Featured Article

# Mastering Antibody Unity in Chinese Patent Applications: Strategies and Case Studies

Antibody drugs are at the forefront of innovation in the biopharmaceutical industry, making them one of the most promising areas for research and development. In a field where patent protection is crucial, the value and importance of antibody patents cannot be overstated. Beyond common challenges like novelty and lack of support, a recurring issue in antibody patent examination is the lack of unity. While this is not an insurmountable barrier to patent approval, dividing a patent containing dozens or even hundreds of antibodies into separate applications is neither practical nor cost-effective. Thus, addressing the unity requirement is vital for securing comprehensive protection for antibody innovations. This article delves into several reexamination cases and current examination practices, offering insights and strategies to effectively tackle unity challenges in antibody patent applications.

## I. Lack-of-Unity is a Common Rejection in Chinese Antibody Patent Examinations

As antibody development technologies advance, the process of screening candidates from vast antibody libraries has become the predominant method for antibody production. Consequently, antibodies in patent applications are increasingly defined by their structural features, such as sequences of critical domains, rather than the previous common way defined by the hybridomas that produce them. When a patent application encompasses multiple library-

derived antibodies without significant shared structural features, applicants frequently encounter examination opinions citing a lack of unity among the claimed antibodies.

This challenge underscores the necessity for strategic approaches in drafting and responding to examination opinions to maintain the broadest possible patent protection. The shift from traditional methods to sequence-based definitions makes it essential for applicants to anticipate potential unity objections and prepare compelling arguments that highlight the underlying commonalities or technical contributions of the antibodies, despite their structural diversity.

## II. Regulations Relating to Unity

Regarding the definition of unity, Article 39 of the Implementing Regulations of the Patent Law stipulates that "Two or more inventions or utility models, which belong to a single general inventive concept and can be filed as one patent application, shall be technically related, and contain one or more identical or corresponding special technical features, where the special technical feature refers to the technical feature that makes a contribution to the prior art as a whole."

Chapter 6 of Part II of the Chinese Patent Examination Guidelines further elaborates: "Two or more inventions belonging to a single general inventive concept shall be technically related, and this technical relationship is reflected in their respective claims in the form of the identical or corresponding special technical features. ... The special technical feature is a concept specifically proposed to assess the unity of a patent application. The special technical feature shall be understood as the technical features that define a contribution which the invention makes to the prior art, that is, the technical features which make the invention, as compared with the prior art and considered as a whole, have novelty and involve an inventive step. Therefore, the expression 'belonging to a single general inventive concept' in Article 31.1 of the Patent Law refers to having the identical or corresponding special technical features."

Chapter 10 of Part II of the Chinese Patent Examination Guidelines also stipulates the principle of unity examination for Markush claims: "Where the Markush elements are for alternatives of compounds, if the following standards are met, they shall be regarded as being of a similar nature, and the Markush claim possesses unity: (1) All alternative compounds possess a common property or function; and (2) All alternative compounds possess a common structure, which constitutes the distinguishing feature between the compounds and those in the prior art, and is essential to the common property or function of the compounds of general formula; or, in the absence of a common structure, all alternative elements belong to the same

class of compounds recognized in the technical field to which the invention pertains. A 'recognized class of compounds' means there is an expectation from the knowledge in the art that members of the class belong to the same class of compounds with the same properties in the context of the claimed invention, i.e., each member are interchangeable, with the expectation that the same intended result will be achieved."

In the revised 2017 edition of Chinese Patent Examination Guidelines, it is stipulated in Section 9.3.1.7 "Monoclonal Antibodies" in Chapter 10 of Part II that "A claim directed to a monoclonal antibody may be defined by specifying structural features", with an exemplary definition provided, wherein the specific sequences of the three light chain CDR regions and the three heavy chain CDR regions of the antibody to be protected are sequentially, explicitly, and close-ended defined. In addition, it is stipulated that "if an antigen is known, an monoclonal antibody of the antigen that is characterized by structural features is significantly different from known monoclonal antibodies in terms of key sequences determining its function and use, and the prior art does not provide technical guidance for obtaining the antibody comprising the above sequences, and the monoclonal antibody produces beneficial technical effects, then the invention of this monoclonal antibody is inventive". This establishes the current requirements in China for inventiveness of antibody inventions, i.e., when the key sequences of the patent antibody differ significantly from those in the prior art, it only requires beneficial technical effects for the antibody to be inventive, while no unexpected technical effect is demanded.

However, the Chinese Patent Examination Guidelines does not give detailed standards for evaluating unity for biological antibodies. Here, we adduce several reexamination cases below, for the purpose of discussing examination insights as well as offering applicants potential strategies for antibody unity issues.

## III. Reexamination Cases

### 1. Common Property + Common Structure

#### a. Reexamination Decision No. 341572 (20221208)

This application requests protection for multiple antibodies against N-terminal pro-brain natriuretic peptide (NT-proBNP), including a newly-discovered antibody and several mutated antibodies further obtained by mutating the new antibody.

The examiner during substantive examination rejected the application for the reason that claims 1-31 do not comply with the unity requirements of Article 31.1of the Chinese Patent Law. The applicant requested reexamination and amended claim 1 as follows: "1. An antibody directed to N-terminal pro-brain natriuretic peptide or functional

fragment thereof, wherein the antibody or functional fragment thereof comprises the following complementarity-determining regions: CDR-VH1: G-Y-X1-F-T-X2-Y-X3-M-H, wherein X1 is T, X2 is N or D, X3 is E, D, or N; CDR-VH2: A-X1-D-P-X2-T-G-G-T-A-Y-S-X3-K-F-K-G, wherein X1 is I, X2 is E, Q, or N, X3 is Q or E; CDR-VH3: X1-R-E-G-D-Y-X2-Y-G-T-X3-D, wherein X1 is T, X2 is F or Y, X3 is I, V, or L; CDR-VL1: R-S-S-Q-T-X1-X2-Y-S-X3-G-N-T-Y-L-E, wherein X1 is I, V, or L, X2 is I, V, or L, X3 is D; CDR-VL2: K-X1-S-N-R-X2-S, wherein X1 is I, V, or A, X2 is F; CDR-VL3: F-Q-X1-S-H-X2-P-P, wherein X1 is G, X2 is L, V, or I; the antibody or functional fragment thereof binds to the N-terminal pro-brain natriuretic peptide antigen with an affinity of KD $\leqslant 9.2\times10^{-8}$ mol/L.".

The examiner during substantive examination holds that: The antibody or functional fragment thereof achieves specific binding to the antigen through a specific combination of 6 CDRs. Changes in CDR combination or changes in some or even one key amino acid within a CDR may significantly alter the binding ability with the antigen. The application only verifies experimentally that a small portion of mutant antibodies comprising 6 CDRs of specific sequences can achieve the claimed technical effect. Additionally, the application fails to demonstrate which amino acids in the antibody CDR sequences are key amino acids that are involved in antigen epitope binding, which amino acids are non-critical amino acids whose mutation does not affect antibody-antigen interaction, or what the combination requirements of amino acid residues at various sites in the CDR is to maintain the spatial structure required for intermolecular interaction. Thus, it would be difficult for those skilled in the art to predict that all the antibody mutants comprising the CDR framework defined in claim 1 achieve the same technical effect. Therefore, the CDR framework in claim 1 cannot be recognized as a special technical feature among the multiple groups of inventions involved in this application.

However, in the reexamination decision, the panel believes that: The multiple groups of antibodies claimed in this application originate from the same monoclonal antibody, all these antibodies can specifically bind to NT-proBNP, with only 1 or 2 amino acid differences at certain sites in each CDR region, while the amino acid sequence at other sites remain identical. That is, the multiple groups of antibodies in this application all carry the mutations described in mutant 1 (the newly-discovered parent antibody) in their CDR regions, and most of their CDR sequences are the same. These identical CDR region sequences constitute the common structure among the multiple groups of antibodies, and this common structure is essential for the specific antibody-antigen binding. Therefore, the common feature among the multiple groups of antibodies claimed in this application lies not only in that they are all anti-NT-proBNP antibodies, but also in that they originate from the same monoclonal

antibody (i.e., mutant 1) and share a common sequence structure in their CDR regions. However, neither Reference Document 1 or 2 discloses or teaches the anti-NT-proBNP antibodies comprising said common structure of CDR regions. Therefore, it cannot be concluded that the common feature as described above is not the special technical feature that define a contribution which the invention makes to the prior art.

It can be seen from the reexamination decision, the multiple NT-proBNP antibodies in this reexamination case have substantially identical CDR region structure, with mutations at only 1 or 2 sites. The common structure of CDR regions is not disclosed by the prior art, and it is expected that this common structure determines the specific binding between antibody and antigen (no existence of teaching-away evidence). Therefore, the claimed antibodies meet the "common property + common structure" standard and possess unity.

**b. Reexamination Decision No. 126053 (20170707)**

This application requests protection for multiple antibodies against K11-linked polyubiquitin, These antibodies share the same light chain CDR3 region, with other 5 CDR regions different from each other. The rejection decision holds that the claimed antibodies in this application do not have unity.

However, in the reexamination decision, the panel believes that: The common technical feature in structure and function of the multiple antibodies in this application is that all these antibodies are isolated antibodies that specifically bind to K11-linked polyubiquitin and comprise the same sequence of HVR-L3 (light chain CDR3), i.e., SEQ ID NO:4 (QQSYTTPPT). … Furthermore, it is widely known in the field that light chain CDR3 plays a crucial role in the antibody-antigen binding. For example, "Antibody Engineering" (2nd Edition) (edited by Zhiwei Dong et al., Beijing Medical University Press, June 2002) discloses that "The binding between an antibody and an antigen mainly involves the CDR surface, on which CDR1 and CDR3 of the heavy chain and CDR3 of the light chain locate centrally, while CDR1-L, CDR2-L, and CDR2-H partially close to the center and partially far from the center. Analysis of the utility of CDRs in antigen binding showed that only the two CDR3s are always involved in antigen binding, indicating the important role of CDR3 in antibody-antigen binding. CDR3 also plays an important role in Fv formation by the interaction between light and heavy chain variable regions. Changes in CDR3 not only affect the structure of the antigen-binding site, but also affect the stereoscopic conformation of Fv." (see pages 46-47, "Antigen Binding" section). Therefore, the importance of light chain CDR3 in antibody-antigen binding is commonly known in the field. As a result, the 16 antibodies in this application all have the function of binding K11-linked

polyubiquitin, and they all have a common HVR-L3 sequence structure that distinguishes them from the prior art and is essential for the function of binding K11-linked polyubiquitin. Therefore, the 16 parallel technical solutions in claims 1 and 7 possess unity.

It can be seen from the reexamination decision, the multiple antibodies in this case have a common light chain CDR3 region structure that distinguishes them from the prior art and plays an important role in the specific antibody-antigen binding. Therefore, the claimed antibodies meet the "common property + common structure" standard and possess unity.

**2. Common Property + Same Class of Compounds**

**a. Reexamination Decision No. 87342 (20150424)**

This application requests protection for multiple antibodies against RSV G protein. The rejection decision holds that the claimed antibodies in this application lack unity.

However, in the reexamination decision, the panel believes that: Based on the description and claims of this application, claims 1-11 request protection for six human monoclonal antibodies, namely 3D3, 3G12, 2B11, 1D4, 1G8, and 10C6. In addition to the common technical feature of binding to RSV virus A2 strain G protein (Ga and Gb), these six human monoclonal antibodies also share the following common technical features: (1) they all bind to the epitope within the residues 160-176 of RSV A2 virus strain G protein; and (2) they all possess the following two specific functions: an EC50 of less than 500ng/ml in the plaque reduction neutralization test (PRNT) and an affinity of less than 1nM to RSV A2 G protein measured by the open/close rate ratio. The epitope targeted by the murine monoclonal antibody disclosed in Reference Document 1 is the G13 epitope of the RSV A2 G protein located within residues 150-173, while the epitope targeted by the applicant's monoclonal antibody is within the 160-176 residues. It is evident that the epitope targeted by the two is different. Also, the Reference Document 1 does not disclose that its monoclonal antibody has the above two functions defined in claim 1. Finally, claim 1 of the present application encompasses six groups of antibodies, forming a Markush claim. Although the six human monoclonal antibodies do not share the same structure, they all target the epitope within the residues 160-176 of RSV A2 G protein and possess the aforementioned two specific functions. In other words, these antibodies may be interchangeable, with the expectation that the same intended result will be achieved, and may be considered as belonging to a recognized class of compounds in the field to which the invention pertains. In the absence of evidence showing that the above six human monoclonal antibodies have been disclosed in the prior art, the six groups of antibodies defined in the present application shall be considered as

belonging to a general inventive concept, possessing unity, and comply with the requirements of Article 31.1 of the Chinese Patent Law.

It can be seen from the reexamination decision, although the multiple antibodies in this case do not share a common structure, they target the same novel epitope, thus have the same properties or functions. Meanwhile, the antibodies are interchangeable, with the expectation that the same intended result will be achieved, and thus may be considered as belonging to a recognized class of compounds in the field to which the invention pertains. Therefore, the antbibodies satisfy the "common property + same class of compounds" standard and possessing unity.

Similarly, where the multiple antibodies in a single application do not share a common structure but target the same novel antigen, these antibodies should also possess unity.

**b. Reexamination Decision No. 110382 (20160606)**

This application requests protection for multiple anti-VEGF antibodies, which were obtained by mutating the CDR regions of a known antibody. The rejection decision holds that the claimed antibodies in this application lack unity.

However, in the reexamination decision, the panel believes that: The claims submitted in the reexamination request were limited to six antibody mutants. Although these six mutants own different structures, they all have reduced immunogenicity and belong to VEGF antibodies with reduced immunogenicity compared to a reference antibody with specific 6 CDR regions. In other words, the above antibodies all have the same property as above. While the Reference Document 1 does not disclose that mutating the CDR regions can reduce the immunogenicity of antibodies, nor does it describe any relationship between CDR region mutations and reduced immunogenicity. Therefore, in the absence of evidence showing that the common technical feature among the multiple technical solutions claimed in claim 1 have been disclosed in the prior art, it cannot be concluded that the common technical feature do not serve as the special technical feature among the multiple technical solutions. Therefore, the parallel technical solutions in claim 1 of the present application belong to a general inventive concept, and thus comply with the requirements of Article 31.1 of the Chinese Patent Law.

It can be seen from the reexamination decision, although the multiple antibodies in this case do not share a common structure, they all belong to mutant antibodies obtained by mutating the CDR regions of the same known antibody and all achieve the effect of reduced immunogenicity. While the prior art does not disclose that mutating the CDR regions of an antibody can reduce its immunogenicity. Therefore, these antibodies are interchangeable, with the

expectation that the same intended result will be achieved, and may be considered as belonging to a recognized class of compounds in the field to which the invention pertains. The multiple antibody mutants in this case satisfies the "common property + same class of compounds " standard and thus possesses unity.

## IV. Strategic Approaches to Overcoming Unity Issues in Antibody Patent Applications

The reexamination decisions discussed earlier generally adhere to the "common property or function + common structure/same class of compounds" standard when assessing unity in antibody patent applications. Ideally, if a group of antibodies within a claim shares a common structure, the argument for unity becomes straightforward: focus on how this shared structure differs from prior art and its crucial role in the antibody' s technical contribution. However, in practice, it's more often the case that multiple antibodies in a single application lack a common structure. When this occurs, it becomes essential to meticulously analyze the description and prior art, identifying how each antibody contributes to improved properties, and the specific structural features underpinning these improvements. By doing so, one can identify connections that categorize the antibodies as belonging to a recognized class of compounds within the same technical field, thus strengthening the argument for unity.

During the drafting stage, it's beneficial to clearly describe the correlation between the structure of the antibodies and the properties thereof in the specification. Highlighting common structural features among the antibodies and explaining how these features contribute to their properties will fortify the argument for unity. Moreover, if it has been clear during drafting that the antibodies within the application do not share a common structure, it is advisable to disclose as much experimental data as possible for each specific patent antibody, such as affinity, specificity, therapeutic activity, and immunogenicity, etc, and to record the same/similar performance improvement of these antibodies (e.g. compared to the same reference antibody). This proactive approach lays the groundwork for later demonstrating how these antibodies belong to "same class of compounds" in order to possess unity.

Addressing unity issues at the drafting stage is crucial. By anticipating potential objections or rejections, applicants can significantly reduce subsequent costs—both in terms of time and financial resources—associated with defending the patent's unity.

Given that Chinese examination practices currently lack detailed standards for assessing unity in antibody patents, the criteria applied can vary from case to case according to our practice. In light of this, we advise applicants and their

representatives to draw on the reexamination cases and response strategies discussed above. Actively engaging with examiners, and when necessary, citing relevant reexamination decisions, can help in crafting strategies that not only address unity issues but also reduce the search burden on examiners, while alleviating the economic pressures on applicants.

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