### PATENTING CRYSTALLINE FORMS OF PHARMACEUTICALS

Using Solid State Science to Claim Form & Substance

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# Pharmaceutical Compound Claims

- Genus > subgenus > compound
  - Familiar with this scheme for chemical compound and composition claims
  - "and salts thereof"
- Not limited to the state of matter, e.g. a crystalline solid
- Pharmaceutical composition and method of treatment

United States Patent [19]	US005432163A [11] Patent Number:	5,432,163
Akhtar et al.	[45] Date of Patent:	Jul. 11, 1995
<ul> <li>[54] ANTI-PROLIFERATIVE AND ANTI-INFLAMMATORY COMPOUNDS: DERIVATIVES OF PENTOSE MONOSACCHARIDES</li> <li>[75] Inventors: M. Nayeem Akhtar, Lansdale; David S. Thomson, Bluebell; Sudershak K. Arora, Lansdale, all of Pa.</li> </ul>	4,735.934 4/1988 Gordon 4,738,953 4/1988 Gordon 4,996,195 2/1991 Ronsen et al 5,157,024 10/1992 Gordon 5,360,794 11/1992 Gordon 5,367,062 11/1994 Arora FOREIGN PATENT DOC	514/25 514/25 514/23 514/23 514/23 514/23 514/25 514/25 514/25
<text><text><text><text><text><equation-block><text><text><text></text></text></text></equation-block></text></text></text></text></text>	<ol> <li>The compound of claim 2, wherein said compound s a xylose derivative.</li> <li>The compound of claim 3, wherein said compound selected from the group consisting of 1,2-O-Isopropylidene-3-O-heptyl-5-O-3'-(N',N'- dimethylaminopropyl)-α,D-xylofuranose,</li> <li>1,2-O-Isopropylidene-3-O-heptyl-5-deoxy-5- aminoheptyl-α,D-xylofuranose,</li> <li>1,2-O-Isopropylidene-3-O-heptyl-5-deoxy-5-N-3'- (N',N'-dimethylaminopropyl)-α,D-xylofuranose,</li> <li>1,2-O-Isopropylidene-3-O-dodecyl-5-O-3'-(N',N'- dimethylaminopropyl)-α,D-xylofuranose,</li> <li>1,2-O-Isopropylidene-3-O-dodecyl-5-deoxy-5- pyrolidinyl-α,D-xylofuranose,</li> <li>1,2-O-Isopropylidene-3-O-dodecyl-5-deoxy-5- pyrolidinyl-α,D-xylofuranose,</li> <li>2-O-Isopropylidene-3-O-doecyl-5-deoxy-5-N'3'- (N',N'-dimethylaminopropyl)-α,D-xylofuranose,</li> <li>2-O-Isopropylidene-3-O-decyl-5-O-3'-(N',N'-dime- thylaminopropyl)-α,D-xylofuranose,</li> <li>2-O-Isopropylidene-3-O-decyl-5-deoxy-5-N-3'- (N',N'-dimethylaminopropyl)-α,D-xylofuranose,</li> <li>2-O-Isopropylidene-3-O-decyl-5-deoxy-5-N-3'- (N',N'-dimethylaminopropyl)-α,D-xylofuranose,</li> <li>2-O-Isopropylidene-3-O-decyl-5-deoxy-5-N-3'- (N',N'-dimethylaminopropyl)-α,D-xylofuranose,</li> <li>2-O-Isopropylidene-3-O-decyl-5-deoxy-5-N-3'- (N',N'-dimethylaminopropyl)-α,D-xylofuranose,</li> </ol>	

- Why are crystalline forms important?
  - Potential upside of finding improved solid form
    - Second generation products
  - Patents, patents, patent\$
    - Research pharma: broaden IP around a drug
      - Extend market exclusivity
    - Generic pharma: to establish their own IP position
      - Freedom to operate
    - They can be listed in the FDA's Orange Book

#### The Patent Examiners are asking:

- Questions of nomenclature
  - Examiners are not comfortable with solid state terminology.
- Questions of technique
  - How do the solid state analytical techniques work?
  - What does the data tell you? What does it not tell you?
  - How much data is needed?
- Questions of patentability
  - Why is the solid state form important?
  - What about a solid state form differentiates it from the prior art?
  - What needs to be included in the specification?, in the claims?



- The pharmaceutical industry is asking:
  - Questions of chemistry
    - What crystalline forms are available for this API?
      - Polymorphs, cocrystals, salts, etc?
  - Questions of value
    - What is this crystalline form worth?
    - Are then beneficial properties?
    - Is it patentable?





- Considerations for patent applications:
  - What is needed for patentability
  - What is needed in the patent specification
  - How to structure the patent claims
- Key is understanding (or predicting) what is needed to get the application allowed



#### **Prior Art**

- The touchstone of patentability/validity
  - Prior knowledge (public)
  - How is the invention different?
- To be patentable, an invention must be:
  - Novel "not anticipated" by the prior art, 35 U.S.C. § 102
  - Unobvious one of ordinary skill would not have known; invention would not have been "obvious" in light of prior art, 35 U.S.C. § 103



#### Prior Art – Anticipation



 In the US, under 35 U.S.C.
 § 102, a person is entitled to a patent unless

- The invention is not novel
  - Already public, prior publication
- Or applicant has lost his/her rights to the invention
  - Waited too long to file the patent application

### Prior Art – Anticipation

#### What constitutes anticipation?

- An invention is anticipated only if <u>each</u> <u>and every element</u> in the claim is found, expressly or inherently, in the prior art
  - Verdegaal Bros., Inc. v. Union Oil Co. of Cal., 814 F.2d 628, 631 (Fed. Cir. 1987).
- Differences between prior art and claims are controlling.

Recent statement by the USPTO:

"Since the final form of a polymorph is uncertain, 103 [obviousness] rejections of the novel form cannot generally be made."

 Polymorphs in Pharmaceutical Solids, J. Andrae, USPTO Biotech-Chem-Pharma Partnership Meeting, Sept. 2, 2009.

#### **Prior Art - Inherent Anticipation**

- A reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.
  - Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991).
- A reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time.
  - Titanium Metals Corp. v. Banner, 778 F.2d 775 (Fed. Cir. 1985).

#### SmithKline Beecham v. Apotex

- Drug: Paroxetine HCI Hemihydrate, the active ingredient in Paxil
- SmithKline's 723 patent
  - Claim 1. "Crystalline Paroxetine hydrochloride hemihydrate."
- Prior Art
  - The '196 patent claims paroxetine and its salts and discloses their antidepressant properties.
  - 1980 Ferrosan developed a process to produce the crystalline hydrochloride salt of paroxetine, or paroxetine hydrochloride (PHC).
  - SmithKline licensed the '196 patent and the PHC technology and began manufacturing PHC.

SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331 (Fed. Cir. 2005).

#### SmithKline Beecham v. Apotex

- SmithKline admitted through its proffered arguments, that producing PHC anhydrate according to the '196 patent inevitably results in the production of at least trace amounts of anticipating PHC hemihydrate.
- Neither Apotex nor SmithKline could then produce PHC anhydrate that did not contain at least trace amounts of PHC hemihydrate.

#### SmithKline Beecham v. Apotex

- SmithKline admitted through its proffered arguments, that producing PHC anhydrate according to the '196 patent inevitably results in the production of at least trace amounts of anticipating PHC hemihydrate.
- Neither Apotex nor SmithKline can presently produce PHC anhydrate that does not contain at least trace amounts of PHC hemihydrate.
- Because the record contains clear and convincing evidence that production of PHC anhydrate in accordance with the '196 patent inherently results in at least trace amounts of PHC hemihydrate, the court held that the '196 patent inherently anticipates claim 1 of the '723 patent.

#### Abbott Labs. v. Baxter

- Drug: Sevoflurane, the anesthetic Ultane<sup>®</sup>
  - Pure sevolfurane degrades in the presence of Lewis acids
  - Claim 1 of the '176 patent recited an anesthetic composition comprising: a quantity of sevoflurane and a Lewis acid inhibitor in an amount effective to prevent degradation by a Lewis acid
    - Listed Lewis acid inhibitors included water
- Abbott Labs. v. Baxter Pharm.
   Prods., Inc., 471 F.3d 1363
   (Fed. Cir. 2006).



#### Abbott Labs. v. Baxter

#### The prior art '211 patent disclosed:

- A technique for purifying sevoflurane for use as a pharmaceutical and particularly as an inhalation anesthetic, which involves the addition of water.
- That if the steps of its Illustration 1, Table 2 were practiced, the result would be sevoflurane that is saturated with water, unable to absorb any more moisture.
- That saturation implies that the sevoflurane contains an amount of water sufficient to prevent it from degrading due to Lewis acids.

#### Abbott Labs. v. Baxter

- At the time, however, knowledge of the beneficial nature of a watersevoflurane mix was wholly lacking in the art.
  - The '211 patent disclosed a particular composition and claims a process for making that composition, but does not teach the advantageous feature of that composition whose discovery led to the patent in suit.
- The lack of knowledge is wholly irrelevant to the question of whether the '176 patent claims something "new" over the disclosure of the '211 patent.
  - Since the '211 patent discloses sevoflurane saturated with water -- i.e., unable to absorb any additional water to further protect it from the degradation reaction -- it anticipates the claims of the '176 patent.
- The claimed property of resistance to degradation is found inherently in the disclosure.



#### 35 U.S.C. § 103(a): A patent may not be obtained, even though the

invention is not identically disclosed or described, if:

- The differences between the subject matter sought to be patented and the prior art are such that...
- ...the subject matter would have been obvious to a person having ordinary skill in the art.

# The determination of obviousness is dependent on the facts of each case.

Sanofi-Synthelabo v. Apotex, 550 F.3d 1075, 1089 (Fed. Cir. 2008).

□ Framing the legal analysis – Graham v. John Deere

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966).

- A court must ask whether the improvement is more than the predictable use (combination) of prior art elements according to their established functions.
- The proper question to have asked was whether a pedal designer of ordinary skill, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to upgrading Asano with a sensor.





KSR Int'l Co. v. Teleflex Inc., 550 US 398 (2007).

#### **Crystalline Form Patent Specifications**

- The patent specification should:
  - Characterize the polymorph itself, e.g.,
    - Physical properties of the form
      - Color, shape, melting point, density, hygroscopicity, water solubility
    - Analytical characteristics
      - Crystal structure: PXRD, single crystal XRD
      - Thermal studies: DSC/TGA
      - Spectral analysis: Raman/IR, solid state NMR
        - Include spectrum but select characteristic peaks
      - Know the limitations of the analytical techniques
        - E.g. Is there variability in peak location or intensity?

#### **Crystalline Form Patent Specifications**

The patent specification should also discuss:

- The utility/activity of the form
  - Therapeutic activity
  - Processing utility
- How to make the form
  - Reproduceablity
- Compositions containing the form
  - The crystalline solid often remains in its solid form
  - Pharmaceutical compositions
    - This is what the infringer will sell.

# Polymorphs – Defining the Form

#### Polymorphs

- Two crystals with the same chemical composition but different internal structure
  - Including different unit cell dimensions and different crystal packing



## Polymorphs – Defining the Form

- Not the compound
  - But a solid state form of the compound
- Not the solid state
  - But a single crystalline form
- The Ultimate Species





U.S. Patent Appl'n 2006/0194,833 A1

#### Polymorphs – Patenting the Form

#### EXAMPLE 7

#### Synthesis of Diol (Molecule 2.1)

Diol (Molecule 4.10 of FIG. 4) (6.191 g, 20.61 mmol) was added to a suspension of freshly prepared Raney Nickel W4 (50 g) in 400 ml of absolute EtOH. After stirring for 1 h at room temperature the reaction mixture was filtered through celite and washed several times with denaturated EtOH. The filtrate was concentrated in vacuo and purification of the residue by column chromatography over silica gel (ethyl acetate) afforded Molecule 2.1 (FIG. 4) as a white crystalline solid (3.696 g, 19.23 mmol, 93%).

"afforded Molecule 2.1 (FIG. **4**) as a white crystalline solid"

- New crystalline form of
  - a known compound
  - Recrystallization
  - Not synthesis
- Question of whether or not the crystalline form was known in the prior art.
  - Issue of novelty/ anticipation

- Claim: Ranitidine HCI (form 2)-- Xantac
  - Independent:
     29-peak infrared
     spectrum
  - Dependent: 32-intensity PXRD
- Infringement proof
  - Single infrared peak at 1045 cm-1

- "It is elementary patent law that all limitations are material."
  - Single peak analysis insufficient
    - Must establish the presence of each limitation

Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562 (Fed. Cir. 1997).

1934: Roger Tory Peterson used arrows in his nature guides to highlight field marks to enable nonexperts to discriminate between confusingly similar species.







#### "Field marks" for Polymorphs?

- Well-chosen Spectroscopic (or other) Properties
  - Limitations that <u>differentiate</u>
    - Not just define
  - Sufficient number of limitations to define the form claimed.
- Confident (but easy) Differentiation
  - Identifying the form should be
    - Straightforward
    - Accessible



"Polymorphism of Molecular Crystals" Professor J. Michael McBride, Department of Chemistry Yale University; Presentation to the USPTO, March 4, 2004

#### □ The "compound" as context

Tris[dihydrobis(1-pyrazolyl)borato]yttrium (III), (H<sub>2</sub>BPz<sub>2</sub>)<sub>3</sub>Y

#### Spectral characterization:

- IR spectrum (Nujol mull) cm<sup>-1</sup>: 2465, 2460, 2445 (BH); 2340, 2310, 2255, 2225 (µ-BH).
- <sup>13</sup>C solid state NMR spectrum having at least two peaks selected from 139, 135 and 104 ppm.

#### □ The claimed invention is:

- 1. Crystalline Tris[dihydrobis(1-pyrazolyl)borato]yttrium (III) having an IR spectrum in Nujol comprising the following characteristic peaks ....
- "Orthogonal" claiming with two techniques.



- Pharmaceutical composition claims
  - Solid state NMR or surface Raman spectroscopy
    - Intact tablet can be examined
    - More appropriate than PXRD?
    - No need to isolate compound from infringing product
      - No risk to changing form
  - Use characteristic peaks of polymorph
    - Choose peaks away from the region containing excipient peaks



- The "form" of a claim to a crystalline form
  - The compound as context (claim preamble)
  - Focus on the form (body of the claim)
    - Meaningful limitations
      - Not something that can be easily avoided
      - Not overly detailed
  - Characteristic" Peaks
    - Not every peak
    - Avoid confusing sparrows
      - Field marks

□ Use this strategy for all types of crystalline form claims.

### Cocrystals – Defining the Form



- The importance of definitions in patents
  - The words of a patent claim define the scope of the intellectual property right.
    - 35 U.S.C. § 112, ¶ 2.
    - Just like the boundaries of a piece of property.
- Various proposed definitions of "cocrystal"
  - Exclude salts, solvates?

# Cocrystals – Defining the Form

- Cocrystal or co-crystal?
  - Definition still under debate and development
    - Even the hyphen!
  - The question is should lawyers or scientists define what is and what is not a cocrystal?
    - Scientists should
    - But, patent lawyers have to



### Cocrystals – Defining the Form

#### Cocrystal - a multicomponent crystal

- Salt a compound formed by replacing hydrogen in an acid by a metal (or a radical that acts like a metal)
- Solvate a crystal structure incorporating either stoichiometric or non-stoichiometric amounts of solvent
- Hydrate a crystal structure incorporating either stoichiometric or non stoichiometric amounts of water
- Clathrate molecules of one substance are completely enclosed within the crystal structure of another
- Molecular Complex a unique crystal structure incorporating stoichiometric amounts of more than one molecule

#### A co-crystal is a crystalline entity in which more than one molecular substance is incorporated into the unit cell.

By convention, this normally excludes:

- Salts. Salts are distinguished by proton transfer, giving electrostatic linkage between oppositely-charged ions.
- Solvates. Solvates are associations of substrates with solvents from which they are crystallized.
   Bonding mechanisms can be similar to those in co-crystals.
- Definitions usually include the stipulation that both (or all) molecular components are solid at room temperature & pressure.
- Visheweshwar, P.; McMahon, J. A.; Bis, J. A.;Zaworotko, M. J. (2006) J. Pharm. Sci. 95(3), 499 – 516.

### **Cocrystals: Defining the Form**

- U.S. Published Application 2008/0051453A1 Bak et al., Sorbic Acid Analog Co-Crystals
  - [0004] In this application, the term "co-crystals" is meant to define [a] crystalline phase wherein at least two components of the crystal interact by hydrogen bonding and possibly by other non-covalent interactions rather than by ion pairing. The primary difference is the physical state of the pure isolated compound. If one component is liquid at room temperature, the crystals are referred to as solvates; if both components are solids at room temperature, the products are referred to as cocrystals (8).



N-(4-(6-4-(trifluormethyl)phenyl)pyrimidin-4-yloxy)benzo[d]thiazol-2-yl)acetamide sorbic acid co-crystal (Example 5).

### Cocrystals – Patenting the Form

- Generally looking for new crystalline forms
- Cocrystal
  - A new composition of matter in and of itself?
    - Is crystallinity needed for patentability?
    - Synthetic approach: A + B -> AB
      - Supra molecular synthesis
      - Not recrystallization
    - Polymorphic forms of the cocrystal
  - Characterization and proof of cocrystal

### Cocrystals – Patenting the Form

- Show that a cocrystal has been formed
  - Comparative data,
    - PXRD, IR, Raman, DSC
    - For example, compare
      - API IR
      - Co-former IR
      - Co-crystal IR
    - What differences exist?



Aptuit Inc.

# Cocrystals – Claiming the Form

- If the cocrystal composition carries patentability
  - Claim as new composition
- □ If the crystalline form carries patentability
  - Same considerations as with polymorphs
- □ If the cocrystal former is a new molecule
  - Independently patentable from the API and the cocrystal
- Generic formula/claims for API and/or co-former may be possible

#### **Cocrystal Patent Strategies**

#### US 2008/0051453A1, Bak et al., Sorbic Acid Analog Co-Crystals

#### -an example of "generic" cocrystal claims

We claim:

1. A pharmaceutical co-crystal comprising:

an active pharmaceutical ingredient; and

a co-crystal agent having the structure R<sup>1</sup>—C(=O)XH, wherein X is O, N(C<sub>1-6</sub>alkyl) or NH and R<sup>1</sup> is a C<sub>3-8</sub>alkyl group containing at least one trans-oriented double bond and being substituted by 0, 1, 2, 3 or 4 groups independently selected from halo, phenyl and hydroxyl.

2. A pharmaceutical co-crystal according to claim 1, wherein the co-crystal agent is selected from sorbic acid, trans-2-hexenoic acid, trans-3-hexenoic acid, trans-4-hexenoic acid, trans-2-butenoic acid, trans-2-pentenoic acid, trans-3-pentenoic acid, trans-2,4-pentadienoic acid.



Example 5: Single crystal structure of N-(4-(6-(4-trifluoromethyl)phenyl)pyrimidin-4-yloxy)benzo[d]-thiazol-2-yl)acetamide sorbic acid co-crystal.

### **Co-crystal Patentability**

- No US cases on the patentability of a co-crystal (yet).
- Anticipation (lack of novelty) not a likely issue given the new composition of matter embodied in a co-crystal.
- Obviousness?
  - Predictable results in view of KSR
  - Different API but common coformer
  - Routine techniques in the art
  - Analogies to other chemical decisions



### Salt Forms



- □ Chemistry 101
  - Acid + base -> salt + water
  - HCI + NaOH -> NaCI + H2O
- Requires an acid/base interaction
  - Involves proton transfer
    - Typically Brønsted acids/bases

### Salt Forms

- Patentability of a specific salt form over generic disclosure
  - Identifying alternative salts for API's
  - Selection of counter-ions
    - Instead of coformers
    - Focuses on different functional groups in API.
- What advantages are achieved with the salt?
  - Increased bioavailability, different dissolution profile, stability, etc.





#### Salt Forms - Patentability

- Prior art disclosure and claims to generic class of compounds
  - "A compound of formula (I) ... and a salt thereof."
  - Typical disclosure and claim
    - Specification may disclose list of salts

- Synthetic approach to salt formation
- Same consideration as cocrystals
  - Patentable new composition of matter?
  - Patentable new crystalline form?

#### Salt Forms – Pfizer v. Apotex

- Drug: Amlodipine besylate
  - Norvasc, to treat hypertension and vasopastic angina
- '303 Patent Claim: The besylate salt of amlodipine.
- Prior art:
  - '909 Patent: Amlodipine maleate and other "pharmaceutically-acceptable anions"
    - But not besylate
  - Besylate salts of other compounds and its benefits

Pfizer, Inc. v. Apotex, Inc., 480 F.3d. 1348 (Fed. Cir. 2007)

#### Salt Forms – Pfizer v. Apotex

- We find this case analogous to the optimization of a range or other variable within the clams that flows from the normal desire of scientists or artisans to improve upon what is already generally known.
- The logical line of testing was to react benzene sulphonate with amlodipine to confirm the presence of a salt and then to verify that its physiochemical properties were adequate.
  - Nothing more than routine application of a well-known problemsolving strategy.

- Three types of crystalline forms:
  - Polymorphs
  - Cocrystals
  - Salt forms
- Three themes discussed:
  - Defining the form
  - Patentability of the form
    - Over the prior art
  - Claiming the form







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- Patent Examiners' questions regarding patentability:
  - Why is the solid state form important?
  - What about the solid state form differentiates it from the prior art?
- Consider: What difference would it make if the claim recited "a crystalline form?"
  - Application of patentability criteria can vary with the type the crystalline form to be patented.

□ So, does the crystalline form (really) matter?

- YES a crystalline form can have its own unique & beneficial pharmaceutical and/or process properties
- YES a crystalline form is not predictable
- YES a crystalline form and the properties tied to that form can give patentability



polymorph 1 stable to shock detonation

polymorph 2 unstable to shock detonation

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