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Superintendencia de Industria y Comercio

Radicado: 15287641 **Folios:** 39

Dependencia: Paten **Fecha:** 2016-09-08 11:12:33

Tipo aplicación: Documentos independientes

T. P.

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

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

Número de expediente: 15-287641

Solicitante : MABXIENCE S.A.

Apoderado: JUAN PABLO CADENA SARMIENTO

Título de la Nueva Creación: FORMULACIONES ALTERNATIVAS PARA POLIPEPTIDOS DE FUSION
TNFR:Fc

Gaceta: 764 DEL 20/MAY/2016 PUBLICACION 845.

2. Datos del Opositor

☐ Persona Natural ☒ Persona Jurídica

LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.

Nombre o denominación /Razón social completa

TITO NOE PARRA MURILLO

Nombre del representante legal

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

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3. Datos del representante o apoderado:

PARRA MURILLO TITO NOE

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Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección del representante

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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 d-e poder general

TOTAL 39

4. Fundamentos de la oposición

Causal: VER ANEXO

Justificación: VER ANEXO

Prórroga:SI X NO

5. Anexos

Comprobante de pago de la tasa para la presentación de la oposición No. 16-0075528 de 3/AGO/16
Poder, si fuere el caso con el que se acredita la representación .

☐ Anexo indicativo de las clases contra las cuales presenta oposición

☐ Pruebas como sustento de la oposición

☐ Copias para el traslado de la oposición. Se anexan 9 folios (Obligatorio indicar cuántos)

☐ Comprobante de pago de tasa por solicitud de prórroga

Comprobante de pago por invocación de notoriedad

Copia de la solicitud y sus anexos en medio magnético.

6. Firma	
TITO NOE PARRA MURILLO	
Nombre del Firmante	Firma
79.579.680 DE BOGOTA	71168 C.S.J.
C.C	Tarjeta Profesional

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



RECIBO DE CAJA

No. 16 - 0075528

Bogotá D.C., Agosto 03 de 2016 - 15:04:06

RECIBIDO DE : LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. - LAFRANCOL S.A. NI 890.301.463

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	750232372	02/08/2016	12.900.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	1632 OPOSICION NUEVA CRACION / PRESENTACION	430.000.00	430.000.00
			\$430.000.00

SON: **CUATROCIENTOS TREINTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

Superintendencia de Industria y Comercio



Radicado: 15287641

Folios : 39

Dependencia: Paten Fecha: 2016-09-08 11:12:33

Tipo aplicación: Documentos independientes

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, Agosto 3 de 2016 - 15:04:09

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

REF:	Expediente: 15 - 287641
TÍTULO SOLICITADO:	FORMULACIONES ALTERNATIVAS PARA POLIPÉPTIDOS DE FUSIÓN TNFR:Fc
PUBLICACIÓN:	GACETA 764 del 20 de junio de 2016, N° de publicación 845.
SOLICITANTE:	MABXIENCE, S.A.
APODERADO:	JUAN PABLO CADENA SARMIENTO
TRÁMITE:	PRESENTACIÓN DE OPOSICIÓN

TITO NOÉ 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.S. LAFRANCOL S.A.S.**, 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 15 - 287641, 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.S. LAFRANCOL S.A.S.**, 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 TÉCNICOS DE LA OPOSICIÓN¹

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, estos son: Novedad, Nivel Inventivo y Aplicación Industrial. 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. Por último, se entiende que una aplicación es susceptible de aplicación industrial cuando su objeto puede ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva.

a. Antecedentes Generales de la Solicitud de Patente

La solicitud de patente relativa al **Expediente N° 15 - 287641**, señala la siguiente prioridad: EP20130166228 del **02/05/2013**.

Esta solicitud de patente pretende proteger en Colombia, **una composición acuosa**, que comprende: un **polipéptido aislado que es una parte que se une a un ligando extracelular de un receptor del factor de necrosis tumoral humano de p75 fusionado a la región Fe de una IgG1 humana**; una **sal presente a una concentración de desde 80 a 130 mM**; y un **tampón acuoso**, en donde el tampón acuoso es tampón de **fosfato de sodio y/o potasio** y en donde el tampón acuoso está presente a una concentración de **20 a 30 mM**; y un **excipiente que es sacarosa** en donde la concentración de sacarosa está **entre 34-80 mg/mL**, caracterizada porque **ni la arginina ni la cisteína se encuentran presentes en la composición**.

Asimismo, la solicitud reivindica una composición acuosa, caracterizada porque comprende: un **polipéptido aislado** que es una parte que se une a un ligando extracelular de un receptor del factor de necrosis tumoral humano de p75 fusionado a la región Fe :le una IgG1 humana; **una sal** presente a una

¹ Informe Técnico elaborado por Q.F. Natalia Soto T., Departamento de Propiedad Industrial – CFR

concentración de desde 80 a 130 mM, en donde la sal no está presente en una concentración de 100 mM; **un tampón acuoso**, en donde el tampón acuoso es **tampón succinato**; y **un excipiente** seleccionado entre el grupo de **trehalosa y sacarosa o una combinación de éstas**, caracterizada porque **el aminoácido libre no se encuentra presente en la composición**. Se indica que dicha sal es **cloruro de sodio**, y que el polipéptido aislado es **etanercept**.

Particularmente, se señala que **el tampón acuoso está presente a una concentración de 15mM a 100mM**, y que **el excipiente es sacarosa presente a una concentración de desde 5 a 80 mg/mL**.

La solicitud también señala que **el pH de la composición es de pH 6.0 a pH 7.0**.

De manera más específica, la solicitud reivindica una composición como cualquiera de las antes descritas, caracterizada porque comprende **50 mg/mL de etanercept, 22 mM de succinato, 90 mM de NaCl, 10 mg/mL de sacarosa, en donde el pH de la composición es pH 6.3**. Asimismo, la solicitud reivindica una composición caracterizada porque comprende **50 mg/mL de etanercept, 25 mM de tampón fosfato de sodio, 90 mM de cloruro de sodio, 34 mg/mL de sacarosa, en donde el pH de la composición es pH 6.3**.

En la memoria descriptiva, la solicitud señala que **la concentración del polipéptido aislado es preferentemente de 10 a 100 mg/mL**, más preferentemente entre 20 y 60 mg/mL, y aún más preferentemente la concentración es alrededor de **25 a 50 mg/mL**. De preferencia, la concentración es **aproximadamente 50 mg/mL**.

Todo lo publicado antes del **02/05/2013** es parte del estado de la técnica.

b. Antecedentes que respaldan nuestra oposición a la Solicitud de patente relativa al Expediente N° 15 - 287641.

1. WO 2011/141926 del 17/11/2011.

"Liquid formulation of polypeptides containing an Fc domain of an immunoglobulin".

Prioridad: IN2010MUM1465 del **10/05/2010**.

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **formulación farmacéutica que comprende un polipéptido que contiene un dominio Fc de una inmunoglobulina** y un inhibidor de la agregación, en donde dicho inhibidor de agregación se selecciona de **ácido aspártico, fenilalanina, ácido glutámico, alanina, histidina y lisina**.

Más específicamente, la solicitud reivindica una **formulación farmacéutica que comprende un polipéptido que contiene un dominio Fc de una inmunoglobulina, un inhibidor de la agregación, un buffer, un surfactante no iónico, un poliol, un estabilizador, un modificador de la tonicidad y un agente quelante.**

Dicho buffer se selecciona de fosfato sodio, histidina, fosfato de potasio, citrato de sodio o potasio, ácido málico, acetato de amonio, tris-(hidroximetil)-aminometano (tris), acetato y dietanolamina o una combinación de los mismos, mientras que dicho poliol se selecciona entre sacarosa, trehalosa, maltosa, manitol, xilitol, maltitol y sorbitol o una combinación de los mismos.

Se indica además que el polipéptido que contiene el dominio Fc de una inmunoglobulina se selecciona entre un anticuerpo monoclonal, una proteína de fusión y un **TNFR:Fc**.

Particularmente, la solicitud reivindica una **formulación farmacéutica de TNFR:Fc** que comprende ácido aspártico, **buffer de fosfato de sodio-potasio**, lisina, **cloruro de sodio, sacarosa**, polisorbato 20 y ácido disodio etilendiaminotetraacético, en donde **el TNFR:Fc está presente en una concentración de 10 mg/mL a 100 mg/mL**. De manera más específica se reivindica una formulación que comprende **25 a 50 mg/mL de etanercept**, 1mM a 50mM de ácido aspártico, 1mM a 50 mM de lisina, **10 mM a 50 mM de fosfato de sodio y potasio, 0.75% a 3% de sacarosa, 50 a 150 mM de NaCl**, 0,1 mM a 2 mM de EDTA, 0.05 mg/mL a 1.0 mg/mL de polisorbato 20 a un **pH de 6.0 a 7.0**.

Este antecedente **le resta nivel inventivo** a la solicitud de **Expediente N° 15 - 287641**.

2. WO 2012/165917 del 06/12/2012.

"Stable liquid formulation of etanercept".

Prioridad: KR20110053890 del **03/06/2011**.

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **formulación líquida de etanercept**, que comprende **etanercept**; y uno o más estabilizadores seleccionados de metionina, lisina, histidina, y sus sales farmacéuticamente aceptables. El **etanercept está presente en una cantidad de 1 a 100 mg/mL**.

La solicitud señala que dicha composición comprende además uno o más compuestos seleccionados entre **un buffer, un agente isotónico**, un excipiente, o un preservante.

Dicho **buffer** se selecciona entre citrato, **fosfato**, **succinato**, tartrato, fumarato, gluconato, oxalato, lactato, acetato, histidina, y Tris. **El buffer está presente en una cantidad entre 0.1 a 100 mM.**

Dicho **agente isotónico** se selecciona de entre **cloruro de sodio**, ácido bórico, borato de sodio, manitol, glicerina, propilenglicol, polietilenglicol, maltosa, **sacarosa**, eritritol, arabitol, xilitol, sorbitol y glucosa.

De manera más específica, la solicitud reivindica una **formulación que comprende 1 a 100 mg/mL de etanercept, 0.1 a 250 mM de metionina o una sal farmacéuticamente aceptable, 0.1 a 100 mM de buffer fosfato, y 1 a 1000 mM de cloruro de sodio.**

En la memoria descriptiva, la solicitud señala que la presente invención se refiere a una **formulación líquida de etanercept (proteína de fusión recombinante p75 TNFR:Fc)**, y más particularmente, a una formulación líquida que comprende uno o más estabilizadores seleccionados de metionina, lisina, histidina y sus sales farmacéuticamente aceptables, **en una cantidad suficiente para reducir los subproductos de etanercept durante el almacenamiento.**

Se indica que la formulación debe tener un **pH de aproximadamente 5 a 7.5 o un pH de aproximadamente 5.8 a 6.8.** En casos específicos, la formulación tiene un **pH de aproximadamente 6.0 a 6.6.**

Se señala además que existen pocos estudios sobre las formulaciones líquidas estables de etanercept, y el único método para estabilizar etanercept que los inventores conocen es el uso de L-arginina en la formulación líquida. Por lo tanto, **existe una necesidad urgente de desarrollar una nueva formulación líquida que sea capaz de mantener de forma estable la actividad de etanercept durante un largo período y que sea más eficaz en la estabilización de etanercept que la formulación conocida que comprende L-arginina.**

La memoria también afirma que los inventores han hecho muchos esfuerzos para desarrollar un método para preparar una formulación líquida capaz de mantener de forma estable la actividad de etanercept. Como resultado, descubrieron que uno o más estabilizantes seleccionados del grupo que consiste en metionina, lisina e histidina muestran efectos notables sobre la estabilización de etanercept en una solución, completando así la presente invención.

Además, se encontró que **la formulación de acuerdo con la presente invención mostró efectos estabilizantes de etanercept que eran equivalentes a o mayor que la de la formulación que comprende L-arginina**, que es la formulación

estable conocida de etanercept. En particular, se descubrió que **la metionina muestra un muy excelente efecto de estabilización de etanercept, mejor que la L-arginina.**

El Ejemplo 2 en la memoria descriptiva muestra el test de estabilidad de formulaciones acuosas de etanercept según la concentración de metionina. La tabla 4 presenta las composiciones 13 y 14 formuladas para ello:

- Formulación 13: **Etanercept 50 mg/mL, solución fosfato 10 mM, NaCl 120 mM, metionina 25 mM (pH 6.3).**
- Formulación 14: **Etanercept 50 mg/mL, solución fosfato 10 mM, NaCl 120 mM, metionina 12.5 mM (pH 6.3).**

Este antecedente **le resta nivel inventivo** a la solicitud de **Expediente N° 15 - 287641.**

3. WO 2012/143418 del 26/10/2012.

"Stable pharmaceutical liquid formulations of the fusion protein TNFR:Fc".

Prioridad: EP20110163171 del **20/04/2011.**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **composición farmacéutica que comprende TNFR:Fc, un buffer citrato y un aminoácido** seleccionado de lisina, prolina y sus sales farmacéuticamente aceptables.

Se señala que dicha composición farmacéutica **comprende además un modificador de la tonicidad**, preferentemente dicho modificador de tonicidad se selecciona de un grupo que consiste en **cloruro de sodio**, cisteína, histidina, glicina, cloruro de potasio, **sacarosa**, glucosa y manitol, más preferentemente el modificador de tonicidad es **cloruro de sodio y/o sacarosa.**

De manera más específica, se desea proteger la composición farmacéutica que comprende de **0.1 a 0.7 mM de TNFR:Fc, 25 a 120 mM de buffer citrato, 15 a 100 mM de lisina, 10 a 100 mM de sacarosa y 5 a 200 mM de cloruro de sodio a pH aproximado de 6.3;** donde el TNFR:Fc es **etanercept.**

En la memoria descriptiva la solicitud señala que la invención se refiere a **formulaciones líquidas farmacéuticas estables de la proteína de fusión TNFR:Fc que comprende diferentes sistemas tampón y estabilizadores.** Se indica además que la invención demuestra que, **mediante la sustitución de,** por ejemplo, el comúnmente utilizado tampón fosfato a un sistema de tampón de

citrato y de la arginina a la lisina como estabilizador, la estabilidad física de TNFR:Fc se pueden mejorar significativamente.

Este antecedente le resta nivel inventivo a la solicitud de Expediente N° 15 - 287641.

4. US 2013/101584 del 25/04/2013.

"Etanercept Formulations Stabilized with Xylitol".

Prioridad: US201161548518P del 18/10/2011.

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **composición farmacéutica acuosa estabilizada que comprende etanercept** y un estabilizador para inhibir la inestabilidad, la agregación por mal plegamiento y/o fragmentación del etanercept, en el que el estabilizador comprende xilitol o una combinación de xilitol y meglumina.

Se señala que dicha composición **comprende además uno o más componentes adicionales** seleccionados de entre **un buffer, un modificador de la tonicidad y un excipiente**.

De manera más específica se desea proteger la **composición opcionalmente libre o esencialmente libre de arginina**, y que comprende aproximadamente **25 a aproximadamente 75 mg/mL de etanercept**; y un estabilizador para inhibir la inestabilidad, la agregación y/o fragmentación del etanercept, en el que el estabilizador es el xilitol en una cantidad que constituye hasta aproximadamente 10% en peso de la composición, y en donde la composición se caracteriza por un análisis SEC en M3 o T2 o T4 de: contenido de monómero mayor que aproximadamente 80% en peso; menos de aproximadamente 3% en peso de agregado (s); y menos de aproximadamente 6% en peso de fragmento 3; **y que tiene un pH de 6,0 a 6,6**.

Particularmente, la solicitud reivindica la composición que comprende alrededor de **25 a 75 mg/mL de etanercept**, aproximadamente 1-10% de xilitol; alrededor de **1 a 30 mM de fosfato de sodio**, opcionalmente hasta 5% de meglumina aproximadamente, opcionalmente hasta alrededor de **100 mM de NaCl**, y opcionalmente hasta **5% de sacarosa aproximadamente**. Más específicamente, dicha composición comprende: aproximadamente **50 mg/mL de etanercept**; alrededor de 10% en peso de xilitol; y **de 10 a 30 mM de fosfato de sodio aproximadamente**; en donde la formulación se caracteriza por un análisis SEC en M3 o T2 o T4 de más de aproximadamente 85% en peso de contenido de monómero.

En la memoria descriptiva, la solicitud señala que **la invención se refiere a composiciones farmacéuticas acuosas estabilizadas con xilitol para el almacenamiento a largo plazo de etanercept**, métodos de fabricación de las composiciones, los métodos de su administración, y kits que contienen el mismo. **La invención incluye formulaciones de etanercept que no requieren arginina para la estabilización.**

Este antecedente **le resta nivel inventivo** a la solicitud de **Expediente N° 15 - 287641**.

5. US 2013/101583 del 25/04/2013.

"Etanercept Formulations Stabilized with Sodium Chloride".

Prioridad: US201161548518P del **18/10/2011**.

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **formulación acuosa de etanercept** estabilizada para reducir la inestabilidad, agregación por mal plegamiento y/o fragmentación de etanerpt, dicha formulación comprende alrededor de **25 a 75 mg/mL de etanercept y uno o más estabilizadores**, en donde los estabilizadores se seleccionan del grupo que consiste en **(i) cloruro de sodio y (ii) cloruro de sodio en combinación con sacarosa o trehalosa; y (iii) una combinación de cloruro de sodio, sacarosa y trehalosa.**

Se señala que dicha formulación comprende además uno o más componentes adicionales seleccionados de entre **un buffer, un modificador de la tonicidad y un excipiente.**

Se señala que, en dicha formulación, el **estabilizador consiste esencialmente de: (a) cloruro de sodio; o (b) cloruro de sodio en combinación con sacarosa; o (c) cloruro de sodio en combinación con trehalosa;** y en el que, la formulación, opcionalmente, **está libre o esencialmente libre de arginina.**

La solicitud reivindica de manera más específica, la formulación que comprende **aproximadamente 25 a 75 mg/mL etanercept, cloruro de sodio en una cantidad de hasta aproximadamente 150 mM, de aproximadamente 1 a fosfato de sodio aproximadamente 30 mM; y aproximadamente 0 a 5% en peso de sacarosa o trehalosa, o combinación de los mismos; en el que la composición tiene un pH de aproximadamente 6,0 a aproximadamente 6,6.**

Particularmente, la solicitud reivindica la formulación que comprende: **aproximadamente 50 mg/mL de etanercept; sobre 75 mM de cloruro de sodio; alrededor de 10 a 30 mM de fosfato de sodio; sobre 3 % en peso de**

sacarosa; la formulación que comprende: aproximadamente **50 mg/mL de etanercept**; **sobre 75 mM de cloruro de sodio**; **alrededor de 10 a 30 mM de fosfato de sodio**; **sobre 3% en peso de trehalosa**; y la formulación que comprende: aproximadamente **50 mg/mL de etanercept**; **sobre 75 mM de cloruro de sodio**; **alrededor de 10 a 30 mM de fosfato de sodio**; **sobre 3% en peso de sacarosa** y que tiene un pH de **alrededor de 6.3 a 6.5**.

Este antecedente **le resta nivel inventivo** a la solicitud de **Expediente N° 15 - 287641**.

6. WO 2013/006454 del 10/01/2013.

"Arginine-free TNFR:Fc-fusion polypeptide compositions and methods of use".

Prioridad: US201161504110P del **01/07/2011**.

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una composición que comprende: **un polipéptido aislado que es una parte que se une a un ligando extracelular de un receptor del factor de necrosis tumoral humano de p75 fusionado a la región Fe de una IgG1 humana**; y una **sal** en una cantidad suficiente para prevenir la agregación del polipéptido aislado, estabilizando por lo tanto la composición, en donde la composición comprende L-arginina a una concentración menor a 1mM.

Se indica que tal composición comprende **alrededor de 10 a 100 mg/mL del polipéptido aislado**, y que dicho polipéptido aislado es **etanercept**.

Asimismo, se señala que la composición comprende además un **tampón acuoso**, y que dicho tampón acuoso es **fosfato de sodio**, histidina, **fosfato de potasio**, citrato de sodio o potasio, ácido málico, acetato de amonio, tris –(hidroximetil) aminometano (tris), acetato, dietanolamina o una combinación de los mismos.

De manera más específica, la solicitud señala que **la sal es cloruro de sodio**, y más específicamente, que dicha sal está presente en una concentración de **aproximadamente 120 a 150 mM**.

La solicitud también señala que dicha composición **comprende además un excipiente**, en donde dicho excipiente es **sacarosa**, lactosa, xilitol, sorbitol, glicerol, **trehalosa**, glucosa, entre otros, o una combinación de los mismos. Más específicamente señala que dicho excipiente es **sacarosa, a una concentración de 0.5% a 1.5%**.

Se indica además que **el pH de la composición es de 5.5 a 7.8 aproximadamente**.

Particularmente, la solicitud reivindica una composición que comprende **50 mg/mL de etanercept, alrededor de 10 mM de fosfato de sodio, aproximadamente 140 mM de cloruro de sodio y aproximadamente de 1% de sacarosa, en donde el pH de la composición es alrededor de 6.0 a 7.0.**

Este antecedente **le resta nivel inventivo** a la solicitud de **Expediente N° 15 - 287641.**

c. Conclusiones

Por todos los antecedentes expuestos (se adjunta una copia de todos los documentos citados en este informe), es evidente que **la solicitud de Expediente N° 15 – 287641 carece de nivel inventivo**, considerando que las formulaciones alternativas para polipéptidos de fusión TNFR:Fc, se desprenden del arte previo.

Siendo, las formulaciones alternativas para polipéptidos de fusión TNFR:Fc, según lo indicado en la solicitud relativa al Expediente N° 15 - 287641, algo que se desprende del estado del arte, se reafirma el fundamento de la carencia de nivel inventivo, pues **el objeto de la invención y los elementos que la componen son conocidos y forman parte del arte previo.**

Por consiguiente, podemos afirmar en forma categórica, que esta solicitud de patente **debe ser denegada**, debido a que **no presenta nivel inventivo** para gozar de un privilegio industrial en Colombia, ya que las formulaciones alternativas para polipéptidos de fusión TNFR:Fc, según lo indicado en esta solicitud de patente, **se desprenden del estado de la técnica.**

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho los artículos 16, 18 y 20 de la Decisión 486 de 2000.

V. ANEXOS

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

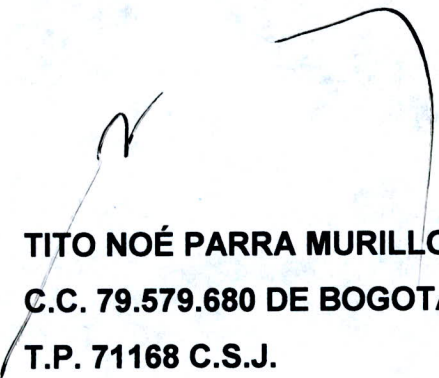
1. Poder para actuar.
2. Certificado de existencia y representación legal de LAFRANCOL S.A.S.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. Los antecedentes mencionados en los fundamentos técnicos.

VI. 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 NOÉ PARRA MURILLO
C.C. 79.579.680 DE BOGOTÁ.
T.P. 71168 C.S.J.

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DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
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Published:

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(54) Title: ALTERNATIVE FORMULATIONS FOR TNFR: FC FUSION POLYPEPTIDES

(57) Abstract: The present invention relates to aqueous stable pharmaceutical compositions suitable for storage of polypeptides that
contain TNFR:Fc.

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ALTERNATIVE FORMULATIONS FOR TNFR: Fc FUSION POLYPEPTIDES

FIELD OF INVENTION

- 5 The present invention relates to aqueous stable pharmaceutical compositions free of some selected amino acids suitable for storage of polypeptides that contain TNFR:Fc.

BACKGROUND OF THE INVENTION

- 10 Therapeutic polypeptide preparations are often stored prior to use. Polypeptides, however, are unstable if stored in aqueous form for extended period of time, particularly in the absence of a stabilizing agent such as arginine. An alternative to relying on aqueous storage is to prepare a dry lyophilized form of a polypeptide, although, reconstitution of a dried polypeptide often results in aggregation or denaturation. This aggregation of polypeptides is undesirable as it may result in immunogenicity.

- 15 A commercially available soluble form of the TNF (tumor necrosis factor) receptor fused to an Fc domain (TNFR:Fc) is known as etanercept. Etanercept (trade name ENBREL®) interferes with tumor necrosis factor (TNF) by acting as a TNF inhibitor. This dimeric fusion polypeptide consisting of the extracellular ligand-binding portion of the human 75 kDa (p75) tumor necrosis factor receptor (TNFR)
20 linked to the Fc portion of human IgG1 is currently formulated with L-arginine and/or L-cysteine as aggregation inhibitor to prevent aggregation of the polypeptide (see EP1478394 B1).

- Nevertheless, arginine can cause serious side effects in some people. A severe allergic reaction, called anaphylaxis, can occur after arginine injections, as well as stomach discomfort, including nausea,
25 stomach cramps or an increased number of stools. Other potential side effects include low blood pressure and changes in numerous chemicals and electrolytes in the blood, such as high potassium, high chloride, low sodium, low phosphate, high blood urea nitrogen and high creatinine levels. In theory, arginine may increase the risk of bleeding, increase blood sugar levels, increase potassium levels and may worsen symptoms of sickle cell disease.

- 30 Cysteine is a non-essential amino acid and is closely related to cystine, as cystine consists of two cysteine molecules joined together. It is an unstable nutrient and is easily converted to cystine. Too much cystine in the body can cause cystinosis, a rare disease that can cause cystine crystals to form in the body and produce bladder or kidney stones. It is also known that people suffering from diabetes
35 and cystinuria may have side-effects with cysteine supplements.

mutually miscible solvents. Further, as used herein, the term "about" means the indicated value $\pm 2\%$ of its value, preferably the term "about" means exactly the indicated value ($\pm 0\%$).

Note that although the composition according to the present invention does not comprise arginine or cysteine (or, preferably, any other amino acid such as proline, glycine, methionine, histidine, serine, valine, lysine, glutamate) alone or added to the composition, the polypeptide itself can contain arginine or cysteine (or any other amino acid such as proline, glycine, methionine, histidine, serine, valine, lysine, glutamate) amino acid residues in its chain.

10 In certain embodiments, the expressed Fc domain containing polypeptide is purified by any standard method. When the Fc domain containing polypeptide is produced intracellularly, the particulate debris is removed, for example, by centrifugation or ultrafiltration. When the polypeptide is secreted into the medium, supernatants from such expression systems can be first concentrated using standard polypeptide concentration filters. Protease inhibitors can also be added to inhibit proteolysis and
15 antibiotics can be included to prevent the growth of microorganisms. In some embodiments, the Fc domain containing polypeptide is purified using, for example, hydroxyapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, and/or any combination of purification techniques known or yet to be discovered. For example, protein A can be used to purify Fc domain containing polypeptides that are based on human gamma 1, gamma 2, or gamma 4 heavy chains
20 (Lindmark et al., 1983, J. Immunol. Meth. 62: 1-13).

Other techniques for polypeptide purification such as fractionation on an ion-exchange column, ethanol precipitation, reverse phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSETM, chromatography on an anion or cation exchange resin (such as a polyaspartic acid
25 column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation can also be utilized depending on the needs. Other polypeptide purification techniques can be used.

In a preferred embodiment, the salt concentration is from 80 to 130 mM, preferably from 90 to 130 mM, such as from 105 to 130 mM, such as about 90 mM, 100 mM or 125 mM. Preferably, the salt
30 concentration (preferably NaCl) is about 90 mM. Regardless of the concentration, the salt is preferably sodium chloride, although other salts such as potassium chloride, sodium citrate, magnesium sulphate, calcium chloride, sodium hypochlorite, sodium nitrate, mercury sulphide, sodium chromate and magnesium dioxide can also be used. This particular range of salt concentrations allows obtaining a composition according to the present invention which is stable at high
35 temperatures, even up to 50°C. In addition, the values in this range are closer to the physiological

11. The composition according to any of items 1 to 10 comprising 50 mg/mL of etanercept, 50 mM sodium phosphate buffer, 60 mg/mL trehalose dihydrate, wherein the pH of the composition is pH 6.2.
12. The composition according to any of items 1 to 10 comprising 50 mg/mL of etanercept, 50
5 mM sodium phosphate buffer, 60 mg/mL sucrose, wherein the pH of the composition is pH 6.2.
13. The composition according to any of items 1 to 10 comprising 50 mg/mL of etanercept, 50 mM sodium phosphate buffer, 60 mg/mL trehalose dihydrate, 0.1 % Polysorbate 20, wherein the pH of the composition is pH 6.2.
14. The composition according to any of items 1 to 10 comprising 50 mg/mL of etanercept, 50
10 mM sodium phosphate buffer, 60 mg/mL sucrose, 0.1 % Polysorbate 20, wherein the pH of the composition is pH 6.2.

CLAIMS

1. An aqueous composition comprising:
 - An isolated polypeptide that is an extracellular ligand-binding portion of a human p75 tumor necrosis factor receptor fused to the Fc region of a human IgG1;
 - 5 - Salt present at a concentration of from 80 to 130 mM; and
 - An excipient selected from the group of trehalose and sucrose or a combination thereof, characterized in that neither arginine nor cysteine are present in the composition.
- 10 2. The composition according to claim 1 wherein the salt concentration is 90 mM.
3. The composition according to any of claims 1 to 2, wherein the salt is sodium chloride.
4. The composition according to any of claims 1 to 3 wherein the isolated polypeptide is etanercept.
- 15 5. The composition according to any of claims 1 to 4, wherein the excipient is sucrose present at a concentration of from 5 to 80 mg/mL.
6. The composition according to any of claims 1 to 5 wherein the composition further comprises an
20 aqueous buffer.
7. The composition according to claim 6, wherein the aqueous buffer is sodium phosphate, potassium phosphate, sodium or potassium citrate, succinic acid, maleic acid, ammonium acetate, tris- (hydroxymethyl)- aminomethane (tris), acetate, diethanolamine, histidine or a
25 combination thereof.
8. The composition according to any of claims 6 or 7, wherein the aqueous buffer is present at a concentration of 15 mM to 100 mM.
- 30 9. The composition according to claim 8 wherein the aqueous buffer is present at a concentration of 20 to 30 mM.
10. The composition according to any one of claims 6 to 9 wherein the aqueous buffer is succinic acid (succinate).
- 35 11. The composition according to any of claims 1 to 10 further comprising one or more excipients.

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

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

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: LIQUID FORMULATION OF POLYPEPTIDES CONTAINING AN FC DOMAIN OF AN IMMUNOGLOBULIN

(57) Abstract: The present invention relates to a liquid formulation of a polypeptide containing an Fc domain of an immunoglobulin which is stabilized to maintain the activity of a polypeptide containing an Fc domain for a prolonged period of time.

WO 2011/141926 A2

HIC Peak 3

6.3 %

7.4 %

15.1 %

The novel formulations of fusion protein are prepared using suitable combination of buffer, an aggregation inhibitors, tonicity modifiers, stabilizers, surfactants, chelating agents and optionally with preservative in suitable combinations thereof.

5

The formulation prepared by the said invention comprises an effective amount of biologically active TNFR: Fc which is used in treating inflammatory diseases in humans. They are preferably used as injectable aqueous solutions.

Claims**We claim**

1. A pharmaceutical formulation comprising a polypeptide containing an Fc domain of an immunoglobulin and an aggregation inhibitor, wherein the aggregation inhibitor is selected from the group consisting of aspartic acid, phenylalanine, glutamic acid, alanine, histidine and lysine.
2. A pharmaceutical formulation comprising polypeptide containing an Fc domain of an immunoglobulin, an aggregation inhibitor, buffer, a non-ionic surfactant, polyol, a stabilizer, a tonicity modifier, and a chelating agent.
3. The pharmaceutical formulation of claim 2, wherein the buffer is selected from the group consisting of sodium phosphate, histidine, potassium phosphate, sodium or potassium citrate, maleic acid, ammonium acetate, tris-(hydroxymethyl)-aminomethane (tris), acetate and diethanolamine or a combination thereof.
4. The pharmaceutical formulation of claim 2 wherein the non-ionic surfactant is selected from the group consisting of a polysorbate-based non-ionic surfactant and a poloxamer-based non-ionic surfactant or a combination thereof.
5. The pharmaceutical formulation of claim 2, wherein the polyol is selected from the group consisting of sucrose, trehalose, maltose, mannitol, xylitol, maltitol and sorbitol or a combination thereof.
6. The pharmaceutical formulation of claim 2, wherein stabilizer is selected from the group consisting of amino acids such as glycine, alanine, lysine, proline and serine and their salts thereof, either alone or in combination.
7. The pharmaceutical formulation of claim 2, wherein the chelating agent is selected from the group consisting of EDTA (ethylenediamine tetraacetic acid), HEDTA (hydroxyethylenediamine triacetic acid), NTA (nitrilotriacetic acid), DTPA (Diethylenetriamine pentaacetate) and citric acid or a combination thereof.
8. The pharmaceutical formulation of claim 2, wherein the tonicity modifier is selected from the group consisting of sodium chloride, potassium chloride, sodium sulfate or a combination thereof.

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

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Published:

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(54) Title: STABLE LIQUID FORMULATION OF ETANERCEPT

(57) Abstract: The present invention relates to a stable liquid formulation of etanercept (recombinant p75 sTNFR:Fc fusion protein), and more particularly, to a liquid formulation comprising one or more stabilizers selected from the group consisting of methionine, lysine, histidine, and pharmaceutically acceptable salts thereof in an amount sufficient to reduce by-product formation of etanercept during storage. The liquid formulation according to the present invention effectively reduces production of etanercept by-products and to stably maintain its pharmaceutical efficacies for long-term storage. Therefore, the reconstitution procedure is not required before administration, and the sterile formulation can be administered to patients to ensure patient safety. Thus, it can be applied to the fields in need of etanercept treatment.

WO 2012/165917 A1

Description

Title of Invention: STABLE LIQUID FORMULATION OF ETANERCEPT

Technical Field

- [1] The present invention relates to a liquid formulation of etanercept (recombinant p75 sTNFR:Fc fusion protein), and more particularly, to a liquid formulation comprising one or more stabilizers selected from the group consisting of methionine, lysine, histidine, and pharmaceutically acceptable salts thereof in an amount sufficient to reduce by-products of etanercept during storage.

Background Art

- [2] Etanercept is a biological inflammation modulator that functions as a competitive inhibitor of TNF- α , binding to cell surface TNF- α receptor, to inhibit TNF- α mediated immune responses. Etanercept is a macromolecule with a molecular weight of approximately 150 kDa, and is a homodimer of two Fc fusion proteins linked by a disulfide bond, each Fc fusion protein consisting of a human soluble p75 TNF receptor coupled to the Fc portion of human immunoglobulin G subclass 1 (Goldenberg, Clinical Therapeutics, 21(1): 75-87, 1999; Moreland et al., Ann. Intern. Med., 130(6): 478-486, 1999).
- [3] This prototypic fusion protein was first synthesized in the early 1990s by Bruce A. Beutler at the University of Texas Southwestern Medical Center, and marketed by Amgen under the trade name of Enbrel in 2002. Etanercept is a TNF- α inhibitor used to treat rheumatoid arthritis, psoriasis, and ankylosing spondylitis, and under clinical trials for the treatment of vasculitis, Alzheimer's disease, and Crohn's disease.
- [4] Like protein drugs, antibody drugs have a very short half life, and chemical and physical denaturation can be easily caused by unfavorable temperature, shear stress, vibration, freeze-thawing, UV exposure, excessive pH change, organic solvents, and microbial contamination. Chemical denaturation includes dimer dissociation, oxidation, deamidation, isomerization, and polymerization, which are influenced by the amino acids constituting the antibody and conditions of the solvent containing the antibody (salt, pH and temperature). Physical denaturation includes loss of tertiary structure, covalent/non-covalent aggregation and adhesion of monomers, which are influenced by hydrophobic patches on the protein surface changed by antibody-containing surrounding environments such as solvents, complex protein structures such as charge distribution, and thermal stability. The physical or chemical denaturation of an antibody causes loss of its physiological activities. Since the denaturation is an irreversible process, antibodies, once denatured, may not recover their native properties to

the initial state, leading to a reduction in their therapeutic efficacies. It has been also suggested that aggregation of monomers causes immune responses. Therefore, many studies have been conducted on antibody formulations containing a physiologically effective amount without aggregates (Ishikawa et al., *Biol. Pharm. Bull.*, 33(8): 1413-1417, 2010; Levin et al., *The Development of Therapeutic Monoclonal Antibody Products*, editors. Boston (MA): BioProcess Technology Consultants, Inc, Chapter 9).

- [5] There are many methods available for preventing protein denaturation in liquid formulations. In some protein drugs, the stability problems are addressed via lyophilization. For instance, U.S. Patent No. 7,592,004 discloses a lyophilized formulation of daclizumab that is stabilized using 5 to 25 mM of a histidine buffer solution (pH 5.5 to 6.5), 0.005 to 0.03% of a non-ionic surfactant, polysorbate and 100 to 300 mM of a non-reducing sugar, sucrose. U.S. Patent Publication No. 2010-0158925 discloses a lyophilized formulation of cetuximab that is stabilized using a histidine buffer solution and lactobionic acid. However, the lyophilization process generates freezing and drying stresses such as formation of ice crystals, pH change, and high concentration of solute, and these stresses may cause antibody denaturation. In addition, since a large-capacity lyophilizer is needed for the lyophilization process during the production, high production costs arise during a large scale of production. Dissolving the lyophilized product in sterile aqueous media for reconstitution before use also poses an inconvenience.
- [6] As an alternative to solve these limitations, a stabilizer is added in liquid formulations for the improvement of antibody stability. Surfactants, serum albumins, polysaccharides, amino acids, polymers, salts or the like are known as stabilizers for proteins including antibodies (Wang, *Int. J. Pharm.*, 185: 129-188, 1999; Wang et al., *J. Pharm. Sci.*, 96(1): 1-26, 2007).
- [7] US Patent Publication No. 2011-0070231 discloses a stable liquid composition of IgG antibody, in which the stable pharmaceutical liquid formulation includes 50 mg/mL or more of daclizumab in 20 to 60 mM of a succinate buffer solution (pH 5.5 to 6.5), 0.02 to 0.04% of polysorbate, and 75 to 150 mM of sodium chloride.
- [8] US Patent Publication No. 2011-0020328 discloses a therapeutically effective amount of anti-CD20 antibody formulation, in which the pharmaceutically stable composition includes 10 to 100 mM of sodium acetate, 25 to 100 mM of sodium chloride, 0.5 to 5% of arginine free base, 0.02 to 0.2 mM of EDTA and 0.01 to 0.2% of polysorbate 80, and its pH is 5.0 to 7.0.
- [9] US Patent No. 7,785,592 discloses a stable formulation, in which 75 mg/mL or more of palivizumab is stabilized by using a histidine buffer solution and glycine without ionic salts and a surfactant, and its stability is maintained at 2 to 8°C for at least 15 months.

residues in antibodies for reaction with the free hydroxyl radicals (Lam et al., J. Pharm. Sci., 86(11): 1250-1255, 1997; Wang, Int. J. Pharm., 185: 129-188, 1999).

- [58] Lysine is an essential amino acid, and has a chemical formula of $C_6H_{14}N_2O_2$ and a molecular weight of 146.19. Lysine is a basic amino acid, and has a pK_1 value of 2.18, pK_2 value of 8.95, pK_3 value of 10.53 and PI value of 9.74.
- [59] Histidine is an essential amino acid with an imidazole functional group having positive charge in its side chain, and has a chemical formula of $C_6H_9N_3O_2$ and a molecular weight of 155.15. Histidine is a basic amino acid, and has a pK_1 value of 1.82, pK_2 value of 9.17, pK_3 value of 6.0 and PI value of 7.59.
- [60] In contrast, L-arginine contained in the known commercially available formulation of etanercept is an essential amino acid, and has a chemical formula of $C_6H_{14}N_4O_2$ and a molecular weight of 174.2. Arginine is a basic amino acid, and has a pK_1 value of 2.17, pK_2 value of 9.04, pK_3 value of 12.48 and PI value of 10.76. That is, methionine, lysine, and histidine used as a stabilizer in the present invention are totally different from arginine as a known stabilizer for etanercept in construct, chemical formula, physicochemical properties, and ionization tendency. The present invention has demonstrated for the first time that amino acids such methionine, lysine, and histidine are the appropriate stabilizers for etanercept.
- [61] The content of the stabilizer in the liquid formulation of the present invention is 0.1 to 250 mM, preferably 1 to 100 mM, and more preferably 5 to 50 mM.
- [62] The liquid formulation of the present invention may further include any material which is generally contained in formulations of protein drugs or antibody drugs to increase etanercept stability according to one or more stabilizers selected from the group consisting of methionine, lysine, histidine, and pharmaceutically acceptable salts thereof except for those deteriorating the function of the present invention. For example, L-arginine known as a stabilizer for etanercept may be added to the liquid formulation of the present invention.
- [63] The liquid formulation according to the present invention may further include a buffer in addition to the stabilizer. As used herein, the term "buffer" refers to the component that improves isotonicity and chemical stability of the formulation, and functions to maintain physiologically suitable pH. The buffer prevents a rapid pH change of the liquid formulation to maintain pH of the solution for the stabilization of etanercept. Preferred examples of the buffer include citrate, phosphate, succinate, tartrate, fumarate, gluconate, oxalate, lactate, acetate, histidine, and Tris, but are not limited thereto. In the specific embodiment, the buffer is a phosphate buffer. The buffer may be used either alone or in combinations of two or more thereof.
- [64] In the various embodiments of the present invention, the formulation should have pH of approximately 5 to 7.5 or pH of approximately 5.8 to 6.8. In the specific em-

stabilizer-free formulation.

[128] Each 0.5 mL of the prepared formulation was put in 1.0 mL glass syringes, sealed, and stored at 50°C. The stabilizer compositions of the formulations are shown in the following Table 9.

[129] Table 9

[Table 9]

	Stabilizer composition
Formulation 17	Methionine 12.5mM +Lysine 12.5mM
stabilizer-free formulation	-

[130]

[131] At 7 days after storage at 50°C, Formulations 17, and stabilizer-free formulation of Table 9 were analyzed by SE-HPLC as example 1 to measure their Total Impurity. The results are shown in Table 10.

[132] Table 10

[Table 10]

	SE-HPLC Total Impurity (%)	
	0 day	7 dyas
Formulation 17	5.2	27.0
stabilizer-free formulation	5.2	32.8

[133]

[134] As shown in the SE-HPLC results of Table 10, when stored at 50°C for 7 days, Formulation 17 containing methionine and lysine as a stabilizer showed Total Impurity of 27%, which is remarkably low, compared to the stabilizer-free formulation showing Total Impurity of 32.8%.

[135] That is, the present invention demonstrated that the formulation comprising methionine and lysine has remarkably effects on the stabilizing of etanercept by reducing the amount of Total Impurity, compared to the stabilizer-free formulation.

[136]

Claims

- [Claim 1] A liquid formulation of etanercept, comprising etanercept; and one or more stabilizers selected from the group consisting of methionine, lysine, histidine, and pharmaceutically acceptable salts thereof.
- [Claim 2] The liquid formulation according to claim 1, wherein the stabilizer is methionine and/or pharmaceutically acceptable salts thereof.
- [Claim 3] The liquid formulation according to claim 1, wherein the stabilizer is present in an amount of 0.1 to 250 mM.
- [Claim 4] The liquid formulation according to claim 1, wherein the etanercept is present in an amount of 1 to 100 mg/mL.
- [Claim 5] The liquid formulation according to claim 1, which have increased storage stability of etanercept compared to the formulation having no stabilizers, by reducing etanercept by-products that are produced due to denaturation during storage.
- [Claim 6] The liquid formulation according to claim 1, which further comprises one or more materials selected from the group consisting of a buffer, an isotonic agent, an excipient, or a preservative.
- [Claim 7] The liquid formulation according to claim 6, wherein the buffer is selected from the group consisting of citrate, phosphate, succinate, tartrate, fumarate, gluconate, oxalate, lactate, acetate, histidine, and Tris.
- [Claim 8] The liquid formulation according to claim 6, wherein the buffer is present in an amount of 0.1 to 100 mM.
- [Claim 9] The liquid formulation according to claim 6, wherein the isotonic agent is selected from the group consisting of sodium chloride, potassium chloride, boric acid, sodium borate, mannitol, glycerin, propylene glycol, polyethylene glycol, maltose, sucrose, erythritol, arabitol, xylitol, sorbitol, and glucose.
- [Claim 10] The liquid formulation according to claim 6, wherein the isotonic agent is present in an amount of 1 to 1000 mM.
- [Claim 11] The liquid formulation according to claim 1, comprising 1 to 100 mg/mL of etanercept, 0.1 to 250 mM of methionine or pharmaceutically acceptable salts thereof, 0.1 to 100 mM of phosphate buffer, and 1 to 1000 mM of sodium chloride.
- [Claim 12] The liquid formulation according to claim 1, comprising 1 to 100 mg/mL of etanercept, 0.1 to 250 mM of lysine or pharmaceutically acceptable salts thereof, 0.1 to 100 mM of phosphate buffer, and 1 to

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(54) Title: STABLE PHARMACEUTICAL LIQUID FORMULATIONS OF THE FUSION PROTEIN TNFR:Fc

(57) Abstract: The present invention relates to stable pharmaceutical liquid formulations of the fusion protein TNFR:Fc comprising different buffer systems and stabilizers. In particular, it could be demonstrated that the physical stability of TNFR:Fc is significantly improved by using a citrate buffer system and lysine as stabilizer.

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Stable pharmaceutical liquid formulations of the fusion protein TNFR:Fc

The present invention relates to stable pharmaceutical liquid formulations of the fusion protein TNFR:Fc comprising different buffer systems and stabilizers. In particular, it could be demonstrated that the physical stability of TNFR:Fc is significantly improved by using a citrate buffer system and lysine and/or proline as stabilizer.

BACKGROUND OF THE INVENTION

Commercial antibodies are commonly formulated in phosphate buffer. Also TNFR:Fc is commonly buffered in sodium phosphate (EP1478394, WO 03/072060 A2). Currently, e.g. the TNFR:Fc protein Etanercept is marketed under the tradename Enbrel[®] having a composition as shown in Table 1.

Table 1 Composition of Etanercept (Enbrel[®])

	[mg/mL]	[mM]
Etanercept	50	0,3
Sucrose	10	29
Sodium chloride	5.8	100
L-arginine hydrochloride	5.3	25
Sodium phosphate monobasic	2.6	19
Sodium phosphate dibasic	0.9	6
WFI	ad 0.5 / 1.0 ml	
pH	6.3 ± 0.2	

Aggregation of antibody products can be controlled by the addition of small amphiphilic molecules. Thereof, L-arginine is the amino acid of choice in suppressing protein interactions in commercial formulations (Baynes et al (2005) 44(12):4919-25; EP1478394). Being a polar additive, it prevents the aggregation of protein folding intermediates.

Like L-arginine, L-lysine is capable of significantly preventing heat- and dilution-induced aggregation of lysozyme (Shiraki et al (2002) J Biochem, 132(4):591-5). L-proline has been established as a stabilizer in liquid immunoglobulin preparations like Sandoglobulin[®] or Privigen[®]. As an hydrophobic amino acid, it is assumed to

SEC Sum DPs	50mMCitrate/ 25mM Lysine	25 mM Citrate/ 25 mM Lysine	Citrate 25mM/ Proline 25mM	Phosphate 25mM/ Lysin 25mM	Phosphate 25mM/ Arginine 25mM
T0	4,0	4,1	4,3	4,7	4,9
1M	10,9	11,4	11,1	15,5	15,4
2M	15,1	15,9	15,1	21,4	20,9
3M	19,5	20,3	19,9	27,5	27,6

CEX Sum APs	50mMCitrate/ 25mM Lysine	25 mM Citrate/ 25 mM Lysine	Citrate 25mM/ Proline 25mM	Phosphate 25mM/ Lysin 25mM	Phosphate 25mM/ Arginine 25mM
T0	8,2	9,0	8,3	9,1	8,8
1M	14,1	14,6	13,6	15,6	15,7
2M	19,0	19,3	18,5	20,5	21,7
3M	28,0	26,8	26,9	29,9	32,4

LIST OF REFERENCES

5 WO 03/072060 A2
EP1478394

Baynes et al, Role of arginine in the stabilization of proteins against aggregation. Biochemistry, 2005 Mar 29;44(12):4919-25.

10 Shiraki et al, Biophysical effect of amino acids on the prevention of protein aggregation. J Biochem, 2002 Oct;132(4):591-5.

15 Bolli et al, L-Proline reduces IgG dimer content and enhances the stability of intravenous immunoglobulin (IVIG) solutions. Biologicals, 2010 Jan;38(1):150-7.

Zheng and Janis, Influence of pH, buffer species, and storage temperature on physiochemical stability of a humanized monoclonal antibody LA298. Int J Pharm, 2006 Feb 3;308(1-2):46-51.

20 Kolhe et al, Impact of freezing on pH of buffered solutions and consequences for monoclonal antibody aggregation. Biotechnol Prog, 2010 May-Jun;26(3):727-33.

Claims

1. Pharmaceutical composition, comprising TNFR:Fc, a citrate buffer and an amino acid selected from the group consisting of lysine and proline and their pharmaceutical acceptable salts.
5
2. The pharmaceutical composition of claim 1, comprising the citrate buffer at a concentration from 25 mM to 120 mM.
- 10 3. The pharmaceutical composition of claim 1 or 2, comprising the amino acid at a concentration from 15 mM to 100 mM, preferably wherein the amino acid is lysine or its pharmaceutical acceptable salt.
- 15 4. The pharmaceutical composition of any of the preceding claims, further comprising a tonicity modifier, preferably wherein the tonicity modifier is selected from the group consisting of sodium chloride, cysteine, histidine, glycine, potassium chloride, sucrose, glucose and mannitol, more preferably wherein the tonicity modifier is sodium chloride and/or sucrose.
- 20 5. The pharmaceutical composition of claim 4, comprising at least one tonicity modifier at a total concentration from 5 mM to 200 mM.
- 25 6. The pharmaceutical composition of any of the preceding claims, further comprising at least one excipient, preferably wherein the at least one excipient is selected from the group consisting of lactose, glycerol, xylitol, sorbitol, mannitol, maltose, inositol, trehalose, glucose, bovine serum albumin (BSA), dextran, polyvinyl acetate (PVA), hydroxypropyl methylcellulose (HPMC), polyethyleneimine (PEI), gelatine, polyvinylpyrrolidone (PVP), hydroxyethylcellulose (HEC), polyethylene glycol (PEG), ethylene glycol,
30 glycerol, dimethylsulfoxide (DMSO), dimethylformamide (DMF), L- serine, sodium glutamate, alanine, glycine, sarcosine, gamma-aminobutyric acid (GABA); polyoxyethylene sorbitan monolaurate, preferably Tween-20;

polyoxyethylene sorbitan monooleate, preferably Tween-80; sodium dodecyl sulphate (SDS), polysorbate, polyoxyethylene copolymer, potassium phosphate, sodium acetate, ammonium sulfate, magnesium sulfate, sodium sulfate, trimethylamine N-oxide, betaine, zinc ions, copper ions, calcium ions, manganese ions, magnesium ions, CHAPS, sucrose monolaurate, and 2-O-beta-mannoglycerate.

7. The pharmaceutical composition of claim 6, comprising the at least one excipient at a total concentration from 0.1 mM to 0.7 mM.
8. The pharmaceutical composition of any the preceding claims, comprising TNFR:Fc at a concentration from 0.1 mM to 0.7 mM.
9. The pharmaceutical composition of any of the preceding claims, wherein said composition further comprises a pharmaceutically acceptable solvent.
10. The pharmaceutical composition of any of the claims 1-8, wherein the composition is lyophilized.
11. The pharmaceutical composition of claim 1,
comprising 0.1 mM to 0.7 mM TNFR:Fc, 25 mM to 120 mM citrate buffer, 15 mM to 100 mM lysine, 10 to 100 mM sucrose and 5 mM to 200 mM sodium chloride at a pH value of about 6.3; or
comprising 0.3 mM TNFR:Fc, 50 mM citrate buffer, 25 mM lysine, 29 mM sucrose and 75 mM sodium chloride at a pH value of about 6.3; or
comprising 0.3 mM TNFR:Fc, 25 mM citrate buffer, 25 mM lysine, 29 mM sucrose and 88 mM sodium chloride at a pH value of about 6.3; or
comprising 0.1 mM to 0.7 mM TNFR:Fc, 25 mM to 120 mM citrate buffer, 15 mM to 100 mM proline, 10 mM to 100 mM sucrose and 5 mM to 200 mM sodium chloride at a pH value of about 6.3; or



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(54) **ETANERCEPT FORMULATIONS
STABILIZED WITH XYLITOL**

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(57) **ABSTRACT**

The invention provides stabilized aqueous pharmaceutical etanercept compositions suitable for long-term storage of etanercept, methods of manufacture of these compositions, methods of administration, and kits containing same.

incorrectly folded etanercept species as determined by HIC; less than about 3 wt % of clipped material by HIC analysis (believed to be fragments of etanercept in which the TNFR portion thereof has been truncated) and a combined amount of correctly and incorrectly folded etanercept of greater than 95 wt % as determined by size exclusion chromatography.

Analysis of Etanercept Formulations

[0116] A. Thermal Stability Storage

[0117] Following dialysis and concentration, samples of the etanercept formulations exemplified above were sterile filtered in a bio safety cabinet. Using sterilized pipettes and autoclaved pipette tips, samples of the etanercept formulations were transferred to pre-labeled and autoclaved 1 mL lyophilization vials. Vials were stoppered with sterile butyl stoppers and crimped with aluminum caps. All vials were then transferred to thermal stability ovens. Samples were subject to two thermal stability regimes: (1) two weeks at 40° C. and (2) four weeks at 25° C. Throughout this specification, these two temperature regimes are denoted "T₂" and T₄," respectively.

[0118] B. Size Exclusion Chromatography (SEC)

[0119] Etanercept formulations disclosed herein were analyzed using the well known technique of Size Exclusion Chromatography (SEC), a high-performance liquid chromatography method in which analytes are separated by size (see Rogner, M. (2000). *Size Exclusion Chromatography. Protein Liquid Chromatography*. M. Kastner. Amsterdam, Elsevier. 61: 89-145.). In order to evaluate thermal stability of the Etanercept samples described above, the samples were examined by a SEC method based on the literature (van Maarschalkerweerd, A., G. J. Wolbink, et al. (2011). "Comparison of analytical methods to detect instability of etanercept during thermal stress testing." *European Journal of Pharmaceutics and Biopharmaceutics* 78(2): 213-221.) The mobile phase buffer was prepared to contain 50 mM sodium phosphate monobasic monohydrate and 150 mM arginine. The pH was adjusted to 6.5 using 1 M HCl. All separations were performed using a Tosoh TSK-Gel SWxl 6 mmx4 cm guard column (cat. no. 8543) attached linearly to a Tosoh TSK-Gel G4000 SWxl 7.8 mmx30 cm (cat. no. 8542). To perform a separation, the columns were brought to room temperature (23° C.) and equilibrated with mobile phase at a flow rate of 0.5 mL/min. 5 microliters of 50 mg/mL etanercept formulation were injected onto the column using an autosampler. The separation was accomplished over 30 minutes at a flow rate of 0.5 mL/minute. Column eluent was monitored at a wavelength of 280 nm during this time.

[0120] C. Integration of Size Exclusion Chromatography Chromatograms

[0121] All integration was performed using Chromeleon software (Dionex). Prior to integration, the SEC chromatogram for a buffer containing no etanercept was subtracted from all chromatograms. All integration was performed between retention times of 12 minutes and 26 minutes. Several parameters were used to define a peak. The minimum area for a detected peak was set to 0.05 mAu*min. The two-dimensional sensitivity for peak detection was set to 0.01 mAu and 75 seconds. Peak shoulders were added manually using a manual integration tool. All detected peaks were manually adjusted in two steps. First, peak baselines (the bottom boundary of the peak) were adjusted to horizontal. Secondly, the vertical positions of the peak baselines were adjusted to that of the chromatogram baseline. The chromato-

gram baseline value was defined as the signal in absence of analyte. The signal in absence of analyte was defined as the absorbance in mAu at 12 minutes retention time.

[0122] D. SEC Fractions of Etanercept Formulations

[0123] In the SEC analysis of etanercept formulations described above, three SEC chromatography fractions were identified and studied. The fractions that were analyzed were, in the order of elution from the SEC column: (1) a high molecular weight fraction representing aggregates of the intact etanercept TNFR:Fc fusion protein likely assembled via non-covalent electrostatic attraction among intact etanercept molecules (hereinafter "aggregate(s)" or aggregate(s) content); (2) monomer content, representing the intact etanercept TNFR:Fc fusion protein (hereinafter referred to as "monomer" or "monomer content"); (3) a fraction likely representing one fragment or a population of fragments of the etanercept molecule in which one portion of the TNFR: molecule fusion protein has become cleaved from the monomer; in the loss of an arm of the Fab portion of the fusion protein at the hinge region of the molecule. The most common fragment or clipped species, as measured by SEC, is referred to as fragment 3. In conducting the SEC analysis, it will be observed that aggregates elute first, followed by monomer, followed by fragment 3.

[0124] The following tables shows the relative amounts of Aggregates, Monomer and fragment 3 determined by SEC analysis as described above.

TABLE 1

SEC ANALYSIS OF MONOMER			
Formulation No.	t ₀	t ₁	t ₂
Commercial Enbrel (comparative) [1:2]	98.81	92.58	87.64
1:17	98.02	93.90	87.53
2:10	98.09	—	87.56
2:11	98.10	—	88.03
2:18	98.10	—	89.19
2:19	98.19	—	89.63

Note:

Amounts reported Tables I, II and III are percentages by weight

T₀ = formulation maintained at 5 C. and analyzed within 24 hours of creation.

T₁ = formulation stored for one week at 40° C.

T₂ = formulation stored for two weeks at 40 C.

TABLE II

SEC ANALYSIS OF AGGREGATES			
Formulation No.	t ₀	t ₁	t ₂
Commercial Enbrel (comparative)	0.09	0.59	1.02
1:17	0.31	0.70	2.17
2:10	0.29	—	2.57
2:11	0.31	—	1.68
2:18	0.29	—	1.53
2:19	0.26	—	1.24

TABLE III

ANALYSIS OF FRAGMENT 3			
Formulation No	t ₀	t ₁	t ₂
Commercial Enbrel (comparative)	0.00	3.30	6.29
1:17	0.00	2.33	4.10
2:10	0.00	—	5.10
2:11	0.00	—	5.68
2:18	0.00	—	4.24
2:19	0.00	—	4.34

HIC Analysis of Etanercept Formulations k

[0125] HIC chromatography may be carried out in a manner known in the art and generally described in U.S. Pat. No. 7,294,481, incorporated herein by reference. Samples are evaluated at t₀ (within 24 hours of preparation at 5° C.) and again after either two weeks of storage at 25° C. (t₂) or after 4 weeks of storage at 25° C. In the HIC chromatograms of the formulations of the present invention, Peak 1 in the HIC chromatogram is believed to be or include "Fragment 3", which is identified and quantified using SEC, as referenced above in the discussion of SEC data; Peak 2 is etanercept monomer as referenced above in the discussion of SEC data; and Peak 3 includes "Aggregate(s)" as referenced above in the discussion of SEC data. It should further be understood that the terms "peak 1", "peak 2" and "peak 3" as used here also constitute a reference to the HIC peak 1, peak 2 and peak 3 referred to and disclosed in FIG. 4 of U.S. Pat. No. 7,294,481 incorporated herein by reference.

[0126] Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is: 5

1. A stabilized aqueous pharmaceutical composition comprising etanercept and a stabilizer to inhibit instability, misfolding aggregation and/or fragmentation of the etanercept, wherein the stabilizer comprises xylitol or a combination of xylitol and meglumine.

2. The composition of claim 1, further comprising one or more additional components selected from a buffer, a tonicity modifier and an excipient.

3. The composition of claim 2 optionally free or essentially free of arginine, and eliciting long term storage stability as characterized by at least one of:

SEC analysis at M₃ or T₂ or T₄ of: monomer content greater than about 90%; aggregates content of less than about 3 wt %; and fragment 3 content less than about 5 wt %; and

HIC analysis at M₃ or T₂ or T₄ wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than about 3 wt. %; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than about 80 wt. %; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than about 20 wt. %.

4. The composition of claim 2, optionally free, or essentially free, of arginine, comprising about 25 to about 75 mg/ml of etanercept; and a stabilizer to inhibit instability, aggregation and/or fragmentation of the etanercept, wherein the stabilizer is xylitol in an amount constituting up to about

10 wt. % of the composition, and wherein the composition is characterized by an SEC analysis at M₃ or T₂ or T₄ of: greater than about 80 wt. % monomer content; less than about 3 wt. % aggregate(s) content; and less than about 6 wt. % fragment 3 content; and having a pH of 6.0 to 6.6

5. The composition of claim 4 eliciting long term storage stability characterized by:

(a) an SEC analysis at M₃ or T₂ or T₄ of greater than about 90 wt. % monomer content; and less than about 3 wt. % aggregate(s) content; and

(b) an HIC analysis at M₃ or T₂ or T₄ wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than about 4 wt. %; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than about 80 wt. %; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than about 20 wt. %; and

6. The composition of claim 3 having an HIC analysis at M₃ or T₂ or T₄ wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than about 1 wt. %; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than about 95 wt. %; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than about 3 wt. %.

7. The composition of claim 3 comprising: about 25 to 75 mg/ml of etanercept; about 1-10 wt. % xylitol; about 1 to 30 mM sodium phosphate; optionally up to about 5 wt. % meglumine; optionally up to about 100 mM NaCl; and optionally up to about 5 wt. % sucrose.

8. The composition of claim 7 comprising: about 1-100 mM NaCl; about 1 to 5 wt. % sucrose; and wherein the stabilizer further comprises meglumine in an amount of about 1-5 wt. % of the composition.

9. The composition of claim 7 comprising: about 50 mg/ml of etanercept; about 10 wt. % xylitol; and 10 to about 30 mM sodium phosphate; wherein the formulation is characterized by an SEC analysis at M₃ or T₂ or T₄ of greater than about 85 wt. % monomer content.

10. The composition of claim 7 comprising: about 50 mg/ml of etanercept; about 10 to 30 mM sodium phosphate; about 1-3 wt. % xylitol; and about 1-3 wt. % meglumine; wherein the formulation is characterized by an SEC analysis at M₃ or T₂ or T₄ of greater than about 85 wt. % monomer content.

11. The composition of claim 7 comprising: about 50 mg/ml of etanercept; about 10-30 mM sodium phosphate; about 1-3 wt. % xylitol; about 1-3 wt. % meglumine; about 1-100 mM sodium chloride; and about 1-4 wt. % sucrose; wherein the formulation is characterized by an SEC analysis at M₃ or T₂ or T₄ of greater than about 85 wt. % monomer content.

12. The composition of claim 7 comprising: about 50 mg/ml of etanercept; about 6 wt. % xylitol; and about 10-30 mM sodium phosphate; wherein the formulation is characterized by an SEC analysis at M₃ or T₂ or T₄ of greater than about 85 wt. % monomer content.

13. The composition of claim 7 comprising about 50 mg/ml of etanercept; about 10-30 mM sodium phosphate; about 2-3 wt. % xylitol; and about 5% sucrose; wherein the formulation is characterized by an SEC analysis at M₃ or T₂ or T₄ of greater than about 85 wt. % monomer content.

14. The composition of claim 3 eliciting long term storage stability as characterized by: an HIC analysis at M₃ or T₂ or T₄ wherein the amount of the composition represented by peak 2



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(54) **ETANERCEPT FORMULATIONS
STABILIZED WITH SODIUM CHLORIDE**

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ABSTRACT

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The invention provides stabilized aqueous pharmaceutical
etanercept compositions suitable for long-term storage of
etanercept, methods of manufacture of these compositions,
methods of administration, and kits containing same.

velocity of 200 cm/h to give a 6 minute residence time. After loading, the column is washed with 2 CV of 25 mM acetate pH 5.5. The product is then eluted with an 8.5 CV, 15% to 85% gradient of 25 mM acetate pH 5.5 to 25 mM acetate, 0.7 M NaCl, pH 5.5. Product collection begins at 0.15 OD (A280, 1.0 cm path length) and collection ends at 50% of peak maximum. The eluate volume is approximately 5 CV. Residual product and contaminants are stripped from the column with 2 CV of 10 mM Tris, 1 M NaCl, pH 8.0 and discarded. The product obtained from the mixed mode column is filtered using a Millipore Opticap XL10, 0.22 μ m Durapore capsule filter, (0.69 m²). The product obtained from this step represents a recovery of about 70% of the Protein A material obtained in Step 2

[0122] Step 3B.

[0123] Mixed Mode Anion Exchange Chromatography.

[0124] A 27.0 L (45 cm diameter $\times$ 17 cm bed height) packed bed GE Healthcare Capto Adhere chromatography column is used to further purify the product obtained in step 3A above. Prior to use, the column is equilibrated with 2 CV of 25 mM Tris, pH 8.0 and sanitized with 2 CV of 0.1 N NaOH, 1M NaCl and neutralized and equilibrated with 2 CV of 25 mM Tris, pH 8.0. Prior to product loading, the column is equilibrated with 3 CV of 10 mM Tris, pH 8.0. The Capto MMC pool from Step 3A above is adjusted to pH 8.1 with $\sim$ 0.045 kg of 1 M Tris, pH 8.3 per kg of pool. The product from Step 3A above was diluted in-line 1:3.8 with WFI to adjust the conductivity to 12.0 mS/cm and pH 8.0. The resulting material is then applied to a column loading of up to 15 g/L media. The column is operated at a linear velocity of 170 cm/h to give a 6 minute residence time. After loading, the column is washed with 2 CV of 25 mM Tris, pH 8.0. The product is then eluted with a 10 CV gradient (20% to 90%) of 25 mM Tris, pH 8.0 to 10 mM Tris, 1 M NaCl, pH 8.0. Product collection is started at 0.15 OD (A280, 1.0 cm path length) and collection ended at 25% of peak maximum. The eluate volume is 4-6 CV. The eluted product is filtered using a commercially available capsule filter and then subjected in a known manner to viral filtration and tangential flow filtration steps. Overall product recovery from step 3B (including the final viral and tangential flow filtration steps) was approximately 68%. Product recovery measured before the filtration steps was about 75%. A schematic representation of HIC data obtained on elution fractions from this step are representing in FIG. 12.

[0125] Analysis:

[0126] The final filtered product obtained in this example is found to have greater than about 90 wt % correctly folded etanercept as determined by HIC; less than 5 wt % incorrectly folded etanercept species as determined by HIC; less than about 3 wt % of clipped material by HIC analysis (believed to be fragments of etanercept in which the TNFR portion thereof has been truncated) and a combined amount of correctly and incorrectly folded etanercept of greater than 95 wt % as determined by size exclusion chromatography.

Analysis of Etanercept Formulations

[0127] A. Thermal Stability Storage

[0128] Following dialysis and concentration, samples of the etanercept formulations exemplified above were sterile filtered in a bio safety cabinet. Using sterilized pipettes and autoclaved pipette tips, samples of the etanercept formulations were transferred to pre-labeled and autoclaved 1 mL lyophilization vials. Vials were stoppered with sterile butyl

stoppers and crimped with aluminum caps. All vials were then transferred to thermal stability ovens. Samples were subject to two thermal stability regimes: (1) two weeks at 40° C. and (2) four weeks at 25° C. Throughout this specification, these two temperature regimes are denoted "T₂" and T₄" respectively.

[0129] B. Size Exclusion Chromatography (SEC)

[0130] Etanercept formulations disclosed herein were analyzed using the well known technique of Size Exclusion Chromatography (SEC), a high-performance liquid chromatography method in which analytes are separated by size (see Rogner, M. (2000). Size Exclusion Chromatography. *Protein Liquid Chromatography*. M. Kastner. Amsterdam, Elsevier. 61: 89-145.). In order to evaluate thermal stability of the Etanercept samples described above, the samples were examined by a SEC method based on the literature (van Maarschalkerweerd, A., G. J. Wolbink, et al. (2011). "Comparison of analytical methods to detect instability of etanercept during thermal stress testing." *European Journal of Pharmaceutics and Biopharmaceutics* 78(2): 213-221.) The mobile phase buffer was prepared to contain 50 mM sodium phosphate monobasic monohydrate and 150 mM arginine. The pH was adjusted to 6.5 using 1 M HCl. All separations were performed using a Tosoh TSK-Gel SWxl 6 mm $\times$ 4 cm guard column (cat. no. 8543) attached linearly to a Tosoh TSK-Gel G4000 SWxl 7.8 mm $\times$ 30 cm (cat. no. 8542). To perform a separation, the columns were brought to room temperature (23° C.) and equilibrated with mobile phase at a flow rate of 0.5 mL/min. 5 microliters of 50 mg/mL etanercept formulation were injected onto the column using an autosampler. The separation was accomplished over 30 minutes at a flow rate of 0.5 mL/minute. Column eluent was monitored at a wavelength of 280 nm during this time.

[0131] C. Integration of Size Exclusion Chromatography Chromatograms

[0132] All integration was performed using Chromeleon software (Dionex). Prior to integration, the SEC chromatogram for a buffer containing no etanercept was subtracted from all chromatograms. All integration was performed between retention times of 12 minutes and 26 minutes. Several parameters were used to define a peak. The minimum area for a detected peak was set to 0.05 mAu $\cdot$ min. The two-dimensional sensitivity for peak detection was set to 0.01 mAu and 75 seconds. Peak shoulders were added manually using a manual integration tool. All detected peaks were manually adjusted in two steps. First, peak baselines (the bottom boundary of the peak) were adjusted to horizontal. Secondly, the vertical positions of the peak baselines were adjusted to that of the chromatogram baseline. The chromatogram baseline value was defined as the signal in absence of analyte. The signal in absence of analyte was defined as the absorbance in mAu at 12 minutes retention time.

[0133] D. SEC Fractions of Etanercept Formulations

[0134] In the SEC analysis of etanercept formulations described above, three SEC chromatography fractions were identified and studied. The fractions that were analyzed were, in the order of elution from the SEC column: (1) a high molecular weight fraction representing aggregates of the intact etanercept TNFR:Fc fusion protein likely assembled via non-covalent electrostatic attraction among intact etanercept molecules (hereinafter "aggregate(s)" or aggregate(s) content); (2) monomer content, representing the intact etanercept TNFR:Fc fusion protein (hereinafter referred to as "monomer" of "monomer content"); (3) a fraction likely rep-

representing one fragment or a population of fragments of the etanercept molecule in which one portion of the TNFR: molecule fusion protein has become cleaved from the monomer; in the loss of an arm of the Fab portion of the fusion protein at the hinge region of the molecule. The most common fragment or clipped species, as measured by SEC, is referred to as Fragment 3. In conducting the SEC analysis, it will be observed that aggregates elute first, followed by monomer, followed by fragment 3.

[0135] The following tables show the relative amounts of Aggregates, Monomer and Fragment 3 determined by SEC analysis as described above.

TABLE I

SEC ANALYSIS OF MONOMER			
Formulation No.	t ₀	t ₁	t ₂
Commercial Enbrel (comparative) [1:2]	98.81	92.58	87.64
xx2:6	98.09	—	87.77
xx2:8	98.07	—	88.38
xx3:10	98.16	—	89.77
xx3:11	98.32	—	89.87
xx3:12	98.33	—	90.92
xx3:13	98.18	—	90.74

Note:

Amounts reported Tables I, II and III are percentages by weight

T₀ = formulation maintained at 5° C. and analyzed within 24 hours of creation.

T₁ = formulation stored for one week at 40° C.

T₂ = formulation stored for two weeks at 40° C.

TABLE II

SEC ANALYSIS OF AGGREGATES			
Formulation No.	t ₀	t ₁	t ₂
Commercial Enbrel (comparative)	0.09	0.59	1.02
2:6	0.30	—	1.81
2:8	0.30	—	1.42
3:10	0.27	—	1.33
3:11	0.20	—	1.24
3:12	0.21	—	0.85
3:13	0.28	—	0.86

Note:

Amounts reported Tables I, II and III are percentages by weight

T₀ = formulation maintained at 5° C. and analyzed within 24 hours of creation.

T₁ = formulation stored for one week at 40° C.

T₂ = formulation stored for two weeks at 40° C.

TABLE III

ANALYSIS OF FRAGMENT 3			
Formulation No	t ₀	t ₁	t ₂
Commercial Enbrel (comparative)	0.00	3.30	6.29
2:6	0.00	—	4.73
2:8	0.00	—	6.29
3:10	0	—	3.76
3:11	0	—	3.59
3:12	0	—	3.68
3:13	0	—	3.88

TABLE IV

SEC MONOMER CONTENT (4 weeks/25° C.)		
Table IV below shows monomer (etanercept) content of etanercept formulations prepared according to the present invention, when stored for four weeks at 25° C. denoted by the symbol T ₄ . In the following table T ₀ represents SEC measurements conducted within 24 hours of formulation preparation, at sample temperature of 5° C.; and T ₄ represents etanercept formulation samples subjected to SEC analysis after 4 weeks storage at 25° C.		
FORMULATION No.	T ₀ Monomer Content	T ₄ Monomer Content
Commercial Enbrel (comparative)	98.15	97.86
3:10	98.16	97.66
3:11	98.32	97.75
3:12	98.33	97.90
3:13	98.18	97.78

TABLE V

SEC AGGREGATES CONTENT (4 weeks/25° C.)		
Table V below shows aggregate(s) content of etanercept formulations prepared according to the present invention after storage for four weeks at 25° C. In the following table T ₀ represents SEC measurements conducted within 24 hours of formulation preparation, at sample temperature of 5° C.; and T ₄ represents etanercept formulation samples subjected to SEC analysis after 4 weeks storage at 25° C.		
FORMULATION No.	T ₀ Aggregate(s) Content	T ₄ Aggregate(s) Content
Commercial Enbrel (comparative)	0.28	0.25
3:10	0.27	0.32
3:11	0.20	0.27
3:12	0.21	0.26
3:13	0.28	0.32

HIC Analysis of Etanercept Formulations

[0136] The following tables (Tables VI and VII) show the results of hydrophobic interaction chromatography ("HIC chromatography") conducted on samples 3:5 and 3:8. HIC chromatography was carried out in a manner known in the art and generally described in U.S. Pat. No. 7,294,481, incorporated herein by reference. Samples were evaluated at t₀ (within 24 hours of preparation at 5° C.) and again after either two weeks of storage at 25° C. (t₂) (see Table VI) or after 4 weeks of storage at 25° C. (t₄) (See Table VII) Peak 1 in the HIC chromatogram is believed to be or include "Fragment 3", which is identified and quantified using SEC, as referenced above in the discussion of SEC data; Peak 2 is etanercept monomer as referenced above in the discussion of SEC data; and Peak 3 includes "Aggregate(s)" as referenced above in the discussion of SEC data. It should further be understood that the terms "peak 1", "peak 2" and "peak 3 as used here also constitute a reference to the HIC peak 1, peak 2 and peak 3 referred to and disclosed in FIG. 4 of U.S. Pat. No. 7,294,481 incorporated herein by reference.

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(54) Title: ARGININE - FREE TNFR : FC- FUSION POLYPEPTIDE COMPOSITIONS AND METHODS OF USE

(57) Abstract: Aspects of the invention are directed to arginine-free polypeptide-containing compositions and methods for treating disorders associated with inflammation or the autoimmune response. In particular, the polypeptide is etanercept.

modified to include one or more limitations found in any other claim that is dependent on the same base claim.

Where elements are presented as lists, *e.g.*, in Markush group format, it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, etc., certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements, features, etc. For purposes of simplicity those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the term "comprising" is intended to be open and permits the inclusion of additional elements or steps.

Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

The term "about" or "approximately" can mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *e.g.*, the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, up to 10%, up to 5%, or up to 1% of a given value. Alternatively, the term can mean within an order of magnitude, for example, within 5-fold, or within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term "about" meaning within an acceptable error range for the particular value should be assumed.

In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the methods of the invention can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

What is claimed is:

CLAIMS

1. A composition, comprising:
an isolated polypeptide that is an extracellular ligand-binding portion of a human p75
5 tumor necrosis factor receptor fused to the Fc region of a human IgG1; and
salt in an amount sufficient to prevent aggregation of the isolated polypeptide, thereby
stabilizing the composition,
wherein the composition comprises L-arginine at a concentration of less than 1 mM.
- 10 2. The composition of claim 1, wherein the composition comprises L-arginine at a
concentration of less than 0.1 mM.
3. The composition of claim 2, wherein the composition comprises L-arginine at a
concentration of less than 0.01 mM.
- 15 4. The composition of claim 3, wherein the composition comprises L-arginine at a
concentration of less than 0.001 mM.
5. The composition of claim 4, wherein the composition is free of L-arginine.
- 20 6. The composition of any of claims 1-5, comprising about 10 mg/ml to about 100 mg/ml
of the isolated polypeptide.
7. The composition of any of claims 1-6, wherein the isolated polypeptide is etanercept.
- 25 8. The composition of claim 1, wherein the composition further comprises aqueous buffer.
9. The composition of claim 8, wherein the aqueous buffer is sodium phosphate, histidine,
potassium phosphate, sodium or potassium citrate, maleic acid, ammonium acetate, tris-
30 (hydroxymethyl)-aminomethane (tris), acetate, diethanolamine or a combination thereof.

10. The composition of claim 8 or 9, wherein the aqueous buffer is present at a concentration of about 1 mM to about 15 mM.
11. The composition of any of claims 1-10, wherein the salt is sodium chloride.
- 5 12. The composition of any of claims 1-11, wherein the salt is present at a concentration of about 120 mM to about 150 mM.
13. The composition of any of claims 1-12, further comprising an excipient.
- 10 14. The composition of any of claims 1-13, wherein the excipient is sucrose, lactose, glycerol, xylitol, sorbitol, Mannitol, maltose, inositol, trehalose, glucose, bovine serum albumin (BSA), human SA or recombinant HA, dextran, PVA, hydroxypropyl methylcellulose (HPMC), polyethyleneimine, gelatin, polyvinylpyrrolidone (PVP), hydroxyethylcellulose (HEC),
- 15 polyethylene glycol, ethylene glycol, glycerol, dimethylsulfoxide (DMSO), dimethylformamide (DMF), proline, L-serine, sodium glutamic acid, alanine, glycine, lysine hydrochloride, sarcosine, gamma-aminobutyric acid, Tween-20, Tween-80, SDS, polysorbate, polyoxyethylene copolymer, potassium phosphate, sodium acetate, ammonium sulfate, magnesium sulfate, sodium sulfate, trimethylamine N-oxide, betaine, zinc ions, copper ions, calcium ions,
- 20 manganese ions, magnesium ions, CHAPS, sucrose monolaurate, 2-O-beta-mannoglycerate or a combination thereof.
15. The composition of any of claims 1-14, wherein the excipient is sucrose.
- 25 16. The composition of any of claims 1-15, wherein the excipient is sucrose at a concentration of from about 0.5% to about 1.5%.
17. The composition of any of claims 1-16, wherein the pH of the composition is about 5.5 to about 7.8.
- 30 18. The composition of claim 1, comprising 50 mg/ml etanercept, about 10 mM sodium

phosphate, about 140 mM sodium chloride, and about 1% sucrose, wherein the pH of the composition is about pH 6.0 to about pH 7.0.

19. The composition of any of claims 1-18, wherein the composition has a commercially-
5 viable shelf life of at least 24 months.

20. The composition of any of claims 1-19, wherein the composition is suitable for subcutaneous administration.

10 21. The composition of any of claims 1-20, wherein the isolated polypeptide is purified.

22. The composition of any of claims 1-21, wherein the composition is sterilized.

23. A composition, comprising:
15 an isolated polypeptide that is an extracellular ligand-binding portion of a human p75 tumor necrosis factor receptor fused to the Fc region of a human IgG1;
aqueous buffer at a concentration of less than 25 mM; and
salt at a concentration of greater than 100 mM,
wherein the composition comprises L-arginine at a concentration of less than 1 mM.

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24. The composition of claim 23, wherein the composition comprises L-arginine at a concentration of less than 0.1 mM.

25. The composition of claim 24, wherein the composition comprises L-arginine at a
25 concentration of less than 0.01 mM.

26. The composition of claim 25, wherein the composition comprises L-arginine at a concentration of less than 0.001 mM.

30 27. The composition of claim 26, wherein the composition is free of L-arginine.

28. A composition, consisting essentially of:
an isolated polypeptide that is an extracellular ligand-binding portion of a human p75
tumor necrosis factor receptor fused to the Fc region of a human IgG1;
aqueous buffer at a concentration of about 10 mM;
5 salt at a concentration of about 140 mM; and
sucrose.
29. The composition of claim 28, wherein the isolated polypeptide is present at a
concentration of 50 mg/mL.
- 10 30. The composition of claim 28 or 29, wherein the polypeptide is etanercept.
31. A method, comprising administering to an individual a composition, comprising:
an isolated polypeptide that is an extracellular ligand-binding portion of a human p75 tumor
15 necrosis factor receptor fused to the Fc region of a human IgG1;
aqueous buffer; and
salt in an amount sufficient to prevent aggregation of the polypeptide, thereby stabilizing
the composition,
wherein the composition comprises L-arginine at a concentration of less than 1 mM.
- 20 32. The method of claim 31, wherein the composition comprises L-arginine at a
concentration of less than 0.1 mM.
33. The method of claim 32, wherein the composition comprises L-arginine at a
25 concentration of less than 0.01 mM.
34. The method of claim 33, wherein the composition comprises L-arginine at a
concentration of less than 0.001 mM.
- 30 35. The method of claim 34, wherein the composition is free of L-arginine.

36. The method of any of claims 31-35, wherein the composition comprises about 10 mg/ml to about 100 mg/ml of the isolated polypeptide.
37. The method of any one of claims 31-36, wherein the polypeptide is etanercept.
- 5 38. The method of any of claims 31-37, wherein the aqueous buffer is sodium phosphate, histidine, potassium phosphate, sodium or potassium citrate, maleic acid, ammonium acetate, tris-(hydroxymethyl)-aminomethane (tris), acetate, diethanolamine or a combination thereof.
- 10 39. The method of any of claims 31-38, wherein the aqueous buffer is present at a concentration of about 1 mM to about 15 mM.
40. The method of any of claims 31-39, wherein the salt is sodium chloride.
- 15 41. The method of any of claims 31-40, wherein the salt is present at a concentration of about 120 mM to about 150 mM.
42. The method of any of claims 31-41, wherein the composition further comprises comprising an excipient.
- 20 43. The method of 42, wherein the excipient is sucrose, lactose, glycerol, xylitol, sorbitol, Mannitol, maltose, inositol, trehalose, glucose, bovine serum albumin (BSC), human SC or recombinant HC, dextran, PVC, hydroxypropyl methylcellulose (HPMC), polyethyleneimine, gelatin, polyvinylpyrrolidone (PVP), hydroxyethylcellulose (HEC), polyethylene glycol, ethylene glycol, glycerol, dimethylsulfoxide (DMSO), dimethylformamide (DMF), proline, L-serine, sodium glutamic acid, alanine, glycine, lysine hydrochloride, sarcosine, gamma-aminobutyric acid, Tween-20, Tween-80, SDS, polysorbate, polyoxyethylene copolymer, potassium phosphate, sodium acetate, ammonium sulfate, magnesium sulfate, sodium sulfate, trimethylamine N-oxide, betaine, zinc ions, copper ions, calcium ions, manganese ions, 25 magnesium ions, CHCPS, sucrose monolaurate, 2-O-beta-mannoglycerate or a combination thereof.
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CERTIFICA

DIRECCIÓN DEL DOMICILIO PRINCIPAL: CRA. 1 NRO. 46 84
MUNICIPIO: CALI-VALLE
TELÉFONO COMERCIAL 1: 6877700
TELÉFONO COMERCIAL 2: 6877700
TELÉFONO COMERCIAL 3: 3155598201
FAX: 6877790
CORREO ELECTRÓNICO: lafrancolsas@lafrancol.com

DIRECCIÓN PARA NOTIFICACIÓN JUDICIAL: CRA. 1 NRO. 46 84
MUNICIPIO: CALI-VALLE
TELÉFONO PARA NOTIFICACIÓN 1: 6877700
TELÉFONO PARA NOTIFICACIÓN 2: 6877700
TELÉFONO PARA NOTIFICACIÓN 3: 3155598201
FAX PARA NOTIFICACIÓN: 6877790
CORREO ELECTRÓNICO DE NOTIFICACIÓN: lafrancolsa@lafrancol.com

CERTIFICA

MATRÍCULA MERCANTIL : 5233-16
FECHA DE MATRICULA EN ESTA CÁMARA: 02 DE OCTUBRE DE 1958
ÚLTIMO AÑO RENOVADO: 2016

CERTIFICA

ACTIVIDAD PRINCIPAL
C2100 FABRICACIÓN DE PRODUCTOS FARMACÉUTICOS, SUSTANCIAS QUÍMICAS MEDICINALES PRODUCTOS BOTÁNICOS DE USO FARMACÉUTICO

ACTIVIDAD SECUNDARIA
C1089 ELABORACIÓN DE OTROS PRODUCTOS ALIMENTICIOS N.C.P.

OTRAS ACTIVIDADES
C1811 ACTIVIDADES DE IMPRESIÓN
N8299 OTRAS ACTIVIDADES DE SERVICIO DE APOYO A LAS EMPRESAS N.C.P.

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 LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA

QUE POR ESCRITURA NRO. 3672 DEL 24 DE AGOSTO DE 2009 NOTARIA TERCERA DE CALI ,INSCRITA EN LA CAMARA DE COMERCIO EL 27 DE AGOSTO DE 2009 BAJO EL NRO. 9876 DEL LIBRO IX ,CAMBIO SU NOMBRE DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. . POR EL DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. SIGLA: LAFRANCOL S.A. .

CERTIFICA

QUE POR ACTA NRO. 124 DEL 30 DE MARZO DE 2012 ASAMBLEA GENERAL ,INSCRITA EN LA CAMARA DE COMERCIO EL 31 DE MAYO DE 2012 BAJO EL NRO. 6645 DEL LIBRO IX ,SE TRANSFORMO DE SOCIEDAD ANÓNIMA EN SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. SIGLA: LAFRANCOL S.A.S. .

CERTIFICA

QUE POR ACTA NRO. 124 DEL 30 DE MARZO DE 2012 ASAMBLEA DE ACCIONISTAS ,INSCRITA EN LA CAMARA DE COMERCIO EL 03 DE DICIEMBRE DE 2012 BAJO EL NRO. 14136 DEL LIBRO IX ,SE APROBO LA ESCISION ENTRE (ESCIDENTE) AMERICAN GENERICS S.A.S. Y (BENEFICIARIA(S)) LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. .

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
E.P. 4274	12/12/1984	NOTARIA NOVENA DE CALI	19/12/1984	73088	IX
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



**Cámara de
Comercio de
Cali**

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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
E.P. 3672	24/08/2009	NOTARIA TERCERA DE CALI	27/08/2009	9876	IX
ACT 116	04/03/2010	ASAMBLEA GRAL ORDINARIA	11/05/2010	5470	IX
E.P. 4421	21/10/2010	NOTARIA TERCERA DE CALI	26/10/2010	12622	IX
E.P. 1786	16/05/2011	NOTARIA TERCERA DE CALI	24/05/2011	6318	IX
ACT 124	30/03/2012	ASAMBLEA GENERAL	31/05/2012	6645	IX
ACT 125	27/07/2012	ASAMBLEA GENERAL DE ACCIONISTAS	23/08/2012	10177	IX
ACT 127	12/12/2012	ASAMBLEA GENERAL DE ACCIONISTAS	13/12/2012	14600	IX
ACT 131	17/06/2013	ASAMBLEA GENERAL DE ACCIONISTAS	24/06/2013	7217	IX
ACT 134	26/09/2014	ASAMBLEA DE ACCIONISTAS	17/10/2014	13923	IX
ACT 135	02/10/2014	ASAMBLEA DE ACCIONISTAS	17/10/2014	13928	IX

CERTIFICA

VIGENCIA: INDEFINIDA

CERTIFICA

OBJETO SOCIAL. LA SOCIEDAD EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ REALIZAR, ENTRE OTROS, LAS SIGUIENTES ACTIVIDADES COMERCIALES Y EMPRESARIALES: 2.1) FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y AFINES. 2.2) LA REPRESENTACIÓN DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. 2.3) FABRICACIÓN, IMPORTACIÓN, DISTRIBUCIÓN Y VENTA DE CUALESQUIERA TIPO DE PRODUCTOS VETERINARIOS. 2.4) LA REALIZACIÓN DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. 2.5) IMPORTAR CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y AFINES Y/O PRODUCTOS INTERMEDIOS O A GRANEL. PARÁGRAFO UNO: EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ 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 EN MUTUO DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN O NO LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS, O CUALESQUIERA OTRAS EMPRESAS DE OTROS OBJETOS SOCIALES. PARÁGRAFO DOS: ADEMÁS DE LAS ACTIVIDADES REFERIDAS EN ESTE ARTICULO, Y LAS ENUNCIADAS EN EL PARÁGRAFO UNO, COMO SOCIEDAD POR ACCIONES SIMPLIFICADA, PODRÁ REALIZAR CUALQUIER ACTIVIDAD LICITA DE COMERCIO EN EL PAÍS O EN EL EXTERIOR, POR EJEMPLO, Y DE MANERA ILUSTRATIVA MÁS NO LIMITATIVA, GESTIÓN DE LICENCIAS, REGISTROS DE EXPORTACIÓN O IMPORTACIÓN, CONVENIOS RELATIVOS A ESAS ACTIVIDADES Y LOS ACTOS RELACIONADOS CON EL MISMO. PARÁGRAFO TRES: POR RAZÓN DE SU OBJETO SOCIAL, LA SOCIEDAD NO PODRÁ CONSTITUIRSE GARANTE NI FIADORA DE OBLIGACIONES DISTINTAS DE LAS PROPIAS NI GARANTIZAR CON SUS BIENES OBLIGACIONES DE TERCEROS, A MENOS QUE LO AUTORICE EN CADA CASO LA ASAMBLEA GENERAL DE ACCIONISTAS CON EL VOTO DE LA TOTALIDAD DE LOS MIEMBROS PRESENTES EN LA REUNIÓN CORRESPONDIENTE.

CERTIFICA

DIRECCIÓN Y ADMINISTRACIÓN. LA DIRECCIÓN Y ADMINISTRACIÓN DE LA SOCIEDAD ESTARÁ A CARGO DE: A) LA ASAMBLEA GENERAL DE ACCIONISTAS; Y B) LOS REPRESENTANTES LEGALES COMO SE

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DESCRIBEN EN SUS CARGOS Y FUNCIONES EN LOS PRESENTES ESTATUTOS.

REPRESENTACIÓN LEGAL. ADMINISTRACIÓN. LA ADMINISTRACIÓN DE LA SOCIEDAD CORRESPONDE AL REPRESENTANTE LEGAL, QUE SE DENOMINARÁ GERENTE, QUIEN TENDRÁ HASTA CINCO SUPLENTE. EL GERENTE Y SUS SUPLENTE SERÁN LOS REPRESENTANTES LEGALES QUIENES SERÁN DESIGNADOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS POR UN TÉRMINO INDEFINIDO Y SE MANTENDRÁN VIGENTES HASTA TANTO ESTOS NO SEAN REMOVIDOS DE SUS CARGOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS. LOS SUPLENTE REEMPLAZARÁN AL GERENTE, DURANTE SUS AUSENCIAS TEMPORALES, ABSOLUTAS O ACCIDENTALES.

FUNCIONES DEL REPRESENTANTE LEGAL.: SON FUNCIONES DEL GERENTE: (A) REPRESENTAR A LA SOCIEDAD ANTE LOS ACCIONISTAS, ANTE TERCEROS Y ANTE AUTORIDADES DE LOS ÓRDENES ADMINISTRATIVO O JURISDICCIONAL, CON FACULTADES PARA TRANSIGIR, COMPROMETER Y DESISTIR Y PARA COMPARECER EN JUICIO; (B) SUPERVISAR EL COMPORTAMIENTO DE LOS EMPLEADOS DE LA SOCIEDAD PARA ASEGURAR EL CUMPLIMIENTO DE SUS OBLIGACIONES. (C) CUMPLIR Y HACER CUMPLIR LAS DETERMINACIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. (D) PRESENTAR, EN LAS REUNIONES ORDINARIAS DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL BALANCE GENERAL DE LOS NEGOCIOS DEL RESPECTIVO EJERCICIO, JUNTO CON EL ESTADO DE RESULTADOS, UN PROYECTO SOBRE DISTRIBUCIÓN DE UTILIDADES O SOBRE CANCELACIÓN DE PÉRDIDAS, JUNTO CON UN INFORME SOBRE EL ESTADO DE LOS NEGOCIOS DE LA SOCIEDAD. (E) SUMINISTRAR A LA ASAMBLEA GENERAL DE ACCIONISTAS LOS INFORMES QUE ÉSTAS LE SOLICITEN. (F) OTORGAR LOS PODERES QUE SEAN NECESARIOS PARA LA DEFENSA O REPRESENTACIÓN DE LA SOCIEDAD. (G) SOMETER LAS DIFERENCIAS QUE PUEDAN SURGIR ENTRE LA SOCIEDAD Y TERCEROS A LA DECISIÓN DE ÁRBITROS Y CONCURRIR A LA DESIGNACIÓN DE DICHOS ÁRBITROS Y DEL APODERADO QUE HAYA DE REPRESENTARLA ANTE EL RESPECTIVO TRIBUNAL. (H) EJERCER LIBREMENTE TODOS LOS ACTOS Y ACUERDOS APROPIADOS Y NECESARIOS PARA EL CUMPLIMIENTO DEL OBJETO SOCIAL, Y (I) EJERCER LAS DEMÁS ATRIBUCIONES QUE LE CONFIEREN LAS LEYES Y LOS ESTATUTOS SOCIALES Y LAS DEMÁS QUE LE CORRESPONDAN EN RAZÓN DE LA NATURALEZA DE SU CARGO.

EL GERENTE REQUIERE AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA LLEVAR A CABO LOS SIGUIENTES ACTOS:

1. CELEBRAR TODA CLASE DE CONTRATOS CUYO OBJETO SEA LA APERTURA DE SUCURSALES, AGENCIAS O DEPENDENCIAS, O LA EMISIÓN DE BONOS DE LA SOCIEDAD.
2. APROBAR, CUALQUIERA SEA SU NATURALEZA, TODOS LOS ACTOS QUE IMPLIQUEN RENUNCIA A DERECHOS DE LA SOCIEDAD, TALES COMO TRANSACCIONES, DESISTIMIENTOS, CONCILIACIONES O ACTOS DE SIMILAR NATURALEZA, CUYA CUANTÍA ABSOLUTA SEA SUPERIOR AL EQUIVALENTE EN MONEDA LEGAL COLOMBIANA A LA SUMA DE QUINIENTOS MIL DÓLARES DE LOS ESTADOS UNIDOS DE AMÉRICA (USD \$500.000.00). EN LOS ASUNTOS DE NATURALEZA LABORAL ESTE REQUISITO SE EXIGIRÁ CUANDO LA REMUNERACIÓN ANUAL DEL RESPECTIVO TRABAJADOR SEA SUPERIOR A SEISCIENTOS CINCUENTA SALARIOS MÍNIMOS LEGALES MENSUALES VIGENTES (650 SMLMV) DE LA REPÚBLICA DE COLOMBIA.
3. INICIAR CUALQUIER ACCIÓN JUDICIAL O ADMINISTRATIVA CUYA CUANTÍA ABSOLUTA SEA SUPERIOR AL EQUIVALENTE EN MONEDA LEGAL COLOMBIANA A LA SUMA DE QUINIENTOS MIL DÓLARES DE LOS ESTADOS UNIDOS DE AMÉRICA (USD \$500.000.00).
4. SUSCRIBIR O REALIZAR CUALQUIER CONTRATO, ACUERDO, ACTO U OPERACIÓN PARA LA ADQUISICIÓN, VENTA, CESIÓN, TRASPASO O DISPOSICIÓN DE ACTIVOS FIJOS DE LA SOCIEDAD CUYO VALOR EN PESOS COLOMBIANOS, O EN CUALQUIER OTRA MONEDA EXCEDA DE UN MILLÓN DE DÓLARES DE LOS ESTADOS UNIDOS DE AMÉRICA (USD \$1.000.000).
5. GRAVAR O ASUMIR CUALQUIER GRAVAMEN SOBRE LOS ACTIVOS FIJOS DE LA SOCIEDAD, CUALQUIERA QUE SEA SU VALOR.



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6. OTORGAR GARANTÍAS POR PARTE DE LA SOCIEDAD PARA GARANTIZAR OBLIGACIONES DE TERCEROS, SALVO POR/AS OBLIGACIONES DE COMPAÑÍAS FINALES DE LA SOCIEDAD.

7. LAS OPERACIONES FINANCIERAS Y BANCARIAS DEBEN REALIZARSE DE ACUERDO CON LAS POLÍTICAS ESTABLECIDAS POR LA ASAMBLEA GENERAL DE ACCIONISTAS, QUIEN CONFORMARÁ UN COMITÉ DE FINANZAS, PARA ESTE FIN.

PARA CALCULAR EL EQUIVALENTE DE LOS MONTOS ANTERIORES EN PESOS COLOMBIANOS, SERÁ USADA LA TASA REPRESENTATIVA DEL MERCADO (TRM) CERTIFICADA POR LA SUPERINTENDENCIA FINANCIERA O LA ENTIDAD COMPETENTE PARA EL DÍA EN QUE SE SUSCRIBA O REALICE LA TRANSACCIÓN.

CERTIFICA

DOCUMENTO: ACTA No. 134 DEL 26 DE SEPTIEMBRE DE 2014

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 17 DE OCTUBRE DE 2014 No. 13926 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

GERENTE

MANUEL CAMILO CAMACHO PEREZ

C.C.80504680

PRIMER SUPLENTE DEL GERENTE

MARIO FRANCISCO PEREZ ANZOLA

C.C.79656956

SEGUNDO SUPLENTE DEL GERENTE

MARIA ISABEL RIVAS PARRA

C.C.52251884

CERTIFICA

DOCUMENTO: ACTA No. 135 DEL 02 DE OCTUBRE DE 2014

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 17 DE OCTUBRE DE 2014 No. 13929 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE

FRANCISCO JAVIER PICART LAURENZ

C.E.399661

CUARTO SUPLENTE DEL GERENTE

TITO NOE PARRA MURILLO

C.C.79579680



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CERTIFICA

DOCUMENTO: ACTA No. 139 DEL 23 DE NOVIEMBRE DE 2015

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 07 DE DICIEMBRE DE 2015 No. 23664 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REVISOR FISCAL

ERNST & YOUNG AUDIT S.A.S.

NIT.860008890-5

CERTIFICA

DOCUMENTO: DOCUMENTO PRIVADO DEL 08 DE JUNIO DE 2016

ORIGEN: ERNST & YOUNG AUDIT S.A.S

INSCRIPCION: 17 DE JUNIO DE 2016 No. 9884 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL

MANUEL ANTONIO RAMIREZ YANTEN

C.C.1117496898

REVISOR FISCAL SUPLENTE

CAROLINA MEJIA SALGADO

C.C.1130620779

CERTIFICA

CAPITAL AUTORIZADO: \$40,000,000,224

NUMERO DE ACCIONES: 3,333,333,352

VALOR NOMINAL: \$12

CAPITAL SUSCRITO: \$24,140,480,940

NUMERO DE ACCIONES: 2,011,706,745

VALOR NOMINAL: \$12

CAPITAL PAGADO: \$24,140,480,940

NUMERO DE ACCIONES: 2,011,706,745

VALOR NOMINAL: \$12

CERTIFICA

CERTIFICA ESPECIAL POR VOLUNTAD DEL USUARIO:

DOCUMENTO: DOCUMENTO PRIVADO DEL 22 ENERO DEL 2015

INSCRIPCION: 11 DE FEBRERO DE 2015 NRO. 1943 DEL LIBRO IX

CONSTA EL GRUPO EMPRESARIAL :



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MATRIZ: ABBOTT INVESTMENTS LUXEMBOURG S.A.R.L.

DOMICILIO: LUXEMBURGO

NACIONALIDAD: LUXEMBURGUESA

ACTIVIDAD: PARTICIPAR DE CUALQUIER FORMA EN CUALQUIER ACTIVIDAD DE TIPO COMERCIAL, INDUSTRIAL, FINANCIERA U OTRA, EN LUXEMBURGO O EN CUALQUIER COMPAÑÍA O EMPRESA EXTRANJERA.

SUBORDINADA: ABBOTT LABORATORIES DE COLOMBIA S.A

NIT: 860002134-8

DOMICILIO: BOGOTA D.C.

NACIONALIDAD: COLOMBIANA.

ACTIVIDAD: IMPORTACION, EXPORTACION, DISTRIBUICION, COMPRA Y VENTA DE TODA CLASE DE MEDICAMENTOS Y PRODUCTOS QUIMICOS Y FARMACÉUTICOS Y ESPECIALIDADES MEDICINALES PARA USO HUMANO Y VETERINARIO.

SUBORDINADA: LABORATORIOS SYNTHESIS S.A.S

NIT; 860000760-1

DOMICILIO: BOGOTA D.C

NACIONALIDAD: COLOMBIANA.

ACTIVIDAD: IMPORTACION, EXPORTACION, FABRICACIÓN, COMERCIALIZACION, DISTRIBUCION Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIENICOS, VETERINARIOS E IMPLEMENTOS MEDICOS.

SUBORDINADA: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.

NIT.890301463-8

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LA FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO, DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO

SUBORDINADA: LAFRANCOL INTERNACIONAL S.AS

NIT: 815003912-2

DOMICILIO: PALMIRA, VALLE.

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: ELABORACIÓN DE OTROS PRODUCTOS ALIMENTICIOS. FABRICACIÓN DE PRODUCTOS FARMACÉUTICOS, SUSTANCIAS QUÍMICAS MEDICINALES PRODUCTOS BOTÁNICOS DE USO FARMACÉUTICO.

SUBORDINADA: AMERICAN GENERICS S A S

NIT. 800223214-9

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TITULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS, ETC.

SUBORDINADA: LABORATORIOS NATURMEDIK S.A.S.

NIT. 800226363-1

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TITULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS, ETC.



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SUBORDINADA: LABORATORIOS PAULY PHARMACEUTICAL S.A.S.

NIT: 800.097.402-6

DOMICILIO: CALI, VALLE

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TÍTULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS ETC.

SUBORDINADA: DISTRIBUCIONES UQUIFA S.A.S.

NIT: 800182021-7

DOMICILIO: CALI, VALLE

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TÍTULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS ETC.

SUBORDINADA: FOCUS PHARMACEUTICAL S.A.S

NIT: 900.104.555-8

DOMICILIO: CALI, VALLE

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TÍTULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS ETC.

SUBORDINADA: LAFRANCOL PERU S.R.L.

DOMICILIO: LIMA

NACIONALIDAD: PERUANA

ACTIVIDAD: DISTRIBUCION Y COMERCIALIZACION DE PRODUCTOS FARMACEUTICOS DE USO HUMANO.

SUBORDINADA: LAFRANCOL DOMINICANA S.A.S.

DOMICILIO: SANTO DOMINGO

NACIONALIDAD: REPUBLICA DOMINICANA

ACTIVIDAD: FABRICACION DE PRODUCTOS FARMACEUTICOS.

SUBORDINADA: LAFRANCOL GUATEMALA S.A.

DOMICILIO: GUATEMALA

NACIONALIDAD: GUATEMALTECA

ACTIVIDAD: PRODUCCION, FABRICACION, EXPORTACION Y DISTRIBUCION DE PRODUCTOS FARMACEUTICOS Y/O ALIMENTICIOS Y NATURALES DE CONSUMO HUMANO Y LA COMERCIALIZACION DE TODA CLASE DE MERCANCIAS POR CUENTA PROPIA O EN NOMBRE DE TERCEROS.

PRESUPUESTO DE CONTROL: ABBOTT INVESTMENTS LUXEMBOURG S.A. R.L ADQUIRIÓ EL 26 DE SEPTIEMBRE DE 2014 UNA PARTICIPACIÓN INDIRECTA DE MAS DEL 50% DEL CAPITAL DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL SAS.

UNA PARTICIPACIÓN INDIRECTA EN EL CAPITAL DE LAS SOCIEDADES ACTUALMENTE REGISTRADAS COMO SUBORDINADAS DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S EN COLOMBIA Y EN EL EXTERIOR (LAS SOCIEDADES SUBORDINADAS A SABER: AMERICAN GENERICS S A S, LABORATORIOS NATURMEDIK S.A.S., LABORATORIOS PAULY PHARMACEUTICAL S.A.S., DISTRIBUCIONES UQUIFA S.A.S., FOCUS PHARMACEUTICAL S.A.S. LAFRANCOL PERU SRL, LAFRANCOL DOMINICANA S.A.S, LAFRANCOL GUATEMALA S.A.)

UNA PARTICIPACIÓN INDIRECTA DE MAS DEL 50% DEL CAPITAL DE LABORATORIOS SYNTHESIS S.A.S, CON DOMICILIO EN BOGOTA E IDENTIFICADA CON NIT: 860000760-1

ABBOTT INVESTMENTE LUXEMBOURG S.A.R.L. TIENE UNA PARTICIPACIÓN DIRECTA DEL MAS DEL 50% EN EL CAPITAL DE ABBOT LABORATORIES DE COLOMBIA S.A SITUACION DE CONTROL QUE FUE REGISTRADA MEDIANTE DOCUMENTO PRIVADO DEL 15 DE OCTUBRE DE 2013, INSCRITO EL 22 DE OCTUBRE DEL MISMO AÑO.

ADEMÁS DEL VÍNCULO DE SUBORDINACIÓN POR PARTICIPACIÓN QUE EXISTE ENTRE ABBOTT INVESTMENTS LUXEMBOURG S.A. R.L, (SOCIEDAD CONTROLANTE) Y LAS SOCIEDADES COLOMBIANAS ABBOTT LABORATORIES DE COLOMBIA S.A., LABORATORIOS SYNTHESIS S.A.S., LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S, Y LAS SOCIEDADES SUBORDINADAS, EN LOS TÉRMINOS DEL NUMERAL 1 DEL ARTÍCULO 261 DEL CÓDIGO DE COMERCIO; EXISTE ENTRE DICHAS SOCIEDADES UNIDAD DE PROPÓSITO Y DIRECCIÓN, SEGÚN LO DISPUESTO EN EL ARTÍCULO 28 DE LA LEY 222 DE 1995. POR LO TANTO, SE CONFIGURA UN GRUPO EMPRESARIAL A PARTIR DEL 26 DE SEPTIEMBRE DE 2014.

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 2016

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.870576-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS FRANCO COLOMBIANO LAFRANCOL SAS UBICADO EN: CL. 36 A NRO. 4 03 DE CALI
FECHA MATRICULA : 02 DE MAYO DE 2013
RENOVO : POR EL AÑO 2016

CERTIFICA

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 30 DE MARZO DE 2016

CERTIFICA

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

LOS ACTOS ADMINISTRATIVOS DE REGISTRO QUEDAN EN FIRME DIEZ (10) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS.

ESTE CERTIFICADO CUENTA CON PLENA VALIDEZ JURIDICA SEGUN LO DISPUESTO EN LA LEY 527 DE 1999. EN EL SE INCORPORAN TANTO LA FIRMA MECANICA QUE ES UNA REPRESENTACION GRAFICA DE LA FIRMA DEL SECRETARIO DE LA CAMARA DE COMERCIO DE CALI, COMO LA FIRMA DIGITAL , LAS CUALES PODRA VERIFICAR A TRAVES DE SU APLICATIVO VISOR DE DOCUMENTOS PDF. LA PERSONA O ENTIDAD A LA QUE USTED LE VA A ENTREGAR EL CERTIFICADO PUEDE VERIFICAR, POR UNA SOLA VEZ, SU CONTENIDO INGRESANDO A <http://www.ccc.org.co/registraya/> Y DIGITANDO EL CODIGO DE VERIFICACION QUE SE ENCUENTRA EN EL ENCABEZADO DEL PRESENTE DOCUMENTO.

EL CERTIFICADO A VALIDAR CORRESPONDE A LA IMAGEN Y CONTENIDO DEL CERTIFICADO CREADO EN EL MOMENTO EN QUE SE GENERO EN LAS SEDES O A TRAVES DE LA PLATAFORMA VIRTUAL DE LA CAMARA.

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CODIGO DE VERIFICACION: 0816RNDZXW

NUMERO DE RADICACION: 20160456121-INT

FECHA DE IMPRESION: VIERNES 19 AGOSTO 2016 11:54:30 AM

PAGINAS: 10 10

DADO EN CALI A LOS 19 DIAS DEL MES DE AGOSTO

DEL AÑO 2016 HORA: 11:54:30 AM

A. M. Z.