Novelty Assessment of Crystal Form Patents in Invalidation Proceedings

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Pharmaceutical crystal forms have become a focus of pharmaceutical research in recent years due to their unique characteristics. Invalidation challenges to patents of pharmaceutical crystal forms have been increasing, but there are relatively few successful cases based solely on the ground of novelty. There are ongoing debates regarding the standards for determining the novelty of pharmaceutical crystal forms. This article attempts to explore the examination criteria for determining the novelty of patents of pharmaceutical crystal forms through analysis of relevant cases in invalidation proceedings.

I. Introduction

Basic pharmaceutical compounds may exist in many different crystal forms. "Drugs with the same chemical structure, due to different crystallization conditions (such as solvents, temperatures, cooling rates), may lead to crystals with different lattice arrangements, which are called polymorphs." [1] Different polymorphs of the same pharmaceutical compound demonstrate different properties and have different effects on druggability and drug efficacy. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) clarifies in a book entitled "*International Technical Requirements for Drug Registration: Quality Section*" that "some new active pharmaceutical ingredients exist in different crystal forms which differ in their physical properties, and under some circumstances, different forms may affect the quality or efficacy of new drug preparations. If different crystal forms may affect the efficacy, bioavailability or stability, appropriate solid crystal forms should be specified." [2] Some scholars have found through studies that the differences in clinical efficacy between domestic and imported drugs, identical drugs manufactured by different enterprises and drugs with the same batch number manufactured by the same enterprise are mostly caused by the change in the state of the crystalline substances of solid chemical drugs [3]. On the one hand, different crystal forms may affect the dissolution and release of a drug due to different *in vivo* dissolution and absorption rates, thereby affecting the efficacy and safety of the drug. On the other hand, different crystal forms may have different stability, hygroscopicity and even shape, which affect the preparation, processing and storage of drugs [4]. It can be seen that studies have shown that there is a direct relationship between drug polymorphism and drug effect and safety. With the continuous deepening of research on drug polymorphism, China has attached more importance to crystal forms of drugs. The Pharmacopoeia of the People's Republic of China (2015 edition) incorporated the research on crystal forms of drugs and the quality control of crystal forms into the guiding principles for the first time. [5] The National Medical Products Administration (NMPA) released the Guiding Principles for Research on Crystal Forms of Chemical Generic Drugs (Draft for Comments) in September 2021. As boosted by both technologies and policies, drug polymorphism has become the focus of small molecule drug research over recent years and a hot spot

for patent challenges.

Recently, in the patent challenges to the active ingredients of drugs—basic compounds, requests for invalidating pharmaceutical crystal form patents are commonly seen. According to incomplete statistics, more than 40% of the patent challenges to the basic pharmaceutical compounds have been targeted to crystal forms of drugs ever since 2019, but there are only a small number of patent challenges posed merely based on the invalidity ground for lack of novelty, which end up with a low success rate. Nevertheless, lack of novelty is still one of the invalidity grounds that invalidation petitioners are reluctant to give up. In the practice of invalidation examination, the author finds that in comparison with the assessment of novelty of patents in relation to basic pharmaceutical compounds, the assessment of novelty of patents in relation to crystal forms of drugs is much more complicated, and there is no consensus reached on the standards of examination in the IP field. For instance, are the rules for assessing the novelty of patents in relation to crystal forms of drugs the same as those for assessing the novelty of patents in relation to basic compounds? Do the difficulties in assessing the novelty of patents in relation to crystal forms of drugs result from legal issues or technical issues? What are the similarities and differences in factual findings between the patents in relation to crystal forms of drugs and the patents in relation to basic compounds when it is judged whether a patent in relation to a crystal form of a drug is disclosed in the prior art? As for the above-mentioned issues, the author attempts to probe into the criteria for assessing the novelty of the patents in relation to crystal forms of drugs by analyzing these cases involving novelty assessment in the invalidation proceedings.

II. Case analysis

The author finds that the focus of disputes over novelty between the two parties concerned lies on two aspects. The first aspect is how to delimit the scope of protection of claims. Some parties concerned hold that the claimed crystal form of a drug is a specific crystal form disclosed in the description, while others think that the scope of protection of claims is not completely equivalent to the specific crystal form of the drug disclosed in the description. The second aspect is that the parties have different understandings of how to judge whether a patent in relation to a crystal form of a drug possesses novelty and whether the crystal form of a drug claimed for protection has been disclosed in the prior art.

1. How to delimit the scope of protection of a patent in relation to a crystal form of a drug

As mentioned above, studies show that the crystal form of a drug has its specialties with respect to the basic compound thereof. However, "crystalline compounds may differ in their physicochemical parameters due to different molecular arrangements, but still fall into the category of compounds".[6] Therefore, the examination of patents in relation to crystal forms of drugs still pertains to the examination of compound patents, and the criteria for assessing novelty thereof are in line with those for assessing novelty of patents in relation to basic compounds of drugs. In the assessment of novelty, the first thing to do is determine the scope of protection of the claims of a patent in relation to a crystal form of a drug, and then a judgment shall be made as to whether the patented crystal form of the drug is disclosed in the prior art. Like other patents, the scope of protection of the patents in relation to crystal forms of drugs shall be defined on the basis of the subject matters of claims and the technical features in the characterizing portions thereof. Different drafting manners of claims may lead to different scopes of protection of claims.

However, in comparison with pharmaceutical compound claims, the delimitation of the scope of protection of pharmaceutical crystal form claims has its own peculiarities. As for the scope of protection of a compound claim, we can generally determine the structure of the compound according to the chemical name or structural formula thereof, thereby delimiting the scope of protection of the compound. However, the scope of protection of a patent in relation to crystal forms of a drug generally cannot be determined merely on the basis of the chemical name thereof. Since there are unified naming conventions for compounds, the chemical structure of a compound can be inferred from the chemical naming thereof. But there are no unified naming conventions for crystal forms of drugs. The naming of a crystal form of a drug is rather arbitrary and has no necessary link to the micro-spatial structure thereof, so the specific micro-spatial structure of the crystal form cannot be determined according to the naming of the crystal form of the drug, such as "Type I crystal". The micro-spatial structure of the crystal form is usually defined by parametric features in the characterizing portion of a claim in the field of crystal forms of drugs. For instance, it is defined by some charac-

teristic peaks (2θ angle or d value) in a powder X-ray diffraction (PXRD) analysis, or a PXRD pattern, or unit cell parameters.[7] These limitations in the characterizing portion ultimately determine what kind of crystal form is claimed. Therefore, the title of a patent in relation to a crystal form of a drug usually defines the crystal of a compound, which usually cannot represent the specific structure of the crystal form; however, the micro-spatial structure of the crystal form is usually defined by parameters in the characterizing portion of the claim, so the characterizing portion which defines the specific micro-spatial structure of the crystal form largely determines the scope of protection of the claim.

The following case 1 is provided to explain that different parameters used in the characterizing portion of a claim will lead to different scopes of protection of a pharmaceutical crystal form claim. Thus, two completely different conclusions may occur in the assessment of novelty of a patent over the same prior art.

[Case 1][8] This case involves a medicinal base compound, 5-Trifluoromethyl-2'-deoxyuridine (i.e. Trifluridine). The description only recites that there is prepared one crystal form of Trifluridine, and the PXRD pattern of the crystal form is shown in Table 1 and Fig. 1 respectively, wherein Table 1 lists the 2θ angles, d values and relative intensities of 36 peaks, and Fig. 1 is demonstrated as follows:

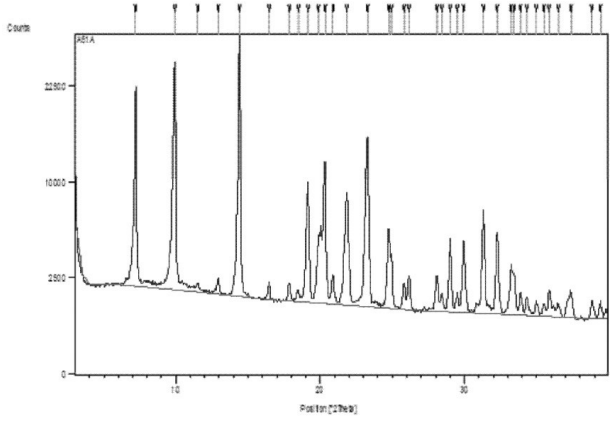
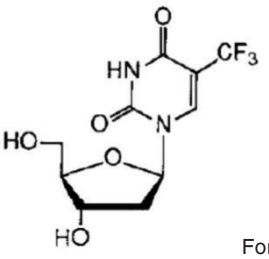


Fig. 1 The PXRD pattern of the crystal form of the drug prepared in Case 1

The data of Table 1 and Fig. 1 are completely the same. And claims in relation to the crystal form of the drug read:

"1. A Trifluridine compound shown in Formula I,



Formula I

characterized in that the Trifluridine compound is in a crystal form, and its X-ray powder diffraction pattern has the characteristic diffraction peaks of 7.21±0.2°, 9.93±0.2°, 14.41°±0.2°, 19.15°±0.2°, 20.33°± 0.2°, 21.84°±0.2°, 23.27°±0.2°, 31.30°±0.2°, 19.88±0.2°, 24.74±0.2°, 24.94°±0.2°, 29.01°±0.2°, 29.94°±0.2°, 32.25°±0.2° and 33.23°±0.2° represented by 2θ angle.

2. The Trifluridine compound according to claim 1, characterized by having an X-ray power diffraction pattern as shown in Fig. 1."

Through comparison between claims 1 and 2, it is found that they both claim the "crystal of the Trifluridine compound", wherein claim 1 defines, in the characterizing portion, fifteen characteristic diffraction peaks represented by 2θ angles in the PXRD pattern, and claim 2 recites "an X-ray power diffraction pattern as shown in Fig. 1" in the characterizing portion. Do the two different ways of said claims define the same scope of protection? The Invalidation Decision in this case determined that claims 1 and 2 have different scopes of protection, on the grounds that "claim 1 only defines a portion of characteristic peaks, without specifying the relative intensity and number of diffraction peaks or the diffraction pattern", "and under such circumstances, the assessment of novelty shall be based on the features defined in the claims, and the specific diffraction data or diffraction patterns that are merely recited in the description shall not be taken for comparison." Therefore, the technical feature of claim 1 which is compared with the reference documents should be the fifteen characteristic diffraction peaks represented by 2θ angles only. Claim 2 defines its feature by the PXRD pattern, with the scope of protection covering the crystal characterized by the PXRD pattern, and its technical feature used for comparison is the PXRD pattern, which includes 2θ angles (d values) of 36 peaks shown in Fig. 1, as well as the features such as the peak shape and intensity as shown in Fig. 1.

The above case indicates that different scopes of protection may be defined if different parameters are adopted

in the characterizing portion of the patent in relation to the crystal form of drug, but the assessment of novelty of such a patent is premised on the determination of the scope of protection of claims, and in particular, those skilled in the art have to judge which technical features are implicitly defined by these parameters from the perspective of technology. At present, a common knowledge in the art is that "just like a human fingerprint, a powder diffraction pattern is composed of the number, position, intensity and geometric topology of diffraction peaks. In the crystalline state, the unit cell parameters determine the number and position of the diffraction peaks of different substances, and the molecules that make up a crystalline substance determine the intensity of each diffraction peak. Those crystal form analyzing methods which only take account of the number and position of the diffraction peaks but ignore the intensity (relative intensity and absolute intensity) thereof are terribly wrong."[9] "If background signals are not considered, the diffraction pattern is composed of three parts, namely the position, shape and intensity of the diffraction peak."[10] Thus, in this case, claims 1 and 2 make a limitation by taking advantage of different parameters, wherein the limitation of claim 1 only recites fifteen PXRD characteristic peaks and therefore only a crystal having these fifteen characteristic peak positions, whereas the limitation of claim 2 only recites the PXRD pattern, which includes the information on not only the positions of the characteristic peaks, but also the number, shape, intensity, etc., of the characteristic peaks. That is to say, the technical features defined in the characterizing portions of the two claims are different in terms of the number and content, thereby leading to two different scopes of protection. In invalidation cases concerning patents in relation to crystal forms of drugs, the crystal form claims often make a limitation using a PXRD pattern, so the claimed crystal form of the patent in relation to a crystal form of a drug is not fully equivalent to the specific crystal form represented by the PXRD pattern, which is prepared according to the description.

2. How to assess whether a patent in relation to a crystal form of a drug possesses novelty

After the determination of the scope of protection of claim, the next step of novelty assessment is to judge whether all the technical features of the claim are disclosed in the prior art. The method for judging whether a patented crystal form of a drug has been disclosed is identical to the method for judging whether a specific compound has been disclosed in the prior art. It can be substantially divided into two circumstances at the legal level: one is to judge whether the patented crystal form of the drug "has been actually disclosed", and the other is to judge whether the protected crystal form of the drug is "presumed to be disclosed".

When judging whether the patented crystal form of the drug "has been actually disclosed", one should usually stand in the position of a person skilled in the art to judge whether each technical feature of the claimed crystal form of the drug has been disclosed in the reference documents. As stated above, if the crystal form of the drug is defined by the position of the PXRD characteristic peak, account shall be taken of whether the position of the characteristic peak of the patented crystal form of the drug has been disclosed in the prior art for the sake of assessment of novelty. If the crystal form of the drug is defined by the full PXRD pattern, consideration shall be given to whether the number and relative intensity of the characteristic peak has been disclosed, in addition to the judgment on whether the position of the characteristic peak has been disclosed in the prior art. When judging whether the position and relative intensity of the characteristic peak "has been disclosed", one should stand in the position of a person skilled in the art to study the connotation of the characteristic peaks that are of identical (substantially identical) position and intensity. The Pharmacopoeia of the People's Republic of China sets forth the following provisions on the identification of crystal forms of drugs, i. e., "as for the identification of crystal forms, the change in such parameters as the number, position (d or 2θ), intensity (relative or absolute), intensity comparison, etc. of diffraction peaks of the test samples are used to identify the state of the crystalline substance. This method is applicable to the identification of various crystalline substances which are all in a crystalline state, in a crystalline state and an amorphous state respectively, or all in an amorphous state. If the crystalline substances of two crystalline samples are determined to be in the same state, a powder X-ray diffraction test should be carried out simultaneously while satisfying the requirements that the two crystalline samples have the same number of diffraction peaks, the error of the 2θ values of the diffraction peak positions is within the range from -0.2° to +0.2°, the error of the relative peak intensity of the diffraction peaks at the same position is within the range of -5% to +5%, and the intensity order of the diffraction peaks should be consistent."[11]

The following two cases illustrate how to judge whether

the features of the patented crystal forms of drugs have been "actually disclosed" in the prior art.

The author still intends to discuss this issue on the basis of Case 1. The petitioner provided E3, which is obtained by downloading the crystal data cif file from E1 and using Mercury software to calculate the crystal diffraction pattern (that is, the PXRD pattern of the crystal in E1). It is argued that E3 discloses the PXRD pattern in claim 1 obtained by means of the Bragg equation through data calculation and conversion. The comparison between the PXRD pattern of the crystal prepared in claim 2 of the patent in suit and that of E3 is shown as follows:

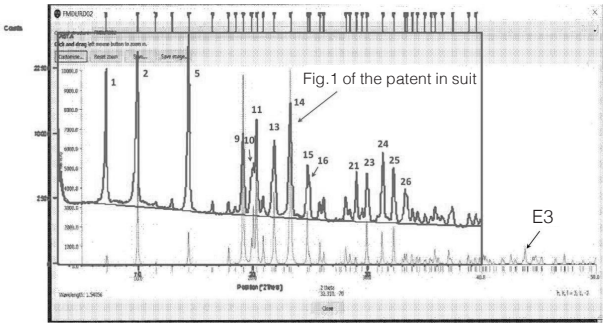


Fig. 2 [Case 1] Comparison of the PXRD patterns between claim 2 of the patent in suit and E3

Table 1: [Case 1] Comparison of characteristic peak data between claim 1 and E3

Diffraction peak number	Claim 1	E3	Central difference
1	7.21±0.2°	7.203	−0.007
2	9.93±0.2°	9.934	0.004
5	14.41±0.2°	14.403	−0.007
9	19.15±0.2°	19.121	−0.029
11	20.33±0.2°	20.300	−0.030
13	21.84±0.2°	21.821	−0.019
14	23.27±0.2°	23.279	0.009
24	31.30±0.2°	31.317	0.017
10	19.88±0.2°	19.866	−0.014
15	24.74±0.2°	24.738	−0.002
16	24.94±0.2°	24.893	−0.047
21	29.01±0.2°	28.990	−0.020
23	29.94±0.2°	29.921	−0.019
25	32.25±0.2°	32.310	0.060
26	33.23±0.2°	33.272	0.042

[Case 1] The Invalidation Decision held that "E3 discloses the positions of fifteen diffraction peaks, which substantially coincide with those of the present patent with the difference of characteristic peaks being less than 0.2°. However, the various peaks are different in terms of intensity. For instance, the No. 5 peak of the present patent is the most intensive one and the fifteen peaks listed in the order of relative intensity (from strong to weak) are peaks Nos. 5, 2, 1, 14, 11, 9, 13, 24, 15, 25, 21, 10, 23, 16 and 26. In contrast, the No. 14 peak of E3 is the most intensive one and the fifteen peaks listed in the order of relative intensity (from strong to weak) are peaks Nos. 14, 9, 11, 2, 13, 10, 15, 25, 5, 24, 10, 16, 26, 21, 1. In addition, there are, in E3, a plurality of peaks missing between 10° and 20° (2θ angle), the number and shape of peaks between 25° and 30° (2θ angle) are different from those in Fig. 1 of the present patent, and there still exist a plurality of diffraction peaks with high relative intensity in addition to the above-mentioned fifteen characteristic diffraction peaks." "The position, shape (geometric topology feature) and intensity of the diffraction peaks all contain the structural information of crystals. As for the crystals of the same organic compound, even if all the diffraction peaks are located in the same position, where the diffraction peaks have different peak shapes, relative intensities and dissimilar order of intensity, it means that the microscopic crystal structures are different and represent different crystal forms, although their unit cell parameters may be quite close."

E1 discloses the fifteen characteristic peaks in claim 1, and the difference in 2θ angle between the characteristic peaks of E1 and claim 1 is less than 0.2°, which is within the error range of the characteristic peaks defined in claim 1, so the Invalidation Decision in Case 1 determined that the crystal form of the compound in claim 1 lacks novelty. As for claim 2, the Invalidation Decision found that the characterizing portion thereof includes thirty-six characteristic peaks (number and position), as well as the information on the shape and intensity (or relative intensity) of each characteristic peak. Since the order of intensity, shape and relative intensity of peaks shown in Fig. 1 according to claim 2 are different from those as shown in the PXRD pattern of the crystal of E3 and many characteristic peaks are not disclosed in E1, the invalidity ground that claim 2 lacks novelty is not tenable.

[Case 2] [12] This case relates to type I crystals of topiroxostat, wherein claim 1 reads "Type I crystals of 4-[5-(pyridin

-4-yl)-1H-1,2,4-triazol-3-yl]pyridine-2-carbonitrile exhibiting characteristic peaks in powder X-ray diffractometry at diffraction angles 2θ of about 10.1°, 16.0°, 20.4°, 25.7°, and 26.7°". The petitioner argued that the crystals of "topiroxostat" prepared in Attachment 2 were the same as those under the protection of the patent in suit, and conducted the powder X-ray detection and analysis of the crystals prepared in Attachment 2 (Note: the preparation and detection tests in Attachment 2 are conducted by an independent third party and recorded in Attachment 3) to obtain the PXRD pattern. The preparation of Attachment 2 was repeated twice to obtain the value of the diffraction angles 2θ of samples. The comparison of the diffraction angles 2θ between the samples and the patent in suit is shown in Table 2:

Table 2: [Case 2] Comparison of characteristic peak positions between claim 1 and the prior art

	Diffraction angles 2θ of characteristic peaks in the powder X-ray diffraction pattern				
Claim 1	10.1	16.0	20.4	25.7	26.7
Sample 1 prepared by repeating Attachment 2	10.2	16.1	20.6	25.9	26.8
Sample 2 prepared by repeating Attachment 2	10.1	16.0	20.5	25.7	26.7

[Case 2] The Invalidation Decision deemed that "through comparison, the positions of the above characteristic peaks all correspond to each other or are within a reasonable error range (the description of the patent in suit recites that '±0.5° of the X-ray diffraction is within an allowable range, and should be covered by the scope of protection of the present invention'). The experimental content of Attachment 3 testifies that the crystal obtained by Example 3 (prior art) of Attachment 2 is identical with the Type I crystal in claim 1 in terms of the defined parameter features, both of which are of the same crystal form, so claim 1 lacks novelty as prescribed by Article 22.2 of the Patent Law. In Case 2, the position differences between the PXRD characteristic peaks disclosed in the prior art and the characteristic peaks defined in claim 1 are all within the error range recognized in the art. Hence, it is deemed that the crystal form of the patent in suit has been disclosed in the prior art.

The above two cases show that in order to determine whether the patented crystal form of the drug has been actually disclosed in the prior art, it is necessary to clarify whether each technical feature in the characterizing portion of the claim has been disclosed by the corresponding feature in the prior art. Under such circumstances, one should stand in the position of a person skilled in the art to decide whether a patented technical feature has been disclosed in the prior art under the standards for identical (substantially identical) crystal forms of drugs adopted by a person skilled in the art. For instance, if the crystal form of a drug is defined by the position data (e.g., d value or 2θ) of the characteristic peaks in the PXRD pattern, the characteristic peak in said position is directly compared with the corresponding one in the prior art to decide whether the former has been disclosed in the prior art, and meanwhile account shall be taken of how large the acceptable error range is when identifying the characteristic peak at the same position during the characteristic peak position detection (for example, according to the explanation in the description of the patent in suit and/or the provision in the "Pharmacopoeia"). If the position of the characteristic peak of the crystal form disclosed in the prior art falls within the error range for the claimed characteristic peak position, it shall be determined that said feature has been substantially disclosed. If the crystal form of the drug is defined by the full PXRD pattern, the simple comparison of the characteristic peaks in terms of position to see whether the technical feature of the patent in suit is disclosed in the prior art is usually not adequate, and it is also necessary to compare the characteristic peaks in terms of number, shape and relative intensity. Only when the above parameters are all disclosed in the prior art can the crystal form of the drug be determined as "having been actually disclosed" in the prior art. The above judgment as to whether the crystal form of the drug has been "actually disclosed" is made under the general rule for novelty assessment, that is, if all the technical features have been disclosed or are deemed as having been substantially disclosed within an error range commonly recognized in the art, it shall be deemed that the technical solution of said claim has been "actually disclosed".

As stated above, although the patents in relation to the crystal forms of drugs still fall within the category of compound patents, the novelty assessment of the patented crystal forms of drugs shall follow, in addition to the general rules, the special rules for assessing the novelty of compounds, i. e., "presumed novelty". However, "presumed

novelty" is somewhat different from "disclosure by means of mention" for compounds. Under Part II, Chapter Ten, Section 5.1 "Presumed Novelty" of the Guidelines for Patent Examination, it is stated that "for a compound claimed in a patent application, if the structural information of a compound, such as the chemical name and the molecular formula (or structural formula), is recited in a reference document so that those skilled in the art think that the claimed compound has been disclosed, the compound lacks novelty, unless the applicant can provide evidence to verify that the compound is not available before the date of filing." As stated above, since the name of the crystal form of a drug cannot reflect its micro-spatial structure, which is characterized by parameters, if the prior art does not disclose the parameter features of the crystal form of the drug, it is only possible to judge whether the patent in suit and the prior art relate to the same crystal form according to the manner to acquire the crystal form of the drug, and further if the patent in suit and the prior art acquire the crystal form in the same or extremely similar way, it is highly likely that they relate to the same crystal form, the prior art is deemed to have disclosed the crystal form of the patent in suit, and the patented crystal form of the drug is "presumed to be disclosed". Under such circumstances, the patentee is obliged to adduce evidence to prove that the two crystal forms are not the same and shall bear the adverse legal consequences if the patentee fails to do so.

[Case 3][13] This case relates to an anhydrous polymorph A of linagliptin, and six specific PXRD characteristic peaks are defined in the characterizing portion of a claim, wherein the first characteristic peak is the most intensive one, and the melting point and lattice parameter are also defined. The description thereof recites "the compound prepared in WO 2004/018468 is present at ambient temperature as a mixture of two enantiotropic polymorphs. The temperature at which the two polymorphs transform into one another is 25±15° C. The pure high temperature form (polymorph A), which can be obtained by heating the mixture to temperatures >40° C., melts at 206±3° C." and "the polymorph B is obtained by cooling to temperatures <10° C". The patent WO 2004/018468 is the family patent document of E1 used by the petitioner, and the compound prepared in WO 2004/018468 is called linagliptin. In E1, the compound is denoted by the reference numeral 142 (a solid with the melting point of 198℃ to 202℃). The petitioner adopted the compound 142 of E1 in order to prove that the anhydrous polymorph A of the patent in suit lacks novelty, whereas the patentee asserted that the melting point of the compound 142 of E1 does not coincide with the melting point of the polymorph A of the patent in suit, and they do not belong to the same crystal.

[Case 3] The Invalidation Decision deemed that "the above-mentioned document WO2004/018468 in the description of the present patent is the family patent of E1. It can be determined according to the above content that the compound 142 of E1 at room temperature should be the mixture of the crystal forms B and A, i.e., E1 has prepared the crystal form A of linagliptin, which is not only of low purity, but also includes the crystal form B. Second, the description of the present patent definitely indicates that the pure crystal form A can be obtained by heating the compound to a temperature greater than 40℃. E1 discloses the melting point (198℃-202℃) of the compound 142, which is greater than 40℃. In view that the method for measuring the melting point in the art is usually to heat the solid compound to a molten state, when the temperature is raised to higher than 40℃ during the melting-point measuring process, E1 has objectively obtained the pure crystal form A, but with specific crystal parameters undefined."

In this case, the characteristic peaks, melting points and lattice parameters defined in the patent in suit are not disclosed in the prior art, such that it is impossible to directly determine whether the technical feature of the patent in suit has been "actually disclosed". But the conditions for acquisition and existence of the solid compound 142 disclosed in E1 are substantially the same as those of the crystal form B of the patent in suit, the rule of "presumed novelty" shall be adopted for novelty assessment. The patent in suit and E1 both relate to the same compound with the identical chemical structure, and they are very likely to obtain the solid products with the same micro-spatial structure under the same conditions. Therefore, it is presumed that the crystal form of the patent in suit has been disclosed in E1. The conditions for obtaining linagliptin prepared in E1 at room temperature (25°C) during the process of measuring the melting point are the same as those for obtaining the crystal form A and the pure crystal form A respectively in the patent in suit. Although E1 does not disclose the crystal parameters of the compound 142, the obtained compound 142 is a solid compound, which exists under the same conditions as those for the crystal form A of the patent in suit and is obtained in the same way. Hence, it is highly likely

that the patent in suit and E1 relate to the same crystal form, and it is presumed that the patent in suit does not possess novelty.

[Case 4] [14] The patent seeks to protect the Form II polymorph of ritonavir, and delimits twenty-one characteristic peaks in the characterizing portions of claims. The method for preparing the Form II polymorph is recited in an example of the description as follows: "Amorphous ritonavir (40.0 g) was dissolved in boiling anhydrous ethanol (100 mL). Upon allowing this solution to cool to room temperature, a saturated solution was obtained. After standing overnight at room temperature, the resulting solid was isolated from the mixture by filtration and was air dried to provide Form II." The petitioner adopted the compound III (namely, ritonavir crystal) to prove that the polymorph of the patent in suit lacks novelty, wherein Example 2 of E1 discloses the method for preparing the compound III as follows: "The residue was dissolved in ethyl acetate and the solvent was distilled once more. The residue was dissolved in ethyl acetate and warmed to about 60°C until a clear solution was obtained. The solution was filtered into a clean 300 gallon reactor and a rinse of ethyl acetate was also filtered into the 300 gallon reactor. Heptane was charged to the ethyl acetate solution in the 300 gallon reactor. The mixture was heated to about 80°C until a clear solution was obtained. The solution was cooled at a rate of less than 25°C per hour to a final temperature of 22°C and was stirred for another 12 hours after the product began to crystallize. The thick slurry was centrifuged in four separate loads to isolate the product. Each isolated load was washed with approximately 45 kg of a solution of ethyl acetate/heptane. The last wash was used to also rinse the reactor. The product was dried in a blender drier under vacuum at 55°C for about 24 hours to provide 101.9 kg of the desired product. m.p. 121-123°C."

[Case 4] The Invalidation Decision deemed that "E1 does not disclose the specific form of the crystal or corresponding powder diffraction pattern, but only discloses the range of the melting point thereof. Furthermore, according to the embodiment of the description of the present patent, the preparing method of Example 2 of E1 is not identical with that of the present application, so it is impossible to judge whether the crystals disclosed in the present patent and E1 are the same or not." "In the crystalline field, different polymorphs can be identified by the known analyzing method……, wherein XRD, crystal lattice parameters and spatial grounds, as well as solid-state nuclear magnetic resonance (NMR), are relatively accurate representation manners. Thus, where the present patent uses the XRD data to represent. Form II and E1 does not disclose the XRD data of the crystal, since the preparation methods of the present patent and E1 are not the same, it is inadequate to prove that the two crystal forms are the same in the absence of further evidence adduced by the petitioner."

Since in the above case, the prior art does not disclose the PXRD parameters of the prepared crystal form so that its crystal form cannot be compared with that of the patent in suit, it cannot be determined that the patented crystal form has been "actually disclosed" and the dispute over novelty is centered on whether the patented crystal form should be "presumed to be disclosed". Since it is highly likely that the same crystal can be obtained by the same crystallization method or extremely close crystallization methods, the typical situation where the rule of "presumed novelty" is applicable to the patents in relation to crystal forms of drugs is that the patent in suit and the prior art adopt quite similar methods for preparing a crystal form so that it can be reasonably presumed that the prepared crystal form products are highly likely to be identical.

In Case 4, the patent in suit dissolves amorphous ritonavir in boiling anhydrous ethanol. Upon allowing this solution to cool to room temperature and stand overnight at room temperature, the resulting solid was isolated from the mixture by filtration and was air dried to provide Form II. In contrast, the prior art uses the mixed solution of ethyl acetate and heptane of ritonavir, and the solution was cooled to 22°C below room temperature, and crystallized, isolated and dried to provide the crystal. Since the dissimilar crystallization solvents of the patent in suit and the prior art are different greatly in properties and crystallization temperature, the methods for preparing crystals thereof are different. In addition, crystallization solvents and temperature are crucial technical means that determine the crystal form. Since the above differences result in that the methods for obtaining crystals of the patent in suit and the prior art are different, it cannot be presumed that the patent in suit has been disclosed in the prior art, and the invalidation petitioner did not fulfill its burden of proof.

It can be known from the above analysis of those cases that, as for the two circumstances for judging whether the patented crystal form of the drug has been disclosed in the prior art, the former applies the general rules for novelty assessment as prescribed in Part II, Chapter Three of the

Guidelines for Patent Examination, i. e., where the patent and the prior art "have completely the same technical content" through comparison, it can be directly determined that the patented crystal form lacks novelty according to the factual findings disclosed in evidence; and the latter makes reference to the high probability rule among the standards of proof for civil evidence in civil litigation, and the rule of "presuming" that a compound lacks novelty in the Guidelines for Patent Examination, i. e., "if the competent people's court, through examination of the evidence provided by a party bearing the burden of proof and in light of relevant facts, is convinced that it is highly likely that the facts to be proved by such evidence have occurred, the people's court shall find that such facts do exist" [15]. If the methods for obtaining a crystal form of the patent and the prior art are exactly the same or quite close to each other, it is highly likely that the patent and the prior art obtain the same crystal according to the facts proved by evidence, thereby presuming that the patented crystal form lacks novelty. If the patentee adduces evidence proving that the prior art cannot obtain the crystal form, the above presumption can be overturned. In this sense, the presumed novelty is a legal determination that exempts one party from the burden of proof according to the case details and transfers the burden of proof for non-existence of the presumed facts to the patentee where there is relatively limited evidence.

III. Conclusion

To sum up, patents in relation to crystal forms of drugs fall into the category of compound patents. The rationales for novelty assessment of these two types of patents are the same, and the judgment as to novelty of a crystal form of a drug and the judgment as to novelty of a compound both require to first determine the scope of protection of claims and the technical solution disclosed in the prior art, and then decide whether a technical fact is disclosed. However, due to the characteristics of the crystal form of the drug, the content and method used for novelty assessment are somewhat special, to be specific:

As for the content, there is no unified standard for the naming of crystal forms of drugs, and no link exists between the naming and the micro-spatial structure thereof. Therefore, different from the factual findings for the novelty of compounds, crystal forms cannot be determined as identical simply because of identical names. Since the micro-spatial structure of a crystal form is determined by its special parameters, such as data on PXRD (or unit cell parameters), the judgment as to whether these parameters have been disclosed in the prior art is the key to judging whether the patented crystal form of the drug possesses novelty. When judging whether the parameters defining the crystal form of the drug have been disclosed, one needs to get to know the rule in the prior art for identifying the same crystal form of the drug. On the one hand, consideration shall be given to the fact that PXRD is a fingerprint identification method for crystal forms of drugs, and the identity of PXRD characteristic peaks does not necessarily lead to the identity of crystal forms. The fingerprint information of the PXRD pattern includes shape and intensity (or relative intensity) of characteristic peaks, in addition to the number and position thereof, which should all be considered in the identification of crystal forms. On the other hand, the PXRD data are obtained by means of testing. Measurement errors inevitably exist due to differences in testing personnel, samples, etc. If the PXRD fingerprint information is within the range of measurement errors recognized in the art, it can be deemed that the crystal forms of the patent and the prior art are the same; or otherwise, they cannot be determined to be the same.

Regarding the judging methods, different from a compound patent which defines the scope of protection of claims by chemical names or chemical structures, a patent in relation to a crystal form of a drug usually defines the scope of protection of claims by parameters. Where the prior art discloses the crystal form parameters, the crystal form parameters of the patent in suit can be compared with those of the prior art under the general rules for novelty assessment to see whether the patent in suit has been "actually disclosed" in the prior art. Where the prior art does not disclose the crystal form parameters, whether the patent in suit has been "actually disclosed" in the prior art cannot be determined under the rules for novelty assessment due to lack of parameter comparison. However, the high probability rule among the standards of proof for civil evidence can be utilized to presume whether the patent in suit has been disclosed in the prior art. The presumption is conducted on whether the method for obtaining the crystal form of the patent in suit is identical or similar to that of the prior art. If the two methods are identical or similar, it is highly likely that the patent in suit and the prior art relate to the same crystal form, and the crystal form of the patent in suit is "presumed

to be disclosed"; or otherwise, the crystal form of the patent in suit is "presumed to be disclosed". Where the crystal form of the patent in suit is "presumed to be disclosed", if there is evidence proving that the crystal form cannot be obtained by the prior art, the above presumption cannot be established. ■

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BRICS Heads of IP Offices Hold Informal Meeting in Geneva, Switzerland

In July, during the 64th Series of Meetings of the Assemblies of the Member States of the World Intellectual Property Organization (WIPO), BRICS heads of IP offices held an informal meeting.

The meeting was chaired by Rory Voller, Commissioner of the Companies and Intellectual Property Commission of South Africa and participated by Shen Changyu, Commissioner of the China National Intellectual Property Administration, Júlio Moreira, President of the National Institute of Intellectual Property of Brazil, Yury Zubov, Head of the Federal Service for Intellectual Property of Russia, and Unnat P. Pandit, Controller General of Office of the Controller General of Patents, Designs and Trademarks.

During the meeting, the offices discussed and reached consensus on issues including progress of the BRICS cooperation roadmap project, BRICS general statements during the WIPO Assemblies, future information communication mechanism and preparatory work for the 15th BRICS Heads of IP Offices Meeting.

Since last year, marked progress has been made in all aspects of IP cooperation among the BRICS countries. Further deepening of communication, mutual learning and pragmatic cooperation are expected to enhance the influence of the BRICS IP cooperation.

Source: CNIPA