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# Discussion on Several Issues Concerning the Inventive step of Patent Applications Related to Biological Sequence

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**Abstract:** ***The examination of inventive step of patent applications for invention for biological sequences follows a three-step method, and in analyzing claims containing administration features, it should avoid considering them as distinguishing features; In addition, the technical solutions of sequential patent applications are holistic and should not be considered separately; The verification of right of priority should be based on its own standards, rather than on the examination criteria of novelty or inventiveness; In addition, for an invention by combination, it is necessary to accurately determine the meaning of "collaboration" in specific applications; When patent applications involve different issues, it is important to avoid confusion between inventive step and supporting issues; Finally, for the technical problems actually solved by the invention, it is not advisable to overly prioritize or "replace" the role or function of the distinguishing features themselves as technical problems.***

**Keywords:** Inventiveness, Right of priority, Distinguishing feature**.**

## 1. Introduction

According to Article 22, paragraph 3 of the Patent Law of the People's Republic of China: "Inventiveness means that, as compared with the prior art, the invention has prominent substantive features and represents a notable progress, and that the utility model has substantive features and represents progress." In patent substantive examination, reexamination of rejections, requests for invalidation, and administrative litigation for patent confirmation, whether a patent application for an invention possess inventive step has always been one of the biggest focal issues. Assessing whether the claimed invention is obvious as compared with the prior art includes the following steps according to the relevant provisions of the "Guidelines for Patent Examination (2023)": 1) Determining the closest prior art; 2) Determining the distinguishing features of the invention and the technical problem actually solved by the invention; 3) Determining whether or not the claimed invention is obvious to a person skilled in the art.

Patent applications for inventions related to biological sequences include themes such as genes, polypeptides, proteins, and involve strategic emerging industries such as biopharmaceuticals and new materials. When confirming whether such patents possess inventiveness, naturally, the three-step method framework needs to be followed. Under this framework, due to the particularity of the field, there are also some distinct characteristics. This article intends to discuss from several points in combination with different cases.

## 2. Accurately Clarifying the Distinguishing Features is of Crucial Importance for the Examination of Inventive Step

According to the "Guidelines for Patent Examination (2023)", The claims shall describe the technical features of the invention or utility model, and the technical features may be either component elements that constitute the technical solution of the invention or utility model, or the interrelations between the elements. The distinguishing features refer to the technical characteristics that differentiate a claimed invention or utility model from the closest prior art. In patent applications for biological sequences, the distinguishing features may be an un-disclosed sequence segment, vector, or excipient, etc. Clarifying the distinguishing features may seem simple, like the difference obtained by subtracting the disclosed technical feature set of the prior art from the technical feature set of the claims, but the actual situation is far from being so straightforward.

**1) In the examination of inventive step of patent applications, the administration features do not constitute distinguishing features**

Case 1: (2016) BJ Administrative Final-Instance Case No. 1762

This case involves an administrative litigation case of administrative disputes over the invalidation of invention patent rights. The patent application number is 200610008639.X, and the name is "Treatment with anti-ErbB2 antibodies". Claim 1 as the review basis is:

1) An article of manufacture, comprising (1) a container, (2) a composition of anti-ErbB2 antibody that binds to epitope 4D5 in the extracellular domain sequence of ErbB2 contained in the container, (3) a label on or associated with the container that indicates that said composition can be used for treating a condition characterized by overexpression of ErbB2 receptor, and (4) a package insert containing instructions to avoid the use of anthracycline-type chemotherapeutics in combination with said composition.

The involved evidence 1 discloses an animal test of a drug composition of rhuMoAb HER2 antibody and paclitaxel (a non-anthracycline antibiotic chemotherapeutic agent) for treating nude mice with xenotransplanted human breast cancer tumors. The appellant believes in the second instance that evidence 1 does not disclose the feature of "avoiding the combined use of anthracycline antibiotics and the antibody." The court of second instance believes that for those skilled in

the art, the role of this drug contraindication is to guide the doctor's medication process and has no substantial impact on the structure and composition of the product itself. Therefore, it should not be considered when determining the protection scope of claim 1.

In the chapter "Novelty of Use Invention of Chemical Product" of the "Guidelines for Patent Examination (2023)", it is clear whether the features related to use such as the administration object, method, route, usage amount, and interval of administration have a limiting effect on the pharmaceutical process. The difference features only reflected in the medication process cannot make the use possess novelty. Because the method of administration to diagnose and treat diseases belongs to the situation where a patent cannot be granted as stipulated in item 3 of paragraph 1 of Article 25 of the Patent Law, the administration feature does not constitute a substantial limitation on the claim.

By extension, for patent applications related to biological sequences, such as claims for pharmaceutical products, the essence of the product lies in the structure/composition. If a feature reflects the structural or compositional features of the product, it has a limiting effect on the claim; otherwise, it has none. For the claims for the preparation method of pharmaceutical products, the technical features that usually limit the preparation method are raw materials, steps, process parameters, equipment, etc. Features regarding the method of pharmaceutical use such as administration object, interval of administration, and administration route. If these features have no direct connection with the pharmaceutical manufacturing method itself and essentially pertain to the pharmaceutical administration behavior towards specific subjects after the pharmaceutical products have been prepared, then, of course, they have no limited effect on the preparation method. For claim of medical use of substance, patent rights can be obtained through the "Swiss-type claim" drafting method. It contains usage features of disease types or features of pharmaceutical manufacturing methods. If such claims involve the behavioral characteristics of administration and has no direct connection with the pharmaceutical process, it has no substantial limiting effect on the claim. Therefore, in the inventiveness examination of product, method, and use type claims, if the administration or pharmaceutical use behavior feature has no substantial impact on the product composition or structure, or has no direct connection with the pharmaceutical method, it does not constitute a distinguishing technical feature from the comparison document.

In patent applications for biological sequences, the realization of technical effects is usually the result of the combined action of multiple factors, and there is often synergy among technical features. When analyzing the distinguishing features between the technical solution of the claim and the closest prior art, technical features cannot be simply separated.

**2) When distinguishing features are closely related, they should not be separated**

Case 2: (2020) SPC Administrative Final-Instance Case of Intellectual Property No. 186

This case involves an administrative litigation case of an administrative dispute over the review of a rejected patent application for an invention. The patent application number is 201180034991.X, and the name is "Live attenuated parvovirus." Claim 1 as the basis for examination is:

1) Live attenuated parvovirus (PV), characterised in that it comprises a capsid gene coding for an amino acid other than Isoleucine at amino acid position 219 of the capsid protein and/or an amino acid other than Glutamine at amino acid position 386 of the capsid protein, characterised in that said parvovirus encodes a capsid protein of CPV serotype 2a, 2b or 2c or a capsid protein of feline parvovirus,and characterized in that said parvovirus is a recombinant parvovirus wherein a DNA fragment of a part of the non-capsid region of said parvovirus is replaced by a homologous DNA fragment of a part of the non-capsid region derived from a second parvovirus, wherein said homologous DNA fragment of said second parvovirus carries an attenuating mutation.

During the trial, the court of first instance held that the sued decision separated the two technical features of "Live attenuated parvovirus, it comprises a capsid gene coding for an amino acid other than Isoleucine at amino acid position 219 of the capsid protein and/or an amino acid other than Glutamine at amino acid position 386 of the capsid protein" (mutation site selection) and "said parvovirus encodes a capsid protein of CPV serotype 2a, 2b or 2c or a capsid protein of feline parvovirus" (virus type selection), and then it was inappropriate to determine that Comparative Document 1 disclosed the technical feature of mutation at amino acid sites 219 and/or 386 in the capsid region as claimed in claim 1 of this application. The court of second instance held that: 1) The amino acid mutation sites in Comparative Document 1 are not limited to positions 219 and 386 of parvovirus CPV2, and it is not explicitly disclosed that mutations at positions 219 and 386 of the capsid protein have an attenuating effect; 2) Although the virus in Comparative Document 1 has an attenuating effect, compared with the difference from wild viruses, it cannot be inferred that the attenuating effect is brought about by mutations at positions 219 and 386, that is, Comparative Document 1 does not implicitly disclose that mutations at positions 219 and 386 have an attenuating effect; 3) This application clearly states that the attenuating effect is brought about by selecting specific virus types through specific mutation sites. In the case where the mutation sites are not only two and the mutation effect is uncertain, the mutation sites and virus types are selective. The sued decision separated the two technical features of mutation site selection and virus type selection in claim 1, determined that Comparative Document 1 disclosed the technical feature of mutation at amino acid sites 219 and/or 386 in the capsid region as claimed in claim 1, failed to accurately determine the distinguishing features of this application compared to the comparative document, so its determination on whether claim 1 of this application possesses inventiveness compared to Comparative Document 1 and 3 and common knowledge is wrong.

In this case, the courts of first and second instance accurately grasped the distinguishing features. Although Comparative Document 1 discloses a parvovirus CPVint (vaccine), and the amino acid at position 219 of the capsid protein amino acid sequence is valine and the amino acid at position 386 is lysine.

From the sequence, it seems that the selection of mutation sites is disclosed. However, when examining the distinguishing features, it is still necessary to consider it within the overall framework of the technical solution and not make a mechanical and fragmented comparison. When making an attenuated vaccine, virus attenuation is the key. If there is no one-to-one causal relationship between virus sequence modification (such as amino acid sequence mutation, deletion, addition, etc.) and the attenuation effect, and it is not known which amino acid changes lead to attenuation, the distinguishing features obtained based on mechanical subtraction will lead to deviations in subsequent technical effect determination, redetermination of technical problem, and whether other comparative documents give technical motivation. This overall consideration stems from the integrity and indivisibility of biological sequence patent technical solutions.

## 3. Verification of Right of Priority is Crucial for Accurately Defining the Time Point of Prior Art

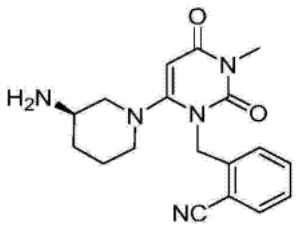
According to Article 22.5, the prior art means any technology known to the public before the date of filing in China or abroad. The prior art includes any technology which has been disclosed in publications in China or abroad, or has been publicly used or made known to the public by any other means in China or abroad, before the date of filing (or the priority date where priority is claimed). Therefore, verification of right of priority is extremely important. According to the "Guidelines for Patent Examination (2023)", general principle on verification of right of priority includes: (1) whether the earlier application, which is used as the basis of the right of priority, involves the same subject matter as that of the later application for which the priority is claimed; (2) whether this earlier application is the first application in which the same subject matter is described; and (3) whether the date of filing of the later application is within twelve months from the date of filing of the earlier application. The same subject matter involves four elements: technical field, technical problem to be solved, technical solution, and prospective effect being the same.

In the process of verification of right of priority, there are special circumstances in the field of biological sequence. Compared with earlier existing technologies, the technical solution recorded in the claims of the prior application as the basis for priority only has some additional features that have no limiting effect on the claims (such as administration features). As mentioned above, such features do not constitute a substantial difference from existing technologies. Then, how should it be considered in verification of right of priority?

Case 3: (2021) SPC Administrative Final-Instance Case of Intellectual Property No. 344

This case involves an administrative litigation case of administrative disputes over the invalidation of invention patent rights. The target patent is "Dipeptidyl peptidase inhibitor for treating diabetes", with patent application number 201210399309.3. The priority data recorded in the patent document is "60/717,558 September 14, 2005 US" and "60/747,273 May 15, 2006 US". It is a divisional application. The application number of its parent case is 200680042417.8, and the application date is September 13, 2006. Claim 1 as the review basis is:

1) Use of compound I in the preparation of a pharmaceutical composition. The pharmaceutical composition is administered orally with a daily dose of 5 milligrams to 250 milligrams of compound I for the treatment of type II diabetes. Compound I has the following structural formula:




and exists in the form of a pharmaceutically acceptable salt or free base.

During the stage of invalidation request, the appealed decision pointed out: "Although claim 1 of this patent limits the oral daily dose of compound I to be 5 milligrams to 250 milligrams, this feature belongs to the administration feature and only reflects the choice in the doctor's medication process. It has no limiting effect on the pharmaceutical process and does not affect the protection scope of the claim. Evidence 4 has disclosed an invention with the same subject matter as claim 1 of this patent. The two prior applications for which this patent claims priority are not the first applications. Claim 1 cannot enjoy the priority right of these two prior applications." In the first instance of administrative litigation, the court of first instance supported the view of the Reexamination Board and held that the appealed decision's determination that the priority of claims 1 - 17 of this patent is not established is correct. During the second instance, the court held that when reviewing novelty and inventiveness, some contents in the claim are regarded as having no substantial limiting effect and are not considered. However, this review standard is not applicable to verification of right of priority. When reviewing whether it belongs to the same subject matter during verification of right of priority, all the contents of the technical solution limited by the patent claim need to be considered, and the standard is "directly and unambiguously derived." Since evidence 4 does not record "the daily dose is 5 milligrams to 250 milligrams" in claim 1 of this patent, this content cannot be directly and unambiguously derived from evidence 4 either. Evidence 4 is not the first application with the same subject matter. The right of priority claimed by claim 1 is established.

From the trial process of this case, it can be known that when verifying right of priority, to judge the same subject matter, it is necessary to closely adhere to the four elements of "technical field, technical problem to be solved, technical solution, and prospective effect". On the one hand, the same subject matter does not require the technical solution recorded in the subsequent application's claims to be reflected mechanically and completely identically in form with the prior application, but follows the standard of being able to be "directly and unambiguously derived" from the prior application. On the other hand, when verifying whether the

prior application is the first application recording the same subject matter, it may be necessary to review whether other prior art earlier than this prior application records the same subject matter. At this time, patentability review criteria such as novelty and inventiveness cannot be introduced. When reviewing novelty or inventiveness, the search for prior art is a search for prior art disclosed earlier than the date of filing (or the priority date where priority is claimed). Verification of right of priority precedes the review of novelty or inventiveness and cannot be mixed with patentability criteria. That is, when discussing the differences between the technical solution recorded in the claims and the prior art, even if the administration feature has no substantial limiting effect in the claims, but in the process of verification of right of priority, when verifying whether other prior art undermines the priority constituent element of "first application", the administration feature cannot be discarded and not considered.

**3) Synergistic Effect in Invention by Combintion**

The "Guidelines for Patent Examination (2023)" defines a invention by combintion as: "An invention by combination refers to a new technical solution made by combining certain known technical solutions to solve a technical problem objectively existing in the prior art. In determining the inventive step of an invention by combination, usually the following factors need to be taken into account: whether those combined technical features functionally support each other, the difficulty or easiness of combination, any technical motivation to make the combination in the prior art, and the technical effect of the combination, etc."

In Chinese patent examination practice, determining the inventive step of an invention by combination needs to comprehensively consider many factors. It is noteworthy that the meanings of function and effect are different. Function is the inherent efficacy of a thing and is determined by the internal element structure. Effect is an extension of function and is closely related to technical solutions and application scenarios. Patent applications for biological sequences contain many inventions by combintion. From a technical principle perspective, biomedical end products are applied to living individuals. Their metabolic pathways, signaling pathways, and action targets are complex. Known product compositions may have antagonistic or synergistic effects. Synergistic enhancement is closely related to the inventiveness of an invention by combination.

Case 4: (2020) SPC Administrative Final-Instance Case of Intellectual Property No. 297

This case involves an administrative litigation case of administrative disputes over the review of rejected invention patent applications. The patent application number is 201180055463.2, and the title is "Composition comprising a peptide and an inhibitor of viral neuraminidase". Claim 1 as the review basis is:

1) Composition comprising:

- a peptide, which consists of 17 adjacent amino acids, wherein the peptide has no TNF-receptor-binding activity and is cyclized; and

- an inhibitor of viral neuraminidase, wherein the inhibitor is a sialic acid analog..

characterized in that the peptide comprises the amino acid sequence CGQRETPEGAEAKPWYC and is cyclized via the C-residues.

The specification of the patent records the test situation in multiple paragraphs and figures. Experimental mice are infected with a certain dose of influenza A strain. Different drugs are administered to infected mice in different groups respectively. The experimental results show that the neuraminidase inhibitor alone produces a moderate effect of reducing pneumonia, and when combined with peptide AP301, it will significantly reduce pneumonia to a much greater extent.

The comparison document 1 discloses a peptide and a composition comprising the peptide. The peptide is composed of 7 to 17 adjacent amino acids and contains a specific hexamer. It has no TNF-receptor-binding activity and is cyclized. It can be used for the prevention and treatment of hyperpermeability, pneumonia or viral lung diseases, especially influenza A virus infection. The comparison document 2 discloses the important role of the viral neuraminidase inhibitors zanamivir or oseltamivir in the prevention and treatment of influenza.

The court of first instance held that: Public knowledge evidence 1 provides the teaching of using the combination therapy of oseltamivir and amantadine to treat avian influenza. Technicians in the relevant field have the motivation to combine drugs targeting different mechanisms of influenza virus. It is easy to think of combining the peptide disclosed in the comparative document 1 and the viral neuraminidase inhibitor disclosed in the comparative document 2 into a composition for the prevention and treatment of influenza virus infection and pneumonia. Obtaining the technical solution of claim 1 by combining comparative document 1, comparative document 2 and common knowledge on the basis of comparative document 1 is obvious to technicians in the relevant field.

The court of second instance held that although the specification mentions the synergistic effect of the peptide component and the neuraminidase inhibitor, it all refers to "under the synergistic effect of the peptide component, improving the effect of the neuraminidase inhibitor", and does not involve "under the synergistic effect of the component neuraminidase inhibitor, improving the effect of the peptide", nor does it involve "under the synergistic effect of the two components, the composition has a technical effect that exceeds the simple addition of separately administering the viral neuraminidase inhibitor and separately administering the peptide". Therefore, based on the disclosed content of the patent application in question, those skilled in the art can only know that administering the composition has a better effect in treating pneumonia infected by influenza A virus than administering the viral neuraminidase inhibitor alone, and will not draw a conclusion that it is better than administering the peptide alone or has a better effect than the simple addition of administering both alone.

In this case, there are several enlightening points. First, regarding how to understand synergy? The concept of synergy was proposed by the German physicist Hermann Haken [3], which refers to the coordinated, cooperative, or synchronous joint action and collective behavior of multiple subsystems in a system. This is the inherent manifestation of the integrity and relevance of the system. Specifically in this case, the connotation and extension of the synergy effect are inseparable from the description and definition in the specification. The synergy effect requires, first, the mutual support of the functions of each technical feature, and second, in terms of technical effects, either a qualitative effect: achieving new effects; or a quantitative effect: the combined technical effect is superior to the sum of the effects of each technical feature. A well-known example of synergy in the biomedical field is the binding of hemoglobin and oxygen. Hemoglobin (Hb) is a protein with a quaternary structure, consisting of 4 subunits, including 2 α-subunits and 2 β-subunits. The binding of hemoglobin and oxygen exhibits positive and negative synergy effects; for the positive synergy effect: when the first oxygen molecule binds to one subunit of hemoglobin, it causes a conformational change in this subunit. This conformational change is transmitted to other subunits through the interfaces between the subunits, increasing the affinity of other subunits for oxygen. By analogy to a certain extent, in the process of patent application layout for biological sequences, when it comes to an invention by combination, in the process of embodying the synergy effect, it is first necessary to clearly define the synergy effect, whether it is that under the synergy of A, the effect of B is enhanced; or under the effect of B, the effect of A is enhanced; or under the synergy of A and B, an effect that originally did not belong to the individual effects of A or B is achieved, or the overall effect is superior to the individual effects of A or B alone. Different recording methods determine the specific implementation methods in the specification and the presentation methods of experimental data. Second, regarding the evaluation of the inventive step of an invention by combination and how to consider the issues of the teaching of the prior art and the ease of combination, the highlight of this case lies in elaborating on the teaching of the prior art from different perspectives. From the perspective of the prior art documents, prior art document 1 discloses: "a peptide and a composition comprising said peptide"; from the perspective of common knowledge, in order to improve the therapeutic effect, it is common knowledge in this field to use drugs targeting different mechanisms of the influenza virus for combined treatment of the influenza virus, and there is no reverse teaching in the prior art that the two cannot be combined; from the relevant paragraphs in the background technology of the invention in this case, a person skilled in the art has the motivation to combine the peptide disclosed in prior art document 1 that "can prevent and treat pneumonia or viral lung diseases" with the viral neuraminidase inhibitor zanamivir or oseltamivir disclosed in prior art document 2 to form a composition. Therefore, when analyzing the inventive step of an invention by combination in the field of biological sequences, in evaluating the teaching of the prior art and the ease of combination, first, it can be seen from the prior art documents whether there is a clear teaching indicating the combination of different technical means; second, it can be seen whether the combination of different technical means can expect its effect, or, in the same technical field, whether the combination of technical means very close to the technical features is common knowledge, as in this case, the treatment of anti-avian influenza virus can adopt the combined use of phosphate oseltamivir and amantadine, which belongs to common knowledge; furthermore, the specification of the application document itself can be comprehensively analyzed. The inventions by combination in the field of biological sequences are inseparable from the exploration of the underlying inventive concept and principle. Different technical features, and the mechanisms they rely on, such as the specific targets of drug action and the signal pathways, may all be disclosed in the background technology. Then, in this case, the technical concept of the invention by combination is very likely to come naturally.

## 4. Clear Definition of the Boundary between Inventiveness and Support

Article 26, Paragraph 4 of the Patent Law stipulates that "The claims shall be supported by the description and shall define the extent of the patent protection sought for in a clear and concise manner." This is the so-called clause regarding "support" and "clear".

In the process of determining invetive step, as described in the Examination Guidelines, the the advantageous effects are important bases for determining whether an invention has "notable progress" and whether a utility model has "progress." Invention patent applications for biological sequences generally require experimental data as evidence, such as cell test data, animal model test data, or clinical trial data. In some cases, there may be a situation where the experimental data and the elucidation of the advantageous effects are not directly and one-to-one corresponding and related, which may further affect whether the technical solution described in the claims is supported by the description. At the same time, when evaluating the constituent element of "notable progress," it may also be impossible to see from the description in the application document whether the solution described in the claims represents notable progress compared with the prior art. In such a situation, it is extremely important to clearly define the different boundaries of the constituent elements of the two legal provisions.

Case 5: (2021) SPC Administrative Final-Instance Case of Intellectual Property No. 448

This case involves an administrative litigation case of an invention patent right invalidation administrative dispute. The target patent is "Endoglucanase STCE and Cellulase Formulations Containing Endoglucanase," with the patent application number 200480036105.7, the application date being October 22, 2004, and the priority date being December 3, 2003. The claim 1 serving as the basis for examination in this case is:

1.a protein consisting of the amino acid sequence represented by SEQ ID NO. 3 and having endoglucanase activity.

Regarding whether the technical solution described in claim 1 is supported by the description and has inventiveness, the appellant in the second instance put forward: "Compared with the technical solution disclosed in Evidence 3, the

distinguishing feature of the patent in this case is that claim 1 seeks to protect the protein represented by SEQ ID NO. 3. However, the description of the patent in this case does not describe the effect of the protein characterized only by the sequence shown in SEQ ID NO. 3. Therefore, the technical effect of the distinguishing feature cannot be confirmed based on the content described in the description of the patent in this case. Therefore, the technical solution protected by claim 1 does not have inventiveness."

Regarding the determination of whether the claim is supported by the description, the second-instance court held that "Examples 3 - 6 verified that STCE1 has endoglucanase activity and stable clarification activity; Examples 7 - 14 expressed the STCE1 gene in the strain IFO31817 in the heterologous host Humicola insolens through genetic engineering technology and verified that the expressed STCE1 has endoglucanase activity and stable clarification activity; Examples 15 and 16 expressed the STCE1 gene in another heterologous host Trichoderma viride through genetic engineering technology." "The examples of the patent in this case have proved the effect of the protein to be protected in claim 1 in three different host cells, further indicating that the target proteins with different glycosylation types and degrees expressed in different host cells all have endoglucanase activity, suggesting that the degree of glycosylation is not a key factor affecting the biological activity of the target protein of the patent in this case." Regarding the determination of whether the claim has inventiveness, it was held that "After reading the description of the patent in this case, a person skilled in the art can know that the distinguishing feature between claim 1 of the patent in this case and the closest prior art is that the protein represented by SEQ ID NO: 3 described in claim 1 of the patent in this case can bring the above-described technical effects described in the description. Therefore, the appellee's decision on the technical problem actually solved by the invention is correct."

In invention patent applications for biological sequences, the issues of support and inventiveness are inseparable from a comprehensive and in-depth interpretation and analysis of the content of the description, but there are obvious differences and emphases between the two. First, regarding support, the position should be from the perspective of a person skilled in the art, and a comprehensive determination should be made based on the overall situation of the existing technology in the field, the content disclosed in the description, and the content limited by the claims. As in this case, although the patent in this case did not determine the full-length sequence of the protein and only confirmed that the expressed protein was consistent with the N-terminal amino acid sequence of endoglucanase STCE1, the construction and expression process adopted conventional means, the sequence of the introduced target gene was determined, and the molecular weight of the finally expressed product was approximately the same as the theoretically expected molecular weight of the target product, so it can be reasonably inferred that the finally expressed protein should have the amino acid sequence shown in SEQ ID NO: 3. In the field of biological sequences and even the entire biomedical field, support issues will appear in various scenarios, such as sequence identity support, Markush claim support, numerical range support, support for naked sequences and modified sequences, etc. However, the essence is still to stand from the perspective of a person skilled in the art, based on the overall situation of the existing technology, closely adhering to all the content described in the description, and determining whether it can be reasonably expected that the technical solution limited in the claims can solve the technical problem claimed to be solved by the invention patent application, and whether the scope of generalization exceeds the technical contribution of the inventor. Second, regarding the determination of inventive step, it is necessary to clearly distinguish the statutory constituent elements of inventiveness from the constituent elements of support and avoid confusion between determination of inventiveness and determination of support issues. As in this case, when determining inventive step, the distinguishing feature between the patent in this case and the closest prior art is accurately defined as the protein represented by SEQ ID NO: 3, and the technical problem actually to be solved by the invention is accurately determined as providing an endoglucanase that is not affected by the hardness of tap water and has stable clarification activity.

Furthermore, in the biomedical field, especially in the field of genetic engineering, there may be a situation where the product to be verified and the solution to be protected are not completely corresponding. The means of obtaining the target protein by genetic engineering is conventional. When eukaryotic cells are used as host cells, whether yeast cells, insect cells, or mammalian cells, there may be post-translational modifications during the expression of the target protein, and the final product often contains glycosylated components. If the patent application intends to protect the naked sequence of a protein or polypeptide and adopts a closed drafting method, while the experimental data is for the modified sequence and is not completely identical to the protection scheme of the claims, how to view the experimental data of such an application and whether it makes the application not meet the statutory constituent element of "notable progress"? It cannot be generalized and needs to be comprehensively analyzed and determined according to the technical field of the application, the technical problem to be solved, the technical means, and the effect. If the modification part has almost no impact on the activity, conformation, interaction with the target, etc. of the protein or polypeptide, and can together with other data described in the description verify and illustrate the effect that the invention intends to achieve, from the perspective of the evidence chain, the relevant experimental data of the modified product has probative force. However, in some scenarios, the situation is more complicated. The claim describes a drug product claim made from a naked sequence, and the description only verifies the modified sequence, and it cannot be seen from the content described in the description the impact of the modification part on the immunogenicity and toxicity of the drug, nor can the degree of impact of the modification part on the interaction relationship between the product and the target be inferred. It is rather difficult for such isolated experimental data to illustrate that the application meets the statutory constituent element of "notable progress." Of course, whether such issues lead to insufficient disclosure of the description is not within the scope of discussion in this article.

## 5. Accurate Definition of Technical Problems

In the three-step method of inventive examination, regarding the technical problem actually solved by the invention, according to the "Patent Examination Guidelines" (2023) [1], first, it is necessary to first determine the distinguishing features of the claimed invention as compared with the closest prior art, and then determine the technical problem that is actually solved by the invention on the basis of the technical effect of the distinguishing features. In practice, it is not very simple to accurately determine the technical problem actually solved by the invention.

Case 6: Supreme People's Court Administrative Judgment of Final Appeal No. 6

This case involves an administrative litigation case of an invention patent application review for rejection and reconsideration. The case involves an invention patent with the application number 201410707259.X and the name "VEGF antagonist formulations suitable for intravitreal administration." The claim 1 serving as the basis for examination is:

A stable ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, which consists of the following:

(a)40 mg/ml of VEGF antagonist, where the VEGF antagonist is a dimer composed of two fusion proteins of SEQ ID NO: 4;
(b)0.03% polysorbate 20;
(c) 10 mM sodium phosphate;
(d) 5% sucrose;
(e) 40 mM sodium chloride, and
(f) water for injection,
pH 6.2 - 6.4,

where at least 90% by weight of the VEGF antagonist is not present in aggregates.

Prior art document 1 discloses an ophthalmic formulation containing a VEGF antagonist (Ranibizumab) and specifically discloses the following technical features: (Dosing Regimen): Ranibizumab (LUCENTIS™) is a VEGF antagonist with an anti-human VEGF Fab fragment; Ranibizumab injection is a formulation for intravitreal injection, and each vial contains 0.7 ml or 0.6 mg/ml (0.3 mg dose level) or 10 mg/ml (0.5 mg dose level) of an aqueous solution of Ranibizumab (pH 5.5), 10 μM histidine, 100 mg/ml trehalose, 0.01% polysorbate 20, and the description discloses that the VEGF antagonist can be a VEGF trap.

Prior art document 2 discloses a VEGF capture agent that can bind and inhibit VEGF activity, and the VEGF small capture agent of this invention can be used to treat any diseases and disorders that can be improved, alleviated, inhibited, or prevented by removing, inhibiting, or reducing VEGF. For a specific VEGF capture agent, the complete capture agent SEQ ID NO: 10 and the dimer of SEQ ID NO: 10 with VEGF affinity are specifically disclosed.

In the review for rejection and reconsideration stage, the appellee's decision held that: compared with the content disclosed in prior art document 1, the technical solution claimed in claim 1 of the present application has the following differences: 1. The components of the ophthalmic formulation claimed in claim 1 of the present application contain specific amounts of sodium phosphate, sucrose, sodium chloride, and water for injection, and do not contain histidine and trehalose. In addition, the contents of the VEGF antagonist and polysorbate 20 are different from those in prior art document 1, and the pH is 6.2 - 6.4; 2. It is defined that the VEGF antagonist is a dimer composed of two fusion proteins of SEQ ID NO: 4, and at least 90% by weight of the VEGF antagonist is not present in aggregates. Based on the effects of the above distinguishing features in the present application, it can be determined that the technical problem actually solved by the present application is to provide a new ophthalmic formulation.

In the first instance stage, the first-instance court confirmed the relevant determination of the appellee's decision. During the second instance trial, regarding the technical problem actually to be solved by claim 1 of the present application, the second-instance court held that: "Prior art document 1 relates to a method for treating intraocular neovascular diseases with a VEGF antagonist, and its inventive purpose is to provide an improved method for administering a therapeutic compound, that is, to provide a new dosing regimen for treating intraocular neovascular diseases. Prior art document 1 does not directly involve the problem of how to prepare a stable, safe, and effective formulation of the therapeutic compound. Moreover, the VEGF antagonist in claim 1 of the present application is a fusion protein dimer, which is a different protein from the VEGF antagonist Ranibizumab in prior art document 1." Eventually, the views of the Reexamination Board and the first-instance court were corrected, and it was considered that the technical problem actually to be solved by claim 1 of the present application is to provide a stable liquid ophthalmic formulation containing a high-concentration different protein antagonist.

During the trial of this case, there are several enlightening points. First, the induction of technical problems should not be too general. If the technical problem is too general, it is very likely to artificially create technical motivation or teaching that does not exist in the prior art documents, resulting in deviation in the examinationt of inventiveness. In this case, one of the differences is exactly a very easy-to-take-for-granted aspect in the biomedical field, that is, the numerical value. The concentration of the VEGF antagonist in the patent in this case is 40 mg/ml, while the concentration of Ranibizumab in prior art document 1 is 0.6 mg/ml (0.3 mg dose level) or 10 mg/ml (0.5 mg dose level). In some patent right confirmation procedures, differences in numerical values or numerical ranges are easily understood and defined as being determined through a limited number of experiments or being considered that such numerical values do not bring unexpected technical effects to the invention. However, this kind of reverse cause and effect may cover up the accurate technical problem. Essentially, in the examination, it is easy to overlook the significance of certain differences limited by numerical values or numerical ranges, and thus ultimately affect the reasonable induction of technical problems. To avoid such deviation, the application document should fully elaborate the inventive concept and straighten out the logical line of technical problem - technical solution - technical effect, which will help the patent

application obtain patent rights in the patent right confirmation process. Second, the role, function, or technical effect of the distinguishing feature itself should not be "substituted" as the technical problem. For example, an invention is to structurally modify a nucleic acid - protein complex, and the distinguishing feature may be that NLS (nuclear localization sequence) is added to both ends of the protein bound to the nucleic acid sequence, and the function is to help bring the nucleic acid sequence into the nucleus and then manipulate or change the DNA in the nucleus. However, the technical problems actually solved by the invention may not only be to bring the nucleic acid sequence into the nucleus, but may also include improving the stability of the nucleic acid - protein complex. Therefore, equating this function with the technical problem actually solved by the invention is incomplete and inaccurate, and thus the evaluation of inventiveness will have a large deviation.

## 6. Conclusion

The examination on inventiveness of invention patent applications for biological sequences has its own characteristics. This article has discussed several issues in the examination on inventiveness and summarized them as follows:

(1) Accurately clarifying the distinguishing technical features is an important part of the examination on inventiveness. For claims that record administration features, such administration features should not be considered as the distinguishing features from the prior art. In addition, for invention patent applications for biological sequences, the technical solutions are holistic, and in the process of examining the distinguishing technical features, the integrity of the solutions should not be separated.

(2) The verification of priority should not refer to the examination standards of novelty and inventiveness. For patent applications that record administration features, the verification of priority still needs to closely adhere to the three requirements pointed out in the Examination Guidelines. If the prior art only fails to disclose the administration features, it still cannot destroy the requirement of "whether this earlier application is the first application in which the same subject matter is described."

(3) For the invention by combination with "synergistic" effects between components, it is necessary to accurately clarify the meaning of "synergy" in specific applications according to the description. Especially in terms of technical effects, it is necessary to accurately examing whether "synergy" means producing new effects, or the combined technical effect is superior to the sum of the effects of each technical feature, or other meanings.

(4) In the inventive examination, it is necessary to clearly define the boundary between the examination of inventiveness and the support of the specification. In the case where the technical solution to be protected by the claim and the object verified by the experimental evidence described in the description are not completely corresponding, it is necessary to comprehensively analyze whether the experimental evidence part can make the solution described in the claim represents notable progress compared with the prior art.

(5) In the process of analyzing technical problems, it is not advisable to make the technical problems too general. Being too general will lead to the creation of technical motivation that does not exist in the prior art, resulting in deviation in the examination of inventiveness. Moreover, the role, function, or technical effect of the distinguishing feature itself should not be "substituted" as the technical problem.

## References

[1] National Intellectual Property Administration, P.R.C. Patent Examination Guidelines: 2023[M]. Intellectual Property Press, 2024.
[2] TANG Tiantian. The Creativity Examination Standard for Combinatorial Inventions in the United States[J]. Patent Agency, 2022(2): 24 - 29.
[3] Haken H. Synergetics [M]. Springer, 1983.