Discussion on Inventive Step Assessment in Cases Involving Invalidation of Pharmaceutical Crystal Inventions

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Due to the development of the China's pharmaceutical industry and the increased requirement for pharmaceutical safety and quality control, invalidation cases involving crystalline forms of drugs have attracted much attention from the industry. Based on some recently concluded cases, this article intends to delve into issues concerning the assessment of inventive step and the allocation of the burden of proof on both parties in the invalidation cases related to crystalline forms of drugs.

The same drug may result in crystalline forms with different spatial structures and molecular arrangements due to different crystallization conditions and processes. This phenomenon is called crystal polymorphism. The phenomenon of crystal polymorphism is of paramount importance to pharmaceutical research and development, mainly because, on the one hand, different crystalline forms may affect the dissolution and release of drugs due to their different *in vivo* dissolution and absorption rates, thereby affecting the efficacy and safety of drugs [2] and, on the one hand, different crystalline forms may affect the preparation, processing and storage of drugs due to their different stability, hygroscopicity and even appearance. Some scholars believe that one of the reasons for the significant difference in efficacy between domestic and imported drugs lies in the crystalline forms of drugs [3]. With the continuous deepening of researches on crystalline drugs, China has placed more emphasis on the issues relating to the crystalline forms of drugs. The Pharmacopoeia of the People's Republic of China (2015) incorporated crystalline form research and quality control into the guiding principles [4] for the first time. In September 2021, the State Food and Drug Administration released the Guidelines for Research on Crystalline Forms of Chemical Generic Drugs (Draft for Comments) [5], aiming to put forward suggestions on the research on crystalline forms of drugs when applying for generic drugs. These are sufficient to show the importance of crystalline form research in the development of drugs.

In practice, since the development and marketing of drugs require a huge number of human and financial resources, for the purpose of recovering R&D costs and maintaining a competitive advantage, on the one hand, innovative pharmaceutical companies tend to lay out multi-level and all-round patent applications for inventions such as compounds and crystalline forms of drugs in a desire to obtain a longer period of exclusivity for pharmaceutical patents by making use of a variety of patent combinations, thereby protecting their R&D achievements, and on the other hand, generic pharmaceutical companies are also prone to "overtaking on the bend" through the R&D of known active compound crystalline forms, so as to gain market shares. Resultingly, the number of patent applications for

crystalline forms of drugs keeps rising year by year, and the number of invalidation cases relating to such patents is on the rise at an increasing rate. In recent years, the invalidation cases related to crystalline forms of drugs have attracted great attention in the relevant industries, and in particular, the criteria for assessing inventive step have provoked heated debates [6]. Having collected invalidation decisions related to crystalline forms of drugs, the authors are in an attempt to delve into those cases for clarifying the rationale for examining the inventive step of this type of inventions.

I. Overall situations of invalidation cases related to crystalline forms of drugs

The authors conducted keyword search in the reexamination and invalidation decision database, gathering 66 invalidation decisions related to crystalline forms of drugs which had been issued from January 2001 to May 2021, and 48 corresponding judgments. Through analysis, it is found that these cases in their entirety demonstrate the following characteristics.

First, the number of invalidation cases is obviously on the rise. Fig. I statistically shows the results according to the date of issuance of invalidation decisions. Within the decade from 2001 to 2010, only eight invalidation decisions were related to crystalline forms of drugs. However, an apparent increase in the annual number of such cases concluded has been observed since 2017. Eight invalidation cases related to crystalline forms of drugs were concluded in the first five months of 2021.

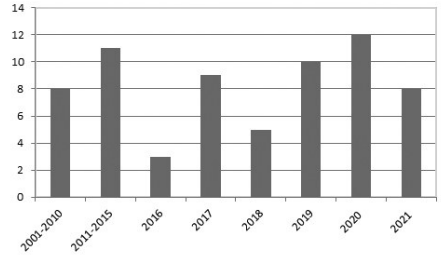

Fig. I Annual number of invalidation cases

Second, these cases focus on disputes over inventive step. As shown in Fig. II, 83% of the grounds for invalidity are related to lack of inventive step, followed by lack of novelty and insufficiency of disclosure.

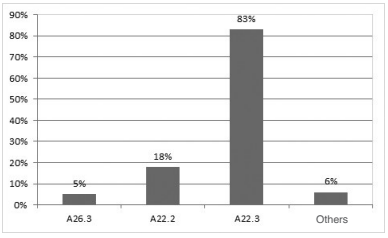

Fig. II Grounds for invalidity

Third, the subject matters of the patents in suit are mostly crystalline forms and salt crystals of compounds. The technical contributions made by the patents in suit to the prior art are the factual prerequisite for judging whether they possess inventive step over the prior art, and are often embodied in the claimed technical subject matters. Fig. III illustrates that a great majority of such cases involve the crystalline forms of the compounds *per se*, followed by salt crystals of compounds. Judging from the characterization of claims, no matter which subject matter is involved, the claimed crystalline forms are mostly characterized with powder X-ray diffraction (PXRD) (see Fig. IV). Judging from the examination conclusions, claims involving the crystalline forms of the compounds *per se* are more likely to be invalidated than those involving salt crystals of the compounds.

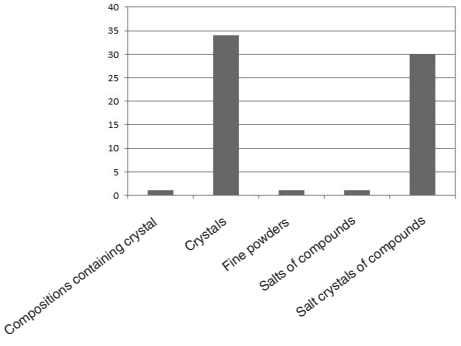

Fig. III Claimed subject matters

Fourth, in the description, the technical effects of an invention involving crystalline forms of a drug are often characterized by the properties related to the developability of crystalline forms, such as solubility and stability. It is found through analysis that the technical effects of the inventions related to crystalline forms of drugs are expressed by either the physiochemical properties that directly affect drugs, such as melting points, solubility and dissolution, or the properties in relation to clinical efficacy of drugs, such as bioavailability. Fig. V illustrates that top five properties used to indicate the technical effects of invention are stability (in-

cluding thermal stability, crystal stability, chemical stability and storage stability), solubility, hygroscopicity, bioavailability and purity, wherein thermal stability is usually characterized by melting point, DSC and TGA, and chemical stability is usually characterized by accelerated tests.

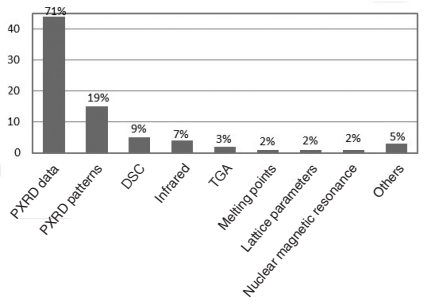

Fig. IV Characterization of claims

Fifth, the patents in suit are improved with respect to the prior art mostly in the aspect of the research on the crystallization of known active compounds or the salt crystallization of known free alkali compounds. The improvements of inventions over the prior art can have a direct impact on the assessment of inventive step. According to the prior art states, the improvements of the patents in suit with respect to the prior art can be divided into the following four types: (1) the compounds *per se* are not known in the prior art, but the patents in suit protect the crystalline forms of new compounds; (2) the compounds *per se* or solid forms thereof are known in the prior art, but the patents in suit protect the crystalline forms of the compounds; (3) one or several crystalline forms of the compounds are known in the prior art, but the patents in suit protect different crystalline forms of the compounds; and (4) the free alkali or salt of the compounds are known in the prior art, but the patents in suit protect the salt (modified salt) crystals of the compounds. As seen in Fig. VI, the largest portion of the pie chart is the third type of the patents in suit accounting for 56% of all the cases, followed by the fourth type.

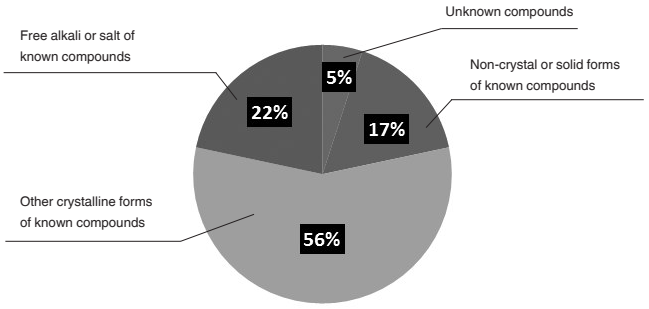

Fig. VI Improvements of the patents in suit over the prior art

Sixth, no data are provided in the description to demonstrate the technical effects of crystalline forms, or though data being provided, the technical effects proved thereby are within the expectation of those skilled in the art, which is the major reason why inventions related to crystalline forms of drugs are declared invalid. Statistics show that in nearly 20% of the invalidated cases, the description of the patent in suit fails to recite any experimental data related to technical effects, and in more than 50% of the invalidated cases, the description of the patent in suit only recites a few data related to technical effects, and the technical effects reflected are within the expectation of those skilled in the art.

Seventh, the administration and the judicature hold

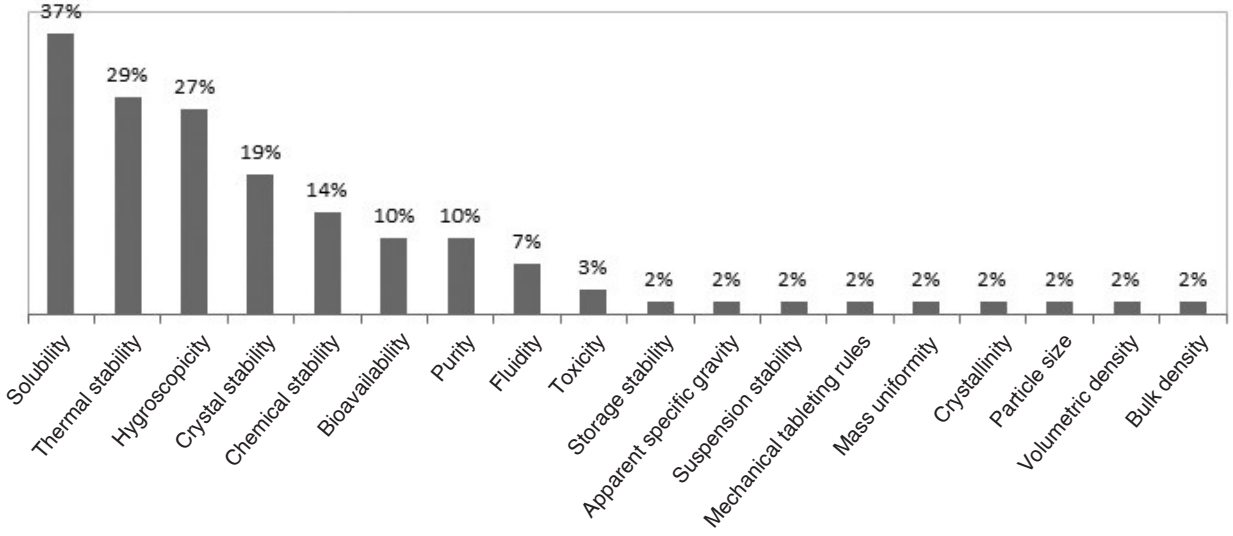

Fig. V Characterization of properties or technical effects of crystalline forms of drugs in the description

highly consistent views on related issues. The 48 judgments which we collected involve 28 invalidation decisions, wherein the judgments concerning the assessment of inventive step of inventions related to crystalline forms all end up with the conclusion of upholding the invalidation decisions.

II. Key points to be examined for assessing the inventive step of invention patents related to crystalline forms of drugs

In practice, most cases concerning invalidation of inventions related to crystalline forms of drugs involve a dispute over the assessment of inventive step. However, there are nearly no disputes between the parties over the selection of the closest prior art, the identification of distinguishing features and the determination of technical problems. The most controversial issues are whether the prior art provides any teaching, and whether the patent in suit achieves any unanticipated technical effect over the prior art. Through analysis, we found that even for those controversial issues, there has been formed a kind of consensus to some extent at present.

1. Almost all the invalidation decisions unanimously determined that the prior art has a strong R&D desire and provides a teaching for crystallization and "crystalline modification" [7] of the known active compounds.

Active pharmaceutical ingredients can exist in different polymorphs, which will in turn affect the quality and efficacy of pharmaceutical preparations. This has appeared in many literatures and has become the common sense in the field of pharmaceutical R&D. For instance, John Haleblian clarified his view in an article titled Pharmaceutical Applications of Polymorphism that "it is clear that probably every organic medicine can exist in different polymorphs and the choice of the suitable polymorph will determine if a pharmaceutical formulation will be chemically or physically stable, or if a powder will tablet or not tablet well, or if the blood level can reach the therapeutic level to give the pharmacologic response desired. Thus, it is time that pharmaceutical companies, as a part of their preformulation studies, identify and study the stability of different polymorphs of each potential new drug, as they do the melting points or other physical characteristics." [8] The guiding committee of the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) once wrote in a book entitled International Technical Requirements for Registration of Pharmaceuticals: Quality Section that "some new active pharmaceutical ingredients exist in different crystalline forms which differ in their physical properties. Differences in these forms could, in some cases, affect the quality or potency of the new drug formulations. In cases where differences have been shown to affect pharmaceutical product performance, bioavailability or stability, then the appropriate solid state should be specified." [9]

In view of the above general knowledge in this field, many invalidation decisions arrived at the following findings: "in the field of crystal chemistry, the primary activity of a compound is closely associated with its chemical structure. On the premise of the identical chemical structure, different crystalline forms vary only in the micro-spatial structure of the compounds. Such a difference generally will not modify the activity of the compound qualitatively. Therefore, ……where the compounds are completely identical in terms of the chemical structure or the same in terms of the core structure, ……, some advantages (such as the relative stability, high purity and good operability that a crystal normally possesses) determined by the crystal and the specific crystal form itself when preparing the compound as a crystal form are known to those skilled in the art. After the completion of the R&D of a compound product, those skilled in the art will normally consider how to pursue further studies on more valuable crystals and prepare other crystals after the preparation of some crystal of the compound, and (inventions related to crystalline forms) are usually achieved by making use of the general properties and effects of crystals known to those skilled in the art and conventional experimental means used for crystal preparation." [10] In the invalidation decision of the Vortioxetine case, the collegial panel also pointed out that "those skilled in the art have been aware of the differences in properties between crystalline drugs and noncrystalline drugs, as well as the advantages of the crystalline drugs over the noncrystalline drugs. As a result, the motivation to prepare active pharmaceutical compounds into crystals is common in the art." [11]

The authors agree on this view. On the one hand, it is determined by the pharmaceutical R&D principle and practice, and on the other hand, it seems that in invalidation cases, the motivation for the R&D of crystalline forms should not be the focal point which petitioners make efforts to

prove.

2. The performance and effect of the pharmaceutical crystalline forms are vital factors to be considered when selecting a crystalline form. Although the inventions of this kind may be unpredictable to some extent, the technical effects thereof in some aspects can usually be expected. This view is embodied in many invalidation decisions.

Crystallization is a crucial means in pharmaceutical R&D to improve the quality of drugs, and crystalline form is a vital indicator of pharmaceutical quality control. In pharmaceutical application, bioavailability is most closely related to crystalline forms, and subject to influence of the properties of crystals, such as solubility, dissolution and stability [12]. For this reason, as far as inventions related to crystalline forms of drugs are concerned, the technical effects of the products related to crystalline forms can be expressed by either the properties concerning the clinical performance of pharmaceuticals, like bioavailability, or the properties concerning the pharmaceutical preparations *per se*, like solubility, dissolution and stability. According to research literature, solids are generally divided into two classes—crystalline and amorphous according to the internal structure thereof. Amorphous solids have higher solubility and dissolution rate, and are highly hydrophilic and easily hygroscopic. Therefore, as compared with crystalline powders, amorphous powders are generally easy to absorb moisture and dissolve [13]. This also means, in general, stable crystals of pharmaceuticals have higher melting point and stability, as well as lower solubility and dissolution rate, than amorphous or metastable crystals, [14] which has been the general recognition in the art.

It is just because of the above-said general recognition that many invalidation decisions determine that "crystals are solid materials whose constituents, such as atoms or molecules, are arranged in a regular, repeating pattern, and which have lattice energy. Crystals are more stable in comparison with non-crystals with the same chemical composition……[15] " "As for the solubility effect, it is well-known in the art that amorphous pharmaceuticals are more soluble than their crystalline counterparts [16]" and "a substance with higher solubility is generally easily hygroscopic [17]".

The authors agree on this view. With the development of the pharmaceutical industry and the deepening of studies on crystalline forms of drugs, the relationship between structure and properties of compounds has been gradually revealed and many universal findings have also been gradually revealed by those skilled in the art. For example, there is a finding that lattice energy empowers crystalline forms of drugs to have higher stability, lower solubility and reduced hygroscopicity than amorphous forms. If an invention is only to make a known active compound from an amorphous form to a crystalline form, the properties or effects obtained thereby are completely within the expectation derived from the above finding. If the invention is granted 20-year exclusivity, it obviously does not match the contributions made by the inventors to the prior art.

3. The crystalline form of the compound is structurally close to the compound itself or its known crystalline form. In order to judge whether there exists an inventive step, one should focus on whether the claimed crystalline form can generate an unexpected technical effect, which is a common view presented in numerous invalidation decisions and court judgements.

Polymorphism refers to different spatial arrangements of the same compound caused by different molecular configurations/conformations or solvate formation. Different crystalline forms of the same compound have completely the same chemical composition with only slight variations in microscopic space. In practice, as for the application of the provisions in Part II, Chapter Ten, Section 6 of the Guidelines for Patent Examination (2010), the invalidation decisions all regarded the crystalline form of the compound in the patent in suit as a compound structurally close to the compound or its known crystalline form, and determined whether an inventive step existed according to whether the crystalline form of the compound achieved an unexpected technical effect. A similar judging rationale also applies to examination of a solvate, which is a pseudopolymorph.

This view was also definitely embodied in the Tiotropium Bromide case tried in the Supreme People's Court. In this case, the Supreme People's Court held that "although crystalline compounds vary in physicochemical parameters due to their different molecular arrangements, they still belong to the category of compounds. Thus, the provision on the inventive step of compounds in the Guidelines for Patent Examination may apply to the assessment of inventive step of new crystalline compounds." In response to the patentee's assertion that "the term 'structurally close' indicates not only the identicalness in chemical structure, but also the proximity in microscopic crystalline structure", the Supreme People's Court stated that "crystalline compounds are of a great variety in terms of the microscopic

crystalline structure. A compound in a solid state may result in different solid crystalline forms due to two or more dissimilar molecular arrangements…… which should not be considered as not structurally close just because of the difference in microscopic crystalline structures…… 'Structurally close compounds' as mentioned in the Guidelines for Patent Examination merely indicate that the compounds must have the same core part or basic ring, and do not involve the comparison of the microscopic crystalline structures", "and in this case, claim 1 seeks to protect a tiotropium bromide monohydrate crystal, Evidence 5a discloses a tiotropium bromide x-hydrate and Evidence 1 discloses a tiotropium bromide crystal. The three substances may be different in terms of the microscopic crystalline structure. But since tiotropium bromide is the basic core part for the three and enables them to have the same activity, they are considered as structurally close on the part of those skilled in the art and therefore belong to the 'structurally close compounds' as mentioned in the Guidelines for Patent Examination." [18] Furthermore, in this case, the Supreme People's Court further clarified that "in the assessment of inventive step of crystals, consideration shall be given to the microscopic crystalline structure *per se*, as well as whether it can achieve an unexpected technical effect."

The authors agree on this view. The provision on the assessment of inventive step of compounds in Part II, Chapter Ten of the Guidelines for Patent Examination (2010) is actually the specific embodiment of the "three-step method" applied to compound inventions. It not only reflects the close relationship between structures and functions or effects in the art, but also demonstrates the general R&D rules in the field of chemical pharmaceuticals. The crystalline form of a compound is much closer to the compound or its another crystalline form than a compound with a similar molecular structure. Therefore, regarding them as "structurally close compounds" in practice is reasonable from the perspectives of technology and legal logic. On this basis, the sure thing to do in the application of the "three-step method" is to place emphasis on whether the inventions of such kind have an unexpected use or effect.

4. Examination on whether the inventions related to crystalline forms of drugs achieve unexpected technical effects shall be condudcted mainly on the basis of evidence adduced by both parties

The judgment on whether the invention has an unexpected technical effect over the prior art shall be made on the basis of the analysis of the patent in suit and the prior art. In the invalidation proceedings, the ascertainment of factual findings inevitably depends on the evidence adduced by both parties.

(1) Provisions related to the burden of producing evidence

Article 64 of the Civil Procedure Law provides for the burden of producing evidence on the party concerned, i.e., "a party concerned shall be liable for providing evidence in support of his or her assertions" [19]. The burden of producing evidence and the burden of proof are two different expressions of the same concept in judicial and academic circles. [20] The burden of producing evidence used in judicial practice is to emphasize the provision of evidence, whereas the burden of proof commonly adopted in juridical theories is to prove the facts of a case by means of evidence. Article 90 of the Interpretation of the Supreme People's Court on Applicability of the Civil Procedure Law of the People's Republic of China incorporates the two terms into "the burden of producing evidence for proof", namely, "a party concerned shall produce evidence to prove the facts on which his or her own claims are based or on which its refutation of the opposite party's claims is based, unless otherwise prescribed by law. Where a party concerned fails to produce any evidence to prove the claimed facts or where the evidence so produced is insufficient to prove the claimed facts prior to the pronunciation of a judgment, the party having the burden of producing evidence for proof shall be liable for unfavorable consequences." [21] This interpretation intends to convey two meanings: in the sense of behaviour, the party concerned has the burden of producing evidence for proof, that is, "the burden of proof always lies with him who alleges"; and in the sense of consequences, the evidence produced by the party concerned shall be sufficient to prove the existence of the facts to be proved, or if the evidence cannot be produced or is insufficient to prove the existence of facts to be proved which the party concerned asserts, the party concerned who bears the burden of proof shall take the adverse consequences.

(2) Allocation of the burden of proving unexpected technical effect in invalidation cases related to crystalline forms of drugs

The above-mentioned provision on the burden of proof is applicable to civil proceedings, as well as invalidation proceedings. In the cases concerning the invalidation of inventions related to crystalline forms of drugs, generally

speaking, where the petitioner adduces the prior art evidence to prove that the compound itself is a known compound, whether the patent in suit has achieved an unexpected technical effect depends on whether both parties have fulfilled their respective burden of proof.

First, account shall be taken of whether the patentee's evidence is sufficient to prove the technical effect of the patent in suit. If the patentee fails to prove the technical effect of the patent in suit, it means that the contribution made by the invention in suit to the prior art only lies in the formation of the crystalline form or salt crystal of the known compound. Under such circumstances, any petitioner's evidence proving that the compound is known in the prior art may deal a fatal blow to the inventive step of the patent in suit. As a result, the patentee has to bear the adverse consequences caused by its failure to provide evidence in support of the technical effect of the patent in suit.

Second, where the patent in suit provides corresponding data demonstrating that the patent has achieved certain technical effects in one or several aspects (such as stability, hygroscopicity, bioavailability), consideration shall be given to whether the petitioner's evidence is sufficient to prove the status of prior art (including a combination of prior art documents). If the petitioner's evidence for proving the prior art status is insufficient to enable those skilled in the art to determine the technical state or level of the prior art, the petitioner usually bears the adverse consequences for failing to produce evidence. The petitioner's evidence for proving the prior art status shall prove not only the state or level of the prior art, but also the scope that can be expected by those skilled in the art based on the state or level of the prior art, i.e., the scope in which the patent in suit is obvious over the prior art. If the petitioner's evidence is insufficient to prove that the patent in suit is obvious over the prior art, the petitioner shall also bear the adverse consequences for failing to produce evidence.

Finally, it is necessary to further observe whether the patentee has made a good rebuttal against the evidence produced by the petitioner, that is to say, whether the patentee has provided sufficient evidence to prove the patent in suit is non-obvious over the prior art. If the patentee fails to produce evidence to overturn the petitioner's request for determining the patent in suit as obvious over the prior art, the patentee shall bear the corresponding adverse consequences.

The above examination rationale can be simply represented in Fig. VII as follows.

(3) The practices of allocation of the burden of proof in invalidation cases concerning crystalline forms of drugs

The allocation of the burden of proof in invalidation cases concerning crystalline forms of drugs is reflected in some invalidation decisions concluded recently.

(a) The patent in suit recites no data concerning technical effects

In the patent invalidation case of "Nintedanib Monoethanesulfonate" [22], the patent in suit differs from Evidence 1 in that the patent in suit seeks to protect a nintedanib monoethanesulfonate hemihydrate crystal, whereas Evidence 1 is directed to nintedanib in the form of free alkali. Upon examination, it was found that Evidence 1 discloses not only

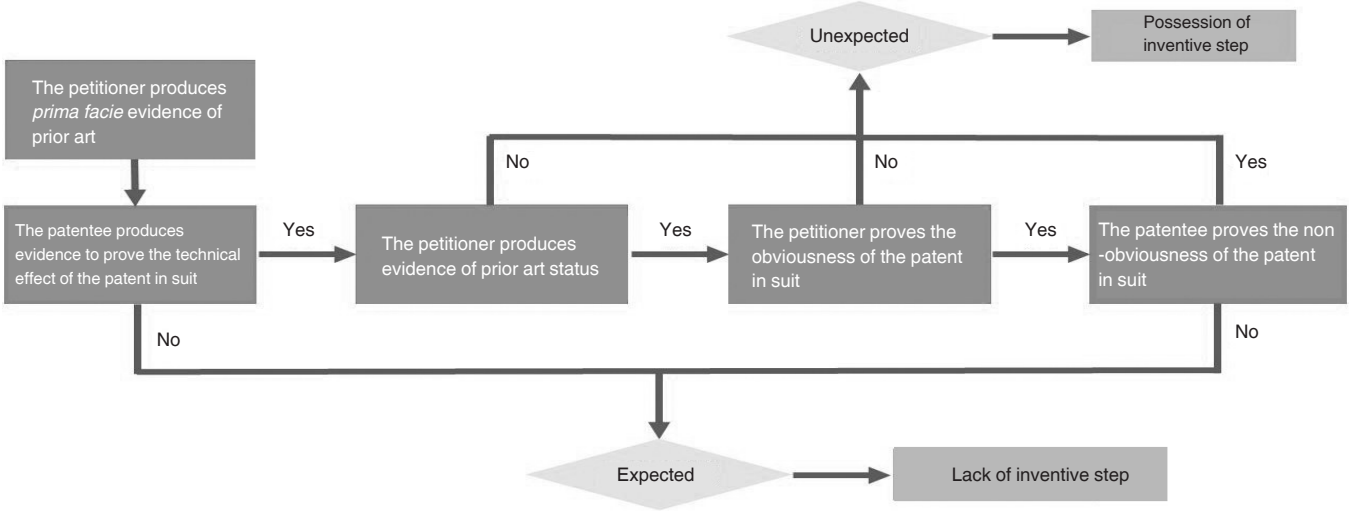

Fig. VII Flowchart setting out the allocation of the burden of proof on both parties

nintedanib in the form of free alkali, but also nintedanib mesylate, Evidence 2 discloses that salt formation is usually used to change the water solubility and hygroscopicity of free alkali compounds, and Evidence 7 discloses that methanesulfonic acid and ethanesulfonic acid are similar in properties and alike in acidity. The patent in suit only generally describes, in the description, that the crystalline pharmaceutical has high pharmacological efficacy, good crystallinity and low amorphization during grinding and compression processes, no hygroscopicity, and is easily soluble in a physiologically acceptable solvent. The description recites the DSC diagram, X-ray powder diffractogram and diffraction data, and unit cell parameters of the crystal, as well as the method for preparing free alkali and monoethylsulfonate crystal, with no experimental data indicating the high pharmacological efficacy of the claimed monoethylsulfonate crystal, or other properties like stability, hygroscopicity and solubility. The Invalidation Decision stated that the technical effects of the patent in suit, such as high pharmacological activity, non-hygroscopicity and high solubility are not proved by the description, and the patentee did not produce other evidence to testify the technical effects, so those skilled in the art are unable to expect that the patent in suit can achieve such technical effects based on the evidence on file. Under such circumstances, the contribution that the patentee has made to the prior art is merely to salt and crystallize nintedanib in the form of free alkali, which is strongly desired and has been taught in the prior art. Hence, in view of Evidences 1, 2 and 7 furnished by the petitioner, the patent in suit was eventually declared invalid due to lack of inventive step.

(b) The petitioner's evidence weakly proves the prior art status

In the patent invalidation case of "Sarpogrelate Hydrochloride" [23], the patent in suit seeks to protect a form II crystal of sarpogrelate hydrochloride. The description of the patent in suit recites that the product prepared by the prior art is actually a mixed crystal (SPG). By means of specific experimental data, the description shows that the form II crystal is chemically stabler than the SPG in the prior art. The petitioner submitted Evidence 2 as the closest prior art, which provides no information about sarpogrelate hydrochloride like its preparation and stability except for sarpogrelate hydrochloride being a white crystalline powder and the melting point thereof. The Invalidation Decision insisted that "those skilled in the art cannot know the stability of sarpogrelate hydrochloride from Evidence 2, and are unable to repeat the experiments of Evidence 2 to verify the crystalline form and chemical stability of the product obtained even if those skilled in the art (including the patentee) read through Evidence 2. Under such circumstances, if the inventive step of the present patent is negated just because of lack of evidence directly proving the technical effect of the present patent over Evidence 2, it is obviously stuck in the logical misunderstanding that cannot be justified, and imposes the unfulfillable responsibility and burden on the patentee. In addition, Evidence 3 to Evidence 5 used by the petitioner to assess the inventive step of the patent in suit in combination with Evidence 2 also fail to provide any teaching that the form II crystal of sarpogrelate hydrochloride demonstrates better chemical stability than the mixed crystal. Therefore, the petitioner's allegation that the patent in suit does not possess inventive step is untenable.

(c) The petitioner's evidence is insufficient to prove that the patent in suit is within the expectation of those skilled in the art.

In the patent invalidation case of "Plinabulin" [24], the patent in suit seeks to protect a plinabulin monohydrate in a crystalline form. The description of the patent in suit recites nine crystalline forms of plinabulin, wherein Form I is plinabulin monohydrate and Form III is the anhydrous form of plinabulin. The experimental data provided in the description show that Form I exhibits better solubility than Form III in the kolliphor and propylene glycol solvent systems, and is the most stable polymorph as compared with other polymorphs and non-hygroscopic in a highly humid environment. The petitioner alleged to assess the inventive step of the patent in suit based on Evidence 2 in conjunction with Evidence 3. Evidence 2 discloses a plinabulin compound, which involves neither the research and improvement of crystalline forms, nor the preparation method, identified data and performance of hydrates. It only schematically shows water molecules in Fig. 40 (see Fig. VIII below).

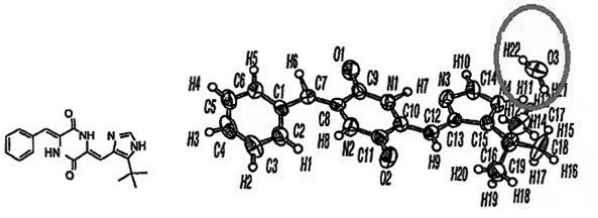

Fig. VIII The structural view of the plinabulin compound in Fig. 40 of Evidence 2

Through comparison, claim 1 of the patent in suit was found to be distinguishable over Evidence 2 in that claim 1 defines the 2θ value of the plinabulin monohydrate crystal, whereas Evidence 2 only discloses plinabulin and schematically shows water molecules in Fig. 40. In view of the experimental data concerning the technical effect as recited in the description, the technical problem actually solved by the patent in suit over Evidence 2 is to improve the solubility of plinabulin in a specific solvent system, and meanwhile empower it with better stability and non-hygroscopicity. The Invalidation Decision concluded that those skilled in the art cannot determine whether the water molecule exists in the unit cell based on Fig. 40 of Evidence 2, nor can they anticipate, in light of Evidence 2 and Evidence 3, the plinabulin monohydrate crystal in a specific crystalline form as disclosed in the patent in suit will have higher solubility (total solubility) than anhydrous plinabulin in a specific solvent system, and meanwhile exhibit better stability and non-hygroscopicity. Considering that the petitioner's evidence is insufficient to show that the patent in suit is expectable by those skilled in the art, the petitioner's allegation that claim 1 lacks inventive step over Evidence 2 in conjunction with Evidence 3 is untenable.

(d) The counter-evidence provided by the patentee is insufficient to overturn the petitioner's preliminary conclusion of obviousness of the patent in suit

In the patent invalidation case of "apatinib" [25], the patent in suit seeks to protect the crystalline form A of apatinib mesylate, and Evidence 6, which is taken as the closest prior art by the petitioner, discloses the solid form of an apaitnib compound. The patent in suit differs from Evidence 6 in that Evidence 6 does not specify the crystalline form of the product. According to the experimental data recited in the description of the patent in suit, there is no obvious difference in chemical properties and stability between the crystalline form A and the counterpart (namely, the crystalline form prepared by Evidence 6), and they are substantially identical in terms of solubility. The Invalidation Decision concluded that the technical problem actually solved by the patent in suit over Evidence 6 is to provide a different crystalline form with better stability. On the one hand, "although Evidence 6 does not focus on the crystalline form of apatinib mesylate or conduct studies on the crystal properties", it can be known under the guidance of Evidence 9, which says "crystalline substances meeting the requirements for pharmaceutical stability can become ideal preponderant crystalline forms of drugs", that "the study of polymorphism and the selection of preponderant crystalline forms of drugs are requisite research projects for solid oral pharmaceuticals. Where Evidence 6 has disclosed one crystalline form of mesylate, those skilled in the art have the motivation to conduct research on polymorphism thereof." On the other hand, in the presence of the crystalline forms of apatinib that are known in the prior art, "seeking for preponderant crystalline forms of drugs that meet the drug production and use demands is a common motivation (of those skilled) in the art, and the crystalline form A of the present patent having a better crystalline stability does not exceed the expectation of those skilled in the art." The patent in suit cannot be deemed as inventive in the event that the counter-evidence submitted by the patentee cannot prove that the patent in suit achieves an unexpected technical effect over the prior art.

The above four cases are merely examples reflecting the rationale for judging unexpected technical effects in recently concluded invalidation decisions concerning crystalline forms of drugs. Although the kernel of each case varies due to different case details, they, as a whole, imply a consistent judging rationale as analyzed in Item 4.(2) "Allocation of the burden of proving unexpected technical effect in invalidation cases related to crystalline forms of drugs". Furthermore, in comprehensive consideration of the historical archives of the 66 invalidation cases, this judging rationale basically has never been changed.

III. Conclusion and suggestions

If patents related to active compounds are basic patents, then invention patents related to crystalline forms of drugs are subservient patents invented on the basis of active compounds. Under some circumstances, whether a compound can end up with the crystalline form of a drug is somewhat unpredictable. But undeniably, researches on crystalline forms of drugs in the pharmaceutical industry have been increasingly deepened to gradually reveal many universal findings. Therefore, the examination criteria for assessing inventive step in invalidation proceedings should, on the one hand, make sure that real contributions to the prior art are protected as appropriate and, on the other hand, prevent so-called "micro-inventions", which are obtained only by conventional crystallization means and expectable by those skilled in the art, from patent protection, which will

otherwise impair the interests of the public.

Firstly, as for examination on the inventive step of inventions related to crystalline forms of drugs, a consistent understanding is that there exist in the prior art a strong R&D desire and motivation for preparing a known compound into a crystalline form, the crystalline form of the claimed compound is structurally close to the compound itself or its polymorph, and the key to judge whether the patent in suit possesses an inventive step lies in whether the patent in suit achieves an unexpected technical effect. If the invention is, in nature, directed to crystallization or salt crystallization of a known compound, both parties should produce evidence with the focus on whether the invention has an unexpected technical effect in the invalidation proceedings. Repetitive proof of a desire or inspiration for crystallization or salt crystallization in the prior art seems to be of no avail.

Secondly, the presentation of detailed experimental data in the description to show the technical effect of the invention related to the crystalline form of a drug is an important factor that qualifies such an invention for a patent possessing an inventive step. The technical effect of the invention related to the crystalline form of a drug can be expressed by either biological properties related to pharmaceutical use or physiochemical properties related to pharmaceutical preparation. If the technical effect demonstrated by the experimental data in the description is expectable by those skilled in the art, the patent in suit can hardly be determined as inventive. Although experimental data later supplemented are also a route to prove the inventive step of the invention, they, if possible, have to satisfy the essential requirements of "disclosure in exchange for protection" and "being derivable from the application documents as originally filed", and pass the strict scrutiny for admissible evidence, which may unavoidably give rise to the loss of opportunities. [26]

Finally, the judgment on whether the technical effects of inventions related to crystalline forms of drugs largely depends on the evidence adduced by both parties. The more detailed the experimental data for proving the technical effect of the patent in suit as provided by the patentee in the description, the greater the burden and difficulty that the petitioner has in proving that the patent in suit lacks an inventive step. On the contrary, if the description fails to provide any experimental data related to the technical effect, it is likely that the petitioner's proof of the compound being known in the prior art suffices to render the patent in suit non-inventive.

All in all, patents related to crystalline forms of drugs are more general than special. The most intuitive feeling the authors have about the investigation of such patent invalidation cases is that the grant of patent for such inventions is not simply premised on the disclosure of conventional technical details, like crystallization or salt formation. Detailed experimental data indicating an unexpected use or effect the patents have over the prior art is a must. ■

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