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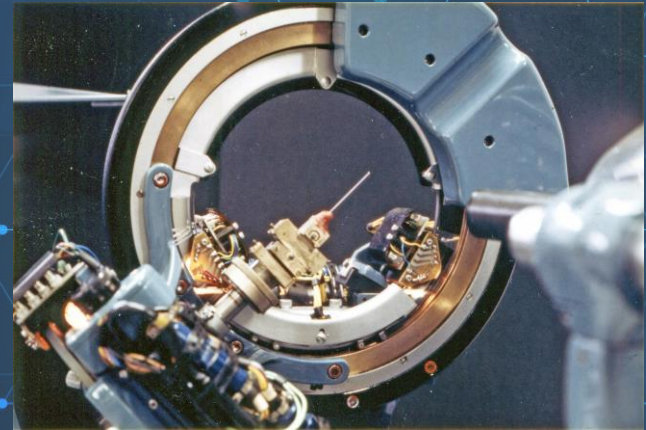
SLW LIFE SCIENCES WEBINAR SERIES

Patenting Solid Forms of Pharmaceuticals

Steven M. Reid, Ph.D., J.D.
Principal



History with Crystals

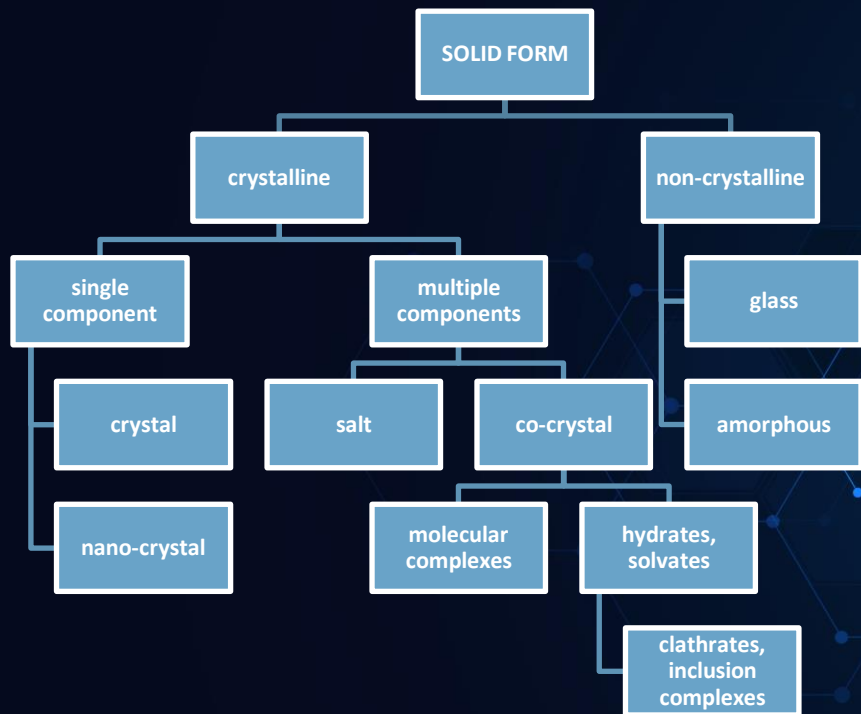


"Close-up of the crystal mounted on a Hilger and Watts Y290 diffractometer" by Prof. David J. Watkin is licensed under CC BY-SA 4.0.

Overview

- What are solid forms?
- Why are they worth patenting?
- Patenting mechanics
- Legal considerations
- Comparisons to EPO, JP, IN, and LatAm practices

Taxonomy of Solid Forms



THE ULTIMATE SPECIES

- Compound *per se* might already be patented, long-known, or both
- Focus is not on the compound, but its solid-state form (polymorph, amorphous solid, co-crystal...)



What are polymorphs?

- Two or more crystals with identical chemical composition but different internal structure.
 - Different crystal packing
 - Different unit cells
- Generally, a compound has only 1 amorphous form:
not a polymorph because not crystalline

Why Patent Solid Forms?

- **Innovators**
 - Extend market exclusivity
 - Shore up IP around a drug, especially commercialized form
- **Generics** can establish own IP position
- **Regulatory:** solid form patents can be listed in FDA Orange Book

EVERGREENING



Drafting Mechanics - specification

- Describe the solid form's advantages
 - Ease of manufacture
 - Flowability, drying, caking
 - Hygroscopicity
- Pharmaceutical importance
 - Physical stability: thermodynamic or kinetic?
 - Chemical stability (shelf life!)
 - Solubility
 - PKD parameters: bioavailability (AUC), C_{max} , etc.

Drafting Mechanics - specification

- Solid forms patents are rich with data
 - Commercializable solid form usually identified during (pre-)clinical development, e.g., salt screen, polymorph screen
 - Studies in mammals (monkey, human): *in vivo* data essentially essential
- Solid forms patents must be rich with biological data
 - Time drafting late enough to capture body of data in application, and not rely only on post-filing declaration if needed
 - CA prohibits all post-filing evidence of non-obviousness
 - CN accepts post-filing evidence only if contemplated in specification

Drafting Mechanics - characterization

- How to make solid form
 - Polymorph, salt, co-crystal screens: solvent(s), temperatures, crystallization conditions, co-formers, etc.
- Physical Properties
 - Color, shape, melting point, density, solubility
- Analytical Data
 - XRPD (the gold standard)
 - Include instrumentation, experimental error, conditions of data collection
 - Cu-K_α radiation at a wavelength of 1.54178 Å
 - 23.2° 2θ ± 0.2° 2θ
 - Crystal structure: single crystal (unit cell parameters)
 - Spectral: IR, Raman, solid state NMR (include spectrum and characteristic peaks)
 - Thermal: DSC, TGA

Drafting Mechanics – use of solid form

- Utility
 - Usually, this is the same as the ‘basic’ compound (API)
 - Therapeutic activity, efficacy
 - Manufacturing utility, e.g., can’t make pure API except by particular solid form
- Compositions comprising solid form
 - Likely the infringing product!
 - Polymorph typically remains in solid form within composition
 - Described excipients must not be liquid. Otherwise, solid form no longer remains.

Fundamental of Claiming

DACTYLOSCOPY FOR THE PATENT ATTORNEY

- Ridge patterns enable identification and differentiation between individuals.
- Focus only on characterizing patterns to establish identity of person, not on person as whole.



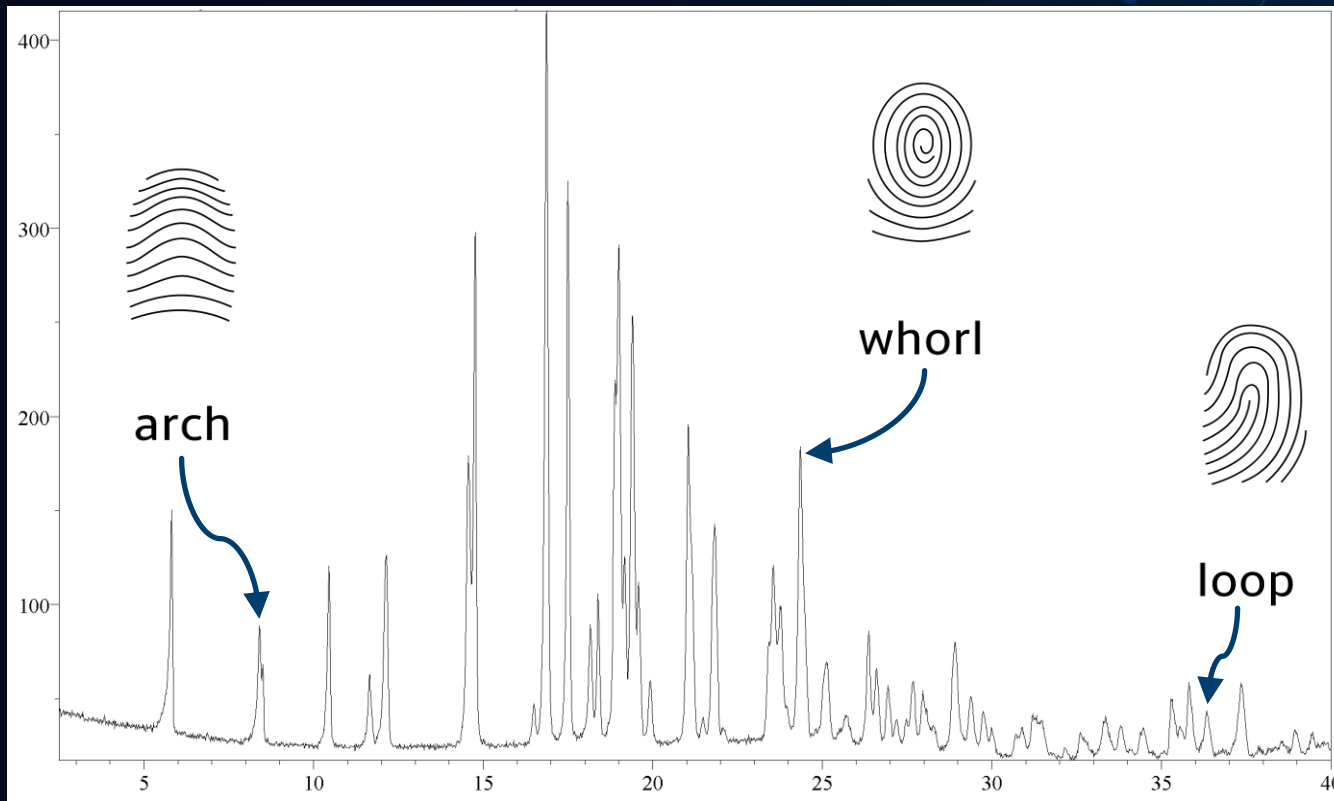
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“Ridge Patterns” for Solid Forms

- Select claim limitations that differentiate between polymorphs; do not merely identify a polymorph
- XRPD is the gold standard
 - Solid form is amorphous: usually one broad signal
 - Solid form is crystalline: many sharp signals from which to choose
- Pick just enough signals to define the unique polymorph. How many?
 - 4 or 5 are sufficient to identify and differentiate between forms. (Careful: must prove each element of claim for infringement!)
 - Some countries require 8 to 10 signals
- Identifying and differentiating polymorphs should be straightforward and accessible (to POSITA, examiners, courts, etc.)

XRPD: The Gold Standard



Elements of the Solid Form Claim

- Compound identity (IUPAC name)
- Characterizing data (XRPD)
 - “signal” instead of “peak”
 - at least 4 signals
 - Experimental error
- Radiation source and wavelength

Crystalline Compound **CHEMICAL NAME** characterized by an X-ray powder diffractogram comprising signals at 4.5, 11.3, 17.7, and 23.5 °2θ ± 0.2 °2θ, as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

Solid Forms and the Law



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Novelty of Polymorphs

- Main issue is whether crystalline polymorph is anticipated, explicitly or inherently, in prior art.
- *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)

“[A] prior art 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.”



Novelty of Polymorphs

- *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373 (Fed. Cir. 2003)

“Inherent anticipation does not require a person of ordinary skill in the art to recognize the inherent disclosure in the prior art at the time the prior art is created.”

reaction stirred at reflux for two hours. The reaction mixture was cooled then dichloromethane (200 ml) added and the layers separated. The aqueous layer was rendered basic by addition of potassium carbonate then re-extracted with dichloromethane (2x200 ml). Organic extracts were combined, dried over anhydrous magnesium sulphate, filtered and concentrated in vacuo to give the title compound as a colourless oil that crystallised on standing to give colourless crystals (15.3 g, 0.07 mol, 59%). ¹H NMR (CDCl₃, 400 MHz) δ: 0.93 (t, 3H), 1.62 (q, 2H), 2.71 (q, 2H), 2.81 (t, 2H), 3.00 (d, 1H), 3.80 (s, 3H), 4.30 (bs, 1H), 4.89 (d, 1H), 6.81 (d, 1H), 6.91 (d, 1H), 6.93 (s, 1H), 7.22 (t, 1H). LRMS; m/z 210. Mpt: 50-51°C. Analysis found C, 67.47; H, 9.02; N, 6.45%. C₁₂H₁₆NO₂•0.2H₂O requires C, 67.70; H, 9.19; N, 6.58%.

Non-Obviousness of Polymorphs

- Structurally similar compounds often *prima facie* obvious variants: showing of unexpected results can rebut.
- Novel polymorphs are patentable without showing unexpected results
- Can't predict polymorph, properties, or how to make





Non-Obviousness of Polymorphs

Grunenthal GMBH v. Alkem Laboratories Ltd. (Fed. Cir. 2019)

- US 7,994,364: claim to Form A of tapentadol HCl
- Prior art:
 - Form B of tapentadol HCl. Not known to exhibit polymorphism.
 - Byrn: conceptual approaches to discovery of polymorphism (screening).
- Dist. Ct.: not invalid as obvious.
- CAFC: affirmed. No reasonable expectation of success.
 - Polymorphism not known for tapentadol HCl. No prior art evidence of any Form A synthesis. No guidance on many polymorphism variables.
 - **“Our decision today does not rule out the possibility that polymorph patents could be found obvious.”**



Non-obviousness of Polymorphs

Pharmacyclics LLC v. Alvogen, Inc. (Fed. Cir. 2022), non-precedential

- US 9,725,455: claim to Form A of ibrutinib with XRPD peaks
- Prior art asserted for obviousness:
 - 2 disclosures of ibrutinib and method of synthesis, but no actual crystalline forms
 - 2 general references on polymorphism, screening
- Dist. Ct.: not invalid as obvious. Motivation to make *a* crystalline form, but not Form A with XRPD peaks. No reasonable expectation of success (unpredictability!).
- CAFC: affirmed. No teaching of ibrutinib crystalline forms and unpredictable polymorph screening results.



Obviousness of Polymorphs

Salix Pharmaceuticals, Ltd. V. Norwich Pharmaceuticals Inc. (Fed. Cir. 2024)

- Claims directed to rifaximin Form β with XRPD peaks
- Single prior art reference's examples described synthesis and crystallization of rifaximin. Crystal not characterized.
- Dist. Ct: obvious because good reason to characterize, it was routine, and prior art would have led POSITA to detect crystal.
- CAFC: affirmed.
 - *Grunenthal* and *Pharmacyclics*: no reasonable expectation to *produce* crystal
 - Here, routine to *characterize* crystal produced by known process.
 - Inherent anticipation argued but not considered (!)
- Correct result, wrong reason.



Patentability of Polymorphs

CLOSE CASE OF ANTICIPATION *Ex Parte Pfrengle*, 2010 WL 4264580 (Bd. Pat. App. & Interf.)

1. Anhydrous crystalline tiotropium bromide which is characterized in that the X-ray powder diagram has values $d = 6.02 \text{ \AA}$; 4.95 \AA ; 4.78 \AA ; 3.93 \AA and 3.83 \AA .

- 102(b) rejection: burden shifting
 - “white crystals” obtained by process very close to Appellants’ process
 - “when PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).
 - No XRPD data. Only melting point.
- 1.132 declaration distinguished claimed and prior art crystals (XRPD and DVS).
- BPAI reversed examiner because declaration evidence rebutted *prima facie* anticipation.



Patentability of Polymorphs

Too CLOSE *Ex Parte Reddy*, 2010 WL 1252093 (Bd. Pat. App. & Interf.)

1. A compound which is a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1.

- 102(b) rejection: burden shifted again.
 - Claimed and prior art processes are same
 - XRPD patterns “are the same and within margins of error of each other.”
- Appellants showed that claimed and prior art forms have different melting points.
- BPAI: AFFIRMED.
 - Mere difference in physical property (mp) is well-known variation
 - Appellants did not claim amount or purity of crystalline form



Lessons from the PTO

- *These* BPAI decisions are non-binding on examiners.
- Discussion with PTO examiner revealed internal effort to harmonize examination
- Disclose and claim at least 2 ‘orthogonal’ sets of data, *e.g.*, XRPD and solid state NMR
- Distinguish over prior art process of synthesis and (re)crystallization to keep burden on PTO to show “sound basis.”



Inventive Step of Polymorphs

- Polymorph is novel because prior art disclosure of compound does not include XRPD lines
- Issue is whether polymorph constitutes inventive step.
- Applicant asserted improved bioavailability and ease in formulation.

EP 03744465.0

1. A crystalline form of [5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt having the formula:

[chemical structure]

and characterized by having an X-ray powder diffraction pattern with peaks at: 6.20, 9.34, 12.16, 12.48, 15.06, 18.26, 18.80, 24.02, 24.46, 26.70, 27.02, 27.48, and 30.86 degrees 2 θ .



Inventive Step of Polymorphs

- EPO unmoved
 - “[T]he provision of a specific crystal form as such does not imply the presence of an inventive step as long as it did not manifest itself in a valuable property in the widest sense, an effect or an increase in the potency of an effect in comparison to the prior art.”
 - Preparation of further crystal forms is “simple routine work” and “does not require an inventive input.”
 - Skilled person can easily prepare further polymorphs of known structure
- Lessons
 - Mere discovery of (new) polymorph may be novel, but not necessarily inventive
 - Must have solid data on a “valuable property”
 - More than mere assertions



Inventive Step of Polymorphs

Sandoz K. K. v. Werner-Lambert Company LLC (2012)

- Invalidation trial before appeal board at JPO
 - Prior art example disclosed compound and possibility of recrystallization, but no obtained crystal.
 - Held: polymorph is inventive.
 - No prior art crystal
 - Improved properties are not predictable

- Sandoz appealed

1. Crystalline Form I atorvastatin hydrate characterized by the following X-ray powder diffraction pattern expressed in the terms of the 2θ , d-spacings, and relative intensities with a relative intensity of > 20% measured after 2 minutes of grinding using $\text{CuK}\alpha$ radiation [table of data] . . .



Inventive Step of Polymorphs

Sandoz K. K. v. Werner-Lambert Company LLC (2012)

- IP High Court reversed
 - Synthesis example + general disclosure of recrystallization = disclosure of claimed polymorph
 - Skilled artisan motivated to try to obtain specific crystalline form
 - Improved properties are highly predictable
 - Held: no inventive step
 - Appeal to Supreme Court denied
- Lessons
 - Data showing pharmacological advantages
 - File before publication of basic patent application
 - Difficult method of making?



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Patentability of Polymorphs

Novartis AG v. Union of India (2013) -- Gleevec

1. [beta-crystalline form of imatinib mesylate]

- Novartis “mailbox” application
 - Pre-grant oppositions by Indian generics
 - Controller rejected application → appeal to Madras High Court
 - Transferred to IP Appellate Board: affirmed
 - Novartis appealed to Supreme Court
- Patent Eligibility: section 3(d)
 - New form of “known substance” without enhancement of efficacy not an invention.
 - Same substances: salts, esters, ethers, polymorphs . . !

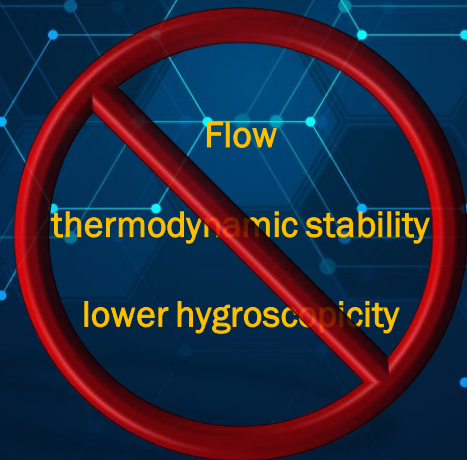


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Patentability Step of Polymorphs

Novartis – “known substance trigger”

- Salt is known substance with known efficacy
- Prior art patent
 - imatinib and general disclosure of pharmaceutical salts
 - deemed to disclose imatinib mesylate
- Claimed crystal is new form of salt
 - beta-form is 30% more bioavailable!





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Patentability of Polymorphs

Novartis – efficacy is key

- Efficacy = “therapeutic efficacy”
- Increased bioavailability is not necessarily increased efficacy
 - Bioavailability: pharmacokinetic parameters
 - Efficacy: pharmacodynamic parameters. Different polymorphs can give rise to different organism responses.



Patentability of Polymorphs*

- CL, MX: patentable, especially if corresponding U.S. or EP claims are patented
- BR, CO, PE, UY: must 'prove' inventive step by solving problem by superior effect/solution
- AR, VN: not patentable

Practice Tips

- Consider overbreadth (“polymorphs thereof”)
 - Might be difficult to defend enablement or written description of crystalline form genus
- Don’t claim too narrowly
 - Claims with too much data are hard to enforce
 - Represent data responsibly: $20.2 \pm 0.2^\circ 2\theta$, not $20.1234^\circ 2\theta$
- Know the prior art
 - Inherency is the major potential weakness
 - Avoid carrying burden at PTO by distinguishing prior art and inventive processes for making polymorph

Practice Tips

- Obtain high quality data
 - Reproducible, good S/N, fully describe instrumentation and collection parameters
 - Difficult to distinguish and identify polymorph if data is poor: enforcement problems
- Formulate a global plan
 - Out of the novelty box isn't enough
 - Hard, tangible advantages of polymorph
 - Chemical and physical data
 - Pharmacodynamics (therapeutic efficacy)
pharmacokinetics (AUC, C_{max} , bioavailability)



Thank you

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