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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

Ref: Expediente No. 00.033.394

Solicitud de Patente de Invención titulada: "NUEVAS FORMAS CRISTALINAS DE UN ANTIBIÓTICO MACRÓLIDO".

Solicitante: PFIZER PRODUCTS INC.

RECURSO DE REPOSICION

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad de la referencia, según consta en el poder adjunto, por medio del presente escrito, y dentro del término legal previsto por el artículo 51 del Código Contencioso Administrativo, me permito interponer RECURSO DE REPOSICIÓN en contra de la Resolución No. 29227, notificada por edicto desfijado el 30 de noviembre de 2006.

1. ANTECEDENTES

La solicitud de patente ventilada en este expediente contiene un capítulo reivindicatorio con 23 reivindicaciones que fue radicado el 03 de octubre de 2006, en respuesta al segundo estudio de fondo expedido por esa Superintendencia (SIC) el 25 de mayo de 2005. Según la resolución No. 29227, dicho capítulo reivindicatorio cumple con las prescripciones establecidas en el artículo 34 de la Decisión 486; sin embargo, en la resolución impugnada, el Despacho niega la totalidad de las reivindicaciones por supuesta falta de nivel inventivo.

2. OBJETO DEL RECURSO

Que se revoque la Resolución recurrida, y en su lugar se conceda el privilegio de patente de invención para las reivindicaciones pendientes de la presente solicitud, o en su defecto aquellas reivindicaciones que cumplan con los requisitos de patentabilidad

3. FUNDAMENTO DEL RECURSO

Con referencia a los argumentos presentados por la SIC para desvirtuar el nivel inventivo de la presente solicitud en la Resolución aquí recurrida, respetuosamente difiero del análisis expuesto, y procedo a dar respuesta a cada uno de dichos argumentos, exponiendo las motivaciones técnicas que desvirtúan completamente la posición de ese Despacho.

3.1. a- La SIC establece que los siguientes documentos afectan el nivel inventivo de la invención reivindicada:

No.	Documento	Fecha publicación
D1	WO9856802	17-12-1998
D2	Farmacia Remington	31-12-1995
D3	Farmacotécnica teórica y práctica	31-12-1981

La patente WO9856802 (**D1**) se relaciona con derivados de homoeritromicina A (fórmula I), sus métodos de síntesis y su aplicación como agentes antibacteriales. Los libros de texto "Farmacia Remington" (**D2**) y "Farmacotécnica teórica y práctica" (**D3**) enseñan que el polimorfismo es una propiedad que se distribuye ampliamente dentro de los compuestos activos, enseñan además que las formas pseudopolimórficas se caracterizan por la absorción de humedad del medio y finalmente explican métodos de caracterización e importancia farmacéutica.

b- De nuevo, el Solicitante acepta que el documento D1 corresponde a una anterioridad que se refiere a materia relacionada con la presente solicitud. D1 se refiere a derivados 9-deoxo-9a-aza-9a-homoeritromicina, entre los que se incluye el compuesto específico CP-472.295 (página 45), los métodos de síntesis de éste (ejemplos 50 y 51) y su purificación por cromatografía. Sin embargo, es necesario que ese Despacho entienda que la presente invención **reclama únicamente algunas formas polimórficas del mencionado compuesto de Fórmula I**

(CP-472.295), pero de ninguna manera el compuesto en general *per se*, esto es, la presente solicitud se refiere a materia novedosa y no sugerida por la anterioridad más cercana. De hecho, en cuanto al compuesto CP-472.295, D1 se refiere únicamente a la configuración amorfa del mismo; dicha anterioridad no menciona o siquiera sugiere la posibilidad de aplicar proceso de recristalizacion alguno para obtener el compuesto de interés en alguna forma cristalina útil. Por lo tanto, es de entender que anteriormente a la presente solicitud, el estado de la técnica más cercano no indicaba o siquiera sugería la posibilidad de obtener polimorfos estables de este compuesto.

En relación con las anterioridades D2 y D3, dichos documentos solo se refieren a la descripción de técnicas generales, experimentales e industriales, que se limitan a brindar definiciones y lineamientos globales de procedimientos farmacotécnicos, dentro de los que se incluyen por ejemplo las técnicas de cristalizacion. Sin embargo, dichos documentos no se refieren de manera particular a los antibióticos macrólidos, y aún menos el compuesto CP-472.295 o los métodos de cristalización específicos para obtener polimorfos de éstos, por lo que de allí es imposible que una persona medianamente versada en la materia encuentre indicaciones inequívocas de cómo obtener las formas cristalinas reivindicadas, o incluso, predecir que tales formas existirían.

Utilizar dichas referencias generales y teóricas como arte previo para intentar desvirtuar el nivel inventivo de materia específica objeto de solicitudes de patente resulta totalmente improcedente, porque conduciría necesariamente a que todo el conocimiento general disponible aplicado por un investigador para el desarrollo de una invención, siempre haría obvia toda invención. Es claro que lo que intenta la SIC es utilizar la teoría general de cristalización y polimorfismo para hacer obvio el desarrollo de nuevos polimorfos; así entonces, me permito cuestionar a ese Despacho si por ejemplo, de manera análoga, invenciones correspondientes a nuevos polímeros resultarían obvias a la luz del conocimiento general de las teorías de polimerización? O, el desarrollo de nuevos semiconductores se derivaría necesariamente del conocimiento general de la teoría y la configuración electrónica de los elementos y combinaciones semiconductoras?

El estudio de solicitudes de patente que conduzca a ese tipo de conclusiones anticipadas corresponde abiertamente a un análisis conocido en el ámbito de patentes como "análisis hindsight". Para entender el análisis equivocado que realiza la SIC, podemos citar el Manual Andino de Patentes, que indica claramente: "...la búsqueda de anterioridades se efectúa a posteriori, tomando como punto de partida la misma invención,...el examinador debe realizar el esfuerzo intelectual de colocarse en la situación que ha tenido que afrontar el técnico con

conocimientos medios en la materia en un momento en que la invención no era conocida, es decir antes de la invención"[1] (mi subrayado). No es apropiado anticiparse a los resultados presentados por la invención, menos aún basándose solamente en el conocimiento de teorías generales, ya que así, siempre resultará "obvio" todo objeto de una solicitud de patente, pues inevitablemente está parecerá derivada de la teoría en que se basa su desarrollo, sin dar mayor importancia al trabajo, intelecto y creatividad involucrados en la invención para llegar a la solución del problema planteado en la solicitud.

Lo anterior hace necesario que ese Despacho brinde más importancia al problema técnico planteado y a los medios realizados para llegar a la solución propuesta al momento de enfocar su análisis, en vez de limitarse a la simple comparación de las características técnicas del producto con alguna anterioridad, o aún peor, deduciendo que una invención específica es obvia a partir del conocimiento general disponible en el estado de la técnica.

En conclusión, las anterioridades D2 y D3 no se relacionan específicamente con la materia de la presente solicitud, dado que en ningún momento se refieren siquiera a compuestos cercanos estructuralmente al CP-472.295 y de ninguna manera anticipan o siquiera sugieren el desarrollo de nuevas formas sólidas del compuesto CP-472.295, de donde además pudiera predecirse o esperarse con una expectativa razonable de éxito su obtención y las propiedades mejoradas e inesperadas. De hecho, es imposible que una persona medianamente versada en la materia pueda predecir con certeza alguna que una nueva forma cristalina, como las reclamadas y caracterizadas en el capítulo reivindicatorio, pueda siquiera existir; más aun, cuando **el arte previo no brinda siquiera indicios** de que dicho compuesto es o no capaz de constituir polimorfos. Además de no ser posible garantizar *a priori* la obtención de formas cristalinas, tampoco es posible predecir cuántas formas son posibles y qué propiedades presentará cierta forma particular. Es decir, algunos compuestos son polimórficos y otros no los son, y no hay un método conocido que permita predecir cuales compuestos podrían proveer formas cristalinas adicionales; igualmente es virtualmente imposible anticipar con aceptable grado de certeza cuál será su estructura tridimensional, cuáles sus propiedades fisicoquímicas (tales como tasa de disolución, higroscopicidad, solubilidad, biodisponibilidad, estabilidad, etc.) y cuál será su actividad biológica. Ni siquiera un conocimiento profundo de la teoría de cristales o una amplia experiencia específica en el área, permitirían a una persona medianamente versada en la materia anticipar inequívocamente los anteriores hechos, basándose en la divulgación del compuesto CP-

[1] Manual para el Examen de Solicitudes de Patentes de Invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina (Manual Andino de Patentes). Documento preparado por la Oficina Internacional de la OMPI. ISBN 9978-43-855-6. 2004. Sección 10.2.1.

472.295 de D1 en su configuración amorfa y la teoría de cristales sólidos, pues solamente con la invención de la presente solicitud se logró la obtención de las formas cristalinas reivindicadas, sin seguir ningún tipo de indicación o enseñanza del arte previo; de hecho, los ejemplos de la presente solicitud describen 3 estructuras cristalinas en los que se pudo determinar diferentes grados de hidratación y para las que su obtención no era posible anteriormente a partir de las enseñanzas del estado de la técnica sin la necesidad de experimentación.

En conclusión, ni D1, ni D2, ni D3, independientemente o en combinación, sugieren los procedimientos para obtener las formas polimórficas reclamadas por la presente invención ni la probable existencia de dichas formas polimorfitas. Es necesario resaltar que aún en respuesta al segundo examen de fondo, **la SIC no demuestra con rigurosidad cuáles son las enseñanzas específicas del arte previo citado, que conllevarían a una persona medianamente versada en la materia a obtener la materia aquí reivindicada**, como por ejemplo, indicaciones claras que lleven a disolver la base libre del compuesto en un solvente seco, o en una mezcla de solventes, o en un solvente no acuoso (p.ej. acetato de etilo, etanol, isopropil eter o mezclas de ellos, conteniendo de 0.05 a 15% o de 1 a 10% de agua), y a luego enfriar la solución, con certeza de poder obtener por cristalización o por deshidratación de la forma monohidratada, las formas cristalinas de interés, con sus características estructurales específicas y las propiedades de estabilidad deseadas.

3.2. a- En la resolución No. 29227, la SIC argumenta que "si bien en **la anterioridad WO9856802 no se insinúan o se sugiere la presencia de cristales o procedimientos de cristalización** es obvio para *un experto medio con conocimientos en el arte* (evidenciados en los libros de texto citados) que el polimorfismo es la capacidad de cualquier elemento o compuesto para cristalizar en la forma de más de una especie cristalina y que las diferentes formas polimórficas de un compuesto dado en general son diferentes en estructura y propiedades como los cristales de dos compuestos distintos..."[2] (mi negrilla y subrayado), para llegar a la conclusión que la producción de los polimorfos reivindicados del compuesto CP-472.295 es obvia, ya que todo técnico medio sabe que el polimorfismo es un fenómeno común, particularmente en los medicamentos y éstos deben determinarse con el fin de producir materia prima aceptable para la industria. Además, los métodos de obtención de polimorfos no imprimen nivel inventivo a una solicitud de patente. Es decir, el trabajo realizado en la presente solicitud

[2] Ver Resolución 29227 del 30 de octubre de 2006 proferida por la Superintendencia de Industria y Comercio, página 4, líneas 16 a 22.

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hace parte de los estudios rutinarios de formulación, que por ningún motivo otorga nivel inventivo a la invención en estudio.

Continúa la SIC argumentando que obtener hidratos y formas anhidras del compuesto CP-472.295 es una derivación evidente del estado de la técnica, ya que cualquier persona medianamente versada en la materia hubiera podido derivarlos de manera evidente a partir de las enseñanzas del arte previo. La presente solicitud se deriva de manera evidente de los conocimientos usuales de un experto medio versado en cristalización y polimorfismo, pues solamente se determinaron las condiciones en que los polimorfos del compuesto CP-472.295 se forman, mediante un juego usual de cambios de solventes y temperatura que si bien, son dispendiosos, no implican una labor creativa, y en donde la conformación del compuesto (no la actividad del investigador) da las propiedades diferentes del mismo.

b- Resulta incomprensible y a todas luces confuso que la SIC acepte que el arte previo más cercano (la anterioridad WO9856802) no contiene sugerencia o indicación alguna acerca de eventuales formas cristalinas del compuesto CP-472.295 o métodos probables para su obtención, pero que al mismo tiempo objete el nivel inventivo aduciendo a que el mismo estado de la técnica conduciría a una persona medianamente versada en la matera a la obtención de dichos polimorfos. Innegablemente esto es una contradicción. Bien indica el Manual Andino de Patentes, que el análisis objetivo de nivel inventivo, responsabilidad de la SIC, debe enfocarse a determinar "si teniendo en cuenta el estado de la técnica en su conjunto, existe alguna indicación que lleve a la persona versada en la materia a modificar o adaptar el estado de la técnica más cercano para resolver el problema técnico, de tal forma que llegue a un resultado que estuviera incluido en el tenor de las reivindicación"[3]. En este caso, claramente el estado de la técnica más cercano corresponde a la anterioridad WO9856802, para la cual la misma SIC determino que no contiene **insinuación o sugerencia de la presencia de cristales o procedimientos de cristalización para el compuesto CP-472.295** y aún menos de los resultados obtenidos con dichos cristales.

Insito en el hecho que para juzgar si una invención se deriva evidentemente del estado de la técnica, el Examinador tiene la carga de probar que la invención carece de nivel inventivo y no puede solo limitarse a establecer las diferencias o similitudes entre la solicitud y dicho estado de la técnica.[4] En el presente caso, no basta con citar la simple existencia del compuesto amorfo

[3] Ibidem ref. 1.
[4] Manual Andino de Patentes. Sección 10.1.

(D1), o literatura general que define el polimorfismo y su importancia (D2 y D3). Solicito a la SIC realice una mención explícita de los elementos contenidos en el estado de la técnica que **insinúen, sugieran y permitan** a una persona medianamente versada en la materia derivar de manera evidente las formas cristalinas reivindicadas de manera directa y sin necesidad de acudir a la experimentación. Claramente, como lo anota la SIC, el arte previo citado no contiene enseñanzas claras o suficientes para predecir la existencia de formas cristalinas del antibiótico CP-472.295 y menos aun métodos para obtenerlas. Una vez más, D1 sólo revela la forma amorfa del compuesto, métodos de preparación y métodos de purificación (cromatografía), mientras que los documentos D2 y D3 sólo proporcionan generalidades acerca de técnicas de polimorfismo y cristalización.

En el análisis del nivel inventivo de una solicitud de patente de invención no es aceptable hacer referencia a elementos aislados del estado de la técnica, como si de armar una colcha de retazos se tratara. Si ese fuese el criterio de nivel inventivo nada sería patentable ya que, como lo ha reconocido el Tribunal Andino de Justicia, nada se inventa de la nada.[5] En este caso, el hecho que pudiera existir eventualmente una mínima motivación general para llevar a cabo trabajo experimental para determinar si hay otras formas polimórficas, no hace el resultado positivo obtenido (es decir la invención) obvio o evidente; si así fuera, el trabajo experimental sería innecesario. **El que sea obvio intentar, no necesariamente hace obvia la invención**. En muchos casos, así como en la presente solicitud, lo que es "obvio intentar" es la variación de todos los parámetros de un proceso dado o el ensayar cada una de muchas posibles alternativas, hasta encontrar un resultado prometedor, para el que el estado de la técnica no proveía indicación de cuáles parámetros eran críticos, o no brindaba orientación de cuál de las muchas elecciones posibles sería exitosa. De hecho, como lo ha indicado la Suprema Corte Canadiense "Muy pocas invenciones tienen resultados inesperados. Prácticamente todo el trabajo investigativo se hace según orientaciones hacia donde el *estado de la técnica* apunta. Así entonces, y basados en la retrospectiva que brinda el estado de la técnica, se podría decir que en muchos casos no hubo creatividad inventiva en un nuevo desarrollo porque siempre se vería cómo logros anteriores apuntarían el camino".[6] Esto quiere decir que por ejemplo, el análisis *canadiense* de obviedad es una evaluación estricta de si una persona versada en la materia hubiera sido guiada directamente y sin dificultad a la solución. El documento "A study of issues relating to the patentability of

[5] Proceso 21-IP-2000, página 8, línea 8 (anexo 3 en mi memorial del 03 de octubre de 2006).
[6] Canadian Supreme Court decision (Faberwerke Hoecht A/G v Halocarbon (Ontario) Ltd (1979), 42 C.P.R. (2d) 145 at 155).

biotechnological subject matter: patentable invention"[7], ilustra claramente este tipo de análisis de la no obviedad en el área biotecnológica, y concluye que el esfuerzo del trabajo investigativo intensivo no es visto como obvio en Canadá, aún más si el estado de la técnica no guía directamente y sin dificultad a la solución. Por ejemplo este documento anota igualmente que aunque la biotecnología es simple en teoría y los pasos y etapas involucradas son *directos y claros*, la "elegante simpleza" de los conceptos esconde "un cúmulo de improbabilidades y obstáculos que de deben ser superados antes de alcanzar resultados exitosos". Esta misma lógica es aplicable en invenciones químicas y farmacéuticas y los Examinadores en estas áreas deben asegurarse que sus objeciones en cuanto al nivel inventivo sean rigurosas y que no caigan fácilmente en la simplicidad del test "obvio intentar"; en particular, esto es cierto cuando se evidencias resultados ventajosos que pueden valorarse como una base objetiva de no obviedad.[8]

Así las cosas, durante el análisis de una solicitud de patente, el Examinador debe poder citar anterioridades que específicamente motiven a una persona versada en el arte a combinar los elementos del estado de la técnica y a intentar las opciones específicas para llegar a la solución inventiva reclamada. No es suficiente alegar que la persona versada podría llegar a la invención, puesto que, como se ha dicho, este criterio desdibujaría por completo el sistema de patentes, elevando el requisito de nivel inventivo a tal punto que nada sería patentable e indicaría que en todos los casos no hubo creatividad inventiva en el desarrollo de nuevas invenciones porque éstas siempre serían vistas cómo logros apuntados por el estado de la técnica.

El hecho de implementar herramientas conocidas en el estado de la técnica no desvirtúa automáticamente el nivel inventivo de una invención. En efecto, dado que es necesario valerse de las herramientas existentes en la técnica para así poder seguir avanzando en los desarrollos tecnológicos. En la resolución impugnada, la SIC parece desatender la jurisprudencia establecida por el El Tribunal de Justicia Andino, que con relación al nivel inventivo en el área de los inventos químicos y biotecnológicos ha manifestado que frecuentemente "...**aplicando procedimientos conocidos** pueden obtenerse resultados inesperados para una persona normalmente versada en la materia...", pero que "...por ello, el juicio del nivel inventivo no

[7] Dr. John R. Rudolph, A Study of Issues Relating to the Patentability of Biotechnological Subject Matter: Table of Contents. Gowling, Strathy & Henderson. http://strategis.ic.gc.ca/epic/internet/inippd-dppi.nsf/en/ip00190e.html. (Anexo 1)

[8] Australian Patent Office. Manual of Practice and Procedures. 1 December 2006. 2.5.3.3.5 "Obvious to Try". http://www.ipaustralia.gov.au/pdfs/patentsmanual/WebHelp/Patent_Examiners_Manual.htm#National/Inventive_Step/2.5.3.3.5_obvious_to_try.htm. (Anexo 2)

puede ser elaborado con criterios generales, sino que dependerá de las especiales circunstancias de cada caso."[9]

Evidentemente, con su análisis *hindsight*, la SIC argumenta en contra de la reivindicación de sólidos cristalinos (polimorfos) utilizando tesis generales que conllevan a entender *a priori* que en su totalidad las nuevas formas cristalinas no son patentables. Por lo tanto, requiero a ese Despacho una respuesta específica de mi pregunta planteada en mi memorial del 03 de octubre de 2006, en cuanto a que si **lo que esa Dependencia sugiere es que las formas cristalinas no son patentables y no corresponderían a invenciones si no a meros decubrimientos**, pues es inevitable entender que esa es ahora la posición de la SIC frente a solicitudes de patente de nuevas formas cristalinas, ya que manifestaciones como las incluidas en la resolución impugnada, asegurando que las formas cristalinas son obvias, debido a que el polimorfismo es una propiedad ampliamente distribuida en los principios activos, conducen directamente a deducir que la SIC tiene un posición predefinida y subjetiva frente al patentamiento de polimorfos. Valga anotar que esta situación es reiterada y generalizada en todos los casos que recientemente reivindican formas cristalinas; al parecer, nos encontramos frente a una determinación de la SIC a no permitir la protección de polimorfos.

En este sentido, y con relación al polimorfismo en general, es importante resaltar que el polimorfismo es un problema vigente en particular para las industrias farmacéutica y de alimentos, ya que solamente algunos polimorfos tienen propiedades deseables (p.ej. estabilidad, biodisponibilidad, disolución, etc), por lo que la patentabilidad de éstos se basa con base en las propiedades ventajosas logradas con nuevas formas cristalinas.[10] Sin embargo, no puede olvidarse que la búsqueda de polimorfos no es completamente predecible, por lo que siempre los científicos investigadores deben explotar intensamente su conocimiento y creatividad con el fin de desarrollar nuevas formas cristalinas. De hecho, no hay un método general para la predicción de estructuras cristalinas a partir de una fórmula molecular; el diseño de sólidos orgánicos que respondan a propiedades deseadas previamente continúa siendo un sueño.[11]

Así las cosas, la investigación de las diferentes formas sólidas de un medicamento, puede conducir al desarrollo de nuevos productos con propiedades mejoradas, tales como velocidad de acción, mayor biodisponibilidad, características de entrega sostenida, ventajas terapéuticas o beneficios en la estabilidad, como ocurre en el presente caso.

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[9] Proceso 105-IP-2000, página 7, líneas 45 a 50 (anexo 4 de mi memorial del 03 de octubre de 2006).
[10] University of Minesota. http://www.chem.umn.edu/groups/siepmann/research/phase.php (Anexo 3)
[11] G.R. Desiraju, Nature Materials, 1, 77-79 (2002) (Anexo 4)

Dado el esfuerzo involucrado en el desarrollo de estas mejoras, y dado que éstas proveen ventajas comerciales competitivas y se derivan directamente de la investigación y creatividad humanas, el sistema de patentes *debe* garantizar su protección. La SIC no puede basarse en apreciaciones subjetivas para privar al inventor de la protección merecida para su desarrollo novedoso y no sugerido por el estado de la técnica. En el mundo entero, las formas cristalinas específicas son consideradas no-obvias y por ende, materia pantentable; si bien en los medicamentos actuales, o las moléculas candidatas a ser medicamentos, es posible encontrar múltiples formas sólidas, algunas similares, algunas drásticamente diferentes en sus características técnicas, estas formas, son todas candidatas para obtener protección vía patentes de manera individual.[12]

Los polimorfos no corresponden a un simple descubrimiento de una nueva forma de una sustancia conocida; los polimorfos reivindicados en la presente solicitud son nuevos productos y su forma cristalina no es una propiedad inherente del material amorfo revelado en D1, de ser así, solcito a ese Despacho indicar cómo a partir del material revelado en D1 es posible inferir los cristales reivindicados. Por el contrario, la intervención humana y la investigación creativa fue necesaria y un elemento fundamental en el desarrollo de las formas cristalinas reivindicadas De hecho, los aunque los métodos de investigación para obtener formas cristalinas son bien conocidos en arte, estos métodos nos lentos, poco eficientes y solo permiten el reconocimiento de una mínima fracción de los posibles cristales de un compuesto dado,[13] por lo que la experticia y creatividad del inventor son una condición obligatoria para obtener cristales con las propiedades deseadas.

Una vez más, insisto en que el carácter no obvio y no evidente de un polimorfo en particular y de los polimorfos de la presente invención yace en el hecho de que es imposible para una persona medianamente versada en el arte, determinar, *a priori*, la existencia de polimorfos específicos para un compuesto dado. (i) no es posible predecir si una forma cristalina específica existe para un compuesto determinado; (ii) no es posible saber, *a priori*, si una forma cristalina específica existe hasta que no se haga el trabajo experimental que conduzca a la obtención de dicho cristal; (iii) no es posible predecir el acercamiento experimental para obtener un cristal de manera eficiente ya que su producción depende de múltiples factores como son la temperatura, la agitación, la velocidad de enfriamiento, la naturaleza del disolvente, la cantidad de disolvente, la pureza del disolvente, etc.; (iv) si el cristal llega a producirse eficientemente, no es posible

[12] Sherry L. Morissette, et. Al., "High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids". Advanced Drug Delivery Reviews 56 (2004) 275– 300. (Anexo 5)
[13] Ibidem ref. 12.

predecir sus parámetros fisicoquímicos, como tampoco es posible predecir cual será por ejemplo su perfil de estabilidad (entre otros, la higroscopicidad). Adicionalmente, quiero anotar que el desconocimiento de las estructuras cristalinas polimorficas específicas reivindicadas en la presente solicitud constituye innegablemente la evidencia de que se está frente a una "estructuras cristalinas inesperadas", con lo cual cumpliría el requisito de patentabilidad de nivel inventivo. La SIC parece rechazar el principio establecido por el Manual Andino de Patentes que establece que un compuesto tiene nivel inventivo cuando (i) el compuesto tiene estructura inesperada, o (ii) cuando el compuesto exhibe un uso o un efecto sorprendente. [14]

3.3. a- La SIC comenta en la resolución impugnada que los resultados referidos en la presente solicitud corresponden a propiedades conocidas por cualquier experto medio y se atribuyen a los hidratos o formas anhidras, es decir, la mayoría de las forma monohidratadas son menos higroscópicas que las anhidras y son susceptibles a perder el agua capturada en condiciones de manipulación, por lo tanto no puede hablarse de propiedades sorprendentes o mejoradas que constituyan indicios de nivel inventivo.

b- Tal como lo indiqué en mi memorial del 03 de octubre de 2006, reitero que la presente solicitud sí presenta resultados mejorados y ventajosos sobre el arte previo más cercano, que una persona medianamente versada en la materia no hubiera podido derivar o predecir de manera evidente a partir de las enseñanzas del estado de la técnica.

La SIC parece desatender abiertamente las indicaciones hechas por el Manual Andino de Patentes, que establece claramente que en relación con el nivel inventivo en áreas de la tecnología, específicamente en química, "ante una objeción por falta de nivel inventivo, el solicitante puede aportar pruebas para apoyar ese nivel inventivo en forma de argumentos o documentos, por ejemplo, (...) **mediante ensayos especialmente comparativos para demostrar la presencia de un efecto técnico o ventaja de la invención, respecto del estado del arte más cercano**" (Negrilla y subrayado propios).[15] Es más, el mismo Manual puntualiza que un compuesto químico o composición química tiene nivel inventivo cuando "... el efecto inesperado puede ser completamente diferente de los descritos para los compuestos similares, **o bien ser igual pero con una mejora en los resultados**" (Negrilla y subrayado propios).[16] Por lo tanto, el requerimiento de nivel inventivo se ve reafirmado cuando a polimorfismo se refiere, si se muestra por ejemplo, cualquier actividad o propiedad mejorada sobre el arte previo.

[14] Manual Andino de Patentes. Sección 10.8.1.
[15] Manual Andino de Patentes. Sección 10.7.
[16] Ibidem ref. 14.

El nivel inventivo de la presente invención se entendería mejor si la SIC enfoca primero su atención en la comprensión del problema superado y la solución suministrada en ese momento por el solicitante, y no incurrir en el error de comprender el problema después de que este ya ha sido resuelto. Tal como lo enseña el Manual Andino de Patentes[17] y lo aplica rutinariamente la Oficina Europea de Patentes, incluso para la evaluación del nivel inventivo de solicitudes que reclaman polimorfos, [18] la aproximación problema-solución permite realizar une reconocimiento objetivo del cumplimiento o incumplimiento del requisito de nivel inventivo en solicitudes de patente.

La aproximación problema-solución se basa en el principio de que toda invención es la solución a un problema técnico persistente, y se realiza de acuerdo a la siguiente metodología:

i) Determinación del arte previo más cercano. Para polimorfos, el arte previo más cercano corresponde usualmente a un documento que reveló anteriormente el mismo compuesto en otra forma, cristalina o no. En el presente caso, claramente el arte previo más cercano corresponde a la patente WO9856802 que reveló el compuesto CP-472,295, pero que no hace referencia a polimorfos del mismo o procedimientos para obtenerlos.

ii) Determinación de las características técnicas que son diferentes al arte previo más cercano. En el presente caso, las diferencias técnicas de la materia reivindicada están dadas precisamente por la estructura misma del cristal que es el elemento diferenciador del compuesto amorfo revelado por D1 y de la que se derivan sus propiedades. Esta diferencia técnica, su estructura cristalina, se estableció claramente por ejemplo por los patrones de difracción de rayos-X, los espectros de calorimentría, las características y posiciones atómicas de la celda unitarias incluidos en las reivindicaciones.

iii) Identificación del problema técnico a solucionar. Para polimorfos, el problema técnico más común es la obtención de una nueva forma física de un compuesto conocido, bien sea para alcanzar el mismo efecto de la forma anterior o para proveer una forma física alternativa con características diferentes y mejoradas. Es válido recordar que es perfectamente aceptable que el problema técnico solucionado no se indique siempre en las

[17] Ibidem ref. 1.
[18] Dr. Sofia Papathoma. Patenting polymorphs at the European Patent Office. Barcelona, June 2006. (http://www.pcb.ub.es/centredepatents/pdf/cursos/dillunsCP/papathoma_polymorphs.pdf) (Anexo 6)

solicitudes de patente,[19] sin embargo, en el presente caso la descripción de la invención definió claramente el interés existente al momento de desarrollar la invención reivindicada de proveer formas no higroscópicas del compuesto CP-472.295 (página 2, líneas 11 y 12), definiendo como no higroscópico un material que absorbe humedad en una proporción inferior a aproximadamente un 0.4% durante 24 horas a una humedad relativa del 90% (página 12, líneas 16 a 20), ya que formas cristalinas con estas características facilitarían la fabricación de formas de dosificación de dicho compuesto (página 16, 19 a 21). Así, podemos definir el problema técnico abordado por la presente solicitud como la obtención formas polímorficas con características mejoradas de baja higroscopicidad y por ende, mayor estabilidad.

iv) Verificar si el problema técnico definido se resolvió con la invención reclamada y si dicha solución resultaría obvia para una persona medianamente versada en la materia. La presente invención proporciona: a) una forma cristalina anhidra de CP-472.295 que es una forma no higroscópica en condiciones de humedad relativa del 87%, por aproximadamente 72 horas a temperatura ambiente; b) una forma cristalina monohidrato de CP-472.295 que es una forma no higroscópica en condiciones de humedad relativa del 87%, por aproximadamente 7 días a temperatura ambiente; y c) una forma cristalina sesquahidrato de CP-472.295 que posee propiedades físicas diferentes a las de las dos formas anteriores (esta forma aparece con un hábito cristalino en forma de varillas con una birrefringencia moderada) y a diferencia del monohidrato, la forma sesquahidrato de CP-472.295 pierde rápidamente agua en condiciones de manipulación de rutina (por ejemplo, 25°C y humedad relativa del 75%). Las anteriores características demuestran que el problema técnico que buscaba resolver la solicitud, se cumple a cabalidad con las 3 modalidades anteriores de la invención reivindicada; estas propiedades ventajosas de baja higroscopicidad constituyen una mejora sobre el arte previo divulgado por D1, ya que permite manejar y almacenar el compuesto a bajo costo y de manera eficiente, y facilita la incorporación de cantidades exactas del compuesto dentro de una gran variedad de formulaciones. Las formas cristalinas de la presente invención logran mejorar el perfil de estabilidad del compuesto CP-472.295 amorfo divulgado por D1, superando las dificultades mencionadas de fabricación y almacenamiento, lo que comprueba el carácter inventivo e mejorado con respecto al arte previo, que por lo demás, no hubiera podido ser anticipado o derivado de manera evidente por una persona medianamente versada en la materia a partir de las enseñanzas del arte previo citado por la SIC.

[19] Manual Andino de Patentes. Sección 10.2.1.

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En conclusión, según la aproximación problema-solución para el análisis del nivel inventivo de la presente solución, éste se reconoce claramente, ya que cualquier persona medianamente versada en el arte aceptaría que el material reivindicado resulta ventajoso sobre lo revelado en el estado de la técnica, arte previo que por lo demás no brindó indicación alguna de la posibilidad de cómo preparar o cómo obtener polimorfos del compuesto CP-472.295, tal como lo afirma la SIC en la resolución impugnada. Adicionalmente, anterior a la presente invención no había conocimiento ni de las formas hidratas o anhidras del compuesto y por lo tanto, no podía predecirse o derivarse del estado de la técnica las propiedades de éstos o en particular del material anhidro.

Si la SIC insiste en su posición de mantener su afirmación en cuanto a que las anteriores características son una derivación del estado del arte, **solcito respetuosamente se enumeren de manera taxativa** los hechos incluidos en el arte previo que conducirían a una persona versada en el arte a obtener específicamente los 3 polimorfos reivindicados del compuesto CP-472.295, con sus estructuras cristalinas definidas y presentando explícitamente las propiedades de estabilidad y baja higroscopicidad referidas anteriormente.

Para terminar, nuevamente, la SIC no cita referencias bibliográficas válidas que sustenten su afirmación en cuanto a que las propiedades derivadas del grado de higroscopicidad de formas cristalinas resultarían obvias para cualquier persona medianamente versada en la materia, de tal forma que una persona medianamente versada en la materia pudiera anticipar *a priori* el comportamiento de las formas cristalinas de la presente invención. Claramente, existen excepciones a la regla planteada por la SIC en cuanto a que las formas monohidratadas son siempre menos higroscópicas que las formas anhidras, pues como lo indiqué en mi memorial del 03 de octubre de 2006, la higroscopicidad está determinada hasta cierto punto por la estabilidad termodinámica de una red cristalina; es decir, no hay motivo para afirmar *a priori* que un monohidrato es siempre más estable que un material anhidro. Por el contrario, es bien sabido que el grado de desorden en un sólido cristalino puede inducir la higroscopicidad,[20] y por lo tanto, la presencia de moléculas de agua en un monohidrato podría desordenar las redes cristalinas haciendo el monohidrato más higroscópico que el material anhidro. En conclusión, no es posible afirmar de manera general y absoluta que todas las formas hidratas de las sustancias son más higroscópicas que las anhidras. De nuevo, un ejemplo de esto puede observase en las diferentes formas sólidas de ácido cítrico, que en su forma monohidratada resulta más higroscópico que en

[20] Makoto Otsuka, Fumie Kato, and Yoshihisa Matsuda, Comparative Evaluation of the Degree of Indomethacin Crystallinity by Chemoinfometrical Fourie-Transformed Near-Infrared Spectroscopy and Conventional Powder X-ray Diffractiometry. AAPS PharmSci. 2000; 2 (1): article 9. DOI: 10.1208/ps020109. (anexo 1 de mi memorial del 03 de octubre de 2006)

su forma anhidra.[21] La SIC debe explicar y sustentar su afirmación referente a que un "experto medio sabe de antemano que la mayoría de los hidratos, incluyendo los de la presente solicitud, tienen a absorber menos agua del medio y a perderla bajo condiciones de manipulación".

3.4. a- La SIC manifiesta en la resolución 29227 que en cuanto a solicitudes de patente de invención, el análisis y calificación se realiza independientemente para cada caso en particular, de tal suerte que si la solicitud de turno reúne los requisitos establecidos en la normativa andina, entonces sí procede a otorgarle el privilegio solicitado.

b- El solicitante entiende que la SIC base su análisis de patentabilidad de manera independiente para cada caso en particular, específicamente en la búsqueda y evaluación de antecedentes que constituyan el arte previo relacionado con una invención específica. Sin embargo, la SIC repetidamente hace afirmaciones generales en casos relacionados con solicitudes de nuevas formas cristalinas, indicando que la aproximación a estos casos no es partícular, sino que corresponde a una posición preestablecida y subjetiva frente al patententamiento de polimorfos. Así entonces, si de evaluar cada caso de manera independiente y objetiva se trata, no se entienden afirmaciones generalizadas contenidas en la resolución impugnada indicando por ejemplo que "es obvio para un experto medio con conocimientos en el arte... que el polimorfismo es la capacidad de cualquier elemento o compuesto para cristalizar en la forma de más de una especie cristalina y que las diferentes formas polimorficas de un compuesto dado en general son diferentes en estructura y propiedades como los cristales de dos compuestos distintos... es decir, debe quedar claro que el trabajo realizado en la presente solicitud hace parte de los estudios rutinarios dentro de la formulación de nuevos productos farmacéuticos, que, contrario a lo que entiende el solicitante, por ningún motivo otorga nivel inventivo a la invención en estudio".[22]

Adicionalmente, y contrario a la nueva y sorprendente posición generalizada de la SIC, representada en la resolución 29227, quiero insistir en que ese mismo Despacho se pronunció en general a favor de la patentabilidad de formas polimórficas de un compuesto, en respuesta a una Acción de Nulidad y Restablecimiento del Derecho contra la resolución No 20167 de 24 de agosto de 2002, proferida por el Superintendente de Industria y Comercio. De nuevo, en la citada respuesta a la acción de nulidad, queda claro que "no es posible considerar ni obvio ni evidente

[21] http://www.jungbunzlauer.com/products-applications/products/citrics/citric-acid/characteristics.html. (anexo 2 de mi memorial de 03 de octubre de 2006)
[22] Ver Resolución 29227 del 30 de octubre de 2006 proferida por la Superintendencia de Industria y Comercio, página 4, líneas 17 a 22 y líneas 26 a 30.

encontrar los parámetros adecuados... para obtener un polimorfo crietalino" (mi subrayado) [23], puesto que éstos deben ser escogidos racional o empiricamente dentro de una gran diversidad de factores, más aun cuando no existen antecedentes en el estado de la técnica que sugieran el método a seguir, como bien ocurre en el presentre caso y se demostró en el análisis referente al nivel inventivo, "puesto que la verdadera dificultad relacionada con el polilimorfismo consiste en asegurar un método de preparación reproducible de un polimórfo específico y el prevenir su transformación espontánea a una forma indeseable, puesto que variaciones mínimas en las condiciones de preparación pueden conducir a la obtención de una forma que no es la más estable o a una que no es la necesaria o deseada" (mi subrayado).[24] Es más, en su concepto, ese Despacho reconoce que "**aunque algunos compuestos pueden formar polimorfos, no enseña de manera general a la persona versada en la materia cuáles compuestos pueden formar estas estructuras cristalinas"** (mi subrayado y negrilla).[25] Por último, ese despacho igualmente estableció que "**en relación con solictudes de patente que traten de formas cristalinas específicas de un compouesto conocido en el pasado, queda claro que su justificación de su protección radica principalmente en la creatividad y racionalidad aplicada para la disposición de las condiciones específicas (el procedimiento) que permita la producción del compuesto cristalino que se diferencia inequívocamente del compuesto comprendido en el estado de la técnica"** (mi subrayado) [26], lo que visiblemente es el caso de la presente invención.

Así las cosas, y de acuerdo con las posición sostenida por ese Despacho en referencia a la protección de formas polimórficas, y siendo que la forma física aquí reclamada posee el nivel inventivo necesario como para acceder a un privilegio de patente, solicito a ese despacho reconsidere su posición y conceda la patente solicitada para las formas cristalinas de la presente invención.

3.5. a- La SIC manifiesta en la resolución No. 29227 que los derechos de patente tienen carácter territorial, es decir, cada oficina de patentes extranjera realiza los exámenes de

[23] Ver página 5, líneas 38 y 39 de la respuesta a una Acción de Nulidad y Reestablecimiento del Derecho contra la resolución No. 20167 de 24 de agosto de 2002, proferida por el Superintendente de Industria y Comercio (anexo 5 de memorial del 03 de octubre de 2006).
[24] Ver página 3, líneas 18 a 22 de la respuesta a una Acción de Nulidad y Reestablecimiento del Derecho contra la resolución No. 20167 de 24 de agosto de 2002, proferida por el Superintendente de Industria y Comercio (anexo 5 de memorial del 03 de octubre de 2006).
[25] Ver página 6, líneas 7 a 9 de la respuesta a una Acción de Nulidad y Reestablecimiento del Derecho contra la resolución No. 20167 de 24 de agosto de 2002, proferida por el Superintendente de Industria y Comercio (anexo 5 de memorial del 03 de octubre de 2006).
[26] Ver página 6, líneas 35 a 40 de la respuesta a una Acción de Nulidad y Reestablecimiento del Derecho contra la resolución No. 20167 de 24 de agosto de 2002, proferida por el Superintendente de Industria y Comercio (anexo 5 de memorial del 03 de octubre de 2006).

patentabilidad a la luz de las disposiciones que los facultan para determinarse se confiere o no un derecho de exclusividad sobre una invención.

b- El hecho de que las patentes sean otorgadas de manera individual e independiente por cada autoridad competente en cada nación, indica que a pesar de que la legislación se ha esforzado por armonizar los requisitos de patentabilidad, existen particularidades en algunos países. Estas diferencias se manifiestan principalmente cuando se trata de excepciones y exclusiones de materia patentable.[27,28] En el caso colombiano, la legislación establece taxativamente la materia que no es considerada como invención y que no puede ser patentable en el territorio andino.[29,30] Adicionalmente, un ejemplo palpable de las diferentes interpretaciones y disposiciones diferenciales que las naciones pueden dar a la legislación armónica de Propiedad Industrial se da con la patentabilidad de los usos, que es aceptada en muchos países incluyendo los Estados Unidos y Europa, mientras que en la Comunidad Andina se entiende que de acuerdo con su legislación, las patentes deben otorgarse solo para productos o procedimientos,[31] y los usos no corresponden a ninguna de estas modalidades. Un ejemplo adicional, más allá del campo de las interpretaciones, lo constituyen disposiciones adicionales incluidas en la legislación que se apartan de la armonización internacional y de la práctica de patentes a nivel mundial, cuando por ejemplo la Decisión 486 incluye un artículo dedicado a evitar el patentamiento de materia conocida basándose en el hecho de haber desarrollado una utilización diferente a la establecida (segundos usos).[32]

Así las cosas, queda claro que las diferencias en las legislaciones de Propiedad Industrial de las diferentes naciones se constituye principalmente por excepciones a patentabilidad o materia que no puede ser considera invención, lo cual es respetado a cabalidad por la presente solicitud de patente. Por el contrario, los conceptos de requisitos de patentabilidad, como el nivel inventivo que debe ostentar una invención para ser patentada, son absolutamente equivalentes y evaluados bajo los mismos parámetros a nivel mundial.

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[27] El Acuerdo sobre los ADPIC, Parte II — Normas relativas a la existencia, alcance y ejercicio de los derechos de propiedad intelectual. Sección 5, Artículo 27. Materia patentable. (http://www.wto.org/spanish/docs_s/legal_s/27-trips_04c_s.htm#5)

[28] OMC – Consejo ADPIC. EXAMEN DE LAS DISPOSICIONES DEL PÁRRAFO 3 b) DEL ARTÍCULO 27. RESUMEN DE LAS CUESTIONES PLANTEADAS Y LAS OBSERVACIONES FORMULADAS. 9 de marzo de 2006. (http://www.wto.org/spanish/tratop_s/trips_s/ipcw369r1.doc)

[29] Artículo 15, Decisión 486.

[30] Artículo 20, Decisión 486.

[31] Artículo 14, Decisión 486.

[32] Artículo 21, Decisión 486.

Por lo tanto, en cuanto a nivel inventivo se refiere, llamo la atención de ese Despacho a la definición de dicho requerimiento realizado por oficinas extranjeras que resultan relevantes en el presente caso. La legislación canadiense establece que la materia definida en las reivindicaciones de una patente no debe resultar obvia para una persona versada en el arte.[33] Por su parte, la legislación australiana determina que una invención involucrará nivel inventivo cuando al compararla con el arte previo, ésta no resulta obvia para una persona versada e el arte relevante a la luz del conocimiento general tal como existía antes de la fecha de prioridad.[34] Así mismo, la legislación estadounidense dispone que una patente no debe ser otorgada para una invención que aunque resulte novedosa, se base en diferencias que sean obvias para una persona versada en la materia.[35] Por último, la legislación china define que el nivel inventivo se presenta cuando una invención comparada con la tecnología existente presenta características notables y un progreso evidente.[36]

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[33] Canadian Patent Act, 1993, c. 15, s. 33: (Source: http://laws.justice.gc.ca/en/P-4/257647.html)

28.3 The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to

(a) information disclosed more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and

(b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.

[34] Australian Patents Act 1990 - Act Compilation (current) - C2006C00620: (http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/framelodgmentattachments/BBFB77E417068985CA257210007DE3DB)

(2) For the purposes of this Act, an invention is to be taken to involve an inventive step when compared with the prior art base unless the invention would have been obvious to a person skilled in the relevant art in the light of the common general knowledge as it existed in the patent area before the priority date of the relevant claim, whether that knowledge is considered separately or together with the information mentioned in subsection (3).

(3) The information for the purposes of subsection (2) is: (a) any single piece of prior art information; or (b) a combination of any 2 or more pieces of prior art information; being information that the skilled person mentioned in subsection (2) could, before the priority date of the relevant claim, be reasonably expected to have ascertained, understood, regarded as relevant and, in the case of information mentioned in paragraph (b), combined as mentioned in that paragraph.

[35] US Patent Laws. TITLE 35 - PART II - CHAPTER 10 > § 103.
(http://www.uspto.gov/web/offices/pac/mpep/documents/appxl_35_U_S_C_103.htm#usc35s103)

Conditions for patentability; non-obvious subject matter. A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[36] Patent Law of the People's Republic of China
(http://www.sipo.gov.cn/sipo_English/flfg/zlflfg/200203/t20020327_33872.htm)

Article 22. Any invention or utility model for which patent right may be granted must possess novelty, inventiveness and practical applicability.

Novelty means that, before the date of filing, no identical invention or utility model has been publicly disclosed in publications in the country or abroad or has been publicly used or made known to the public by any other means in the country, nor has any other person filed previously with the Patent Administration Department Under the State Council an application which described the identical invention or utility model and was published after the said date of filing.

Inventiveness means that, as compared with the technology existing before the date of filing, the invention has prominent substantive features and represents a notable progress and that the utility model has substantive features and represents progress.

Así las cosas, deseo subrayar que las 4 anteriores legislaciones han otorgado patentes en relación con la invención de la presente solicitud: patente estadounidense US 6.583.274 (anexo 6 de mi memorial del 03 de octubre de 2006), patente canadiense CA 2.372.206 (anexo 7 de mi memorial del 03 de octubre de 2006), patente australiana AU 772283 (anexo 8 de mi memorial del 03 de octubre de 2006) y aprobación de la patente por la autoridad china que ha sido anunciada.

Ahora bien, el artículo 18 de la Decisión 466 considera 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.[37] Así entonces, la evaluación del requisito de nivel inventivo es claramente equivalente entre las legislaciones ejemplificadas anteriormente y la legislación colombiana, por lo que resulta a todas luces inconsecuente e incoherente que en 4 de esas jurisdicciones se acepte el carácter inventivo de la invención reivindicada, pero en la colombiana, aunque conceptualmente el significado sea el mismo, se niegue, por lo de más basándose en premisas subjetivas, tal como lo demostré anteriormente.

De nuevo, aunque las concesiones de patentes en oficinas de otros países no son vinculantes en el sentido que obliguen a la SIC a tomar una decisión en el mismo sentido, es completamente cierto que los criterios de patentabilidad en los que deben fundamentarse el análisis de solicitudes de patente, en particular en cuanto al nivel inventivo se refiere, son análogos globalmente, y concesiones en otras jurisdicciones sugieren el cumplimiento de dichos requisitos, ya que claramente, los criterios de evaluación y estudio aplicados para determinar la novedad y nivel inventivo resultan equivalentes a los que la Superintendencia debe emplear, establecidos de manera semejante por las legislaciones de patentes a lo largo del mundo entero. Tan cierto es lo anterior, que además el Manual Andino de Patentes, al comentar el Artículo 46 de la Decisión 486, establece que una Oficina nacional competente podrá reconocer los resultados de exámenes de novedad o de patentabilidad efectuados respecto a la solicitud extranjera equivalente, como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad.[38] En el mismo sentido, es importante anotar que el mismo Tribunal Andino de Justicia ha citado a la

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Practical applicability means that the invention or utility model can be made or used and can produce effective results.

[37] Artículo 18.- Decisión 486: 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.

[38] Manual Andino de Patentes, Capítulo III, 7.3.

jurisprudencia de las Cámaras de Apelación de Oficina Europea de Patentes como antecedentes aplicables a la Decisión 486.[39]

De nuevo, aunque dichas patentes no son vinculantes para la oficina nacional, sí corresponden a un fuerte y claro indicio sobre el cumplimiento de los requisitos de patentabilidad de la invención reivindicada, puesto que como se demostró, los requisitos de novedad y nivel inventivo son requisitos universales y objetivos que se evalúan alrededor del mundo bajo estándares equivalentes.

Así las cosas, solcito respetuosamente a ese despacho pronunciarse claramente sobre los hechos y elementos concluyentes que conducen a la SIC a evaluar el nivel inventivo de una manera diferente a la realizada por ejemplo por las oficinas canadiense, australiana, estadounidense y china. No se entiende como pueden todas estas oficinas de manera independiente llegar a la misma conclusión, y la SIC a una exactamente contraria, aunque la legislación que define el requisito de nivel inventivo sea equivalente entre todas estas jurisdicciones.

4. Para terminar, de conformidad con lo establecido en el artículo 59 del Código Contencioso Administrativo, solcito respetuosamente que todos y cada uno de los puntos planteados en el presente recurso (en particular, los puntos 3.1 a 3.5) sean resueltos de manera individual, completa y motivada, respecto de las razones de hecho, derecho y/o conveniencia que lleven a esa Superintendencia a adoptar la decisión que estime frente a la solicitud aquí formulada.

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[39] Ver por ejemplo:

- Proceso 193-IP-2005, página 12, donde se cita que "el Tribunal a manera de orientación h a tomado como referencia criterios de las Cámaras de Recursos de la Oficina Europea de Patentes (OEP)" para el análisis de la falta de novedad.
- Proceso No. 216-IP-2003, página 11, donde se menciona a manera de referencia la interpretación y el alcance que dan las directivas de la Oficina Europea de Patentes al término terapia.
- Proceso No. 118-IP-2005, página 15, done donde el Tribunal cita a manera de referencia que "a partir de la "decisión adoptada en el caso T-506/95, las Cámaras han establecido que el estado de la técnica más próximo es aquel que...".
- Proceso 69-IP-2005, página 12, donde el Tribunal explica que "para analizar la existencia de nivel inventivo, las Cámaras de Recursos han adoptado el método llamado de "acercamiento problema-solución" (problem and solution approach)".
- Proceso No. 101-IP-2005, página 9, donde el Tribunal cita "a título de referencia, el criterio de las Cámaras de Recursos, según el cual los manuales u obras básicas deben formar parte de los conocimientos generales del experto medio".

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5. NOTIFICACIÓN

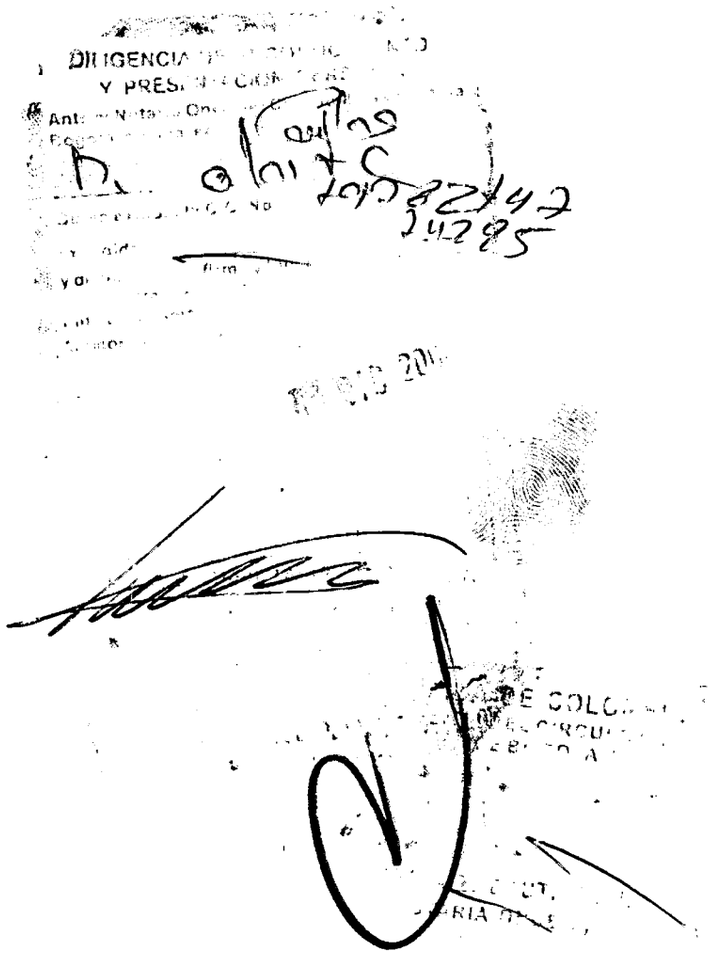
Recibiré notificaciones en mis oficinas ubicadas en el World Trade Center, Calle 100 No. 8A-37, Torre A, Piso 10, de Bogotá.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74295.

Anexos:

- **Anexo 1** - Apartes relevantes de: Dr. John R. Rudolph, A Study of Issues Relating to the Patentability of Biotechnological Subject Matter: Table of Contents. Gowling, Strathy & Henderson.
- **Anexo 2** - Australian Patent Office. Manual of Practice and Procedures. 1 December 2006. 2.5.3.3.5 "Obvious to Try".
- **Anexo 3** – University of Minesota. http://www.chem.umn.edu/groups/siepmann/research/phase.php
- **Anexo 4** - Apartes relevantes de: G.R. Desiraju, Nature Materials, 1, 77-79 (2002)
- **Anexo 5** - Apartes relevantes de: Sherry L. Morissette, et. Al., "High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids". Advanced Drug Delivery Reviews 56 (2004) 275– 300.
- **Anexo 6** - Dr. Sofia Papathoma. Patenting polymorphs at the European Patent Office. Barcelona, June 2006.



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Intellectual Property Policy

A Study of Issues Relating to the Patentability of Biotechnological Subject Matter: Executive Summary

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Executive Summary

Biotechnology is an important area of research, development and commercial activity. The prospects for commercial development in this area are considerable especially considering that so many sectors of the economy are affected by it. *Chapter 1* of the Report provides an overview of this situation and discusses the fact that Canada is currently well positioned to be a leader in Biotechnology. It goes on to suggest that the Patent system which helped to fuel the growth of the field may not be the best means by which to sustain the growth. This is explained as being due to a number of fundamental aspects of biotechnological subject matter which make it different from all other fields of technology. Consequently, the Report queries whether the patent system is the appropriate vehicle for securing intellectual property rights. A summary of objectives for the Report is provided which serve to focus the scope of the Report to the issues of "invention", "non-obviousness" and "novelty" as they relate to the patentability of biotechnological subject matter.

In order to set the stage for subsequent discussion, in *Chapter 2* "biotechnology" is broken down into three basic categories of subject matter which are encompassed by the term. These are the bio-matter itself which includes parts of biotechnology; methods and processes for making bio-matter; and, the uses of bio-matter of biotechnology. The chapter provides a brief review of basic biology and genetics in respect of the broad divisions of biotechnology in order to assist the reader in understanding the nature of the subject matter which is at the heart of the issue of invention in biotechnology.

Chapter 3 of the Report provides a discussion of the "concept" of invention from a somewhat philosophical perspective with a view to considering whether the subject matter of biotechnology can, at any level, be considered an invention. The discussion provided in the chapter is based on the perceptions and perspectives of the author drawing on a background in the medical sciences and patent law to analyze the issue. A discussion in relation to creation and discovery as those concepts relate to invention is provided with a conclusion that invention is a sub-set or separate class which shares features of both creation and discovery. One of the key elements proposed as a distinguishing feature of invention over creations and discoveries is the element of utility or applicability. It is concluded that invention is very much a subjective assessment and that there is nothing unusual or different about the subject matter of biotechnology which would result in a finding that there could not be

biotechnological invention.

A more pragmatic and substantive analysis of the question of invention in biotechnology is presented in *Chapter 4* where the Report provides discussion on the elements of patentable invention as this concept is understood in Canadian practice. An overview of the philosophical basis for the patent system is first provided with the preliminary recitation of the current definition of "invention" as found in the Canadian *Patent Act*. The Report then considers wh ether biotechnology subject matter fits within the scope of the legislative definition highlighting in particular, exceptions to proper subject matter including methods of medical treatment, human beings and higher life forms.

In respect of higher life forms, the enumerated categories which describe the "proper subject matter" of statutory invention are discussed with particular attention to the terms "manufacture" and "composition of matter." In this part, discussion is provided with respect to the scope of patent protection which may be available in respect of biotechnological subject matter with an example of a higher life form highlighted. Related issues such as the problem of progeny are discussed with specific reference to the potential for infringement by progeny and the problems of infringement analysis under the doctrine of equivalents.

The Report then turns to the questions of statutory invention which necessarily flow once proper subject matter has been found. These questions are contained in the elements of "novelty", "utility" and "obviousness." Each of these elements is discussed briefly with an overview of the current Canadian position or standards in respect of their evaluation or assessment. The Report then examines whether biotechnological invention fits within those standards, with an emphasis on those aspects which are of particular concern in biotechnology. The Report concludes that there is nothing about biotechnology that requires a review of the standard of utility as applied in Canada. Further the Report concludes that the only unusual aspect of biotechnology in respect of analysis of the element of novelty is in respect of products of nature. Consequently, issues relating to the "product of nature" doctrine are discussed in greater detail.

Arising from the determination of non-obviousness, the chapter provides consideration of the "worth a try" doctrine and *desideratum* inventions are considered as they are stated to be intermingled with the analysis of the "worth a try" doctrine. Following this is a consideration of the "technicians skilled in the art." The discussion under this heading quickly focuses on the expertise of Examiners in the Patent Office as it is these individuals who are called upon daily to assess this element of the test for non-obviousness.

The Report concludes in this chapter that with respect to invention in biotechnology the "skilled technician" is likely to be a Ph.D. researcher and may more likely be a composite research team. This is a direct result of the complexity of the subject matter of biotechnology. The Report also concludes that the mere complexity of biotechnological subject matter should not be the basis upon which a change is sought or brought to the standard of non-obviousness.

Chapter 5 is the final chapter and it presents the recommendations of the Report. In this chapter the Report indicates that there are three outstanding issues which, arguably, are preventing Canada from being a world leader with respect to providing rights to innovators in biotechnology. Namely, the question of patentability of higher life forms; the patentability of products of nature; and the problems with progeny.

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The Report recommends that higher life forms be patentable and recommends amendments to the *Patent Act*, in order to achieve this result. As a consequence of this recommendation, the Report provides a farmer's exemption with respect to the potential problems with progeny. Also introduced is a proposal to limit patentability of higher life forms to non-human subject matter.

The Report also recommends that the current Canadian standards applied in the assessment of novelty and non-obviousness are acceptable and need not be changed in order to accommodate biotechnological innovation.

Finally, the Report recommends that in order to further encourage the biotechnology industry in Canada, a separate piece of legislation should be enacted in order to encourage research and development with respect to "products of nature."

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Intellectual Property Policy

308b)A Study of Issues Relating to the Patentability of Biotechnological Subject Matter: Patentable Invention

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Chapter 4 - Patentable Invention

Section 4.2

New, Useful and Unobvious - Does Biotechnology Fit?
Specific Issues of Patentability

Then the remaining elements of statutory invention which must be considered are whether the subject matter has novelty, is useful and is unobvious. There are separate considerations in respect of each of these remaining elements and these will now be discussed. However, what is set out below provides only a brief overview of the guiding principles by which these elements are assessed regardless of the subject matter. Under each heading specific issues peculiar to biotechnology will be discussed in detail.

A. Utility

According to the enumerated definition of invention utility is the last mentioned element. It requires that the subject matter under consideration must be useful i.e., it must have utility. Caselaw supports the view that inventions, which are the subject of a patent, are, *prima facie*, presumed to be useful.(144) This accords with the definition of invention given above in the discussion of the concept of invention, however, the question in patent law is if mere utility/applicability is enough. Arguably it is enough. Indeed, Canadian caselaw suggests that there must simply be some practical utility, if not a commercial aspect. In the words of Mr. Justice Dickson (as he was then) in *Consulboard Inc. v. MacMillan Bloedel (Saskatchewan) Ltd.*,(145) quoting with approval from an authoritative British legal reference material (Halsbury):

> "...the practical usefulness of the invention does not matter, nor does its commercial utility, unless the specification promises commercial utility, nor does it matter whether the invention is of any real benefit to the public, or particularly suitable for the purposes suggested....[I]t is sufficient utility to

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C. Non-obviousness

An important consideration and the one which, by itself or in conjunction with issues relating to novelty, is more likely to hamper making a finding that there is patentable invention is the consideration of non-obviousness. As indicated above, this element of invention is derived from the judiciary(174) and in spite of many formulations used by our Courts when dealing with the different aspects of the question of "invention", it is clear that they are searching for an answer to the issue of obviousness. Many Canadian decisions also refer to inventiveness, or, the so-called "inventive step"(175). However, the analysis inevitably returns to whether the invention was obvious.This is hardly surprising. Obviousness, after all, is intimately related to the issue of novelty or newness because if something is obvious then it is not likely to be considered to be new. Yet, something can be new in the literal sense of the word even though it was obvious because it was never actually produced in a tangible form before. But as the Courts have correctly interpreted, this is not the type of "new" contemplated by Parliament which is willing to exchange a 17-20 year right to prevent others from practising an invention for the knowledge behind the "new" subject matter. The newness that the *Patent Act* seeks to protect must be imbued with this further quality which has been formulated by the Canadian judiciary into the concept of non-obviousness.

The test, for non-obviousness in Canada was well formulated in a the Federal Court of Appeal in *Beloit Canada Ltd. v. Valmet OY*.(176) at p 294, by Mr. Justice Hugessen. (177) His Lordship said as follows:

> "The test for obviousness is not to ask what competent inventors did or would have done to solve the problem. Inventors are by definition inventive. The classical touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right. The question to be asked is whether this mythical creature (the man in the Clapham omnibus of patent law) would, in light of the state of the art and of common general knowledge as at the claimed date of invention, have come directly and without difficulty to the solution taught by the patent. It is a very difficult test to satisfy."

Thus the question which must be answered in considering whether there is invention is whether the skilled technician(178) with "the state of the art and of common general knowledge(179) as at the claimed date of invention"(180) is able "...[to] come directly and without difficulty to the solution(181) taught by the patent."

Invention in biotechnology has arguably been more susceptible to attacks on the basis of obviousness given the underlining perceptions that many of the products are "products of nature" and because many procedures and methods which are used to prepare products of nature have become fairly standard and well known. Intermixed with these problems is the fact that the examiners concerning biotechnology cases are usually highly academically trained and consequently arguably taking a more sophisticated view to addressing this issue. Consequently the report will now examine these three closely related issues which are of concern with respect to addressing the non-obviousness inquiry.

The Worth a Try Doctrine

The inquiry relating to the obviousness of an invention is closely associated with the question of predictability in so far as it concerns questions of whether the "invention" was "worth a try" based on the prior art available to one who is skilled in the art. Notwithstanding that the "reasonable predictability" assessment is employed to help delineate the scope of a patentable invention,(182) it is an inevitable part of the obviousness assessment to determine whether in fact, it can be said that the predictability question if answered in the affirmative, confirms that the invention is obvious and was "worth a try." If something was worth a try, then the result is arguably predictable, i.e., the result is expected, or obvious.

In the U.K. the standard of obviousness on this point is that the skilled person would have thought that the invention was "well worth trying in order to see whether it would have beneficial results."(183) It has been stated differently in respect of a research groups but amounts to the same test: Would the research group] have been directly led to try the idea that it might well produce a useful result."(184)

In the United States, the formulation of the Courts is put in the words "would it have been obvious to try." This conclusion by a court on the issue of obviousness must only be arrived at where the prior art clearly indicates that it would, in fact, be obvious to try. This has also been formulated as a "reasonable expectation of success"(185) From the decision *in Re Wright* (1988)(186) the Federal Circuit reversed a decision of the Board of Patent Appeals and Interferences holding "the question is whether what the inventor did would have been obvious to one of ordinary skill in the art attempting to solve the problem upon which the inventor was working."(187) In other words, an invention is patentable, or non-obvious unless the prior art suggests the actual result which is claimed in the invention. This approach is in most respects, except for the specific wording, quite similar to the English test.(188) The key feature is that the idea to be tried must led to a useful result. Notwithstanding this approach, the "obvious to try" doctrine had caused considerable trouble for invention in biotechnology in the United States because patents were refused for DNA sequences coding for amino acid sequence where the protein amino acid sequence had been published. On this basis the U.S. PTO would issue a rejection on the basis that creating the corresponding DNA would have been obvious or "worth a try". Even where only a partial amino acid sequence was available.(189)

In Canada, this doctrine is tied to the aspect of the obviousness inquiry discussed above which relates to being led "directly and without difficulty to the solution." The leading case in Canada on this doctrine is *Faberwerke Hoecht A/G v. Halocarbon (Ontario) Ltd.*(190) where Mr. Justice Pigeon speaking for the majority of the Supreme Court of Canada first quoted from the trial level decision where it was held that the defence urged by the defendant, that carrying out the patented process was "worth a try" in the light of the prior art, failed. He then quoted Mr. Justice Jackett of the Federal Court of Appeal who overturned the trial judge on this point. Jackett, C.J. stated:

> "I do not think that the learned trial Judge's assumption is correct as a universal rule. I would not hazard a definition of what is involved in the requirement of "inventive ingenuity" but, as it seems to me, the requirement of "inventive ingenuity" is not met in the circumstance of the claim in question where the "state of the art" points to a process and all that the alleged inventor has done is a certain whether or not he process will work successfully."(191)

In response to this, Mr. Justice Pigeon stated the Canadian position on this doctrine:

> "In my view this statement of the requirement of inventive ingenuity puts it much too high. Very few inventions are unexpected discoveries. Practically all research work is done by looking in directions where the "state of the art" points. On that basis and with hindsight, it could be said in most cases that there was no inventive ingenuity in the new development because everyone would then see how the previous accomplishments pointed the way. The discovery of penicillin was, of course, a major development, a great invention. After that, a number of workers went looking for other antibiotics methodically testing whole families of various micro-organisms other than *penicillium notatum*. This research work was rewarded by the discovery of a number of antibiotics such as chlormycetin...as mentioned in *American Cyanamid Co. v. Berk Pharmaceuticals Ltd.*,[1976] R.P.C. 231, where Whitford, J., said (at p.257): "A patient searcher is as much entitled to the benefits of a monopoly as someone who hits upon an invention by some lucky chance or inspiration". I cannot imagine patents obtained for antibiotics and for various processes for their production being successfully challenged on the basis that the discovery of penicillin pointed the way and there was no inventive ingenuity in the search for other antibiotics and in the testing and the development of processes."

His Lordship then went on to quote various formulations of the test of obviousness. (192) Consequently, diligent, "sweat of the brow" work in a directed manner is likely not to be viewed as obvious in Canada. It is the view of this author that of the three approaches, namely, the U.S.'s "would it have been obvious to try"; the U.K.'s "was it well worth trying in order to see if it would have beneficial results" and the Canadians "to come directly and without difficult to the solution" the Canadian view is the most sensible. It is also least likely to do harm to biotechnological inventions seeking patent protection while recognizing that certain inventions will be obvious where the prior art leads directly to the invention, this view also recognizes that other inventions, which while seemingly obvious, such as *desideratum* inventions, are likely to be considered as non-obvious.

Desideratum Inventions

Inextricably linked with the "worth a try", "obvious to try" assessment are so-called *desideratum* inventions. These are the inventions where it is clear that a certain product or process or method is desired, and the route to achieving the result is also fairly straight forward, or at least appears to be. For example, in respect of research directed toward developing proteins, the research project typically begins with the discovery that a particular protein performs some desirable function. Understanding how this protein functions requires scientists to extract the target protein from a natural source. Subsequently, once the target protein has been purified, a next step is isolating the gene that expresses this protein and placing that gene in a suitable environment so as to allow for the production of the protein in large quantities. (193) While all of these steps seem fairly straightforward, as one commentator has suggested, in biotechnology the technology is simple in theory, but the elegant simplicity of concept hides "a mass of uncertainties and practical hurdles which need to be overcome before success can be achieved."(194)

Earlier, the ethnobotanical approach to invention was discussed and such an approach can arguably be classified as a *desideratum*, although, such "inventions" are also, equally, not as easy to achieve. This is particularly true in cases where the approach to invention is "prospecting." In many respects this approach is really no

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Updates

Part Amended	Amendment Reason	Updated
2.13.10.1 Guidelines for Using IPRP/IPERs and Other Foreign Examination Reports (FERs) in Examination	The information contained in Annex E (Guidelines for Using FERs) has been incorporated into 2.13.10.	1 December 2006
Suggestions for Manual	Updated link to Improvement Log (Improvement Log issue P568)	1 December 2006
1.1.19 Annexes A-Z 1.2.10 Annexes A-C 1.4.8 Annexes A-B 1.5.7 Annex A 1.6.7 Annexes A.1, A.2, A.3-C 1.7.11 Annexes A-C 1.8.12 Annexes A-G	Inclusion of informative titles on Annexes (for the Contents LHS screen of Robohelp) (Improvement Log issue P278)	1 December 2006
1.1.12.3 Reporting 1.3.8.2 Box I Basis of Opinion/ Report	Distinguish between ISO and IPEO and update links	1 December 2006
1.3.8.7 Box VI Certain Documents Cited	Clarification of priority dates for Box VI	1 December 2006
1.1.4.9 Issuing the Invitation to Pay Additional Search Fees	Correct and update links.	1 December 2006
1.2.4 Unity of Invention	Update to current procedure	1 December 2006

2.14.4.4 Replacing a Request for Standard Examination with a Request for Modified Examination 2.14.4.5 Fee Payable on Varying the Type of Examination	Updating procedures to be followed when a request for standard examination is replaced with a request for modified examination.	1 December 2006
2.1.2 Product Quality Standards	Revised Quality Standards	1 December 2006
1.3.8.5 Box IV Unity of Invention	Correct Link in 1.3.8.5.	1 December 2006
2.23.13.1 General Comments 2.23.13.10 Amendments to "other filed documents" (Including Basic Documents)	Clarifying that the abstract of a PCT application cannot be amended during the national phase.	1 December 2006
1.2.1 Procedural Outline - International Type Search 1.2.3 Classification and Search Indication	Changing instructions for paper-based Art 15(5) procedures to PAMS/electronic based procedures. (Improvement Log issues P264 & P280)	1 December 2006
2.11.2.3.10 Swiss Claims	Insertion of omitted text.	1 December 2006
2.13.8.2.4 Citing Non-Patent Literature 2.13.8.2.5 Forwarding Patent Literature with Reports	Clarification of procedures that should be followed when an applicant or attorney requests copies of patent or non-patent literature.	1 December 2006
1.3.8.1 Front Page and Notification Application Details	Correction of a Volume 1 error in relation to filling out IPER/IPRPII forms regarding attached annexes. (Improvement Log issue P373)	1 December 2006
2.5.1.4.2 Operation of Section 7	Correction of typographical errors.	1 December 2006
1.8.8.2 Examination Procedure	Clarification of when it is appropriate to cite matter contained in an FER	1 December 2006
1.1.12.5.8 Date of Actual Completion of the Search	Link to IPE Quality Checklist added	1 December 2006

2.22.6.2 Conclusion of Re-examination Otherwise	Updated to include procedures for the handling of Ecases.	1 December 2006
2.11.3.7 Inclusion of References	Clarifying that background or prior art documents referred to in a specification should be publicly available.	1 December 2006
2.31.4.6 Ground (3): Subsections 18(2) and (3)	Deletion of the text 'lichens'.	1 December 2006
Annex A - Section 104 Amendments During Opposition or Section 28 Proceedings: Check Sheet Annex B - Assembling Accepted Specifications Guidelines Annex C - Assembling Specifications Guidelines: Voluntary Amendments	Correction of minor typographical errors. Annexes converted to HTML format.	1 December 2006
2.13.9.2 Original Searching	The paragraph which indicates that the search should be made of complete specifications filed up to 12 months from the filing date of the specification under examination has been changed to reflect current practice.	1 December 2006
2.7.2.4 The Issue of Repeatability	Changes to add that the requirement of repeatability for a life form may be met through a deposit under the Budapest Treaty.	1 December 2006
2.7.2.3 Best Method of Performance of an Invention Involving a Life Form	Changes to provide specific examples of methods that may be used to produce a new life form.	1 December 2006
2.7.2.2 Some Specific Requirements for the Written Description of Plant Varieties	Changes to explain that colour photographs, with reference to a standard horticultural chart may be used to meet the full description requirement for a plant variety.	1 December 2006
2.7.2.1 General Requirements of the Description	Changes to 2.7.2.1 to explain that an applicant wishing to rely on the Budapest Treaty for full description must also provide some written description of the features of the invention in the specification.	1 December 2006
2.7.1 General Considerations and Definitions	Changes refer to the specific exclusions in sec 18(2) and 18(30 of the Patents Act and summarise the conclusions drawn from Ranks Hovis McDougall Ltd's Application on patenting of life forms.	1 December 2006
All Annexes in Volume 4	Informative titles for the Annexes	1 December 2006

1.1.11 Search Procedure 2.5.2.5.5 Would the Person Skilled in the Art Consider it Obvious 2.5.2.5.6 Inventive Step Objections Involving a Combination of Documents Annex E - Guidelines for Using IPRP/IPERs and FERs in Examination	Amendment in light of our agreed practice re mosaicing.	1 November 2006
2.13.5.9 Considering Subsection 45(3) Search Results	Clarifying that an applicant must file sec 45(3) search results, regardless of whether the Office is already aware of the results or whether they include only 'A' documents.	1 November 2006
2.9.2.2 Short History of Manner of Manufacture 2.9.2.5 Discoveries, Ideas, Scientific Theories, Schemes and Plans 2.9.2.10 Business Methods	Revision of the manual in the light of the Fed Ct decision, Grant v Commissioner of Patents, 18 July 2006.	1 November 2006
2.11.2.2 Rules of Construction	Correction of minor typographical errors.	1 November 2006
2.4.4.5 Resiling from Acknowledged Prior Art 2.11.10 Provisional Specifications s 40(1) 2.12.1 Priority Date of Claims 2.12.2 Priority Date Issues Specific to Associated Applications 2.13.8.1 Restriction of the Extent of the Report 2.13.8.2.1 Degree of Specificity Required When Reporting 2.13.8.2.4 Citing Non-Patent Literature 2.13.8.2.6 "Whole of Contents" Approach 2.13.9.3 Restricting the Search 2.13.9.4 Discontinuing the Search 2.13.9.5 Reserving the Search 2.13.11.1 Notifications 2.17.5 Published Documents	Replacement of 'sec 45(1)(b)' with 'sec 45(1)(c)'. The manual incorrectly referred to sec 45(1)(b) through not having being updated when the Patents Act was amended in 2000.	1 November 2006
2.11.5.4 Different Combinations of Intergers	Correction of spelling error in title	1 November 2006
2.13.14 Copying of Material and Copyright Implications	Correction of hyperlinks to the Copyright Act	1 November 2006

2.15.12 Objections Based on Sec 45(3) Search Results 2.15.13 Objections Based on a Sec 27 Notice 2.15 Annex A (deleted)	Inclusion of procedures that should be followed when the final date for acceptance for an Ecase requires updating.	1 November 2006

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2.5.3.3.5 "Obvious to Try"

The decision of the High Court in *Aktiebolaget Hassle v Alphapharm Pty Ltd* [2002] HCA 59 (12 December 2002) established that the "obvious to try" test which had been applied in the lower court decisions on this matter and in numerous UK decisions was not part of Australian law. The majority of the High Court explicitly rejected the approach taken in cases decided under the 1977 UK Act which equate the "obvious to try" approach with "worth a try" and "well worth trying". They found that the United States law on obviousness was to be preferred as it was more consistent with that adopted in the Australian decisions in *3M v Beiersdorf* [supra] and *Wellcome Foundation v VR Laboratories* [supra].

In the US, any criterion which adopts a notion of "obvious to try" has been rejected in a long series of decisions on '103 of the 1952 US Act. The US decision in re *O'Farrell* 853 F 2d 894 (1988) distinguished the tests of "obvious to try" and "obvious" by referring to two kinds of errors which occur when applying the standard of "obvious to try":

"In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.....in others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."

The Canadian approach is similar to the US. A key Canadian Supreme Court decision (*Faberwerke Hoecht A/G v Halocarbon (Ontario) Ltd* (1979), 42 C.P.R. (2d) 145 at 155) noted that:

"Very few inventions are unexpected discoveries. Practically all research work is done by looking at directions where the "state of the art" points. On that basis and with hindsight, it could be said in most cases that there was no inventive ingenuity in the new development because everyone would then see how the previous accomplishments pointed the way."

As a consequence, the Canadian test for obviousness is a stringent test of whether a skilled worker would have been led "directly and without difficulty to the solution". A paper "A study of issues relating to the patentability of biotechnological subject matter: patentable invention" (available on the Internet) discussed this test specifically in relation to biotechnology and concluded that diligent "sweat of the brow" work in a directed manner is not likely to be viewed as obvious in Canada. The paper noted that while biotechnology is simple in theory and the steps straight forward, the "elegant simplicity" of the concepts hide "a mass of uncertainties and practical hurdles which need to be overcome before success can be achieved". The same logic would also apply to chemical or pharmaceutical patents and

examiners in all these areas should ensure that their inventive step objections are properly taken and that they do not stray into the "obvious to try" test. This is particularly true where there have been "unexpected results" as this is often an objective basis for establishing non-obviousness in law.

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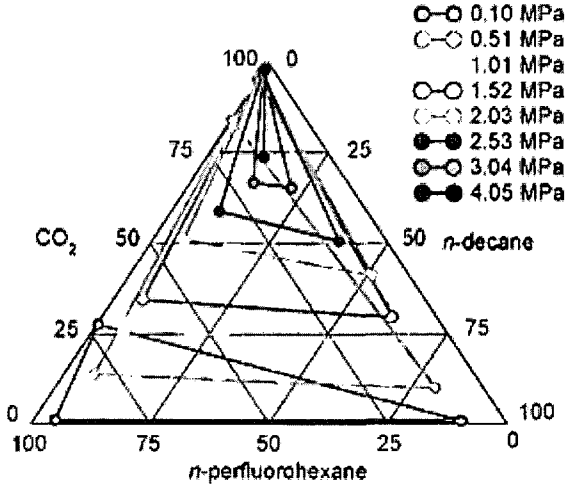
Phase Equilibria

Phase equilibria play a central role in most chemical processes ranging from fractional distillation of organic mixtures, extraction with selective solvents, to crystallization of specfic forms of drug molecules. In fact, such separation processes are often dominating productions costs for many chemicals and pharmaceuticals. The prediction of phase equilibria of multicomponent mixtures is one of the grand challenges for molecular simulation requiring both accurate force fields and efficient sampling algorithms. The ternary liquid-liquid-vapor phase diagram below was predicted from a simulation of a three-component mixture that may find potential use for biphasic catalytic systems. At elevated pressures, carbon dioxide swells the two liquid phases and these expanded phases become more miscible. Above the upper critical solution pressure, the catalytic reaction can progress rapidly in the single liquid phase. Thereafter, the pressure is lowered and phase separation occurs. Thus, the separation of the fluorous catalyst (soluble in the fluorocarbon phase) from the organic products (soluble in the hydrocarbon phase) is greatly facilitated.



In the area of phase equilibria, the Siepmann group's research interestes are directed toward tunable solvents, adsorbed films, and polymorphism and solvate formation of pharmaceutical solids. There is great need to develop environmentally benign and highly tunable process solvents that can replace chlorinated or fluorinated solvents. Molecularly-thin fluid films adsorbed on solid substrates play a central role for lubrication and as

protective surface coating. Polymorphism, the ability of a given molecule to crystalize into different solid forms or to form crystalline solvates upon addition of stochiometric amounts of solvent, is an important problem for the pharmaceutical and food industries because certain polymorphs have desirable properties (e.g., stability, bioavailability, or dissolution characteristics) and individual polymorphic forms may be patentable. One of the continuing scandals of science, as emphasized by John Maddox (former editor of *Nature*), is that there is no general method for the predicition of crystal structures from molecular formulae, and that designing organic solids with specific and desired properities remains only a dream [G.R. Desiraju, *Nature Materials*, **1**, 77-79 (2002)].

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Chemistry Department Research News:

- February 23, 2000: Molecular Modeling of Supercritical Fluid Extraction
- September 6, 2000: Solute Partitioning Between Water and (Dry or Wet) 1-Octanol
- July 10, 2002: Solvation of Napthalene in Supercritical Carbon Dioxide: Are Large Negative Partial Molar Volumes Related to Local Density Enhancements?
- July 9, 2003: Temperature Dependence of Transfer Properties: Importance of Heat Capacity Effects
- Jan 5, 2005: Simulating Green Solvents
- February 1, 2006: Simulating Fluid Phase Equilibria of Water from First Principles

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Recent Phase Equilibria Publications:

B.L. Eggimann, J.I. Siepmann, and L.E. Fried,
'Application of the TraPPE force field to predicting isothermal pressure-volume curves at high pressures and high temperatures,'
Intl. J. Thermophys., submitted for publication.

N. Rai, J.L. Rafferty, and J.I. Siepmann,
'Prediction of the bubble point pressure for the binary mixture of ethanol and 1,1,1,2,3,3,3-heptafluoropropane from Gibbs ensemble Monte Carlo simulations using the TraPPE force field,'

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Cryptic crystallography

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A method for predicting crystal structures from just molecular formulae has eluded scientists for more than 50 years. The problem is currently being addressed by two very different approaches. But which one is more likely to succeed?

A molecule can be defined, in strictly geometrical terms, as a group of atoms in which the distance from any one atom to at least one other in the group is much smaller than any distance between atoms in different groups. Such a definition was given nearly 50 years ago by the great Russian crystallographer Alexander I. Kitaigorodskii[1,2]. Interactions between atoms within a molecule are therefore much stronger, by almost two orders of magnitude, than those between atoms from different molecules. This is why we have a far less precise idea about the ways in which molecules assemble in condensed media than we have about the ways in which atoms bond within molecules. Trying to establish *a priori* exactly how molecules come together in crystals is in fact a very difficult problem, and is known by the name 'crystal structure prediction' (CSP). CSP is a problem of formidable proportions because the solution requires a complete understanding of the mechanism for crystallization — the ultimate goal of solid-state supramolecular chemistry.

The problem is stated easily enough. Given the structural formula of a small organic molecule with fewer than, say, 20 non-hydrogen atoms (A), and with no more than two or three conformationally flexible carbon–carbon or carbon–A bonds, is it possible to predict its crystal structure with the kind of accuracy that is obtained with an X-ray diffractometer? In other words, we are looking to predict the size of the crystal unit cell, correct to about two decimal places, the space group symmetry, and the positions of all the atoms in the asymmetric unit. Research groups from all over the world have taken up this challenge and much of their effort has been streamlined in the form of two blind tests conducted by the Cambridge Crystallographic Data Centre (CCDC) in 1999 and 2001. The crystal structures of three molecules were determined, and the results held in confidence by an independent referee. Some 18 groups were invited to submit up to three ranked predictions for each molecule within four months. To keep things 'easy', the crystal structures were restricted to the ten most common space groups, to have only a single molecule in the asymmetric unit, and to be ordered and unsolvated. Yet, out of a total of nearly 75 predictions made in the two tests combined, the number of correct predictions was fewer than ten. No research group predicted all three structures correctly in either of the two tests[3,4].

Figure 1 **Two-dimensional closest packing as seen in M. C. Escher's 'Horsemen'. For molecules to come together in this way, all portions of their surfaces must be equally 'sticky'. The presence of a few 'stickier' regions leads to distortions from ideal close packing, and eventually to a breakdown of the geometrical model.**

Back in 1988, John Maddox (former editor of *Nature*) pointed to the need for CSP in materials research[5]. He wrote that it was "one of the continuing scandals" that a general method for the prediction of crystal structures from molecular structures was not yet available. This provocative piece was much quoted in articles devoted to the emerging subject of crystal engineering — the dream of designing organic solids with specific and desired properties[6]. Later, in 1996, Philip Ball wrote that "a large part of the scandal remains"[7]. Maddox was hopeful at the time about predicting structures for extended inorganic solids,

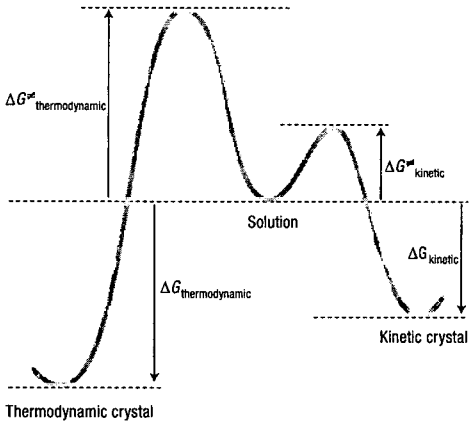

Figure 2 **The Curtin–Hammett principle: the most stable or the fastest? The route to the kinetically favoured crystal would be the fastest, because the activation energy (G) barrier to that state is lower ($\Delta G^{\neq}_{kinetic}$). The thermodynamically favoured crystal would take longer to form because the activation barrier is much higher ($\Delta G^{\neq}_{thermodynamic}$), but it would be more stable because the final energy state is the lowest. If the same crystalline form is both kinetically and thermodynamically favoured, polymorphism is highly unlikely.**

but for organic molecular solids one can say that, 15 years on, the situation has not changed greatly[8]. Because we still lack a general and accurate method for CSP, there is no known example of a designed crystalline molecular material in wide technological use. Perhaps it was not appreciated how difficult CSP really is.

The original, and by far the more popular, approach to CSP is based on geometry and goes back to Kitaigorodskii[1,2]. Interactions between molecules are assumed to be very weak and lacking in directionality; it is further assumed that all interactions taper off at longer distances in roughly the same way. In this isotropic model, crystal structures are governed by close packing. The structure that makes the most economical use of space is the best one, and molecules crystallize so that the bumps in the surface of one fit into the hollows in the surface of the other (Fig. 1). Using this model as a starting point, computational techniques can generate several hypothetical crystal structures that approximately satisfy these close-packing conditions[9]. These calculations generate many putative structures, maybe up to 20, within 2 kJ mol^{-1} of the lowest energy structure, known as the 'global minimum'[10]. The number of structures generated is large because the intermolecular interactions are weak.

Of course, most molecules do not live in these idealized isotropic conditions, and so the proponents of this school of thought introduce various modifications into their calculations to take into account the electrostatic and directional effects that are unquestionably present in organic crystals. Hydrogen bonding, being the prime example of such effects, is very important in crystal structures. Molecules that can hydrogen bond always do so, and this needs to be taken into account in CSP. Some of the resulting computations are quite sophisticated, but in the end, the close-packing approach has two, seemingly insurmountable, problems.

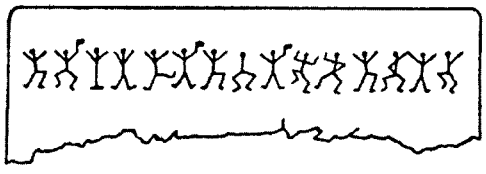

Figure 3 **Cryptology and crystallization: hidden but definite. Crystallography needs its own Sherlock Holmes to crack the secrets of molecules as they assemble into crystals.**

"Dancing Men" sourced from *The Complete Adventures of Sherlock Holmes* by Sir Arthur Conan Doyle. Published by Martin Secker and Warburg Ltd, London, 1981.

First, the fluctuations and variations in the interactions are too numerous to handle properly, and depend on molecular structural features that may be quite remote from the site of the interactions themselves[11]. Second, the global minimum structure is not the observed structure because kinetic effects dominate. In other words, one cannot be sure of getting the best structure; usually it is the one that can be obtained the most quickly.

All chemical reactions are subject to the dictates of thermodynamics and kinetics — how far and how fast. Most chemical reactions that require the making and breaking of covalent bonds are kinetically controlled. On the other hand, supramolecular reactions that take place in solution are thermodynamically controlled and take place under conditions close to equilibrium[12]. But crystallization is different from other supramolecular reactions in that it is kinetically controlled. Like other kinetic processes, the outcome of crystallization depends a great deal on experimental variables such as temperature, solvent, rates of heating and cooling, impurities and shock. A particular crystal form may not be the global minimum in terms of free energy, but it may be the most common outcome because it is kinetically dictated by the reaction conditions.

The appearance of these 'local minimum' structures during crystallization makes a mockery of methods that look only for the global minimum. In the 1950s, David Y. Curtin and Louis P. Hammett showed that kinetic products may dominate, or even be formed exclusively in chemical reactions[13]. The Curtin–Hammett principle states that the distribution of products in a reaction that has many pathways need bear no relation to the relative stability of those products. Exactly the same rule holds for crystallization. Given a collection of molecules that can come together in many ways, the favoured route has little to do with the stability of the final ensemble, but rather with how fast this route can be travelled (Fig. 2). But if kinetics and not thermodynamics dominates, then a full dynamic treatment is required in CSP. This is beyond our most fanciful dreams. State-of-the-art dynamic simulations are now in the millisecond range, whereas crystal growth may take hours or even days. The maximum cluster size handled by the calculations may be around 10,000 atoms, of which 50% are surface atoms, and so the objects being modelled will have little in common with real crystals. In short, the events that take place during crystallization cannot be modelled computationally.

If *ab initio* prediction of kinetically controlled crystal forms is impossible, what is the solution? It is a basic rule of cryptology that even the most difficult of codes can be broken if a sufficient number of examples is available. Sherlock Holmes was able to decipher the sinister meaning of the messages in the *The Adventure of the Dancing Men*, because he started with the correct assumption that the figures occurring the most often in the bizarre messages corresponded to the letters 'S' and 'E', which occur the most frequently in the English language (Fig. 3). The same fingerprinting approach may be adopted in CSP.

Consider for example, molecule I, which was used in the 2001 CCDC blind test (Fig. 4). This molecule can, in principle, assemble into crystals in one of two ways through what is called the dimer synthon, II, or

the catemer synthon, III. The term 'synthon' or 'supramolecular synthon' refers to small, stable structural units that are readily accessed during crystallization[14]. The dimer is more stable than the catemer, but a crystal that contains the catemer grows more quickly. This is because the catemer can propagate by generating hydrogen bonds, which are strong and directional. In contrast, the dimer can associate with other dimers only through weak van der Waals interactions.

If we now check the Cambridge Structural Database, a depository of more than 250,000 accurately determined small molecule crystal structures (http://www.ccdc.cam.ac.uk/prods/csd/csd.html), we will find that a majority of molecules that are similar to molecule I give catemers rather than dimers. Coupling this information with computations that are generated using the close-packing approach (and that predict a crystal structure based on a dimer) results in a new ranking of the structures from which the experimental catemer structure hopefully emerges as the winner[15]. In the search for kinetically controlled crystal structures, such a method is on a surer footing than mere computations because it relies in part on experimental data. If a particular kind of structure has been formed often enough in the past, it is more likely that it will reappear.

But many questions remain. What is meant by molecular similarity? Is the identification of similar molecules a subjective matter? What parts of a molecule are the most critical in terms of defining the crystal structure that is ultimately formed? How large a database of crystal structures is required before most molecular recognition situations are covered? And most critically, what happens when more than one crystal form occurs experimentally?

The question of polymorphism — when more than one crystalline form exists — takes the difficult problem of CSP to an even higher level. Crystallization is a highly specific event, so how do alternative pathways become viable[16]? We know they do because for some categories of molecules, polymorphism is not rare. About 10% of organic substances may yield polymorphs easily, with another 20–30% possibly occurring if more exotic experimental conditions are used (such as high and low temperatures and pressures, hydrothermal methods, laser irradiation, annealing, supercritical liquids and unusual solvents). A plausible scenario is one in which either or both of the kinetic and thermodynamic forms are obtained during recrystallization. Many commercial substances, such as drugs or dyestuffs, produce many polymorphs, making this issue of critical importance to industry.

So CSP is not only a great scientific challenge, but has many implications in the chemical industry in areas such as catalysis, pharmaceuticals and separation. A reliable and general method for the CSP of polymorphic forms of a drug would transform the multibillion-dollar pharmaceutical industry. Perhaps, and given the great fundamental and practical importance of CSP, a good case can be made for a much bigger coordinated international effort to solve this problem, bringing CSP into the league of protein folding and the Human Genome project. In the context of CSP of polymorphs, pertinent questions are: (1) Is it possible to determine from the molecular structure whether a compound will be polymorphic? (2) If so, how many polymorphs will it have? (3) Under what conditions will these polymorphs be obtained? (4) Can one predict from the molecular structure whether a compound will crystallize with the solvent of crystallization, especially water? (5) Under what conditions will these pseudopolymorphs, or hydrates, be obtained?

These are very hard questions, but then the whole issue of CSP is full of extreme difficulty: the interactions between molecules are numerous, weak and variable; the supramolecular behaviour of a functional group acutely depends on the nature and even the locations of other functionalities in the molecule; there are many closely packed, low-energy structures; one can never really tell in advance whether polymorphism will occur or not; kinetics competes with thermodynamics; and one has no way of knowing from the molecular structure whether the kinetic structure would also be favoured thermodynamically. Research problems in CSP and crystal engineering are like the Himalayan Mountains. One tackles them because they are there, and one doesn't give up. But then, one comes face to face not only with Everest, but also with killers like Makalu, Lhotse and Annapurna — and in those magnificent ranges, peaks less than 20,000 feet are not even named.

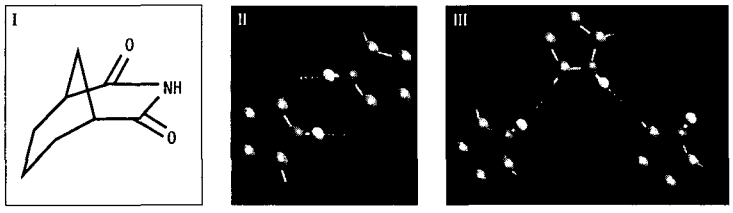

Figure 4 **A simple imide molecule in the 2001 CCDC blind test (I), and two alternative supramolecular synthons (II and III) that it can form. Synthon III was found in the experimental structure.**

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High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids

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Received 21 August 2003; accepted 6 October 2003

Abstract

The concepts of high-throughput (HT) screening and combinatorial synthesis have been integrated into the pharmaceutical discovery process, but are not yet commonplace in the pharmaceutical development arena. Emerging strategies to speed pharmaceutical development and capture solid form diversity of pharmaceutical substances have resulted in the emergence of HT crystallization technologies. The primary type of diversity often refers to polymorphs, which are different crystal forms of the same chemical composition. However, diverse salt forms, co-crystals, hydrates and solvates are also amenable to study in HT crystallization systems. The impact of form diversity encompasses issues of stability and bioavailability, as well as development considerations such as process definition, formulation design, patent protection and regulatory control. This review highlights the opportunities and challenges of HT crystallization technologies as they apply to pharmaceutical research and development.

Keywords: High-throughput; Crystallization; Polymorph; Solvate; Salt; Co-crystal

Contents

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doi:10.1016/j.addr.2003.10.020

1. Introduction

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug [1]. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties. Discovery and characterization of the diversity of solid forms of a drug substance provide options from which to select a form that exhibits the appropriate balance of critical properties for development into the drug product. Importantly, the desired properties may vary with each mode of delivery (i.e., oral, pulmonary, parenteral, transdermal, etc.), such that the solid form may differ for each optimized dosage form. Given these options, the choice and design of pharmaceutical solid forms can be critically important to successful drug development.

Solid form discovery and design depends on the nature of the molecule of interest and type of physical property challenges faced in its development. The preferred solid form is generally the thermodynamically most stable crystalline form of the compound [1,2]. However, the stable crystal form of the parent compound may exhibit inadequate solubility or dissolution rate resulting in poor oral absorption, particularly for water-insoluble compounds. In this case, alternative solid forms may be investigated. For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability [1,3,4]. Like the parent compound, pharmaceutical salts may exist in several polymorphic, solvated and/or hydrated forms.

Most APIs and their salts are purified and isolated by crystallization from an appropriate solvent during the final step in the synthetic process. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the process(es) used to generate supersaturation and promote crystallization [1,5–13]. The most notable variables of composition and processing are summarized in Table 1. Solid form screening is used to understand the effects that these variables have on the polymorphic outcome of a crystallization experiment, so that a robust process can be identified to produce the desired crystal form. Traditionally, the study of solid form diversity of active compounds has relied on the use of a variety of common process methods for generation of new forms, coupled with modern characterization methods for analysis of the solids produced [2,14]. Most often, however, a combination of solvent recrystallization (cooling or evaporative, as well as slurry conversion) and thermal analysis (e.g., hot stage microscopy, differential scanning calorimetry) are employed for initial form screening. Such methods are inherently slow and only allow exploration of a small fraction of the composition and process space that can contribute to form diversity. Before suggesting a form for development, scientists may have carried out only a few dozen crystallization experiments and possibly prepared a handful of different salts of a compound. The main reasons for the limited number of experiments are the constraints on availability of compound and scientists' analytical capacity in a given time frame, and they are therefore often forced to make form selection decisions on incomplete data. Accordingly, it is not surprising that unexpected and undesired outcomes can, and do, occur later on in development.

Despite more than a century of research [15], the fundamental mechanisms and molecular properties that drive crystal form diversity, specifically the nucleation of polymorphic forms, are not well under-

Table 1
Crystallization composition and processing variables [1,2,8]

Composition type		Process variables[a]				
Polymorph/ solvates	Salts/ co-crystals	Thermal	Anti-solvent	Evaporation	Slurry conversion	Other variables
▪ Solvent/ solvent combinations	▪ Counter-ion type	▪ Heating rate	▪ Anti-solvent type	▪ Rate of evaporation	▪ Solvent type	▪ Mixing rate
▪ Degree of supersaturation	▪ Acid/base ratio	▪ Cooling rate	▪ Rate of anti-solvent addition	▪ Evaporation time	▪ Incubation temperature	▪ Impeller design
▪ Additive type	▪ Solvent/ solvent combinations	▪ Maximum temperature	▪ Temperature of anti-solvent addition	▪ Carrier gas	▪ Incubation time	▪ Crystallization vessel design (including capillaries, etc.)
▪ Additive concentration	▪ Degree of super-saturation ▪ Additive type and concentration ▪ pH ▪ Ionic strength	▪ Incubation temperature(s) ▪ Incubation time	▪ Time of anti-solvent addition	▪ Surface-volume ratio	▪ Thermal cycling and gradients	

[a] Applicable to all types of screens.

stood [13,16]. As a result, predictive methods of assessing polymorphic behavior of pharmaceutical compounds by ab initio calculations remain a formidable challenge. Even in cases where the existence of a crystalline form is predicted, the stability relative to other crystalline packing arrangements has been difficult to estimate with accuracy [17]. Moreover, the prediction of packing structures for multicomponent (e.g., solvates, hydrates, co-crystals) or ionic systems is not yet possible [17]. Due to these limitations, solid form discovery remains an experimental exercise, where manual screening methods are employed to explore form diversity of a compound.

Control over solid form throughout the drug development process is of paramount importance. Reliable preparation and preservation of the desired form of the drug substance must be demonstrated, and has become increasingly scrutinized by regulatory agencies as more sensitive and quantitative solid-state analytical methods have become available [18]. Many strategies to influence and control the crystallization process to produce the solid form of interest have been reported. Some examples include stereochemical control using tailor-made auxiliaries [19–21], targeted solvent recrystallization [22–24], and templating using a variety of surfaces (e.g., organic single crystal substrates [25], surfaces of metastable crystal faces [25,26], inorganic crystal surfaces [27] and polymeric materials [28]). Recent studies have also begun to uncover the role of reaction byproducts and other impurities in determining polymorphic outcome and crystal properties [29–32], and in fact, it has been shown that in some cases such species can stabilize metastable crystal forms [33,34]. In addition, new processing methods continue to be developed to improve discovery and characterization of new forms, including precipitation by supercritical fluid [35,36], laser induced nucleation [37–39] and capillary crystallization [40–42]. However, there remains a lack of fundamental understanding of the nucleation process and the specific factors that contribute to crystallization of diverse forms of a compound [13,21,23]. In order to fully control the crystallization process, the link between the physical or chemical processes that influence nucleation and crystal growth needs to be better established. It is in this area that new experimental methodologies have the potential to enable development of this knowledge base.

There is reason to believe that the already complicated landscape of pharmaceutical solid forms will become even more complex in the future. It is now increasingly appreciated that hydrogen bonded co-crystal structures between active agents and molecules other than water or solvent can be prepared. For example, co-crystals of aspirin, *rac*-ibuprofen and

rac-flurbiprofen have been prepared by disrupting the carboxylic acid dimers using 4,4′ -bipyridine [43]. These structures are formally molecular compounds (or co-crystals) but do not involve formation of covalent bonds or charge transfer from or to the active substance. Recent demonstrations of these principles with drug compounds have been published [43–45].

Exploration of a given compound's polymorphs, hydrates, solvates, salts, co-crystals and combinations of all of these appears intractable by conventional experimental methods, and as the number of potential methods for exploring and controlling crystal form diversity continue to expand, existing strategies will become increasingly inadequate. In an effort to understand form diversity in a more comprehensive manner, high-throughput (HT) crystallization systems have recently been developed. This methodology uses a combinatorial approach to solid form generation, where large arrays of conditions and compositions are processed in parallel. Experiments are performed at small scale to reduce the material demand and to afford the largest number of conditions possible. The large number of crystallization trials performed in these experiments reflects the reality that nucleation rate has an extremely non-linear dependence on the experimental conditions, and as such, the probability of a chance occurrence of a particular form is increased by a HT approach. Supersaturation (solubility) and induction time of the various possible solid forms are independently controlled by these conditions, resulting in highly non-linear time dependence of crystallization. In addition, the combinatorial approach permits exploration of a chemical continuum, where use of many solvent mixtures may allow one to assess what underlying physical or chemical processes are required to produce a particular solid form. Once a variety of conditions that can be used to produce a given crystal form on the microscale are identified in the HT screen, scale-up studies are typically conducted to optimize the process for laboratory scale production.

In this review, the development and application of novel HT crystallization technologies for exploration of solid form diversity are discussed. The operational features of a fully integrated, automated HT crystallization system are presented, highlighting the design requirements for hardware and software components, as well as general specifications for consumables. Case studies are used to illustrate the benefits and capabilities of the approach, including salt selection in early lead optimization (ELO) and pre-clinical development, polymorph and solvate screening in highly polymorphic systems, comprehensive discovery of crystal forms to reduce the risk of late displays of polymorphism, comparison of experimental and predictive methods of solid form discovery, and engineering of co-crystals. The need for post-screening characterization of crystal forms to enable ranking and selection of the most suitable form for development is briefly reviewed. Finally, the implications of HT crystallization technologies on the future of solid form screening processes, intellectual property protection and regulatory compliance are discussed.

2. Development of high-throughput crystallization technologies

HT crystallization systems have been developed to more rapidly and comprehensively explore the multiparameter space that contributes to solid form diversity [40,46–51]. In its simplest description, HT crystallization can be broken down into three key experimental steps: *design* of experiment (DOE), *execution* of experimental protocols and *analysis* of data. Systems designed to carry out these experiments generally consist of both hardware and software components that drive and track experimentation, and permit data storage, retrieval and analysis. Such systems should be designed to be flexible and scalable to ensure that a variety of experimental procedures can be carried out either serially or concurrently. Thus, the system can be employed at various stages of drug development, where differences exist in the quality and quantity of compound available. While it is highly desirable to have the ability to mine and model experimental data, and to use the subsequent knowledge to guide further experiments, not all HT crystallization systems are equipped with these features. In Section 3, the hardware and software considerations for design and development of a fully integrated, informatics-driven HT crystallization system are described.

While the concepts of HT screening are widely applied in the pharmaceutical industry, most notably in the drug discovery arena [52], the application of

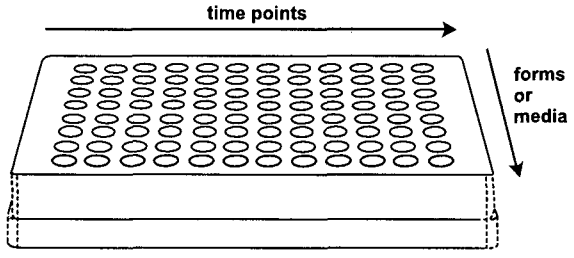

Fig. 10. Schematic of a 96-well dissolution filter plate.

for the longest time point desired is dispensed first and the shortest one comes last. Instead of varying the form along one axis of the plate, one can choose to study the dissolution of a single form into several different media (see Fig. 10). Equilibrium solubility can be determined in a variety of solvents and at different temperatures using a similar principle to the dissolution plate. A demonstration has been provided using automated React-IR analysis [109]. Other functional parameters, such as solid-state stability and thermal properties, can be adapted to HT. Such systems for ranking the stability of forms generated from HT crystallization await publication and review at a future date.

5. Summary and outlook

HT crystallization methodologies are capable of screening hundreds or thousands of crystallization conditions in parallel using small amounts of compound for the identification and characterization of diverse forms of active pharmaceutical ingredients. As demonstrated by numerous case studies from several stages of pharmaceutical development, such technologies have begun to show promise in enabling more comprehensive exploration of solid form diversity. The technologies are likely to provide a landscape of potential operating conditions from which scientists and engineers can design robust and scalable processes for transfer to manufacturing.

The ability to conduct extensive crystallizations with small amounts of material using a variety of solvents, additives and conditions necessarily generates large sets of data. However, the information by itself is of limited value, unless it can be properly analyzed. In order to extract maximum knowledge from the studies, it is essential to have the ability to design experiments, track samples in the process, collect the data in a relational database, and mine the information using statistical techniques and models in property space that assist the scientist to maximize the value of the data. Such models attempt to fit an output variable to physical properties or descriptors using techniques similar to those used in traditional quantitative structure activity relationships (QSAR). These models can be *carefully* extended to mixtures containing compounds that were not included in the original experiments if validation suggests that the models are sufficiently stable. Significant models that are found in the analysis of the data can be stored in the database for later retrieval and use to direct iterative experiments. The power of this approach becomes increasingly more visible when several properties are being co-optimized, as can be very important in the pharmaceutical development process where such properties as oral bioavailability, stability and processability need to be reconciled. The availability of a map of conditions that lead to the formation of different forms (salts, hydrates, solvates, polymorphs, co-crystals) of the drug can be valuable to the process chemists or engineers as they develop scalable processes to produce materials suitable for development and registration.

For many years, the value of composition of matter (CoM) patents on new chemical entities, including where appropriate, pharmaceutically acceptable salts, has been well appreciated. However, it is only within the last decade or so that the application of CoM patents has been significantly extended to cover all forms of the compound, including hydrates, solvates, co-crystals and polymorphs. Unlike salts, which for the most part can be prophetically claimed based on an understanding of the chemical structure of the compound and its ionization constants, the existence and identity of hydrates, solvates, co-crystals and polymorphs have defied prediction. Therefore, in order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials.

In general, discrete crystal forms are considered non-obvious and patentable. Given the diversity and greater complexity of chemical structures of today's

drug candidates [110], coupled with the advanced technology to identify novel forms, it is common to find multiple forms of drugs [61], some similar, some dramatically different in terms of their in vivo performance. These forms are all candidates for separate intellectual property protection. Therefore, it is incumbent on the innovator of a new drug candidate to identify and patent these forms in order to optimally protect their investment in the compound. Recent case studies suggest that identifying and patenting all forms of new chemical entities should be a primary strategy of all innovators of novel drugs. In this regard, the use of HT crystallization technologies for rapid, comprehensive discovery and characterization of solids form diversity offers significant advantages for the development of a strong intellectual property position.

With the advent of HT crystallization methods, appreciation for the landscape of physical form for drug development has begun to change. Use of these systems has the potential to facilitate drug development by saving valuable time in selecting the optimal physical or chemical form of a given compound. HT systems that generate rich datasets offer the ability to develop a more fundamental understanding of the crystallization process, based on knowledge generated from large numbers of experiments on diverse compounds. Having such information at an early stage minimizes the risk of process modifications resulting in form changes and provides the opportunity to gain more comprehensive intellectual property coverage. In addition, comprehensive form data help address important regulatory questions related to the number of solid forms of an API and the relationships between them.

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Patenting Polymorphs at the European Patent Office

Dr. Sofia Papathoma

Patent examiner in directorate 2.1.17
Pure & Applied Organic Chemistry

Barcelona, June 19th-21st 2006

Polymorphs / Pseudopolymorphs

- Polymorphs are different crystalline forms of the same compound resulting from different arrangements of the molecules in the solid state.
- They differ from each other in their physicochemical parameters but not in their chemical composition.
- Often, however, solvates and hydrates are treated like polymorphs of the unsolvated crystal form (pseudopolymorphs).

Main patentability criteria for polymorphs

- Clarity (Article 84 EPC)
- Disclosure of the invention (Article 83 EPC)
- Novelty (Article 54 EPC)
- Inventive step (Article 56 EPC)
- Unity of the invention (Article 82 EPC, Rule 30 EPC)

Clarity

- Article 84 EPC:

„The claims shall define the matter for which protection is sought. They shall be clear and concise and supported by the description."

Note: It is the claims and not the application as a whole, which must define the scope of protection.

Inventive step

- Article 56 EPC:

„ An invention shall be considered as involving an inventive step, if, having regard to the state of the art, it is not obvious to a person skilled in the art. "

- At the EPO, inventive step is assessed according to the problem-solution approach.
- The problem-solution approach is based on the principle, that every invention is the solution of a technical problem.

Inventive step

1. Determine the closest prior art
2. Determine the technical difference
3. Determine the inferred technical effect

↓

4. Establish the objective technical problem to be solved
5. Check that the problem was solved

↓

6. Assess whether it would have been obvious to solve the objective problem by the claimed invention

Inventive step

The closest prior art:

- A document disclosing subject-matter for the same or similar technical purpose and having the most technical features in common with the claimed invention.
- For polymorphs, the closest prior art is usually a document disclosing the same compound in different crystalline or non-crystalline (or undefined) form.
  - If several crystalline forms are already known, that with the most similar properties (e.g. physical, biological) is chosen.

Inventive step

The technical problem:

- Objective criteria must be used to determine, which technical problem has been solved:
  - based on what is actually shown in the application, and
  - in the light of the closest prior art.
  - The objective problem may differ from the subjective technical problem presented by the applicant.
- For polymorphs, the most common technical problems to be solved are:
  - the provision of an alternative physical form of a known compound to achieve the same technical effect, or
  - the provision of a further physical form of a known compound with different or improved properties (e.g. bioavailability, stability, etc.).

Inventive step

Common knowledge:

- Polymorphs differ in their properties e.g. melting point, density, chemical reactivity and stability, solubility and dissolution rate.
- Systematic investigation of a compound to determine whether it is prone to polymorphism is routine practice in pharmaceutical pre-formulation studies (Caira 1998).
- Every compound has different polymorphic forms and, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound (McCrone 1965).
- Instance of polymorphism appear not to be uncommon in areas such as pharmaceutical products, dyes and explosives, i.e. where materials are repeatedly prepared under conditions that may vary slightly from time to time (Bernstein 2002).

Inventive step

Example:

- The technical problem may be the provision of an alternative with substantially the same effect.
- In many cases, a mere alternative of a known crystal form may be an obvious solution of this technical problem, because:
  - compounds of similar molecular structure have similar properties
  - polymorphs have identical molecular structure
  - polymorphism is common enough to justify routine screening
  - any new polymorph of the same compound would solve the problem.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: **0-33394** EDICTO No. **18009**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución** No. **29227** de **30-OCT-2006**. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención a la creación denominada: "NUEVAS FORMAS CRISTALINAS DE UN ANTIBIÓTICO MACRÓLIDO".

ARTICULO SEGUNDO: Notificar personalmente al doctor Carlos R. Olarte en su calidad de apoderado de la sociedad Pfizer Products Inc., o a quien haga sus veces, el contenido de la presente resolución, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición ante el Superintendente de Industria y Comercio al momento de notificarse o dentro de los 5 días hábiles siguientes.

NOTIFIQUESE Y CUMPLASE
Dada en Bogotá D.C., a los 30 OCT. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **17-NOV-2006**_____ Este edicto se desfija hoy **30-NOV-2006** a las cinco (5:00 p.m.) _____
Secretaría General Ad-Hoc
EDICTO No. **18009**