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Act. 400 OPOSIOBSERVTER Folios: 53

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- ☒ Patente de Invención.
☐ Patente de Modelo de Utilidad.
☐ Diseño Industrial.
☐ Esquema de Trazado para Circuitos Integrados.
☐ Marcas de Productos o Servicios.

- ☐ Marca Colectiva.
☐ Marca de Certificación.
☐ Lema Comercial.

②

**SOLICITUD
PUBLICADA**

Número del expediente: 09-053-058

Solicitante: WYETH

Apoderado: ALVARO CORREA ORDONEZ

Título de la nueva creación o denominación del signo: COMPRESIDOS BICAPA
DE ESTRÓGENO/SERM Y ESTRÓGENO/PROGESTINA

Gaceta: 608

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE

Nombre: PROCAPS S.A.

Dirección: CALLE 80 No. 78b-201

Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución: BARRANQUILLA

Teléfono: 371 99 00 Fax: 373 08 18
E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Número 890.106.527-5

**REPRESENTANTE
O APODERADO**

Nombre: CIELO ANGELA PEÑA
RODRIGUEZ

Dirección: CARRERA 13 No. 119-95

Teléfono: (571)213 12 13 Fax: (571)612 19 79
E-mail: negocios@optimum-co.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número 51.940.252 TP 82701

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación:

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

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZ

FIRMA: _____

C.C. 51.940.252

TP. 82701



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 09 053058
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPRIMIDOS BICAPA DE ESTRÓGENO/SERM Y
ESTRÓGENO/PROGESTINA."
Solicitante : WYETH
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 608 del 30 de septiembre de 2009

Yo, **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **82701** del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "**COMPRIMIDOS BICAPA DE ESTRÓGENO/SERM Y ESTRÓGENO/PROGESTINA**", cuyo titular es **WYETH**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

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

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 22 de mayo de 2009 reivindicando prioridad bajo la solicitud US20060867715P del 2006-11-29; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 608 del 30 de septiembre de 2009, cuya publicación internacional corresponde a la WO2008067387 del 2005-02-24.

2.2. La solicitud colombiana 09 053058 objeto de la presente oposición, se refiere a comprimidos bicapa que comprenden por lo menos un estrógeno en una primera capa y un agente terapéutico en una segunda capa, y a procesos para su preparación; donde el comprimido bicapa que comprende: (a) una primera capa que comprende por lo menos un estrógeno; y (b) una segunda capa que comprende uno o más agentes terapéuticos seleccionados del grupo que consiste de un

modulador del receptor de estrógeno selectivo y un gestágeno; en donde: dicha primera capa comprende de aproximadamente 20% a aproximadamente 45% en peso de dicho comprimido; y dicha segunda capa comprende de aproximadamente 55% a aproximadamente 80% en peso de dicho comprimido; y, en donde dicho estrógeno comprende estrógenos conjugados.

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

- D1: WO03077923 publicada el 25 de septiembre de 2003.

2.4. Ahora bien, el documento D1, particularmente en la descripción revela una forma de dosificación oral adecuado para entregar una dosis combinada de progesterona y que a la entrega a través del tracto gastrointestinal ofrece una concentración en sangre de alrededor de 0,1 ng / ml a alrededor de 400 ng / ml de progesterona, donde la forma de dosificación comprende una combinación que incluye (a) una primera forma sólida que comprende de 25 mg a 500 mg de progesterona micronizada en compañía de polietilenglicol con un peso molecular promedio de alrededor de 1000 a 10.000 y que constituyan al menos el 30% de dicho primer estado sólido, y (b) una segunda zona de forma sólida que comprende un estrógeno. Particularmente, en la página 16, líneas 6 a 10 la anterioridad D1 revela formulaciones de estrógeno y progesterona comprimido para formar una forma de dosificación, tal como una tableta de varios niveles, en el que de cada capa



representa una progesterona o una formulación de estrógeno. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.5. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 053058 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.6.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 29 de noviembre de 2006 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, comprimidos bicapa que comprenden por lo menos un estrógeno en una primera capa y un agente terapéutico en una segunda capa, sobre el cual busca protección en el capítulo reivindicatorio.

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

industrial.". La solicitud pretendida no cumple con los tres requisitos de patentabilidad.

2.8. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada "COMPRIMIDOS BICAPA DE ESTRÓGENO/SERM Y ESTRÓGENO/PROGESTINA", cuyo titular es WYETH, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 608 del 30 de septiembre de 2009.

3. PRUEBAS

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

- D1: WO03077923 publicada el 25 de septiembre de 2003.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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



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

4.3. En las demás normas concordantes.

5. ANEXOS

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

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

- D1: WO03077923 publicada el 25 de septiembre de 2003.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita



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Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas
en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13.12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79

E-mail: negocios@optimum-co.com - www.optimum-co.com

Bogotá Colombia



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CAMARA DE COMERCIO
DE BARRANQUILLA
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA"-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." "PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI MITADA"-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." "PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----
NIT: 890.106.527-5.

libro respectivo, la sociedad antes mencionada -----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996 otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada -----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A. -----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT N°: 890.106.527-5.

MATRÍCULA MERCANTIL: 24,802.



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CAMARA DE COMERCIO
DE BARRANQUILLA
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Dirección para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y

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farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

C E R T I F I C A

CAPITAL

Nro Acciones

Valor Acción

Autorizado

\$*****2,000,000,000 *****2,000,000 *****1,000

Suscrito

\$*****1,229,071,000 *****1,229,071 *****1,000

Pagado

\$*****1,229,071,000 *****1,229,071 *****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se

***** C O N T I N U A *****



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PROCAPS S.A.-----

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requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S.A.-----
NIT: 890.106.527-5.

ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

CC.*****7,463,982

CC.*****7,461,324

CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot
2. Minski Deitel Daniel
3. Minski Sharon

CC.*****72,219,541

PA.*990,212,082,805

C E R T I F I C A



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CAMARA DE COMERCIO
DE BARRANQUILLA
12*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S.A. -----
NIT: 890.106.527-5.

Revisor Fiscal Ppal.
Vargas Pertuz Ana Isabel

CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 151 del 31 de Marzo de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 30 de Julio de 2009 bajo el No. 151,129 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre
Suplente del Revisor Fiscal.
Duarte Diaz David

Identificación

CC.*****73,115,965

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo, -----

y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, -----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, -----

3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, -----
obrando como Presidente y Representante Legal de la sociedad C.F.

NATURMEGA S.A., que obrando en su condición de Presidente y -----
Representante Legal de la sociedad PROCAPS S.A., el presidente -----

debidamente facultado por los Estatutos Sociales y por el Maximo Organó Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN -----

MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con

las facultades que se transcriben a continuación: a.- Para que -----
representen a la sociedad PROCAPS S.A. ante todo tipo de -----

autoridades administrativas y jurisdiccionales, en asuntos de -----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria,

tributaria, policiva, administrativa y fiscal. b.- Contestar y -----
presentar demandas, requerimientos, recursos, pedir y aportar -----

pruebas, recibir, notificarse, ejercer la acción de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que -----

cursen contra la sociedad, allanarse en nombre de la sociedad en
los asuntos que sean necesarios, transigir, desistir, sustituir,

renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, -----

transaccionales, judiciales o extrajudiciales o extrajudiciales,
cualquiera que sea su cuantía, para lo cual las apoderadas deben

aportar la autorización simple y escrita del Representante legal
de la sociedad. d.- Podrán presentar solicitudes de devolución y/o

compensación de impuestos, ventas y rentas, recibir los pagos por
las devoluciones y adelantar todo trámite o proceso administrativo

ante la DIAN, de tal forma que en ningún momento quede sin -----
representación legal de la sociedad. PODERES ESPECIALES: a.- Se -----

confiere poder especial amplio y suficiente a las personas que se
determinan seguidamente, que conforman el grupo A y B, para, para

***** C O N T I N U A *****



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CAMARA DE COMERCIO
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12*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), ----- liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO ----- CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN ----- VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA ----- DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO ----- CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----- amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA ----- CC.No.8.715.941, para que en nombre y representación de PROCAPS ----- S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto quedan facultados para firmarlas, como también los demás documentos relacionados con ellas, ----- notificarse, aportar y solicitar las pruebas que sean necesarias. c.- Otorgar poder especial amplio y suficiente al señor MARLON ----- TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representación de ----- PROCAPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los trámites o registros de Comercio ----- Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ----- ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ----- representación de PROCAPS S.A., endosen los títulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ----- (1.000.000.000.00) M.L. CUARTO: El representante legal de la ----- sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General ----- Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaría 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008 bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condición de Presidente y Representante Legal de la Sociedad PROCAPS S.A., confiere por medio de este instrumento ----- publico Poder especial Amplio y Suficiente a la doctora MILENA -----

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.-----

ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y representación de PROCAPS S.A., suscriba declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad en el giro normal de sus negocios y operaciones sociales, por tanto queda facultada para firmar, como tambien los demas documentos relacionados con ellas, notificarse, aportar y solicitar las pruebas que sean necesarias.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 27 de Marzo de 2009.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles despues de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

m. p. j. p.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-053058- -00003-0000

Fecha: 2009-12-28 12:58:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 53

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 94,457

FECHA : DICIEMBRE 15 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	RECIBO DE CAJA			56603	31/07/2009	540,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			56604	31/07/2009	540,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS	219,000.00
		TOTAL :	\$ 219,000.00

SON: DOSCIENTOS DIEZ Y NUEVE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-053058-00003-0000

Fecha: 2009-12-28 12:58:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 53

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800173089-2

CERTIFICACION DE EXCEDENTE : 09 - 81,204
FECHA : OCTUBRE 28 DE 2009

===== CONSIGNACION =====

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	RECIBO DE CAJA			32048	29/04/2009	203,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			64132	31/08/2009	106,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			64138	31/08/2009	68,000.00

===== CONCEPTO =====

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	69,000.00
		TOTAL :	\$ 69,000.00

SON: SESENTA Y NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 09 053.058, titulada "**COMPRIMIDOS BICAPA DE ESTRÓGENO/SERM Y ESTRÓGENO/PROGESTINA**", cuyo titular es **WYETH**, publicada en la gaceta No. 608 del 30 de septiembre de 2009.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 3 días del mes de Diciembre de 2009.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.

NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA
ALFONSO LUIS AVILA FADUL
DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO
El suscrito Notario certifica que este escrito fue presentado
personalmente por

WALTER TANAKA TATEKAWA

Identificado con: GF2SL 928 de PAENARA

Quiero declarar que su contenido es cierto y que la firma puesta en
él es suya.

04 DIC. 2009 FIRMA

NOTARIO TERCERO DE BARRANQUILLA



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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 September 2003 (25.09.2003)

PCT

(10) International Publication Number
WO 03/077923 A1

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31/57

(21) International Application Number: PCT/US02/07562

(22) International Filing Date: 14 March 2002 (14.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): **WATSON PHARMACEUTICALS, INC.** [US/US]; 311 Bonnie Circle, Corona, CA 92880 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **TAN, Domingo, Y.** [US/US]; 4 Carson, Irvine, CA 92620 (US).

(74) Agents: **WEGNER, Harold, C.** et al.; Foley & Lardner, Washington Harbour, Suite 500, 3000 K Street, N.W., Washington, DC 20007-5109 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/077923 A1

(54) Title: PROGESTERONE ORAL DRUG DELIVERY SYSTEM

(57) Abstract: Provided is an oral dosage form suitable to deliver a combined dosage of progesterone and which upon delivery through the gastrointestinal tract provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone; said dosage form comprising a combination that includes (a) a first solid form comprising from about 25 mg to about 500 mg micronized progesterone in a solid polyethylene glycol carrier having an average molecular weight of from about 1000 to 10,000 and constituting at least about 30 % of said first solid form; and (b) a second solid form comprising an estrogen.

PROGESTERONE ORAL DRUG DELIVERY SYSTEM

FIELD OF THE INVENTION

5 This invention relates to oral dosage forms of hormones and methods for their delivery to subjects needing hormone therapy.

SUMMARY OF THE INVENTION

10 In a first embodiment, there is provided an oral dosage form suitable to deliver a combined dosage of progesterone and which upon delivery through the gastrointestinal tract provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone; said dosage form comprising a combination that includes (a) a first solid form comprising from about 25 mg to about 500 mg micronized progesterone in a solid polyethylene glycol carrier
15 having an average molecular weight of from about 1000 to 10,000 and constituting at least about 30 % of said first solid form; and (b) a second solid form comprising an estrogen. In one embodiment, the polyethylene glycol carrier comprises from about 45 % to about 65 % weight of the first solid form. In a further embodiment, the second solid form (b) contains from about 0.25 mg to about 5 mg of estradiol.

20 In a further embodiment, the solid polyethylene glycol carrier comprises a mixture of polyethylene glycol 1450, polyethylene glycol 3350 or polyethylene glycol 8000. In a preferred embodiment there is provided an oral dosage form suitable to deliver a combined dosage of progesterone and an estrogen via the gastrointestinal tract which upon oral administration provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml
25 progesterone; said dosage form comprising a combination that includes (a) a first solid form containing from about 25 mg to about 500 mg micronized progesterone, said caplet having been derived from the extrusion of a polymer matrix extruded from a mixture comprising micronized progesterone in a solid polyethylene glycol carrier which is a mixture of

polyethylene glycol 1450, polyethylene glycol 3350 or polyethylene glycol 8000, the micronized progesterone having first been dispersed in molten polyethylene glycol, and, after cooling to a solid form, having extruded, said mixture constituting from about 45 % to about 65 % weight of said first solid form; and (b) a second solid form which contains from about 0.25 mg to about 5 mg of estradiol. In a preferred embodiment, the oral dosage form is provided with said first solid form as a caplet and said second solid form as a tablet.

In a second aspect of the invention, there is provided a method of providing an oral dosage of a combination therapy of progesterone and estradiol which comprises administering to a patient an oral dosage form suitable to deliver a combined dosage of progesterone and an estrogen via the gastrointestinal tract which upon oral administration provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone; said dosage form comprising a combination that includes (a) a first solid form containing from about 25 mg to about 500 mg micronized progesterone, said caplet having been derived from the extrusion of a polymer matrix extruded from a mixture comprising micronized progesterone in a solid polyethylene glycol carrier which is a mixture of polyethylene glycol 1450, polyethylene glycol 3350 or polyethylene glycol 8000, the micronized progesterone having first been dispersed in molten polyethylene glycol and, after cooling to a solid form, having been extruded, said mixture constituting from about 45 % to about 65 % weight of said first solid form; and (b) a second solid form which contains from about 0.25 mg to about 5 mg of estradiol.

The invention features a solid oral dosage form of progesterone comprising a therapeutically effective amount of micronized progesterone and a solid polymeric carrier, wherein the dosage form, upon oral administration, provides a therapeutically effective amount of progesterone to a subject. A preferred solid polymeric carrier is a mixture of polyethylene glycols of molecular weight ranging from about 1,000 to about 10,000. Preferably, progesterone dosage forms of this invention can be prepared by injection molding techniques. Further, the dosage form can be prepared for immediate release or controlled release. The

dosage form can be a tablet, capsule, caplet, encapsulated pellets, encapsulated granules, powder, or encapsulated powder. These dosage forms can be provided as unit dosage forms.

In some preferred aspects, the polyethylene glycol is polyethylene glycol 1450, polyethylene glycol 3350 or polyethylene glycol 8000, or a mixture thereof.

5 In some aspects, the cellulose ether is a hydroxyalkyl cellulose, carboxyalkyl cellulose, or a mixture thereof. In some preferred aspects, the cellulose ether is hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, carboxyethyl cellulose, hydroxypropylmethyl cellulose, cellulose acetate trimellitate, or a mixture thereof.

In one specific aspect, an oral progesterone unit dosage form is provided which
10 comprises micronized progesterone and a solid polymeric carrier, wherein the dosage form, upon oral administration, provides a therapeutically effective amount of progesterone to a subject, wherein, the dosage form comprises from about 25 mg to about 500 mg of micronized progesterone per dose; the solid polymeric carrier constitutes from about 45 % to about 65 % weight of the dosage form and comprises a mixture of polyethylene glycol 1450, polyethylene
15 glycol 3350 or polyethylene glycol 8000.

In another specific aspect, a combination dosage form is provided which comprises an oral progesterone dosage form and an estrogen dosage form, wherein the combination dosage form is a capsule which encloses the progesterone dosage form and the estrogen dosage form;

the oral progesterone dosage form is a caplet comprising micronized
20 progesterone and a solid polymeric carrier, which progesterone dosage form, upon oral administration, provides a therapeutically effective amount of progesterone to a subject, and the progesterone dosage form comprises from about 25 mg to about 500 mg of micronized progesterone per dose and the solid polymeric carrier constitutes from about 45 % to about 65 % weight of the progesterone dosage form and comprises a mixture of polyethylene glycol
25 1450, polyethylene glycol 3350 or polyethylene glycol 8000, and the therapeutically effective amount of progesterone represents a blood concentration of from about 0.1 ng/ml to about 400 ng/ml

and the oral estrogen dosage form is an estradiol tablet comprising estradiol from about 0.25 mg to about 5 mg of estradiol.

This invention further provides a hormone replacement therapy by administering a dosage form described above to a subject in need of progesterone or a combination of progesterone and estrogen. The method of this invention may be used for treating or preventing various conditions, including, but not limited to, infertility related to non-receptive uterus, premenstrual tension, ovulation, primary dysmenorrhea and endometriosis, habitual abortion, respiratory depression in the Pickwickian syndrome, secondary amenorrhea, dysfunctional uterine bleeding, preeclampsia and toxemia of pregnancy, sexual infantilism, and post-menopausal symptoms.

DETAILED DESCRIPTION OF THE INVENTION

A. General Techniques

One of ordinary skill in the art would readily appreciate that the pharmaceutical formulations described herein can be prepared by applying known pharmaceutical manufacturing procedures. Such formulations can be administered to the subject with methods well-known in the pharmaceutical arts. Thus, the practice of the present invention will employ, unless otherwise indicated, conventional techniques of pharmaceutical sciences including pharmaceutical dosage form design, drug development, and pharmacology, as well as of organic chemistry, including polymer chemistry. Accordingly, these techniques are within the capabilities of one of ordinary skill in the art and are explained fully in the literature (See generally, for example, Remington: The Science and Practice of Pharmacy, Nineteenth Edition. Alfonso R. Gennaro (Ed.): Mack Publishing Co., Easton, PA, (1995), hereinafter REMINGTON, incorporated by reference herein in its entirety).

B. Definitions

As used herein, certain terms may have the following defined meanings.

As used in the specification and claims, the singular forms *a*, *an* and *the* include plural
5 references unless the context clearly dictates otherwise. For example, the term *a*
pharmaceutical may refer to one or more pharmaceuticals for use in the presently disclosed
formulations and methods.

The term *pharmaceutical* generally refers to any known pharmacologically active agent
as well as its pharmaceutically acceptable salt, prodrug such as an ester or an ether, or a salt of
10 a prodrug, or a solvate such as ethanolate, or other derivative of such pharmacologically active
agent. These salts, prodrugs, salts of prodrugs, solvates and derivatives are well-known in the
art.

In addition, this invention contemplates the use of polymorphic, isomeric (including
stereoisomeric, geometrically isomeric and optically isomeric) and anomeric forms of the
15 pharmaceuticals described herein.

The terms *pharmaceutical* and *drug* as used herein are identical in meaning and thus are
used interchangeably.

The term *pharmaceutical carrier* or simply *carrier* as used herein refers to a
composition that contains and or delivers a pharmacologically active agent and is generally
20 considered to be otherwise pharmacologically inactive.

By *solid polymeric carrier* is meant a carrier that comprises a polymer or a mixture of
polymers that is substantially free of oil. A formulation is *substantially free of oil* when the
formulation does not constitute an oil or a mixture of oils primarily to dissolve or disperse a
given drug in the formulation. Inclusion of any combination of polymers or oils which would
25 destroy the solid nature of the said first form is excluded from the scope of the invention.

Formulation is a pharmaceutical term of art that includes a carrier and a pharmaceutical. Formulation is a broad term and includes the compositions that may or may not have been processed into a dosage form which is ultimately administered to a subject. For example, formulation includes the compositions that are mixed in preparation for manufacturing a dosage form.

A *dosage form*, as used herein refers to a formulation that is ready for administration to a subject. As used herein, it specifically refers to solid dosage forms, including, but not limited to, tablets, capsules, caplets, powders, pellets, and granules. The term also includes multilayered tablets wherein a given layer may represent a different drug. The term also includes powders, pellets and granules that are encapsulated. The powders, pellets, and granules may be coated with a suitable polymer or a conventional coating material to achieve, for example, greater stability in the gastrointestinal tract, or to achieve the desired rate of release. Moreover, the capsule comprising the powder, pellets or granules may be further coated. The tablet, or the caplet may also be scored to facilitate division of dosing.

Alternatively, the dosage forms of the present invention may be unit dosage forms wherein the dosage form is intended to deliver one therapeutic dose per administration.

The term *pharmaceutically acceptable* means that the ingredient that is being qualified is compatible with other ingredients of the formulation and not injurious to the patient. Several pharmaceutically acceptable ingredients are known in the art and official publications. For example, THE UNITED STATES PHARMACOPEIA describe the analytical criteria for assessing the pharmaceutical acceptability of numerous ingredients of interest. Unless otherwise indicated, the ingredients used in the present invention are pharmaceutically acceptable.

Injection molding refers to a process for producing oral solid dosage forms wherein a predetermined amount of the formulation comprising a carrier and a pharmaceutical (along with optional adjuvants) are injected into a mold at a certain temperature and pressure and the mold is cooled and the oral solid dosage form is collected. Optionally, the mold can be packed

with additional amount of the formulation material during the cooling cycle. In some aspects, the dosage form is a tablet or a caplet.

A *therapeutically effective blood level* refers to the blood level of a drug in a subject that is necessary to provide a therapeutic benefit to the subject. The therapeutically effective blood level may vary depending on the therapeutic benefit desired, as well as other variables such as the subject's age, weight, metabolism, physiological conditions such as gastrointestinal motility, renal clearance, etc. The therapeutically effective blood level may be achieved in one or more administrations, applications or dosages. Determination of the dosing needed to achieve a therapeutically effective blood level for a given therapy or treatment is well within the ordinary skill in the pharmaceutical arts.

In the context of hormone replacement therapy, therapeutically effective amount of progesterone is that amount of progesterone effective for one or more of the following, preventing estrogen-induced endometrial hyperplasia in post menopausal women, inducing bleeding in secondary amenorrhea, and reducing endometrial hyperplasia and dysfunctional bleeding in women suffering from such bleeding disorders.

The various therapeutically effective blood levels for various treatments are known in the art. See, for example, de Lignieres, B., Oral Micronized Progesterone, Clin. Ther., 21(1): 41-60 (1999), which is incorporated by reference. The therapeutically effective blood levels may range from about 0.1 ng/ml to about 100 ng/ml or more, depending on the condition being treated and the individual patient-related variables such as age, weight, metabolic activity, etc. See, also for example, the U.S. Patent No. 5,543,150, which is incorporated by reference, which describes some of the therapeutic serum levels.

The term *blood level* is used interchangeably with terms such as blood concentration, plasma level, plasma concentration, serum level, serum concentration, serum blood level and serum blood concentration.

C_{max} refers to the maximum serum concentration of progesterone following the oral administration of the solid oral dosage form to patients.

25

Normalized C_{max} refers to the value obtained by dividing C_{max} into the dosage strength of the solid oral dosage form of progesterone. For example, if the maximum serum concentration of progesterone is 14 ng/ml following the oral administration of a solid oral dosage form containing 200 mg of micronized progesterone, the C_{max} is 14 ng/ml and the
5 *normalized C_{max}* is 0.07 ng/ml/mg.

AUC refers to the area under the curve that tracks the serum concentration (ng/ml) of progesterone over a given time following the oral administration of the solid oral dosage form to patients. AUC can be measured from 0 to 12 hours or from 0 to 24 hrs following the administration and in these cases are referred to as AUC₍₀₋₁₂₎ or AUC₍₀₋₂₄₎, respectively.

10 *Normalized AUC* is obtained by dividing the AUC into the dosage strength of the solid oral dosage form of progesterone. For example, if the AUC₍₀₋₁₂₎ is 160 hr.ng/ml following the oral administration of a solid oral dosage form containing 200 mg of micronized progesterone, the *normalized AUC₍₀₋₁₂₎* is 0.8 hr.ng/ml/mg.

The term *administration* refers to a method of delivering a formulation to a desired site.
15 Specifically, oral administration refers to ingesting a drug by swallowing or chewing.

Subject as used herein refers to a human, both male and female, or an animal (preferably a mammal) that can benefit from the administration of the progesterone formulations of the present invention.

Concentrations, amounts, and other parameters of various components of this invention
20 are often presented in a range format throughout this application. The description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as 0.1 to 100
25 should be considered to have specifically disclosed subranges such as 0.1 to 1, 0.4 to 10, 1-25, 10-50, 25-60, 40-65, 60-80, 70-100, etc, as well as individual numbers within that range, for

example, 0.1, 0.4, 1, 5, 7, 11, 15, 19, 22, 28, 35, 39, 44, 60, 65, 78, 84, 89, 95, etc. This applies regardless of the breadth of the range and regardless of the units under consideration.

C. The Dosage Forms

5 This invention provides oral progesterone dosage forms comprising micronized progesterone and a solid polymeric carrier, wherein the dosage forms, upon oral administration, provide a therapeutically effective blood level of progesterone to a subject. The currently available oral progesterone dosage forms comprising micronized progesterone are oil-based and thus do not comprise a solid polymeric carrier.

10 The oral dosage forms of the present invention can be processed into an immediate release or a sustained release dosage form. Immediate release dosage forms may release the progesterone in a fairly short time, for example, within a few minutes to within a few hours. Sustained release dosage forms may release the progesterone over a period of several hours, for example, up to 24 hours or longer, if desired. In either case, the delivery can be controlled
15 to be substantially at a certain predetermined rate over the period of delivery.

 The oral dosage forms of the present invention can be processed into dosage forms such as tablets, capsules, caplets, powders, encapsulated pellets, encapsulated granules, or encapsulated powders. These dosage forms can be coated with a polymeric or other art-known coating materials to achieve, for example, greater stability on the shelf or in the gastrointestinal
20 tract, or to achieve control over drug release. Such coating techniques and materials used therein are well-known in the art. For example, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid-methacrylic acid ester copolymers, cellulose acetate trimellitate, carboxymethylethyl cellulose, and
25 hydroxypropylmethyl cellulose acetate succinate, among others, can be used to achieve enteric coating. Mixtures of waxes, shellac, zein, ethyl cellulose, acrylic resins, cellulose acetate, silicone elastomers can be used to achieve sustained release coating. See, for example, Remington, *supra*, Chapter 93, for other types of coatings, techniques and equipment.

Additionally, the tablet or caplet dosage form can be scored to facilitate easy break-off to adjust the dosage as needed. The tablets can also be multi-layered, each layer representing a different drug or a different concentration of the same drug. Alternatively, the dosage forms of the present invention can be prepared as unit dosage forms which are intended to deliver one therapeutically effective dose per administration.

General methods and equipment for preparing tablets, capsules, pellets, and powders are well-known in the art. See, Remington, *supra*, Chapters 91 and 92.

The present progesterone dosage forms constitute commonly used pharmaceutical excipients to form a stable natural progesterone product without the use of allergenic ingredients such as peanut oil. Further, since the dosage forms of the present invention deliver the natural progesterone, as opposed to synthetic progestins, the undesirable effects of synthetic progestins on liver function and carbohydrate metabolism can be avoided. Additional advantages of these dosage forms include dosing flexibility, convenience, greater patient compliance in a clinical setting and the attendant benefits of improved clinical outcomes.

Various aspects of this invention are described below in greater detail.

a) Progesterone

Progesterone is a steroid hormone secreted primarily from the corpus luteum of the ovary during the latter half of the menstrual cycle. Chemically, progesterone is pregn-4-ene-3,20-dione. Progesterone may exist in two crystalline forms of equal physiologic activity and which are readily interconverted. The α -form is orthorhombic (prisms from dilute alcohol) with $a:b:c = 0.750:1.0:0.905$. These crystals are reported to have a melting point of 127-131 °C. The β -form is orthorhombic (needles) with $a:b:c = 0.563:1.0:0.275$. These β -form crystals are reported to have a melting point of 121 °C. Merck Index, 12th Edition, pp 1335-1336, Merck & Co., Inc., White House Station, NJ (1996). This invention contemplates

using progesterone of either D-form or L-form or a mixture thereof. Accordingly, the term progesterone as used herein refers to either D-form or L-form or a mixture thereof.

The pharmaceutical dosage forms according to the invention constitutes micronized progesterone. Micronized progesterone refers to a white or creamy white crystalline
5 particulated powder that is practically insoluble in water, wherein virtually all (i.e., greater than 90 %) of the individual progesterone particles in the powder have been reduced in size to less than about 25 microns in diameter, or in the case of non-round particles, to less than about 25 microns in their largest dimension. In some aspects, virtually all (greater than 90 %) of the micronized progesterone particles have particle sizes of less than 10 microns, and a majority
10 (e.g. 78 %) of these particles have particle sizes of less than 5 microns.

Micronized progesterone is available from commercial sources such as Berlichem, a division of Schering AG, and from the Upjohn Company. Alternatively, micronized progesterone can be prepared from bulk progesterone in a radiator mill (jet air micronizer) by techniques well-known in the art. For a description of the micronization techniques and
15 machines, see, for example, U.S. Patent Nos. 2,032,827 and 4,018,388.

In a preferred embodiment, the dosage form contains from about 50 mg to about 500 mg progesterone per dose. In another preferred embodiment, the dosage form contains from about 10 % to about 70 % (more preferably from about 15 % to about 60 %) by weight of micronized progesterone.

20

b) The Carrier

The present dosage forms comprise a solid polymeric carrier to deliver micronized progesterone. The solid polymeric carrier may constitute at least 30 % by weight of the first solid form that is made up of the micronized progesterone and solid polymeric carrier. from
25 about 1 % to about 80 % by weight of the dosage form. In preferred embodiments, the polymeric carrier constitutes from about 20 % to about 70 % by weight of the dosage form. In

even more preferred aspects, the polymeric carrier constitutes from about 30 % to about 65 % by weight of the first solid form.

Polyethylene glycol is available in various grades under several trademarks including Carbowax® PEG 200, 300, 400, 540 Blend, 900, 1000, 1450, 3350, 4000, 4600, 8000 and
5 compound 20M from Union Carbide Co., USA and Poly Glycols® E series from Dow chemical Co., USA. The various grades available under a given trademarks represent differences in molecular weight and viscosity.

In one aspect, the carrier is a mixture of polyethylene glycols having a molecular weight of from about 100 to about 20,000. In another aspect, the carrier is a mixture of
10 polyethylene glycols having a molecular weight of from about 1000 to about 10,000. In some aspects, the polyethylene glycol is polyethylene glycol 1450, polyethylene glycol 3350 or polyethylene glycol 8000, or a mixture thereof.

It is to be understood that adding additional components to the polymers may be contemplated which is envisioned within the scope of the invention provided there is no
15 deleterious effect on the overall composition and effective therapeutic provision of medication. Thus, in another aspect, the carrier may include a mixture of polyvinylpyrrolidones having a mean molecular weight ranging from 2,500 to 3,000,000 or more. There are many commercially available polyvinylpyrrolidone polymers suitable for the purposes of this invention. In another aspect, the carrier is a cellulose ether. Some exemplary cellulose ethers
20 may include hydroxyalkyl cellulose (such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, cellulose acetate trimellitate etc), and carboxyalkyl celluloses (such as carboxymethyl cellulose, carboxyethyl cellulose, etc) or a mixture thereof. In some aspects, the carrier may include adjuvants such as opacifiers, bulking agents, sweeteners, stabilizing agents, etc. Examples of opacifiers include titanium dioxide, Talc, calcium
25 carbonate, behenic acid, and cetyl alcohol. Examples of bulking agents include starch, microcrystalline cellulose, calcium sulfate, calcium phosphate, and lactose. Examples of sweeteners include aspartame, saccharin, sodium cyclamate and Xylitol. Examples of

stabilizing agents include alginic acid glycerylmonostearate, hydroxypropyl cellulose, magnesium, aluminium silicate, and propylene glycol.

The above carriers can be used to prepare dosage forms of this invention that can release the progesterone immediately, i.e., within a few minutes to within a few hours, or in a sustained manner, i.e., over a period of 24 hours or longer if desired. The dissolution rate of the progesterone dosage form can be influenced by including adjuvants such as surfactants to the dosage form. Such surfactants may include sodium lauryl sulfate, glyceryl monooleate, sorbitan ester, docusate sodium, and cetrimide. The surfactant may constitute from about 0.1% to about 5 % by weight of the dosage form. In one aspect, for example, a polyethylene glycol dosage form of the present invention as described herein may comprise about 2.5 % by weight sodium lauryl sulfate to provide an immediate release dosage form.

In the case of sustained release dosage forms, additional solid carriers can be used, including, but not limited to, gums, acrylic resins or a mixture thereof.

15 c) Combination Dosage Form Comprising Progesterone and an Estrogen

In a further aspect, this invention provides a combination dosage form that comprises an oral progesterone dosage form as described above and an oral estrogen dosage form. Such a combination dosage form can be a tablet, capsule, caplet, powder, encapsulated pellets, encapsulated granules, or encapsulated powder. For example, the combination dosage form can be a capsule which encloses the progesterone dosage form and the estrogen dosage form. The progesterone dosage form and the estrogen dosage form can in turn be independently a tablet, capsule, caplet, powder, encapsulated pellets, encapsulated granules, or encapsulated powder. Alternatively, the progesterone and estrogen can be formulated together into one dosage form such as a powder or a tablet which can be further encapsulated or coated.

Thus, in one aspect, the combination dosage form is a capsule that encapsulates a progesterone tablet and an estrogen tablet. In another aspect, the combination dosage form is a

capsule that encapsulates a progesterone tablet and an estrogen powder. The desired dosage form can be chosen depending on the treatment on hand, as well as the desired order of release of the progesterone and the estrogen. For example, by choosing a progesterone caplet and an estrogen powder to prepare a combination capsule, one can achieve a quicker release of estrogen (because the estrogen is a powder) and a slower release of progesterone (because the progesterone caplet requires dissolution first). Selection of the proper dosing and the dosage form for a given treatment is well within the ordinary skill in the art.

Such combination oral dosage forms are feasible because of the development of the oral progesterone dosage forms of the present invention that comprise a solid polymeric carrier.

The solid polymeric carrier, unlike the oil-base of the existing dosage forms, allows the production of an oral progesterone dosage form that is of sufficiently small size to facilitate its inclusion, along with an estrogen oral dosage form, in a dosage form such as a capsule to create a dosage form for combination hormone therapy. Thus, a combination of estradiol and progesterone can now be obtained in one oral dosage form by placing, for example, one caplet of progesterone and one tablet of estradiol into a capsule such as a size #1 gelatin capsule.

The estrogen that can be used for the combination dosage form described above can be any one or more of the estrogens that are known in the art. For example, the estrogen can be natural estrogens or their congeners such as estradiol, estrone, estropipate, ethinyl estradiol, quinestrol, or conjugated estrogens. Synthetic estrogens that may be used include dienestrol, diethylstilbesterol, and mestranol. Preferably, the estrogen is estradiol. The estrogen dosage can be from about 0.1 mg to about 10 mg per unit dosage form. The determination of an appropriate dose for a given treatment is within the ordinary skill in the art. For additional details, one may refer to Remington, *supra*, Chapter 64.

D. Methods of Making

a) Injection Molding – A method of preparing progesterone oral dosage forms comprising micronized progesterone and a solid polymeric carrier

The oral solid dosage form of progesterone is prepared with a technique known as injection molding. For a general description of this technique, see for example, U.S. Patents Nos. 3,432,592, 4,801,460, 4,806, 337, 5,004,601, and 5,082,655, and Cuff, G. and Raouf, F., *Pharmaceutical Technology*, 96-106 (1998), all of which are incorporated by reference
5 herein in their entirety.

Briefly, polyethylene glycols are melted and micronized progesterone is dispersed into the molten polyethylene glycol carrier. The micronized progesterone constitutes at least 30 % of the mixture.. After the dispersion of the progesterone, a small amount of adjuvants such as titanium dioxide (as an opacifier) or pregelatinized starch (as a bulking agent) may be added to
10 the mixture. The melted mixture is cooled down through a lentilling machine to form flakes of lentils. Lentils or even larger sized intermediate flakes can be prepared by melt granulation, lentilling and/or milling. The lentils and the intermediate flakes are passed through a screen of appropriate sieve size to form smaller pieces of lentils. These lentils are made into oral solid dosage forms such as tablets and caplets with techniques known to those skilled in the art, such
15 as injection molding.

During injection molding, a mold is closed and clamped to prevent it from opening. The formulation comprising the pharmaceutical and its carrier is injected into the cavities of the mold through a nozzle. The amount of material that is injected into the mold is controlled by moving a screw to a predetermined distance inside the mold. The screw may be displaced
20 to facilitate packing of additional material into the mold cavities to fill the void generated when the mold cools after the first injection. The various parameters of the injection and packing steps, such as packing time, packing pressure, injection rate, and injection pressure can be adjusted. The mold is cooled and the screw is returned to its pre-injection position. The mold is opened and the molded parts (in this case, the solid unit dosage forms) are ejected. See Cuff
25 and Raouf, *supra*.

The molded dosage form can be scored with conventional techniques. Alternatively, the mold can be set such that scoring is accomplished through the molding process.

Other techniques known in the art may also be employed to prepare the solid dosage form, including, but not limited to, compression molding, tableting, and extrusion. See, for example, Remington, *supra*, Chapters 91-94.

5 **b) Combining Progesterone and Estrogen in One Dosage Form**

A combination dosage form comprising progesterone and estrogen dosage forms can be prepared by first preparing the progesterone and estrogen formulations or dosage forms separately and then combining them. In one aspect, progesterone and estrogen formulations can be compressed together to form one dosage form, for example, a multilayered tablet
10 wherein each layer represents a progesterone or an estrogen formulation. Alternatively, the progesterone dosage form and the estrogen dosage form can be encapsulated in one capsule. For example, one caplet of progesterone and one tablet of estradiol may be placed into a size # 1 hard shell gelatin capsule using an MG encapsulation machine fitted with custom built parts.

Methods of preparing estrogen formulations are well-known in the art. See,
15 Remington, *supra*, Chapters 91-93. For example, the estrogen formulation can be prepared by direct compression method. In this method, the required quantities of estrogen and a portion of anhydrous lactose are mixed together in a blender. The remaining anhydrous lactose, and, optionally, different types of color aluminum lake, are premixed by passing through a size 20 screen. Other ingredients such as microcrystalline cellulose and polacriline potassium may be
20 added to this mixture. The granulation may be lubricated with magnesium stearate. The granules are then made into tablets on a rotary tableting machine fitted with appropriate punches and dies to achieve the desired tablet size, thickness, and hardness.

Estrogen may constitute from about 0.5 % to about 5 % by weight of the tablet, depending on the type of estrogen and the therapeutically effective estrogen blood levels
25 needed for a given treatment. In one example, estradiol constitutes about 1.29 % of the weight of the mixture so that a tablet containing 1 mg of estradiol weighs about 80 mg and has a diameter of about 7/32 inch. The thickness of a tablet weighing 80 mg is about 0.107 inch.

In one example, the progesterone formulation is a caplet and the estrogen formulation is an estradiol tablet and the combination dosage form is a capsule. Thus, one caplet of progesterone and one tablet of estradiol may be filled into a size #1 capsule using an MG encapsulation machine that is fitted with custom built parts. As described above, individual formulations of progesterone and estrogen can be varied, including, but not limited to, tablets, powders, granules, and pellets. Thus, in other examples, the combination dosage form may be a capsule comprising a progesterone tablet and an estradiol powder.

Different progesterone and estrogen combination formulations have been made possible by the progesterone formulation comprising a solid polymeric carrier. For example, preparation of a combination dosage form with a capsule of standard size 1 is now feasible. A size 1 capsule has an internal diameter of about 0.253 inch and an internal length of about 0.748 inch when fully closed. With the present invention, a progesterone caplet of up to a length of about 0.545 inch and an estradiol tablet of up to a thickness of about 0.115 inch can be placed end to end within a size 1 capsule.

E. Administration

The pharmaceutical dosage forms of this invention can be administered to patients needing hormonal therapy requiring progesterone, either as a replacement or as a supplement. The effective amount of progesterone per dosage form can vary widely, in accordance with the needs of the patient, a dosage of from about 50 to about 500 milligrams per dosage form. The method of administration generally involves swallowing, sucking, or chewing a dosage form of the present invention. Alternatively, the dosage form can be held in the mouth, under the tongue, or next to a cheek for sufficient period such that an effective amount of the progesterone is released from the dosage form. Additional methods of administering oral dosage forms are well known in the art.

The dosage forms of the present invention can be administered to treat or prevent a variety of conditions. Such conditions include infertility related to non-receptive uterus,

premenstrual tension, ovulation, primary dysmenorrhea and endometriosis, habitual abortion, respiratory depression in the Pickwickian syndrome, secondary amenorrhea, dysfunctional uterine bleeding, preeclampsia and toxemia of pregnancy, sexual infantilism, and post-menopausal symptoms.

- 5 The invention described herein is further illustrated by the following non-limiting examples.

EXAMPLES

10 Example 1: Progesterone Oral Caplets, 200 mg

The composition for preparing progesterone oral caplets constituting 200 mg of progesterone per caplet is provided in Table 1 below.

TABLE 1

15

Component	mg/caplet	% (by weight)
Micronized progesterone	200.0	43.10
Polyethylene glycol 1450	56.6	12.20
Polyethylene glycol 3350	163.3	35.20
Polyethylene glycol 8000	41.8	9.00
Titanium dioxide	2.3	0.50
TOTAL	464.0 mg	100.0 %

The required quantities of polyethylene glycol 1450, polyethylene glycol 3350 and polyethylene glycol 8000 were melted into an appropriate size heated kettle. The molten

mixture was mixed for 5-10 minutes. Titanium dioxide was passed through a size 20 mesh into the molten mixture and the mixture was stirred for additional 10 minutes. Micronized progesterone was dispersed into the kettle while mixing. After all the micronized progesterone has been added, the mixture was continuously stirred with the turbine speed on for
5 approximately 50 minutes. The material was transferred into a lentilling machine to form flakes or lentils. The flakes or lentils were passed through a comminuting machine (Fitzpatrick) to provide smaller pieces of lentils.

The caplets were molded using injection-molding technology. Methods of injection molding, the necessary equipment, and operating conditions are well known in the art. See,
10 for example, U.S. Patents Nos. 4629621, 4744976, 4774074, 4806337, and 5082655, which are incorporated by reference.

The method was carried out using an all electric, 50-ton model ACT-50 injection molding machine. The lentils were fed into the hopper of an injection molding machine (ACT 50-D Cincinnati Milacorn). The caplets were prepared using 0.68" x 0.23" capsule shaped
15 cold runner mold and cavity inserts. The barrel temperatures were set to a temperature range of 130 -150 °F. The shot size was set from 0.8 to 0.9 inch. The mold chillers were set to a temperature of 8-10 °C.

The mold was then closed using semi-automatic mode and the selected mold cavities were filled with material flowing at 0.1 to 0.4 inch per second and at an injection pressure of
20 1000 to 1200 pounds per square inch. At the end of the 8 to 12 second injection time and the 1 to 3 second pack pressure of 100 - 500 pounds per square inch, the mold cooling time of 10 to 14 seconds allowed the extruder to return to the starting shot size position of 0.8 to 0.9 inch. The cooling timer timed out, allowing the mold to open 8 inches and the injection cycle pulses 2 to 4 times at a speed of 5 to 12 inches per second. At the same time the ejection cycle was
25 operating, an air blast of 40 to 80 psi was directed at the spray to assure it was clear from the mold before starting the next cycle. After several cycles of running in the semi-automatic

37

mode, with all caplet parts injecting into the collection bin, the automatic cycle mode could be activated. Cycle stability would be reached after running for approximately 5 minutes.

Example 2: Progesterone Oral Caplets, 200 mg

- 5 The composition for preparing progesterone oral caplets constituting 200 mg of progesterone per caplet is provided in Table 2 below.

TABLE 2

Component	mg/caplet	% (by weight)
Micronized progesterone	200.00	51.55
Polyethylene glycol 1450	38.80	10.00
Polyethylene glycol 3350	131.74	33.95
Polyethylene glycol 8000	15.52	4.00
Titanium dioxide	1.94	0.50
TOTAL	388.00 mg	100.00 %

- 10 Oral caplets constituting 200 mg of progesterone per caplet were prepared according to the process set forth in Example 1 except that during the injection molding process, mold cavities of 0.545" x 0.240" were used.

Example 3: Progesterone Oral Caplets, 200 mg

- 15 The composition for preparing progesterone oral caplets constituting 200 mg of progesterone per caplet is provided in Table 3 below.

TABLE 3

Component	mg/caplet	% (by weight)
Micronized progesterone	200.00	51.55
Polyethylene glycol 1450	40.16	10.35
Polyethylene glycol 3350	116.40	30.00
Polyethylene glycol 8000	29.48	7.60
Titanium dioxide	1.94	0.50
TOTAL	388.00 mg	100.00 %

The procedure for preparing 200 mg progesterone oral caplets was as described above
5 in Example 2.

Example 4: Progesterone Oral Caplets, 150 mg

The composition for preparing progesterone oral caplets constituting 150 mg of
progesterone per caplet is provided in Table 4 below.

TABLE 4

Component	mg/caplet	% (by weight)
Micronized progesterone	150.00	38.66
Polyethylene glycol 1450	54.32	14.00
Polyethylene glycol 3350	146.82	37.84
Polyethylene glycol 8000	34.92	9.00
Titanium dioxide	1.94	0.50
TOTAL	388.00 mg	100.00 %

5 The procedure for preparing 150 mg progesterone oral caplets was as set forth in Example 2.

Example 5: Progesterone Oral Caplets, 150 mg

10 The composition for preparing progesterone oral caplets constituting 150 mg of progesterone per caplet is provided in Table 5 below.

TABLE 5

Component	mg/caplet	% (by weight)
Micronized progesterone	150.00	38.66
Polyethylene glycol 1450	51.07	13.16
Polyethylene glycol 3350	147.32	37.97
Polyethylene glycol 8000	37.67	9.71
Titanium dioxide	1.94	0.50
TOTAL	388.00 mg	100.00 %

The procedure for preparing 150 mg progesterone oral caplets was as set forth in Example 2.

5

Example 6: Progesterone Oral Caplets, 75 mg

The composition for preparing progesterone oral caplets constituting 75 mg of progesterone per caplet is provided in Table 6 below.

TABLE 6

Component	mg/caplet	% (by weight)
Micronized progesterone	75.00	18.75
Polyethylene glycol 1450	67.00	16.75
Polyethylene glycol 3350	152.00	38.00
Polyethylene glycol 8000	24.00	6.00
Pregelatinized starch (Starch 1500)	80.00	20.00
Titanium dioxide	2.00	0.50
TOTAL	400.00 mg	100.00 %

The procedure for preparing 75 mg progesterone oral caplets was as set forth in
5 Example 2 except that Example 6 has pregelatinized starch as an additional ingredient.

Example 7: Progesterone Oral Caplets, 200 mg

The composition for preparing progesterone oral caplets constituting 200 mg of
progesterone per caplet is provided in Table 7 below.

TABLE 7

Component	mg/caplet	% (by weight)
Micronized progesterone	200.00	43.10
Polyethylene glycol 1450	56.60	12.20
Polyethylene glycol 3350	163.30	35.20
Polyethylene glycol 8000	41.80	9.00
Titanium dioxide	2.30	0.50
TOTAL	464.00 mg	100.00%

The above-listed quantities of polyethylene glycol 1450, polyethylene glycol 3350 and
5 polyethylene glycol 8000 were melted into an appropriate size heated kettle. The molten
carrier was mixed for 5-10 minutes. Titanium dioxide was added through a size 20 mesh into
the molten mixture and the mixture was stirred for additional 10 minutes. Micronized
progesterone was dispersed into the kettle while mixing. After all the micronized progesterone
has been added, stirring was continued for another 30 minutes. The material was then poured
10 onto a sheet of aluminum foil and allowed to cool and harden. The hard sheet was then passed
through screen #20. The milled material was encapsulated using size 0 capsules.

Example 8: Progesterone Oral Caplets, 100 mg

The composition for preparing progesterone oral caplets constituting 100 mg of
15 progesterone per caplet is provided in Table 8 below.

TABLE 8

Component	mg/caplet	% (by weight)
Micronized progesterone	100.00	52.63
Lactose monohydrate (Fast Flo #316), NF	57.70	30.37
Microcrystalline cellulose (Avicel PH102), NF	17.10	9.00
Croscarmellose sodium, (Ac-Di-Sol), NF	5.70	3.00
Sodium lauryl sulfate, NF	3.80	2.00
Povidone, NF	3.80	2.00
Colloidal silicon dioxide, NF	0.60	0.30
Magnesium stearate, NF	1.30	0.70
*Ethyl alcohol anhydrous (SD3A)	21.00	
TOTAL	190.00 mg	100.00%
*Ethyl alcohol anhydrous is evaporated during processing.		

The required quantities of micronized progesterone, lactose monohydrate, croscarmellose sodium, sodium lauryl sulfate and microcrystalline cellulose were transferred into an appropriate size mixer and mixed for 10 minutes. Povidone was dissolved in ethyl alcohol while the powders were being mixed. The powders were granulated with the povidone solution and the mixing continued until a moist granular mass was formed. Additional ethyl alcohol was added if needed to reach granulation and point. The granulation was transferred to a tray dry oven and dried at 55 °C for 10-15 hrs or until loss on drying was not more than 2.0%. The dried granules were passed through a size 20 mesh screen together with colloidal silicon dioxide. Next, the milled granulation was lubricated by mixing with the required

quantities of magnesium stearate in a suitable blender. The granulate was then compressed to 190 mg per tablet on a rotary tableting machine using 1/4 inch flat faced beveled edge toolings. To make a 200 mg progesterone capsules, 2 tablets of progesterone 100 mg were filled into each size 0 hard shell gelatin capsules.

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Example 9: Preparation of Estradiol Tablet, USP, 1 mg

The composition for preparing an estradiol tablet constituting 1 mg estradiol per tablet is provided in Table 9 below.

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TABLE 9:

Component	mg/tablet	% (by weight)
Estradiol, micronized, USP	1.03	1.290
Anhydrous lactose, NF	60.00	75.000
Microcrystalline cellulose (Avicel PH102)	16.00	20.000
Polacrillin potassium, NF	2.40	3.000
Magnesium stearate, NF	0.40	0.500
D&C Red #30 (27 %) aluminum lake	0.06	0.075
FD&C Blue #1 (13 %) aluminum lake	0.06	0.075
D&C Yellow #10 (18 %) aluminum lake	0.04	0.050
TOTAL	80.00 mg	100.00%

Partial quantity of anhydrous lactose (e.g., about 17 %), the required quantities of D&C Red #30 (27 %) aluminum lake, FD&C Blue #1 (13 %) aluminum lake, D&C Yellow #10 (18 %) aluminum lake were passed through a size 20 mesh screen. The required quantities of estradiol and the remaining quantities of anhydrous lactose were transferred into

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an appropriate size mixer and were mixed for 10 minutes. The required quantities of microcrystalline cellulose, polacriline potassium and the milled colored mixtures were added into the lactose/estradiol mixture and the composition was mixed for 10 minutes. The granulate was then lubricated by mixing with the required quantities of magnesium stearate in the same mixer. The granulate was then compressed to 80 mg per tablet using 7/32" round flat faced beveled edge tooling on a rotary tabletting machine. The thickness range of the tablets was 0.104" to 0.112" and hardness range of the tablets is 2-6 Kp.

Example 10: Bioavailability of Progesterone Caplet

10 A pilot, single-dose, two period, randomized crossover study was conducted in healthy post-menopausal women to determine the relative oral bioavailability of two progesterone products under fasting conditions. The methodology for conducting randomized crossover studies are well-known in the medical and pharmaceutical arts.

15 Figure 1 shows the results of the experiment. In Figure 1, "A" represents the data for a capsule formulation of progesterone 200 mg of the present invention (hereinafter referred to as Watson progesterone) and "B" represents the data for commercially available formulation, Prometrium® 100 mg (x 2). The formulation is the same as in Example 1 except that the lentils were passed through a size 20 mesh and encapsulated in size 0 capsules.

20 Figure 1 shows that the mean peak progesterone concentrations (Cmax) reached were 20.04 ± 14.09 and 19.60 ± 17.89 ng/ml following administration of the Watson progesterone and Prometrium® respectively. The means were not found to be statistically different as assessed by ANOVA (analysis of variance). The time to reach peak progesterone concentration (Tmax) was 2.31 ± 1.71 hrs for the Watson progesterone and 1.44 ± 0.32 hrs for Prometrium®. The means were not found to be statistically different at a p value of 0.05 or less. Area under the curve (AUC) (0-t) following administration of the Watson
25 progesterone and Prometrium® were not found to be statistically different as assessed by ANOVA (analysis of variance). AUC (0-t) or the area under the drug concentration versus

time curve, from time zero to the last measured concentration (12 hours), was calculated by the linear trapezoidal method.

This study showed that there were no statistically significant differences in the mean peak progesterone concentration (C_{max}), mean time to reach peak progesterone concentration (T_{max}), and Area under the curve (AUC) between the Watson solid oral progesterone formulation and the FDA approved oil based oral progesterone formulation, Prometrium®, following a single administration to healthy postmenopausal women.

Example 11: Bioavailability of Progesterone Caplet when Administered with Estradiol

A pilot single dose, three period, randomized crossover study was conducted in 12 healthy postmenopausal women to determine the relative oral bioavailability of two progesterone products under fasted conditions. The study involved administration of a single progesterone caplet (300 mg), a single estradiol tablet (1 mg) or a combination of the estradiol tablet and the progesterone caplet.

The progesterone caplet resulted in a C_{max} of 75.78 ± 5.3 ng/mL of plasma progesterone, with a T_{max} of 2.62 ± 1.5 hours and an $AUC_{(0-24)}$ of 211.1 ± 127 ng.hr/ml. The normalized C_{max} is 0.25 ng/mL and the normalized AUC is 0.7 ng.hr/ml/mg. The normalized data was obtained by dividing the corresponding data with the dose.

The combination capsule resulted in a C_{max} of 122.98 ± 157.9 ng/mL of plasma progesterone with a T_{max} of 1.88 ± 0.98 hours and an $AUC_{(0-24)}$ of 276.6 ± 251.4 ng.hr/ml. The normalized C_{max} is 0.41 ng/mL and the normalized $AUC_{(0-24)}$ is 0.9 ng.hr/ml/mg.

The above data indicate that the normalized C_{max} of progesterone from the combination capsule (0.41 ng/ml) is about 60 % higher than the normalized C_{max} for the progesterone-only caplet (0.25 ng/ml). Similarly, the normalized AUC for progesterone from the combination capsule (0.9 ng.hr/ml/mg) is about 30 % higher than the AUC for progesterone from the progesterone-only caplet (0.7 ng.hr/ml/mg). These are surprising

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results and suggest that higher C_{max} and AUC levels of progesterone can be achieved by providing progesterone in a solid oral dosage form having a solid polymeric carrier and in combination with an estrogen.

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We claim:

1. An oral dosage form suitable to deliver a combined dosage of progesterone and estradiol which upon delivery through the gastrointestinal tract provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone, said dosage form comprising a combination that includes (a) a first solid form comprising from about 25 mg to about 500 mg micronized progesterone in a solid polyethylene glycol carrier having an average molecular weight of from about 1000 to 10,000 and constituting at least about 30 % of said first solid form; and (b) a second solid form comprising an estrogen.
2. An oral dosage form of claim 1 wherein said polyethylene glycol carrier comprises from about 45 % to about 65 % weight of the component (a).
3. An oral dosage form of claim 1 wherein said second solid form (b) contains from about 0.25 mg to about 5 mg of estradiol.
4. An oral dosage form of claim 1 wherein said solid polyethylene glycol carrier comprises a mixture of polyethylene glycol 1450, polyethylene glycol 3350 or polyethylene glycol 8000.
5. An oral dosage form suitable to deliver a combined dosage of progesterone and an estrogen via the gastrointestinal tract which upon oral administration provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone; said dosage form comprising a combination that includes (a) a first solid form containing from about 25 mg to about 500 mg micronized progesterone, said first solid form having been derived from the extrusion of a polymer matrix extruded from a mixture comprising micronized progesterone in a solid polyethylene glycol carrier which is a mixture of polyethylene glycol 1450,

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polyethylene glycol 3350 or polyethylene glycol 8000, the micronized progesterone having first been dispersed in molten polyethylene glycol and, after cooling to a solid form, having been extruded, said mixture constituting from about 45 % to about 65 % weight of said first solid form; and (b) a second solid form which contains from about 0.25 mg to about 5 mg of estradiol.

6. An oral dosage form of claim 5 wherein said first solid form is a caplet and said second solid form is a tablet.

7. A method of providing an oral dosage of a combination therapy of progesterone and estradiol which comprises administering to a patient an oral dosage form suitable to deliver a combined dosage of progesterone and an estrogen via the gastrointestinal tract which upon oral administration provides a blood concentration of from about 0.1 ng/ml to about 400 ng/ml progesterone; said dosage form comprising a combination that includes (a) a first solid form containing from about 25 mg to about 500 mg micronized progesterone, said first solid form having been derived from the extrusion of a polymer matrix extruded from a mixture comprising micronized progesterone in a solid polyethylene glycol carrier which is a mixture of polyethylene glycol 1450, polyethylene glycol 3350 or polyethylene glycol 8000, the micronized progesterone having first been dispersed in molten polyethylene glycol and, after cooling to a solid form, having been extruded, said mixture constituting from about 45 % to about 65 % weight of said first solid form; and (b) a second solid form which contains from about 0.25 mg to about 5 mg of estradiol.

INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/US 02/07562

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/565 A61K31/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 05807 A (NOVO NORDISK) 2 March 1995 (1995-03-02) claims 1-5,8,9 ---	1-3,5-7
A	US 3 862 311 A (L.J.LEESON) 21 January 1975 (1975-01-21) claims ---	1-7
A	WO 97 04749 A (LABORATOIRS EFFIK) 13 February 1997 (1997-02-13) claims 1,7,9,11,14-20,24,25 example I --- -/--	1-7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

13 November 2002

Date of mailing of the international search report

20/11/2002

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/07562

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 11749 A (WARNER-LAMBERT) 24 June 1993 (1993-06-24) claims page 6, line 24 - line 30 page 7, line 8 - line 11 page 7, line 24 - line 28 -----	1-7
A	US 3 828 106 A (H.W.RUDEL) 6 August 1974 (1974-08-06) claims examples column 5, line 3 - line 28 -----	1-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/07562

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/07562

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9505807	A	02-03-1995	AU 7530594 A BR 9407306 A CA 2169840 A1 CN 1132478 A CZ 9600425 A3 WO 9505807 A1 EP 0789560 A1 FI 960749 A HU 74167 A2 JP 9501682 T LT 96010 A ,B NO 960653 A NZ 271617 A PL 313113 A1 SK 19396 A3	21-03-1995 08-10-1996 02-03-1995 02-10-1996 12-06-1996 02-03-1995 20-08-1997 19-02-1996 28-11-1996 18-02-1997 25-06-1996 19-02-1996 26-11-1996 10-06-1996 05-03-1997
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WO 9311749	A	24-06-1993	AT 157864 T AU 3142693 A DE 69222182 D1 DE 69222182 T2 DK 617612 T3 EP 0617612 A1 ES 2109377 T3 GR 3025501 T3 IL 104179 A JP 7504162 T MX 9207390 A1 NZ 245483 A PT 101132 A ,B SG 43179 A1 WO 9311749 A1 US 2001044409 A1 ZA 9209789 A	15-09-1997 19-07-1993 16-10-1997 26-02-1998 14-04-1998 05-10-1994 16-01-1998 27-02-1998 20-11-1997 11-05-1995 01-06-1993 21-12-1995 31-03-1994 17-10-1997 24-06-1993 22-11-2001 23-06-1993
US 3828106	A	06-08-1974	NONE	

2020
Bogotá, D.C.,

Doctor:
Álvaro Correa Ordóñez
Apoderado

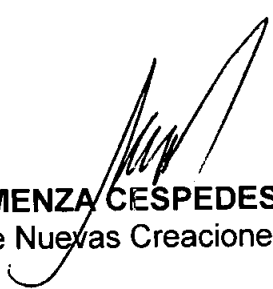
Oficio N°: 088771

ASUNTO:	Radicación PCT N°	09-53058
	Trámite	011
	Evento	378
	Actuación	440
	Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor Tito Noe Parra Murillo, en su calidad de apoderado de Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

El anterior oficio fue notificado por fijación en lista de fecha, 16 JUL. 2010.

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2020
Bogotá, D.C.,

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Apoderado

Oficio N°: 08878

ASUNTO: Radicación PCT N° 09-53058
Trámite 011
Evento 378
Actuación 440
Folios 008

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Cielo Ángela Peña Rodríguez, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

El anterior oficio fue notificado por fijación en lista de fecha, 16 JUL. 2010.

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