition of claim 1 wherein the oil is a mineral oil.

3. The composition of claim 1 wherein the base form of phenylephrine is from about 0.5% by weight to about 5% by weight of said composition.

4. The composition of claim 1 which includes from 0.25% by weight to 0.5% by weight of an anti-bacterial agent.

5. The composition of claim 1 which includes from about 0.1% by weight to 0.05% by weight of an anti-fungal agent.

6. The composition of claim 1 which includes from about 0.1% by weight to about 0.05% by weight of an anti-oxidant.

7. The composition of claim 1 which includes from about 0.1% by weight to about 0.05% by weight of a preservative.

8. The composition of claim 1 wherein the oil is a vegetable oil.

9. The composition of claim 8 wherein the oil is sesame seed oil.

10. A method of ocular drug delivery of phenylephrine which has a base form and acid/salt form, which comprises:

placing said phenylephrine in its unionized base form;

suspending from about 0.5% by weight to about 5.0% by weight of said phenylephrine in a non-toxic pharmaceutically acceptable oil selected from the group consisting of mineral oil and edible vegetable oil; and

topically delivering a unit dose of said suspension which is unionized base form of phenylephrine to the eye for preferential absorption in comparison with acid and salt forms of said drug.

11. The method of claim 10 wherein said oil is a vegetable oil.

Description

BACKGROUND OF THE INVENTION

The present invention relates to a novel pharmaceutical composition containing the base form of phenylephrine. Phenylephrine has the formula 3-hydroxy-.alpha.-[(methylamino)methyl]benzyl alcohol.

Phenylephrine is a well-known pharmaceutically active amine whose principal use in the field of ophthalmology is as a mydriatic. There are, however, certain known disadvantages associated with the use of phenylephrine as a mydriatic agent. Those disadvantages, involving systemic side effects, have limited the use of this highly effective drug. Thus, in spite of the fact that it is one of the most effective mydriatics available, its use is significantly limited because of the significant side effects which may occur in some individuals treated with phenylephrine. Those unwanted significant side effects range from hypertension, syncope, and even in some cases to myocardial infarction, leading to death.

Phenylephrine HCl is a very hydrophilic drug used in the eye for its mydriatic and capillary decongestion effects. Because of its hydrophilic characteristics, it poorly penetrates the epithelium of the cornea, therefore, a relatively high concentration, 2.5% or 10%, must be applied to the eye topically to achieve a potent effect. As a result of applying a large dose which is poorly absorbed, the earlier mentioned significant systemic side effects may occur. However, because phenylephrine is such an effective mydriatic agent, despite the potential risk of adverse side effects, there is a continuing need for its use. In the past there have been some attempts to prepare prodrugs of phenylephrine in order to minimize the side effect risk. While the preparation of prodrugs is often advantageous, it is not without disadvantages from time to time. For example, there is an increased cost factor with the preparation of prodrugs of phenylephrine. Accordingly, it can be seen that there is a continuing and real need for a technique which allows one to use phenylephrine in a topical ocular dose form which maximizes mydriatic effectiveness so that lower levels of the active drug can be employed.

Clearly, then, there is a need to reduce the systemic side effects of phenylephrine. Theoretically this could be accomplished by increasing the ocular absorption and thereby reducing systemic absorption. However, the reduction in systemic side effects is an indirect effect of improved ocular absorption. This is exemplified by the fact that even though ocular absorption may double from 2 to 4%, systemic absorption decreases from 98% to only 96%, which is not a significant decrease with respect to systemic side effects. Nevertheless, by increasing the absorption two-fold, the dose can be reduced by one-half to achieve the same therapeutic effect and in this manner systemic effects can be reduced substantially.

This invention has as its primary objective the development of new and useful phenylephrine topical compositions which when used at mydriatically effective levels allow a lower dosage level to be

instilled in the eye, leading to decreased side effect risk.

Another objective of the present invention is to provide a safe and pharmaceutically effective mydriatic which is a combination of phenylephrine in the base form and a vegetable oil carrier.

Yet another objective of the present invention is to prepare a mydriatic composition for topical ocular treatment, useful in ophthalmic diagnosis and surgery, which uses phenylephrine in the base form, allowing it to be more effectively absorbed than in the acid form.

Another objective of the present invention is to provide an ocular composition which will allow phenylephrine to be used in its base form to produce a local or systemic physiological effect, similar to that achieved by much higher concentrations of acid or salt forms of phenylephrine.

An even further objective is to develop a drug delivery system for phenylephrine, adopted to improve the drug absorption, and yet maintain drug potency.

The method and manner of accomplishing these and other objectives of the present invention will become apparent from the detailed description which will follow hereinafter.

SUMMARY OF THE INVENTION

This invention relates to topical phenylephrine composition useful as a mydriatic. Phenylephrine, in its base form, is suspended in an oil suspension, either a mineral oil or vegetable oil. As a result, when used topically, the oil suspension overwhelms the buffer capacity of the tears, so that the base form actually raises the pH of the tears thereby promoting the formation of the un-ionized base form phenylephrine which is preferentially absorbed into the eye quicker than the ionized acid or salt form. Since the base form is more quickly absorbed across the cornea than the acid form, lower dosage levels can be used, reducing the risk of adverse systemic effects.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a pupil dilation study for phenylephrine base form in comparison with phenylephrine acid form at the same molar concentration, 0.045 molar, and in the same sesame oil vehicle.

FIG. 2 shows a comparison study of phenylephrine and phenylephrine hydrochloride in sesame oil at 0.115 molar concentrations.

FIG. 3 shows a similar study at 0.5 molar concentrations of phenylephrine base and phenylephrine acid form in sesame oil.

DETAILED DESCRIPTION OF THE INVENTION

One successfully obtains the objects of the present invention by preparing a topical ocular medicament containing phenylephrine in an oil suspension system. Importantly, the phenylephrine must be in the base form, as opposed to the acid or acid salt form. In other words, the phenylephrine must be in the un-ionized form. In the past phenylephrine has always been used in its salt form since the latter is soluble and stable in buffered aqueous vehicles. In fact, the use of the base form in buffered aqueous vehicles produces the same amount of ionized species as produced from the salt form. Regardless of the initial pH of the phenylephrine salt (or base) form in the aqueous solution, the buffer capacity of the tears would overwhelm the pH of the instilled aqueous drop and poor absorption would result. In the past it has been common to use nontoxic salt forms of phenylephrine prepared by reacting it with inorganic

acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, and the like. Such acid/salt forms can be used in aqueous systems or often in the form of a viscous gel for placement in the conjunctival sac. However, the amount of phenylephrine used in such acid systems must necessarily be high, i.e. up to 10%. Conventionally, it had been thought necessary to achieve an effective mydriosis to use the high concentration of the acid form to overcome both the known poor penetration characteristics of the epithelium of the cornea and the natural buffering effect of tears.

It has now been surprisingly found that the base form of phenylephrine can be used to provide mydriatically effective topical dose compositions. In accordance with this invention, while applicant does not wish to be bound by any theory, it is believed that the base form of phenylephrine suspended in an oil suspension simply overwhelms the buffer capacity of the tears. As a result there is a high available amount of un-ionized phenylephrine which is preferentially absorbed. This only occurs in an oil suspension, not in aqueous systems, where because of the buffer capacity of tears, the pH remains unchanged.

Generally it has been found that the topical compositions of this invention may be satisfactorily prepared using either a mineral oil or an edible vegetable oil. Preferred oil suspensions include the usual triglyceride vegetable oils, preferably the edible oils such as sesame seed oil, cottonseed oil, soybean oil, coconut oil, rapeseed oil, peanut oil, olive oil, palm oil, palm kernel oil, corn oil, castor oil, sunflower seed oil, wallflower oil, and pilchard oil. The preferred oil is sesame seed oil.

The dosage of phenylephrine in the mydriatic composition of the present invention can comprise from about 0.25% by weight of the composition up to about 10% by weight of the composition which is to be topically applied to the eye. Preferably the composition is from about 0.5% by weight of the phenylephrine up to about 5% by weight of the phenylephrine. The balance of the composition is primarily the oil. However, besides the drug itself, other typically state of the art formularies such as stabilizing agents, wetting agents, anti-oxidants, preservatives, etc. may be added. For example, one may use from 0.25% to 0.5% of an anti-bacterial agent (chlorobutanol), from 0.01% to 0.05% of an anti-fungal agent (propylparaben, methylparaben), from 0.01% up to 0.05% of a wetting agent (poloxamer series) and from 0.01% to 0.05% of an anti-oxidant (alpha-tocopherol, BHA and BHT).

The following examples are offered to further illustrate but not limit the formulations of the present invention.

EXAMPLE 1

Formation of Phenylephrine Base

Phenylephrine HCl (0.3 g, 1.47 mmole) was dissolved in 3 ml of water in a test tube to which was added 1 ml of ammonia T.S. The interior of the test tube was rubbed with a glass rod to initiate the precipitation of the free base. The phenylephrine was separated by filtration and washed with about 1 ml of ice-cold water and finally dried over silica gel for 16 hours. IR (KBr) measurements were made to confirm the preparation of the phenylephrine base.

EXAMPLE 2

Preparation of an Oil Suspension of Phenylephrine and Phenylephrine HCl

	Ingredients % (w/w composition)
	Phenylephrine or phenylephrine 1-10% HCl, U.S.P.

Pluronic P-103* 0.05% Chlorobutanol 0.025-0.5% Methylparaben 0.05% Propylparaben 0.01%
Alphatocopherol** 0.05% Sesame Oil qs 100%

*polyethylenepolypropylene glycol or poloxamer P103 (Wyandotte Corp., Wyandotte, Michigan) **or
other suitable oil soluble antioxidant, i.e., BHT 0.03% or BHA 0.02%

Preparation

The pluronic P-103 was added to phenylephrine or phenylephrine HCl and mixed well. Preferably, the drug powders are micronized. Each of the remaining ingredients were dissolved in about 80% of the sesame oil. If any of the ingredients are not fully dissolved, the sesame oil can be heated to about 50.degree. for a few minutes. Upon cooling, any residual particles will be dissolved. About 10% of the sesame oil was added to the pluronic-drug mixture and triturated until the powder was wetted and well dispersed. The remainder of the sesame oil was added with stirring or trituration to form the final product which is dispensed to the patient's eye in drop form. Both phenylephrine and phenylephrine HCl form suspensions in sesame oil.

EXAMPLE 3

Mydriatic Experiments

The right eye of a normal adult New Zealand Rabbit (3-4 months) was used to measure mydriasis. A flood of diffuse light was placed at a fixed distance from the rabbit eye. The initial pupillary diameter prior to administering eye drops was about 3-4 mm. Changes in pupil diameter were measured from photographs taken with a 35 mm single lens reflex camera equipped with a close-up lens. Pupil diameters were measured at time 0 through about 5 hours. A dosing volume of 10 .mu.l was administered to the right eye of a group of eight rabbits. A three day rest period was allowed between instillations of each formulation. Each rabbit received each formulation one time.

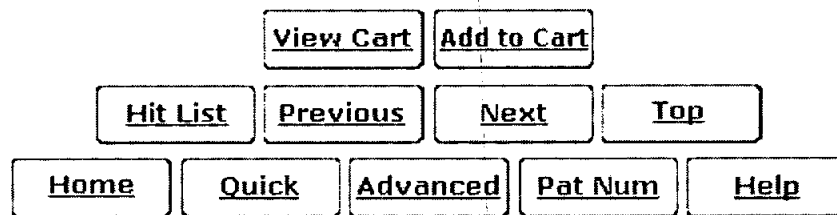
FIGS. 1-3 show the results of the tests demonstrated in Examples 1-3. There it can be seen that an equimolar concentration of phenylephrine and phenylephrine hydrochloride were compared at 0.045, 0.115 and 0.5 molar. These molarities represent 1, 2.5 and 10% w/v based upon phenylephrine hydrochloride. At each concentration, the phenylephrine base yielded a greater degree of mydriasis than the hydrochloride salt at all concentrations tested.

It can therefore be seen that one can now prepare topical ocular dose form compositions of phenylephrine containing *phenyleprine* at less than the ordinary 10% used in the acid form composition. Moreover, it is absorbed more quickly across the eye and achieves better dilation of the pupil than same level concentrations of the acid form. As a result, compositions can be dropped down in their phenylephrine content to within the range of from 1% to 5% and still get the same mydriatic effect as those now commercially utilized. Because the concentration level is lower, the systemic side effect risk is also lower.

While not yet having been tested, it is possible that this same drug delivery system will work for other ocular drugs such as sodium sulfacetamide, pilocarpine, epinephrine, and in particular, whenever a weak base or weak acid drug is used in concentrations above 1%. Thus it can be seen that the invention accomplishes all of its stated objectives.

* * * * *

Images



☒ [US Patent & Trademark Office, Patent Full Text and Image Database]				
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☒ [Image]				

(6 of 8)

United States Patent
Phillips , et al.

4,816,264
March 28, 1989

Sustained release formulations

Abstract

Drug delivery systems which exhibit sustained release properties when administered are produced using a "dual control" system which employs polymeric agents in core and membrane portions.

Inventors: **Phillips; Reginald** (Montclair, NJ), **Bikkina; Krishnayya** (Edison, NJ), **Khan; Sadath U.** (Mine Hill, NJ)

Assignee: **Warner-Lambert Company** (Morris Plains, NJ)

Appl. No.: **06/871,643**

Filed: **June 6, 1986**

Current U.S. Class: **424/468** ; 424/480; 424/482; 424/494; 424/495; 424/497; 427/2.19

Current International Class: A61K 9/20 (20060101); A61K 9/28 (20060101); A61K 009/22 (); A61K 009/36 (); A61K 009/16 ()

Field of Search: 424/472,468,480,482,494,495,497 427/3

References Cited [Referenced By]

U.S. Patent Documents

<u>4008719</u>	February 1977	Theeuwes et al.
<u>4014334</u>	March 1977	Theeuwes et al.
<u>4252786</u>	February 1981	Weiss et al.
<u>4309996</u>	January 1982	Theeuwes
<u>4320759</u>	March 1982	Theeuwes
<u>4389393</u>	June 1983	Schor et al.
<u>4434153</u>	February 1984	Urquhart et al.

4519801

May 1985

Edgren

4610870

September 1986

Jain et al.

Foreign Patent Documents

1568837

Jun., 1980

GB

Other References

"Coating of Tablets and Small Particles with Acrylic Resins by Fluid Bed Technology", K. Lehmann & D. Dreher, Int. J. Pharm. Tech. & Prod. Mfr., 2 (4) 31-43, (1981). .

"The Application and Processing of Acrylic Coatings in Form of Aqueous Dispersions Compared with Organic Solutions" Klaus Lehmann, Eripainos:Acta Pharmaceutica Fennica, No. 4/1982..

Primary Examiner: Lusignan; Michael

Attorney, Agent or Firm: Olevsky; Howard Daignault; Ronald A.

Claims

We claim:

1. In combination, a drug suitable for oral delivery and a delivery system for sustained release dosage of said drug comprising:

(a) a core portion containing about 70 to 90% by weight of the drug and an effective amount of a cellulosic gelling polymer; and

(b) a semipermeable membrane around said core containing effective amounts of a water soluble cellulosic polymer and a water insoluble acrylic polymer; said combination having 65 to 80% by weight drug and 20 to 30% by weight of the combination of gelling and membranal polymeric binders of the combination.

2. The delivery system of claim 1 whenever the core contains hydroxyethyl cellulose.

3. The delivery system of claim 2 wherein the drug is procainamide hydrochloride.

4. A process for producing solid dosage forms which exhibit sustained release properties when administered which comprises the steps of:

(1) producing a solid core containing effective amounts of at least one drug and at least one cellulosic gelling polymer, and

(2) coating the core of step (1) with at least one semipermeable coating which contains effective amounts of water soluble cellulosic and water insoluble acrylic polymer components.

5. The process of claim 4 wherein the gelling polymer comprises hydroxy ethyl cellulose.

6. The process of claim 4 wherein there is added the steps of:

(3) coating the product of step (2) with a polymeric color coat, and

(4) coating the product of step (3) with a polymeric clear coat.

7. The process of claim 6 wherein the gelling polymer comprises hydroxyethyl cellulose.

Description

BACKGROUND

The self-administration of oral dosage forms is fought with many non-compliance problems. While some patients do not like the taste or mouthfeel of certain dosage forms, others simply forget to take drugs or other orally-administered beneficial substances.

This invention deals with a dosage form which need be taken no more than twice in a twenty-four hour period. Optimally it need be administered only once a day.

THE INVENTION

It has been discovered that certain binders and coating systems, when used together, result in a "dual control" mechanism which prolongs the release of drugs and other beneficial substances for up to 12 hours and more.

In one preferred embodiment, procainamide hydrochloride is mixed with a hydrocolloid gelling polymer such as hydroxyethyl cellulose, and conventional additives such as sugar and fillers, and shaped into a core. This core is then coated with a semipermeable membrane containing a mixture of a hydroxypropyl cellulose polymer, Eudragit E30D (a 30% dispersion of methacrylate ester copolymer in aqueous media), conventional coating additives such as an antifoam agent, polyethylene glycol, and filler.

The core alone gives drug release in 8 to 9 hours. The core/membrane combination gives sustained release properties over a period of 12 hours or more.

In another embodiment, the coated sustained release product described above is further coated with a color coat and a clear coat.

ADVANTAGES

The invention has several advantages over other dosage forms. Primarily, it helps to assure patient compliance in the self-administration or oral dosages because only 1 or 2 dosages need be taken per day.

Secondly, the "dual" nature of the system virtually eliminates the likelihood that the drug or other bioaffecting agent will be "dumped" into the recipient's system soon after swallowing. The invention is of particular benefit in the administration of antiarrhythmics, antihypertussives and other drugs whose sustained action is important to their efficacy.

Other aspects and advantages of the invention will become apparent from the following description.

DESCRIPTION OF THE INVENTION

The heart of the invention is a delivery system for drugs or other beneficial agents. While the term "drug" is used, it should be noted that the invention is equally applicable to vitamins, minerals, and other beneficial agents to be discussed in greater detail infra. The delivery system of the invention contains two parts:

- (1) A tablet core produced by mixing drug and a gelling polymer shaping and hardening, pre drying, and
- (2) A semipermeable membrane or coating which surrounds the core.

It is the combination of a polymer-bound core and a polymeric membrane outside the core which results in the flow release of the active component(s) from the case of the delivery system. The resultant composite is then useful as an ingestible tablet or pellet.

THE CORE

The core portion of the novel dosage system contains at least one beneficial substance or drug and at least one gelling polymer.

By "beneficial substance," applicants mean any agent or combination of agents which, when absorbed by the body, evokes a response which mitigates against one or more disease states or symptoms or otherwise improves the health of the individual to whom it was administered. In general, any drug, pro-drug, vitamin, mineral or functionally equivalent substance can be used.

The drugs or other beneficial substances used herein may be selected from a wide variety of molecules and their acid addition salts. Both organic and inorganic salts may be used provided the drug maintains its medicament value and is soluble in the solvent. Exemplary acid salts include hydrochloride, hydrobromide, orthophosphate, benzoate, maleate, tartrate, succinate, citrate, salicylate, sulfate, and acetate.

Suitable categories of drugs that may be employed in the instant composite may vary widely and generally may include any stable drug combination. Illustrative categories and specific examples include:

- (a) Antitussives, such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, and chlophedianol hydrochloride;
- (b) Antihistamines, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, and phenyltoloxamine citrate,
- (c) Decongestants, such as *phenylephrine* hydrochloride, phenylpropanolamine hydrochloride, pseudophedrine, hydrochloride ephedrine; and
- (d) Various alkaloids, such as codeine phosphate, codeine sulfate and morphine.
- (e) Antihypertensives
- (f) Antiarrhythmics

(g) Antiinflammation agents

(h) Antibacterials

(i) Vitamins

(j) Mineral supplements, such as potassium chloride and calcium carbonates and the like. Mixtures are operable.

Useful drugs include, but are not limited to: procainamide, hydrochloride, meclofenamic acid, gemfibrozil, diphenhydramine, diphenhydramine HCl, and the like.

Mixtures of beneficial substances can be employed.

The gelling polymers used to bind the drug in the core portion are generally polymer materials which form gels or colloids. It is believed that this polymeric ingredient yields a gel within or adjacent to the core when it comes in contact with an aqueous media such as that inside a subject who ingests the dosage form.

Useful gelling polymers are those bearing molecular weight of about 270,000 to about 1,150,000, preferably about 860,000 to about 1,150,000. Furthermore, these polymers should have an intrinsic viscosity of from about 90 to about 4,000 cps, preferably about 1500, to 4000 cps, in about 1% aqueous solution.

Typically, these polymers are cellulosics, although a portion or all of any cellulosic gelling polymer can be replaced with one or more of such polymers as polyvinyl acetate phthalate, polyvinyl pyrrolidone, polyethylene oxide and the like.

Useful cellulosics include ethers, esters and gums. Thus, hydroxy ethyl cellulose (types H, HH, H4, MH, M,L) hydroxypropyl cellulose (types HF, EF, LF, MF), hydroxy propyl methylcellulose (types E4M, F4M, K4M, K15M, E15LV, XD), cellulose acetate phthalate, carboxymethyl cellulose, sodium carboxymethyl cellulose, and the like. Mixtures are operable.

The key feature of the gelling polymer is its solubility and its propensity to form a membrane in aqueous environments.

The core or central portion can also contain conventional excipients and additives which function to facilitate in processing and/or storage. Thus, colorants, colorants, flavors, perfumes, sweeteners, surfactants, lubricants, stabilizers and the like, as well as mixtures of two or more of these, can be employed.

Typically, the structure employed will comprise sugar. Some or all of the sugar may be replaced by at least one sugar substitute, e.g., aspartame, saccharin, or the like.

Fillers, when present, will be pharmaceutically acceptable. Various conventional additions, e.g. sugar, silica dioxide, magnesium stearate, and the like can be used herein. Thus, silicas of various kinds, e.g., colloidal silica and/or Cab-O-Sil are operable.

One or more lubricants, wetting agents, etc. can also be employed.

Magnesium stearate is one preferred component of the substrate part of the composite delivery system.

In the core portion, the drug content will be about 70 to about 90 wt %, preferably 76.9 to 83.3%.

SEMIPERMEABLE MEMBRANE

The outer shell or membrane adjacent to the central core of the instant delivery system contains a combination of at least two polymeric coating materials.

The first of such materials may be one of the gelling polymers employed in the core of the system. Thus, the cellulose and other vinyl polymers discussed above are operable. Cellulose are preferred. Hydroxypropyl cellulose is highly preferred.

The second polymeric material used in the semipermeable membrane is an aqueous dispersion resin of acrylic character. Preferred resins are the Eudragits.RTM. made by Rohm Pharma and the Aquacoats.RTM. made by FMC Corporation. Eudragit E30D.RTM. is highly preferred.

The membrane or outer coating layer may also contain a variety of convention excipients. Thus, antifoam agents, fillers, lubricants, colorants, surfactants, stabilizers, plasticizers, sweeteners, flavoring agents and the like and mixtures thereof may be employed.

Useful additions of this include Antifoam AF.RTM. made by Dow Chemical Co. polyethylene glycol 3550, Mistron.RTM. talc from Whittaker and the like.

The exterior or outer membrane can be the final coating applied to the dosage form. However, the use of one or more additional coating layers such as color coats, polishing coats, clear coats and other conventionally used coats is contemplated.

The final dosage form will be a solid orally-administrable form. While tablets or pills are preferred, the delivery system may comprise pellets, caplets and the like of oval, elliptical, spherical or other conventional shapes.

The final composition of the dosage form will be such that it will contain about 65 to about 80, preferably about 70.9 to about 77.0 weight percent drug, about 20 to about 30, preferably about 22.4 to about 28.6, binder component (including gelling and membranal polymeric binders) and about 2 to about 3 weight percent excipient(s).

Generally, the total film coat per tablet, in a tablet embodiment, will be from about 5 to about 10 wt %, preferably about 5 to about 6 wt %.

EXAMPLES

The following examples illustrate the invention:

EXAMPLES 1-3

Table I sets forth three preferred embodiments of compositions for tablet cores and film coatings produced in accordance with the invention.

TABLE I	Tablet Cores	Dose 500 mg	750 mg	1000 mg
	Procainamide Hydrochloride USP	76.90%	83.30%	
	83.30% Hydroxethyl Cellulose NF	2.60%	1.70%	1.70%
	Type 250 H NF Purified Water USP	q.s.	q.s.	

q.s. Silicon Dioxide, Colloidal NF 0.20% 0.20% 0.20% Magnesium Stearate, NF 0.30% 0.40% 0.40%
 Film Coat Composition Hydroxypropyl Cellulose NG 3.00% 3.00% 3.00% Antifoam 0.30% 0.30%
 0.30% Polyethylene Glycol 3350 NF 0.60% 0.70% 0.70% Eudragit E30D 25.00% 20.00% 20.00% Talc
 8.00% 6.00% 6.00% Purified Water 63.10% 70.00% 70.00% Total Film Coat Per Tablet 5.50% 6.00%
 5.50% w/w w/w w/w _____

EXAMPLE 4

This example illustrates the preparation of 500 mg procainamide hydrochloride tablets.

500.00 grams procainamide hydrochloride was passed through a Fitzmill #N00RH screen with impact at highspeed. The powder was loaded into a planetary mixer 130 grams hydroxy ethyl cellulose, type "H" was added and the powder was blended for 5 minutes to a loose density of 0.36g/ml.

A solution was made up using 17.00g or g.s. sugar and 20.00 ml or q.s. purified water. The blended powder mixture was granulated using this solution and additional water as needed. Core was taken not to over overwet the granulate.

The granulate was spread on paper-lined trays and dried overnight in forced air ovens at 50-55.degree. C. to a L.O.D. of about 0.6 (+-.0.3%).

The dried material was mixed with 1.00 g. colloidal silica, and 2.00g. magnesium stearate and passed through a Fitzmill #2A RH screen with knives at medium speed to give a final granulation have a loose density of 0.58 g/ml. This granulate was then tumble blended for 5 minutes in a P-K blender. 650 mg of the blended product was compressed in using 0.375".times.0.630" elliptical punches to yield elliptical tablets having 12-15 kp hardness and 0.290-0.294" thickness.

The coating of the cores produced above was carried out as follows:

A. Semipermeable membrane subcoat

The basic recipe calls for the use of 250 g. of solution to coat 1 kg. of tablets.

6.3 g of antifoam AF Emulsion was mixed well with 1325.1 g purified water. 12.6 g of polyethylene glycol 3350 was added and mixing continued until the PEG dissolved. 63.0 g. of hydroxypropyl cellulose was dispersed into the mixture and was allowed to hydrate with mixing for 30 minutes. 525.0 g. Eudragit E 30D was added and mixing continued at moderate speed. 168.0 g. of Mistron spray talc was added with continued mixing throughout the coating process. The subcoat, as first coat(ing) is then in place.

B. Color Coat

About 150 g. of color coating solution is needed to coat 1 kg of tablets. 2.52 g. antifoam emulsion and 1068.48 g. purified water was mixed to create a vortex. 189 g. Opadry yellow colorant was added slowly and mixed for 30 minutes.

C. Clear Coat

About 65 g. of clear coating solution is needed to coat 1 kg. of tablets. 0.1638 g. vanillin and 10.92 g. polyethylene glycol 3350 were dissolved in 507.62 g. purified water. 27.3 g. hydroxy ethyl cellulose was added and mixed until it dissolved.

APPLICATION OF COATINGS

Typically, the coating are applied to cores in quantities of about 5 to 6 wt. % sub-coat, followed by about 2 to 2.5 wt. % color coat and about 0.5 wt. % clear coat using a 24" Accela Cota pan and the following parameters:

	COLOR	CLEAR	SUB-COAT	COAT	COAT
	Pan Load (kg)	6 to 8	6 to 8	6 to 8	Pan Speed (rpm) 14
14 14	Inlet Air Temp. (.degree.C.)	60-80	60-80	60-80	Tablet Bed Temp. (.degree.C.) 36-38 37-39 37-39
Fluid Nozzle L3B L3B L3B	Air Nozzle	66 PD	66 PD	66 PD	Atomizing Pressure (psi) 40 40 40
Cylinder Pressure (psi)	50 50 50	Spray Rate (ml/min)	25-40	20-30	20-30

The resultant tablets were ellipitical in shape, had a vanillin odor and a yellow color.

EXAMPLE 5

Using similar procedures to those and in Example 4 tablets were made using the following compositions.

Tablet Core Compositions (1000 tablets) _____ Procainamide Hydrochloride USP 750.00 g Hydroxyethyl Cellulose NF, Type "H" q.s. or 130.00 g Sugar, Granulated NF Special (Bottler's Grade) 15.00 g Purified Water USP q.s. or 30.00 ml Silicon dioxide, Colloidal NF/Cab-O-Sil M-5 2.00 g Magnesium Stearate, NF - Mallinkrodt q.s. or 3.00 g 900.00 g

TABLET COATING COMPOSITIONS

_____ A. Sub-Coat Hydroxypropyl Cellulose NF 3.0 q.s. Antifoam AF Emulsion, Medical 0.3 q.s. Polyethylene Glycol 3350 NF 0.7 q.s. Eudragit E30D 20.00 q.s. Mistron Spray Talc 6.00 q.s. Purified Water USP 70.00 q.s. To Make About: 954.00 g B. Color Coat: Opadry Orange YS-1-2563 15.00 q.s. Antifoam AF Emulsion, Medical 0.20 q.s. Purified Water USP 84.80 q.s. To Make About 973.10 g C. Clear Coat: Vanillin USP 0.03 q.s. Hydroxyethyl Cellulose NF, Type L 5.00 q.s. Polyethylene Glycol 3350 NF 2.00 q.s. Purified Water USP 92.97 q.s. To Make About 978.00 g _____

EXAMPLE 6

Using procedures similar to those used in Example 4, one thousand tablets were made using the following compositions:

_____ Tablet Cores: Procainamide Hydrochloride USP 1000.00 g Hydroxyethyl Cellulose NF, Type "H" q.s. or 173.30 g Sugar, Granulated NF, Special (Bottler's grade) 20.00 g Purified Water USP q.s. or q.s. or 40.00 ml Silicon dioxide, Colloidal NF/Cab-O-Sil M-5 q.s. 2.70 g Magnesium Stearate, NF - Mallinkrodt q.s. or 4.00 g To Make: 1200.00 g _____

TABLET FILM COATINGS: Wt. %

_____ A. Sub-Coat: Hydroxypropyl Cellulose NF 3.0 q.s. Antifoam AF Emulsion, Medical 0.3 q.s. Polyethylene Glycol 3350 NF 0.7 q.s. Eudragit E30D 20.0 q.s. _____

EXAMPLE 7

TABLET CORES:

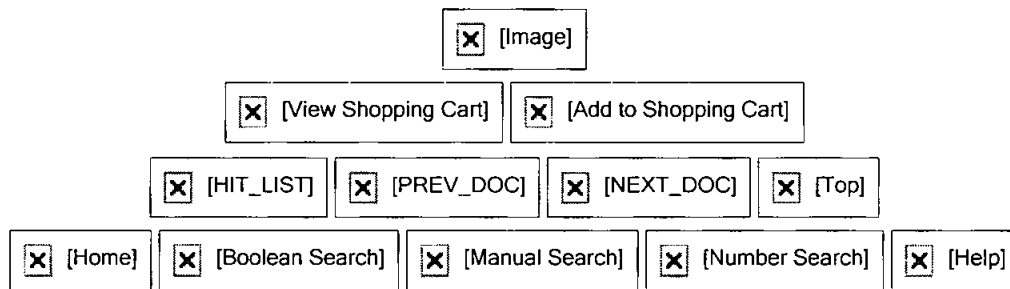
TABLET FILM COATING: Wt %

EXAMPLE 8

The results of the study are given in Table II.

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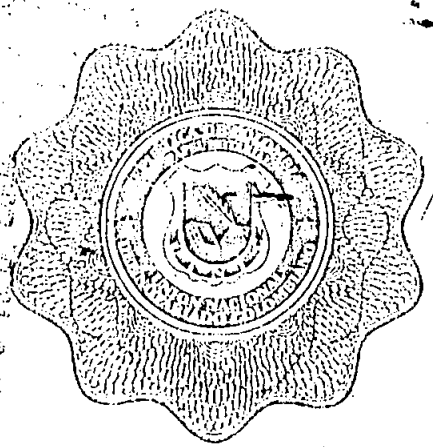
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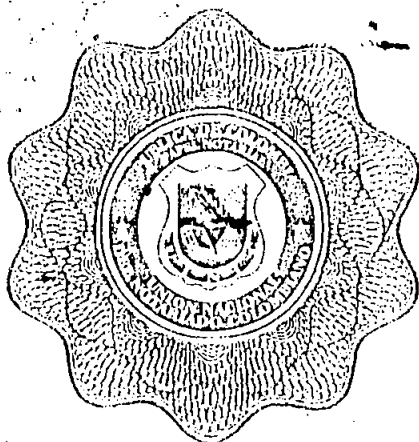
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DEL DOS MIL DOS (2002). - - - - -
ACTOS: PODER GENERAL. - - - - -
OTORGADO POR: LAFRANCOL S.A. SOCIEDAD DEBIDAMENTE
REPRESENTADA POR JUAN MARIA RENDON GUTIERREZ. - - - - -
A: TITO NOE PARRA MURILLO. - - - - -
EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL,
DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA,
ANTE MI, DIANA BEATRIZ LOPEZ NOTARIA TREINTA Y TRES
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QUE SE CONSIGNA EN LOS SIGUIENTES TERMINOS: - - - - -
COMPARECIERON: JUAN MARIA RENDON GUTIERREZ, mayor de
edad, vecino de Bogotá, identificado con la cédula
de ciudadanía número 17.125.100 de Bogotá
manifestó: - - - - -
PRIMERO.- Que obra en su carácter de Representante
Legal en nombre y representación de LAFRANCOL S.A. sociedad
comercial organizada y existente conforme a las leyes
colombianas, con domicilio y sede principal en Cali,
constituida mediante escritura pública número mil
cuatrocientos treinta y cuatro (1434) de la Notaria Cuarta
(4ª) de Cali del veintinueve (29) de septiembre de mil
novecientos cincuenta y ocho (1958), reformada en distintas
oportunidades, según consta en el certificado expedido por
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17 JUL 2002
DIANA BEATRIZ LOPEZ
NOTARIA

COPIA
BOGOTA D.C.

instrumento, concede **PODER GENERAL**, amplio y suficiente a **TITO NOE PARRA MURILLO**, mayor de edad, soltero, vecino de Bogotá, identificado con la cédula de ciudadanía número 79.579.680 de Bogotá, abogado en ejercicio, portador de la T.P. No. 71168 del C.S.J., domiciliado en Bogotá D.C., República de Colombia, con dirección en Diagonal 107 # 36 - 45 de la misma ciudad, como su representante con poder general amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de **LAFRANCOL S.A.**, a cuyo efecto lo autorizo, para que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las del orden administrativo, contenciosos - administrativo y judicial, en todo lo concerniente a los siguientes asuntos: - - - - -

a) En cuanto a marcas, lemas, enseñas comerciales, depósito de nombres comerciales, diseños industriales y modelos de utilidad, patentes de invención y derechos de autor para que solicite su registro o depósito, lleve los procesos respectivos hasta su culminación, haga solicitudes, solicite traspasos, cesiones, modificaciones o correcciones, solicite prórrogas, preste caución, solicite renovaciones, inscriba afectaciones, acuerdo comercialización y licencias de uso, desista de solicitudes, presente derechos de petición, responda cualquier requerimiento o auto, presente recursos, presente demandas, intervenga en procesos administrativos y jurisdiccionales, asista audiencias, presente



y solicite pruebas, conteste demandas, proteja en general los derechos y prioridades, formule observaciones, presente acciones de oposición, de cancelación,

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b) Para que en todos los asuntos arriba determinados, tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C. y normas pertinentes del Código Contencioso Administrativo, pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos, de todos los asuntos antes mencionados que se tramitar ante la Superintendencia de Industria y Comercio, los Tribunales Contencioso Administrativos, Consejo de Estado y jurisdicción penal, civil o comercial. - - - - -

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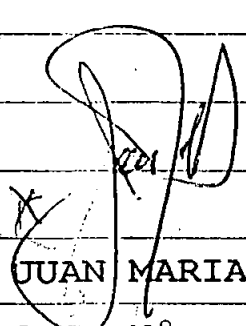
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17 JUL 2009

NOTARIA TREINTA Y TRES
BOGOTÁ D.C. COLOMBIA
DIANA BEATRIZ LOPEZ
NOTARIA

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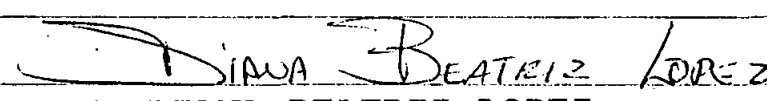

JUAN MARIA RENDON GUTIERREZ

C.C. N°.

TEL. N°.

LAFRANCOL S.A.

NIT. -


DIANA BEATRIZ LOPEZ


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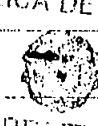
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33 ★  ★ 33

DIANA BEATRIZ LOPEZ
NOTARIA



REPUBLICA DE COLOMBIA
CERTIFICADO DE EXISTENCIA Y REPRESENTACION
EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE CALI

CERTIFICA

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL : ---K 1 46 84
DIRECCION NOTIFICACION JUDICIAL: ---K 1 46 84
CIUDAD: CALI
MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTUBRE DE 1958
DIRECCION ELECTRONICA : lafrancolsa@lafrancol.co
DIRECCION WEB : www.lafrancol.com
AFILIADO

CERTIFICA

NIT : 890301463-8

CERTIFICA

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI
, INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL
LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL
S.A.

CERTIFICA

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.INS	LIBRO
E.P. 1104	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	19467	
E.P. 2309	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	20089	
E.P. 1725	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	24528	
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	26360	
E.P. 2422	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963	26717	
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964	28406	
E.P. 101	31/01/1966	NOTARIA CUARTA DE CALI	01/02/1966	31039	
E.P. 552	21/03/1968	NOTARIA CUARTA DE CALI	01/04/1968	35711	
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI	16/01/1973	2975	IX
E.P. 1956	30/05/1973	NOTARIA CUARTA DE CALI	13/06/1973	4337	IX
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI	28/11/1973	5994	IX
E.P. 5579	12/11/1973	NOTARIA CUARTA DE CALI	28/11/1973	5995	IX
E.P. 4406	30/09/1974	NOTARIA CUARTA DE CALI	28/11/1974	10887	IX
E.P. 192	03/02/1978	NOTARIA CUARTA DE CALI	14/02/1978	25355	IX
E.P. 3479	07/09/1979	NOTARIA CUARTA DE CALI	19/09/1979	34204	IX
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E.P. 1155	21/05/1985	NOTARIA SEPTIMA DE CALI	03/06/1985	76917	IX
E.P. 1553	20/06/1986	NOTARIA SEPTIMA DE CALI	08/07/1986	85997	IX
E.P. 1458	09/06/1987	NOTARIA SEPTIMA DE CALI	24/12/1987	3508	IX
E.P. 7222	14/12/1988	NOTARIA TERCERA DE CALI	19/12/1988	13847	IX
E.P. 4530	04/09/1989	NOTARIA TERCERA DE CALI	07/09/1989	21508	IX
E.P. 3865	02/08/1990	NOTARIA TERCERA DE CALI	13/08/1990	31708	IX
E.P. 8305	13/12/1995	NOTARIA TERCERA DE CALI	23/01/1996	557	IX
E.P. 4559	16/11/1999	NOTARIA TERCERA DE CALI	26/11/1999	7911	IX

E.P. 6.004	02/12/2004	NOTARIA TERCERA DE CALI	14/12/2004	13371	IX
E.P. 6241	27/12/2006	NOTARIA TERCERA DE CALI	19/01/2007	625	IX
E.P. 389	07/02/2008	NOTARIA TERCERA DE CALI	19/02/2008	1880	IX
E.P. 1907	11/05/2009	NOTARIA TERCERA DE CALI	26/05/2009	5950	IX

CERTIFICA

VIGENCIA: 29 DE SEPTIEMBRE DEL AÑO 2057

CERTIFICA

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISIOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES, ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DOS (2) AÑOS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTES: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTES: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMMLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL

DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS. EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

GERENTE GENERAL Y REPRESENTANTE LEGAL
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

PRIMER SUPLENTE DEL GERENTE
THER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE
ROBERTO M. VENTURA CRISPINO
C.C.9086003

CERTIFICA

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2032 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE
JAN PABLO REYES VILLAMIZAR
C.C.80419709

CERTIFICA

DOCUMENTO: ACTA No. 112 DEL 25 DE MARZO DE 2008
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 03 DE MARZO DE 2009 No. 2453 DEL LIBRO IX

FUE (RON) _NOMBRADO (S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

SEGUNDO RENGLON

ROSA VICTORIA VENTURA DE VISBAL

C.C.38992048

TERCER RENGLON

CARLOS ANTONIO ESPINOSA PEREZ

C.C.16684716

SUPLENTE

PRIMER RENGLON

JUAN MARIA RENDON GUTIERREZ

C.C.17125100

SEGUNDO RENGLON

ROBERTO M. VENTURA CRISPINO

C.C.9086003

TERCER RENGLON

ISABEL CRISPINO DE VENTURA

C.C.29402071

CERTIFICA

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE (RON) NOMBRADO (S) :

REVISOR FISCAL

ALFREDO LOPEZ & CIA. LTDA

NIT.800026893-5

CERTIFICA

DOCUMENTO: DOCUMENTO PRIVADO DEL 08 DE MAYO DE 2008

ORIGEN: ALFREDO LOPEZ & CIA LTDA

INSCRIPCION: 23 DE MAYO DE 2008 No. 5771 DEL LIBRO IX

FUE (RON) NOMBRADO (S) :

REVISOR FISCAL PRINCIPAL
ALFREDO LOPEZ CAMPO
C.C.8241912

REVISOR FISCAL SUPLENTE
ANDERSON DAVID RODRIGUEZ REYES
C.C.16916373

CERTIFICA

CAPITAL AUTORIZADO: \$10,000,000,000
NUMERO DE ACCIONES: 1,000,000,000
VALOR NOMINAL: \$10
CAPITAL SUSCRITO: \$7,500,000,000
NUMERO DE ACCIONES: 750,000,000
VALOR NOMINAL: \$10
CAPITAL PAGADO: \$7,500,000,000
NUMERO DE ACCIONES: 750,000,000
VALOR NOMINAL: \$10

CERTIFICA

DOCUMENTO: DOCUMENTO PRIVADO DEL 30 DE ABRIL DE 2004
INSCRIPCION: 03 DE MAYO DE 2004 No. 4859 DEL LIBRO IX

DOCUMENTO: DOCUMENTO PRIVADO DEL 29 DE ABRIL DE 2005
INSCRIPCION: 06 DE MAYO DE 2005 No. 4983 DEL LIBRO IX

DOCUMENTO: DOCUMENTO PRIVADO DEL 15 DE JUNIO DE 2006
INSCRIPCION: 21 DE JUNIO DE 2006 No. 7526 DEL LIBRO IX

DOCUMENTO: DOCUMENTO PRIVADO DEL 01 DE NOVIEMBRE DE 2006
INSCRIPCION: 28 DE NOVIEMBRE DE 2006 No. 13380 DEL LIBRO IX

DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE DICIEMBRE DE 2006
INSCRIPCION: 21 DE DICIEMBRE DE 2006 No. 14301 DEL LIBRO IX

DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE DICIEMBRE DE 2007
INSCRIPCION: 21 DE DICIEMBRE DE 2007 No. 13604 DEL LIBRO IX

CONSTA EL GRUPO EMPRESARIAL:

CONTROLANTE
LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
IT. 890301463-8

DOMICILIO: CALI VALLE
NACIONALIDAD: COLOMBIA

ACTIVIDAD: A) LA FABRICACION, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACIÓN DE CASAS FABRICANTES NACIONALES O EXTRANJERAS

DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACIÓN, DISTRIBUCIÓN Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACIÓN DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PUEDE LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAÍCES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAÍCES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD, DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

SUBORDINADA

AMERICAN GENERICS S A

NIT. 800223214-9

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTÍCULO 27 DE LA LEY 222.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LAFRANCOL INTERNACIONAL S.A.

NIT. 815003912

DOMICILIO: PALMIRA VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. POSEE EL 40% Y LABORATORIOS PAULY PHARMACEUTICAL S.A. POSEE EL 40% Y AMERICAN GENERICS S.A. POSEE EL 19.97%

ACTIVIDAD: REALIZACIÓN DE ACTIVIDADES DESDE LA ZONA FRANCA, LAS CUALES CONSISTEN EN LA PRESTACIÓN DE TODO TIPO DE SERVICIOS ASÍ COMO DISTRIBUIR, VENDER, COMPRAR, IMPORTAR, EXPORTAR Y ALMACENAR TODO TIPO DE MATERIAS PRIMAS, PRODUCTOS TERMINADOS Y SEMITERMINADOS RELACIONADOS CON LA INDUSTRIA DE ALIMENTOS, COSMÉTICA Y FARMACÉUTICA.

SUBORDINADA

LAFRANCOL PERÚ S.A

DOMICILIO: LIMA LIMA

NACIONALIDAD: PERU

PRESUPUESTO DE CONTROL: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. POSEE EL 93.0%

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LABORATORIOS PAULY PHARMACEUTICAL S A

NIT. 800097402-6

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTÍCULO 27 DE LA LEY 222.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO

SUBORDINADA

LAFRANCOL (USA) CORP

DOMICILIO: ESTADOS UNIDOS

NACIONALIDAD: ESTADOS UNIDOS

PRESUPUESTO DE CONTROL: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. POSEE EL 65.25%

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

GAMAR SOCIEDAD LIMITADA

NIT. 890312050-7



DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL E, ARTICULO 27 DE LA LEY 222.

ACTIVIDAD: TODAS LAS ACTIVIDADES RELACIONADAS CON LAS ARTES GRAFICAS.

SUBORDINADA

LAFRANCOL GUATEMALA S.A.

NIT. 4088707

DOMICILIO: GUATEMALA

NACIONALIDAD: GUATEMALA

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTICULO 27 DE LA LEY 222

ACTIVIDAD: PRODUCCIÓN, FABRICACIÓN, EXPORTACIÓN Y DISTRIBUCIÓN DE PRODUCTOS FARMACÉUTICOS Y/O ALIMENTICIOS Y NATURALES DE CONSUMO HUMANO Y LA COMERCIALIZACIÓN DE TODA CLASE DE MERCANCÍAS POR CUENTA PROPIA O EN NOMBRE DE TERCEROS.

SUBORDINADA

DISTRIBUCIONES UQUIFA LTDA

NIT. 800182021-7

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTICULO 27 DE LA LEY 222

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS Y ALIMENTOS FUNCIONALES DE CONSUMO HUMANO

SUBORDINADA

LABORATORIOS NATURMEDIK S A

NIT. 800226363-1

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTICULO 27 DE LA LEY 222.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE CONSUMO HUMANO.

SUBORDINADA

FOCUS PHARMACEUTICAL

NIT. 900104555

DOMICILIO: BOGOTA DISTRITO CAPITAL

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTICULO 27 DE LA LEY 222.

ACTIVIDAD: DESARROLLO, FABRICACIÓN O PRODUCCIÓN, DIRECTAMENTE O A TRAVÉS DE TERCEROS EN CUALQUIER MODALIDAD NEGOCIAL, LA COMERCIALIZACIÓN Y DISTRIBUCIÓN NACIONAL O INTERNACIONAL, DE TODA CLASE DE ARTÍCULOS DE GÉNERO FARMACÉUTICO, ESPECÍFICAMENTE DE MEDICAMENTOS.

SUBORDINADA

LAFRANCOL DOMINICANA S.A.

DOMICILIO: SANTO DOMINGO REPUBLICA DOMINICANA

NACIONALIDAD: REPUBLICA DOMINICANA

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTICULO 27 DE LA LEY 222.

ACTIVIDAD: FABRICACIÓN DE PRODUCTOS FARMACÉUTICOS.

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO. 5234-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL

UBICADO EN: ---K 1 46 84 DE CALI

RENOVO : POR EL AÑO 2009

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.369809-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S A UBICADO EN: --K 1 46A 70 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL AÑO 2009

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.369810-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S A UBICADO EN: ---K 1A 46 A 32 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL AÑO 2009

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734908-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A UBICADO EN: CRA. 1A NRO. 46A 28 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734911-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A UBICADO EN: CRA. 1B NRO. 46A 121 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734913-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A UBICADO EN: CRA. 3 NRO. 47 25 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 25 DE MARZO DE 2009

CERTIFICA

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.

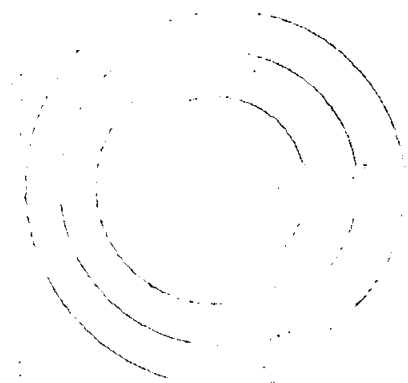
LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.



DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.
DADO EN CALI A LOS 18 DIAS DEL MES DE JUNIO DEL AÑO 2009 HORA: 12:59:58

EL SECRETARIO

[Handwritten signature]



CAMARA
DE COMERCIO
DE CALI