Kluwer Patent Blog

Inventiveness of Pharmaceutical Polymorph Patents in China

Jiao Yuxin (ZY Partners), Hui Zhang (Baker & McKenzie), and Yi Wei (Zy Partners) · Thursday, May 4th, 2017

Pharmaceutical polymorph patents are regarded as effective means and important secondary pharmaceutical patents to extend the life cycle of pharmaceutical patent protection. However, the inventiveness evaluation criteria for pharmaceutical polymorph patents have become much stricter in China while the amount of patent application keeps soaring.

The clinical research of pharmaceutical polymorphs commenced in 1950s internationally though, it was until in mid-1990s did Chinese research institutions and pharmaceutical enterprises recognize the importance of pharmaceutical polymorphs after the first awareness of the significant efficacy difference between imported nimodipine and the homemade one.

In China, no specific rules over pharmaceutical polymorph patents are provided in the *Patent Law* or the *Patent Examination Guidelines,* rooms are left for authorities to exercise discretional power on deciding whether an application for pharmaceutical polymorph patent is inventive or not. In patent examination practice, China in the early days had a lower threshold for authorization of pharmaceutical polymorph patents than European countries and the US. However, the threshold has increasingly heightened in recent years, and as a result, a large portion of authorized pharmaceutical polymorph patents were invalidated by the Patent Reexamination Board ("**PRB**") for failing to satisfy the present examination requirement. Based on a review of recent court administrative judgments over re-examination or invalidation decisions made by the PRB, we astonishingly observed that the PRB and the courts denied the inventiveness of almost all pharmaceutical polymorph patents with overwhelmingly consistent examination standards.

Pharmaceutical polymorph patents share general properties with chemical product patents and meanwhile hold their particularities. This article would summarize the current inventiveness examination standards for pharmaceutical polymorph patents in China and propose some strategic suggestions for potential patent applicants.

I. Current Examination Standards over Inventiveness of Chinese Pharmaceutical Polymorph Patents

There are two sets of rules for inventiveness assessment under the *Patent Examination Guidelines,* both of which come to the same conclusion that, whether a polymorph invention can produce unexpected technical effect is the core evaluation standard.

1. **General Standard: the "Three-Step Approach"**

1.1 **Relevant Rules**

Article 22.3 of the current *Patent Law of the People's Republic of China (2009*) stipulates that: *"Inventiveness means that, compared with the existing technologies, the invention possesses prominent substantive features and indicates remarkable advancements, and the utility model possesses substantive features and indicates advancements."*

Section 3 of Chapter 4 in Part II of the *Patent Examination Guidelines* (2017) clarifies the general procedures and standards for inventiveness assessment, i.e., (1) determining the closest prior art; (2) determining the distinguishing features of the invention and the technical problem actually solved by the invention; and (3) determining whether or not the claimed invention is obvious to a person skilled in the art. The above-mentioned is referred to as the "Three-Step Approach" and the general rule in assessing patent inventiveness.

Section 5 of Chapter 4 in Part II of the *Patent Examination Guidelines* (2017) further provides supplementary factors to be considered to avoid arbitrary denial of inventiveness of a patent following the "Three-Step Approach". These factors include whether an invention produces unexpected technical effect, overcomes a technical prejudice or achieves commercial success, etc.

1.2 **Examination Standard**

When applying the "Three-Step Approach" for polymorph patents, it is generally presumed that there is a universal technical motivation in the prior art to prepare the crystal form of active pharmaceutical ingredients. From a storage perspective, crystal is a comparatively stable form for easier preservation and transportation; from an availability perspective, if there is demand in the prior art to improve the stability and purity of an amorphous compound, a person skilled in the art would apparently know that a crystal form of a certain compound can be precipitated from a solution, and be motivated to prepare crystalline products for reducing impurity; from an application effect perspective, a crystal with higher stability and higher purity would naturally possess higher bioavailability.

In short, following the "Three-Step Approach", it is generally recognized as an "obvious" technical solution to prepare a new polymorph based on a known compound or a known polymorph, given that there has been an obvious motivation, the preparation process of polymorph is generally mature and the technical effects can be anticipated. The assessment of inventiveness of polymorph patents will then need to conduct a further "unexpected technical effect" evaluation.

2. **Special Standard for Chemical Inventions**

2.1 **Relevant Rules**

Since polymorph is a type of chemical products, the inventiveness assessment of polymorph patents can follow the below special provisions on examination of chemical inventions in Chapter 10 of Part II of the *Patent Examination Guidelines* (2017). That is,

"For a compound that is similar in structure to a known compound, it must have unexpected use or effect. The said unexpected use or effect may be a use different from that of the known compound, the substantive progress or improvement of a known effect of a known compound, or a use or effect which is not clear in the common general knowledge or cannot be deduced from the common general knowledge."

2.2 **Examination Standard**

There were debates on whether a claimed polymorph is similar in structure to a known compound or a known polymorph in prior arts. A decision made by the Chinese Supreme People's Court (see below) clarified that the similarity evaluation should be based on the chemical structure of the core active element rather than the microcosmic crystalline structure of the polymorph. Accordingly, a crystal form of a known compound would be regarded to have similar structure with the compound and its amorphous and crystal forms. The differences in microcosmic crystalline structure of different polymorphs are only considered if such microcosmic crystalline structure brings "unexpected technical effect".

Standard for "Unexpected Technical Effect"

3.1 **Relevant Rules**

Section 5.3, Chapter 4 of Part II of the *Patent Examination Guidelines* (2017) stipulates that: "*An invention produces an unexpected technical effect means that, as compared with the prior art, the technical effect of the invention represents a "qualitative" change, that is, new performance; or represents a "quantitative" change which is unexpected. Such a qualitative or quantitative change cannot be expected or inferred by the person skilled in the art in advance*."

"New performance" appears to be a decisive element, which is supposed to be different from existing effects in the prior art (qualitatively different) or be of effects which cannot be expected or inferred by a person skilled in the art compared with the known effects disclosed in the prior art (quantitatively different).

3.2 **Examination Standard**

For pharmaceutical polymorphs, the conventional effects usually include stability, purity and good bioavailability that are commonly known as advanced properties of polymorphs in pharmaceutical preparations. Unexpected technical effect requires that, a significant quantitative change is achieved to any of the said conventional effects which exceeds the expectation of a person skilled in the art, or a new and unexpected property is achieved which amounts to a "qualitative" change.

II. Relevant Judicial Practice

1. ***Boehringer Ingelheim Pharma GmbH & Co KG v. PRB and Jiangsu Chia-tai Tianqing Pharmaceutical Co. Ltd (No. 86 IP. Adm. 2011)***

No. 86 Precedent involves a Chinese invention patent ZL01817143.5, filed on September 28, 2001 and authorized on October 5, 2005. The involved patent claims a crystalline tiotropium bromide monohydrate, its preparation process, its pharmaceutical formulation and its use in treating a disease. The patent was invalidated by the PRB based on two pieces of prior art, one disclosing the chemical name and molecular formula of x hydrate of tiotropium bromide, and the other disclosing a series of compounds which can treat the same disease and an anhydrate crystal of tiotropium bromide and its preparation process. The PRB believed that the patent did not achieve unexpected technical effect over the prior art. The PRB decision was affirmed by the trial and appellant courts, and the patentee eventually brought the case to the Supreme People's Court to petition for a retrial. The patentee's major appeal grounds include that the structure of the claimed polymorph shall not be regarded similar to those in the prior art, and the crystalline structure *per se* is unobvious.

The Supreme People's Court dismissed the retrial petition, explaining in its ruling that, *there is diversity of crystalline structure of one compound, and one compound may form different solid polymorphs based on two or more molecular arrangements. However, because not all the polymorphs will lead to prominent substantial feature and obvious progress, it could not conclude that polymorphs are not similar in structure only based on different crystalline structure. That is to say, "compounds with similar structure" under the "Patent Examination Guidelines" refers in particular to compounds having the same core element or the same basic ring, without the comparison of the microcosmic crystalline structure itself. When judging a crystal's inventiveness, the microcosmic crystalline structure should be considered together with whether it has unexpected technical effect.*

2. **Statistical Analysis of Judicial Assessment of Inventiveness of Pharmaceutical Polymorph Patents**

2.1 **Analytical Samples**

In order to review the judicial situation regarding inventiveness examination of pharmaceutical polymorph patents in China, the author retrieved by the keywords "pharmaceutical", "inventiveness" "polymorph" and "crystal" in the databases of IP House, PKU Law, and on the IP Precedent Guiding Service Platform, and identified eight judicial precedents in total (counted in the number of final judgments to avoid repeated calculations). The eight judicial precedents are taken as samples in the following analysis.

The eight judicial precedents were made between 2010 and 2016, including one decision issued by the Supreme People's Court (the above mentioned), six made by Provincial Courts, and one made by an Intermediate Court. Among the samples, two of them are judicial review of the PRB's rejection of two pharmaceutical polymorph patent applications and six of them are judicial review of the PRB's decisions on invalidation of six pharmaceutical polymorph patents.

2.2 **Observations and Speculations**

2.2.1 The determinations on the inventiveness of pharmaceutical polymorph patents are fully consistent.

In the eight judicial precedents, Chinese courts at all levels denied the inventiveness of pharmaceutical polymorph patents.

2.2.2 The legal grounds for denying the inventiveness of pharmaceutical polymorph patents are highly unified.

Among the eight decisions, four of them were applied the general standard of "Three-Step Approach" plus the "Unexpected Technical Effect" examination; and the rest four were applied the special inventiveness standard for chemical compounds. In both circumstances, "unexpected technical effect" was examined and denied. The decisions show that, the examination standards for inventiveness of pharmaceutical polymorph patents are broadly consistent between PRB and courts and among Chinese courts at all levels.

2.2.3 The examination standards for inventiveness of pharmaceutical polymorph patents have significantly changed.

We notice that, the six invalidated patents involved were granted between 2000 and 2009, and that the final judgments denying their inventiveness were made between 2010 and 2016. The results reflect the substantial change of the examination standards for inventiveness of pharmaceutical polymorph patents in recent years.

In the past time when the patents were granted, it was at the initial stage of polymorph studies in China. A generally accepted understanding at that time was that, even though a person skilled in the art could expect the improvement in certain properties of a compound by producing a crystal form, whether a polymorph could be obtained and what polymorph would be obtained were unpredictable for a known compound disclosed in the prior art, which might bring non-obviousness to the polymorphic invention. Therefore, the patent examination office generally recognized the inventiveness of pharmaceutical polymorph patents at that time.

In the recent years, the progress of polymorph research and development brought changes to minds of examiners and judges, who have gradually reached consensus, as reflected by the eight decisions. That is, a deeper understanding of the importance of pharmaceutical polymorphs provides stronger motivation to a person skilled in the art to study polymorphs, so that it becomes a routine for a person skilled in the art to prepare polymorphs based on a known compound. Moreover, the richer experience in polymorph preparation makes it much easier to obtain a new polymorph. Therefore, the standard for inventiveness review of polymorph inventions is substantially raised.

2.2.4 Retroactivity in inventiveness evaluation is improper.

It is a natural process that technology development causes changes of patent examination practice. However, whether a stricter examination standard can apply to invalidate a patent that was granted following a less strict examination standard is an issue worthy of attention.

It is a universal practice that whether a patent has inventiveness shall be evaluated from the technical level and the cognitive level of a person skilled in the art before the filing date or the priority date. The approach of using the present stricter examination standard to invalidate granted patents appears inconsistent to the said examination norm.

III. Suggestions

As mentioned above, “unexpected technical effect” is an essential factor for inventiveness assessment of pharmaceutical polymorph patents. Accordingly, this article intends to make some suggestions from the perspective of technical effect.

1. “Qualitative change” of technical effect should be exploited more to qualify polymorph patent applications. Since stability, purity and bioavailability of a polymorph are considered to be conventional, “new performances” of a new polymorph are preferred to be introduced in the application. Taking an example of bioactivity, if a new polymorph is able to bring reduction of side effects, change of indications or suitable groups, it will have better chances to be accepted that the new polymorph has a “new performance”, and accordingly shows a “qualitative change” of the technical effect.
2. “Qantitative changes” of technical effects achieved by a new polymorph has to have unpredictability. For example, based on the common knowledge in the art, between stability and solubility there exists a relation of mutual restriction; however, if it is proven with experimental data in the original application that a new polymorph can simultaneously improve the stability

and solubility of a drug, it will be recognized that such “quantitative change” is a “unexpected technical effect” of the new polymorph.

3. Finally, it is worth noting that “unexpected technical effect” can only be the technical effects specified in or can be directly determined from the original disclosure of application documents. According to the examination practice, any experimental data submitted after the filing date to prove the technical effect will hardly be taken into consideration for inventiveness evaluation.

To make sure you do not miss out on regular updates from the Kluwer Patent Blog, please subscribe here.

This entry was posted on Thursday, May 4th, 2017 at 10:00 am and is filed under China, Pharma, Pharmaceutical patent
You can follow any responses to this entry through the Comments (RSS) feed. Both comments and pings are currently closed.