Challenges and Strategies for Patenting New Solid Forms

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### Outline

- Introduction to new solid form patents
- What information should be in the specification?
- What types of patent claims should be included?
- Orange Book listing
- Patent term extension
- Patentability requirements
- Cases related to the novelty of polymorphs
- Cases related to obviousness issues for salts and polymorphs
- Concluding remarks
New Solid Forms

- Salts
- Solvates or hydrates (pseudopolymorphs)
- Polymorphs
- Combinations of the categories above
Importance of New Solid Form Patents

• Approximately 51% of the new molecular entities approved by the FDA between 1985-2005 with at least one patent have claims to polymorphs, isomers, prodrugs, esters, or salts (or 24% where there is not an NCE patent)

• Secondary patents generate additional patent life of about 4-6 years beyond the chemical compound patent.

• Secondary patent without chemical compound patents but with independent secondary patents generate additional patent life of about 7-10 years.

Specification

• Written description and enablement (description of the invention, along with information related to how to make and use the invention)

• Describe how to make and use the new solid form

• Normally would include multiple solid forms if discovered in screening, not only the new form of interest

• Screening protocol

• Scaled up preparative procedure for the new solid form of interest

• Characterization data

• Instrument parameters

• Information regarding the variation in data
  • Typically ±0.2° for XRPD peaks, ± 3°C for DSC
Characterization of the New Solid Form

- X-ray crystallographic methods (XRPD)
  - 2-theta, peak intensity
- Thermal methods (TGA, DSC)
- Dynamic vapor sorption (DVS)
- Solid state spectral methods (NMR)
- Other parameters (solubility, density)
- Pharmacokinetic parameters (e.g., formulation patents)
What Types of Patent Claims

- Composition of matter claims to new solid form
- Formulations of new solid forms (pharmaceutical composition claims)
- Method of treatment using new solid forms
- Process of making new solid form
A Note about Claims

• Compound claims
  • Need language “or a pharmaceutically acceptable salt thereof”
  • Covers solvates and polymorphs of the compound or salt without explicit claim language
  • Avoid terms like “or a pharmaceutically acceptable solvate thereof”, “or a pharmaceutically acceptable polymorph thereof”, etc.

• New solid form claims
  • Covers just the specified polymorph
  • Broadest claim covers form by name/identifier
  • Include some claims that recite characteristics
New Solid Form Claims

- Theoretical NCE called Compound A

**Salt claims:**
1. A salt of Compound A, which is Compound A hydrochloride.

**Solvate claims:**
1. A monohydrate of Compound A.
2. Compound A hydrochloride hemihydrate.
1. A solid form, which is Form I of Compound A.

2. The solid form of claim 1, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at about 15.4°.

3. The solid form of claim 1, having an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 15.4°, about 31.1°, about 33.1°, and about 33.4°.

4. The solid form of claim 1, having an X-ray powder diffraction pattern substantially as shown in Figure 1.
5. The solid form of any one of claims 1 to 3, having a differential scanning calorimetry (DSC) thermogram comprising an endothermic peak at about 135 °C.

6. The solid form of any one of claims 1 to 3, having a differential scanning calorimetry (DSC) thermogram substantially as shown in Figure 2.

7. The solid form of any one of claims 1 to 6, having a thermogravimetric analysis (TGA) substantially as shown in Figure 3.
New Solid Form Claims - Compositions

8. A pharmaceutical composition comprising the solid form of any one of claims 1 to 7, and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition comprising the solid form of any one of claims 1 to 7, wherein said solid form is present in said composition in an amount of at least about 90% by weight.

10. A pharmaceutical composition consisting essentially of the solid form of any one of claims 1 to 7.

11. The solid form of any one of claims 1 to 7, which is substantially purified.

12. The solid form of any one of claims 1 to 7, which is crystalline.
13. A process for preparing the solid form of any one of claims 1 to 7, said process comprising precipitating said crystalline form from a solution comprising Compound A and ethanol.


15. A method of treating rheumatoid arthritis, comprising administering to said patient the solid form of any one of claims 1 to 7.
A Note About XRPD Data

• Important to have a reproducible, robust XRPD pattern, where there are not impurities or other polymorphs present

• As for any claim: the fewer limitations there are, the easier it is to prove infringement
  • *Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418 (Fed. Cir. 1994) where the patentee failed to prove infringement of its claim to a crystalline form of cefadroxil monohydrate because they could not show that the allegedly infringing product was characterized by all, or even most, of the 37 X-ray diffraction peaks recited in the claim

• General choose 2-theta peaks for claim drafting based on peak intensity

• Peak intensity can vary greatly from sample to sample and instrument to instrument. Thus, it is generally wise not to incorporate peak intensity data into the claims, but should be present in the specification, along with a Figure showing the XRPD pattern.
Orange Book Listing

• Patents on active ingredients in drug product ("drug substance" patents)
  • If new solid form is approved by FDA, can list the patents claiming the approved solid form

• Formulations and compositions of the drug product ("drug product" patents)
  • Include pharmaceutical composition claims covering the approved solid form

• Methods of treatment for the listed drug
  • Include method of treatment claims with the approved indication and approved solid form

• Cannot list process of manufacture claims
Patent Term Extension (PTE)

- First permitted commercial marketing or use of the drug product’s active ingredient
- While multiple patents may cover a single FDA approved product, only one patent can enjoy a PTE for a single regulatory review period
- Half the time spent in clinical trials plus the entire time the product was undergoing FDA review, minus any time where the applicant failed to act with due diligence, not to exceed 14 years
- Types of patents eligible for PTE
  - A product, method of using a product, or a method of manufacturing a product
  - Would include an approved salt form or solid form
  - *Pfizer Inc. v. Dr. Reddy’s Labs, Ltd.*, 359 F.3d 1367 (Fed. Cir. 2004) (allowed extension of claims to amlodipine maleate where approved salt was amlodipine besylate, interpreting the therapeutically active agent *in vivo* as amlodipine)
Requirements For Patentability

• Definiteness
  • The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention
  • Terms “about” and “substantially as shown in” – include information in the specification re the variation
    • Typically ±0.2° for XRPD peaks, ± 3°C for DSC

• Written Description
  • Describe the invention in such a way to show that the inventor had possession of the invention
    • Detailed procedures, characterization data, and instrument parameters will be useful later to show infringement

• Enablement
  • Describe the invention such that a person skilled in the art to which it pertains can make and use the invention without undue experimentation.
Requirements for Patentability

• Novelty
  • Exceptions: Disclosures made 1 year or less before the effective filing date of the claimed invention - Unless the disclosure was made by the inventor or joint inventor or by another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor; or the subject matter disclosed had, before such disclosure, been publicly disclosed by the inventor or a joint inventor or another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor.

• Non-obviousness
  • the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.
  • But….Patentability shall not be negated by the manner in which the invention was made.
Anticipation

- Explicit or inherent
- Whether the reference discloses every limitation of the claim explicitly or inherently

- New solid forms – generally worried about inherent anticipation

- Does the prior patent for the NCE or other publication necessarily and inevitably result in the new solid form?
SmithKline Beecham Corp. v. Apotex Corp.

- Paroxetine HCl hemihydrate
- Active ingredient in SKB’s Paxil®

**4,721,723**
1. Crystalline paroxetine hydrochloride hemihydrate.

- Prior art method makes the anhydrate, and inevitably results in trace amounts of the hemihydrate

*SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005)
In re Armodafinil Patent Litigation Inc.

- Cephalon’s drug Nuvigil® - Form I polymorph of armodafinil (also known as (-)-modafinil)

- 7,132,570 - “Methods for the Production of Crystalline Forms and Crystalline Forms of Optical Enantiomers of Modafinil”

3. A laevorotatory enantiomer of modafinil in a polymorphic form that produces a powder X-ray diffraction spectrum comprising reflections at 15.4, 31.1, 33.1 and 33.4 degrees 2.\theta.

7. A Form I polymorph of (-)-modafinil.

8. A pharmaceutical composition \textit{comprising} a Form I polymorph of (-)-modafinil according to claim 7.

9. A pharmaceutical composition \textit{consisting essentially of} a Form I polymorph of (-)-modafinil according to claim 7.

10. A process for preparing a Form I polymorph of (-)-modafinil comprising the steps of: (a) providing a solution of (-)-modafinil dissolved in a hot solvent; (b) rapidly cooling the solution from step (a) to produce crystals; (c) filtering the crystals; (d) drying the crystals; and (e) obtaining the crystals of said Form I polymorph of (-)-modafinil, wherein the solvent of step (a) is selected from water, methanol, absolute ethanol, absolute ethanol plus 3% water (v/v), and ethanol denatured with toluene plus 3% water, (v/v, based on the total volume of ethanol and toluene).
Novelty

- Whether Preparation I from prior patent produced Form I armodafinil or a composition consisting essentially of Form I armodafinil
- The defendant’s expert completed two experiments
  - First experiment produced pure Form I, but the court noted that the expert did not heat the solution to 30-40°C for dissolution as called for in Preparation I and subjected the produced to extensive vacuum drying not called for in Preparation I
  - Second experiment produced a mixture of 90% Form II and 10% of Form I
- Third experiment by Plaintiff’s scientists resulted in amorphous material
- Fourth experiment attempting to duplicate the plaintiff’s experiments obtained Form I with impurities, but made changes to heating and cooling rates (Preparation I lacked detail on these rates and recrystallization solvent)
Claims are Novel

- Defendants did not show that Form I *necessarily and inevitably* results, because “variations in the Preparation I process—variations not detailed in that Preparation—lend to different outputs”
- First experiment did not use temperature in Preparation I for dissolution step
- Second experiment did not produce a composition consisting essentially of Form I
  - 90% Form II produced
  - No further purification steps described
- Third experiment produced amorphous material
- Fourth experiment – did not test a representative range of conditions
Recommendations

• Attempt to determine whether your prior NCE patent inherently discloses the new solid form prior to filing your secondary patent
  • Typically less of an issue where the new solid form is a polymorph of a solid form not disclosed in your original patent

• Include a detailed preparative procedure for the preferred solid form with complete characterization
Obviousness - 35 U.S.C. § 103

• A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.

• Patentability shall not be negated by the manner in which the invention was made.
The *Graham* Factors

- Obviousness is determined by reference to 4 factual inquiries:
  1. the scope and content of the prior art;
  2. the differences between the claimed invention and the prior art;
  3. the level of ordinary skill in the art; and
  4. other objective indicia of non-obviousness, such as commercial success of the claimed invention, long felt but unmet need, failure of others.

KSR International v. Teleflex, Inc.*

Supreme Court, April 30, 2007
Opinion authored by Justice Kennedy


• Case dealt with car acceleration pedals, not chemical compounds
Tightened the Standards Re Obviousness

- Rejected the “rigid application” of “teaching, suggestion or motivation” (aka “TSM”) test:
  1. the reference(s) teach or suggest all of the claim limitations;
  2. some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference(s) or to combine the teachings; and
  3. a reasonable expectation of success that the combination would work

- Still must provide “some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”

- Sometimes “obvious to try” might suffice
  - “When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.”
New Salt Forms

- Amlodipine besylate (Norvasc®)

4,879,303

1. The besylate salt of amlodipine.

2. A pharmaceutical composition comprising an antihypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 together with a pharmaceutically acceptable diluent or carrier.

3. A tablet formulation comprising an anti-hypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.
Development of Salt

• Original patent on amlodipine filed March 11, 1982
  • Disclosed hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts
  • Maleate salt was identified as preferred
• In 1982, the discovery group designated amlodipine maleate as the drug substance for development
• In 1984, a scientist at Pfizer noted that the maleate salt had two issues:
  • (1) chemical instability; and
  • (2) stickiness of tablet formulation.
• He decided to test seven other potential anions to resolve these issues: hydrochloride, mesylate, besylate, lactate, succinate, and acetate
• Besylate salt was found to have better stability and stickiness
• In 1986, filed new patent application to besylate salt and selected the besylate tablet formulation for further development
Motivation to Select Besylate Salt

• On appeal, the Federal Circuit found the besylate salt obvious
• A person of ordinary skill in the art would have been motivated to choose the besylate salt
  • Michael addition caused instability of the maleate salt; a skilled person would be motivated to eliminate the double bound
  • At the time, there were 53 FDA-approved, commercially marketed anions; a skilled person would be motivated to start from those
    • Court: What if I sic my phalanx of zealous scientists on that list and then come up with a product. Would that be a logical thing for me to do? The Witness: It would be logical to try that.
  • The Pfizer scientist expect 7 of those 53 anions to have improved stability and stickiness, including the besylate salt
  • Numerous references pointing to besylate salts as preferred for stability reasons; a skilled person would be motivated to narrow the genus of 53 anions to one including besylate
Reasonable Expectation of Success

- The court rejected the argument that it was generally unpredictable as to whether a particular salt would form and what its exact properties would be, noting that “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.”

- The court noted that the Pfizer scientist believed that the besylate salt would be improved over the maleate salt:
  - Q. And when you chose these salts ... you believed that if you could, in fact, make an amlodipine salt out of them, these might be a cure for the problems you were having with maleate, correct?
  - A. Indeed.
Obvious-To-Try

- Not numerous parameters to try (finite list)
  - 53 anions
  - Prior art references suggested narrowing to besylate
- The court also noted that this is “not the case where the prior art teaches merely to pursue a ‘general approach that seemed to be a promising field of experimentation’ or ‘gave only general guidance as to the particular form of the claimed invention or how to achieve it’”
- The court noted that on “the particularized facts of this case, consideration of the ‘routine testing’ performed by Pfizer is appropriate because the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing
  - Pfizer had argued that obviousness cannot be negatived by the manner in which the invention was made (e.g., by the existence of routine methods of screening)
- The court analogizes the selection of the besylate salt to the optimization of a range
No Unexpected Results

• The court is required to consider evidence of unexpected results, which is a form of secondary considerations.
• In the case of compounds or new solids forms, the new form should be compared to the closest prior art.
• In this case, the court disputed whether the maleate salt was actually the closest prior art salt to the claimed besylate salt.
• Further, the court states that the improved stability and stickiness were not unexpected, because there was no evidence of what would be expected in the first place.
Contrary Result

- Bupropion HBr (Aplenzin®)

7,553,992
3. A crystalline compound of the formula:

![Chemical Structure]

having the powder X-ray diffraction pattern shown in FIG. 58.

7,569,610
1. A method of treating depression, comprising administering an effective amount of bupropion hydrobromide to treat depression to a subject in need thereof.
Development of Bupropion HBr

- Bupropion was previously marketed as the HCl salt under the trademark Wellbutrin®
- Stability issues with the HCl salt – no more than 18 month shelf life
- HBr salt chosen for development
- Various advantages
  - Doubled shelf life
  - Reduced risk of seizures
  - Ability to formulate a single tablet at all dosage strengths (including the highest dosage)
  - Improved resistance to dose dumping
  - Easier manufacturability due to reduced corrosivity
Salt selection is an unpredictable art, citing several articles:

- "Selecting a salt form that exhibits the desired combination of properties is a difficult semiempirical choice”
- “There is yet no reliable way of predicting exactly what effect changing the salt form ... will have on its biological activity ....”;
- “Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound”
- “the ability to predict which salt forms will have desirable properties is essentially nonexistent”

Availability of high-throughput screening does not negate this:

- While HTP screening would have allowed one to create and test many salts at once, it would not have allowed one to reasonably predict the individual properties of the resulting salts in advance
- Federal Circuit has rejected the argument that obviousness can be based on the availability of after-the-fact testing
No Motivation to Develop HBr Salt

- References did not suggest that switching to an HBr salt would increase stability (e.g., Gould, “Salt Selection of Basic Drugs”)
  - Increasing hydrophobicity, but proposes using a carboxylic acid in lieu of a mineral acid like HBr
  - Using an acid with a higher \( pK_a \), but HBr has a lower \( pK_a \) than HCl
  - Raising melting point, but difficult to predict which acid will give a higher melting point (in any case, bupropion HBr has a lower melting point than bupropion HCl)
- Other references also would not motivate a skilled person to substitute HBr for HCl
Significant Unexpected Advantages

- Various advantages over the HCl salt were unexpected
  - Doubled shelf life
  - Reduced risk of seizures
  - Ability to formulate a single tablet at all dosage strengths (including the highest dosage)
  - Improved resistance to dose dumping
  - Easier manufacturability due to reduced corrosivity
Distinguished Facts From Pfizer Case

• The court noted that, in Pfizer, “numerous prior art teachings specifically indicated that switching to the besylate salt would result in improved stability over the maleate salt”

• By contrast, the court felt that there was not a similar showing that switching from an HCl salt to a HBr salt would result in the improved stability
Obviousness of Salt Forms

- More subject to a challenge based on obviousness than NCE patent or, as we shall see, polymorph patents

- Unexpected results may be critical to patentability – document advantages in specification
Polymorphs

- Nuvigil® - Form I polymorph of armodafinil (also known as (-)-modafinil)

7,132,570

7. A Form I polymorph of (-)-modafinil.

8. A pharmaceutical composition comprising a Form I polymorph of (-)-modafinil according to claim 7.

9. A pharmaceutical composition consisting essentially of a Form I polymorph of (-)-modafinil according to claim 7.

Arguments Made Regarding Obviousness

- A person of ordinary skill in the art would have:
  - (1) been motivated to identify the most stable polymorph of armodafinil—Form I—for use in a pharmaceutical composition;
  - (2) expected to obtain the most stable polymorph of armodafinil using well known and merely routine techniques and predictable steps;
  - (3) known that the D-spacings and 2–Theta values recited in the asserted claims are intrinsic to Form I and would have been measured using routine techniques; and
  - (4) been motivated to make a pharmaceutical composition consisting essentially of Form I.
Existence of a Polymorph is Unpredictable

• Publications at the time discussing polymorphic crystallization experiments noted that: “[t]here are no failsafe methods to predict the extent of polymorphism of a given compound”, and “[u]nlike 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 ... polymorphs have defied prediction”

• Even if there were a way of predicting that a compound would be polymorphic and what the crystal structures might be, the evidence presented shows that person of skill would not know how to make a specific polymorph or predict its properties.

• For armodafinil, the court found that a researcher could not predict (a) whether it would exhibit polymorphism; or (b) what recrystallization conditions would generate a particular crystalline form
No Reasonable Expectation of Success

- The court also noted that there was no way to tell whether the Preparation I white crystals of the prior patent were polymorphic.
- The court disagreed with the defendants' assertion there would be a reasonable expectation of success in finding Form I because it would have been easy to obtain.
- Motivation to find a stable form does not mean that there is a reasonable expectation of success in finding one.
  - “Dr. Bernstein explained that the motivation of a skilled artisan to find the “most stable form” of armodafinil would be no different than the motivation to find an effective drug with the lowest toxicology profile, which likewise does not render obvious a specific drug that has the lowest toxicology profile.”
- Other considerations, beyond thermodynamic stability are involved in the calculus that leads to the selection of a polymorph or solid form for use in a pharmaceutical product.
  - E.g., solubility.
Existence of Polymorphic Screening

- The defendants argued that it was ‘a simple and routine matter…to identify the most stable polymorph’ using polymorphic screening.
- The plaintiffs argued that crystallizing new polymorphs often requires hundreds to thousands of experiments that analyze the effects of various parameters such as temperature, solvent and solvent mixtures, mixing time, cooling rates, stirring rates, and concentrations, as well as methods and processes for precipitation, cooling, evaporation, slurry, and thermo-cycling.
  - May 2002 article - 7,776 crystallization experiments, representing 2,592 unique conditions, were used in experiments for polymorphs of acetaminophen.
- The court agreed with the plaintiff, noting that the “number of crystallization conditions was so large that, even if a “most stable” crystal form could have been predicted, a person of ordinary skill in the art would not have a defined, finite set of reasonably predictable experiments or variables and would have had to rely on trial and error experimentation.
Contrast with *Pfizer* Case

- Unlike the general notion to find a new or improved crystal form, in *Pfizer* “it [was] not the case where the prior art teaches merely to pursue a general approach that seemed to be a promising field of experimentation or gave only general guidance as to the particular form of the claimed invention or how to achieve it.”
- Instead, a limited number of pharmaceutically acceptable salt anions would have been known to the skilled artisan, who was “capable of further narrowing that list of 53 anions to a much smaller group ... with a reasonable expectation of success.”
- “Obvious to try” is not equivalent to obviousness in every case, particularly where, as here, the prior art provided at most general motivation to conduct trial and error experimentation in a decidedly unpredictable field.
Polymorph Patents

• Polymorph patents tend to be stronger than salt patents, because of the lack of ability to predict whether a given compound or salt will display polymorphism
• Must take care that a polymorph is not inherently disclosed in any prior patent or publication (i.e., that the polymorph does not result from a prior synthetic procedure)
• Include evidence of unexpected or improved properties in the specification
• Include claims reciting the percentage of the polymorph in a composition and claim to compositions consisting essentially of the polymorph as fallback positions to avoid potential novelty issues
Thank you!

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