Polymorphism of Active Pharmaceutical Ingredients: the border between a real quality issue and an effective patent tool

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Crystal forms @ Bologna -
The sixth Workshop on Crystal forms

Bologna – January 19th, 2012
Polymorphism of organic compounds

- Known since 1967 (JP 19670830 by Fuji Photo Film Co.): mp 117-119 °C
Polymorphism is a very well known property of organic compounds

- Crystalline form A (octahedral) mp 142°C (DSC)
- Crystalline form B (plate) mp 126 °C (DSC)


Google search for melting point of Variacrol blue A

Results reported in the first 5 pages
Polymorphism is a very well known property of organic compounds

Crystalline form A (octahedral) mp 142°C (DSC)
Crystalline form B (plate) mp 126.5 °C (DSC)


- File registry C.A.: no mention of crystalline forms; mp 128°C

- Aldrich Catalog: mp 128 – 130 °C
Items

- Polymorphs & Patents in the API field (namely generic drugs)
- Polymorphism of intermediates
- Polymorphism of API
- Quantitative determination of crystalline forms
Premise

- A glance into the generic pharmaceutical products arena
- No blame on anyone
Polymorphism of APIs

Polymorphic forms of a drug substance can have different chemical and physical properties:

- Melting point
- Chemical reactivity
- Apparent solubility
- Dissolution rate
- Optical and mechanical properties
- Vapour pressure
- Density

Guidelines for industry
ANDAs: Pharmaceutical Solid Polymorphism – Chemistry, Manufacturing and Controls Information
FDA – CDER – July 2007
Polymorphism of APIs

The different chemical and physical properties can have an impact on:

- Manufacturing of the drug product
- Drug product stability
- Dissolution
- Bioavailability

Guidelines for industry
ANDAs: Pharmaceutical Solid Polymorphism – Chemistry, Manufacturing and Controls Information
FDA – CDER – July 2007
Polymorphism of APIs

Polymorphism can affect the quality, safety and efficacy of the drug product.
Polymorphism of APIs: oral IR formulations

- Are there known polymorphs with different apparent solubility?
- If yes, but they are highly soluble as defined by Biopharmaceutics Classification System, polymorphic form specifications are unnecessary for both drug substance and drug product.

Guidelines for industry
ANDAs: Pharmaceutical Solid Polymorphism – Chemistry, Manufacturing and Controls Information – Attachment 1 – Decision Tree 1
FDA – CDER – July 2007
Patent

It consists of a set of exclusive rights granted by a state to an inventor for a limited period of time in exchange for the public disclosure of an invention.

The patent system has been conceived to promote innovation.
Patentable inventions

- New
- Involve an inventive step
- Susceptible of industrial application

European patent convention 2000 (EPC 200)
Polymorphs patents

New:

- is it really new?
- which crystalline form is described in the prior art (patent and scientific literature known before the filing of the patent application)?
- which crystalline form is obtained following the plain teaching of the prior art?

European patent convention 2000 (EPC 200)
Case 1: Zonisamide

Anti-epileptic drug

Known since 1978 Onho et al, US 4,172,896 by Dainippon Pharmaceuticals

In 2004 a Paragraph IV ANDA application could be filed
Generic medicines in USA: Paragraph IV

- USA is the main market for generic products
- A six months market exclusivity can be obtained by the first generic company proving that the patent exclusivity granted to the drug originator was not due (paragraph IV)
- It is a unique opportunity for a generic drugs produce (six months of high level margins)
- The filing has very tight rules, namely for the timing
Zonisamide: the key intermediate

US 4,172,896 DAINIPPO PHARMACEUTICALS

US 7,291,742 DIPHARMA

US 4,172,896 DAINIPPO PHARMACEUTICALS
Opportunity for a paragraph IV filing on March 27, 2004

Many generic companies attempted the paragraph IV filing

On March 13\textsuperscript{th} 2003 (WO 2003/020708) and March 11\textsuperscript{th} 2004 (WO 2004/020419) two patent applications (by a relevant generic APIs producer) were published claiming 5 crystalline forms (overall) of the sodium salt intermediate
Zonisamide: crystalline forms of the key intermediate

- The product is known since 1978.

- No mention is made in the prior art of the key intermediate crystal forms.

- Which is the crystalline form obtained according to the preparation methods published prior to the filing of the previously mentioned patent applications?

- How long could it take to clarify the issue? At which cost for the company?

- Are our customers ready to accept this patent risk?
In order to avoid any issue with the competitor, Dipharma developed an alternate route not requiring the intermediate sodium salt.

A patent application, even if it is not fully sound, has the power to influence the competition, because the generic companies (customers) are very sensitive to the potential patent risks (cost of the lawsuit).
Crystalline forms of API intermediates: Rabeprazole case

Rabe-750

Allegrini et al Eur. Pat Appl. 1,921,075 (Dipharma)
Crystalline forms of the key intermediates: Rabeprazole

Solubility in the reaction mixture: 0.163 % w/w

Solubility in the reaction mixture: 0.064 % w/w

G. Razzetti, C. Valdiskovic and P. Allegrini unpublished results
Case 2 - ARMODAIFINIL

- Armodafinil is the (R) enantiomer of Modafinil API
- The chemical entity was disclosed and claimed in EP 233106 filed on January, 19 1987
- The patent naturally expired in 2007
- No mention is made to crystalline form(s)
- In 2002 the originator filed a new patent application disclosing Armodafinil polymorphs and a process for their preparation.

Nuvigil

Treatment of Narcolepsy and sleep disorders
The patent application was filed in France (FR 284909)

The original claim 1 is:
1. Procédé de préparation de formes cristallines des énantiomères optiques du modafinil, comprenant les étapes suivantes:
   i) dissoudre l'un des énantiomères optiques du modafinil dans un solvant autre que l'éthanol ;
   ii) cristalliser l'énantiomère du modafinil ;
   iii) récupérer la forme cristalline de l'énantiomère du modafinil ainsi obtenue.

The corresponding polymorphs are claimed in the subsequent lines:
- Form II in claim 17
- Form III in claim 19
- Form IV in claim 21

In addition several solvates are also claimed
Case 2 - ARMODAFINIL

- Why «a solvent different from ethanol?»

- Because according to the basic product patent (Preparation 1/d) the final product is...

recristallise dans l’éthanol.

- The situation seems quite clear:
  - In ethanol crystalline form I is obtained
  - Form I is not new because is the product obtained following the plain teaching of the prior art (EP 233106)
  - So only the other polymorphs could be claimed
Which crystalline form is obtained by crystallizing Armodafinil in Ethanol?

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Recrystallization Procedure</th>
<th>Form Obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/2502</td>
<td>(-)-modafinil was synthesized by ammonolysis of methyl (-) benzhydrylsulfinylacetate in MeOH and water. 100 g of the crude product was taken up in 500 ml absolute EtOH, heated to reflux, filtered, allowed to come to room temperature, then cooled in an ice bath. Crystals were filtered and dried. Yield 77 g. M.P. (inst.)= 153-154°C. These crystals were then dissolved in 500 ml absolute ethanol, heated to reflux, then left to cool to room temperature, with stirring. The crystals were filtered and dried. M.P. (inst.)= 163-164°C. PXRD analysis performed about 1 month later with a PW1840(Cu) diffractometer.</td>
<td>Form I</td>
</tr>
<tr>
<td>1/0054(a)</td>
<td>Crystals of (-)-modafinil were obtained by the same double recrystallization procedure set forth for Example 5/2502, on a larger scale. 163.5 g of product was obtained. M.P. (inst.)= 164°C. PXRD analysis performed about 9 months later with a PW1840(Cu) diffractometer.</td>
<td>Form I/ Form IV mixture</td>
</tr>
<tr>
<td>1/0054(b)</td>
<td>Sample of Example No. 1/0054(a) (supra) taken from storage re-analyzed by PXRD 5 years later with a PW1840(Cr) diffractometer.</td>
<td>Form I</td>
</tr>
<tr>
<td>1/0920</td>
<td>(-)-modafinil was synthesized by ammonolysis of methyl (-) benzhydrylsulfinylacetate in MeOH and water. 365.8 g of crude product was taken up in 1.83 L of denatured EtOH (w/2.5% toluene) and heated to 75°C to dissolve, then allowed to crystallize. 162 g of these crystals were taken up in 810 ml denatured EtOH (w/2.5% toluene), and heated to reflux. Solution was allowed to cool on bench top for 10 minutes, then transferred to an ice bath. Crystals were filtered and dried under vacuum at 30°C. M.P. (inst.)= 163°C PXRD analysis performed 10 days later with a PW1840(Cr) diffractometer.</td>
<td>Form I</td>
</tr>
</tbody>
</table>
Which crystalline form is obtained by crystallizing Armodafinil in Ethanol?

| ON II/149 E | Step a: (-)-modafinil was synthesized by ammonolysis of methyl (-) benzhydrilsulfinylacetate in MeOH and water. 66 g of crude product was taken up in 330 ml absolute EtOH, heated to reflux, filtered, and the hot filtrate immediately cooled in an ice bath. Crystals were filtered and dried under vacuum at 35°C. Yield 57 g.  
Step b: 7.85 g of product from Step a was mixed with 115 ml absolute EtOH and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. M.P. (inst.)= 162°C. PXRD analysis with a PW1840(Cr) diffractometer. | Form I |
| ON II/149 H | 5 g of product from II/149 E Step a, was mixed with 80 ml denatured EtOH (w/2.5% toluene) and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. M.P. (inst.)= 156°C. PXRD analysis with a PW1840(Cr) diffractometer. | Form II |
| ON II/150 A | Step a: product from II/149 E Step a, was dissolved in a mixture of acetone, ethyl acetate, methanol, isopropanol, absolute ethanol, and propanol. The solvents were evaporated under vacuum using a rotator. The residue was dissolved in absolute ethanol, cooled to 20 °C, then placed in an ice bath. Crystals were filtered and dried in an oven.  
Step b: About 5 g of the product from II/150 A, Step a, was mixed with 70 ml denatured EtOH(w/2.5% toluene) + 3% H₂O and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. PXRD analysis with a PW1840(Cr) diffractometer. | Form I |
| ON II/150 B | About 5 g of the product from II/150 A, Step a, was mixed with 70 ml absolute EtOH + 3% H₂O and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. PXRD analysis with a PW1840(Cr) diffractometer. | Form I |
But, stemming from the original priority document, several patent extension were filed:

In Europe:

- EP 1,572,635A1 with the same claims of the original document
- EP 2,343,275A2 claiming crystalline form I and processes for its preparation

In the USA:

- A granted patent (US 7,132,570) related to Form I
Case 2 - ARMODAFINIL

US 7,132,570 main claims are:

1. A laevorotatory enantiomer of modafinil in a polymorphic form that produces a powder X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings: 8.54, 4.27, 4.02, 3.98 (Å).

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

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).
Quantitation of patented crystalline forms

The presence of traces of different crystalline forms in general is not regarded as a relevant quality issue of a drug, because:

- The alternate crystalline form is not a real impurity of the API
- It could affect the bioavailability, to an extent that is a fraction of its content
- Some exceptions are possible in the case of chemically unstable crystalline forms
Traces of patented polymorphs: the single crystal claim construction

Under 35 U.S.C. § 271(a), any infringement, even *de minimis* infringement, is actionable.
Thus, where a patent claim covers a crystalline form *per se*, presence of that crystalline form at any level - even trace levels - in the API entering the U.S. could subject a party to infringement liability.

[SKB vs Apotex 403 F.3d 1331 (Fed. Cir. 2005)]
Liability: quantitation of damages

No case law. 2 possible approaches:

1- proportional to the amount of patented polymorph

2- proportional to the loss of revenues
Conclusions

- Polymorphs can affect quality safety and efficacy of drug products
- They can be regarded as inventions provided that they are new and useful
- Patent and patent applications related to polymorphism are a potent tool for life cycle management of pharmaceutical products and for the competition in the generic arena
Acknowledgements

- Giovanni Minardi
- Eleonora Rezoagli
- Gabriele Razzetti
- Chiara Vladiskovic
Back-up slides
Biopharmaceutic Drug Classification

Highly soluble: is the maximum dosage soluble in 250 ml or less of water at pH 1.0 – 7.5?

L.X Yu et al., Pharmaceutical Research, Vol 19, No. 7, July 2002
Polymorphs patents

- Involve an inventive step (not obvious). Problem and solution approach
  - determining the closest prior art
  - establishing the «objective technical problem» to be solved
  - Considering whether or not the claimed invention, starting from the closest prior art and the objective technical problem, would have been obvious to the skilled person

Dipharma’s founder Mario Biazzi invented the world’s best continuous plant for nitroglycerine production, a solution which was widely acclaimed by the press for its advantages in safety and productivity. He also founded SAFEX International, an industry association whose goal is to improve the safety in the explosives industry.
1949
Incorporation of “Dinamite S.p.A.”

1990
Name changed to “Dinamite Dipharma”

2004
Name changed to “Dipharma Francis S.r.l.”
Dipharma today

- Four production sites, all FDA-inspected
- 498 employees
- € 120 Mio in product sales (2010)
- 60 years of experience in handling complex and hazardous chemical processes safely
- Over 125 patents or patent applications filed
cGMP production sites

Baranzate, Milan
Dipharma
FDA inspected since 1970

Caronno, Varese
Dipharma
FDA inspected since 1978

Mereto, Udine
Dipharma
FDA inspected since 1980

Malta
Amino Chemicals
FDA inspected since 2002
Consolidated Sales (M)

Employees and jobs
498 qualified resources (28/02/2011)

Total employment in manufacturing
(source: ILO)
G-7 countries (yearly average, in millions)
-13%

Dipharma (yearly average)
+7.7%
Internal IP Department

- Filing of new patent applications
- New non-infringing synthesis routes
- Periodic monitoring of the "freedom-to-operate" position

New patent applications filed