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Media Center > Insights > Patent

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CNIPA's new tweak over inventiveness assessments of co-solvent compound crystals

Wu Xiaohui, October 15, 2024, first published by MIP

Wu Xiaohui of Wanhuida Intellectual Property explains why a recent decision on inventiveness assessments of co-solvent compound crystals heralds a significant shift in focus by the CNIPA, with implications for pharmaceutical patent strategies

The invention patent for drug crystal forms has been a key cog in chemical products research and a critical building block in the patent portfolio of pharmaceutical corporations. Invalidation decision No. 580021 made by the CNIPA on June 21 2024 offers a glimpse into the agency's shift of focus and its latest inventiveness assessment practice regarding co-solvent compound crystals, which merits analysis and dissection.

Case summary

AstraZeneca owns patent No. 200780024135.X (the Patent at Issue), which relates to the S-propylene glycol hydrate of Dapagliflozin, a prescription drug for type 2 diabetes. On August 9 2023, Nanjing Huaxun Intellectual Property Consulting Co., Ltd. (the Petitioner) initiated an invalidation action, mainly challenging the inventiveness of the Patent at Issue, among others. On June 21 2024, the CNIPA issued the aforesaid invalidation decision to maintain the validity of the patent.

Claim 1 of the Patent at Issue sought to protect the crystalline structure of the compound in formula Ia (i.e., S-propylene glycol hydrate of Dapagliflozin) and specified the powder X-ray diffraction pattern.

The Petitioner cited multiple pieces of evidence – including the Dapagliflozin L-phenylalanine complex disclosed in evidence 1 or 2 as the closest prior art, combined with evidence 4–8, 16–18, and common knowledge – to argue that claim 1 lacks inventiveness. Evidence 9-11 was adduced by the Petitioner for the purpose of proving common knowledge.

The panel started with identifying the difference between claim 1 and evidence 1, finding that claim 1 seeks to protect the crystalline structure of formula Ia and specifies the powder X-ray diffraction pattern, while evidence 1 discloses the Dapagliflozin L-phenylalanine complex form. Based on the distinguishing features, the technical problem actually solved by claim 1, relative to evidence 1, is to provide the crystalline structure of Dapagliflozin shown in formula Ia. The key issue in this case could be boiled down to whether the evidence on record suffices to substantiate that for the Dapagliflozin L-phenylalanine complex, it is obvious to introduce S-propylene glycol and water to form a co-solvent compound.

The panel then parsed through the evidence submitted by the Petitioner, concluding that:

- Evidence 1 discloses the Dapagliflozin L-phenylalanine complex. However, due to the different chemical structures and physicochemical properties of L-phenylalanine and propylene glycol, a person skilled in the art would be unable to envisage forming a solvent compound of Dapagliflozin with propylene glycol, based on this evidence.
- Although evidence 4 highlights the advantages of propylene glycol solvent compounds, the enumerated compounds differ significantly in terms of structure and properties from Dapagliflozin. On top of that, evidence 4, which makes no mention of S-propylene glycol solvent compounds, fails to provide sufficient technical guidance.
- Evidence 5–8 involves drugs that share no similarities in chemical structure and physicochemical properties with Dapagliflozin, thus offering no technical inspiration.
- Evidence 9–11 pertains to general research methods for polymorphs and does not involve specific

Time： Oct 15 2024

applications of S-propylene glycol solvent compounds, thus providing no technical guidance.

As regards the inventiveness assessment, the panel delved into the potential industrial value generated by the Patent at Issue. The panel opined that the differential scanning calorimetry thermal analysis diagram in the description of the patent shows that the endothermic peak of the (S)-PG crystalline structure of formula Ia is at 71.43°C, while that of the (R)-PG crystalline structure of formula Ib is at 52.29°C.

These results indicate that the (R)-PG crystalline structure of formula Ib may melt at a temperature that is slightly above room temperature or during the drug formulation process, leading to uncontrollable drug formulation quality. This is a technical problem that needs to be addressed at the industrial application level. In contrast, the endothermic peak of the (S)-PG crystalline structure of formula Ia, as involved in claim 1, is markedly higher so as to solve the above technical problem and thus possesses industrial application value.

Therefore, even if a person skilled in the art uses propylene glycol to prepare a Dapagliflozin solvent compound, they would not conceive that S-propylene glycol, as opposed to R-propylene glycol, could solve the technical problems present in industrial applications.

Ultimately, the panel concluded that the technical evidence on record does not provide any technical guidance for the preparation of Dapagliflozin as an S-propylene glycol hydrate. The Petitioner's argument that claim 1 lacks inventiveness, based on evidence 1 disclosing the Dapagliflozin L-phenylalanine complex as the closest prior art, was untenable.

Comments on the CNIPA's inventiveness assessments of co-solvent compound crystals

This case is very intriguing, as it diverges from the CNIPA's past practice.

The CNIPA used to assess the inventiveness of drug crystal form inventions by taking into account:

- Whether there is technical teaching in the prior art; and
- Whether the patent at issue has achieved unexpected technical effects compared with the prior art.

Based on such methodology, the panel tends to believe that there is a research need and technical teaching for crystallisation and recrystallisation of known compounds in the prior art. As the crystal form of a compound and the compound per se, as well as a new crystal form and the known crystal forms thereof are deemed structurally similar, the presence of inventiveness would hinge on whether the claimed drug crystal form has unexpected technical effects. Solvates, as pseudo-polymorphs, are also subject to similar examination criteria.

It is therefore quite creative that the subject decision – based on the disclosed content of the evidence, especially the differences in structure and physicochemical properties between the compounds involved and the crystal form compound at issue – shifts its focus back to whether the prior art provided technical teaching for preparing Dapagliflozin as an S-propylene glycol hydrate, rather than whether the Patent at Issue achieved unexpected technical effects. Specifically, in assessing the common knowledge evidence, the decision found that it only involves general research methods for polymorphs but fails to include the specific application of S-propylene glycol solvates to drug compounds to improve certain properties.

The panel therefore concluded that a person skilled in the art could not obtain technical teaching from the cited common knowledge, and the prior art did not directly indicate a general motivation to form this crystal.

This decision provides an alternative examination route, which could be attributable to the structural differences between the Dapagliflozin S-propylene glycol solvate and its compound, as well as the industrial value generated therefrom. In a nutshell, the very core of an inventiveness assessment of crystal form patents lies in the presence of specific and clear technical teaching in the prior art, which is to be ascertained by factoring in the disclosures made by such prior art.