

## FORMULARIO ÚNICO DE OPOSICIÓN

①

## OPOSICIÓN A:

- |                                                                        |                                                  |
|------------------------------------------------------------------------|--------------------------------------------------|
| <input checked="" type="checkbox"/> Patente de Invención.              | <input type="checkbox"/> Marca Colectiva.        |
| <input type="checkbox"/> Patente de Modelo de Utilidad.                | <input type="checkbox"/> Marca de Certificación. |
| <input type="checkbox"/> Diseño Industrial.                            | <input type="checkbox"/> Lema Comercial.         |
| <input type="checkbox"/> Esquema de Trazado para Circuitos Integrados. |                                                  |
| <input type="checkbox"/> Marcas de Productos o Servicios.              |                                                  |

②

Número del expediente: 09-139.945

Solicitante: **NOVARTIS A.G.**

**SOLICITUD  
PUBLICADA**

Andarado: **CARLOS REYNALDO OLARTE GARCIA**

Título de la nueva creación o denominación del signo: FORMAS AMORFAS  
ESTABILIZADAS DE MESILATO DE IMATINIB

Gaceta: 624

**③ OPOSICIÓN PRESENTADA POR:**

|                              |                                                                                                                                                                                         |                                                                                                                                                                                                                                       |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SOLICITANTE                  | Nombre: <b>LABORATORIOS SYNTHESIS S.A.S.</b><br>Dirección: <b>Carrera 44 N° 20 C 73</b><br>Nacionalidad o Domicilio: <b>COLOMBIA</b><br>Lugar de Constitución: <b>BOGOTÁ</b>            | <b>IDENTIFICACION</b><br>C.C. <input type="checkbox"/> NIT <input checked="" type="checkbox"/><br>C.E. <input type="checkbox"/> Otro <input type="checkbox"/><br>Cual _____<br>Número <u><b>860.000.760-1</b></u>                     |
|                              | Teléfono: <b>3692222</b> Fax: <b>3693542</b><br>E-mail: _____                                                                                                                           |                                                                                                                                                                                                                                       |
| REPRESENTANTE<br>O APODERADO | Nombre: <b>ELINA ISaura MORENO BOHORQUEZ</b><br>Dirección: <b>CARRERA 104 N°119-95 OF 104</b><br>Teléfono: <b>2131213</b> Fax: <b>6121979</b><br>E-mail: <b>negocios@optimum-co.com</b> | <b>IDENTIFICACION</b><br>C.C. <input checked="" type="checkbox"/> NIT <input type="checkbox"/><br>C.E. <input type="checkbox"/> Otro <input type="checkbox"/><br>Cual _____<br>Número <u><b>51.975.664</b></u> TP <u><b>83823</b></u> |

## Ⓐ FUNDAMENTOS DE LA OPOSICIÓN:

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

**Causa:** No cumple con los requisitos de patentabilidad.

Siano operatori:

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

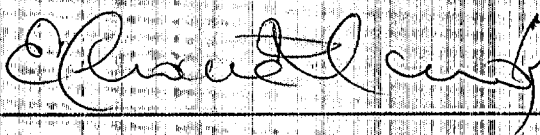
⑥ ANEXOS

- ☒ 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: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA:



C.C. 51'975.664

TP. 83823



Derecho de la Competencia, Propiedad  
Industrial y Comercio Exterior

Señor Jefe,

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 09 139945

Asunto : Oposición a la solicitud de patente de Invención titulada  
"FORMAS AMORFAS ESTABILIZADAS DE MESILATO  
DE IMATINIB"

Solicitante : NOVARTIS AG.

Opositora : LABORATORIOS SYNTHESYS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 624 del 20 de enero de 2011

Yo, *ELIANA ISaura MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **83823** del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESYS S.A.S** 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 "FORMAS AMORFAS ESTABILIZADAS DE MESILATO DE IMATINIB", cuyos titulares son **NOVARTIS AG**, 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 IMATINIB. 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 07 de diciembre de 2009 reivindicando prioridad bajo la solicitud EP20070109816 del 2007-06-07; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 624 del 20 de enero de 2011, cuya publicación internacional corresponde a la WO2008154262 del 2008-12-18.

2.2. La solicitud colombiana 09 139945 objeto de la presente oposición se refiere a la forma amorfa estabilizada de la sal de adición de ácido metansulfónico de 4-(4-metilpiperazin-1-ilmetil)-N-[4-metil-3-(4-(piridin-3-il)-pirimidin-2-ilamino)-fenil]-benzamida, composiciones farmacéuticas tales como cápsulas o tabletas que contienen esta forma, el uso de dicha forma en métodos de diagnóstico o,

preferiblemente, para el tratamiento terapéutico de animales de sangre caliente, especialmente seres humanos, y al uso de principio de formulación estabilizando la forma amorfa de mesilato de Imatinib como un intermediario para la preparación de composiciones farmacéuticas.

2.3. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: *“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”*, tenemos que 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 afectan la patentabilidad de la presente solicitud:

- D1: US2006275372 publicada el 07 de agosto de 2003.
- D2: WO 2004106326 publicada el 09 de diciembre de 2004.

2.4. Ahora bien, el documento D1, se refiere a composiciones en nanopartículas de mesilato de imatinib, o una sal o un derivado del mismo. Las partículas de mesilato de imatinib de la composición tienen un tamaño efectivo de partícula promedio de menos de unos 2000 nm y son útiles en el tratamiento de la leucemia mieloide crónica, tumores del estroma gastrointestinal y enfermedades relacionadas; Dicho documento D1, de forma particular en la descripción (ver ejemplo 1) revela nanopartículas de mesilato de imatinib en un estado amorfo estable para el tratamiento de la leucemia. En una realización (ejemplo 1) el molido conjunto con estabilizadores de superficie se describe, sin embargo, sin indicación de si es o no el producto final amorfo. No obstante, moler conjuntamente es uno de los procesos

conocidos anteriormente que conducen a un estado amorfo (como se describe en la solicitud objeto de la presente oposición); la solicitud objeto de la presente oposición no es novedosa pues lo reclamado ya era parte de arte anterior.

2.5. Por su parte, el documento D2 se refiere a polimorfos de mesilato de imatinib, a los procesos para su preparación y a las composiciones farmacéuticas que los contienen, donde dicho documento D2 revela de forma particular en la descripción, pagina 2 líneas 1 -5 y en los ejemplos 6,7 y 8 una composición amorfa estable de mesilato de imatinib.

2.6. Tomando los documentos D1 y D2 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir de dicho documento D1 por sí solo, o en combinación con D2, concebir una forma amorfa estabilizada de mesilato de imatinib, composiciones farmacéuticas tales como cápsulas o tabletas que contienen esta forma, el uso de dicha forma en la medicina, y al uso del principio de formulación estabilizando la forma amorfa de mesilato de Imatinib como un intermediario para la preparación de composiciones farmacéuticas. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 139945 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1. CARENCIA 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, 07 de junio de 2007 ya era conocido, pues como se demostró, eran parte del arte anterior con base en los documentos D1, nanopartículas de mesilato de imatinib en un estado amorfo estable para el tratamiento de la leucemia, utilizando el proceso de molido conjunto con estabilizadores de superficie; sobre lo cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 07 de junio de 2007, a partir del documento D1 por sí solo, o en combinación con D2, un experto en la materia puede llegar de manera evidente a nanopartículas de mesilato de imatinib en un estado amorfo estable, o a mesilato e imatinib en un estado amorfo estable; sobre lo cual busca protección en el capítulo reivindicatorio.

2.9. 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 dos de los tres requisitos de patentabilidad.

2.10. 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 “FORMAS AMORFAS ESTABILIZADAS DE MESILATO DE IMATINIB”, cuyos titulares son NOVARTIS AG, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 624 del 20 de enero de 2011.

### 3. PRUEBAS

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

- D1: US2006275372 publicada el 07 de agosto de 2003.
- D2: WO 2004106326 publicada el 09 de diciembre de 2004.

### 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

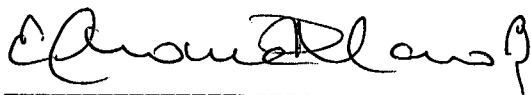
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **LABORATORIOS SYNTHESYS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
  - D1: US2006275372 publicada el 07 de agosto de 2003.
  - D2: WO 2004106326 publicada el 09 de diciembre de 2004.

**6. NOTIFICACIONES**

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

1

## **PODER ESPECIAL**

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Gerente de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Bogotá (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **09 139.945**, titulada "**FORMAS AMORFAS ESTABILIZADAS DE MESILATO DE IMATINIB**", cuyo titular es **NOVARTIS AG**, publicada en la gaceta No. 624 del 20 de enero de 2011.

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

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

Dado y Firmado en Bogotá (Colombia) a los \_\_\_\_ días del mes de \_\_\_\_ de 2011.

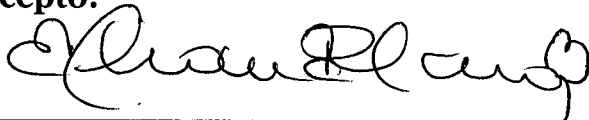
**LABORATORIOS SYNTHESIS S.A.S.**

Cédula de Extranjería: No. 319788.

NIT: 860.000.760-1

Gerente

Acepto:



**ELIANA ISAURA MORENO BOHÓRQUEZ**

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



28



# DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Circulo de Bogotá,

*Juan Alberto Palacios Aragon*  
quien exhibió la C.E. *39988*

Expedida en *Ma* y

declaró que la firma y huella que aparecen en el presente documento son suyas y que el contenido del mismo es cierto.

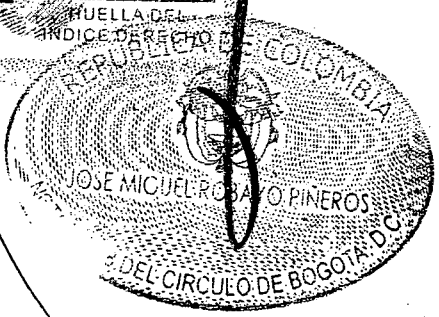
**07 ABR 2011**

BOGOTÁ, D.C.

FIRMA

EL NOTARIO

NOTARIA DIECIOCHO DEL CIRCULO DE BOGOTÁ D.C.  
HUELLA SE AUTENTICA POR SOLICITUD DEL INTERESADO



*[Handwritten signature]*

## SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

-/-



## RECIBO DE CAJA

No. 11 - 0034867

Bogotá D.C., Abril 14 de 2011 - 15:54:15

RECIBIDO DE : LABORATORIOS SYNTHESIS S.A.S.

NI 860.000.760

## \*\*\* Soporte del Pago \*\*\*

| TIPO PAGO    | BANCO           | CUENTA    | No. PAGO  | FECHA PAGO | VR. PAGO   |
|--------------|-----------------|-----------|-----------|------------|------------|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 328250392 | 12/04/2011 | 304.000.00 |

## \*\*\* Conceptos Pagados \*\*\*

| CANT | RENTISTICO                                              | CONCEPTO                      | Vr. UNDITARIO | Vr. CONCEPTO |
|------|---------------------------------------------------------|-------------------------------|---------------|--------------|
| 1    | 50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES | 12 MARCAS Y LEMAS COMERCIALES | 304.000.00    | 304.000.00   |
|      |                                                         |                               |               | \$304.000.00 |

SON: \*\*TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE\*\*

Responsable: \_\_\_\_\_

Recibo de Caja Aplicado al Expediente No. \_\_\_\_\_

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



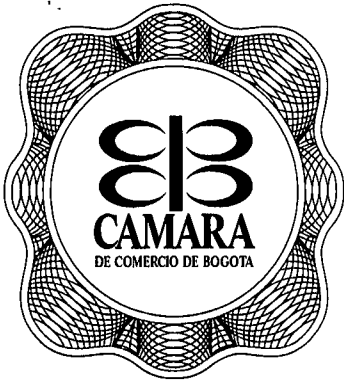
No. 09-139945- -00004-0000

Fecha: 2011-04-14 16:06:10 Dep. 2020 DIR.NUEVASCR  
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI  
Act. 400 OPOSIOBSERVTER Folios: 50

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Linea: 018000-910165 Call Center: (571) 6513240

, Abril 14 de 2011 - 15:54:15



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CAMARA DE COMERCIO DE BOGOTA

SEDE SALITRE

18 DE FEBRERO DE 2011

HORA 17:37:24

R030552045

HOJA : 1 DE 6

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

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

CERTIFICA:

NOMBRE : LABORATORIOS SYNTHESIS S A S

N.I.T. : 860000760-1

DOMICILIO : BOGOTA D.C.

CERTIFICA:

MATRICULA NO: 00008059 DEL 23 DE MARZO DE 1972

CERTIFICA:

DIRECCION DE NOTIFICACION JUDICIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL DE NOTIFICACION JUDICIAL :

synthe@synthesis.com.co

DIRECCION COMERCIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL COMERCIAL :

synthe@synthesis.com.co

CERTIFICA:

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

CERTIFICA:

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

CERTIFICA : \_

QUE POR ESCRITURA PUBLICA NUMERO 6491 OTORGADA EN LA NOTARIA 1. - DE BOGOTA EL 24 DE DICIEMBRE DE 1.981, INSCRITA EN ESTA CAMARA DE COMERCIO EL 12 DE MARZO DE 1.982, BAJO EL NUMERO 113.297 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE "LABORATORIOS SYNTHESIS - BALAVOINE Y CIA. S.C.A" POR EL DE "LABORATORIOS SYNTHESIS LTDA. Y CIA. S.C.A" E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

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

CERTIFICA:

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

CERTIFICA:

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

CERTIFICA:

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

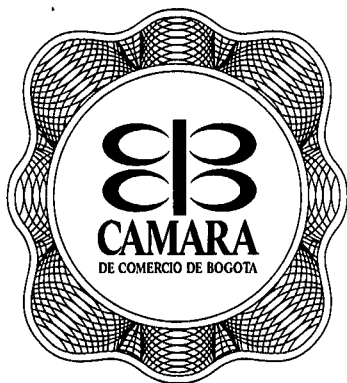
CERTIFICA:

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

CERTIFICA:

REFORMAS:

| ESCRITURAS NO. | FECHA        | NOTARIA | INSCRIPCION             |
|----------------|--------------|---------|-------------------------|
| 4471           | 18-XII-1.956 | 8 BTA.  | 22-XII-1.956 NO. 36.077 |
| 3322           | 31-XII-1.958 | 8 BTA.  | 12-I-1.959 NO. 42.034   |
| 2322           | 22-IX-1.961  | 8 BTA.  | 29-IX-1.961 NO. 51.161  |
| 290            | 2-II-1.967   | 6 BTA.  | 24-II-1.967 NO. 71.304  |



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CAMARA DE COMERCIO DE BOGOTA

SEDE SALITRE

18 DE FEBRERO DE 2011

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HOJA : 2 DE 6

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|      |              |              |                          |
|------|--------------|--------------|--------------------------|
| 8545 | 16-XII-1.967 | 6 BTA.       | 26-I-1.968 NO. 75.041    |
| 4679 | 20-XII-1.967 | 8 BTA.       | 26-I-1.968 NO. 75.042    |
| 3010 | 14-V-1.968   | 6 BTA.       | 30-V-1.968 NO. 76.244    |
| 2931 | 4-V-1.970    | 6 BTA.       | 18-V-1.970 NO. 84.983    |
| 5656 | 13-VII-1.970 | 6 BTA.       | 13-VIII-1.970 NO. 86.126 |
| 3487 | 15-VII-1.971 | 3 BTA.       | 29-VII-1.971 NO. 90.980  |
| 4638 | 10-VII-1.984 | 11 BTA.      | 27-VIII-1.984 NO.157.001 |
| 1443 | 14-III-1.985 | 11 BTA.      | 26- III-1.985 NO.167.627 |
| 724  | 11- II-1.985 | 1 BTA.       | 21- II-1.985 NO.165.940  |
| 4836 | 11-VIII-1986 | 1 BTA.       | 23- IX -1.986 NO.197.784 |
| 5659 | 15- IX -1986 | 1 BTA.       | 23- IX -1.986 NO.197.784 |
| 6326 | 16- X -1987  | 1 BTA.       | 23- X -1.987 NO.221.604  |
| 5164 | 21-VIII-1990 | 1 BTA.       | 3- IX -1.990 NO.303.579  |
| 9244 | 23-XII- 1991 | 1 STAFE.BTA. | 8-I -1.992 NO.351.255    |
| 8145 | 15- X - 1992 | 1 STAFE.BTA. | 16- X-1.992 NO.382.488   |
| 1374 | 26- III-1993 | 1 STAFE.BTA. | 19- III-1993 NO.399972   |
| 3120 | 01-VI-1.995  | 1A.STAFE BTA | 23-VI- 1.995 NO.498.060  |
| 5435 | 17-IX-1.996  | 1A.STAFE BTA | 30-IX- 1.996 NO.556.909  |
| 5435 | 17-IX-1.996  | 1A.STAFE BTA | 01- X- 1.996 NO.557.146  |
| 5435 | 17-IX-1.996  | 1A.STAFE BTA | 02- X- 1.996 NO.557.301  |
| 5942 | 7-X -1.996   | 1A.STAFE BTA | 11- X- 1.996 NO.558.222  |
| 6305 | 24-X--1.996  | 1A.STAFE BTA | 07-XI--1.996 NO.561.207  |
| 6929 | 25-XI-1.996  | 1A.STAFE BTA | 12-XII-1.996 NO.565.961  |
| 787  | 19-II-1.997  | 1A.STAFE BTA | 25-II -1.997 NO.575.141  |
| 1024 | 28-II-1.997  | 1A.STAFE BTA | 31-III-1.997 NO.579.245  |

CERTIFICA:

REFORMAS:

| E.P. NO. | FECHA      | NOTARIA | CIUDAD      | FECHA      | NO. INSC. |
|----------|------------|---------|-------------|------------|-----------|
| 0007110  | 1997/10/28 | 0001    | BOGOTA D.C. | 1997/11/06 | 00609204  |
| 0001896  | 1998/03/16 | 0001    | BOGOTA D.C. | 1998/04/01 | 00628368  |
| 0002924  | 1998/04/21 | 0001    | BOGOTA D.C. | 1998/05/18 | 00634309  |
| 0002377  | 2000/06/14 | 0001    | BOGOTA D.C. | 2000/06/20 | 00733626  |
| 0000SIN  | 2004/06/22 | 0000    | BOGOTA D.C. | 2004/06/28 | 00940785  |
| 117      | 2010/04/30 | 0000    | BOGOTA D.C. | 2010/06/10 | 01390261  |
| 120      | 2010/08/18 | 0000    | BOGOTA D.C. | 2010/08/26 | 01409241  |

|     |            |      |             |            |          |
|-----|------------|------|-------------|------------|----------|
| 120 | 2010/08/30 | 0000 | BOGOTA D.C. | 2010/09/13 | 01413659 |
| 120 | 2010/07/29 | 0000 | BOGOTA D.C. | 2010/11/19 | 01429837 |

CERTIFICA:

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

CERTIFICA:

OBJETO SOCIAL: EL OBJETO DE LA SOCIEDAD ES EL EJERCICIO DE TODAS LAS ACTIVIDADES COMERCIALES PARA: 1) LA IMPORTACIÓN, EXPORTACIÓN, FABRICACIÓN, COMERCIALIZACIÓN, DISTRIBUCIÓN Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, VETERINARIOS E IMPLEMENTOS MÉDICOS. 2) CUALQUIER OTRA ACTIVIDAD LÍCITA DE COMERCIO RELACIONADA CON SU OBJETO SOCIAL PRINCIPAL Y TODO LO QUE SE RELACIONA CON LA IMPORTACIÓN DE LOS BIENES Y EQUIPOS NECESARIOS PARA EL DESARROLLO DE SU OBJETO SOCIAL. 3) TENER LA REPRESENTACIÓN EN COLOMBIA DE EMPRESAS O SOCIEDADES ESTABLECIDAS FUERA DEL TERRITORIO COLOMBIANO, CUYO OBJETO SEA SIMILAR O COMPLEMENTARIO. EN DESARROLLO DE SU OBJETO SOCIAL PRINCIPAL, LA SOCIEDAD PODRÁ ADELANtar Y CELEBRAR LOS SIGUIENTES ACTOS Y CONTRATOS: A) EXPORTAR E IMPORTAR, AGENCIAR, DISTRIBUIR, COMERCIALIZAR, COMPRAR O VENDER A COMISIÓN O CONSIGNACIÓN O DE CUALQUIER OTRA FORMA O MODALIDAD, TODA CLASE DE EQUIPOS, APARATOS, BIENES AL POR MAYOR O AL DETAL, Y SERVICIOS RELACIONADOS CON SU ACTIVIDAD. B) GRAVAR EN CUALQUIER FORMA LOS BIENES DE SU PROPIEDAD MUEBLES O INMUEBLES, DAR EN PRENDA LOS PRIMEROS O HIPOTECAR LOS SEGUNDOS PARA GARANTIZAR OBLIGACIONES DE LA SOCIEDAD. C) CONSTITUIR APODERADOS QUE LE REPRESENTEN, ASOCIARSE CON OTRAS COMPAÑÍAS DE LA MISMA O PARECIDA NATURALEZA Y EN GENERAL REALIZAR TODA CLASE DE OPERACIONES COMERCIALES O CIVILES Y EJECUTAR O CELEBRAR TODA CLASE DE CONTRATOS O ACTOS DEL MISMO ORDEN, YA SEAN INDUSTRIALES, COMERCIALES O FINANCIEROS ENCAMINADOS A ALCANZAR LOS FINES QUE SE PROPONEN. D) ADQUIRIR, ENAJENAR, ADMINISTRAR, RECIBIR O DAR EN ARRENDATARIO O A CUALQUIER TÍTULO, TODA CLASE DE BIENES MUEBLES E INMUEBLES. E) INTERVENIR ANTE TERCEROS O ANTE LOS ACCIONISTAS MISMOS COMO ACREEDORA O COMO DEUDORA EN TODA CLASE DE OPERACIONES DE CRÉDITO, DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRESTAMOS. OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR Y NEGOCIAR EN GENERAL TÍTULOS VALORES RECIBIRLOS EN PAGO; G) CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES.

CERTIFICA:

CAPITAL:

\*\* CAPITAL AUTORIZADO \*\*



\*01\*



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CAMARA DE COMERCIO DE BOGOTA

SEDE SALITRE

18 DE FEBRERO DE 2011

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HOJA : 3 DE 6

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VALOR : \$20,000,000,000.00  
NO. DE ACCIONES : 20,000,000.00  
VALOR NOMINAL : \$1,000.00

**\*\* CAPITAL SUSCRITO \*\***

VALOR : \$17,633,742,000.00  
NO. DE ACCIONES : 17,633,742.00  
VALOR NOMINAL : \$1,000.00

**\*\* CAPITAL PAGADO \*\***

VALOR : \$17,633,742,000.00  
NO. DE ACCIONES : 17,633,742.00  
VALOR NOMINAL : \$1,000.00

**CERTIFICA:**

REPRESENTACION LEGAL: GERENCIA LA CUAL SERÁ ASUMIDA POR UN GERENTE Y UN SUBGERENTE QUIENES TENDRÁN REPRESENTACIÓN LEGAL DE LA SOCIEDAD.

**CERTIFICA:**

**\*\* NOMBRAMIENTOS \*\***

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

**NOMBRE**

**IDENTIFICACION**

**GERENTE**

PALACIOS LUIS ALBERTO

C.E. 000000000319788

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

**NOMBRE**

**IDENTIFICACION**

**SUBGERENTE**

MUÑOZ MARTINEZ ORLANDO

C.C. 000000008317044

**CERTIFICA:**

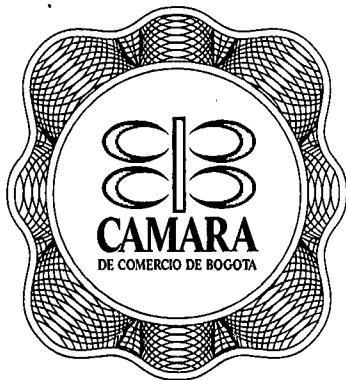
FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A SU CARGO LA ADMINISTRACIÓN INMEDIATA DE LA SOCIEDAD, ASÍ COMO LA REPRESENTACIÓN LEGAL DE LA MISMA Y EN TAL VIRTUD LE ESTÁN ASIGNADAS LAS SIGUIENTES FUNCIONES Y ATRIBUCIONES: A) LLEVAR LA REPRESENTACIÓN DE LA

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

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 654 DE LA NOTARIA 01 DE BOGOTÁ D.C., DEL 20 DE FEBRERO DE 2009, INSCRITA EL 02 DE MARZO DE 2009 BAJO EL NO. 15209 DEL LIBRO V, COMPARECIO ORLANDO MUÑOZ MARTINEZ IDENTIFICADO CON CEDULA DE CIUDADANIA NO. 8.317.044 EN SU CALIDAD DE DELEGADO GENERAL SUPLENTE DEL SOCIO GESTOR LABORATORIOS SYNTHESIS LTDA.,

POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL SEÑOR ANDRÉS FERNANDO MOLLAJOLI CENTURION, IDENTIFICADO CON CÉDULA DE EXTRANJERÍA NO. 351.283 QUE EN NOMBRE DE LA SOCIEDAD QUE REPRESENTO, ACTUÉ CON LAS MÁS AMPLIAS FACULTADES EN LA REPÚBLICA DE COLOMBIA, EN LOS SIGUIENTES ASUNTOS 1. PARTICIPAR EN CALIDAD DE SOCIO, ACCIONISTA O EMPRESARIO EN PERSONAS JURÍDICAS COLOMBIANAS, CONSTITUIDAS O POR CONSTITUIRSE, EN EL PORCENTAJE QUE LA APODERADA AQUÍ NOMBRADA ESTIME CONVENIENTE A NUESTROS INTERESES, CON FACULTAD PARA ENTREGAR LAS SUMAS CORRESPONDIENTES AL PAGO DEL MISMO; 2. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE



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CAMARA DE COMERCIO DE BOGOTA

SEDE SALITRE

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LAS AUTORIDADES COLOMBIANAS; 3. REPRESENTAR A LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., EN LAS REUNIONES ASAMBLEA GENERAL O JUNTAS EN LAS CUALES TENGA INTERÉS; 4. EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRÉSTAMOS DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS, OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR, Y NEGOCIAR EN GENERAL TÍTULOS VALORES Y RECIBIRLOS EN PAGO; 5. CELEBRAR ASÍ MISMO OPERACIONES RELACIONADAS CON LA PROTECCIÓN DE SUS BIENES, NEGOCIOS Y PERSONAS A SU SERVICIO; 6. CELEBRAR CONTRATOS DE CUENTAS EN PARTICIPACIÓN, SEA COMO PARTÍCIPE ACTIVA O COMO PARTÍCIPE INACTIVA; 7. TRANSIGIR, DESISTIR Y APELAR DECISIONES DE ÁRBITROS O DE AMIGABLES COMPOREDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES; 8. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. 9. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEA CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES; 10. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. 11. NOTIFICARSE VÁLIDAMENTE DE AQUELLOS ACTOS DEL ORDEN ADMINISTRATIVO O JUDICIAL QUE SE FORMULEN CONTRA LA SOCIEDAD, ASÍ CÓMO ABSOLVER INTERROGATORIOS CON CAPACIDAD PARA CONFESAR; 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SYNTHESIS LTDA & CIA S.C.A. 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SÍNTESIS LTDA. & CIA S.C.A., RECAUDAR O RECIBIR POR SUS FRUTOS Y CELEBRAR TODA CLASE DE CONTRATOS RELACIONADOS CON LA ADMINISTRACIÓN. 13. ENAJENAR, ADQUIRIR, PERMUTAR, GRAVAR, ARRENDAR BIENES MUEBLES, PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTIIESIS LTDA & CIA S.C.A, SIN LÍMITE DE CUANTIA. 14. ENAJENAR, PERMUTAR, ADQUIRIR, GRAVAR, ARRENDAR BIENES MUEBLES E INMUEBLES PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL

SALARIO MÍNIMO LEGAL MENSUAL MAS ALTO EN LA FECHA DE CELEBRACIÓN Y TENGA RELACIÓN DIRECTA CON EL DESARROLLO SOCIAL, ASÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DE LA SOCIEDAD GESTORA. 15. TOMAR DINERO EN MUTUO, CON FACULTAD PARA ESTIPULAR TODO TIPO DE INTERESES, PLAZOS Y DEMÁS CONDICIONES Y CELEBRAR CONTRATOS DE CUENTA CORRIENTE; 16. GIRAR, ORDENAR GIRAR, ENDOSAR, PROTESTAR, OTORGAR, ACEPTAR ORDENAR AVALÚOS Y HACER TODA CLASE DE NEGOCIOS RELACIONADOS CON TÍTULOS VALORES CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL SALARIO MÍNIMO LEGAL MENSUAL MÁS ALTO EN LA FECHA DE SU CELEBRACIÓN, SÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DEL REPRESENTANTE LEGAL DE LA SOCIEDAD GESTORA. 17. PRESENTAR DECLARACIÓN DE RENTA, PATRIMONIO, IMPUESTOS A LAS VENTAS EN ADMINISTRACIÓN DE IMPUESTOS NACIONES Y MUNICIPALES E INTERPONER LOS RECURSOS Y DECLARACIONES PERTINENTES CONTRA ACTOS DE DICHA ADMINISTRACIÓN CON FACULTAD PARA DEFENDER LOS INTERESES DE LA SOCIEDAD EN ÉSTA MATERIA. 18. DESIGNAR APODERADO ESPECIAL PARA CADA PROCESO JUDICIAL O ADMINISTRATIVO. 19. PRÉSENTAR RECURSOS POR VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR 20. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES 21. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES 22. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA REPÚBLICA DE COLOMBIA

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 3511 DE LA NOTARIA 18 DE BOGOTA D.C., DEL 8 DE SEPTIEMBRE DE 2010, INSCRITA EL 1 DE OCTUBRE DE 2010 BAJO EL NO. 00018604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE BOGOTA, EN SU CALIDAD DE GERENTE DE LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL A OLGA VICTORIA PRIETO ZAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.308 DE BOGOTA PARA QUE EN NOMBRE DE LA SOCIEDAD LABORATORIOS SYNTHESIS S.A.S., PROMUEVA Y DEFIENDA LOS INTERESES DE LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE, EN TODA ESPECIE DE GESTIONES Y ACTUACIONES ANTE LAS AUTORIDADES ADMINISTRATIVAS O JURISDICCIONALES Y EN ESPECIAL PARA: A. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS. B. TRANSIGIR, DESISTIR Y APELAR A DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C. ADELANTAR CUALQUIER TIPO DE TRÁMITE ANTE EL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES. D. RECIBIR NOTIFICACIÓN DE TODAS LAS PROVIDENCIAS QUE SE EXPIDAN DENTRO DE LOS DIFERENTES TRÁMITES E INTERPONER LOS RECURSOS PROPIOS DE LA VÍA GUBERNATIVA. E. REPRESENTAR



QUE POR DOCUMENTO PRIVADO DE REVISOR FISCAL DEL 28 DE JUNIO DE 2010,  
INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397034 DEL LIBRO IX,  
FUE (RON) NOMBRADO (S) :

NOMBRE  
REVISOR FISCAL PRINCIPAL  
AGUILLON ROJAS SANDRA MILENA  
REVISOR FISCAL SUPLENTE

IDENTIFICACION  
C.C. 000000047436442

PRADA SANCHEZ NUBIA MARCELA  
C.C. 000001032358923  
QUE POR ACTA NO. 119 DE ASAMBLEA DE ACCIONISTAS DEL 22 DE JUNIO DE  
2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397026 DEL LIBRO  
IX, FUE (RON) NOMBRADO (S):

NOMBRE  
REVISOR FISCAL PERSONA JURIDICA  
DELOITTE & TOUCHE LTDA

IDENTIFICACION  
N.I.T. 000008600058134

CERTIFICA:

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

CERTIFICA:

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

CERTIFICA:

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS:

NOMBRE : CARDIOPHARM

MATRICULA NO : 00537358 DE 3 DE MARZO DE 1993

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

\*\*\*\*\*

NOMBRE : GENERICS

MATRICULA NO : 00664623 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

\*\*\*\*\*

NOMBRE : MASCOTT

MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

\*\*\*\*\*

NOMBRE : ONCOPHARM

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994



EL PRIMER AÑO DE CONSTITUCION DE SU EMPRESA, DE 50% EN EL SEGUNDO AÑO Y DE 25% EN EL TERCER AÑO. LEY 590 DE 2000 Y DECRETO 525 DE 2009.

RECUERDE INGRESAR A [www.supersociedades.gov.co](http://www.supersociedades.gov.co) PARA VERIFICAR SI SU EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,

VALOR : \$ 3,700

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

A handwritten signature in black ink, appearing to read "J.ausem", is written over the text. The signature is stylized with a long horizontal stroke extending to the left.

# Anexo 1



US 20060275372A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2006/0275372 A1****Jenkins et al.**(43) **Pub. Date: Dec. 7, 2006**(54) **NANOPARTICULATE IMATINIB MESYLATE FORMULATIONS****Related U.S. Application Data**(75) Inventors: **Scott Jenkins**, Downingtown, PA (US);  
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**ELAN DRUG DELIVERY, INC.****C/O FOLEY & LARDNER LLP****3000 K STREET, N.W.****SUITE 500****WASHINGTON, DC 20007-5109 (US)**(51) **Int. Cl.****A61K 31/506** (2006.01)**A61K 9/14** (2006.01)(52) **U.S. Cl.** ..... **424/489; 977/906; 514/252.18**

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**ABSTRACT**(73) Assignee: **Elan Pharma International Limited**(21) Appl. No.: **11/446,565**(22) Filed: **Jun. 5, 2006**

The present invention is directed to a nanoparticulate compositions of imatinib mesylate, or a salt or derivative thereof, having improved pharmacokinetic profiles and reduced fed/fasted variability. The nanoparticulate imatinib mesylate particles of the composition have an effective average particle size of less than about 2000 nm and are useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

## NANOPARTICULATE IMATINIB MESYLATE FORMULATIONS

### CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119(e) of U.S. provisional application No. 60/687,146, filed on Jun. 3, 2005, which is incorporated by reference herein in its entirety.

### FIELD

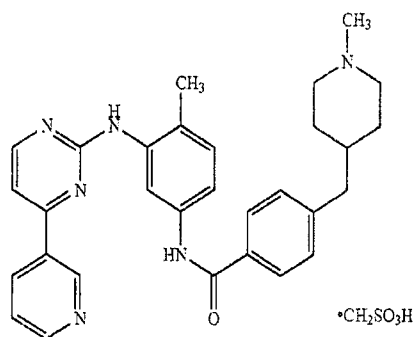
[0002] The invention relates generally to compounds and compositions useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases. More specifically, the invention relates to nanoparticulate imatinib mesylate compositions. The nanoparticulate imatinib mesylate compositions have an effective average particle size of less than about 2000 nm.

### BACKGROUND

#### A. Background Regarding Imatinib Mesylate

[0003] Imatinib mesylate, chemically known as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methane-sulfonate, has a molecular formula of  $C_{29}H_{31}N_7O_4CH_4SO_3$ , and a molecular weight of 589.7.

[0004] Imatinib mesylate has the chemical structure shown below:



[0005] Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Imatinib mesylate is soluble in aqueous buffers  $\leq$  pH 5.5 and slightly soluble to insoluble in neutral to alkaline aqueous buffers. In non-aqueous solvents, imatinib mesylate is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

[0006] Imatinib mesylate is commercially available under the trade name Gleevec® as film-coated tablets, manufactured by Novartis Pharma Stein AG (Stein, Switzerland), and distributed by Novartis Pharmaceuticals Corporation (East Hanover, N.J.). Gleevec® is available in strengths containing imatinib mesylate in amounts equivalent to 100 mg or 400 mg of imatinib free base. Gleevec® contains inactive ingredients that include colloidal silicon dioxide; crospovidone; hydroxypropyl methylcellulose; magnesium

stearate; and microcrystalline cellulose with tablet coatings having ferric oxide, red; ferric oxide, yellow; hydroxypropyl methylcellulose; polyethylene glycol and talc.

[0007] Imatinib mesylate is indicated for the treatment of Philadelphia chromosome positive chronic myeloid leukemia (CML) and Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

[0008] Gleevec® is generally prescribed in dosages of 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. Additionally Gleevec® is recommended at dosages of 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. Gleevec® is generally prescribed to be administered orally, with a meal and a large glass of water, with doses of 400 mg or 600 mg administered once daily, and dosages of 800 mg administered as 400 mg twice a day.

[0009] Imatinib mesylate compounds have been disclosed, for example, in U.S. Pat. No. 5,521,184 to Zimmermann for "Pyrimidine Derivatives and Processes for the Preparation Thereof" and United States Patent Application No. 2004/0127571 to Bhalla et al. for "Method of Treating Leukemia with a Combination of Suberoylanilide Hydromaxic Acid and Imatinib Mesylate". Both of these references are hereby incorporated by reference.

[0010] Imatinib mesylate has high therapeutic value in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors, and related diseases. However, because conventional, non-nanoparticulate imatinib mesylate tablets are only very slightly soluble in water at 37° C., the dissolution of conventional imatinib mesylate tablets is reduced in the fasting state as compared to the fed state. Thus, imatinib mesylate has limited bioavailability in the fasting state as compared to the fed state, which limits the therapeutic outcome for all treatments requiring imatinib mesylate.

#### B. Background Regarding Nanoparticulate Active Agent Compositions

[0011] Nanoparticulate active agent compositions, first described in U.S. Pat. No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of imatinib mesylate.

[0012] Methods of making nanoparticulate active agent compositions are described in, for example, U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

[0013] Nanoparticulate active agent compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" U.S. Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray

Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticle Aggregation During Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticle Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticle X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticle Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticle Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticle NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticle Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328 for "Nanoparticle Diagnostic Diatrizoate Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticle Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticle Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticle Diagnostic Mixed Carboxylic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticle Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticle Compo-

sitions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticle Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticle Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticle Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticle Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticle Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form;" U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticle Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,428,814 for "Bioadhesive Nanoparticle Compositions Having Cationic Surface Stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" and U.S. Pat. No. 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract;" U.S. Pat. No. 6,592,903 for "Nanoparticle Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,582,285 for "Apparatus for sanitary wet milling;" U.S. Pat. No. 6,656,504 for "Nanoparticle Compositions Comprising Amorphous Cyclosporine;" U.S. Pat. No. 6,742,734 for "System and Method for Milling Materials;" U.S. Pat. No. 6,745,962 for "Small Scale Mill and Method Thereof;" U.S. Pat. No. 6,811,767 for "Liquid droplet aerosols of nanoparticle drugs;" and U.S. Pat. No. 6,908,626 for "Compositions having a combination of immediate release and controlled release characteristics;" U.S. Pat. No. 6,969,529 for "Nanoparticle compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" U.S. Pat. No. 6,976,647 for "System and Method for Milling Materials;" all of which are specifically incorporated by reference. In addition, U.S. Patent Publication No. 20020012675 A1, for "Controlled Release Nanoparticle Compositions;" U.S. Patent Publication No. 20050276974

for "Nanoparticulate Fibrate Formulations;" U.S. Patent Publication No. 20050238725 for "Nanoparticulate compositions having a peptide as a surface stabilizer;" U.S. Patent Publication No. 20050233001 for "Nanoparticulate megestrol formulations;" U.S. Patent Publication No. 20050147664 for "Compositions comprising antibodies and methods of using the same for targeting nanoparticulate active agent delivery;" U.S. Patent Publication No. 20050063913 for "Novel metaxalone compositions;" U.S. Patent Publication No. 20050042177 for "Novel compositions of sildenafil free base;" U.S. Patent Publication No. 20050031691 for "Gel stabilized nanoparticulate active agent compositions;" U.S. Patent Publication No. 20050019412 for "Novel glipizide compositions;" U.S. Patent Publication No. 20050004049 for "Novel griseofulvin compositions;" U.S. Patent Publication No. 20040258758 for "Nanoparticulate topiramate formulations;" U.S. Patent Publication No. 20040258757 for "Liquid dosage compositions of stable nanoparticulate active agents;" U.S. Patent Publication No. 20040229038 for "Nanoparticulate meloxicam formulations;" U.S. Patent Publication No. 20040208833 for "Novel fluticasone formulations;" U.S. Patent Publication No. 20040195413 for "Compositions and method for milling materials;" U.S. Patent Publication No. 20040156895 for "Solid dosage forms comprising pullulan;" U.S. Patent Publication No. U.S. Patent Publication No. 20040156872 for "Novel nimesulide compositions;" U.S. Patent Publication No. 20040141925 for "Novel triamcinolone compositions;" U.S. Patent Publication No. 20040115134 for "Novel nifedipine compositions;" U.S. Patent Publication No. 20040105889 for "Low viscosity liquid dosage forms;" U.S. Patent Publication No. 20040105778 for "Gamma irradiation of solid nanoparticulate active agents;" U.S. Patent Publication No. 20040101566 for "Novel benzoyl peroxide compositions;" U.S. Patent Publication No. 20040057905 for "Nanoparticulate beclomethasone dipropionate compositions;" U.S. Patent Publication No. 20040033267 for "Nanoparticulate compositions of angiogenesis inhibitors;" U.S. Patent Publication No. 20040033202 for "Nanoparticulate sterol formulations and novel sterol combinations;" U.S. Patent Publication No. 20040018242 for "Nanoparticulate nystatin formulations;" U.S. Patent Publication No. 20040015134 for "Drug delivery systems and methods;" U.S. Patent Publication No. 20030232796 for "Nanoparticulate polycosanols formulations & novel polycosanols combinations;" U.S. Patent Publication No. 20030215502 for "Fast dissolving dosage forms having reduced friability;" U.S. Patent Publication No. 20030185869 for "Nanoparticulate compositions having lysozyme as a surface stabilizer;" U.S. Patent Publication No. 20030181411 for "Nanoparticulate compositions of mitogen-activated protein (MAP) kinase inhibitors;" U.S. Patent Publication No. 20030137067 for "Compositions having a combination of immediate release and controlled release characteristics;" U.S. Patent Publication No. 20030108616 for "Nanoparticulate compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" U.S. Patent Publication No. 20030095928 for "Nanoparticulate insulin;" U.S. Patent Publication No. 20030087308 for "Method for high throughput screening using a small scale mill or microfluidics;" U.S. Patent Publication No. 20030023203 for "Drug delivery systems & methods;" U.S. Patent Publication No.

20020179758 for "System and method for milling materials;" and U.S. Patent Publication No. 20010053664 for "Apparatus for sanitary wet milling," describe nanoparticulate active agent compositions and are specifically incorporated by reference.

[0014] Surface modified nanoparticles and compositions thereof useful for treating cancer and other neoplastic diseases have been described, for example, in U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anti-cancer Nanoparticles".

[0015] Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

[0016] There is a need in the art for imatinib mesylate formulations which overcome the fed/fasted absorption variability, along with other problems, observed with conventional imatinib mesylate dosage forms. The present invention, which overcomes such problems, relates to a nanoparticulate composition comprising imatinib mesylate, or a salt or derivative thereof for the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

## SUMMARY

[0017] The compositions disclosed herein typically include nanoparticulate imatinib mesylate, or a salt or derivative thereof, having an effective average particle size of less than about 2000 nm and at least one surface stabilizer. The surface stabilizer is typically adsorbed on or associated with the surface of the nanoparticulate imatinib mesylate particles. Optionally, the compositions may include a pharmaceutically acceptable carrier and any suitable excipients.

[0018] The nanoparticulate compositions of imatinib mesylate, or a salt or derivative thereof, disclosed herein may be effective in the treatment of a number of disease or conditions, including but not limited to chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

[0019] A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized.

[0020] Another aspect of the invention is directed to pharmaceutical compositions comprising particles of a nanoparticulate imatinib mesylate, or a salt or derivative thereof, at least one surface stabilizer, and a pharmaceutically acceptable carrier, as well as any desired excipients.

[0021] One embodiment of the invention encompasses a nanoparticulate imatinib mesylate composition, wherein the pharmacokinetic profile of the nanoparticulate imatinib mesylate is not affected by the fed or fasted state of a subject ingesting the composition.

[0022] In yet another embodiment, the invention encompasses a nanoparticulate imatinib mesylate composition, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

[0023] Another embodiment of the invention is directed to nanoparticulate imatinib mesylate compositions comprising one or more additional compounds useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors, and related diseases.

[0024] This invention further discloses a method of making the nanoparticulate imatinib mesylate composition. Such a method comprises contacting the nanoparticulate imatinib mesylate, or a salt or derivative thereof, with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate imatinib mesylate composition having an effective average particle size of less than about 2000 nm. The one or more surface stabilizers can be contacted with a nanoparticulate imatinib mesylate, either before, during, or after size reduction of the imatinib mesylate particle.

[0025] The present invention is also directed to methods of treatment including but not limited to, the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases, using the novel nanoparticulate imatinib mesylate compositions disclosed herein. Such methods comprise administering to a subject a therapeutically effective amount of a nanoparticulate imatinib mesylate, or a salt or derivative thereof. Other methods of treatment using the nanoparticulate compositions of the invention are known to those of skill in the art.

[0026] Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0027] The present invention is directed to nanoparticulate compositions comprising an imatinib mesylate, or a salt or derivative thereof. The compositions comprise an imatinib mesylate, or a salt or derivative thereof, and preferably at least one surface stabilizer adsorbed on or associated with the surface of the drug. The imatinib mesylate, or a salt or derivative thereof, particles have an effective average particle size of less than about 2000 nm.

[0028] Advantages of the nanoparticulate imatinib mesylate compositions of the invention as compared to a conventional, non-nanoparticulate composition of the same imatinib mesylate formulation, include, but are not limited to: (1) smaller tablet size or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) increased bioavailability; (4) substantially similar pharmacokinetic profiles of the imatinib mesylate compositions when administered in the fed versus the fasted state; (5) bioequivalency of the imatinib mesylate compositions; (6) an increased rate of dissolution for the imatinib mesylate compositions; (7) the imatinib mesylate nanoparticles of the present invention redisperse upon addi-

tion thereof to a solution; and (8) the imatinib mesylate compositions can be used in conjunction with other active agents useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

[0029] The present invention also includes nanoparticulate imatinib mesylate compositions, or a salt or derivative thereof, together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (e.g., intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments, or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

[0030] A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules, and the solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof. A solid dose tablet formulation is preferred.

[0031] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0032] The term "effective average particle size of less than about 2000 nm," as used herein, means that at least about 50% of the nanoparticulate imatinib mesylate particles have a size of less than about 2000 nm, by weight (or by other suitable measurement technique, such as by number, volume, etc.) when measured by, for example, sedimentation flow fractionation, photon correlation spectroscopy, light scattering, disk centrifugation, and other techniques known to those of skill in the art.

[0033] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0034] As used herein with reference to stable imatinib mesylate nanoparticulate particles, "stable" connotes, but is not limited to one or more of the following parameters: (1) the particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise significantly increase in particle size over time; (2) that the physical structure of the particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the particles are chemically stable; and/or (4) where the imatinib mesylate has not been subject to a heating step at or above the melting point of the imatinib mesylate in the preparation of the nanoparticles of the present invention.

[0035] The term "conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2000 nm. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2000 nm.

[0036] The phrase "poorly water soluble drugs" as used herein refers to those drugs that have a solubility in water of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, or less than about 1 mg/ml.

[0037] As used herein, the phrase "therapeutically effective amount" shall mean that drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

#### A. Preferred Characteristics of the Nanoparticulate Imatinib Mesylate Compositions of the Invention

##### [0038] 1. Increased Bioavailability

[0039] The nanoparticulate imatinib mesylate, or a salt or derivative thereof, formulations of the invention are proposed to exhibit increased bioavailability, and require smaller doses as compared to prior conventional imatinib mesylate formulations.

[0040] In one embodiment of the invention, the nanoparticulate imatinib mesylate composition, upon administration to a mammal, produces therapeutic results at a dosage which is less than that of a non-nanoparticulate dosage form of the same imatinib mesylate composition.

##### [0041] 2. Improved Pk Profiles

[0042] The invention also preferably provides compositions comprising nanoparticulate imatinib mesylate, or a derivative or salt thereof, having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the compositions comprising imatinib mesylate, or a salt or derivative thereof, preferably includes, but is not limited to: (1) a  $C_{max}$  for imatinib mesylate, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the  $C_{max}$  for a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage; and/or (2) an AUC for imatinib mesylate, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage; and/or (3) a  $T_{max}$  for imatinib mesylate, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the  $T_{max}$  for a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage.

[0043] In one embodiment, a composition comprising a nanoparticulate imatinib mesylate exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage, a  $T_{max}$  not greater than about 50%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the  $T_{max}$  exhibited by the non-nanoparticulate imatinib mesylate formulation.

[0044] In another embodiment, the composition comprising a nanoparticulate imatinib mesylate exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage, a  $C_{max}$  which is at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the  $C_{max}$  exhibited by the non-nanoparticulate imatinib mesylate formulation.

[0045] In yet another embodiment, the composition comprising a nanoparticulate imatinib mesylate exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage, an AUC which is at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate imatinib mesylate formulation.

[0046] In one embodiment of the invention, the  $T_{max}$  of imatinib mesylate, when assayed in the plasma of the mammalian subject, is less than about 6 to about 8 hours. In other embodiments of the invention, the  $T_{max}$  of imatinib mesylate is less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after administration.

[0047] The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of imatinib mesylate or a salt or derivative thereof. The compositions can be formulated in any way as described herein and as known to those of skill in the art.

##### [0048] 3. The Pharmacokinetic Profiles of the Imatinib Mesylate Compositions of the Invention are not Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

[0049] The invention encompasses imatinib mesylate compositions wherein the pharmacokinetic profile of imatinib mesylate is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of drug absorbed or the rate of drug absorption when the nanoparticulate imatinib mesylate compositions are administered in the fed versus the fasted state.

[0050] For conventional imatinib mesylate formulations, i.e., GLEEVEC®, the absorption of imatinib mesylate is increased when administered with food. This difference in absorption observed with conventional imatinib mesylate

formulations is undesirable. The imatinib mesylate formulations of the invention overcome this problem, as the imatinib mesylate formulations reduce or preferably substantially eliminate significantly different absorption levels when administered under fed as compared to fasting conditions.

[0051] Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor subject compliance an increase in the medical condition for which the drug is being prescribed may be observed.

[0052] 4. Bioequivalency of Imatinib Mesylate Compositions of the Invention When Administered in the Fed Versus the Fasted State

[0053] The invention also provides a nanoparticulate imatinib mesylate composition in which the administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

[0054] The difference in absorption of the imatinib mesylate compositions of the invention, when administered in the fed versus the fasted state, preferably is less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

[0055] In one embodiment of the invention, the invention encompasses compositions comprising at least one nanoparticulate imatinib mesylate composition, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by  $C_{max}$  and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMA). Under U.S. FDA guidelines, two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and  $C_{max}$  are between 0.80 to 1.25 ( $T_{max}$  measurements are not relevant to bioequivalence for regulatory purposes). To show bioequivalency between two compounds or administration conditions pursuant to Europe's EMA guidelines, the 90% CI for AUC must be between 0.80 to 1.25 and the 90% CI for  $C_{max}$  must be between 0.70 to 1.43.

[0056] 5. Dissolution Profiles of the Imatinib Mesylate Compositions of the Invention

[0057] The nanoparticulate imatinib mesylate compositions, or a salt or derivative thereof, of the invention are proposed to have unexpectedly dramatic dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. To improve the dissolution profile and bioavailability of the imatinib mesylate it would be useful to increase the drug's dissolution so that it could attain a level close to 100%.

[0058] The imatinib mesylate compositions of the invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the composition is

dissolved. In other embodiments of the invention, at least about 30% or at least about 40% of the imatinib mesylate composition is dissolved within about 5 minutes. In yet other embodiments of the invention, at least about 40%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of the imatinib mesylate composition is dissolved within about 10 minutes. Finally, in another embodiment of the invention, preferably at least about 70%, at least about 80%, at least about 90%, or at least about 100% of the imatinib mesylate composition is dissolved within about 20 minutes.

[0059] Dissolution is preferably measured in a medium which is discriminating. Such a dissolution medium will produce two very different dissolution curves for two products having very different dissolution profiles in gastric juices; i.e., the dissolution medium is predictive of in vivo dissolution of a composition. An exemplary dissolution medium is an aqueous medium containing the surfactant sodium lauryl sulfate at 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. The rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

[0060] 6. Redispersibility Profiles of the Imatinib Mesylate Compositions of the Invention

[0061] An additional feature of the imatinib mesylate, or a salt or derivative thereof, compositions of the invention is that the compositions redisperse such that the effective average particle size of the redispersed imatinib mesylate particles is less than about 2 microns. This is significant, as if upon administration the imatinib mesylate compositions of the invention did not redisperse to a substantially nanoparticulate size, then the dosage form may lose the benefits afforded by formulating the imatinib mesylate into a nanoparticulate particle size.

[0062] This is because nanoparticulate active agent compositions benefit from the small particle size of the active agent; if the active agent does not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated active agent particles are formed, owing to the extremely high surface free energy of the nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

[0063] Moreover, the nanoparticulate imatinib mesylate compositions of the invention exhibit dramatic redispersion of the nanoparticulate imatinib mesylate composition particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a biorelevant aqueous media such that the effective average particle size of the redispersed imatinib mesylate composition particles is less than about 2 microns. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

[0064] Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less

than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. See e.g., Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res.*, 14 (4): 497-502 (1997).

[0065] It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (i.e., weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, etc.

[0066] Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 N, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 N HCl or less, about 0.01 N HCl or less, about 0.001 N HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

[0067] Electrolyte concentrations of 0.001 N HCl, 0.01 N HCl, and 0.1 N HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 N HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

[0068] Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts+sodium, potassium and calcium salts of chloride, acetic acid/acetate salts+sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts+sodium, potassium and calcium salts of chloride, and citric acid/citrate salts+sodium, potassium and calcium salts of chloride.

[0069] In other embodiments of the invention, the redispersed particles of imatinib mesylate, or a salt or derivative thereof, (redispersed in water, a biorelevant media, or any other suitable media) have an effective average particle size of less than about less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-

scattering methods, microscopy, or other appropriate methods. Such methods suitable for measuring effective average particle size are known to a person of ordinary skill in the art.

[0070] Redispersibility can be tested using any suitable means known in the art. See e.g., the example sections of U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

[0071] 7. Imatinib Mesylate Compositions Used in Conjunction with Other Active Agents

[0072] The imatinib mesylate, or a salt or derivative thereof, compositions of the invention can additionally comprise one or more compounds useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases, or the imatinib mesylate compositions can be administered in conjunction with such a compound. Examples of such compounds include, but are not limited to, anti-cancer agents such as mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens. For example, additional compounds may include gefitinib, pertuzamib, paclitaxel, cisplatin, carboplatin, gemcitabine, bevacizumab, temozolomide, sunitinib, leflunomide, docetaxel, imatinib, lapatinib, canertinib, doxorubicin, vatalanib, sorafenib, leucovorin, capecitabine, cetuximab, and combinations thereof.

#### B. Nanoparticulate Imatinib Mesylate Compositions

[0073] The invention provides compositions comprising particles of imatinib mesylate, or a salt or derivative thereof, and at least one surface stabilizer. The surface stabilizers preferably are adsorbed on, or associated with, the surface of the imatinib mesylate particles. Surface stabilizers especially useful herein preferably physically adhere on, or associate with, the surface of the nanoparticulate imatinib mesylate particles, but do not chemically react with the imatinib mesylate particles or itself. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

[0074] The present invention also includes imatinib mesylate, or a salt or derivative thereof, compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (e.g., intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

[0075] 1. Imatinib Mesylate Derivatives

[0076] The compositions of the invention comprise imatinib mesylate, an imatinib mesylate derivative or a salt thereof. The particles of imatinib mesylate, or a salt or derivative thereof, can be in a crystalline phase, a semi-crystalline phase, an amorphous phase, a semi-amorphous phase, or a combination thereof.

[0083] Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulose, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-*n*-methylpyridinium, anthryl pyridinium chloride.

cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

[0084] Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide,  $C_{12-15}$  dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)<sub>2</sub> ammonium chloride or bromide, N-alkyl ( $C_{12-18}$ ) dimethylbenzyl ammonium chloride, N-alkyl ( $C_{14-18}$ ) dimethylbenzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and ( $C_{12-14}$ ) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl( $C_{12-14}$ ) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzene-alkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide,  $C_{12}$ ,  $C_{15}$ ,  $C_{17}$  trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyl dimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), bezalkonium chloride, stealkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaryl Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

[0085] Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry*

(Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry*, (Marcel Dekker, 1990).

[0086] Nonpolymeric surface stabilizers are any nonpolymeric compound, such as bezalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula  $NR_1R_2R_3R_4^{(+)}$ . For compounds of the formula  $NR_1R_2R_3R_4^{(+)}$ :

[0087] (i) none of  $R_1-R_4$  are  $CH_3$ ;

[0088] (ii) one of  $R_1-R_4$  is  $CH_3$ ;

[0089] (iii) three of  $R_1-R_4$  are  $CH_3$ ;

[0090] (iv) all of  $R_1-R_4$  are  $CH_3$ ;

[0091] (v) two of  $R_1-R_4$  are  $CH_3$ , one of  $R_1-R_4$  is  $C_6H_5CH_2$ , and one of  $R_1-R_4$  is an alkyl chain of seven carbon atoms or less;

[0092] (vi) two of  $R_1-R_4$  are  $CH_3$ , one of  $R_1-R_4$  is  $C_6H_5CH_2$ , and one of  $R_1-R_4$  is an alkyl chain of nineteen carbon atoms or more;

[0093] (vii) two of  $R_1-R_4$  are  $CH_3$  and one of  $R_1-R_4$  is the group  $C_6H_5(CH_2)_n$ , where  $n \geq 1$ ;

[0094] (viii) two of  $R_1-R_4$  are  $CH_3$ , one of  $R_1-R_4$  is  $C_6H_5CH_2$ , and one of  $R_1-R_4$  comprises at least one heteroatom;

[0095] (ix) two of  $R_1-R_4$  are  $CH_3$ , one of  $R_1-R_4$  is  $C_6H_5CH_2$ , and one of  $R_1-R_4$  comprises at least one halogen;

[0096] (x) two of  $R_1-R_4$  are  $CH_3$ , one of  $R_1-R_4$  is  $C_6H_5CH_2$ , and one of  $R_1-R_4$  comprises at least one cyclic fragment;

[0097] (xi) two of  $R_1-R_4$  are  $CH_3$  and one of  $R_1-R_4$  is a phenyl ring; or

[0098] (xii) two of  $R_1-R_4$  are  $CH_3$  and two of  $R_1-R_4$  are purely aliphatic fragments.

[0099] Such compounds include, but are not limited to, bezalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride (Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, diethyldimethylammonium chloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oleyl ether phosphate, diethanolammonium POE (3) oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stealkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyqua-

temium-1, procaine hydrochloride, cocobetaine, stearylalkonium bentonite, stearylalkonium hectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

[0100] The surface stabilizers are commercially available and/or can be prepared by techniques known in the art. Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

[0101] The imatinib mesylate composition and surface stabilizer may be present in the pharmaceutical compositions disclosed herein at any suitable ratio (w/w). For example, in some embodiments the pharmaceutical compositions include the imatinib mesylate composition and the surface stabilizer at a ratio of about 20:1, 15:1, 10:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1 (w/w), or any range defined by said ratios (for example, but not limited to about 20:1-2:1, about 10:1-4:1, and about 8:1-5:1).

#### [0102] 3. Other Pharmaceutical Excipients

[0103] Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

[0104] Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

[0105] Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

[0106] Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

[0107] Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such as benzalkonium chloride.

[0108] Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatosee DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

[0109] Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

[0110] Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

#### [0111] 4. Nanoparticulate Imatinib Mesylate Particle Size

[0112] The compositions of the invention comprise nanoparticulate imatinib mesylate, or a salt or derivative thereof, particles which have an effective average particle size of less than about 2000 nm (i.e., 2 microns), less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0113] By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the imatinib mesylate particles have a particle size of less than the effective average, by weight (or by other suitable measurement technique, such as by volume, number etc.), i.e., less than about 2000 nm, 1900 nm, 1800 nm, etc., when measured by the above-noted techniques. In other embodiments of the invention, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the imatinib mesylate particles have a particle size of less than the effective average, i.e., less than about 2000 nm, 1900 nm, 1800 nm, 1700 nm, etc.

[0114] In the present invention, the value for D50 of a nanoparticulate imatinib mesylate composition is the particle size below which 50% of the imatinib mesylate particles fall, by weight (or by other suitable measurement technique, such as by volume, number etc.). Similarly, D90 is the particle size below which 90% of the imatinib mesylate particles fall, by weight (or by other suitable measurement technique, such as by volume, number etc.).

#### [0115] 5. Concentration of Imatinib Mesylate and Surface Stabilizers

[0116] The relative amounts of imatinib mesylate, or a salt or derivative thereof, and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, upon the particular imatinib mesylate selected, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, etc.

[0117] The concentration of the imatinib mesylate can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined dry weight of the imatinib mesylate and at least one surface stabilizer, not including other excipients.

[0118] The concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the imatinib mesylate and at least one surface stabilizer, not including other excipients.

[0119] 6. Exemplary Nanoparticle Imatinib Mesylate Tablet Formulations

[0120] Several exemplary imatinib mesylate tablet formulations are given below. These examples are not intended to limit the claims in any respect, but rather to provide exemplary tablet formulations of imatinib mesylate which can be utilized in the methods of the invention. Such exemplary tablets can also comprise a coating agent.

| Exemplary Nanoparticle<br>Imatinib Mesylate Tablet Formulation #1 |                        |
|-------------------------------------------------------------------|------------------------|
| Component                                                         | g/Kg                   |
| Imatinib Mesylate                                                 | about 50 to about 500  |
| Hypromellose, USP                                                 | about 10 to about 70   |
| Docusate Sodium, USP                                              | about 1 to about 10    |
| Sucrose, NF                                                       | about 100 to about 500 |
| Sodium Lauryl Sulfate, NF                                         | about 1 to about 40    |
| Lactose Monohydrate, NF                                           | about 50 to about 400  |
| Silicified Microcrystalline Cellulose                             | about 50 to about 300  |
| Croscopidone, NF                                                  | about 20 to about 300  |
| Magnesium Stearate, NF                                            | about 0.5 to about 5   |

[0121]

| Exemplary Nanoparticle<br>Imatinib Mesylate Tablet Formulation #2 |                        |
|-------------------------------------------------------------------|------------------------|
| Component                                                         | g/Kg                   |
| Imatinib Mesylate                                                 | about 100 to about 300 |
| Hypromellose, USP                                                 | about 30 to about 50   |
| Docusate Sodium, USP                                              | about 0.5 to about 10  |
| Sucrose, NF                                                       | about 100 to about 300 |
| Sodium Lauryl Sulfate, NF                                         | about 1 to about 30    |
| Lactose Monohydrate, NF                                           | about 100 to about 300 |
| Silicified Microcrystalline Cellulose                             | about 50 to about 200  |
| Croscopidone, NF                                                  | about 50 to about 200  |
| Magnesium Stearate, NF                                            | about 0.5 to about 5   |

[0122]

| Exemplary Nanoparticle<br>Imatinib Mesylate Tablet Formulation #3 |                        |
|-------------------------------------------------------------------|------------------------|
| Component                                                         | g/Kg                   |
| Imatinib Mesylate                                                 | about 200 to about 225 |
| Hypromellose, USP                                                 | about 42 to about 46   |
| Docusate Sodium, USP                                              | about 2 to about 6     |

-continued

| Exemplary Nanoparticle<br>Imatinib Mesylate Tablet Formulation #3 |                        |
|-------------------------------------------------------------------|------------------------|
| Component                                                         | g/Kg                   |
| Sucrose, NF                                                       | about 200 to about 225 |
| Sodium Lauryl Sulfate, NF                                         | about 12 to about 18   |
| Lactose Monohydrate, NF                                           | about 200 to about 205 |
| Silicified Microcrystalline Cellulose                             | about 130 to about 135 |
| Croscopidone, NF                                                  | about 112 to about 118 |
| Magnesium Stearate, NF                                            | about 0.5 to about 3   |

[0123]

| Exemplary Nanoparticle<br>Imatinib Mesylate Tablet Formulation #4 |                        |
|-------------------------------------------------------------------|------------------------|
| Component                                                         | g/Kg                   |
| Imatinib Mesylate                                                 | about 119 to about 224 |
| Hypromellose, USP                                                 | about 42 to about 46   |
| Docusate Sodium, USP                                              | about 2 to about 6     |
| Sucrose, NF                                                       | about 119 to about 224 |
| Sodium Lauryl Sulfate, NF                                         | about 12 to about 18   |
| Lactose Monohydrate, NF                                           | about 119 to about 224 |
| Silicified Microcrystalline Cellulose                             | about 129 to about 134 |
| Croscopidone, NF                                                  | about 112 to about 118 |
| Magnesium Stearate, NF                                            | about 0.5 to about 3   |

### C. Methods of Making Nanoparticle Imatinib Mesylate Compositions

[0124] The nanoparticle imatinib mesylate, or a salt or derivative thereof, compositions can be made using, for example, milling, homogenization, precipitation, cryogenic, or template emulsion techniques. Exemplary methods of making nanoparticle active agent compositions are described in the '684 patent. Methods of making nanoparticle active agent compositions are also described in U.S. Pat. No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,665,331 for "Co-Microprecipitation of Nanoparticle Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Pat. No. 5,662,883 for "Co-Microprecipitation of Nanoparticle Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Pat. No. 5,560,932 for "Microprecipitation of Nanoparticle Pharmaceutical Agents;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

[0125] The resultant nanoparticle imatinib mesylate compositions or dispersions can be utilized in solid or liquid dosage formulations, such as liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast

melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, etc.

**[0126]** 1. Milling to Obtain Nanoparticulate Imatinib Mesylate Dispersions

**[0127]** Milling an imatinib mesylate, or a salt or derivative thereof, to obtain a nanoparticulate dispersion comprises dispersing the imatinib mesylate particles in a liquid dispersion medium in which the imatinib mesylate is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the imatinib mesylate to the desired effective average particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. A preferred dispersion medium is water.

**[0128]** The imatinib mesylate particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, imatinib mesylate particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the imatinib mesylate/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

**[0129]** 2. Precipitation to Obtain Nanoparticulate Imatinib Mesylate Compositions

**[0130]** Another method of forming the desired nanoparticulate imatinib mesylate, or a salt or derivative thereof, composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving the imatinib mesylate in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

**[0131]** 3. Homogenization to Obtain Nanoparticulate Imatinib Mesylate Compositions

**[0132]** Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Pat. No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." Such a method comprises dispersing particles of an imatinib mesylate, or a salt or derivative thereof, in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size of an imatinib mesylate to the desired effective average particle size. The imatinib mesylate particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the imatinib mesylate particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the imatinib mesylate/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

**[0133]** 4. Cryogenic Methodologies to Obtain Nanoparticulate Imatinib Mesylate Compositions

**[0134]** Another method of forming the desired nanoparticulate imatinib mesylate, or a salt or derivative thereof, composition is by spray freezing into liquid (SFL). This technology comprises use of an organic or organoaqueous solution of imatinib mesylate with stabilizers, which is injected into a cryogenic liquid, such as liquid nitrogen. The droplets of the imatinib mesylate solution freeze at a rate sufficient to minimize crystallization and particle growth, thus forming nanostructured imatinib mesylate particles. Depending upon the choice of solvent system and processing conditions, the nanoparticulate imatinib mesylate particles can have varying particle morphology. In the isolation step, the nitrogen and solvent are removed under conditions that avoid agglomeration or ripening of the imatinib mesylate particles.

**[0135]** As a complementary technology to SFL, ultra rapid freezing (URF) may also be used to create equivalent nanostructured imatinib mesylate particles with greatly enhanced surface area. URF comprises an organic or organoaqueous solution of imatinib mesylate with stabilizers onto a cryogenic substrate.

**[0136]** 5. Emulsion Methodologies to Obtain Nanoparticulate Imatinib Mesylate Compositions

**[0137]** Another method of forming the desired nanoparticulate imatinib mesylate, or a salt or derivative thereof, composition is by template emulsion. Template emulsion creates nanostructured imatinib mesylate particles with controlled particle size distribution and rapid dissolution performance. The method comprises an oil-in-water emulsion that is prepared, then swelled with a non-aqueous solution comprising the imatinib mesylate and stabilizers. The particle size distribution of the imatinib mesylate particles is a direct result of the size of the emulsion droplets prior to loading with the imatinib mesylate a property which can be controlled and optimized in this process. Furthermore, through selected use of solvents and stabilizers, emulsion stability is achieved with no or suppressed Ostwald ripening. Subsequently, the solvent and water are removed, and the stabilized nanostructured imatinib mesylate particles are recovered. Various imatinib mesylate particles morphologies can be achieved by appropriate control of processing conditions.

**[0138]** Published International Patent Application No. WO 97/144407 to Pace et al., published Apr. 24, 1997, discloses particles of water insoluble biologically active compounds with an average size of 100 nm to 300 nm that are prepared by dissolving the compound in a solution and then spraying the solution into compressed gas, liquid or supercritical fluid in the presence of appropriate surface modifiers.

D. Methods of Using the Nanoparticulate Imatinib Mesylate Compositions of the Invention

**[0139]** The invention provides a method of increasing the plasma levels of an imatinib mesylate, or a salt or derivative thereof, in a subject. Such a method comprises administering to a subject an effective amount of a composition according to the invention comprising nanoparticulate imatinib mesylate compositions.

**[0140]** In one embodiment of the invention, the imatinib mesylate composition, in accordance with standard pharma-

cokinetic practice, preferably produces a maximum blood plasma concentration profile in less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after the initial dose of the composition.

[0141] The compositions of the invention are useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases. The imatinib mesylate, or a salt or derivative thereof, compounds of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, optically, ocularly, parenterally (e.g., intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (e.g., powders, ointments or drops), or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

[0142] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0143] The nanoparticulate imatinib mesylate, or a salt or derivative thereof, compositions may also comprise adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[0144] Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0145] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to an imatinib mesylate, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[0146] Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0147] 'Therapeutically effective amount' as used herein with respect to an imatinib mesylate, dosage shall mean that dosage that provides the specific pharmacological response for which an imatinib mesylate is administered in a significant number of subjects in need of such treatment. It is emphasized that 'therapeutically effective amount,' administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a 'therapeutically effective amount' by those skilled in the art. It is to be further understood that imatinib mesylate dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

[0148] One of ordinary skill will appreciate that effective amounts of an imatinib mesylate can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of an imatinib mesylate in the nanoparticulate compositions of the invention may be varied to obtain an amount of an imatinib mesylate that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered imatinib mesylate, the desired duration of treatment, and other factors.

[0149] Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

[0150] The following prophetic example is given to illustrate the present invention. It should be understood, however, that the spirit and scope of the invention is not to be limited to the specific conditions or details described in this example but should only be limited by the scope of the claims that follow. All references identified herein, including U.S. patents, are hereby expressly incorporated by reference

## EXAMPLE 1

[0151] The purpose of this example was to prepare a composition comprising a nanoparticulate imatinib mesylate or a salt or derivative thereof.

[0152] An aqueous dispersion of 5% (w/w) imatinib mesylate, combined with one or more surface stabilizers, such as hydroxypropyl cellulose (HPC-SL) and dioctylsulfosuccinate (DOSS), could be milled in a 10 ml chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, Pa.; see e.g., U.S. Pat. No. 6,431,478), along with 500 micron PolyMill® attrition media (Dow Chemical Co.) (e.g., at an 89% media load). In an exemplary process, the mixture could be milled at a speed of 2500 rpms for 60 minutes.

[0153] Following milling, the particle size of the milled imatinib mesylate particles can be measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. For a successful composition, the initial mean and/or D50 milled imatinib mesylate particle size is expected to be less than 2000 nm.

[0154] It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

1. A stable nanoparticulate composition of imatinib mesylate, or a salt or derivative thereof, comprising:

(a) particles of imatinib mesylate, or a salt or derivative thereof, having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer.

2. The composition of claim 1, wherein the imatinib mesylate particles are selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi amorphous phase, and mixtures thereof.

3. The composition of claim 1, wherein the effective average particle size of the imatinib mesylate particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

4. The composition of claim 1, wherein the composition is formulated:

(a) for administration selected from the group consisting of oral, pulmonary, rectal, colonic, parenteral, intracasternal, intravaginal, intraperitoneal, ocular, optic, local, buccal, nasal, and topical administration;

(b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, and capsules;

(c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formula-

tions, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or

(d) any combination of (a), (b), and (c).

5. The composition of claim 4, further comprising one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

6. The composition of claim 1, wherein:

(a) imatinib mesylate, or a salt or derivative thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of imatinib mesylate, or a salt or derivative thereof and at least one surface stabilizer, not including other excipients;

(b) the surface stabilizer is present in an amount selected from the group consisting of about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of imatinib mesylate, salt, or derivative thereof and at least one surface stabilizer, not including other excipients; or

(c) a combination thereof.

7. The composition of claim 1, further comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

8. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a non-ionic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

9. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, non-crystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl  $\beta$ -D-glucopyranoside; n-decyl  $\beta$ -D-maltopyranoside; n-dodecyl  $\beta$ -D-glucopyranoside; n-dodecyl  $\beta$ -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- $\beta$ -D-glucopyranoside; n-heptyl  $\beta$ -D-thiogluconoside; n-hexyl  $\beta$ -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl  $\beta$ -D-glucopyranoside; octanoyl-N-methylgluca-

mide; n-octyl- $\beta$ -D-glucopyranoside; octyl  $\beta$ -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipids, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide,  $C_{12-15}$ dimethyl hydroxyethyl ammonium chloride,  $C_{12-15}$ dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)<sub>4</sub> ammonium chloride, lauryl dimethyl (ethenoxy)<sub>4</sub> ammonium bromide, N-alkyl ( $C_{12-18}$ )dimethylbenzyl ammonium chloride, N-alkyl ( $C_{12-14}$ )dimethylbenzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and ( $C_{12-14}$ ) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkylamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, N-alkyl( $C_{12-14}$ ) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide,  $C_{12}$  trimethyl ammonium bromides,  $C_{15}$  trimethyl ammonium bromides,  $C_{17}$  trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride, dimethyl ammonium chlorides, alkyl-dimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

10. The composition of claim 1, wherein the composition is bioadhesive.

11. The composition of claim 1, wherein the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

12. The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

13. A composition comprising imatinib mesylate, or a salt or a derivative thereof, wherein upon administration to a human the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

14. The composition of claim 13, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

15. A stable nanoparticulate composition of imatinib mesylate, or a salt or derivative thereof, comprising:

(a) particles of imatinib mesylate, or a salt or derivative thereof, having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer,

wherein upon administration to a mammal the composition produces therapeutic results at a dosage which is less than that of a non-nanoparticulate dosage form of the same imatinib mesylate, or salt or derivative thereof.

16. A composition of imatinib mesylate, or a salt or derivative thereof, comprising imatinib mesylate or a salt or derivative thereof wherein the composition has:

(a) a  $C_{max}$  for imatinib mesylate, or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration that is greater than the  $C_{max}$  for a non-nanoparticulate formulation of the same imatinib mesylate, or a salt or derivative thereof, administered at the same dosage;

(b) an AUC for imatinib mesylate, or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration that is greater than the AUC for a non-nanoparticulate formulation of the same imatinib mesylate, or a salt or derivative thereof, administered at the same dosage;

(c) a  $T_{max}$  for imatinib mesylate, or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration that is less than the  $T_{max}$  for a non-nanoparticulate formulation of the same imatinib mesylate, or a salt or derivative thereof, administered at the same dosage; or

(d) any combination of (a), (b), and (c).

17. The composition of claim 1, additionally comprising one or more active agents useful for the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

18. The composition of claim 17, wherein the active agent is selected from a group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

19. A method for preparing imatinib mesylate, or a salt or derivative thereof, comprising contacting particles of imatinib mesylate, or a salt or derivative thereof with at least one surface stabilizer for a time and under conditions sufficient

to provide a nanoparticulate imatinib mesylate composition having an effective average particle size of less than about 2000 nm.

20. The method of claim 19, wherein the contacting comprises grinding, wet grinding, homogenization, freezing, template emulsion, precipitation, or a combination thereof.

21. A method for treating of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases comprising administering a stable nanoparticulate composition of imatinib mesylate, or a salt or derivative thereof, comprising:

(a) particles of imatinib mesylate, or a salt or derivative thereof, having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer.

22. The method of claim 21, wherein the effective average particle size of the particles of imatinib mesylate, or a salt or derivative thereof, is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

\* \* \* \* \*

# Anexo 2

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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, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, 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, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations 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, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, 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, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

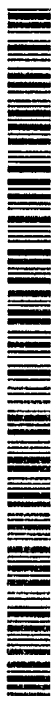
## Published:

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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.

(54) Title: NOVEL POLYMORPHS OF IMATINIB MESYLATE

(57) Abstract: The present invention relates to novel polymorphs of imatinib mesylate, to processes for their preparation and to pharmaceutical compositions containing them.



WO 2004/106326 A1

## NOVEL POLYMORPHS OF IMATINIB MESYLATE

### FIELD OF THE INVENTION

5

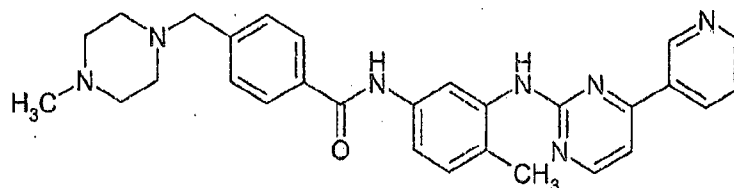
The present invention relates to novel polymorphs of imatinib mesylate, to processes for their preparation and to pharmaceutical compositions containing them.

10

### BACKGROUND OF THE INVENTION

Imatinib, chemically 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide, is represented by the following structure:

15



20

Imatinib and its salts are anti-tumor agents, which were disclosed in US 5,521,184. Two crystalline modifications ( $\alpha$ -form and  $\beta$ -form) of imatinib mesylate were mentioned in WO 99/03854.

WO 99/03854 mentioned amorphous imatinib mesylate, but it did not make any reference to hydrate of imatinib mesylate.

25

We have discovered a stable novel crystalline form of imatinib mesylate. The novel form is at least as stable as the reported forms,  $\alpha$ - and  $\beta$ -forms. The novel crystalline form is stable over the time and has good flow properties and so, the novel crystalline form is suitable for formulating imatinib mesylate.

30

Amorphous forms of pharmaceutical products are usually known to have better dissolution properties than their crystalline forms. If amorphous form of a pharmaceutical product is stable enough, it can be formulated to a pharmaceutical composition having good dissolution properties.

We have discovered hydrate of imatinib mesylate.

We have also discovered a sufficiently stable non-hygroscopic amorphous form of imatinib mesylate hydrate. So, amorphous form of imatinib mesylate hydrate can be utilized to prepare stable pharmaceutical dosage forms having good dissolution properties.

One object of the present invention is to provide a stable novel crystalline form of imatinib mesylate, hydrate of imatinib mesylate and amorphous imatinib mesylate hydrate.

Another object of the present invention is to provide processes for preparing the novel crystalline form of imatinib mesylate, hydrate of imatinib mesylate and amorphous imatinib mesylate hydrate.

Still another object of the present invention is to provide pharmaceutical compositions containing the novel crystalline form of imatinib mesylate, hydrate of imatinib mesylate and amorphous imatinib mesylate hydrate.

#### DETAILED DESCRIPTION OF THE INVENTION

As used herein, room temperature refers to about 25°C to 30°C.

In accordance with the present invention, there is provided a novel crystalline form of imatinib mesylate, designated as form H1, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 9.9, 11.1, 16.3, 17.3, 18.1, 19.1, 19.6, 20.3, 21.1, 21.9, 23.2, 23.6, 24.2, 24.9, 25.6, 26.0, 27.3, 27.9, 28.9, 29.4, 30.4 and 30.5 degrees. Figure 1 shows typical form H1 x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of imatinib mesylate form H1. Imatinib free base is dissolved in a chlorinated solvent, methanesulfonic acid is added and imatinib mesylate form H1 is isolated.

Examples of chlorinated solvents are chloroform, methylene dichloride, ethylene dichloride and a mixture thereof. Preferable solvents are chloroform and methylene dichloride.

Imatinib free base may be dissolved in the chlorinated solvents at room temperature or at an elevated temperature.

The quantity of methanesulfonic acid per mole of imatinib free base is not critical but preferably at least one mole of methanesulfonic acid per mole of imatinib free base is used to obtain maximum yield of imatinib mesylate.

5 Methanesulfonic acid can be added to the solution of imatinib free base in chlorinated solvent preferably between about 5°C to reflux temperature, more preferably between room temperature to reflux temperature. Most preferably, methanesulfonic acid is added at room temperature.

Then, the precipitated imatinib mesylate form H1 is collected by filtration or centrifugation.

10 In accordance with the present invention, an another process is provided for preparation of imatinib mesylate form H1. A mixture of imatinib mesylate and a chlorinated solvent is stirred for about 10 hours to 48 hours and imatinib mesylate form H1 is isolated.

15 Examples of chlorinated solvents are chloroform, methylene dichloride, ethylene dichloride and a mixture thereof. Preferable solvents are chloroform and methylene dichloride.

Imatinib mesylate in a previously known crystalline or amorphous form may be used in the process. Imatinib mesylate hydrate obtained by the process described below may also be used. Particularly  $\alpha$ -form,  $\beta$ -form or amorphous  
20 imatinib mesylate may be used.

Preferably, the mixture of imatinib mesylate and a chlorinated solvent is stirred between about 5°C to reflux temperature, more preferably between room temperature to reflux temperature, for about 24 hours to 48 hours.

Then imatinib mesylate form H1 is collected by filtration or centrifugation.

25 In accordance with the present invention, there is provided a novel hydrate of imatinib mesylate. The water content of the hydrate of imatinib mesylate is between 2.0 to 3.2% by weight of hydrate of imatinib mesylate, typically between 2.2 to 2.9% by weight of hydrate of imatinib mesylate.

The amorphous form of imatinib mesylate hydrate, designated as  
30 amorphous imatinib mesylate hydrate, is characterized by having broad x-ray diffraction spectrum as in figure 2.

In accordance with the present invention, a process is provided for preparation of imatinib mesylate hydrate.

Imatinib mesylate hydrate is prepared by dissolving imatinib mesylate in a mixture of a suitable solvent and water and removing the solvents from the solution.

Imatinib mesylate in a crystalline or amorphous form may be used in the process. Particularly  $\alpha$ -form,  $\beta$ -form or amorphous imatinib mesylate may be used.

The suitable solvent is selected from the group consisting of alcohols, e.g., methanol, ethanol, isopropyl alcohol; ketones, e.g., acetone; acetonitrile; and a mixture thereof.

The solvent may be removed from the solution by vacuum drying or spray drying to give amorphous imatinib mesylate hydrate. The drying time and the drying temperature depend on the solvent used in the process. For example if the solvent is methanol, the solvent and water can be removed at about 50°C for about 9 hours.

Imatinib free base and imatinib mesylate obtained by the previously known methods may be used in the above processes.

In accordance with the present invention, there is provided a pharmaceutical composition comprising imatinib mesylate form H1 and a pharmaceutically acceptable carrier or diluent.

In accordance with the present invention, there is provided a pharmaceutical composition comprising imatinib mesylate hydrate and a pharmaceutically acceptable carrier or diluent. Amorphous imatinib mesylate hydrate may also be used in the composition.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction spectrum of imatinib mesylate form H1.

Figure 2 is a x-ray powder diffraction spectrum of amorphous imatinib mesylate hydrate.

x-Ray powder diffraction spectrum was measured on a Bruker axs D8 advance x-ray powder diffractometer having a copper-K $\alpha$  radiation.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

Example 1

Imatinib free base (5.0 gm) is dissolved in chloroform (50 ml) at room temperature and then methanesulfonic acid (0.75 ml) is added. The contents are stirred for 5 hours at room temperature and separated crystals are filtered and dried to give 5.0 gm of imatinib mesylate form H1.

Example 2.

The mixture of Imatinib mesylate ( $\alpha$ -form, 5.0 gm) and chloroform (150 ml) is heated to 50°C and stirred for 36 hours at this temperature. Then the contents are cooled to 25°C, maintained for 5 hours at room temperature and filtered and dried to give 4.5 gm of imatinib mesylate form H1.

Example 3

The mixture of Imatinib mesylate ( $\beta$ -form, 5.0 gm) and chloroform (150 ml) is heated to 50°C and stirred for 36 hours at this temperature. Then the contents are cooled to 25°C, maintained for 5 hours at room temperature and filtered and dried to give 4.3 gm of imatinib mesylate form H1.

Example 4

Imatinib free base (5.0 gm) is dissolved in methylene dichloride (50 ml) at room temperature and then methanesulfonic acid (0.75 ml) is added. The contents are stirred for 5 hours at room temperature and filtered and dried to give 4.9 gm of imatinib mesylate form H1.

Example 5

The mixture of Imatinib mesylate (5.0 gm) and methylene dichloride (150 ml) is heated to 50°C and stirred for 5 hours at this temperature. Then the contents are cooled to 25°C, maintained for 25 hours at room temperature and filtered to give 4.6 gm of imatinib mesylate form H1

Example 6

Imatinib mesylate form H1 (3.5 gm) is dissolved in a mixture of methanol (25 ml) and water (5.0 ml) at room temperature. The solution is subjected to

vacuum drying at about 50°C for 9 hours to give 3.0 gm of amorphous imatinib mesylate hydrate.

#### Example 7

- 5           Example 6 is carried out using imatinib mesylate ( $\alpha$ -form) instead of imatinib mesylate form H1 to give imatinib mesylate hydrate.

#### Example 8

- 10           Example 6 is carried out by subjecting the solution to spray drying instead of vacuum drying to give amorphous imatinib mesylate hydrate.

We claim:

1. A crystalline imatinib mesylate form H1, characterized by an x-ray powder diffraction spectrum having peaks expressed as  $2\theta$  at about 9.9, 11.1, 16.3, 17.3, 18.1, 19.1, 19.6, 20.3, 21.1, 21.9, 23.2, 23.6, 24.2, 24.9, 25.6, 26.0, 27.3, 27.9, 28.9, 29.4, 30.4 and 30.5 degrees.
2. A crystalline imatinib mesylate form H1 as defined in claim 1, further characterized by a x-ray powder diffraction spectrum as in figure 1.
3. A process for preparation of imatinib mesylate form H1 as defined in claim 1, which comprises the steps of:
  - a) dissolving imatinib free base in a chlorinated solvent;
  - b) adding methanesulfonic acid; and
  - c) isolating imatinib mesylate form H1 by filtration or centrifugation;wherein the chlorinated solvents is selected from chloroform, methylene dichloride, ethylene dichloride and a mixture thereof.
4. A process according to claim 3, wherein the chlorinated solvent is chloroform.
5. A process according to claim 3, wherein the chlorinated solvent is methylene dichloride.
6. A process for preparation of imatinib mesylate form H1 as defined in claim 1, which comprises the steps of:
  - a) mixing imatinib mesylate and a chlorinated solvent; and
  - b) isolating imatinib mesylate form H1 by filtration or centrifugation;wherein the chlorinated solvent is selected from chloroform, methylene dichloride, ethylene dichloride and a mixture thereof.
7. A process according to claim 6, wherein the chlorinated solvent is chloroform.
8. A process according to claim 6, wherein the chlorinated solvent is methylene dichloride.
9. Imatinib mesylate hydrate.
10. Imatinib mesylate hydrate of claim 9, wherein water content of the hydrate of imatinib mesylate is between 2.0 to 3.2% by weight of hydrate of imatinib mesylate.

- 46
11. Imatinib mesylate hydrate of claim 10, wherein water content of the hydrate of imatinib mesylate is between 2.2 to 2.9% by weight of hydrate of imatinib mesylate.
  12. Imatinib mesylate hydrate of claim 11, wherein water content of the hydrate of imatinib mesylate is about 2.5% by weight of hydrate of imatinib mesylate.
  13. A process for preparation of imatinib mesylate hydrate of claim 9, which comprises the steps of:
    - a) dissolving imatinib mesylate in a mixture of a suitable solvent and water;
    - b) removing the solvents from the solution formed in (a) either by vacuum drying or by spray drying;wherein the suitable solvent is selected from alcohols, ketones, acetonitrile and a mixture thereof.
  14. A process according to claim 13, wherein the solvent is removed by vacuum drying.
  15. A process according to claim 13, wherein the solvent is removed by spray drying.
  16. A process according to claim 13, wherein the alcohol is selected from methanol, ethanol and isopropyl alcohol; and the ketone is acetone.
  17. A process according to claim 13, wherein the suitable solvent is methanol.
  18. A process according to claim 13, wherein the suitable solvent is ethanol.
  19. Amorphous imatinib mesylate hydrate.
  20. Amorphous imatinib mesylate hydrate of claim 19 characterized by a x-ray powder diffraction spectrum as in figure 2.
  21. Amorphous imatinib mesylate hydrate of claim 19, produced according to the process described in claim 13.
  22. A pharmaceutical composition comprising imatinib mesylate form H1 of claim 1 and a pharmaceutically acceptable carrier or diluent.
  23. A pharmaceutical composition comprising imatinib mesylate hydrate of claim 9 and a pharmaceutically acceptable carrier or diluent.
  24. A pharmaceutical composition comprising amorphous imatinib mesylate hydrate of claim 19 and a pharmaceutically acceptable carrier or diluent.

Fig. 1/2

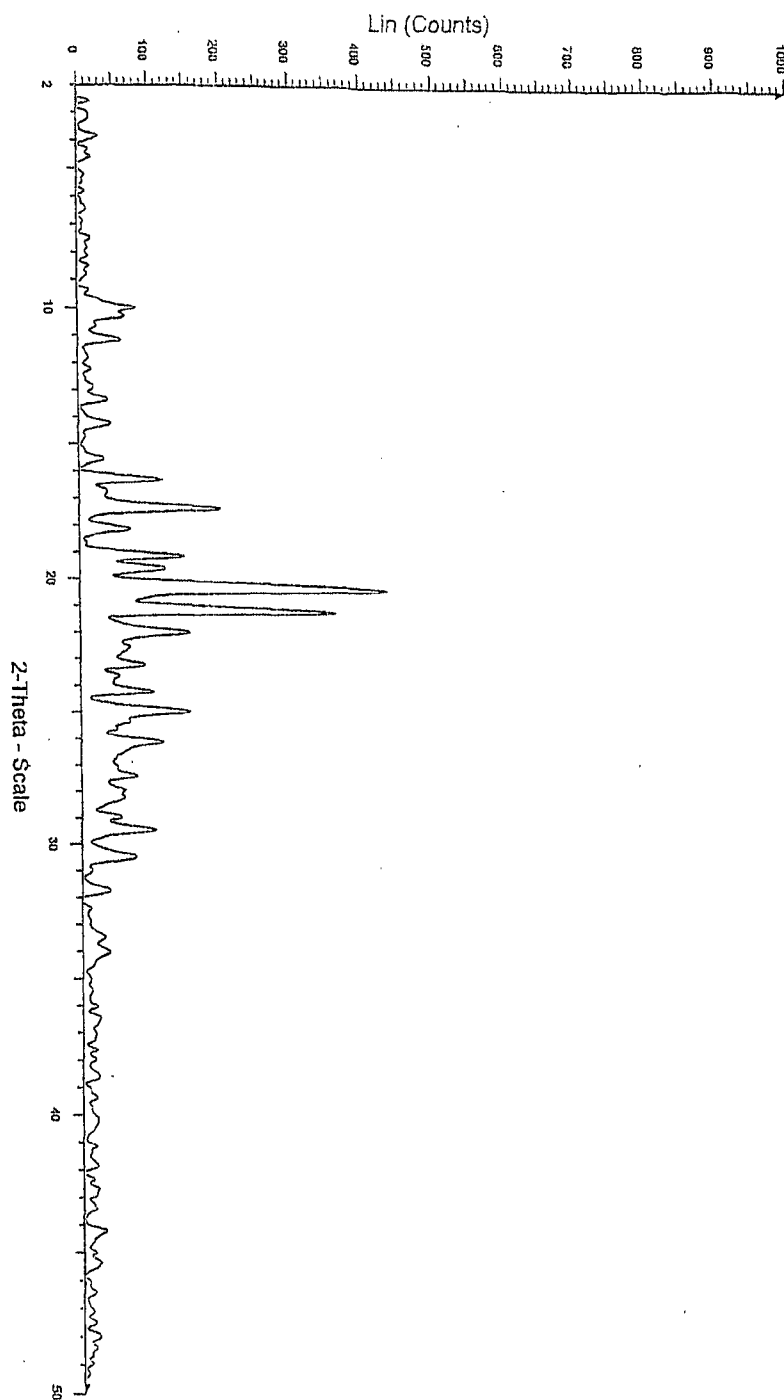
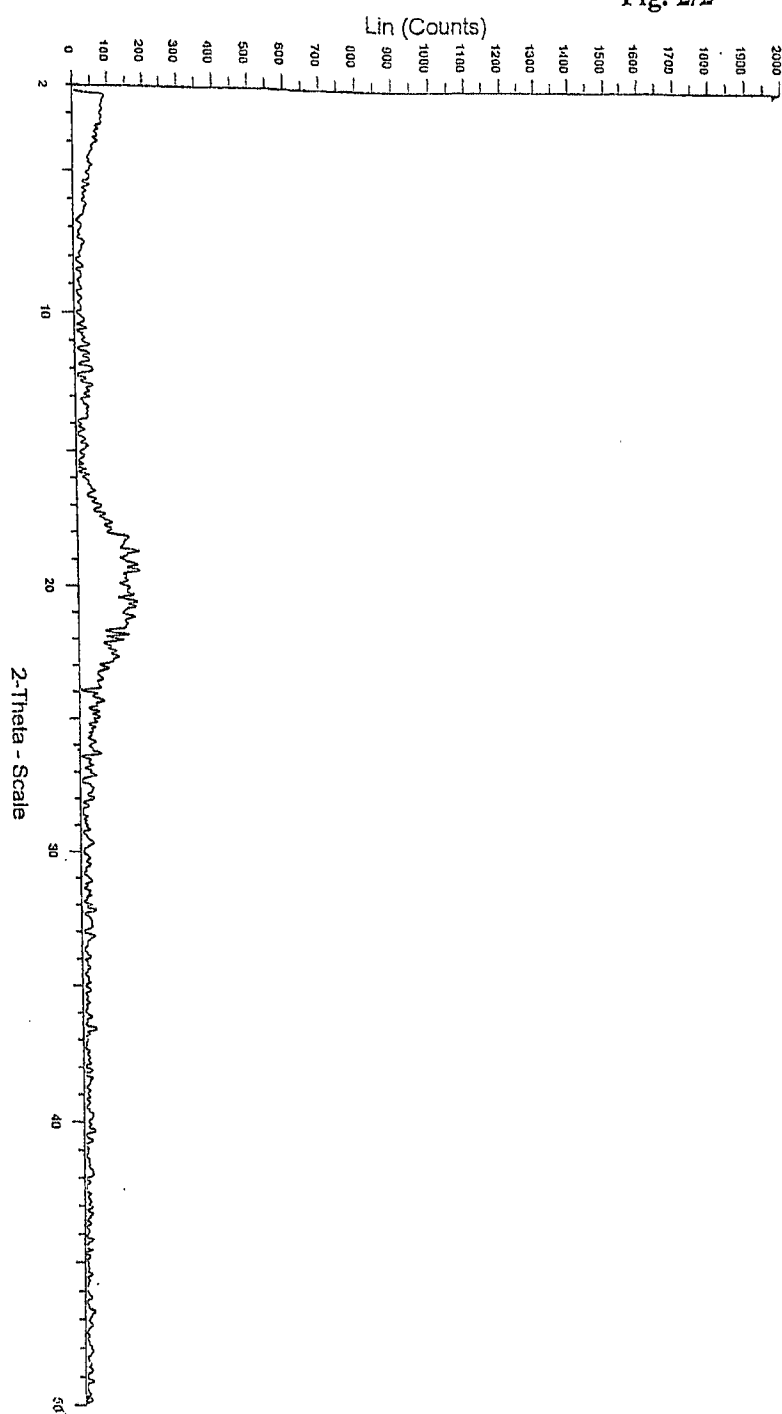


Fig. 2/2



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IN 03/00206-0

| CLASSIFICATION OF SUBJECT MATTER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                               |                                                                                  |
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| IPC <sup>7</sup> : C07D 401/14, A61K 31/506                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                               |                                                                                  |
| 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 <sup>7</sup> : C07D, A61J                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                               |                                                                                  |
| 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 practicable, search terms used)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                               |                                                                                  |
| REGISTRY, CAPLUS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                               |                                                                                  |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                               |                                                                                  |
| Category                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Citation of document, with indication, where appropriate, of the relevant passages                                                            | Relevant to claim No.                                                            |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | WO 99/03854 A (NOVARTIS ERFIND VERWALT GMBH; NOVARTIS AG) 28 January 1999 (28.01.99) ; cited in the application<br><i>the whole document.</i> | 1-24                                                                             |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | US 5521184 A (CIBA GEIGY CORP; ZIMMERMANN JUERG) 28 May 1996 (28.05.96) ; cited in the application.<br><i>example 21.</i>                     | 1-24                                                                             |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                               |                                                                                  |
| * Special categories of cited documents:<br>„A“ document defining the general state of the art which is not considered to be of particular relevance<br>„E“ earlier application or patent but published on or after the international filing date<br>„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)<br>„O“ document referring to an oral disclosure, use, exhibition or other means<br>„P“ document published prior to the international filing date but later than the priority date claimed<br>„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<br>„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<br>„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<br>„&“ document member of the same patent family |                                                                                                                                               |                                                                                  |
| Date of the actual completion of the international search<br>13 February 2004 (13.02.2004)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                               | Date of mailing of the international search report<br>10 March 2004 (10.03.2004) |
| Name and mailing address of the ISA/AT<br>Austrian Patent Office<br>Dresdner Straße 87, A-1200 Vienna<br>Facsimile No. 1/53424/535                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                               | Authorized officer<br>MÜLLER-HIEL R.<br>Telephone No. 1/53424/434                |

## INTERNATIONAL SEARCH REPORT

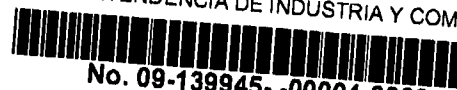
Information on patent family members

International application No.

PCT/IN 03/00206-0

| Patent document cited<br>in search report |   |         | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---|---------|---------------------|----------------------------|---------------------|
| US                                        | A | 5521184 |                     | CY A 2229                  | 2003-04-18          |
|                                           |   |         |                     | LU A 90908                 | 2003-04-30          |
|                                           |   |         |                     | DE I 10299016I             | 2002-08-29          |
|                                           |   |         |                     | NO A 931283                | 1993-10-04          |
|                                           |   |         |                     | SK B 280620B               | 2000-05-16          |
|                                           |   |         |                     | KR B 261366                | 2000-08-01          |
| WO                                        | A | 9903854 |                     | DK T 998473T               | 2004-02-02          |
|                                           |   |         |                     | CN B 1134429B              | 2004-01-14          |
|                                           |   |         |                     | ID A 24093                 | 2000-07-06          |
|                                           |   |         |                     | DE D 69818674D             | 2003-11-06          |
|                                           |   |         |                     | RU C 2206012               | 2003-07-10          |
|                                           |   |         |                     | AT T 251152T               | 2003-10-15          |

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-139945-00004-0000

Fecha: 2011-04-14 16:06:10 Dep. 2020 DIR.NUEVASCR  
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Señor Jefe,

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 09 139945  
Asunto : Oposición a la solicitud de patente de Invención titulada  
"FORMAS AMORFAS ESTABILIZADAS DE MESILATO  
DE IMATINIB"  
Solicitante : NOVARTIS AG.  
Opositora : LABORATORIOS SYNTHESYS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 624 del 20 de enero de 2011

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **83823** del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESYS S.A.S** 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 "FORMAS AMORFAS ESTABILIZADAS DE MESILATO DE IMATINIB", cuyos titulares son NOVARTIS AG, 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 IMATINIB. 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 07 de diciembre de 2009 reivindicando prioridad bajo la solicitud EP20070109816 del 2007-06-07; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 624 del 20 de enero de 2011, cuya publicación internacional corresponde a la WO2008154262 del 2008-12-18.

2.2. La solicitud colombiana 09 139945 objeto de la presente oposición se refiere a la forma amorfa estabilizada de la sal de adición de ácido metansulfónico de 4-(4-metilpiperazin-1-ilmetil)-N-[4-metil-3-(4-(piridin-3-il)-pirimidin-2-ilamino)-fenil]-benzamida, composiciones farmacéuticas tales como cápsulas o tabletas que contienen esta forma, el uso de dicha forma en métodos de diagnóstico o,

preferiblemente, para el tratamiento terapéutico de animales de sangre caliente, especialmente seres humanos, y al uso de principio de formulación estabilizando la forma amorfa de mesilato de Imatinib como un intermediario para la preparación de composiciones farmacéuticas.

2.3. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: *“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”*, tenemos que 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 afectan la patentabilidad de la presente solicitud:

- D1: US2006275372 publicada el 07 de agosto de 2003.
- D2: WO 2004106326 publicada el 09 de diciembre de 2004.

2.4. Ahora bien, el documento D1, se refiere a composiciones en nanopartículas de mesilato de imatinib, o una sal o un derivado del mismo. Las partículas de mesilato de imatinib de la composición tienen un tamaño efectivo de partícula promedio de menos de unos 2000 nm y son útiles en el tratamiento de la leucemia mieloide crónica, tumores del estroma gastrointestinal y enfermedades relacionadas; Dicho documento D1, de forma particular en la descripción (ver ejemplo 1) revela nanopartículas de mesilato de imatinib en un estado amorfo estable para el tratamiento de la leucemia. En una realización (ejemplo 1) el molido conjunto con estabilizadores de superficie se describe, sin embargo, sin indicación de si es o no el producto final amorfo. No obstante, moler conjuntamente es uno de los procesos

conocidos anteriormente que conducen a un estado amorfo (como se describe en la solicitud objeto de la presente oposición); la solicitud objeto de la presente oposición no es novedosa pues lo reclamado ya era parte de arte anterior.

2.5. Por su parte, el documento D2 se refiere a polimorfos de mesilato de imatinib, a los procesos para su preparación y a las composiciones farmacéuticas que los contienen, donde dicho documento D2 revela de forma particular en la descripción, página 2 líneas 1 -5 y en los ejemplos 6,7 y 8 una composición amorfa estable de mesilato de imatinib.

2.6. Tomando los documentos D1 y D2 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir de dicho documento D1 por sí solo, o en combinación con D2, concebir una forma amorfa estabilizada de mesilato de imatinib, composiciones farmacéuticas tales como cápsulas o tabletas que contienen esta forma, el uso de dicha forma en la medicina, y al uso del principio de formulación estabilizando la forma amorfa de mesilato de imatinib como un intermediario para la preparación de composiciones farmacéuticas. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 139945 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1. CARENCIA 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, 07 de junio de 2007 ya era conocido, pues como se demostró, eran parte del arte anterior con base en los documentos D1, nanopartículas de mesilato de imatinib en un estado amorfo estable para el tratamiento de la leucemia, utilizando el proceso de molido conjunto con estabilizadores de superficie; sobre lo cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 07 de junio de 2007, a partir del documento D1 por sí solo, o en combinación con D2, un experto en la materia puede llegar de manera evidente a nanopartículas de mesilato de imatinib en un estado amorfo estable, o a mesilato e imatinib en un estado amorfo estable; sobre lo cual busca protección en el capítulo reivindicatorio.

2.9. 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 dos de los tres requisitos de patentabilidad.

2.10. 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 “FORMAS AMORFAS ESTABILIZADAS DE MESILATO DE IMATINIB”, cuyos titulares son NOVARTIS AG, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 624 del 20 de enero de 2011.

### 3. PRUEBAS

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

- D1: US2006275372 publicada el 07 de agosto de 2003.
- D2: WO 2004106326 publicada el 09 de diciembre de 2004.

### 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 **LABORATORIOS SYNTHESYS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
  - D1: US2006275372 publicada el 07 de agosto de 2003.
  - D2: WO 2004106326 publicada el 09 de diciembre de 2004.

## 6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

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