SLW Life Sciences Webinar

Patenting Solid Forms Pharmaceuticals Revisited

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June 9, 2026

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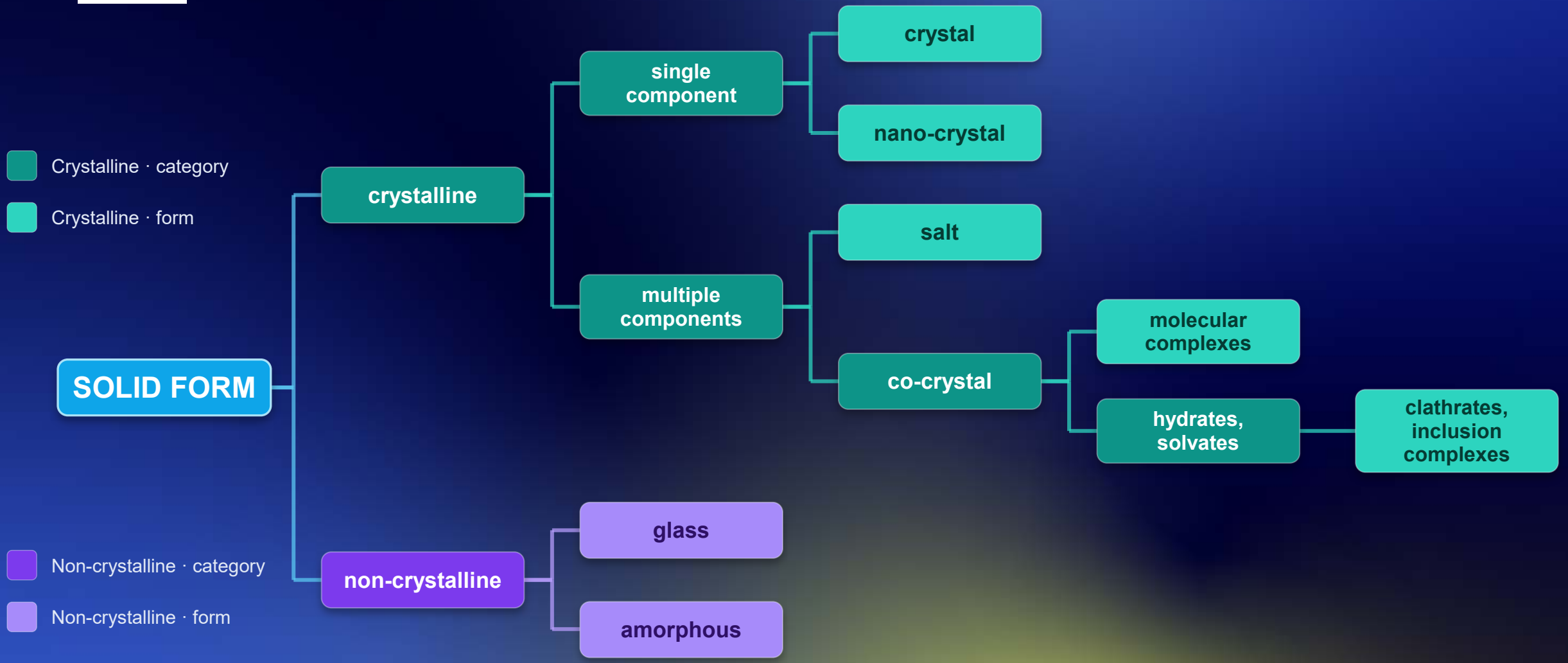
Overview

- What are solid forms?
- Why are they important?
- Why are they worth patenting?
- Patenting mechanics
- Legal considerations and jurisdictional issues

Important Definitions

- Polymorphism – a different arrangement and/or conformation of the molecules in a crystal lattice
- Amorphous – a disordered arrangement of molecules not having a crystal lattice
- Solvates – a crystal form containing a stoichiometric or nonstoichiometric amount of a solvent
  - Hydrate – the solvent is water

Taxonomy of Solid Forms



Importance of Crystalline Polymorphs

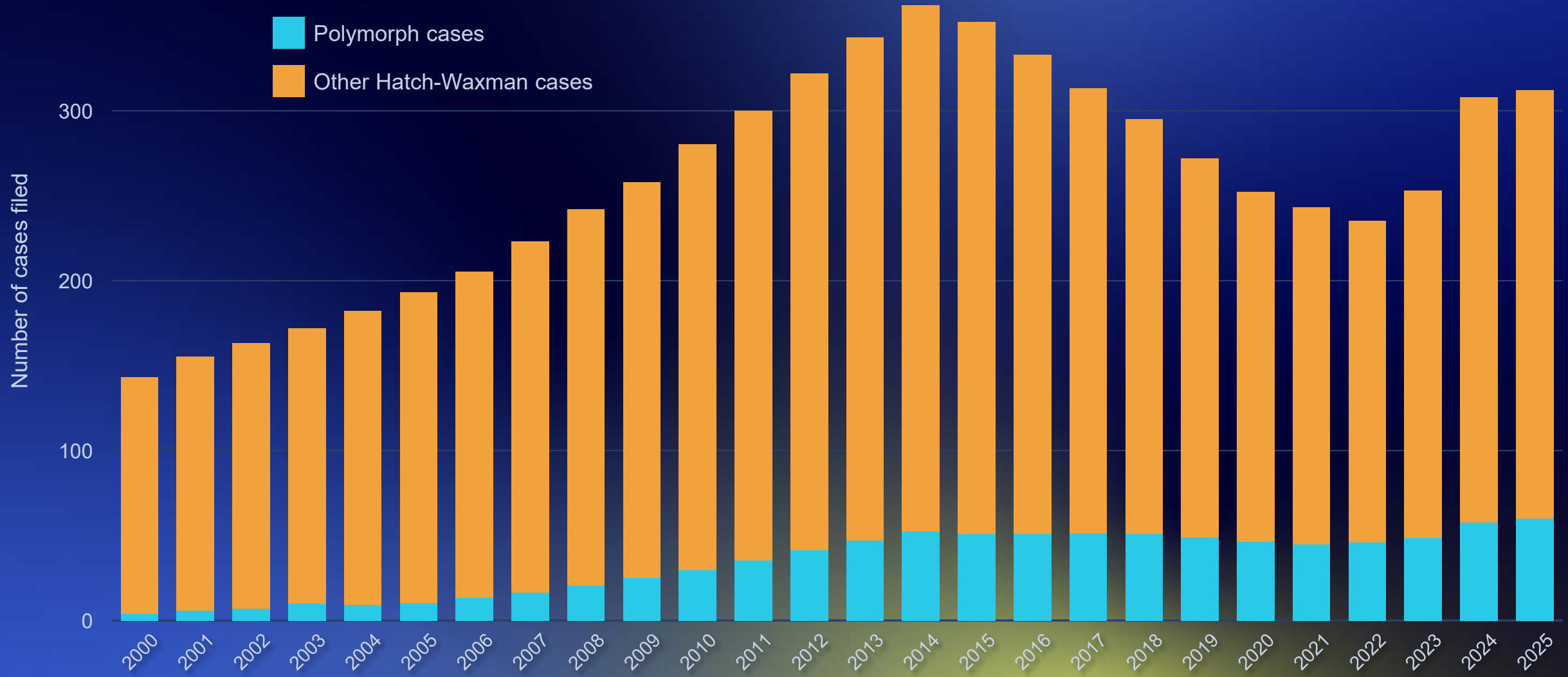
- Regulatory Considerations
  - US Food and Drug Administration
    - Guidance for Industry
    - “ANDAs: Pharmaceutical Solid Polymorphism”
    - Sameness requirement between generic and branded compositions
  - European Medical Agency
    - ICH Q6A – consideration of polymorphism in setting specifications and quality control
    - ICH Q8 – identification of physiochemical properties, including crystal structure, that affect drug performance
    - ICH Q11 – drug substance development

Importance of Crystalline Polymorphs

- Innovators
  - Extend market exclusivity
  - Additional IP protection for a drug substance/product

- Generic Producers
  - Non-infringement of protected drug substance
  - Separate IP position for generic product
  - Sameness requirement for the branded product
    - PK and PD parameters

Importance of Crystalline Polymorphs



Importance of Crystalline Polymorphs

- Why does polymorphism matter?
  - Ritonovir (Norvir®)
    - HIV/AIDS protease inhibitor
    - Two years after launch new polymorph formed during minor adjustment in production
    - Much lower dissolution rate
  - Rifaximin (Xifanan®)
    - Broad spectrum antibiotic
    - Two different polymorphs known
    - Very different *in vivo* pharmacokinetic profiles due to differences in solubility and dissolution profile

Importance of Crystalline Polymorphs

- Newman and Wenslow, “Solid form changes during drug development: good, bad, and ugly case studies,” *AAPS Open* (2016) **2:2**
  - DOI 10.1186/s41120-016-0003-4
  - Open access
- Case studies on how crystal polymorphism had a very significant impact on both drug development and in product life cycle management.

Drafting the Specification

- Formation conditions to ensure enablement
- Enough data to ensure novelty and written description
- Definitions to avoid indefiniteness

- Describe the advantages
  - Ease in manufacturing
  - Formulation – flowability, drying, caking
  - Hygroscopicity

Drafting the Specification

- Pharmaceutical Importance
  - Physical stability – thermodynamic and/or kinetic?
  - Chemical stability – shelf life, storage conditions
  - Solubility – dissolution profile, immediate release vs extended release
  - PKD parameters – AUC, PK/PD profile

- Biological Data
  - Often useful during prosecution in “inventive step” jurisdictions
  - Does the PK/PD profile distinguish the claimed form from other forms?

Drafting the Specification

- Pharmaceutical Importance
  - Will the crystalline form be the FDA/EMA approved form?
  - Will the crystalline form be the infringing generic?
  - Even with IV or dissolved medicaments, solid forms are usually used during purification of the API
    - Will the claimed crystalline form be prepared during manufacture of the final drug product

Drafting the Specification

- Characterization
  - Composition – single API, salt form, solvate, etc.
  - Formation method – recrystallization conditions (i.e., solvents, temperature, time)
  - Crystal structure – single crystal diffraction, powder x-ray diffraction (PXRD)
  - Physical properties – melting point, dissolution rate, density
  - Thermal properties – differential scanning calorimetry (DSC), thermogravimetric (TGA)

Drafting the Specification

- Characterization
  - Spectroscopy – solid state FTIR, solid state Raman
  - Stability – transformation rates between different states
  - Biological Data – PK and PD profile, AUC, C_{max}, etc.

Claim Drafting

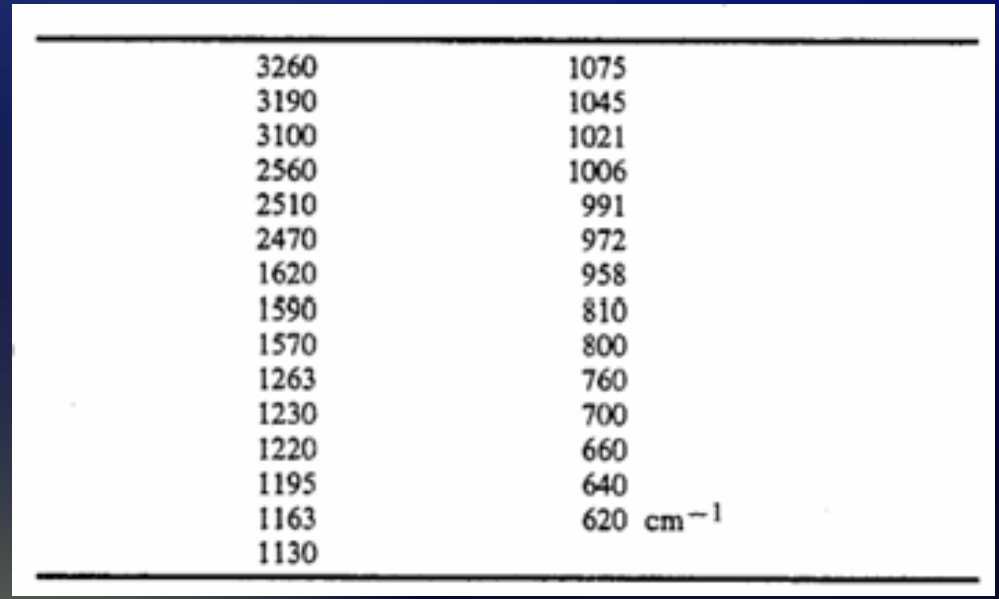
- Claims must find the balance between too specific and too general.
  - Rifle shot, not “needle”
  - Also not shotgun blast as with NCE application

- Must also draft claims, or have support in the specification for claims, that are appropriate for the jurisdiction.

Claim Drafting – too narrow

- *Glaxo, Inc. v. Novopharm Limited* 931 F.Supp. 1280 (ED NC 1996).
- Glaxo failed to prove infringement (affirmed at CAFC)

- Claim 1 of US 4,521,431: Form 2 ranitidine hydrochloride characterised by an infra-red spectrum as a mull in mineral oil showing the following main peaks:



3260	1075
3190	1045
3100	1021
2560	1006
2510	991
2470	972
1620	958
1590	810
1570	800
1263	760
1230	700
1220	660
1195	640
1163	620 cm^{-1}
1130	

Claim Drafting – too narrow

- *Glaxo, Inc. v. Novopharm Limited*
  - Claim 2 of US 4,521,431: Form 2 ranitidine hydrochloride according to claim 1 further characterised by the following x-ray powder diffraction pattern expressed in terms of "d" spacings and relative intensities (1) (s=strong, m=medium, w=weak, v=very, d=diffuse) and obtained by the Debye Scherrer method in a 114.6 mm diameter camera by exposure for 12 hours to CoK_a radiation and for 3 hours to CuKa radiation:

d (Å)	I	d (Å)	I
10.73	m	3.40	2 w
6.50	3 vwd	3.35	2 vwd
6.13	m	3.25	wd
5.83	s	3.12	2 vw
5.63	3 vwd	3.04	2 vwd
5.42	s	2.97	3 vwd
5.06	2 vw	2.93	3 vwd
4.92	w	2.88	3 vwd
4.59	2 vw	2.81	vwd
4.40	s	2.72	vwd
4.28	w	2.66	3 vwd
3.91	wd	2.47	2 vwd
3.79	s	2.44	vw
3.71	m	2.34	2 vwd
3.60	vwd	2.30	3 vwd
3.46	m	2.21	2 vwd

Claim Drafting – too narrow

- *Glaxo, Inc. v. Novopharm Limited*
  - “Clearly, the Court cannot entertain Glaxo's argument that sightings by its experts of one or two small "peaks" in Novopharm's ANDA indicate the presence of Form 2, a substance claimed in the '431 and '133 patents by no less than twenty-nine main infra-red peaks and thirty-two main x-ray d-spacings. As a matter of law, an area ratio test dependent on the presence of a single claimed infra-red peak out of twenty-nine such peaks claimed in the patent is insufficient to prove infringement.” 931 F.Supp. 1280, 1290 (ED NC 1996).

Claim Drafting

- Dactyloscopy for the 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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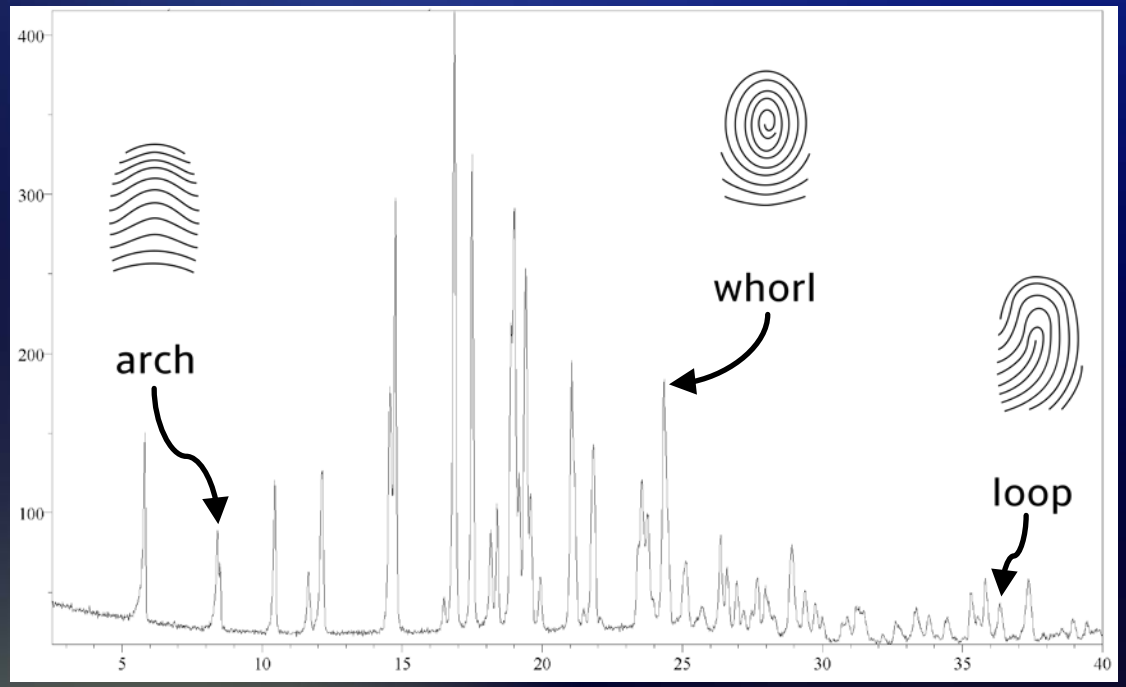
Claim Drafting

- Dactyloscopy for the Attorney
  - Select claim limitations that differentiate between polymorphs; do not merely identify a polymorph
  - Pick just enough signals to define the unique polymorph. How many?
  - Identifying and differentiating polymorphs should be straightforward and accessible (to POSITA, examiners, courts, etc.)

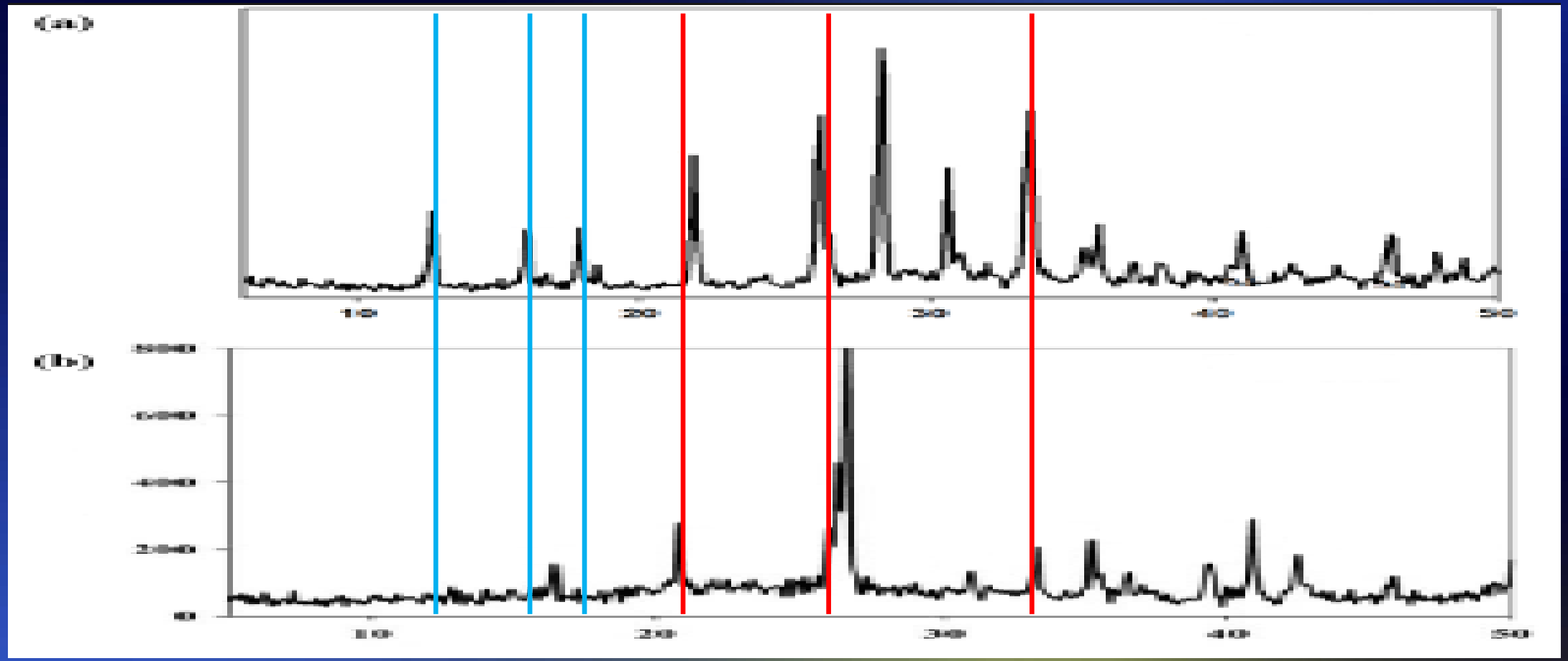


Claim Drafting

- Optimal situation when drafting
  - Obtain multiple polymorphs AND their XRPD diffractograms.

- Stack diffractograms with 2θ (x-axis) alignment
  - Identify peaks amongst diffractograms with similar 2θ values
  - Select 3-4 peaks unique to the claimed polymorph

Claim Drafting



Claim Drafting

- Elements of an optimal claim
  - Unambiguously identify the molecule – IUPAC, structure, salt form, etc.
  - Clearly identify the radiation source and wavelength
  - Clearly identify the experimental error in the instrument
  - Claim elements fortified by support and data in the specification with examples and high-quality spectra

Claim Drafting

- Claim 1: A crystal form of [NAME] having an X-ray powder diffraction pattern characterized by **peaks** at 2θ angles of 10.1 ± 0.2, 20.7 ± 0.2, and 30.4 ± 0.2 determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

- Claim 1: A crystal form of [NAME] having an X-ray powder diffraction pattern characterized by **signals** at 2θ angles of 10.1 ± 0.2, 20.7 ± 0.2, and 30.4 ± 0.2 determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

- The specification must clearly define the difference between a signal and a peak – signal to noise ratio (e.g. 3:1) or functional maxima.

Claim Drafting

- Claim 2: The crystal form according to claim 1, further comprising X-ray powder diffraction **peaks** at 2θ angles of 15.4 ± 0.2, 25.1 ± 0.2, and 35.9 ± 0.2.

- Claim 2: The crystal form according to claim 1, further comprising X-ray powder diffraction **signals** at 2θ angles of 15.4 ± 0.2, 25.1 ± 0.2, and 35.9 ± 0.2.

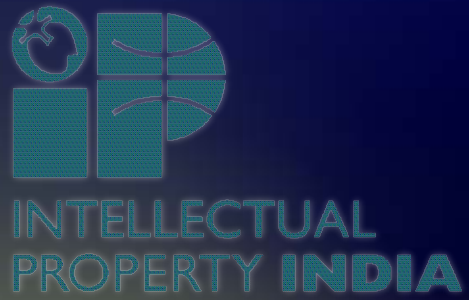
- Never assume that all crystalline polymorphs have been identified.
  - Atorvastatin calcium has 70+ known crystalline forms.

Claim Drafting

- Claim 3: A crystal form of [NAME], said crystal form prepared by recrystallization in a solvent mixture of [solvent 1] and [solvent 2], wherein… [recrystallization conditions and solvent ratios].

- Product by process claims can provide an additional layer of protection.
  - Process claims can implicate § 271(g) (Process Patent Infringement) when manufacturing is performed overseas and then imported into the United States.

Legal Considerations



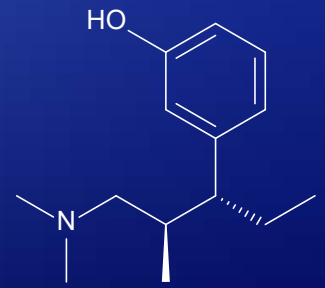
Legal Considerations

- Anticipation/ Novelty – in most instances the amorphous form has already been disclosed; would the amorphous form anticipate the crystalline form?
  - Crystal forms have different physical and/or biological properties
- Obviousness/Inventive Step – innovators are required to study new chemical entities, so they would naturally discover them during development
  - Not all molecules have crystalline polymorphs
  - Not all crystalline polymorphs have different properties as compared to the amorphous form
- Inherency – why isn't the crystalline form inherent based on a disclosure of an amorphous form?
  - Crystalline forms require special conditions to form that do not occur in nature, especially if prepared in salt form from nonaqueous solvents
  - Prior art description of making and isolating crystal, but not characterizing crystal, could be inherent disclosure of claimed polymorph.

Jurisdictional Issues

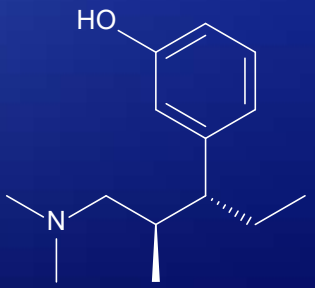
- Inventive step versus obviousness
  - Inventive step focus is on where development starts and the steps that lead to the final product
  - Obviousness focus is on the final product with minimal consideration for how it was reached

Grunenthal GMBH v. Alkem Laboratories, Ltd.



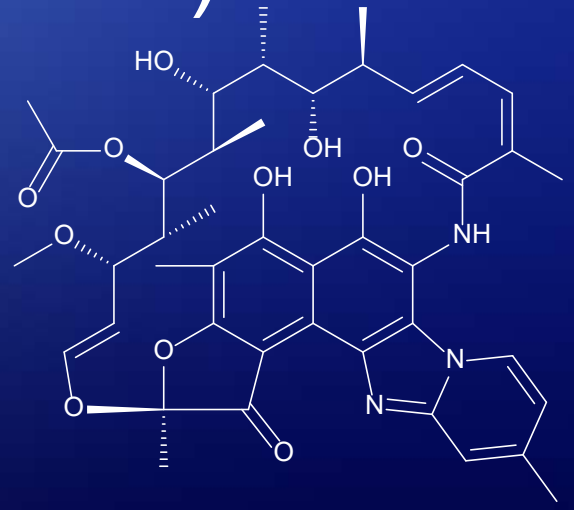
- Tapentadol hydrochloride (Nucynta®)
- US 7994364 claim 1: 1. A crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu Kα radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2.
- Challenger argued obviousness based on:
  - numerous references disclosing polymorphs in general and
  - FDA guidance requiring that a brand owner evaluate polymorphism in a new chemical entity OR
  - Byrn article: conceptual approaches to discovery of polymorphism (screening options).

Grunenthal GMBH v. Alkem Laboratories, Ltd.



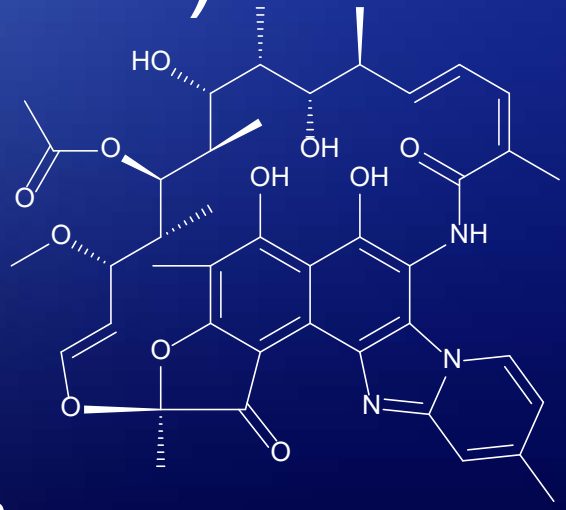
- District Court Question: Can a routine method applied to a known substance produce a non-obvious product?
- Alkem appeal based on finding of nonobviousness by the Distict Court
- Federal Circuit affirmed the District Court
- There was no reasonable expectation of success in making or finding the claimed polymorph.
- "Our decision today does not rule out the possibility that polymorph patents could be found obvious."

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



- Rifaximin (Xifaxan®)
- District Court found the claimed polymorph **inherently disclosed** in the prior art and routine characterization would have identified it.
- CAFC: “The difference between the prior art and the claims is thus effectively nothing more than the performance of routine characterization to identify the polymorphic forms that result from the known [prior art] processes.”

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



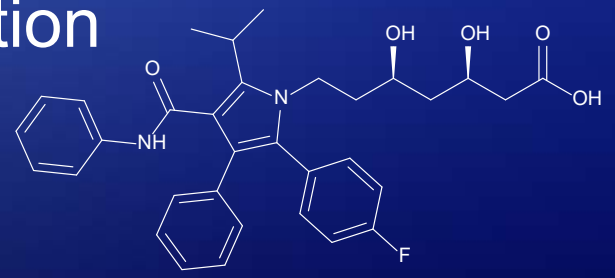
- CAFC affirmed: “There thus appears to be no dispute that the claimed polymorph can be readily produced from the crystallization conditions disclosed in [the prior art] and that it would have been well within the abilities of the skilled artisan to procure and characterize the β form of rifaximin.”

- CAFC hinted that claimed polymorph was not novel but emphasized lack of characterization in the prior art rather than the lack of novelty.

- Emphasized the fact dependent nature of the decision and analysis.
  - With an early disclosure of the molecule, mostly likely in a large genus, be cautious about including too specific **purification and isolation conditions**.

EP 1148049 – T 0777/08

- Atorvastatin – appeal of revocation during opposition



  - The approved API is the calcium salt
  - Patents on the original API were the closest prior art
  - The amorphous API had several problematic properties during formulation – flowability and ease of drying
  - It is well known in the art that crystal forms have different physical properties than the amorphous form.
  - It is well known in the art that crystal forms often have better flowability and drying than amorphous forms.
  - There might be trade-offs in good and bad properties between amorphous and crystalline forms.
  - No inventive step.

EP 1148049 – T 0777/08

- Atorvastatin – appeal of revocation during opposition

  - The approved API is the calcium salt
  - Patents on the original API were the closest prior art
  - Polymorphism is well-known in the art
  - Innovators are required to investigate polymorphism as part of the drug development process
  - Screening is a well-known and virtually automated
  - No inventive step

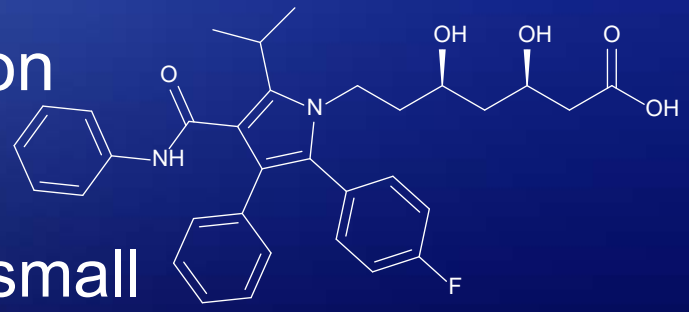
EP 1148049 – T 0777/08

- Atorvastatin – appeal of revocation during opposition

  - "…in the absence of any technical prejudice…the mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving an inventive step (contrary to the statement in the patent in suit, paragraph [0011]." Decision at § 5.2, ¶ 5 (pg. 11).

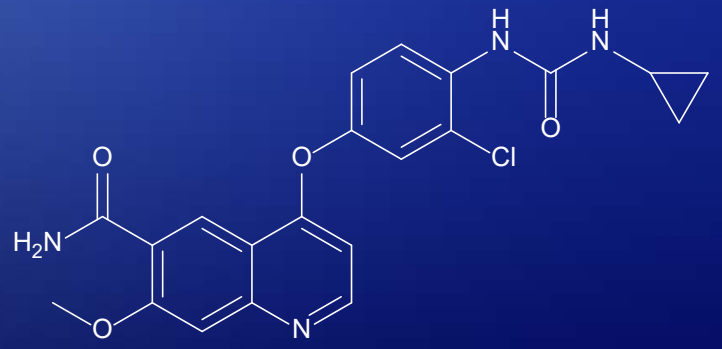
EP 1148049 – T 0777/08

- Atorvastatin – appeal of revocation during opposition



- The prior art references were general references on small molecule chemistry
  - Bavin, “Polymorphism in Process Development,” *Chemistry & Industry*, **21**, 527 (1989)
  - Bryn, *et al.,* “Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations,” *Pharm. Res.*, **12(7)**, 945 (1995)
  - Hancock, *et al*., “Characteristics and Significance of the Amorphous State in Pharmaceutical Systems,” *Pharm. Res.*, **12(6)**, 799 (1995)

EP 04807580.8 - T 0643/12

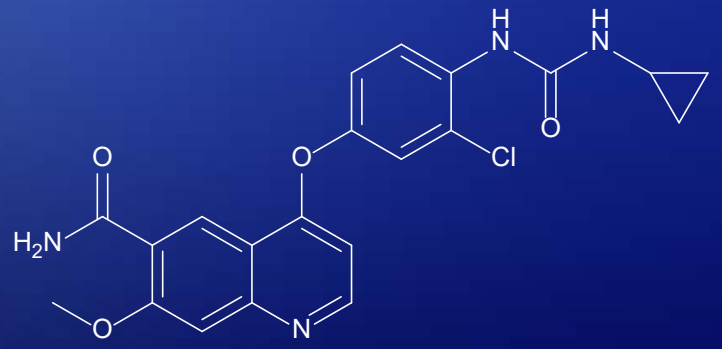


- Lenvatinib (Lenvima®)

- Appeal of rejection by Examining Division
  - ED cited in part to T 0777/08 in the rejection

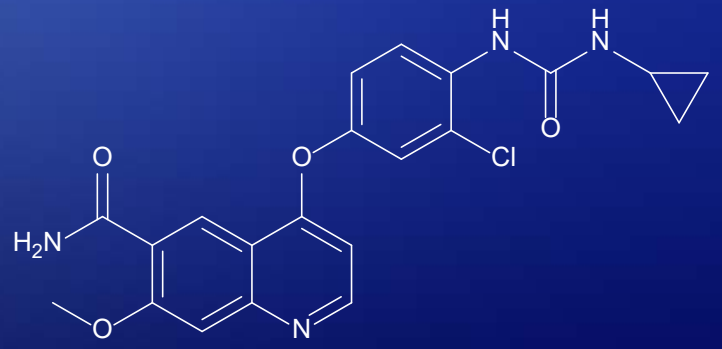
- Rejection was reversed
  - Contrasted the application to T 0777/08
  - Emphasized the technical problem addressed in the claims

EP 04807580.8 - T 0643/12



- Lenvatinib (Lenvima®)
- In the specification, the technical problem was explicitly defined as “the provision of Lenvatinib in a form having an improved dissolution rate and bioavailability, low hygroscopicity, and good stability.”
- Supporting data evaluating these properties in the examples. Multiple polymorphs discovered and tested – only one claimed.

EP 04807580.8 - T 0643/12



- Lenvatinib (Lenvima®)

- Distinguished from T 0777/08
  - "…the mesylate salt claimed would not have been expected to deliver the desired ***combination*** of properties. Moreover, the skilled person would not have expected that any arbitrary crystalline salt form of Lenvatinib would be equally suitable in this respect." Decision at § 5.3.

T 0777/08 vs T 0643/12

- There was a clear technical problem in T 0643/12 with extensive supporting data.
  - Numerous polymorphs prepared and tested. Best one for formulation with the most desirable properties was selected for patenting.
- In T 0777/08, it was primarily about claiming a polymorph for the sake of a polymorph and extending patent protection.

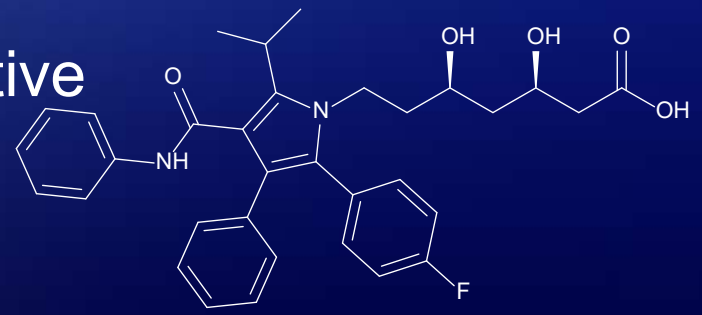
- Lesson: patent owner must control the technical question, and in the specification there must be a clear technical problem that is solved by the crystalline polymorph. Data illustrating both successful and unsuccessful attempts to solve the problem is especially strong.

EPO Open Question

- Will the UPC change anything?
- Stay tuned over the next several years to find out.

JP 3296564 - Atorvastatin

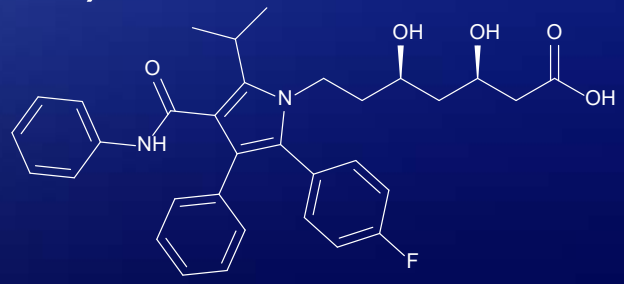
- *Sandoz K. K. v. Werner-Lambert Company LLC* ((IPHC), Case No. Hei 23 (Gyo-Ke) 10445 (2012))
  - Appeal Board at JPO upheld claims as being inventive
  - Improved properties are not predictable



- IP High Court Reversed
  - Skilled artisan motivated to try to obtain specific crystalline form
  - Improved properties are highly predictable
  - Held: no inventive step
  - Supreme Ct. denied petition for appeal

JP 3296564 - Atorvastatin

- *Sandoz K. K. v. Werner-Lambert Company LLC* ((IPHC), Case No. Hei 23 (Gyo-Ke) 10445 (2012))



- Lessons
  - If the procedure to obtain the crystalline polymorph is routine, then a skilled person would perform it.
  - Not inventive to perform trial and error crystallization and characterization.
  - Whether or not a claimed invention has **remarkable effects** is considered an important aspect in determining if an inventive step is present
  - Important to include data illustrating how the polymorph is superior in one or more properties compared to the other known forms.
  - Post filing data is not always permitted, so it should be included in the original application

CN 201580047368.6 - Fruquintinib

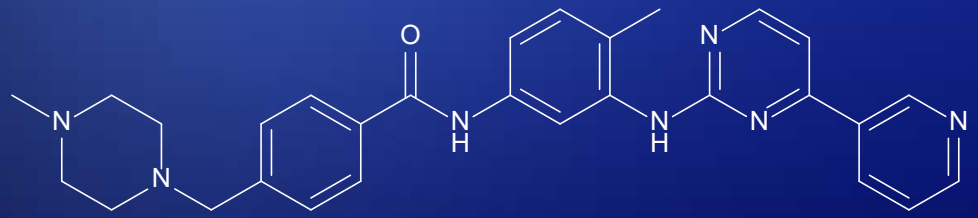
- *Chengdu Sino-Strong v. CNIPA* (Beijing IP Court (2024))
  - CNIPA denied the application
    - Polymorph screening was routine
    - Insufficient comparative effect: claimed polymorph had **better stability** than the prior art.
    - An "**unexpected technical effect**" with clear superiority over the prior art is required for patentability
  - Beijing IP Court Reversed
    - "**Better technical effect**" is sufficient to support patentability
      - Practical usability, commercial viability, significant investment in finding and developing the polymorph
    - Considered a significant doctrinal shift

Chinese Approach

Court Level	Approach
CNIPA (Patent Office)	Unexpected effect required with clear superiority over the prior art; very strict
Beijing IP Court (2024)	“Better technical effect”; less strict and more flexible
Supreme People’s Court	Established the “unexpected effect required” standard and has not been changed.

India – Gleevec® (Imatinib)

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

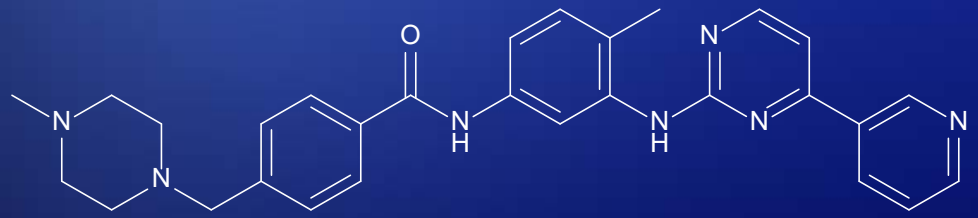


  - Pre-Grant Opposition by generic producers
    - Pre-grant oppositions by Indian generics
    - Controller rejected application → appeal to Madras High Court
    - Transferred to IP Appellate Board: affirmed
    - Novartis appealed to Supreme Court

INTELLECTUAL PROPERTY INDIA

India – Gleevec® (Imatinib)

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



  - Patent Eligibility: section 3(d)
    - New form of "known substance" without enhancement of efficacy not an invention.
    - Same substances: salts, esters, ethers, polymorphs
  - 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
    - Bioavailability is not improved therapeutic efficacy
  - Lesson
    - **Efficacy**: PK/PD parameters (C_{max}, AUC, etc). Different polymorphs can give rise to different organism responses.

INTELLECTUAL PROPERTY INDIA

Summary of All Jurisdictions

Major Jurisdictions

Jurisdiction/System	Difficulty	Core Standard	Key Issues / Obstacles
India	Very High	Section 3(d)	Requires therapeutic efficacy; polymorphs presumed unpatentable
China (CNIPA)	High	Inventive step	Routine crystallization presumed obvious
China (Courts)	Moderate	Inventive step	Emerging 'better effect' standard
Japan	High	Inventive step + enablement	Strict reproducibility requirements
United States	Low-Moderate	Anticipation	More permissive; unpredictability helps
EPO (Europe)	Moderate	Problem-solution	Requires technical effect

Europe (National)

Jurisdiction/ System	Difficulty	Core Standard	Key Issues / Obstacles
Germany	Moderate	EPO-aligned	Technical effect required
France	Moderate	EPO-aligned	Predictability analysis
Italy	Moderate	EPO-aligned	Routine screening vulnerability
Spain	Moderate	EPO-aligned	Strict comparison methodology
UK	Moderate	EPO + UK case law	Flexible obviousness approach
UPC	Unknown		

Summary of All Jurisdictions

East Asia & SE Asia

Jurisdiction/System	Difficulty	Core Standard	Key Issues / Obstacles
South Korea	Moderate-High	Inventive step	Unexpected effects required
Taiwan	Moderate-High	Inventive step	Strong data requirements
Singapore	Moderate	EPO-influenced	Accepts polymorphs with data
Malaysia	Moderate	EPO-style	Documentation critical
Thailand	Moderate-High	Strict pharma policy	Secondary patents disfavored
Indonesia	Moderate-High	Strict examination	Evergreening concerns
Philippines	Moderate	EPO-like	Data-driven
Vietnam	Moderate-High	Strict inventive step	Incremental improvements disfavored

Latin and South America

Jurisdiction/System	Difficulty	Core Standard	Key Issues / Obstacles
Brazil	Moderate-High	Inventive step	Health policy overlay
Argentina	Very High	Restrictive	Secondary patents often rejected
Chile	Moderate	Inventive step	Accepts with strong data
Colombia	Moderate-High	TRIPS-based	Public health scrutiny
Peru	Moderate-High	Andean framework	Derivative skepticism
Ecuador	Very High	Public policy	Secondary patents denied
Uruguay	Moderate	Developing	Limited precedent
Paraguay	Moderate	Developing	Unpredictable outcomes

Summary of All Jurisdictions

Central America and Mexico

Jurisdiction/System	Difficulty	Core Standard	Key Issues / Obstacles
Mexico	Moderate	Inventive step	Data-driven but flexible
Costa Rica	Moderate-High	TRIPS strict	Derivative scrutiny
Panama	Moderate	Flexible	Limited case law
Guatemala	Moderate-High	Strict	Low transparency
Honduras	Moderate	Developing	Data required
El Salvador	Moderate	Strict	Limited precedent
Nicaragua	Moderate	TRIPS-based	Uncertain enforcement
Dominican Republic	Moderate	Flexible	Variable outcomes

African Systems

Jurisdiction/System	Difficulty	Core Standard	Key Issues / Obstacles
ARIPO	Moderate	EPO-influenced	Accepts polymorphs with data
OAPI	Moderate	French/EPO hybrid	Limited scrutiny
South Africa	Low	Formal system	No substantive examination
Egypt	Moderate-High	TRIPS-based	Growing scrutiny
Morocco	Moderate	EU-aligned	Accepts with effect
Tunisia	Moderate	Developing	Limited case law
Kenya	Moderate-High	Health policy	Anti-evergreening trend
Nigeria	Moderate	Weak exam	Variable outcomes
Ghana	Moderate	Developing	Limited precedent
Ethiopia	Very High	Restrictive	Pharma patents constrained

Summary of All Jurisdictions

Middle East

Jurisdiction/System	Difficulty	Core Standard	Key Issues / Obstacles
Saudi Arabia	Moderate	EPO-like	Accepts polymorphs
UAE	Moderate	Flexible	Developing system
Israel	Moderate	EPO-like	Mature system
Turkey	Moderate	EPO-aligned	Predictability analysis
Iran	Moderate-High	Restrictive	Limited foreign filings

CIS/Eurasia

Jurisdiction/System	Difficulty	Core Standard	Key Issues / Obstacles
Russia	Moderate	EPO-like	Variable application
Ukraine	Moderate-High	Developing	Limited clarity
Kazakhstan	Moderate	EPO-influenced	Fragmented system

Global Polymorph Patenting

Key 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
  - Identify target jurisdictions during drafting
  - Novelty often isn’t enough
  - Hard, tangible advantages of polymorph
  - Include as much data as possible in the application

Key Practice Tips

- Claiming Strategy
  - Overlapping and narrowing layers of dependent claims
  - Method of formation and recrystallization conditions
- Know the prior art
  - Inherency can be a problem
  - Clearly distinguish the claimed polymorph from the prior art

Thank you

These materials are for general informational purposes only. They are not intended to be legal advice, and should not be taken as legal advice. They do not establish an attorney-client relationship.