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## Patentability of Pharmaceutical Polymorphs in Europe



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### Introduction

**A**s a follow up to our recent article on pharmaceutical polymorphs and their patentability in the United States<sup>1</sup>, we now address the patentability of pharmaceutical polymorphs in Europe where the issue is more nuanced. With the economic size of Europe and the number of countries covered under the European Patent Convention (EPC), its importance to the pharmaceutical industry cannot be overlooked.

Polymorphism is the ability of a crystalline material to exist in more than one solid or crystalline form. Patent protection for a polymorphic form of a drug or clinical candidate has the potential to extend the patent protection of a drug and extend its market exclusivity. It may also serve as an additional basis to enforce the patent owner's rights against a putative generic manufacturer due to differences in the chemical and biological properties between different polymorphs. For an introduction to crystal polymorphism, and its importance in

the pharmaceutical industry in general, please see our previous article.<sup>1</sup>

### Did Polymorph Claims Just Die in Europe?

In May 2011, the Technical Board of Appeal of the European Patent Office (hereinafter the "Board") issued a very significant decision in upholding the Opposition Division decision revoking patent EP1148049B1 which claimed a polymorphic form of atorvastatin.<sup>2</sup> The revocation was on the ground of a lack of inventive step pursuant to Articles 52(1) and 56 of the EPC.<sup>3</sup> Article 52(1) states that "[e]uropean patents shall be granted for any inventions, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of industrial application."<sup>4</sup> Article 56 states "[a]n invention shall be 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."<sup>5</sup> Under United States law, the closest equivalent for a lack of inventive step is obviousness in lieu of the prior art under 35 USC § 103.

As an initial determination in the Opposition Proceeding, the original patents for the amorphous form of atorvastatin were cited as the closest prior art.<sup>6</sup> Two different lines of reasoning using overlapping references were developed to hold that the patent lacked an inventive step.

<sup>1</sup> See article in March, 11, 2016, issue of Bloomberg BNA's Pharmaceutical Law & Industry Report. (14 PLIR 386, 3/11/16)

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<sup>2</sup> Atorvastatin calcium is sold under the tradename Lipitor® by Pfizer, Inc.

<sup>3</sup> Case T 0777/08 – 3.3.01 issued on 24 May 2011 with Warner-Lambert Company, LLC as Patent Proprietor and Teva Pharmaceuticals Industries, Ltd. as Opponent.

<sup>4</sup> <http://www.epo.org/law-practice/legal-texts/html/epc/2013/e/ar52.html> (accessed on January 13, 2016).

<sup>5</sup> <http://www.epo.org/law-practice/legal-texts/html/epc/2013/e/ar56.html> (accessed on January 13, 2016).

<sup>6</sup> WO/1994/016693 and EP0409281B1

For the first line of reasoning, the Board determined that the existence of polymorphism was a well-known issue of concern in the pharmaceutical industry.<sup>7</sup> It was also well-known that it is advisable to screen for polymorphs early in the drug development process because both European and American regulators require “appropriate” information about polymorphs during the approval process.<sup>8</sup> Finally, a person skilled in the art would know how to screen for polymorphs.<sup>7,8</sup> Paragraph [0011] in the description of the patent states “[w]e have now surprisingly and unexpectedly found that atorvastatin can be prepared in crystalline form.”<sup>9</sup> The Board then concluded that

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]).

Surprising and/or unexpected results are common hallmarks of an inventive step or non-obviousness under both European and American law, but this conclusory statement was not accepted at face value simply because it was written in the application.

For the second line of reasoning, the decision noted that the patent holder did not rely solely on the existence of the polymorph to support the inventive step. In the technical problem to be solved, the Patent Proprietor asserted that a new form of atorvastatin having improved filterability and drying characteristics was desirable as compared to the amorphous form.<sup>10</sup> The Board reasoned that it is well known in the art that crystalline forms have different physical characteristics than an amorphous form, including both filterability and ease of drying.<sup>7,8,11</sup> Amorphous forms are known to be more soluble and have a greater bioavailability, but “[c]rystalline products are generally the easiest to isolate, purify, dry and, in a batch process, handle and formulate.”<sup>7</sup> A person skilled in the art would recognize that there might be a trade-off between the positive and negative aspects of a polymorph. The existence of possible negative consequences does not mean that a polymorph was not “obvious to try . . . with a reasonable expectation of success without involving any inventive ingenuity.”<sup>12</sup> Furthermore, although the Board recognized that there might be other possible means to solve the filterability and drying problem, the “arbitrary selection from a group of equally suitable candidates cannot be viewed as involving an inventive step.”<sup>13</sup> In other words, selecting one possible solution to a problem out of a group of known possible solutions does not involve an inventive step. Similar rationale is found in

the *KSR International v. Teleflex, Inc.* decision in the United States.<sup>14</sup>

Both lines of reasoning, and the references cited in support, would be applicable to almost any pharmaceutical polymorph patent or pending application. Bavin,<sup>7</sup> Byrn,<sup>8</sup> and Hancock<sup>11</sup> are general references on small molecule polymorphism in regards to pharmaceuticals that do not refer to atorvastatin specifically and could be prior art to any presently filed application and many already issued patents. While this decision suggests that polymorphs might be much more difficult to patent in Europe, the manner in which it has been applied is the important issue.<sup>15</sup>

## Polymorph Patents Allowed

Decision T 0643/12<sup>16</sup> overturned the rejection by the Examining Division of an application for a polymorph of lenvatinib mesylate.<sup>17</sup> In their appeal, the Applicant stated that the technical problem to be solved was “the provision of lenvatinib in a form having an improved dissolution rate and bioavailability, low hygroscopicity, and good stability.”<sup>18</sup> Support for this description was found in the application in two places. First, the specification stated that:

[0004] It is an object of the present invention to provide a crystalline form of the salt of 4-(3-chloro-4-(cyclopropyl-aminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarbox-amide or the solvate of the salt which has high usability as a medicament and a process for preparing the same.<sup>19</sup>

Second, and most importantly, data in the application compared the stability, hygroscopicity, bioavailability, and dissolution rate for multiple salts and crystal forms. The Board distinguished this case from T0777/03 in § 5.4.3 of the decision by suggesting that “the mesylate salt claimed would not have been expected to deliver the desired **combination** of properties (*emphasis added*). Moreover, the skilled person would not have had a reasonable expectation that any arbitrary crystalline salt form of lenvatinib would be equally suitable in this respect.”<sup>20</sup>

The decision cited several pieces of prior art showing that the search for a salt form of a weakly basic molecule would not involve an inventive step. However, the technical problem involved a series of interrelated and

<sup>14</sup> *KSR International v. Teleflex, Inc.*, 127 S.Ct. 1727, 1742 (2007) (“When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.”)

<sup>15</sup> In searching Office Actions and PTAB decisions at the USPTO, this author has not found this line of reasoning presented. One can only wonder if (more likely when) it will happen and how the PTAB and US Courts will decide. With closer collaboration between patent offices worldwide, especially with the new Global Dossier Initiative, this author expects to see it sooner rather than later.

<sup>16</sup> Case T 0643/12-3.3.01 issued on 18 June 2014 with Eisai R&D Management Co., Ltd. as the Applicant.

<sup>17</sup> Lenvatinib is marketed under the tradename of Lenvima® by Eisai.

<sup>18</sup> T 0643/12-3.3.01 at § 5.3.

<sup>19</sup> EP0698623A1 at [0004].

<sup>20</sup> T 0643/12-3.3.01 at § 5.4.3.

<sup>7</sup> M. Bavin, *Chemistry & Industry*, 21 August 1989, 527- 529.

<sup>8</sup> S. Byrn *et al.*, *Pharmaceutical Research*, July 1995, 12(7), 945 – 954.

<sup>9</sup> EP0409281B1 at [0011].

<sup>10</sup> EP0409281B1 at [0006].

<sup>11</sup> B. C. Hancock *et al.*, *Pharmaceutical Research*, June 1995, 12(6), 799 – 806.

<sup>12</sup> T 0777/08 at pg. 12 ¶ 2.

<sup>13</sup> T 0777/08 at pg. 13 ¶ 1.

sometimes inversely related properties that did not correlate with each other. One reference cited by the Applicant stated that “the selection of the salt form that exhibits the desired combination of properties remains a difficult semi-empirical choice.”<sup>21</sup> Because of the interrelationship between the four different properties and the difficulties that would be associated with optimizing each one simultaneously, the application was found to have an inventive step.

There are several important takeaways from this decision. First, the technical problem to be solved must be described in the application, even if it is only implicit. Second, the problem cannot be one that is routinely associated with polymorphs. A common formulation and manufacturing issue that is routinely solved by use of a polymorph may not be enough. Third, and most importantly, the data included in the application should be specifically related to the technical problem. The data showed that certain salt and crystal forms had desirable properties while others did not.

Decision T 0517/14<sup>22</sup> affirmed the Opposition Division decision to uphold the allowance of a patent for a polymorph of ibandronate sodium.<sup>23</sup> The technical problem described was the provision of “a polymorphically stable form of ibandronate sodium” because it was well known that several of the known polymorphs would interchange on standing.<sup>24</sup> Although some of the known polymorphs had similar solubility and dissolution properties, there was no reason to infer that other polymorphs would be equivalent.

In arguing against an inventive step, the Opponent relied on T 0777/08 when they suggested that a person skilled in the art would be aware of the existence of stable polymorphs. Finding a new, stable polymorph “could not be regarded as an unexpected property in the sense of decision T 777/08.”<sup>25</sup> The Patent Proprietor argued that the prior art documents, including those that disclosed the amorphous form and other polymorphic forms, did not provide any guidance as to the new stable polymorph. In agreeing with the Patent Proprietor and upholding the patent, the Board cited the similarity between the preparation conditions for the numerous known polymorphs. Using either a water/methanol or water/acetone recrystallization solvent mixture leads to multiple different polymorphs, some of which were stable and some of which were not. The conditions to generate the numerous different polymorphs were very similar, so there was no expectation of success in finding a stable polymorph based on conditions similar to those that produce unstable ones.

An important takeaway from this decision is that finding a polymorph just for the sake of finding one does not have an inventive step. In this case, there was a legitimate, demonstrable need for a stable polymorph due to the lack of stability in known polymorphs. The small difference in the conditions for generating a

stable form versus an unstable form also supported the inventive step determination.

Decision T 1422/12,<sup>26</sup> an appeal of a rejection by the Examining Division for an application for a polymorph of Tigecycline,<sup>27</sup> illustrates another argument for allowance. The initial rejection was based, in part, on T0777/08.<sup>3</sup> In overturning the rejection, the Board distinguished this application from T0777/08:

The facts of the present case are clearly distinguishable from those leading to the decision T 777/08 (*loc. cit.*) which stated (see Headnote I) that “**in the absence of any unexpected property**, the mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving an inventive step” (emphasis added in the decision).<sup>28</sup>

The Applicant submitted that the problem to be solved was an improved stability toward epimerization citing to paragraphs [0009] – [0010] in the application as filed:

[0009] Generally, the crystalline solid has improved chemical and physical stability over the amorphous form, and forms with low crystallinity. They can also exhibit improved hygroscopicity, bulk properties, and/or flowability.

[0010] The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to *improve the performance characteristics* of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. There is a need in the art for crystalline Tigecycline and polymorphic forms thereof (emphasis added).<sup>29</sup>

The Examining Division rejected the Applicant’s description of the technical problem; however, despite not even mentioning epimerization in the application, the Board accepted that the improved “performance characteristics” in the application included improved stability toward epimerization. They wrote:

[t]hat the more *specific* problem of improved stability with respect to epimerisation is not mentioned in the application as originally filed is irrelevant (see T 39/93, point 5.3.5, *loc. cit.*), since improvement of stability by avoidance of epimerisation, and, as a consequence, improved biological activity, is clearly recognizable [sic] by the skilled person as a desirable effect for a tetracycline antibiotic. As a consequence, the Board does not agree with the conclusions of the Examining Division regarding the for-

<sup>21</sup> Gould, P. L., “Salt Selection for Basic Drugs,” *Int. J. Pharmaceutics*, 33(1-3), 201-217 (1986).

<sup>22</sup> Case T 0517/14-3.3.01 issued on 19 June 2015 with Teva Pharmaceutical Industries, Ltd as the Patent Proprietor and Hexal AG and Help AG as the Opponents.

<sup>23</sup> Ibandronate sodium is marketed under the tradename Boniva® by Hoffman-La Roche.

<sup>24</sup> T 0517/14 at pg. 43, § 5.3.

<sup>25</sup> T 0517/14 at pg. 12.

<sup>26</sup> Case T 1422/12 – 3.3.10 issued on 11 April 2013 with Teva Pharmaceutical Industries, Ltd. as the Applicant.

<sup>27</sup> Tigecycline is sold under the name Tygacil® by Pfizer, Inc.

<sup>28</sup> T 1422//12 at pg. 8, § 2.6.2

<sup>29</sup> T 1422/12 at pg. 3¶ 1.

mulation of the technical problem and thus allows the definition given . . .<sup>30</sup>

Once the Board accepted the Applicant's definition of the technical problem, they also accepted declarations by the inventors supporting the increased stability of the polymorph. Although epimerization was a known problem with the amorphous form of Tigecycline and many other tetracycline antibiotics, there was no suggestion in the prior art that a crystalline form would be more stable to epimerization. Furthermore, the prior art taught that previous attempts to solve the epimerization problem using different methods were unsuccessful.<sup>31</sup> Because an amorphous form of Tigecycline was already on the market, this suggested that previous routine attempts to screen for polymorphs were unsuccessful, and it reduced the motivation to search for a polymorphic form.

There are two important takeaways from this decision. First, there must be a specific technical problem that the Applicant is trying to solve with the polymorph, and it cannot be one routinely associated with polymorphs. Traditional formulation problems that are commonly resolved via different polymorphic forms may not be enough. Second, support for the technical problem must be found in the specification of the application when filed even if that support is very weak and generalized.

### Polymorph Patent Denied

Decision T 2007/11,<sup>32</sup> where the Board upheld the rejection by the Examining Division of an application for a polymorph of imatinib mesylate ethanol solvate,<sup>33</sup> illustrates the importance in drafting the application and describing the technical problem properly. The Applicant argued that the technical problem was the preparation of a crystalline form of imatinib that had improved flowability and "was especially attractive for pharmaceutical formulations, due to its unique shape (habit), smaller particle size and the narrower particle size distribution. Excellent flowability was achieved due to the unique shape and could be retained even with small particles."<sup>34</sup> This formulation of the technical problem was rejected by both the Examining Division and the Board because there was no supporting data in the application. The Examples in the description of the application included 46 methods for producing different polymorphic forms and one example of a pharmaceutical formulation. There was no data as to flowability testing, shape, particle size measurement, or particle

size distribution.<sup>35</sup> Because there was no support for the purported advantages of the new polymorph, the technical problem was "reformulated in a less ambitious way. In view of [the prior art, the technical problem] can merely be seen as the provision of a further crystalline form of imatinib mesylate."<sup>36</sup> Once the technical problem was rephrased as such, the end result was predictable. The Board cited both T0777/08<sup>3</sup> and some of the same prior art therein<sup>8</sup> when they upheld the rejection.

There are two important takeaways from this decision. First, regardless of how vague the description of the technical problem to be solved, there must be some supporting data in the specification to back it up. Speculation and conclusory statements without support will not be accepted. This data must be included when the application is initially drafted. Second, "[t]he board cannot accept the appellant's argument that there was inventive merit merely because the skilled person could not have been certain that a further crystalline form of imatinib mesylate existed or that such a form would have different and even advantageous properties."<sup>37</sup> The inventive step is focused on the process by which the invention is derived, not the end result.<sup>38</sup> The Applicant must control the discussion of the technical problem and the manner in which it was solved to show there is an inventive step. Allowing the Board to control the argument and phrasing of the technical problem was fatal for this application.

### Conclusion

Pharmaceutical polymorphs provide an excellent way for a company to further protect a small molecule drug in order to recoup the billions of dollars that go into research and development, thereby enabling further research and development. To ensure optimum worldwide coverage, it is critically important that the application be drafted in a manner that complies with the requirements of as many targeted markets as possible. Even before the application is drafted, it is important to consider the requirements of the many different jurisdictions and prepare accordingly. Evidence of unexpected results or the provision of data supporting the solution to a significant technical problem – one not traditionally associated with small molecule polymorphism – must be included in the application to establish an inventive step. Europe is an important market for many pharmaceutical products, so drafting an application with the best chance for allowance requires an expert with the proper knowledge and experience.

<sup>30</sup> T 1422/12 at pg. 7¶ 1.

<sup>31</sup> US-A-5 675 030, column 1, lines 39-62, and claims 1 and 13.

<sup>32</sup> Case T 2007/11-3.3.01 decided on 7 October 2014 with Sincor, Inc. as the Applicant.

<sup>33</sup> Imatinib is marketed under the tradename Glivec® (Europe) or Gleevec® (USA) by Novartis.

<sup>34</sup> T 2007/11 at pg. 15, § 7.3.

<sup>35</sup> See the Examples in WO 2007/136510 A2 (or PCT/US2007/010321).

<sup>36</sup> T 2007/11 at pg. 17, § 7.6.

<sup>37</sup> T 2007/11 at pg. 18, § 7.7.2.

<sup>38</sup> The end result of the inventive process is scrutinized under the novelty requirements of the EPC, not the inventive step. In the cases described herein, the novelty of the polymorph was seldom an issue.