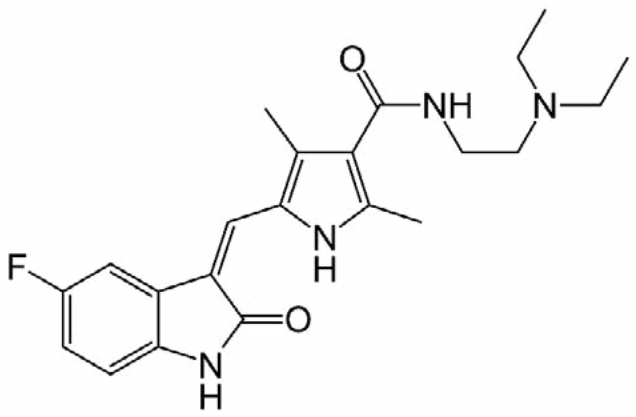
Crystal-form patents in China

Following the invalidation of sunitinib crystal-form patent in China, **Toby Mak** discusses the level of inventiveness required in China compared to the corresponding European patent opposition. He also looks at the trend of invalidation of crystal-form patents in various jurisdictions and provides some suggestions on how to increase the chances of surviving invalidation attacks against crystal-form patents.

Sunitinib patent invalidated in China – crystal-form patent facing difficulties on inventiveness

Sunitinib is a drug for treating cancers in the stomach, intestine, kidney and pancreas, marketed by Pfizer under the name Sutent®. Below is the chemical structure of Sunitinib.



There are three US patents directed to Sutent® according to the US Orange Book:

1) US6573293 has a Markush claim, with claim 7 specifically directed to sunitinib itself;
2) US7125905 is directed to the L-malate salt of sunitinib, which is the exact compound in the drug Sutent® on the market; and
3) US7211600 is directed to the method of treatment by sunitinib.

The CN family member of US6573293 and US7125905 is CN1329390C ('390, ZL 01807269.0), whose full term expired on 15 February 2021.

US7211600 does not have a CN equivalent.

Similar to many other drugs, there are more patents covering the drug Sutent®. One of these is CN100439360C ('360, ZL 02815892.X, CN family member of US7435832 and EP1419151), with the following details:

- The claims are directed to a specific crystal form of sunitinib malate (with specific powder X-ray diffraction peak values), and the method of making such crystal form.
- The full term expiry is 13 August 2022.
- This '360 was invalidated by the Re-examination and Invalidation Department (RID, formerly known as the Patent Re-examination Board) of the China National Intellectual Property Administration on 2 April 2021.
- The invalidation petitioner was CSPC Pharmaceutical Group Co., Ltd. (CSPC), a Chinese pharmaceutical company with assets of RMB(¥) 49 billion (about £5.5 billion), and over 27,000 employees.
- In 2019, CSPC tried but failed to invalidate the above '390 directed to the chemical structure of Sutent® on the basis of obviousness. The basis of the RID's (the Patent Re-examination Board back then) ruling was that the structure of claim 1 of '390, which was a Markush claim, is substantively different from the closest piece of prior art WO99/61422A1. Specifically, in claim 1 of '390, R6 is -C(O)N(R11)(CH_2)$_n$R12, which was not disclosed by WO99/61422A1.
- The invalidation decision of '360 in China appears to be pending an appeal at the Beijing IP Court.

Opposition of the corresponding EP1419151B of '360

The corresponding EP1419151B of '360 survived after opposition. It was attacked on various grounds:

- Added matter –unsuccessful attack on minor wordings such as 'about' and 'pharmaceutical'.
- Sufficiency –unsuccessful attack that the specification provided information on how to obtain the crystal at issue.
- Priority – It was argued that the inventor as the applicant was not identified when the priority US provisional application was filed. This allegation was dismissed as the patentee proved that such information could be supplied after filing in the US without affecting the provisional application date. On the other hand, the attack on the main request of the patentee against the differences between the numeric values of two diffraction angles in the priority document from those in claim 1 (specifically due to rounding up of values at the first decimal in claim 1) was successful.
- Novelty –unsuccessful attack that the references did not mention any solid form of L-malic acid salt of sunitinib, which is the subject of the patent, or its synthetic method.
- Inventive step – While the main reference did mention L-malic acid salt of sunitinib, no preparation and characteristics of such L-malic acid salt of sunitinib were described. Because of this, the attack was unsuccessful on the basis that the prior art did not provide a concrete chemical entity to modify and to compare to solve the technical problem of bad filterability of the crystals of the free base of sunitinib, which was further supported by post-filing data submitted by the patentee of repeating an example in the main reference. Such post-filing data showed that the free base crystal of sunitinib were small with poor filterability in gram and kilogram scale. By contrast, the crystal form I of L-malic acid salt of sunitinib in the claims was shown by the post-filing data to have good filterability with full compatibility with commercial manufacturing processes. The specification also recited that this crystal form I has good solid-state stability, low hygroscopicity, and good solubility. The post-filing data was found by the EPO opposition division to be 'convincing and does not have any doubt that the skilled person can repeat these experiments using common general knowledge'.

Invalidation of '360 in China

Claim 1 of '360 is:

1. Anhydrous crystal of malic acid salt of N-[2-(diethylamino)ethyl]-5-[(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide, wherein the crystal has characteristic diffraction peaks at .39 11.90, 13.16, 15.92, 16.79, 17.18, 19.40, 20.30, 21.26, 21.68, 22.13, 22.91, 24.17, 25.46, 26.06, 26.96, 27.56, 32.27, 32.93, and 34.43 degrees two-theta in a powder X-ray diffraction pattern.

The other independent claims either refer to claim 1 or recites the diffraction peaks above.

In the 2021 invalidation of '360, the crystal-form patent of Sutent®, the RID's invalidation reasons were:

- Different from the EPO, the RID considered that the technical problem to be solved by the crystal form I of sunitinib in claim 1 was to provide a crystal form of a specific salt of sunitinib.
- Although FIG. 3 of '360 illustrated that 'The more crystalline polymorph, Crystal Form I is of low hygroscopicity, absorbing less than 0.5% water across the 0-90% relative humidity range. The less crystalline polymorph, Crystal Form II, is very hygroscopic, absorbing over 15% water over the 0-90% relative humidity range.', and Fig. 4 illustrated that 'the two crystal forms are monotropic, although degradation occurs after the crystals melt. Monotropism is confirmed by the conversion of Crystal Form II to Crystal Form I in a room temperature slurry', the RID stated that according to WO01/45689A2, a person skilled in the art has the motivation to select a sunitinib compound and acid including malic acid to form a pharmaceutically acceptable salt based on its teachings to further optimise the properties of the pharmaceutical compound [Note: However, WO01/45689A2 did not mention anything related to hygroscopicity.]
- It is well known in the art that salting organic bases could improve physical and chemical properties, and the corresponding selection principles and methods are also well known, while amine salts are generally crystalline.
- It is also obvious to a person skilled in the art to routinely select a possible suitable salt form and obtain a specific crystal form combined with common knowledge in the art.
- Based on common general knowledge evidence in the art (two Chinese and two English review references on the topic of chemical pharmaceuticals), how to select an appropriate salt form and further screen a crystalline form for pharmaceutical compounds, and decision analysis method for salt form screening, are known in the art.
- Regarding good solid-state stability and low hygroscopicity of crystal form I of '360, the RID stated the following:
  - The data in the specification 'lack proof', and even if such data was considered, such did not exceed the

expectation of the general requirements for drugs.
  - Such improved properties could be expected, as 'If a crystal type has a higher crystallinity than another crystal type, it usually means an improvement in a series of properties such as higher melting point, more regular crystal grains, better stability and less moisture absorption, and so on.' As such, such improvements could be expected by a person skilled in the art.
- Regarding good solubility of crystal form I of '360, while the RID agreed that formation of salt crystals would reduce the solubility of the salt, such depends on the specific combination of free base, salt type and crystal form. As the solubility of the malic acid salt of sunitinib itself was not provided and compared with its crystal form I, existing data could only show that the improvement in solubility is due to the formation of the malic acid salt, but not necessarily due to the crystallization to form crystal form I.
- Regarding ease of filtration in large-scale operations, the counterevidence submitted by the patentee, which was the post-filing data submitted at the opposition of EP1419151B, was accepted and considered by the RID, although such was not contained in the original disclosure. The RID also stated that during the development of the crystal form I in claim 1, attention had been paid to the change in the particle size of sunitinib after salt and crystal formation, and the influence on the filtration in large-scale operations during the research process according to the recitation in the original disclosure. However, the RID stated that 'especially for high melting point crystal, such apparently has the advantage of more regular grains than the amorphous state or the low melting point crystal, and therefore the advantage of being easier to handle in the preparation process is also obvious.'
- Based on the above, the RID considered that the advantages of crystal form 1 of sunitinib including good solid-state stability, low hygroscopicity, good solubility, and ease filtration in large-scale operations are all advantages that could be expected by a person skilled in the art. As such, crystal form 1 of sunitinib is only an obvious selection that could be made by a person skilled in the art using known techniques.

Observations

Acceptance of post-filing data

It is encouraging to see that the RID accepted and considered the post-filing data, evidencing that post-filing data is now acceptable in China. Although the allowance of post-filing data has been specified in the Chinese Patent Examination Guidelines since 2017, it is the general notion that submission of post-filing data is not allowed in China (partly due to general unacceptance among the examiners, and many examiners will try to pick the smallest problem to reject the post-filing data, like irrelevance, not exact correspondences with the conditions in the original disclosure, and so on). This invalidation decision shows the opposite. It is not clear, however, whether the RID acceptance is affected by the plain acceptance of such data at the EPO.

Formulation of technical problem

One key factor leading to the differences in the outcomes in Europe and China is the formulation of the technical problem:

- EPO – The provision of a further solid form of sunitinib which has improved filterability in large scale while having other good properties such as solid-state stability, good solubility and log hygroscopicity.
- CN RID – To provide a crystal form of a specific salt of sunitinib.

With the technical problem being set to be so general, and with the extensive knowledge in the art on crystallinity, the invalidation of '360 could be expected. Even improvement of filtration was determined by the RID to be expectable, as better crystallinity is expected to produce larger crystals that are easier to be filtered.

Technical effects of new crystal forms that could be expected

The RID may have a point that the following are technical effects that could be expected from a new crystal form with higher crystallinity:

- Better stability
- Higher melting point
- Larger crystal grain, resulting in improved ease of filtration

On the other hand, improved solubility and less moisture absorption (reduced hygroscopicity) may not be directly linked to higher crystallinity of a new crystal form. It is not clear what the basis of the RID's decision in '360 is; how reduced hygroscopicity is directly linked to higher crystallinity? I would not be surprised if this point was used in the appeal against the invalidation decision of '360.

Regarding improved solubility, the RID dismissed this point on the basis that 'the solubility of the malic acid salt of sunitinib itself was not provided and compared with its crystal form I.' It appears that if the patentee could provide the solubility of the malic acid salt of sunitinib itself for comparison, this point may be considered, which again may be used in the appeal.

Crystal-form patents face high invalidation risks in China

Invalidation decisions of crystal-form patents in the last ten years:

Invalidation results				
Jurisdiction	Totally invalid	Partially valid	Totally valid	Decision not reached
China	19	7	4	17
European Patent Office (EPO)	30	3	48	25
US	2	3	3	2
Japan	1	0	0	0
India	3	0	6	3
South Korea	13	2	5	28

The total number of invalidation attempts in the US, Japan and India may be too few to be of statistical significance. While at the European Patent Office (EPO) there appears to be a higher chance to maintain the validity of a crystal-form patent, the opposite is true for China and South Korea. I have reviewed other relevant Chinese decisions and observed that the principles in the invalidation decision is generally applied in China. That is, relying only on improved qualities related to stability, for example operability, portability, storage, and so on (CN ZL 00802360.3; ZL 200610002509.5) could lead to the invalidation of a granted crystal-form patent. Merely providing an alternative crystal form is almost certain to be not good enough (as a crystallographer myself – while studying for my PhD – I have to admit making new crystal forms is a lot easier than before).

On the other hand, if the improved property of the new crystal form may be argued to be not directly related to the increased crystallinity, for example improved solubility, delivery, efficacy, then the chance of grant and/or surviving through invalidation challenge could be much improved, at least in China. In such case, however, proper comparison data should be provided, preferably in the specification. In the case of '360, not only the comparison data on improved solubility between malic acid salt of sunitinib and the free base sunitinib should be provided, but also the comparison data between amorphous malic acid salt of sunitinib and crystal form I should also be provided.

It appears that China has a higher inventiveness standard than other jurisdictions. Specifically, in order for a technical effect achieved by an invention to be unexpectable, such effect should not be known to be directly related to the change of property of the invention.

Special thanks to Darts-IP for providing invalidation decision data of the last ten years for China, EPO, the US, Japan, India, and South Korea. Author: Toby Mak, Tee & Howe Intellectual Property Attorneys ©2022