Featured Article

The 'Precision' Breakthrough of Chinese Medical Use Patents

— Examining Standards and Practical Strategies from the Perspective of 'Patient Subgroups'

As the era of 'one-size-fits-all' medication gradually fades, precision medicine has propelled drug innovation into a new arena of 'personalized medicine'. Traditional disease classification, based on gross anatomy and clinical manifestations, can no longer accommodate the fine segmentation of patient populations brought about by multi-dimensional biomarkers such as genes, proteins, and metabolites. However, China's patent examination has changed very little, and it still uses "indication" as one of the examination criteria, that is, only if it is recognized as a "new disease" can it open up patent protection space for personalized medicine.

In China, according to the guidelines for examination, claims to protect indications must be written as medicinal use claims in Swiss type, such as "use of compound X in the preparation of a drug for the treatment of Y disease". In such a claim, only the indication/disease and the characteristics related to preparing the drug (including active ingredients) are considered as technical features, while the characteristics related to use of the drug, such as the object of administration, the mode of administration, the route, the dosage and the time interval, are generally not recognized as having a limitation effect on the

claims. However, for patents that have discovered a specific patient subgroup with outstanding therapeutic effects, whether the patient subgroup can be recognized as a new disease or whether it has a limiting effect on the disease is not clearly stipulated in the guidelines. Therefore, it is a difficult point in examination practice and one of the most controversial topics in pharmaceutical industry. Through the following related cases, this paper not only presents examination yardstick for whether the patient subgroup has a limiting effect, but also provides a breakthrough route for pharmaceutical companies.

Case 1

Patient subgroups defined by physiological indicators

Application No. CN201480035471.4, Reexamination Decision No. 1348965, Decision Date September 5, 2023

Claim 1 of this patent relates to use of a peptide compound in the preparation of a drug for treating cancers of mammals with a white blood cell count (WBC) of less than 10,000/μL. D1 has disclosed the same peptide compound (CBP501) for cancer treatment but did not restrict the patient's white blood cell count (WBC) level.

The focus of this case is whether the restriction of the white blood cell count (WBC) constitutes a different disease.

The panel believes that a WBC < 10,000/μL is within the normal physiological range (for humans: 4,000-10,000/μL; some animals such as goats and horses are also within this range). Various factors can alter the number of white blood cells, and differences in white blood cell counts may only reflect the patient's physical condition at a certain time, rather than being a clear marker for disease classification. On the one hand, the white blood cell counts defined in the claims of this application are all within the generally accepted normal ranges in the field; on the other hand, the applicant has not provided evidence to show that the existing technology classifies diseases such as tumors based on white blood cell counts. The applicant has failed to demonstrate that the differences in WBC counts distinguish the disease defined in this application from that disclosed in D1. Therefore, the limitation of WBC count essentially only describes certain individual patients and does not correspond to clinically known indications. The response to CBP-501 caused by the different WBC counts is a factor that doctors need to consider in clinical medication processes, rather than a characteristic in the pharmaceutical preparation process. Hence, claim 1 lacks novelty.

Case 2

Patient subgroups defined by physiological indicators

Patent No. CN200980104713.X, Patent Invalidation Announcement Decision No. 568709, Decision Date: December 22, 2023

Claim 1 of this patent relates to use of Degarelix in the preparation of a drug for treating subjects with prostate cancer at the metastatic stage, wherein the treatment comprises an initial dose of 160-320 mg Degarelix and subsequently administering a maintenance dose of 60-160 mg every 20-36 days, wherein the subjects have a pre-treatment baseline serum alkaline phosphatase (S-ALP) level of approximately over 150 IU/L.

The panel holds that the limitations on the initial dose, maintenance dose, and administration frequency in claim 1 only relate to administration regime of the drug. In essence, they pertain to the specific methods of administering the drug to the human body, which does not have a direct and necessary correlation with the pharmaceutical preparation process. These limitations reflected in the drug administration process do not constitute technical characteristics of the use claim and is not limiting the claim.

The patent holder argues that the dual limitations in claim 1 with prostate cancer at the metastatic stage and the pretreatment baseline serum alkaline phosphatase level actually specify prostate cancer patients with bone metastases, which constitutes a new therapeutic application.

The panel opines that there is no evidence to prove that there is a consensus in the relevant technical field that the S-ALP indicator can be used to classify prostate cancer, nor is there evidence that prostate cancer patients with an average baseline S-ALP of 150 IU/L, 200 IU/L, or 300 IU/L belong to a new subtype of prostate cancer. On the contrary, there is evidence that healthy individuals and patients with other diseases can also have S-ALP levels reaching 150 IU/L, 160 IU/L, or even above 200 IU/L, indicating that S-ALP levels are difficult to use as a single indicator for prostate cancer classification. In the absence of definite evidence proving that, before the priority date of this patent, the relevant technical field acknowledged S-ALP baseline levels as a single indicator for prostate cancer progression, and as a single indicator to measure therapeutic effects, the changes in S-ALP levels after treatment in patients with metastatic prostate cancer for specific baseline S-ALP levels, as verified by this invention, belong to the analysis of physiological indicators during patient treatment, and do not define new indications nor characterize corresponding therapeutic effects, making it impossible to determine the inventiveness of the claim.

Author's Summarization

In the above two cases, although the examination conclusions denied the classification of indications based on physiological indicators, the panel made judgment based on evidence rather than simply rejection. By analyzing evidence from both positive and negative perspectives, the panel concluded that the recited physiological indicators cannot constitute a classification of indications.

Case 3

The pathological mechanism has not changed the indications.

Application No. 201710863043.6, Reexamination decision No. 310604, Decision date June 1, 2022.

Claim 1 of this application pursues protection of use of compound A or its pharmaceutically acceptable salts in preparation for normalizing the cartilage damage state in animals including treated mammals suffering from cartilage diseases, where the cartilage diseases are osteoarthritis associated with damage, injury, or impairment of articular cartilage.

D3 has disclosed compound A was used in Phase II clinical trials for osteoarthritis, but does not explicitly mention its effect on cartilage damage.

The key dispute in this case is whether the limitation 'normalizing the cartilage damage state' distinguishes it from the prior art. Is osteoarthritis associated with damage, injury, or impairment of articular cartilage a different form of osteoarthritis?

The panel holds that 'associated with damage, injury, or impairment of articular cartilage' in claim 1 describes the inherent pathological changes of osteoarthritis and does not limit it to a new disease different from the conventional understanding of osteoarthritis. Moreover, 'normalizing the cartilage damage state' is an explanation of the intrinsic mechanism of compound A for treating osteoarthritis and does not limit it to a new disease different from that disclosed in comparison document 3. Therefore, claim 1 lacks novelty.

Case 4

The therapeutic mechanism has not changed the indications.

Application No. CN202010930505.3, Reexamination Decision No. 1514670, Decision Date December 22, 2023.

Claim 1 of this application aims to protect use of a flavonoid composition comprising specific concentrations 100 μmol/L Icariside II and 30 μmol/L Kaempferol in the preparation of a drug for treating vitiligo by promoting the survival of melanocytes and keratinocytes.

The applicant believes that the therapeutic mechanisms of this application and D1 are different. The technical solution formed by

combining D1 and D2 involves the use of Icariside II and Kaempferol to treat vitiligo caused by a reduction in melanin due to autoimmune factors, whereas this application is directed towards reducing oxidative stress levels in vitiligo, developing an antioxidant stress drug for the treatment of vitiligo. The applicable situations, therapeutic mechanisms, and treatment methods of the two are completely different.

The view of the panel is that the therapeutic mechanism is merely the discovery of the causes of the disease, which cannot change the types of diseases in medical use. The diseases treated in both D1 and this application are vitiligo, and there is no differentiation in the existing technology between vitiligo caused by autoimmune factors and that caused by oxidative stress factors. Furthermore, the limitation of this medical use does not allow the claimed composition to have a different structure and/or composition. It is evident that the limitation of 'vitiligo by promoting the survival of melanocytes and keratinocytes' cannot be distinguished from the vitiligo disclosed in D1.

Author's Summarization

Regardless of the pathological mechanisms or therapeutic mechanisms, they are recognized in patent practices as not having a limiting effect on the disease, unless there is evidence proving that different mechanisms have caused changes in the disease or the therapeutical effects.

Case 5

Patient subgroup constitutes a new indication - Evidence is king

Patent No. 2018800305082, Allowance Date: October 29, 2024

Claim 1 of this patent relates to "use of a peptide of SEQ ID No: 2 in the manufacture of a medicament for the treatment of cancer in an HLA-A*0201-positive patient having a tumor expressing TElomerase Reverse Transcriptase (TERT), wherein said tumor is non-immunogenic and wherein said peptide of SEQ ID No: 2 induces a CTL response against the cryptic TERT572 peptide of SEQ ID No: 1, and said patient has a non-small cell lung cancer (NSCLC)."

The examiner stated in the second office action that claim 1 defines "the tumor is non-immunogenic" and "the peptide of SEQ ID NO:2 induces a CTL response against the cryptic TERT572 peptide of SEQ ID No:1", but the latter limitation is only related to the mechanism of action of the peptide of SEQ ID NO:2, and the former limitation does not distinguish a different disease. It is evident that the above limitations do not impact the drug to be prepared, the disease to be treated, or the process of preparing the drug. Therefore, D1 has essentially disclosed all the technical features of this claim, and the technical solution of D1 belongs to the same technical field as the claimed invention, solving the same technical problem, and is capable of

producing the same technical effect. Thus, this claim lacks novelty.

The applicant argued with the submission of two pieces of evidence published before the priority date, demonstrating that non-immunogenic tumors and immunogenic tumors are different types of tumors, that is, they belong to different diseases/disorders. The evidence revealed that non-immunogenic tumors lack tumor T cell infiltration due to the absence of tumor antigens, defects in antigen presentation, lack of T cell activation, and defects in homing to the tumor bed by experimental data. It also revealed that non-immunogenic tumors respond differently to immunotherapy compared to immunogenic tumors. Following favorable evidence, the examiner accepted that non-immunogenic tumors define a different disorder, thereby granting a patent right.

Author's Suggestions

To ensure that patient subgroups can be recognized to have formed different indications, it is recommended to consider providing more indicators and relative data, which the clinical trial requirements related to, while drafting an application, so that they correspond better with the indications. Moreover, it is recommended to describe the therapeutic effects of patient subgroups in detail and support them with experimental data, highlighting the difference in treatment response from other patients.

Epilogue

The blueprint for precision medicine is grand and inspiring, yet in the patent arena examiners usually pose a single, blunt question: does the “patient subgroup” you depict rewrite the indication, or is it already accepted industry-wide as a distinct disease? To answer in the affirmative, the applicant must marshal convincing evidence that the subgroup’ s pathology is different, its therapeutic response is different, and so on. Only then can this query be turned into a positive statement, allowing a pharmaceutical company to transform "personalized medicine" into a "patent moat. " Otherwise, even flawless experimental data will ultimately fail to secure protection because it "imposes no limitation", leaving the drug development outside the patent fence, bereft of capital support, and doomed to fail in the marketplace.

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Ms. Wu is skilled in patent application drafting, office action responses, reexamination, invalidation, administrative litigation, patent due diligence and freedom-to-operate investigation, patent analysis and other services. She has accumulated rich patent legal service experience in the fields of pharmacy, life sciences, chemistry, materials science and other technologies. In addition to handling Chinese patent applications, Ms. Wu also has the qualification to handle US patent applications. Ms. Wu also cooperates with local lawyers to complete patent agency services in Europe, Canada, Australia, India, Brazil and other countries and regions in the patent application granting procedure.

Ms. Wu has rich experience in Chinese and English drafting. She was selected as one of the first batch of high-level talents in the patent agency industry (patent document drafting type) by the All-China Agents Association in 2013. The international application PCT/CN2014/091138 she drafted was included in the "National Excellent Invention Patent Application Agency Case Selection (2016)". The invention patent invalidation case (invention name: "Phenylpiperazine derivatives as serotonin reuptake inhibitors") represented by Ms. Wu was selected as one of the top ten cases of patent reexamination and invalidation by the China National Intellectual Property Administration in 2022.