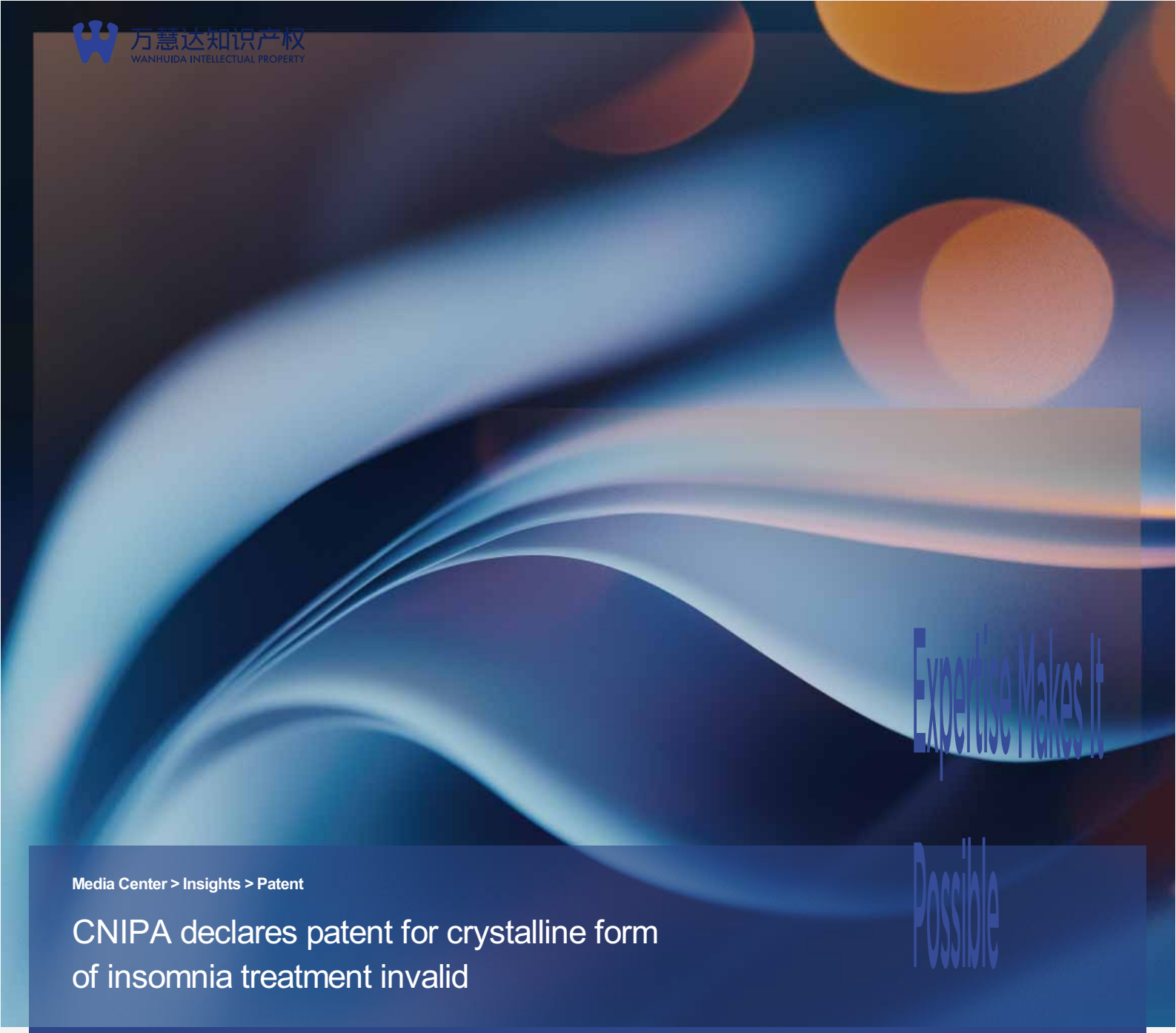

CNIPA declares patent for crystalline form of insomnia treatment invalid

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CNIPA declares patent for crystalline form of insomnia treatment invalid

Yue Guan, March 10 2025, first published by MIP

On February 25 2025, the CNIPA issued an invalidation decision, No. 584735, declaring the patent for the crystalline form of the drug lemborexant invalid.

Lemborexant, also known by its trade name Dayvigo, was developed by Eisai Co. Ltd. (Eisai) and is clinically used to treat insomnia. First approved by the US Food and Drug Administration in December 2019, lemborexant has been marketed in the US, Japan, Canada, Australia, and Hong Kong. The marketing application that Eisai filed in mainland China in January 2024 is expected to be approved in 2025. The global sales revenue of lemborexant reached $2.6 billion in 2023.

The patent at issue – which was initially owned by Crystal Pharmaceutical (Suzhou) Co., Ltd. – changed hands to Bergen Pharmaceutical, LLC (Bergen) in May 2021. The invalidation request was filed by the original drug company, Eisai (the petitioner), on June 19 2024, presumably because the patent portfolio built by the patentee around lemborexant would impede Eisai's exploitation of lemborexant in China. The invalidation action therefore aimed to remove the patent at issue and to clear the path for Eisai's marketing of lemborexant in China.

The invalidation proceeding

Eisai's invalidity action is mainly predicated on the following grounds:

The claimed crystalline is disclosed by the prior manufacture process patent of lemborexant (Evidence 1), and the experiment report (Evidence 2) indicates that the crystalline of the product obtained by following the prior process is identical to the crystalline claimed by the patent. That is, the claimed crystalline is disclosed by the implied contents of Evidence 1 that can be derived directly and unambiguously from the disclosure by a person skilled in the art. The crystalline thus does not possess novelty when compared with Evidence 1.
Leaving aside the facts proven by Evidence 2, the patent at issue failed to prove the following: (i) lemborexant has other crystalline forms, and (ii) there are unexpected technical effects created by the crystalline. Therefore, the claimed crystalline does not possess an inventive step over Evidence 1.

As counterevidence, Bergen filed an experiment report to show that the claimed crystalline is not necessarily obtained by following the process in Evidence 1 and pointed out that the synthesis steps to produce lemborexant in Evidence 1 are not strictly followed as described in Evidence 1. Bergen also adduced evidence to prove that lemborexant has an amorphous form, underlining that the hygroscopicity and in vitro dissolution rate of the crystalline are unexpected when compared with the amorphous form. Based on these reasonings, Bergen argued that the crystalline has not been disclosed and is non-obvious over Evidence 1.

The CNIPA's methodology in reaching its conclusion

The CNIPA delved into the patentability assessment of the crystalline using a layered approach.

First, the CNIPA determined that Eisai has demonstrated, by a preponderance of evidence, that following the procedures set forth in Evidence 1 will necessarily and inevitability result in the formation of the claimed crystalline, and the claimed crystalline does not possess novelty.

Second, the CNIPA determined that even without Evidence 2, based on the description of the patent at issue, it cannot be concluded that the crystalline has unexpected technical effects when compared with the amorphous

form. The CNIPA therefore concluded that the crystalline does not possess an inventive step.

With respect to novelty, the CNIPA deemed that experiments to follow the steps disclosed in the prior art could be appropriately detailed by a person skilled in the art based on their conventional cognition, and it would be neither scientific nor reasonable to carry out experiments in a manner that is completely consistent with the methods described in the prior literature.

The CNIPA found Evidence 2 to be preponderant, compared with the counterevidence. Specifically, the CNIPA found that the differences between the experiment disclosed by Evidence 2 and Evidence 1 are mainly related to the compound synthesis process, which has no material effect on the subsequent solid precipitation generating the crystalline. Therefore, the argument that Evidence 2 cannot represent the result of Evidence 1 has no merit.

In addition, the CNIPA held that the patentee's experiment failed to follow the steps of Evidence 1 due to the following reasons:

The colour of the key raw material 'acid' is light orange, and the nuclear magnetic resonance spectrum shows the existence of certain impurities, which may cause side reactions and thus affect the product composition;
The experiment does not include the important steps of heating to dissolve the reaction mixture and then cooling in the precipitation procedure, which may influence the generation of the crystalline; and
A solid form is not obtained by adding the poor solvent n-hexane to the solution, corroborating that Evidence 1 could not be successfully replicated.

In assessing the inventiveness, the CNIPA opined that:

Bergen failed to prove that lemborexant prepared by Evidence 1 is another crystalline form; consequently, unexpected technical effects of the crystalline can only be evaluated by comparison with the amorphous form;
It can be expected that the structural characteristics of the crystalline and amorphous forms dictate the improvement of physical and chemical stability, compressibility, grinding stability, flowability, and solvent residue of the crystalline compared with the amorphous form; and
Regarding the better hygroscopicity and in vitro dissolution rate of the crystalline over the amorphous form, the patent did not describe the effects, and the patentee did not submit control experiments.

The implications of the CNIPA's decision

The CNIPA provides some guidance as to how experiment evidence should be scrutinised. In the invalidation decision, it explicitly states "in the absence of any questions raised by the patentee regarding the substantive content in Evidence 2 (except for the method different from Evidence 1), it would be insufficient if the panel were to exclude Evidence 2 from consideration, merely because the experimenters failed to appear in court for questioning."

This suggests that in assessing the authenticity of experiment evidence, the panel shall not only look into its formality, but also take into account any legitimate doubts raised by the adverse party over substantive matters, as well as the level of high probability of the evidence, so as to make a comprehensive assessment.

Also, the CNIPA applied the preponderance of evidence standard in reviewing the evidence furnished to underpin opposite conclusions regarding the same fact to be proven. For example, the panel did not stop short of negating the novelty of the crystalline based on Evidence 2; instead, it went farther to compare the probative force of the two experiment reports, making the obviousness conclusion of the crystalline more convincing. It stated that "compared to the differences in raw materials and experimental procedures between counterevidence 4 and evidence 1, the differences in filtration and other processes between evidence 2 and evidence 1 have little impact on the final experimental results, and will not substantially affect the crystallisation of lemborexant. Therefore, evidence 2 has a stronger probative force than counterevidence 4."

The decision sheds light on matters such as proving implicit technical contents of the prior art and inventiveness assessment for pharmaceutical crystalline inventions. Applicants could also take heed of the guidance offered by the CNIPA to refine their pharmaceutical patent filing strategy.