"Patentes de formas polimórficas de principios activos farmacéuticos: *Poli-morfismo* de las patentes"

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INVENT FARMA

Contenido:

- ✓ Aspectos regulatorios
  - Requerimientos de las Agencia Regulatorias

- ✓ IP
  - Nomenclatura
  - Patentabilidad
  - Infracción

GENERICS bulletin
THE BUSINESS NEWSLETTER FOR THE GENERIC MEDICINES INDUSTRY

News@Genericsbulletin 2 September 2010 Issue 322

Osteoporosis Drugs

US court upholds Evista ruling

An Indiana district court was right to rule last year that two particle-size patents protecting Eli Lilly's Evista (raloxifene) 60mg tablets until 10 March 2017 were invalid, the US Court of Appeals for the Federal Circuit has decided. The Court of Appeals also backed the district court's rejection of Teva's attacks on the validity of four method-of-use patents that protect the osteoporosis brand up to 2 March 2014 (Generics bulletin, 16 October 2009, page 12).

Discussing the particle-size patents 6,458,811 and 6,894,064, the Court of Appeals said Lilly had failed to prove that the district court had erred in finding the patents invalid for a lack of written description. "The patent specification only discloses measurements of bulk raloxifene," the court pointed out, adding that a skilled person would have learned nothing about particle sizes in finished-dose formulations.

Lilly said it would "review its legal options regarding this aspect of the ruling". G

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Polymorphisms and Patent, Market, and Legal Battles: Cefdinir Case Study

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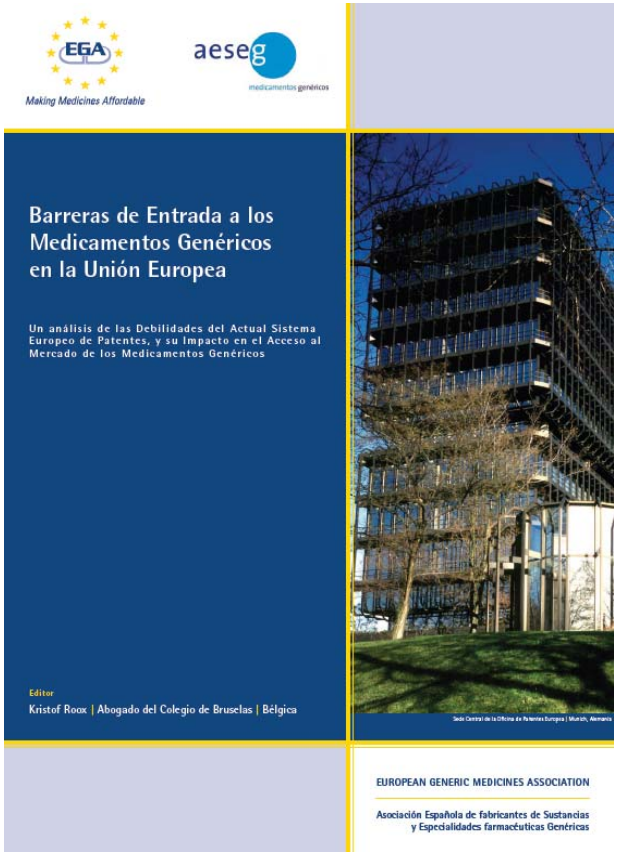
In this context, the filing of patents claiming new crystalline forms, usually 4-6 years after the original product patent, is a typical strategy applied by such companies to extend patent protection. This patent protection approach by big pharma forces generic bulk producers to discover and file patents on new polymorphs if they want to market the drug after expiry of the product patents.

From our direct experience, an interesting example is Cabergoline (Parkinson's disease): the originator and generic companies claimed up to 14 crystalline forms and solvates. What is the meaning of all these patent applications? Where is the advantage with respect to the previously reported crystalline forms or solvates?

Organic Process Research & Development **2007**, 11, 64-72



http://www.egagenerics.com/doc/BarrerasInforme_ES_web.pdf

CITALOPRAM HBr (CIPRAMIL ®, Lundbeck)

EP 1 169 314 and its divisional EP 1227 0088 dealing with the **crystalline base of citalopram and its use for purification**

The patent was granted and innovator initiated more than 30 court cases in 9 European countries.

Several generic companies faced interim injunctions and others decided simply not to enter the market

PERINDOPRIL ERBUMINE (Coversyl ®, Servier)

Servier has been granted patents on alpha (most thermodinamically stable), beta and gamma polymorphs of perindopril erbumine.

UK Court granted preliminary injunctions against generic companies: Apotex, Lupin, Teva, Krka and Niche

EP1296947 was **revoked by EPO after opposition and appeal (T1753/06) and by the UK Courts**.

Apotex was awarded £17.5 million for damages[1]

Source: Patent-related barriers to Market entry for generic medicines in the European Union. European Generic Medicines Association. May 2008.

[1][2008] EWHC 2347 (Ch) Case No: HC 06 C03050 Mr Justice Norris. 9 October2008

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Teva sues to block rivals to generic sertraline

Patent disputes in US courts usually involve originator companies suing their generic rivals. But now Teva Pharmaceutical Industries is suing a number of other generics firms to protect US patents that it claims cover the ways to make crystalline forms of sertraline HCl, the active ingredient in Pfizer's Zoloft tablets.

Although Pfizer lost US patent protection for Zoloft last June, Teva did not launch its generic sertraline until last September after a delay caused by manufacturing issues. The move triggered a six-month generic marketing exclusivity award to the first filer. Thus, Teva has the exclusive rights to market the generic until February 6th.

In a number of lawsuits filed in the US District Courts of New Jersey, Delaware, the Southern District of New York, and Maryland, Teva has targeted those firms with pending ANDAs, plus companies that make the active ingredient. Teva alleges that they infringe its patent on processes for making sertraline HCl tablets.

The suits have apparently been filed in order to keep generic rivals from launching soon after Teva's exclusivity ends. Teva's current competition consists solely of an authorised generic from Pfizer, through its Greenstone division.

The suits claim infringement of four patents covering the manufacturing of crystalline forms of sertraline: Patent Nos 6,600,073 (expiring June 2020), 6,500,987 (November 2019), 6,495,721 (November 2019), 6,495,721 (May 2020) and 6,897,340 (April 2030). The '073 and '987 claim processes for polymorphic Form V, while the '721 and '340 cover polymorphic Form II, Teva says

In legal documents, Teva has indicated that the lawsuits involve its generic rivals Pliva, Novartis's generics unit Sandoz, Apotex, Merck KGaA's Genpharm, Lupin, Cipla and Zydus Cadila. They also include the manufacturers Invagen and Hetero Drugs.

These firms represent just a handful of companies listed on the FDA's website as having obtained tentative approval for their versions of generic sertraline. These include Dr Reddy's, Genpharm, Mylan, Roxane, Apotex, Zydus, Watson, Pliva, Purepac, Invagen, Ranbaxy, Sun Pharma and Aurobindo.

In its complaint against Andrx, filed in a district court in New Jersey, Teva states: "On information and belief, the sertraline HCl API contained in defendant's tablets is or will be Form II or Form V – sertraline HCl Forms I, II and V are the only crystalline forms that are practical to use in a pharmaceutical tablet – Form I is claimed by an unexpired US patent assigned to Pfizer, and thus it is unlikely that [the] defendant will attempt to market products containing that polymorph."

Teva went on to say that it is not aware of any commercially viable process to manufacture Form V sertraline that is not covered by one or more claims of the '987 and/or '073 patent. It added that it had been unsuccessful in obtaining from any source a sample of the defendant's tablets, and that, even if it could obtain such a sample, no analytical technique would allow it to establish definitively that any of the four patents would not be infringed.

"For this reason, plaintiffs cannot conclusively determine whether defendants' tablets infringe the patents unless and until defendant discloses to plaintiffs the method by which the sertraline HCl API contained therein is or will be made," it noted. Teva believes that its lawsuit will aid in the process of discovery. The complaints against the other generic rivals contain similar allegations.

Recently, Novartis's Lek unit sued Bristol-Myers Squibb and Watson over alleged infringement of US patents covering crystalline forms of the sodium salt of pravastatin sodium, the key ingredient in Pravachol (*Scrip* No 3223, p 15). More than a half dozen firms also have ANDA approvals and sell generic pravastatin, and it is not known whether Lek will initiate any additional complaints.

opinic

Why we are discussing about polymorphic forms in pharmaceutical products?

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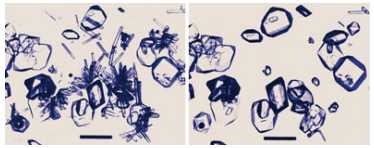
Pharmaceutical product

Competitors develop new forms



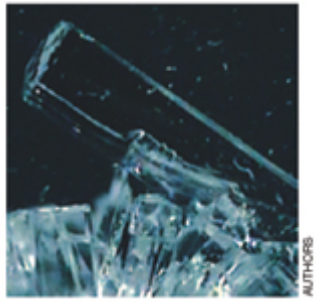
Patent Protection (monopoly)

Differences in properties between solid forms of the same compound are used to justify the novelty and non-obviousness.

Regulatory authorities require information and characterisation of solid forms

Characteristics of solid forms may have influence on properties of the product:

- bioavalability
- stability
- manufacture, etc.



Value of patents claiming polymorphic forms for generic companies

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Even though polymorph patents may not keep a competitor completely off the market, it may still have a comercial value if the amorphous or non-infringing crystalline form is inferior to the crystalline form (even if it is considered bioequivalent for marketing approval):

- Usually crystalline forms are preferred for pharmaceutical compositions
- Changes in pharmaceutical form (tablets to capsules), excipients, manufacturing process or conditions, packaging, etc.
- longer development times, less stability, etc.

Regulatory issues. Ritonavir Case

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Ritonavir is an inhibitor of HIV protease with activity against the human immunodeficiency virus.

Approved by FDA in 1996 and marketed by Abbot Laboratories

two formulations: Oral solution (80 mg/ml) and Capsules (100mg).

Soft gelatin capsules were subsequently developed.

After 2 years on the market a new thermodinamically stable polymorph began to precipitate

This proved to have lower solubility with greatly reduced bioavailability

Removal of the product from the market for almost a year

FDA CDER Chemistry review. Application No. 20-945

In July 1998, Abbott notified the FDA that they had experienced manufacturing difficulties with the semi-solid capsules. During manufacturing of the product, a new polymorphic form of ritonavir (Form II) which is less soluble than the known Form I ritonavir appeared in the capsules, resulting in failure of dissolution testing. Abbott later reported that Form II also appeared in the oral solution and in the soft gelatin capsules. As a result of this problem, the semi-solid capsules were removed from the market, the shelf life and storage condition for the oral solution were changed from 24 months at 5^0 C to 6 months at 25^0 C through supplements, and the soft gelatin formulation was modified. The latter two actions were taken to ensure adequate solubility of ritonavir in these formulations. A "not approvable" action was taken on NDA 20-945 in November 1998 due to insufficient CMC data on a modified soft gelatin formulation to address the quality, stability and performance of the new product. Information required for a resubmission was recommended in the FDA letter dated November 23, 1998.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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Development of new active substances

ICH Q6A (http://www.ich.org/cache/compo/276-254-1.html)

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES
Q6A

3.3.1 New Drug Substances

c) ***Polymorphic forms****:* Some new drug substances exist in different crystalline forms which differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. **Differences in these forms** could, in some cases, affect the quality or performance of the new drug products. In cases where **differences exist** which have been shown to affect drug product performance, bioavailability or stability, then the **appropriate solid state should be specified**.

Applicable to new drug substances (human and veterinary) and generics

http://www.ema.europa.eu/htms/human/humanguidelines/quality.htm

Regulatory requirements

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Risk of inadvertent polymorphic change

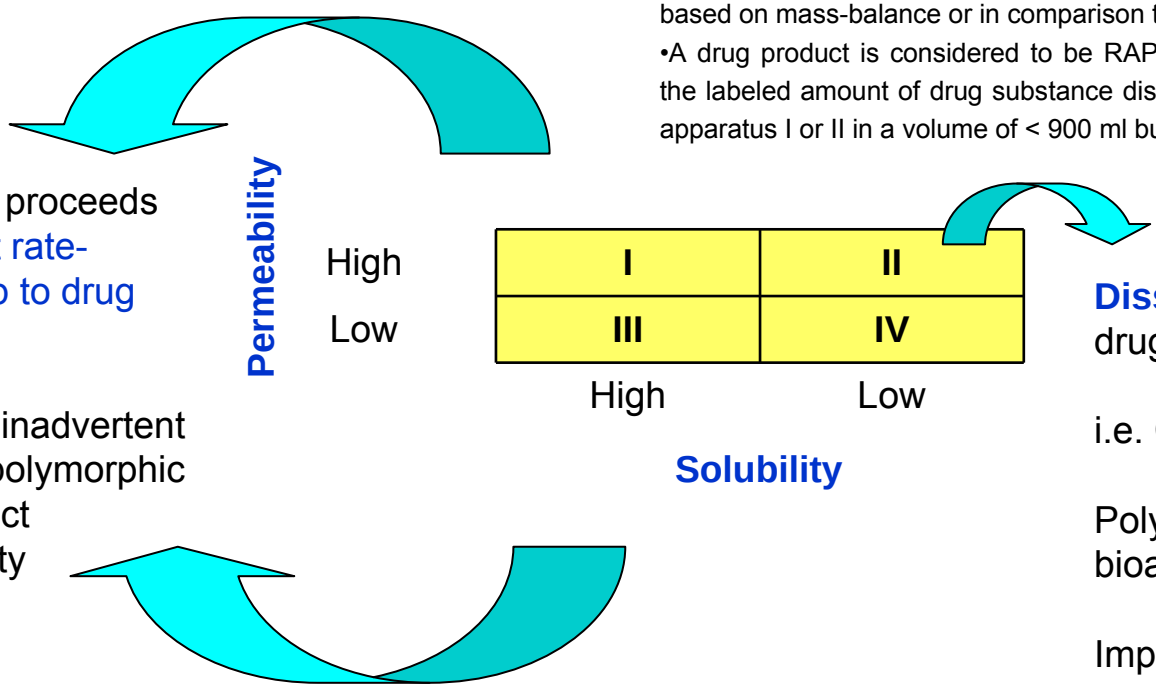
Biopharmaceutics Classification System (BCS)

CLASS BOUNDARIES

•A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5.

•A drug substance is considered HIGHLY PERMEABLE when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.

•A drug product is considered to be RAPIDLY DISSOLVING when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.



Dissolution proceeds rapidly. Not rate-limiting step to drug absorption

Low risk of inadvertent change in polymorphic form to affect bioavalability

Dissolution rate-limiting step to drug absorption

i.e. Carbamazepine

Polymorphic forms may affect bioavailability

Important to **incorporate controls on polymorphic forms**

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm128219.htm

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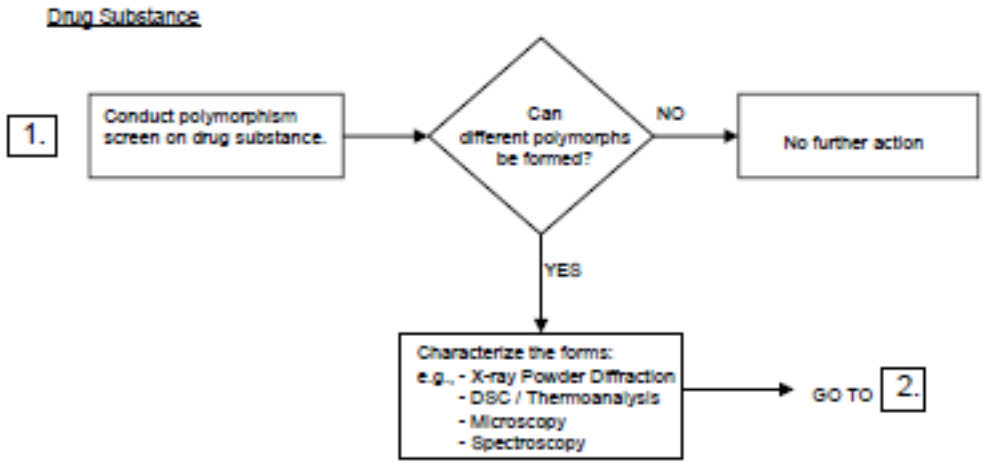
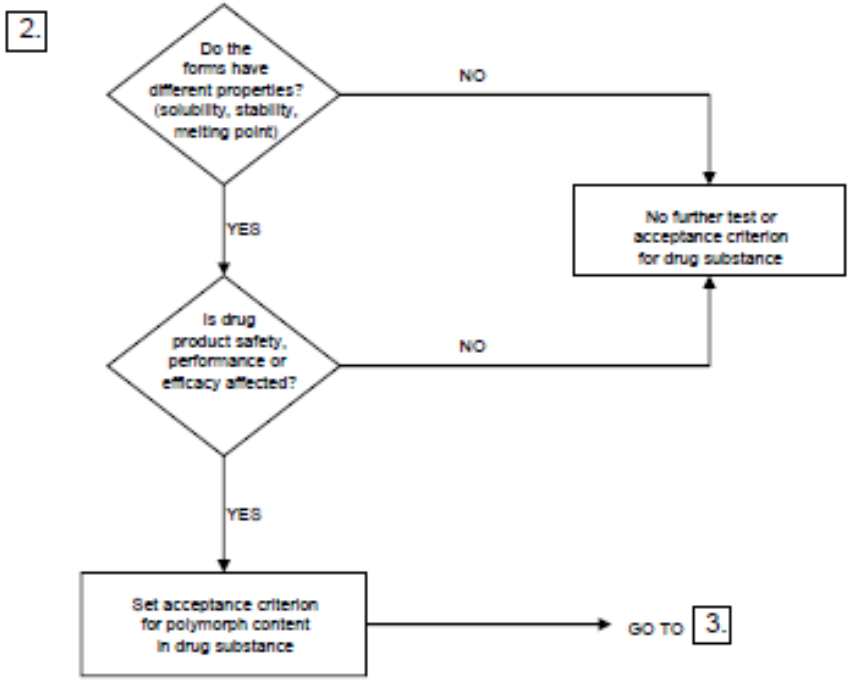
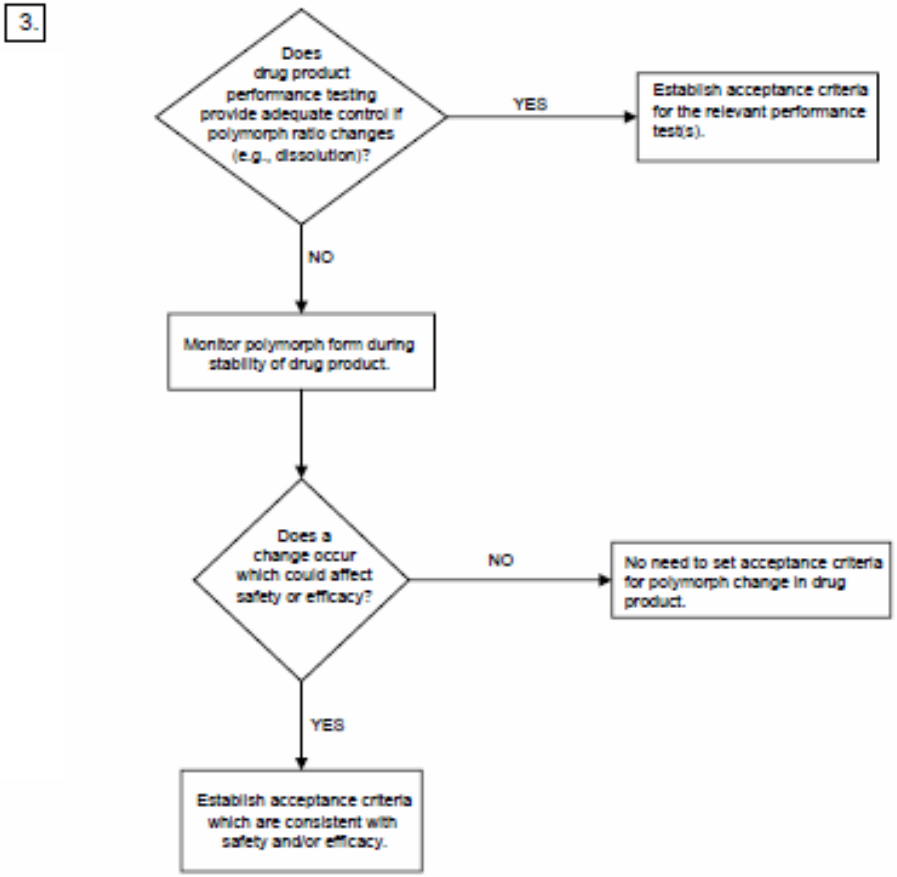
Decision trees #4(1) through 4(3) provide additional guidance on when, and how, polymorphic forms should be monitored and controlled.

DECISION TREE #4: INVESTIGATING THE NEED TO SET ACCEPTANCE CRITERIA FOR POLYMORPHISM IN DRUG SUBSTANCES AND DRUG PRODUCTS



Regulatory requirements





Regulatory issues

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Regulatory authorities require information on the effect of polymorphism:

- how you can be sure it is this polymorphic form and not another one, about the stability and risk of interconversion …

- Which **polymorphic form is present in the innovator tablet**?

- If it is not proved that your finished product has the same polymorphic form than innovator, you must argue by literature articles that **the polymorphic form has no influence on the solubility, bioavailability so on pharmacokinetic property of this active substance and consequently of the finished product.**

- During ICH stability it must be proved that there is no change of the polymorphic form of active substance

    - You must also prove that the **manufacture process** (compression) does not change the polymorphic form of the active substance.

    - A **control of polymorphism at the end of shelf life should be performed.**

    - The possibility/ risk for conversion of drug substance to other modifications of the drug substance should be discussed.

- The **influence of the polymorphic** form on solubility of API, **stability**, melting point, etc., should be studied as physicochemical and physical characteristics may differ.

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FDA Guidance:
ANDAs: Pharmaceutical Solid Polymorphism. Chemistry, Manufacturing, and Controls Information

Section 505(j)(2) of the Act specifies that an ANDA must contain, among other things, information to show that the active ingredient in the generic drug product is the "same as" that of the RLD.

Specifically, 21 CFR 314.92(a)(1) provides that the term "same as" means, among other things, "**identical in active ingredient(s).**"

differences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals within the meaning of the Act and FDA regulations.

each ANDA applicant is required to demonstrate that, among other things, the drug product exhibits sufficient stability and is bioequivalent to the RLD.

Value of secondary patents in US

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These patents are listed on the “Orange Book”. Patents that can be listed are:

- ✓ Product patents
- ✓ composition patents
- ✓ use patents
- ✓ patents on polymorphic forms (Under *Medicare Presciption Drug, Improvement and modernization Act 2003*)

When filing a ANDA a generic company has to certify that non of the patents listed in OB:

i) **Patent information on the drug has not been filed**

ii) **Patent has already expired**

iii) **The product will not be marketed before expiry of patents listed in OB**

iv) **The patent is not valid or will not be infringed**

FDA considers different salts a different product. Application under 505(b)(2)

More requirements than a “regular” ANDA

Not elegible for 180-days of exclusivity

Options for developing generic drugs

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Art. 10.2.(b) of EU Directive 2004/27:

"The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant."

Marketing of a different salt as generic product:

Innovator	**Generics**
Lipitor ® Atorvastatin Calcium	Atorvastatin Magnesium
Plavix® Clopidogrel Bisulfate	Clopidogrel Besylate, HCl, base
Seroxat ® Paroxetine HCl	Paroxetine mesylate
Norvasc ® Amlodipine besylate	Amlodipine maleate

Particular case: Orally inhaled products

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GUIDELINE ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP) INCLUDING THE REQUIREMENTS FOR DEMONSTRATION OF THERAPEUTIC EQUIVALENCE BETWEEN TWO INHALED PRODUCTS FOR USE IN THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN ADULTS AND FOR USE IN THE TREATMENT OF ASTHMA IN CHILDREN AND ADOLESCENTS

London, 22 January 2009
Doc. Ref. CPMP/EWP/4151/00 Rev. 1

New active substance are required to undergo a full development programme regardless ot the type of device for which the new active substance is inhaled

For abridge applications….may be considered acceptable if the product satisfies **all of the following criteria** (compared with the reference product):

• The product contains the **same active substance** (i.e. same salt, ester, etc.)

•The active substance is in the solid state (powder, suspension): any differences in crystalline structure and/or polymorphic form should not influence the dissolution characteristics, the performance of the product or the aerosol particle behaviour.

Contenido:

- ✓ Aspectos regulatorios
  - Requerimientos de las Agencia Regulatorias

- ✓ IP
  - Nomenclatura
  - Patentabilidad
  - Infracción

General Patentability requirements

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According to European Patent Convention (EPC), an invention is patentable (Art. 52(1)) if :

- It is novel over the prior art (Art. 54 EPC):

  Prior art is defined as everything made available before the filing (priority) date of the application by means of a written or oral description, by use or in any other way.

- It involve an inventive step

- It has industrial applicability

In US: utility, novelty and non-obviousness

But the rules and regulations of patents differ from country to country.

For example in India, the Indian Patent Act Section 3(d) lists what are not inventions:

"*The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property ….*"

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NOVELTY

In order to determine if an invention (polymorph) is patentable, the first step is to compare it with the prior art.

Main problems to determine the (lack of) novelty:

- **nomenclature of forms described**
- **poor description of prior art. Reproducibility (Enabling disclosure)**
- **Prior art disclosures difficult to locate. Hiden in regulatory information**
- **Prior use. Effective date??**

Nomenclature of polymorphic forms

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"Part of the difficulty encountered in searching and interpreting the literature on polymorphic behaviour of materials is due to inconsistent labelling of polymorphs. In many cases, the inconsistency arises from lack of an accepted standard notation."

Berstein, J. Polymorphism in Molecular Crystals. 2002

"It was probably one of the low points of my career, *when we spent 30 minutes arguing whether the word should be spelled co-crystal or cocrystal.*
[…] has even suggested quasipolymorph, and others have put forth elaborate terms such as solvatomorph, hydratomorph, and pseudopolymorphic solvate…"

War of the words. Chemical&Engineering News, 2007, 85 (25), 28-29

Nomenclature of polymorphic forms

Invent Farma

Inconsistent labelling of polymorph:

- **Arabic** (1,2,3..) or **Roman** (I, II, III…) numerals
- lower or upper case **latin** (a,b,c…or A, B, C) or lower case **Greek** (α,β,γ, …)
- by names descriptive of **properties** (red form, low-temperature polymorph, metastable…etc)
- other:

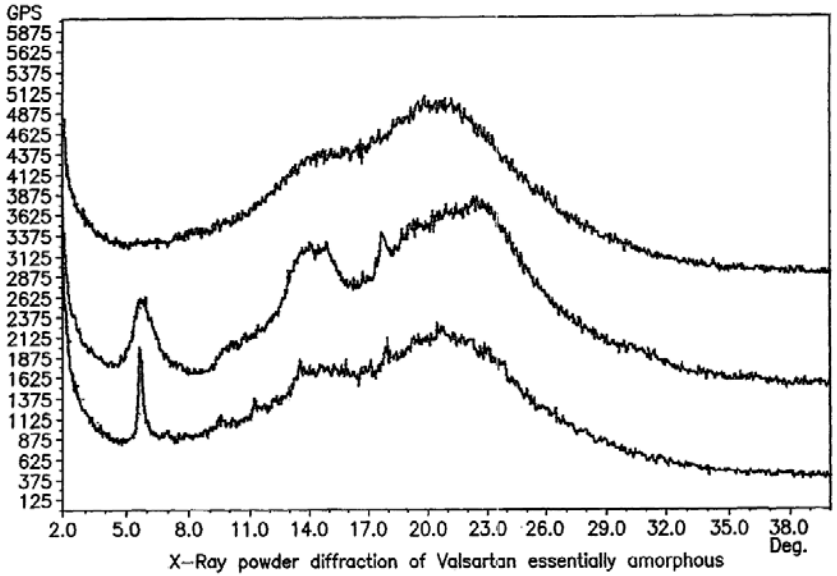

Fig. 1

Inconsistent labelling. Patents and regulatory information. Aripiprazole (Abilify®)

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(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 April 2003 (03.04.2003)

PCT

(10) International Publication Number
WO 03/026659 A1

Also, Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (October 6-8, 1996) state that, aripiprazole anhydride crystals exist as type-I crystals and type-II crystals; the type-I crystals of aripiprazole anhydride can be prepared by recrystallizing from an ethanol solution of aripiprazole, or by heating aripiprazole hydrate at 80°C; and the type-II crystals of aripiprazole anhydride can be prepared by heating the type-I crystals of aripiprazole anhydride at 130 to 140°C for 15 hours.

- 112 -

CLAIMS

1. Hydrate A of aripiprazole wherein said Hydrate has a powder x-ray diffraction spectrum which is substantially the same as the following powder x-ray

13. Aripiprazole Anhydride Crystals B having low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.40% or less after placing said drug substance for 24 hours in a dessicator maintained at 100%.

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Abilify. For information on changes after approval please refer to module 8.

Aripiprazole can exist in several crystalline forms, Form I was chosen for the development and commercialisation..

Inconsistent labelling. Patents of the same family: Olanzapine

Invent Farma

US 20010018071A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2001/0018071 A1**

Cochran et al. (43) **Pub. Date: Aug. 30, 2001**

(54) **ORAL 2-METHYL-THIENO-BENZODIAZEPINE FORMULATION**

(76) Inventors: **George Randall Cochran**, Plainfield, IN (US); **Tommy Clifford Morris**, Indianapolis, IN (US)

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(21) Appl. No.: **09/766,218**

(22) Filed: **Jan. 19, 2001**

Related U.S. Application Data

(60) Division of application No. 09/144,188, filed on Aug. 31, 1998, now Pat. No. 6,190,698, which is a division of application No. 08/716,922, filed on Sep. 20, 1996, now Pat. No. 5,919,485, which is a continuation-in-part of application No. 08/410,465 filed on Mar. 24, 1995, now abandoned.

Publication Classification

(51) **Int. Cl.**[7] **A61K 9/36**; A61K 31/551

(52) **U.S. Cl.** **424/479**; 514/220

(57) **ABSTRACT**

The invention provides a pharmaceutically elegant solid oral formulation of olanzapine and a process for making such formulation.

[0011] Unfortunately, anhydrous Form II olanzapine is metastable and is therefore not well suited for commercial use in pharmaceutical formulations. Applicants have discovered that the pharmaceutically elegant anhydrous Form I olanzapine can be formulated in its substantially pure form as a stable solid oral preparation. Such formulation provides assurance of a uniform pharmaceutically elegant product substantially free of Form II impurity in order to comply with regulatory requirements.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 0 733 367 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
25.09.1996 Bulletin 1996/39

(51) Int Cl.[6]: **A61K 31/55**, A61K 9/28

(21) Application number: **96301997.1**

(22) Date of filing: **22.03.1996**

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE

(30) Priority: **24.03.1995 US 410465**

(71) Applicant: **ELI LILLY AND COMPANY**
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  Indianapolis, Indiana 46205 (US)

(74) Representative: **Hudson, Christopher Mark**
Lilly Industries Limited
European Patent Operations
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Windlesham Surrey GU20 6PH (GB)

(54) **Oral olanzapine formulation**

(57) The invention provides a pharmaceutically elegant solid oral formulation of olanzapine and a process for making such formulation. The formulation comprises olanzapine as an active ingredient intimately mixed with a bulking agent; binder, disintegrant, a dry binder to assure adequate friability, and a lubricant; wherein such solid oral formulation is coated with a polymer selected from the group cosisting of hydroxypropyl methylcellulose, hydroxyethyl cellulose, methylhydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, dimethylaminoethyl methacrylatemethylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer, methylcellulose, and ethylcellulose.

It is especially preferred that the formulation contain the most stable anhydrous form of olanzapine, referred to herein as Form II; however, other forms of olanzapine are contemplated. Form II has a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

Describing polymorfic forms

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1.2 Polymorphs are treated as inventions defined by parameters. The physical data provided in claim 2 are the ones of the X-ray powder diffraction pattern. Since these data are the essential technical features allowing to defined the claimed polymorph versus the already crystalline form known from **D1**, these need to be accurate. The presence of the term "about" is detrimental for such a definition (Article 6 PCT and Guidelines II-5.38 PCT). For an appropriate definition, a defined range of reading error should be provided for every single peak.

It may happen that in the relevant prior art a different parameter, or no parameter at all, is mentioned. If the known and the claimed products are identical in all other respects…then in the first place an objection of lack of novelty arises.

(GL C-IV, 9.6)

Describing polymorfic forms

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Techniques to characterise crystalline forms:

ICH Q6 A.3.3.1 New drug substances.

Physicochemical measurements and techniques are commonly used to determine whether multiple forms exist:

- **Analytical Techniques**
  - **melting point including hot-stage microscopy**
  - **solid state IR**
  - **X-ray powder diffraction**
  - **thermal analysis procedures like DSC, TGA, DTA**
  - **raman spectroscopy**
  - **solid state NMR.**
  - **optical microscopy**

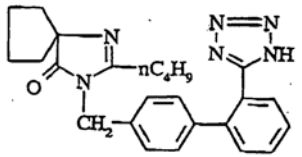
Claiming polymorphic forms. Types of claims

EP717616

14. Formoterol fumarate dihydrate having a particle size less than 10 µm, which when subjected to water-containing vapour gives off heat of less than 0.5 J/g.

WO99/67236

1. Un composé cristallin de formule :



(I)

ayant un habitus cristallin tel que le rapport entre la longueur et la largeur des cristaux soit compris entre 1:1 et 10:1 et dont la chargeabilité mesurée par tribogénération varie entre 0 et -10 nanocoulomb/g.

WO2010/004578

24. Paliperidone having porous texture and irregular shape morphology, seen through the microscope as shown in figure-3a.

ES 2 304 335 T3

REIVINDICACIONES

1. Una forma E de atorvastatina de magnesio que tiene un espectro de RMN de ^{13}C en estado sólido que contiene valores: 122,0, 128,9 y 137,8 ppm.

2. Una forma E de atorvastatina según la reivindicación 1, que tiene un espectro de RMN en ^{19}F en estado sólido que contiene valores: -113,2,0, -118,9 y -122,1 ppm.

Claiming polymorphic forms

Invent Farma

EP 993 455 B1

Claims

1. Crystalline polymorph form 1 descarbonylethoxy-loratadine essentially free of polymorph form 2 and **characterized by** the following x-ray powder diffraction pattern having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") at approximately:

d spacing (±0.04)	RI
9.04	Weak
6.42	Weak
5.67	Weak
5.02	Weak
3.58	Weak

8. Crystalline polymorph form 2 descarbonylethoxy-loratadine substantially free of polymorph form 1 and **characterized by** the following x-ray powder diffraction pattern having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") at approximately:

d spacing (±0.04)	RI
8.34	Weak
6.87	Medium
6.20	Medium
4.90	Medium

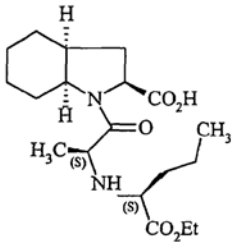
Claiming polymorphic forms

Invent Farma

EP1296947 B1

Claims

1. α crystalline form of the compound of formula (I) :



. $tBuNH_2$ (I),

characterised by the following powder X-ray diffraction diagram, measured using a diffractometer (copper cathode) and expressed in terms of inter-planar distances d, Bragg's angle 2 theta, intensity and relative inter (expressed as a percentage with respect to the most intense ray) :

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
7.680	11.50	390	8.8
8.144	10.85	230	5.2
9.037	9.78	4410	100
10.947	8.08	182	4.1
13.150	6.73	82	1.9
13.687	6.46	83	1.9
14.627	6.05	582	13.2
15.412	5.74	770	17.5
16.573	5.34	1115	25.3
17.357	5.10	340	7.7
18.109	4.89	193	4.4
19.922	4.45	306	6.9
20.609	4.31	375	8.5
21.412	4.15	226	5.1

(continued)

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
21.832	4.07	217	4.9
22.158	4.01	483	11
22.588	3.93	386	8.8
23.323	3.81	107	2.4
24.200	3.67	448	10.2
24.727	3.60	137	3.1
25.957	3.43	125	2.8
26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

How many peaks have to be included in a claim?

- **Several peaks in order to distinguish from prior art**
- **Few peaks to get a good protective scope.**

Claiming polymorphic forms

Invent Farma

"…. I see no reason to suppose that the reader would understand the figures in the table to be of absolute precision. The reader would take a set of very similar, if not exactly similar, peaks to be those of the crystalline form claimed by the patentee. ***No exact match is called for****."*

Perindopril UK. Servier vs. Apotex [2008] EWCA Civ 445. Supreme Court. Jacob L.J.

Value of intensities?

T1753/06. (EP1296947 B1)

"4.5.2. Le Chambre note que les diagrammes expérimetaux ainsi que le diagramme simulé, bien qu'ils soient presque identiques, ***présentent des légères variations****….*

4.5.3. …le Chambre considère que les pics ayant une intensité très faible sont les pics les plus sujets aux influences provoquées par le preparation de l'échantillon, l'appareillage pour la mesure du diagramme, les bruits de fond…

…Donc, ***l'intensité ne peut pas servir comme caractéristique distinctive*** *et une variaction de l'intensité des pics dans les diagrammes expérimentaux n'indique pas la formation d'une forme cristalline différente."*

Novelty. Prior art

Invent Farma

EPO Guidelines C-IV, 9.1:

"An invention is considered to be new if it does not form part of the state of the art"

Disclosed in a single document. It is not permissible to combine separate items of prior art together

Explicitely described or implicit (may require reproduction to know what is really described)

Enabling disclosure?

i.e. Finasteride EP0823436.- T 0605/02:

Third party observations filed.Reproduction of prior art to obtain Form I.

Patent withdrawn

"As it has never been contested that forms I and II of Finasteride disclosed in document (1) correspond with both presently claimed polymorphic forms, the question arises, whether such disclosure destroys the novelty of present Claims 1 and 2

….. in the absence of any indication of how form I may be obtained,…

…thus, document (1) is not an enabling disclosure of how to prepare either claimed form of Finasteride, document (1) is not a novelty-destroying disclosure for present Claims 1 and 2."

Novelty. Prior art

Quality of figures

THE FOURTH JAPAN-KOREA SYMPOSIUM
ON
SEPARATION TECHNOLOGY

October 6 ~ 8, 1996

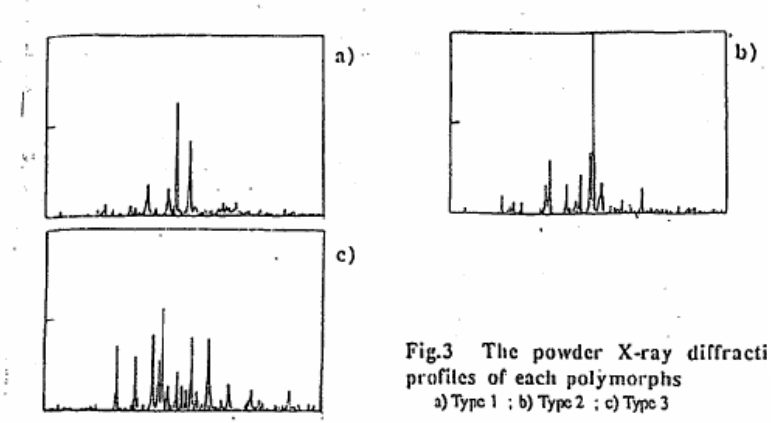
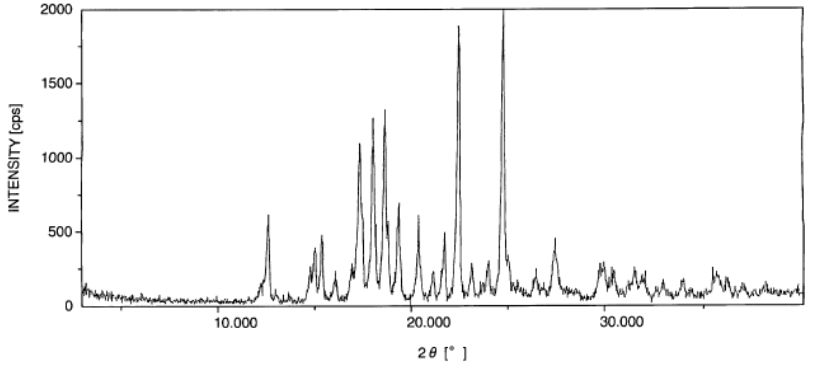


Fig.3 The powder X-ray diffracti
profiles of each polymorphs
a) Type 1 ; b) Type 2 ; c) Type 3

WO 03/026659

FIG.3



3/31

PCT/JP02/09858

Figure 3 is a powder x-ray diffraction diagram of the Aripiprazole Hydrate A obtained in Example 1.

Novelty. Comparison with prior art

Invent Farma

Comparison with prior documents

Prior art does not always describe the product in a manner that can be used to compare

> *9. "…**For simply comparing the cited prior art ('341) with the patent would not reveal lack of novelty and probably not obviousness. You need the technical input of experts both in the kind of chemistry involved and in powder X-ray diffraction and some experimental evidence in order to see just how specious the application for the patent was…"**.*

Perindopril UK. Servier vs. Apotex [2008] EWCA Civ 445. Supreme Court. Jacob L.J.

Novelty. Comparison with prior art

Invent Farma

Development of Drug Substances as Mixture of Polymorphs: Studies to Control Form 3 in Casopitant Mesylate

Zadeo Cimarosti,*,† Carlo Castagnoli,† Marco Rossetti,‡ Mirka Scarati,‡ Caroline Day,§ Brendan Johnson,⊥ and Pieter Westerduin†

Chemical Development, Medicines Research Centre, GlaxoSmithKline, Verona, Italy, Pharmaceutical Development, Medicines Research Centre, GlaxoSmithKline, Verona, Italy, Chemical Development, Medicines Research Centre, GlaxoSmithKline, Stevenage, U.K., Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, RTP, U.S.A.

During process development studies it was discovered that what was initially considered a single crystalline phase, Form 1, was actually a mixture of two different forms, Form 1 and Form 3. A retrospective analysis of all the key drug substance batches clearly indicated that Form 3 was always present as minor component in mixture with Form 1. Furthermore any attempt to generate either pure Form 1 or pure Form 3 failed.

Reproduction of prior art processes

Invent Farma

Is really possible to reproduce the prior art?

[2009] EWCA Civ 1188. Floyd L.J. Calcipotriol UK Appeal

Issue (1) Anticipation by Example 4 of the acne use patent.

*16. There never was any dispute what it was that Sandoz had to prove: **that the inevitable result of carrying out example 4 is that the monohydrate would result.** ...*

18. Experience shows that some parties attacking patents simply do not follow this straightforward path. Instead they depart from the prior art. …

Reproduction of prior art. Inevitable result.

Invent Farma

*19. Here the experiment suffered from two vices. First the obvious precaution of ensuring a **seed-free environment** was not taken. On the contrary it was seeded (it is not suggested deliberately so) with monohydrate (Judgment [76]). **Second the recipe of example 4 was simply not followed.** Why was never explained. Example 4 uses MC903 ... made by the process of example 5 of WO/00834 ... Sandoz used calcipotriol made by a company called Teva, made by a process which was never disclosed and devised years after the Patent. **That product had different impurities.***

*22. The **failure to use MC903** was one of the reasons why the Dutch court, Case No. 306029/HA 08-733), refused to accept a case of inevitable result (see 4.6). […]*

*23. The Judge did not think the failure to start with MC903 was in itself fatal. He thought that the skilled team would read the example as saying "start with the anhydrate compound howsoever made". But that meant, he reasoned, that Sandoz had to **show that howsoever the anhydrous calcipotriol was made (and so with an undefined range of possible impurities) the inevitable result would be the monohydrate**. The target was much bigger than if you had to use MC903. And Sandoz had simply failed even to attack that wider target.*

Reproduction of prior art.

Invent Farma

At which scale has to be reproduced?

laboratory scale?
pilot plant/ industrial?

Perindopril UK Case. Servier sued Apotex and others for infringement of EP-1.296.947-B1.

Apotex alleged that following the EP308341 the alpha form would inevitably be produced.

26. I turn to the experiments conducted for the purpose of this case. Apotex relied on four. Three were repeated at the request of Servier. ***Because experience has shown that experiments conducted for the purpose of litigation are apt to be biased****, under English procedure, a party who wishes to rely upon an experiment which he has carried out, must give notice to the other side giving details and* ***he must allow the other side to see a repetition of the experiment if it so wishes****.*

Here Apotex relied on two experiments. ***Experiment 1 was on a laboratory scale and Experiment 2 on scale of '341 (which was called "pilot").*** *These were repeated with Servier representatives present. So there were four in all relating to '341.*

[2008] EWCA Civ 445. Jacob L.J. Perindopril UK Appeal

Reproduction of prior art.

Invent Farma

Prior art does not provide clear indications on the conditions to be used

EP-308.341-A

STADE 3D : Sel de tert.butylamine de l'acide {[(éthoxycarbonyl) - 1 butylamino - (S)] - 2 propionyl (S)} - 1 octahydroindole carboxylique - 2 (2S, 3aS, 7aS)

Dans un réacteur placer 140 litres environ d'acétate d'éthyle et 10 kg d'acide {[éthoxycarbonyl) - 1 butylamino - (S)] - 2 propionyl (S)} - 1 de l'acide octahydroindole carboxylique - 2 (2S, 3aS, 7aS) obtenu précédemment. Additionner progressivement 2,20 kg environ de tert.butylamine, porter à reflux jusqu'à dissolution totale ; filtrer. Refroidir, filtrer et sécher.
Rendement : 95 %

Time of reflux?

Cooling rate?

Final temperature?

The person reproducing the prior art has to:

- use the common general knowledge at the “prior art date”
- can not invent to reach at the desired product

In Apotex case, the protocol for the experiments was created by an **independent expert who had been provided with ‘341 but not the patent in suit.**

Reproduction of prior art.

Prior art does not provide clear indications on the conditions to be used

Mr. Justice Pumfrey (**[2007] EWHC 1538 (Pat)**. Perindopril. Servier vs. Apotex:

"*For the purpose of anticipation, the prior documents must enable something which inevitably falls within the claim. Where the prior art does not describe the end to be achieved,* ***it is illegitimate to employ a refinement of technique or whatever to cause the desired result to be achieved****. Where the sufficiency of a disclosure of a method is under discussion,* ***of course the skilled person is entitled to do such preliminary work and carry out such uninventive refinements, without undue effort, with a view to producing a product falling within the claim."***

T1753/06. R.4.13: "*Le chambre ne peut pas contester que l'exemple 3D du document (1) ne divulgue pas en détail le mode de filtration, de refroidissement et de séchage, étapes qui sint en général usuelles. Par conséquent,* ***l'homme du metier en reproduisant l'exemple antérieur doit determiner de la façon de mettre en oeuvre ces étapes compte tenu de ses connaissances générals et du but à atteindre dans le document considéré…"***

Novelty. Prior use

Information made available by Regulatory agencies on web sites:

European Medicines Agency (EMA): http://www.ema.europa.eu

FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Drug Details

Drug Name(s)	ABILIFY (Brand Name Drug)
FDA Application No.	(NDA) 021436
Active Ingredient(s)	ARIPIPRAZOLE
Company	OTSUKA
Original Approval or Tentative Approval Date	November 15, 2002
Chemical Type	1 New molecular entity (NME)
Review Classification	S Standard review drug

- There are no Therapeutic Equivalents
- Approval History, Letters, Reviews, and Related Documents
- Label Information
- Medication Guide

Novelty. Prior use

Invent Farma

Also available for veterinary products

http://www.ema.europa.eu

SCIENTIFIC DISCUSSION

1 SUMMARY OF THE DOSSIER

Trocoxil, chewable tablets for dogs, contain mavacoxib as the active substance and the triangular shaped tablets are presented in five different strengths (6 mg, 20 mg, 30 mg, 75 mg, 95 mg). They are intended for treatment of pain and inflammation associated with degenerative joint disease in dogs in cases where continuous treatment exceeding one month is indicated. The Applicant for this veterinary medicinal product is Pfizer Ltd, United Kingdom.

Development Pharmaceutics

Trocoxil has been developed as chewable tablets for once-a-month dosing for dogs. The strengths in focus have been changed during development but the tablets applied for are 6 mg, 20 mg, 30 mg, 75 mg and 95 mg. All strengths are manufactured from a common blend containing 5 % w/w of mavacoxib. Five crystalline forms (I to V) of mavacoxib exist and are distinguished by powder X-ray diffraction. There are two crystalline non-solvated forms and three solvated forms. No hydrates exist. Form I is used for the formulation and is an anhydrous, non-solvated and non-hygroscopic form. The

The main problem is to **prove the publication date**

Novelty. Prior use

EP1467712B MicardisPlus®

the opponent tries to use the information published at FDA website as prior art

Claims

1. A bilayer pharmaceutical tablet comprising a first layer containing telmisartan in at least 90% amorphous form in a dissolving tablet matrix comprising a basic agent and a water soluble diluent, and a second layer containing hydrochlorothiazide in a disintegrating tablet matrix.

D1c was a chemistry review report established by the centre of drug evaluation and research for the drug NDA 21-162 which dated itself 17.10.2000. This date however most likely did not correspond to the date of public access, because in principle data submitted to the FDA was confidential. It was not clear when D1c was made available to the public and where the document originated from.

For D1d the situation was similar to D1c apart from the fact that this document had a date stamp of 15.09.2000. This date may, however, be the date of receipt at the FDA or any other arbitrary date. In any way, this date was no evidence for the public access or availability.

Provisional opinion as to the grounds of opposition

1. Article 100(a) EPC, Article 54 EPC

The opposition division is of the preliminary opinion that the availability of D1a-D1d to the public at the filing date does not appear to be proven so that D1a-D1d do not appear to be relevant for the purpose of novelty.

Novelty. Inherent anticipation. Paroxetine (1/3)

Invent Farma

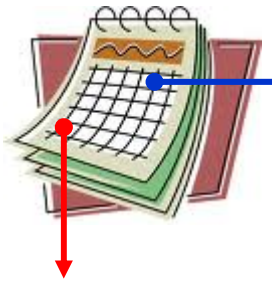
US. Paxil®.

Paroxetine hydrochloride anhydrate. First prepared in 1970 by Ferrosan .

During scale up a new form of Paroxetine hydrochloride appeared.

Hemihydrate of Paroxetine HCl marketed since 1983

Expiry dates in USA



Anhydrate: 1992

Hemihydrate: 2006

Apotex filed an ANDA to market Paroxetine HCl anhydrate containing a PIV certification (patent not infringed)

District Court: **Found patent valid but not infringed**

Court of Appeals of Federal Circuit: **Patent invalid**:

Clinical trials: Prior use (reversed)

Inherent anticipation (similar to EP implicit disclosure)

GSK asserted that Apotex will infringe by manufacturing PHC anhydrate tablets that necessarily contain, by a conversion process discussed below, at least trace amounts of PHC hemihydrate

Novelty. Inherent anticipation. Paroxetine (2/3)

Invent Farma

To show that manufacture of PHC anhydrate tablets necessarily creates PHC hemihydrate, SmithKline proffered expert testimony on the so-called ***"seeding"*** *or* ***"disappearing polymorph"*** *theory. Under this theory, Ferrosan may have originally created a crystalline compound, namely PHC anhydrate, in a relatively unstable form. For presently unknown reasons, the PHC anhydrate "morphed" into a more stable form, namely the PHC hemihydrate discovered in SmithKline's facilities. With this new form or polymorph in existence, SmithKline's experts explained,* ***the general environment became "seeded" with crystals of PHC hemihydrate****. In this seeded environment, the* ***PHC anhydrate converts to the PHC hemihydrate upon its inevitable contact with seeds of PHC hemihydrate****.* ***In other words, the creation of pure PHC anhydrate became extremely difficult, if not impossible; the old polymorph, PCH anhydrate, has effectively disappeared in its pure form because it changes naturally into the new polymorph, PCH hemihydrate.***

SmithKline argues that practicing the '196 patent infringes claim 1 of the '723 patent, but that the '196 patent does not anticipate claim 1 of the '723 patent. SmithKline uses the "disappearing polymorph" theory to justify its apparently inconsistent positions. …

403 F.3d 1331 . U.S. CAFC. 8 April 2005,

Novelty. Inherent anticipation. Paroxetine (3/3)

Invent Farma

The record shows, and SmithKline admits 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****.*

…..this court holds, based on the undisputed facts, that claim 1 of the '723 ***patent is invalid for inherent anticipation by the '196 patent*** *under § 102(a). Apotex is, therefore, not liable for infringing claim 1 of the '723 patent. This court affirms the district court's judgment.*

403 F.3d 1331 . U.S. CAFC. 8 April 2005,

Novelty. Reproduction of prior art. Inevitable result

"Seed crystals, they're in the air. You can't see them. You can't smell them. You can't taste them. You also can't detect them, they're there, and these seed crystals fall out of the sky, and they're very intelligent because they know when you are running one of these Example 32 experiments. They fall out of the sky and fall in your reaction beaker...Well I submit that if one believes in Santa Claus we might believe in these seed crystals, but if we're beyond that, we're not going to believe in these seed crystals . . ."

Part of the opening statement by the counsel for Novopharm in the first ranitidine hydrochloride case against Glaxo in August 1993.

Bernstein J. Chap. 14. Polymorphism in the Pharmaceutical Industry. Ed. Rolf Hilfiker

Invent Farma

EPO Guidelines, C-IV.11.1 General

An invention is considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. Novelty (see IV, 7) and inventive step are different criteria. The question – "is there inventive step?" – only arises if the invention is novel.

"It is at least this author's opinion that every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound."

McCrone 1965. In Bernstein J. Polymorphism in Molecular Crystals.

Obviousness

Problem-and-solution approach

Determine Closest prior art
Determine technical difference
Determine the inferred technical effect

Establish the objective technical problem
Check that the problem was solved

Assess wehter it would have been obvious to solve the objective problem by the claimed invention

(Usually) same compound, for the same technical purpose, different crystalline, or non-crystalline or undefined form.

Provide alternative stable form of a known compound to achieve the same effect

Obvious
Unexpected or non-obvious effect required

Provide further form of known compound with different property

No reasonable expectation

No obvious

Inventive step. Surprising effect

(22) Date de dépôt: **06.07.2001**

Surprising technical effect over prior art?

(30) Priorité: **06.07.2000**

EP 1 296 947 B1

Alpha

[0006] La demanderesse a présentement trouvé qu'un sel particulier du perindopril, le sel de tert-butylamine, pouvait être obtenu sous une forme cristalline bien définie, parfaitement reproductible et présentant notamment des caractéristiques intéressantes de filtration, de séchage et de facilité de formulation.

EP 1 294 689 B1

Beta

[0006] La demanderesse a présentement trouvé qu'un sel particulier du perindopril, le sel de tert-butylamine, pouvait être obtenu sous une forme cristalline bien définie, parfaitement reproductible et présentant notamment des caractéristiques intéressantes de formulation.

EP 1 296 948 B1

Gamma

[0006] La demanderesse a présentement trouvé qu'un sel particulier du perindopril, le sel de tert-butylamine, pouvait être obtenu sous une forme cristalline bien définie, parfaitement reproductible et présentant notamment des caractéristiques de formulation.

Inventive step. Obvious to try?

Invent Farma

WO2005080381

3. The present application does not meet the criteria of Article 33(1) PCT, because the present subject-matter does not involve an inventive step in the sense of Article 33(3) PCT.

Documents D1 and D2, which are regarded as being the closest prior art, disclose crystalline forms of ondansetron and their use in the treatment of nausea and vomiting (D1, claims 11 and 28; D2, p. 5, paragraph 2).

The problem underlying the present application is seen in the provision of alternative forms of ondansetron for the same therapeutic application (see present description, p. 1, lines 6-14).

Since the pharmaceutical effect of a pharmaceutically active ingredient is based on its molecular structure rather than its solid state properties, it would be obvious for the person skilled in the art to screen for further crystalline forms of ondansetron as a solution to the above-mentioned problem. Present Form E is therefore considered to be an obvious alternative to the known high-melting forms of D1 (Form B) and D2 (Form II).

An inventive step cannot therefore be acknowledged, in the absence of evidence showing that present Form E has unexpected properties with respect to the closest prior art forms of D1 (Form B) or D2 (Form II). With the letter of 01.02.2006, the applicant provided evidence of the stability of Form E. No comparative tests were, however, provided.

Obviousness

Invent Farma

Having regard to Regulatory issues is obvious to perform a polymorphism screening?

ICH Q6A

Decision trees #4(1) through 4(3) provide additional guidance on when, and how, polymorphic forms should be monitored and controlled.

Note: These decision trees should be followed sequentially. Trees 1 and 2 consider whether polymorphism is exhibited by the drug substance, and whether the different polymorphic forms can affect performance of the drug product. Tree 3 should only be applied when polymorphism has been demonstrated for the drug substance, and shown to affect these properties. Tree 3 considers the potential for change in polymorphic forms in the drug product, and whether such a change has any effect on product performance.

Common General Knowledge

Invent Farma

About crystal forms

- The common general knowledge would include the basics of crystallisation as follows.
- A compound is said to exist in polymorphic form if it crystallises into more than one arrangement in the crystal lattice.
- It was **well known and accepted** that different crystal forms of the same compound (whether true polymorphs or solvates or hydrates) can have **different physicochemical properties**.
- These properties include solubility, dissolution rate, stability and processing characteristics. In consequence the bio-availability of the drug can be dependent on the crystal form as well.
- In general, crystallisation is an empirical process. **It is not possible to predict in advance** whether a particular compound will crystallise, or whether it will form an amorphous solid.
- A given compound may fail to crystallise even where similar compounds are known to crystallise. If a given compound crystallises in one way, it is **not possible to predict** what if any other forms it might exist in, or whether it will form solvates.
- Inducing a compound to crystallise for the first time, or into a new crystalline form, involves choosing the correct conditions which themselves **cannot be predicted in advance**.
- **Seemingly trivial matters such as impurities**, may influence the result.

Mr. Justice Floyd. [2009] EWHC 996 (Pat). UK Patents Court . Leo vs. Calcipotriol

Invent Farma

About screening for polymorphs

- A **polymorph screen** involves crystallising an API from a variety of solvents and solvent mixtures and characterising the resulting crystals for evidence of polymorphism or pseudopolymorphism.

- Nevertheless, well before 1993, standard formulation textbooks were teaching with varying degrees of emphasis that, in the preformulation stage of pharmaceutical development, **one should actively look for polymorphs**

- The immediate objective in looking for alternative crystal forms is not research conducted solely or even primarily to find something better. The objective is to establish that when you make and sell the product it is not going to change into something different. …. Nevertheless, as we shall see when we come to the relevant regulatory guidelines, **what is said to be important is to demonstrate stability under the actual process and storage conditions. To look more widely for polymorphs would not be regarded by the skilled team as mandatory**.

- I conclude that the skilled team would know in 1993, as part of its general knowledge, that full polymorph screening was an available step to take …. **That does not mean that it would be obvious to conduct such a full polymorph screen in all circumstances**. The skilled team would consider in any individual case how difficult such experiments were, and the prospects of finding useful results. However, the skilled team would appreciate the importance of checking for the possibility of polymorph or solvate formation under the actual process and storage conditions proposed

Mr. Justice Floyd. [2009] EWHC 996 (Pat). UK Patents Court . Leo vs. Calcipotriol

Obviousness

Invent Farma

Calcipotriol Appeal. Jacob L.J. Accepted that:

•full polymorph screening using a range of solvents and conditions was a systematic investigation to discover whether a compound came in other forms.

•This process was not required by regulators

•Crystallising analogues was difficult and that Leo Pharma's past experience had not indicated it was worthwhile for any purpose at all.

•It was not universal practice to conduct a polymorph screen

•The skilled team would not regard such a screen as mandatory

CONCLUSION: THE SKILLED TEAM WOULD NOT CARRY OUT A FULL SCREEN

NOT OBVIOUS

Source: Bratin Roy. Leo Pharma A/S vs Sandoz Ltd.- Whither the Single European Patent. Europ. Int. Prop. Rev. 2010, 178.

Obviousness

Invent Farma

"In my opinion, the evidence of the state of the knowledge at the date of the invention, that is the discovery of the hemyhidrate form and the fact that it had beneficial properties for the manufacture of crystalline paroxetine hydrochloride, ***does not indicate that others skilled in the art would have known the way in which to create, notice and document the benefits of the hemihydrate form****….*

As noted above, the test for obviousness is stringent. It requires the capable but non-imaginative skilled person to look at the common knowledge in the art at the date of the invention and immediately, without imaginative ingenuity, reach at the described invention."

SKB vs Genepharm. Paroxetine (Canda). Ms. Heneghan J. 2003 FC 1248

Invent Farma

When and where?

• During **examination** by filing Third party observations (Art. 115 EPC).

• After grant: filing an **opposition** (Art.100 EPC).

• After opposition: **invalidation proceedings before national courts**.

Problems:

- In some countries infringement and validity are assessed separately
- Different Courts may reach at a different conclusion

Challenging the validity of patents

Invent Farma

In Calcipotriol case. (EP (UK) No. 0 679 154

High Court of Justice. Patent Court. Mr. Justice Floyd:

*"The parties are in dispute over the Patent elsewhere. The **Dutch court**, has rejected Sandoz' invalidity attack …... a **German court** had held the patent invalid on the basis of an obviousness attack different to the one pursued before me. …... If there were a **supra-national court** of the kind currently proposed, able to decide on disputes about the validity of patents for the whole of Europe, **conflicting results of this kind between courts of first instance could be avoided**."*

High Court of Justice. Court of Appeal. Jacob L.J.:

*"This appeal falls to be dismissed. I only add a couple of points. This is yet another case where validity has to be assessed by **several national courts**. We have reached the same result as that in Holland at first instance (where the argument was in part different). The Bundespatentgericht has gone the other way – but **working on different prior art**, prior art which Sandoz in this country abandoned. Different results in different countries based on different cases is, of course, explicable. It is an unfortunate state of affairs, **curable only by a single European Patent Court.**"*

US. Paroxetine SKB vs. Apotex

District Court

… limited claim 1 to PHC hemihydrate in commercially significant amounts. …. The trial record contained uncontested testimony that a PHC anhydrate-hemihydrate mixture would need to possess a percentage of PHC hemihydrate in the "**high double digits**" **if the hemihydrate component were to contribute any commercial value**. …

Federal Circuit:

Having interpreted claim 1 to **cover PHC hemihydrate without further limitation**,

In summary, this court reverses the claim construction of the district court and holds that claim 1 of the '723 patent **covers any amount of crystalline** paroxetine hydrochloride hemihydrate without further limitation. … this court affirms the district court's finding that Apotex's PHC anhydrate product will infringe claim 1

Infringement Canada

66] In construing the claim in issue, the Court must identify the essential elements of that claim. …

The key to purposive construction is therefore the identification by the court, with the assistance of the skilled reader, of the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of his invention...

[67] … that task is challenging since the claim contains only four words and reads as follows: "crystalline paroxetine hydrochloride hemihydrate".

[68] … We have found that amorphous paroxetine hydrochloride is a hygroscopic solid of poor handling qualities.

The purposive approach to construction ….. The hemihydrate is described as being stable and non-hygroscopic …. It is **not** sensible to interpret the claim as **covering minuscule and minute amounts of crystalline paroxetine hydrochloride hemihydrate** which, according to the expert evidence, is now extremely widespread since the discovery of the product in 1984, due to the prevalent use of the drug and the factors of seeding and conversion.

[75] … **Claim 10 means crystalline paroxetine hydrochloride hemihydrate when it is found in a drug in sufficient quantity that it improves the handling properties of such drug during manufacture.**

Source: http://decisions.fct-cf.gc.ca/en/2003/2003fc1248/2003fc1248.html

Infringement of patent claiming polymorphs

Invent Farma

Claim Construction.

According to Art. 69 EPC and its protocol for interpretation:

- **Scope determined by claims**
- **Description used to resolve ambiguities**

- Usually a polymorph is not a new product. It is a new physical form of a known chemical product.
- It is developed **to solve a techical problem**
- A different polymorphic form, may not solve the same problem at all

Infringement of patent claiming polymorphs

Invent Farma

Which is the maximum amount of polymorph B (patented) in a pharmaceutical composition of polymorph A (Free)?

B is patentable (probably) because of the new properties/features and solve a techincal problem that A does not solve

Trace amounts of B (claimed polymorph) in A is an act of infringement?

- In US: YES
- In Canada: No
- in EU???

•Which levels are detectable?

- **Which technique has to be used to determine the presence of patented polymorph?**
- **limit of detection?**

• The presence of traces may have a seeding effect. Polymorphic stability has to be proved over the shelf life of the product (Regulatory requirement!!!)

Conclusions

Invent Farma

Regulatory

- It is important to characterise the crystalline forms and to know their properties
- Consider the risk of inadvertent change of polymorphic forms and its effect on the product

Value for patentees

- Follow-up patents are useful to keep off competitors from market or to delay their entry

Patentability

- There is no standard or generally accepted notation for polymorphs
- Prior art descriptions usually does not provide enough information to compare with new inventions
- Although there are systematic approaches to polymorph screening is not obvious to perform them and to understand the results obtained

Invent Farma

Litigation:

- Prior art disclosures. Repeat exactly the prior art process (if possible!!):
  - same scale
  - using same procedure
  - Impurities……
- Environment is seed-free
- **claim construction???**

Conclusions

9. The upshot of all this is that were the patent valid, Servier's monopoly in practice would last until 2020. But, as the Judge held and we confirm, it is invalid. And very plainly so. It is the sort of patent which can give the patent system a bad name. I am not sure that much could have been done about this at the examination stage. There are other sorts of case where the Patent Office examination is seen to be too lenient. But this is not one of them. For simply comparing the cited prior art ('341) with the patent would not reveal lack of novelty and probably not obviousness. You need the technical input of experts both in the kind of chemistry involved and in powder X-ray diffraction and some experimental evidence in order to see just how specious the application for the patent was. *The only solution to this type of undesirable patent is a rapid and efficient method for obtaining its revocation. Then it can be got rid of before it does too much harm to the public interest.*

Perindopril UK. Servier vs. Apotex [2008] EWCA Civ 445. Supreme Court. Jacob L.J.

Gracias

Preguntas ?

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