Polymorphs at the CNIPA – Are They Inventive Over Prior Art Forms of the Same Chemical Formulae?

Featured Article

On July 4, 2021, National Medical Products Administration ("NMPA") and China National Intellectual Property Administration ("CNIPA") co-issued the "Measures for the Implementation of the Early Resolution Mechanism for Drug Patent Disputes (Interim)" ("Implementation Measures"), marking that the Chinese version of the drug patent linkage system has entered a practical stage. However, according to Rule 5 of the Implementation Measures, polymorph (crystal form) patents are not included in the scope of the drug patents to be listed in the NMPA's drug patent linkage platform.

It is well known that to file an application for regulatory market authorization of a drug, it is necessary to submit the drug crystal form information. According to the Implementation Measures, a crystal form patent dispute, if any, cannot be resolved before the drug obtains its market authorization, which makes the drug crystal form patent in a very special position. For example, if a generic drug company successfully challenges originated drug patents and therefor obtains a market exclusivity according to the Implementation Measures, the drug may still not be successfully marketed due to a potential infringement of a crystal form patent, and thus cannot fully enjoy the economic benefit brought by the market exclusivity.

Therefore, drug polymorph patents are important in the battlefield between branded and generic drug companies, even they are excluded to be listed in the NMPA's drug patent linkage platform.

In examining the patentability for polymorph claims, inventive step is the most important consideration. In this article, the author attempts to analyze the current examination standard of inventive step of polymorph claims.

I. Technical background of polymorph patents

In the process of new drug development, the first step is to find active compounds. However, most of the newly discovered active compounds cannot be directly prepared into usable drugs due to poorly properties such as solubility, bioavailability, and stability. Therefore, technicians often modify the properties, such as solubility, dissolution rate, bioavailability, stability (chemical stability, thermal stability, melting point, crystal stability), hygroscopicity, processability or the like, of the active compounds by salt formation and crystallization, making the compounds suitable for preparing into final available drug products. Therefore, salt formation and crystallization have become necessary steps in the development of new drugs.

II. Examination considerations for polymorph claims

According to the examination standard from many new invalidation decisions, for salt form and crystal form patents, CNIPA generally holds that one skilled in the art would have the motivation to investigate the salts and crystal forms of already known active compounds. However, the motivation to investigate salts and crystals does not necessarily mean that claims directed to salt forms and crystal forms lack inventive step. The key lies in whether the claimed salt forms and crystal forms achieve unexpected technical effects.

What would be constituted as unexpected? Here, the author investigates the determination of unexpected technical effects by analyzing the following two invalidation cases concluded by CNIPA.

III. Case overview

Case 1: Vortioxetine invalidation case (No. 48337 invalidation decision)

Vortioxetine is a new serotonin reuptake inhibitor (SRI) developed by H•Lundbeck, which is mainly used for the treatment of depression.

Claim 1 of the patent at issue relates to the β crystal form of vortioxetine hydrobromide. In the specification of the patent, examples specify preparation and characterization of various salts of vortioxetine and different crystal forms of vortioxetine hydrobromide. The description further provides the β crystal form of vortioxetine hydrobromide is more stable and has lower solubility than the others, and a combination of low hygroscopicity and proper solubility is attractive.

The closest prior art, evidence 1, only discloses vortioxetine free base. The difference between claim 1 of the patent at issue and evidence 1 lies in the β crystal form of vortioxetine hydrobromide. Whether the β crystal form of vortioxetine hydrobromide achieves unexpected technical effects over the closest prior art becomes the focus of the dispute.

The invalidation requester asserts: (1) based on existing evidence, the hygroscopicity, solubility and stability of the β crystal form of vortioxetine hydrobromide can be expected; and (2) the β crystal form of vortioxetine hydrobromide fails to achieve any unexpected technical effects over other salts and crystal forms, and is obtained by a routine screening of salt forms and crystal forms.

The panel at CNIPA disagrees, and states the following:

As for the known compound of vortioxetine, one skilled in the art would have the motivation to investigate its acid addition salts and the crystals of the salts, which, however, does not necessarily render the salt forms, crystal forms, and crystal forms of salts of the compound unpatentable. The key lies in whether the crystal form of the salt claimed by this patent achieves unexpected technical effects.

As for the unexpected technical effects, based on the facts recorded in the description of this patent, β crystal of vortioxetine hydrobromide of this patent achieves high thermal stability and can reach the "slightly hygroscopicity" and "slightly soluble" level as stipulated by the Pharmacopoeia.

On the basis of the vortioxetine free base, this patent also prepares and investigates the crystal form of the free base as well as a variety of different salts and crystal forms of the salts, and measures the melting point, hygroscopicity and solubility of each of the substances. **Through the analysis and comparison of the melting point, hygroscopicity and solubility data of various salt crystals, compared with other salt forms, the α crystal form and β crystal form of vortioxetine hydrobromide achieve relatively low hygroscopicity and relatively high solubility as well as a higher melting point (stability). This comprehensive performance is unexpected by one skilled in the art over numerous salts and crystals provided in this patent.**

Case 2: Lenvatinib invalidation case (No. 48337 invalidation decision)

Lenvatinib is an anti-tumor drug developed by Eisai, and is mainly used for the treatment of

liver cancer.

Claim 1 of the patent at issue claims lenvatinib mesylate crystal (C). The description recites that the purpose of the patent is to provide crystals of lenvatinib salt with high applicability as pharmaceuticals. The crystals of lenvatinib salts have excellent properties in terms of physical properties (dissolution rate, hygroscopicity, chemical stability) and kinetics (bioavailability). The description discloses seven (7) different salts and crystals, and the dissolution rate, hygroscopicity, chemical stability and bioavailability of 5 salts and crystals therein. During an invalidation proceeding, the patentee further supplements the hygroscopicity data of hydrochloride and hydrobromide, and the bioavailability data of mesylate crystal (C). The patentee holds that lenvatinib mesylate crystal (C) of this patent achieves the technical effects of significantly improved dissolution rate and bioavailability as well as low hygroscopicity and good solid stability. Accordingly, the patentee holds that lenvatinib mesylate crystal (C) achieves comprehensive performance, which is unexpected.

In this regard, a panel at CNIPA states the following:

Regarding the solubility properties and bioavailability, the mesylate crystal (C) is not optimal, i.e., does not reach the degree of unexpected. As for the hygroscopicity, evidence M teaches that for organic bases, the non-hygroscopicity of corresponding organic acid salts is superior than that of inorganic acid salts such as hydrochloride and sulfate. Therefore, the non-hygroscopic effect of mesylate crystal (C) can be expected by one skilled in the art. As for the solid stability, the data of the solid stability of mesylate crystal (C) is comparable with that of ethanesulfonate crystal (β), and thus this technical effect does not reach an unexpectedly high degree.

As for the comprehensive performance held by the patentee, the experimental data recorded in this patent and the supplementary experimental data submitted by the patentee do not fully reflect the comprehensive performance of the above four aspects of the different salts and crystals, and the evidence in the case is insufficient to support the comprehensive performance of mesylate (C) is better than other salts.

IV. Our thoughts

The results of the above two cases are opposite. Why? It might be answered from the "unexpected technical effects" provided in the Patent Examination Guidelines.

Chapter 4, Section 5.3 of Part II of Patent Examination Guidelines stipulates: *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.*

Thus, it is believed that the assessment of the unexpected technical effects of crystal form patents should first determine whether there is a qualitative change (that is, whether a new performance is generated), and then determine whether the quantitative change is beyond expectation if there is no qualitative change.

i. Regarding determination of a qualitative change

For this situation, it is required to compare the technical effects of a crystal form with the technical effects of its active compound to determine whether the change in the technical effect brought by crystallization conforms to the general knowledge of one skilled in the art. If the change of technical effect is beyond the general knowledge and the newly produced effect is beneficial for the pharmaceutical process or medication process, this change should be regarded as a qualitative change, and thus has unexpected technical effects.

However, in practice, only a few crystalline patents conform to this situation. More patents

rely on determining whether the quantitative change is beyond expectations.

ii. Regarding determining a quantitative change

As for determining a quantitative change, the difficulty lies in the comparison benchmark, i.e., how to find the benchmark for evaluating quantitative changes is crucial for determining unexpected technical effects.

Since the structure and properties of each compound are different, the degree of quantitative change of certain properties after salt formation and crystallization are not identical yet. Therefore, a certain degree of quantitative change brought by salt formation and crystallization may be considered as achieving unexpected effects for a certain compound, but not for another. Therefore, there is no universal benchmark for determining the unexpected effect of the crystal form, and the benchmark still needs to be determined case by case.

Regarding how to determine the comparison benchmark for evaluating quantitative changes, the author holds that the following perspectives can be considered. As mentioned in many invalidation decisions, one skilled in the art have the motivation to investigate the salt forms and crystal forms of the active compound after obtaining the active compound. In other words, it is easy for one skilled in the art to obtain the salt forms and crystal forms of the compound. Therefore, the general level of the crystal forms obtained by the salt formation and crystallization of the compound is the level that can be expected by one skilled in the art. Therefore, this general level can be used as a benchmark for determining whether the quantitative change of crystal form is beyond the expectations.

Alternatively, from another point of view, the research of crystal forms by technicians actually is the screen of the salt forms and crystal forms of the active compound. Therefore, from the perspective of selection invention, whether the target crystal form has an unexpected quantitative change also needs to compare it with the general level of salt forms and crystal forms of the compound. This also reflects that using the general level of salt forms and crystal forms of the compound as a benchmark for determining quantitative change is reasonable.

In practice, since the panel makes the judgement between two parties, and the panel neither has the ability nor the responsibility to actually verify the objective general level of salt forms and crystal forms of the active compound. Therefore, the general level should be reflected based on the description of the crystal form patent and the evidence submitted by both parties.

Taking vortioxetine case as an example, the patentee in this case provides partial or complete data of the properties of 17 salt forms and crystal forms in total. Among them, compared with all other salt forms and crystal forms, only α crystal form and β crystal form have a higher melting point (stability), lower hygroscopicity and proper water solubility, and the combination of these three properties allows α crystal form and β crystal form available for preparing into tablets and used in actual treatments. In contrast, one or more of the melting point, hygroscopicity, and water solubility of other salt forms and crystal forms cannot reach the required level, which makes them improper to be prepared into tablets. The data of these salt forms and crystal forms in the description can reflect that the general level of crystal forms and salt forms of vortioxetine is that the three properties are hard to reach the level required for tablets at the same time. Since the three properties of α crystal form and β crystal form reach the required levels at the same time, these two crystal forms show unexpected technical effects.

As for the lenvatinib case, the patentee in this case provides data of the properties of 5 salt forms and crystal forms in total. Among them, in terms of dissolution rate and bioavailability, the crystal (C) only shows a general level and is comparable with other crystals and salts. For

hygroscopicity, all organic acid salts are non-hygroscopic, whereas all inorganic acid salts are hygroscopic. However, since the evidence M demonstrates that the non-hygroscopicity of organic acid salts is superior over inorganic acid salts, the advantages in non-hygroscopicity can be expected by the evidence M. Therefore, according to the existing evidence provided by the patentee, in crystal forms of organic acid salts, the performance of crystal (C) is only at a general level, lower than ethanesulfonate crystal (β) and comparable with mesylate cystal (A). Moreover, compared with inorganic acid salts, except for non-hygroscopicity, crystal (C) also fails to show unexpected improvement in dissolution rate and bioavailability. Through analysis of existing data, crystal (C) only reaches the general level reflected by other salt forms and crystal forms, thus fails to show unexpected technical effects.

To sum up, the author attempts to analyze the standard for determining the inventive step of the crystal form patent with reference to vortioxetine and lenvatinib cases. The author holds that the key of the unexpected technical effect of the crystal form patent is not to prove that the crystal form achieves certain effects, but to prove that **compared with the general level of crystal forms of the active compound**, the crystal form achieves better effects which are beneficial for the pharmaceutical process or medication process. In other words, the key of unexpectation lies in "**comparison**". The author hopes that the above analysis can provide a consideration for drafting patent application or dealing with invalidation cases.

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For more information, please contact the author of this article:

CHANG ,Yuxuan: Patent Attorney, Attorney at Law: ltbj@lungtin.com

CHANG ,Yuxuan
Patent Attorney,
Attorney at Law

Mr. Chang has expertise in patent application preparation and prosecution, patent reexamination, patent invalidation, administrative litigation, and patent analysis etc. He is very experienced in patent cases in technical areas of pharmaceutical science, chemistry, material, chemical engineering, medical device and environmental protection. Mr. Chang has represented many large companies at home and abroad in over 1000 patent cases.

隆天知識產權
LUNG TIN IP ATTORNEYS

18th Floor, Tower B, Grand Place, No 5, Huizhong Road,
Chaoyang District, Beijing 100101, P. R. China
Tel: 0086-10-84891188 Fax: 0086-10-84891189
Email: LTBJ@lungtin.com Web: www.lungtin.com