Technical Effect and Determination of Inventive Step of Crystal Form Patents

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The provision on inventive step is essentially to protect the creative efforts made by an inventor for acquiring a technical solution. Therefore, generally speaking, consideration shall be given to whether the acquisition of the technical solution is obvious when deciding whether a disputed patent possesses an inventive step. However, there are also exceptions in practice. For pharmaceutical patents, especially crystal form patents, technical effects are of great significance in the determination of inventive step. In practice, a majority of crystal form patents are determined to involve an inventive step after their technical effects are taken into account. An in-depth discussion will be conducted on the role of technical effects in the determination of inventive step of crystal form patents and the specific ways to assess the technical effects.

I. Role of technical effects in the determination of inventive step of crystal form patents

The assessment of inventive step of pharmaceutical patents, especially crystal from patents, is different from that of patents in other fields as the former places more emphasis on the technical effects, rather than the technical solutions alone. In other words, regardless of whether the acquisition of the technical solution *per se* requires creative efforts, the technical solution can generally be considered as involving an inventive step as long as it achieves a better technical effect.

This approach is embodied in the reexamination and invalidation decisions issued by the China National Intellectual Property Administration (CNIPA) and the courts' judgments, and is normally expressed as, e.g., that "for a certain known compound, those skilled in the art have the motivation to study its acid addition salts and salt crystals; however, it does not mean that the salt forms, crystal forms and crystal forms of salts of the compound possess no inventive step. The key is to decide whether the salt crystals claimed in the disputed patent achieve an unexpected technical effect."

The fundamental reasons why technical effects play a vital role in the determination of inventive step of pharmaceutical patents lie in the significance of drug research and development (R&D) to the public health and the need to protect the interests of the pharmaceutical industry. Typically, the R&D level of the pharmaceutical industry determines the level of disease treatment to a considerable extent and is in close association with the health of general public. Therefore, conferring strong protection on the pharmaceutical industry is crucial to the public interest. But what is unignorable is that the drug R&D is characterized by high investment and high failure rate. It usually takes ten or even decades of years and costs one or several billions of dollars to develop a new medicine. But even so, the complexity of human bodies renders the R&D of such medicines quite uncertain. In practice, the R&D of some medicines has to be stopped even at Phase III clinical trials, such that a large amount of previous investment cannot be recovered. Thus, only by providing comprehensive and strong protection for drug-related patents can R&D entities as a whole generate expectations of higher profits and therefore be motivated to invest in R&D.

As far as crystal form patents are concerned, although crystal forms are normally prepared by conventional methods, it is undeniable that even with a conventional preparation method they cannot be obtained without multiple trials, and whether a crystal form that meets pharmaceutical

needs can be obtained is uncertain and requires significant investments to test. Where the R&D of crystal forms is usually one of the essential steps in pharmaceutical development, the investments in the R&D of crystal forms must be protected to guarantee the R&D entities with anticipated economic returns, in such a way to incentivize the pharmaceutical R&D and industrial development for the sake of the public interest. Considering that technical effects are more closely linked to industrial interest than technical solutions, it is necessary and reasonable to highlight the role of technical effects in the determination of inventive step for crystal form patents.

II. Specific ways to assess technical effects

Generally speaking, a technical solution can have various technical effects. So does a crystal form patent. Whether the technical effects need to be selected, how to make a selection and how to weigh up these different effects are issues that must be faced in the determination of inventive step of crystal form patents. By analyzing said issues from the perspective of industrial interests, it can be known that since the profits from medicines mainly come from revenues generated after their launch into the market, the technical effects that need to be taken into consideration for the above issues are those related to the developability.

To be specific, there is usually one or at most a limited number of developable crystal forms. The same compound may have multiple crystal forms. One crystal form may be superior to other crystal forms in terms of one or more physicochemical properties. However, even though a crystal form with no prospect of developability may be better in terms of one or several physicochemical properties, it is unnecessary to render it under protection. Thus, the inventive step of said crystal form does not need to be determined.

Although it is not known for sure which crystal form has developability, and particularly it is difficult to more accurately predict, in the patent substantive examination and re-examination procedures, which crystal form may be launched into market in the future, there are still rules to follow. Judgments can usually be made on the basis of some conventional physicochemical properties, like purity, melting point, hygroscopicity and solubility. That is to say, specific, not general, physicochemical properties shall be taken into account in the comparison of technical effects of crystal form patents.

In an individual case, the technical effects in relation to the developability may usually be considered from the following aspects: first, the determination of the technical effect of the disputed crystal form; second, the determination of the technical effect of the reference technical solution; and third, the determination of the weights of different technical effects.

1. Determination of the technical effect of the disputed crystal form

As for the crystal form patent in dispute, the technical effect can be most directdly known from the description. For instance, in the Sunitinib case, the description provides the effect data of the crystal form in claim 1, including non-hygroscopicity, solubility, melting point and solid stability, wherein the crystal form is of low hygroscopicity, absorbing less than 0.5% water across the 0-90% relative humidity range, melts at about 196℃ and has the solubility that is determined to be 5mg/ml. Regarding the solid state stability of the crystal form, it was evaluated by high pressure liquid chromatography (HPLC) as follows: "four week data after aging at 60℃/ambient relative humidity, 60℃/75% relative humidity, and 80℃/ambient relative humidity showed no significant degradation. Powder X-ray diffraction on two-week samples also indicated no change in crystal form." [1]

Of course, if the corresponding data are not recorded in the description, the patentee can also supplement experimental data in support of the relevant technical effect. However, whether the supplementary experimental data can be accepted depends on whether they comply with the following provision in Part II, Chapter Ten, Section 3.5 of the Guidelines for Patent Examination: "[w]ith respect to the experimental data submitted after the date of filing by the applicant for the sake of meeting the requirements of, e.g., Articles 22.3 and 26.3 of the Patent Law, they shall be examined by the examiner. The technical effect proved by the supplementary experimental data should be one that can be derived by a person skilled in the art from the disclosure of the patent application".

The kernel of the provision is to determine whether the technical effect can be "derived" from the description. Generally speaking, as long as those skilled in the art can preliminarily know that the technical effect proved by the supplementary experimental data is the technical effect of the claims in dispute based on the description and their cognitive capabilities, it can be determined that the technical ef-

fect can be derived from the description unless there exists evidence to the contrary or sufficient reason to doubt it. It should be noted that the technical effect is not required to be derived from the description unambiguously, but can be further proved by the supplementary experimental data.

In the Cariprazine case, claim 1 of the patent in dispute is directed to Form I crystals of cariprazine monohydrochloride salt. The patentee supplemented experimental data to further prove the technical effect that the crystal form in dispute has a high purity. Purity is only touched upon in para. 0014 of the description as follows: "the hydrochloride salt is particularly preferred, as it may be prepared in the highest yield and highest purity. Another advantage of the monohydrochloride salt that it can readily be prepared using standard solvents and reaction conditions." Although it is difficult to unambiguously determine that the patent in dispute definitely has the above technical effect in the absence of specific experimental data, the court held that the patentee can still supplement the experimental data in the invalidation and litigation proceedings to further prove the technical effect. [2]

Attention should be drawn to the fact that the technical effects derived from the description shall be the effect of all technical solutions within the scope of the claim in dispute. To put it another way, if the technical effects recited in the description can only be produced by part of the claimed technical solutions, the technical effects should not be determined to be derived from the description.

In the Sitagliptin case, the court revoked the Decision on Invalidation mainly on the grounds that the technical effect as determined in the Decision on Invalidation cannot be produced by all the technical solutions of claim 1 of the patent in dispute. In this case, claim 1 of the patent in dispute is directed to the monohydrate of the dihydrogenphosphate salt of sitagliptin. The Decision on Invalidation found that the thermal stability and crystal form stability of the crystalline monohydrate of the dihydrogenphosphate salt of sitagliptin are unexpected, thereby rendering claim 1 of the patent in dispute inventive. The technical effects were determined in accordance with the graphs shown in Figs. 4 and 5 of the description. Figs. 4 and 5 only involve particular crystal forms, whereas the crystalline monohydrate of the dihydrogenphosphate salt as defined in claim 1 of the patent in dispute covers all the crystal forms of the monohydrate of the dihydrogenphosphate salt. Based thereon, the court held that in the absence of relevant evidence and reasonable grounds, it cannot be determined from the description of the patent in dispute that all the crystalline monohydrates of the dihydrogenphosphate salt of sitagliptin as defined in claim 1 have properties identical to those of the specific crystals in Figs. 4 and 5 as prepared in the embodiments of the description of the patent in dispute. Therefore, the court did not agree with the conclusion of the Decision on Invalidation that "the evidence on file does not suffice to prove that the technical effects (thermal stability and crystal form stability) of the crystalline monohydrate of the dihydrogenphosphate salt of sitagliptin of the patent in dispute are expectable". [3]

Where a technical effect can be produced by all the technical solutions, whether the supplementary experimental data are admissible depends on whether the technical effect is the technical contribution made by the inventor prior to the filing date of the invention in dispute, and whether the technical effect can be confirmed by those skilled in the art. If the above requirements are satisfied, the technical effect proved by the supplementary technical data will usually be considered in the assessment of inventive step. Or otherwise, the technical effect will not be taken into consideration at all as it is regarded merely as an assertion.

In the Cariprazine case, the patentee supplemented the experimental data as Counter-exhibits 1 and 2 to prove purity; but Counter-exhibits 1 and 2 did not indicate any specific time when the experiments were conducted. Under such circumstances, the court determined that Counter-exhibits 1 and 2 cannot prove that the patentee had obtained the specific data about purity recited in the patent in dispute before the filing date thereof. For this reason, the experimental data were not accepted by the court in this case. [4]

2. Determination of the technical effect of the reference technical solution

As known from the above analysis, the developability is a factor to be considered in the determination of the technical effect of the disputed technical solution, as well as in the determination of the technical effect of the reference technical solution. The prerequisite for judging the developability is that there are specific data on the technical effect of both the disputed technical solution and the reference technical solution. If a reference document only discloses the technical effect of the reference technical solution in general, it cannot be concluded that the disputed technical solution does not have a better technical effect with respect to the

reference technical solution. In other words, where the effect data related to the developability are recited in the description of the patent in dispute, if the invalidation petitioner in an invalidation case cannot adduce evidence proving the effect data of the closest prior art, he or it shall bear the consequences of failure to produce evidence.

In the Sunitinib case, the invalidation petitioner failed to adduce evidence proving the effect data of the closest prior art. In this regard, the court found that the description of the patent in dispute provides the effect data of the crystal form in claim 1 in relation to the developability, such as non-hygroscopicity, solubility, melting point and solid stability, but the invalidation petitioner failed to adduce evidence proving the specific effect data of sunitinib free base (i.e., Compound 16 in Exhibit II-2) in the closest prior art. Hence, the invalidation petitioner's assertion that claim 1 of the patent in dispute does not have unexpected technical effects cannot be established. [5]

A similar situation also occurs in the "beta crystal form of vortioxetine" case. The court found that where Exhibit 1, as the closest prior art, merely indicates the pharmaceutical properties, not physicochemical properties, of vortioxetine free base, those skilled in the art may have the general knowledge of the basic physicochemical properties of salified or crystallized free base, for example, a compound that is salified to be an ionic compound has a melting point higher than that of a free substance, or organic salt drugs are more hygroscopic than free organic bases. These general properties may have an impact on the R&D direction, but are of no substantial significance to developability. Accordingly, with no further evidence proving the physicochemical properties of the free base of vortioxetine, the court was not persuaded by the invalidation petitioner's assertion that the patent in dispute produces no unexpected technical effects based on the general properties.

In addition, it is particularly noteworthy that in the comparison of the technical effects of crystal form patents, work shall be done to compare the disputed crystal form with the closest prior art, as well as other crystal forms if recited in the description. After all, from the perspective of industrial interests, if the disputed crystal form has worse technical effects as compared with other crystal forms recited in the description, thereby rendering it impossible to be developed, there is no need to put it under protection even though it demonstrates better technical effects with respect to the closest prior art.

For instance, in the "alpha crystal form of vortioxetine" case, although the invalidation petitioner failed to adduce evidence proving the physicochemical properties of the free base of vortioxetine in the closest prior art, so that the technical effects of the patent in dispute and Exhibit 1 cannot be compared, the Decision on Invalidation did not directly draw the conclusion that the patent in dispute involves an inventive step, but compared the alpha crystal form of vortioxetine in the patent in dispute with other crystal forms thereof recited in the description instead. On the premise of finding that the alpha crystal form of vortioxetine in the patent in dispute has better technical effects than other crystal forms thereof, the patent in dispute was determined to involve an inventive step. [6]

3. Determination of the weights of different technical effects

Another issue that needs to be considered in the comparison of technical effects is how to determine the overall technical effect of a particular crystal form, that is, how to determine the weights of different physicochemical properties, where it has better physicochemical properties in one or some aspects but poor performance in other aspects in comparison with other crystal forms. For the reasons as mentioned above, this issue shall also be judged from the perspective of the developability, which means that the overall technical effect needs to be judged on the basis of the importance of different physicochemical properties to developability.

In the "beta crystal form of vortioxetine" case, in consideration of the objective indicators of physicochemical properties of said crystal from alone, rather than the weights of these different physicochemical properties in the technical effects of the crystal form, the invalidation petitioner asserted that the beta crystal form of vortioxetine of the patent in dispute is not the best crystal from in terms of comprehensive properties with respect to the crystal form of hydrochloride and alpha crystal form of hydrobromide, and therefore should not be determined to involve an inventive step.

However, the court rejected the invalidation petitioner's argument after analyzing the technical effects from the perspective of developability, holding that although the beta crystal form of the patent in dispute is better than the crystal form of hydrochloride in terms of hygroscopicity (0.6% and 1.5% respectively), but worse than the latter in terms of melting point and solubility (231°C, 236°C, and 1.2mg/ml and 3mg / ml respectively), the crystal form of hydrochloride

seems to be superior to the patent in dispute in terms of two physicochemical properties. Therefore, it appears that the crystal form of hydrochloride, not the patent in dispute, should have better technical effects; however, that is not the case. Although the melting point of the crystal form of hydrochloride is slightly higher than that of the patent in dispute, it does not make any difference for the pharmaceutical processing as long as a certain melting point is reached. The difference between the crystal form of hydrochloride and the beta crystal form of the patent in dispute in terms of the melting point in this case is a good example. Although the crystal form of hydrochloride is obviously better than the patent in dispute in terms of solubility, such a defect of the patent in dispute can be overcome by means of micronization in the pharmaceutical processing. To say the least, disregarding the above factor, the patent in dispute is slightly soluble according to the Pharmacopoeia and complies with the relevant pharmaceutical requirements. Thus, the two physicochemical properties of the beta crystal form of the patent in dispute will not have any substantial impact on the pharmaceutical processing or the preparations *per se*. However, things are different for hygroscopicity, which has a vital influence on both the pharmaceutical processing and preparations because it directly affects the stability of active pharmaceutical ingredients and preparations. The crystal form of hydrochloride has a higher hygroscopicity than that of the beta crystal form of the patent in dispute. This difference significantly affects the storage of the active pharmaceutical ingredients and can hardly be fully compensated through relevant processes during the pharmaceutical processing. Therefore, the beta crystal form of the patent in dispute is obviously superior to the crystal form of hydrochloride in terms of the comprehensive effect from the aspect of developability.

Furthermore, for the same reasons as above, the difference between the patent in dispute and the alpha crystal form of hydrobromide in terms of melting point has no substantial impact on pharmaceutical processing. Their difference in solubility can be compensated by the preparation processes and complies with the requirement for slight solubility in the Pharmacopoeia. Although the alpha crystal form of hydrobromide has a hygroscopicity of 0.3%, which is better than 0.6% of the patent in dispute, both of them are at the "slightly hygroscopic" level according to the Pharmacopoeia and meet the requirements of the Pharmacopoeia. It can be seen that as far as the properties related to developability are concerned, the beta crystal form of the patent in dispute and the alpha crystal form of hydrobromide both produce good technical effects. Hence, both the collegial panel and the court determined that the beta crystal form of the patent in dispute possesses an inventive step according to the determination of the technical effects.[7]

The author: Judge of Beijing Intellectual Property Court

[1] See the Administrative Judgment No. Jing73xingchu 15973/2021.

[2] See the Administrative Judgment No. Jing73xingchu 6015/2021.

[3] See the Administrative Judgment No. Jing73xingchu 7397/2021.

[4] See supra note 2.

[5] See supra note 1.

[6] See the Administrative Judgment No. Jing73xingchu 14001/2021.

[7] See the Administrative Judgment No. Jing73xingchu 14004/2021.

CNIPA and DPMA Extend PPH Pilot Program

The China National Intellectual Property Administration (CNIPA) and the German Patent and Trade Mark Office (DPMA) have jointly decided to extend their Patent Prosecution Highway (PPH) pilot program for another three years from 23 January 2024 to 22 January 2027. The pertinent requirements and procedures governing applicants' PPH requests at the two offices still follow the established procedures to file a request to the DPMA for PPH Pilot Program between the DPMA and the CNIPA.

The extension of the CNIPA-DPMA PPH pilot program will continuously advance China-Germany communication and cooperation in IP, serve both Chinese and German innovators by accelerating the patent examination process and deepen the two offices' cooperation in patent examination.

Source: CNIPA