Exploration and Practice of Patent Protection Rules for Nucleic Acid Drugs in China[1]

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I. Introduction

After decades-long evolution, nucleic acid drugs have finally ushered in their "highlight moment" — the 2023 Nobel Prize in Physiology or Medicine once again affirmed the significant value of nucleic acids as drugs; and in 2024 when the investment market went cold, nucleic acid drugs have bucked the trend and received a number of patent transfer and corporate merger offers worthy of "one hundred million Chinese yuan" or "one hundred million US dollars"[2], which demonstrates a new trend that new quality productive forces lead the rapid development of the biopharmaceutical industry.

From 2018 when the first nucleic acid interference drug was approved for marketing to December 2024, twenty-four nucleic acid drugs (three of which have exited the market) and eight nucleic acid vaccines have been approved for marketing worldwide, more than two hundred have been approved for clinical trials, and the indications have also gradually expanded from rare diseases to common chronic diseases. With the expansion of market, it is expected that the market size thereof may reach ten billion US dollars in the next five years[3]. In recent years, nucleic acid drug industrial zones have been established in Kunshan of Jiangsu Province, Daxing District of Beijing, Fengxian District of Shanghai, Tianjin Economic Development Zone, etc., which have gradually formed corresponding production and research clusters. Following small molecule drugs and antibody drugs, nucleic acid drugs are becoming the third-generation drugs supporting the development of the biopharmaceutical industry.

Along with the vigorous development of technology and industry, the number of patent applications for nucleic acid drugs has surged domestically and internationally. Take nucleic acid interference drugs for example. The number of patent applications for nucleic acid interference drugs all over the globe has reached up to more than 9,000, wherein patent applications filed in China in 2022 and 2023 both accounted for more than 50% of the annual patent applications worldwide, ranking second in terms of the cumulative number of patent applications on the globe. While proactively seeking patent protection, innovative entities have also put forward their demands for changes in the patent system and adjustments to examination criteria, in hope of enhancing the predictability of patentability and stability of patent rights. At the current stage, it is the right time to clarify the patent protection rationales for such drugs and expound the protection rules compatible with the industrial de-

acid-based-therapeutics-market，2024年12月16日訪問。

[4] JPO《專利審查基準》的附件B特定技術領域適用例中的第2章"生物相關發明"第2.1(1)(e)、5.3(1)(i)節，https://www.jpo.go.jp/e/system/laws/rule/guideline/patent/handbook_shinsa/document/index/app_b2_e.pdf，2024年12月16日訪問。

[5] 黃利、朱薈彬："歐洲核酸藥物專利保護政策分析與思考"，《中國專利與商標》，2024年第4期。

[6] 第58530號無效宣告請求審查決定書（專利號201580072874.0）。

[7] 第89100號複審決定書（專利申請號201110035346.1）。

[8] 第1600294號複審決定書（專利申請號202111044203.7）。

[9] 第563156號無效宣告請求審查決定書（專利號201810143112.0）。

[10] 第89185號複審決定書(專利申請號201110105532.8)。

[11] 專利申請號201180026298.8。

[12] (2016)粵民終1094號民事判決書。

velopment process.

II. Prominent issues in relation to patent protection of nucleic acid drugs in China

First, the examination of patents in grant and invalidation proceedings is the foundation for the generation of patent rights and the source of patent protection. Through sorting out and investigating the current patent examination status of nucleic acid drugs, it can be clearly seen that the disputes mostly focus on how to define the scope of protection of inventions, how to determine the height of innovation and how to reasonably delimit the scope of protection of rights that are in line with technical contributions made, and the major reasons underlying these disputes lie in that patent acquisition rules are still in need of improvement, and related guiding cases are still lacking. In practice, for assessment of patents in relation to nucleic acid drugs, reference is usually made to those in relation to pharmaceutical compounds directly, in such a way that the technical characteristics of nucleic acid drugs *per se* can hardly be reflected accurately and policy requirements for intellectual property protection in new fields and new formats are hardly enforced in an effective manner, which in turn affects the consistency between standards and their actual implementation.

Second, patent infringement determination is a crucial step in patent protection. Patents in relation to nucleic acid drugs involve relatively professional technical principles and experimental data, which results in technical and legal difficulties in patent infringement determination. There are also huge controversies over the application of the doctrine of equivalents and few relevant precedents. Consequently, there is formed no reasonable expectation in the industry, thereby leading to various confusions about infringement determination and Freedom to Operate.

III. Connection between the technical characteristics of nucleic acid drugs and patent protection rules

As noticed by the industry, issues concerning the application of law where new technologies, new fields and new formats are formed have always been heatedly discussed and tricky. The authors are in an attempt to link the technical characteristics of nucleic acid drugs with the application of patent law closely in a bid to form crystal clear rules for patent protection.

A deep understanding of the technical characteristics of nucleic acid drugs is the foundation for objectively understanding inventions, accurately clarifying technical contributions and reasonably defining the scope of protection. At present, nucleic acid drugs can be mainly divided into two categories: small nucleic acid drugs and mRNA, wherein the small nucleic acid drugs include nucleic acid interference drugs (siRNA), antisense oligonucleotides (ASO), artificial miRNA (amiRNA), small activating RNA (saRNA), etc., and mRNA is further divided into mRNA drugs and mRNA vaccines. Patents involving the above subject matters demonstrate a series of common technical characteristics, which decides that they are subject to consistent rules for patent protection. Nucleic acid interference drugs, for example, are obviously different from the "compounds" and "genes" (namely, "encoding genes"), as well as representative biological macromolecules (e. g., "monoclonal antibodies"), as stipulated in the Guidelines for Patent Examination, in a series of distinctive characteristics, which are mainly embodied in the following three aspects: "multi-level structural characteristics", "trivial and contradictory prior art information" and "obscure structure-activity relationship".

First, nucleic acid interference drugs usually have structural characteristics at three levels, i. e., basic naked sequence, modification method and ligand selection, each of which has different impacts on the effect. The *in vitro* silencing effect mainly depends on its basic naked sequence, chemical modification is primarily aimed to enhance *in vivo* stability or other favorable properties, and the delivery system mainly has the cell membrane penetration effect and is also related to the specificity recruitment of nucleic acid molecules in organs and/or tissues. The silencing effect, stability and membrane penetration effect all have an impact on the final therapeutic effect to various degrees. It can be seen that the *in vivo* functional activity mainly depends on the overall effect of the basic naked sequence, modification method and ligand selection, or in other words, the verified *in vivo* technical effect of an invention results from the joint action of the basic naked sequence, modification method and ligand selection, and meanwhile the *in vivo* long-term mechanism of nucleic acid interference drugs is directly associated with chemical modification, delivery,

dosage, administration, etc., thereof.

Second, the so-called sequence design "rules" disclosed in the prior art are usually derived from limited samples summarized by different innovative entities from their own perspectives using non-public statistical methods. The conclusions drawn thereby are over-general and impertinent, and there are many exceptions to these rules. Therefore, such "rules" are susceptible to contradiction and incompatibility, and can hardly provide clear technical guidance for sequence design, such that nucleic acid interference drug products created on the basis of such a design do not necessarily have the expected functional activities, and it is still necessary to obtain candidate products through high throughput screening in the process of research and development and have them verified through further experiments.

Third, the structure-activity relationship of nucleic acid interference drug molecules is often unclear, which does not suffice to evaluate the predictability of technical effects. Drug molecules for different target sequences may have different activity levels. Even the same drug molecule may demonstrate greatly different activities *in vitro* and *in vivo*. In the process of research and development, it is still necessary to further select candidate products with higher activity *in vitro* through *in vivo* experiments. What's more, the functional activity of the same drug molecule also varies greatly in different delivery systems *in vivo*.

Based on the above analysis, we make a comparison between the structural characteristics of the nucleic acid drugs, monoclonal antibodies and encoding genes.

	Nucleic acid drugs	Antibodies	Encoding genes
Structural clue	Reverse complement of the target sequence	Randomly prepared and obtained by screening	Identical function, High homology
Structural hierarchy	Naked sequence Modification method Ligand selection	Six CDR regions Framework regions Constant regions	Encoding region Structural domain/ structural unit
Structural variation	Appropriate extension along the target sequence Position effect	Replacement of Fc region/CDR transplantation	Single mutation may lead to loss of activity

Table 1 Structural characteristics of nucleic acid drugs, monoclonal antibodies and encoding genes

The above technical characteristics determine that the basic patent examination principles that are applicable to inventions with those subject matters can be roughly summarized as follows: "to differentiate different structural levels and experimental levels", "to expand the scope of protection cautiously" and "to consider the prior art as a whole". To be specific:

First, account shall be taken of the structural hierarchy defined in the claims of the invention, as well as the level and degree of the effect experiment recited in the description of the invention. As for the claimed nucleic acid molecules, it is required to distinguish whether their structural hierarchy is nucleic acid molecules expressed solely by the naked sequence, or those modified and/or matched with the delivery system. When construing the technical features of the technical solution, consideration shall be given to not only the structural characteristics of each hierarchy itself, but also the combination relationship between various hierarchies. Different structural hierarchies may provide nucleic acid molecules with new functional effects, and affect the most basic inhibitory activity to varying degrees. As for the claimed nucleic acid molecules having different structural hierarchies, it is necessary to pay attention to whether the description recites the corresponding effect experiments, and differentiate the *in vitro* experiments and/or *in vivo* experiments essential for verifying different types of functional effects, with the focus on the identification of the effects that can only be verified by *in vivo* experiments. On this basis, efforts shall be made to correctly understand the content disclosed in the description and the technical solutions defined in the claims, as well as the correspondences therebetween.

Second, a prudent attitude shall be adopted when examining claims that are overly broad in generalization so as to avoid granting the right to the claims, the technical effect of which cannot be predetermined. As for the drafting manners that include the terms "comprising/including" and "hybridization" and other variants, it is usually required to examine whether the patent description adequately verifies the functional effects of various nucleic acid molecules within the scope of protection of the claims, and analyze and take into account the reasonability of the limitations on sequence length according to information disclosed in the description. Accordingly, as for the interpretation of the scope of protection of the claims in infringement determination, it is required to bear in mind the technical characteristics in

this field, together with the substantive contribution of the invention, to expand the scope of protection of the claims moderately under the doctrine of equivalents.

Third, in the inventive step assessment, we should draw special attention to the overall technical information disclosed in the prior art, and avoid either citing a portion of mutually contradictory technical contents in the prior art in an isolated and one-sided manner or extracting segmented phrases from the overall technical solution in the prior art as the teaching in the assessment of inventive step of the invention. For instance, consideration shall be given to whether the nucleic acid drug molecule sequence disclosed in the prior art is one of the hundreds of roughly disclosed candidate sequences or a specific preferred molecule purposefully selected and verified and whether the sequence design rule disclosed in the prior art is one of the mutually contradictory or incompatible rules or a clear rule directed to a specific target, all of which have an important impact on the assessment of obviousness of the invention.

IV. Comparison of rules for protecting nucleic acid drug patents in various countries

Issues in relation to nucleic acid drugs, which are a representative of new technical fields, are heatedly discussed in patent protection practices in various countries. Since it is a relatively new topic, only the Japan Patent Office (JPO) has definitely set forth the provisions on nucleic acid interference drugs (RNAi) in the Examination Guidelines for Patent: "A non-coding nucleic acid may be described by specifying the nucleotide sequence. Further, a non-coding nucleotide may be described by specifying the target gene. Example 1: A probe whose nucleotide sequence is represented by SEQ ID No. X. Example 2: An siRNA targeting XX gene whose nucleotide sequence is represented by SEQ ID No. X." and "in a case where a nucleotide sequence of a gene A is publicly known, if it is not difficult to select a target domain, an invention of an antisense nucleic acid or siRNA to the gene A does not involve an inventive step. However, if the antisense nucleic acid or siRNA has advantageous effects that a person skilled in the art cannot expect, the invention of said antisense nucleic acid or siRNA involves an inventive step." [4] No written provisions are stipulated by the United States Patent and Trademark Office (USPTO) and the European Patent Office (EPO).

Through sorting out and analyzing a great number of cases, we can summarize the following rules: as for the tendency from basic patents and platform patents at the beginning of technological development to the later application-oriented patents, the patents granted in various countries have undergone a process in which the scope of protection has been narrowed down from broad protection to precise protection; and meanwhile, the USPTO has also narrowed down the scope of patent-eligible subject matters, clarifying that naturally existing DNA and corresponding oligonucleotide primers are not subject matters susceptible for patent protection, which directly led to the fact that the related US patents filed later all clearly define the chemical modifications of nucleic acid sequences. However, the EPO and JPO have not made any adjustment to the relevant policies.

Although various patent offices hold substantially the same views on the rationales for assessing novelty and inventive step, which has aroused wide concerns, there still exist a series of obvious differences. The Table 2 (see next page) is a comparative analysis of standard practices of the USPTO, EPO and JPO in the examination of nucleic acid interference drugs.

Regarding patent infringement determination, there are several cases under trial in Europe and the United States. In April 2023, Arbutus and Genevant filed a lawsuit in the United States against Pfizer and BioNTech on the grounds that the production and sale of the mRNA-LNP COVID-19 vaccine, Comirnaty, have infringed on five patents of Arbutus and Genevant. In August 2024, Moderna also filed a lawsuit against Pfizer and BioNTech in the United States and Germany simultaneously, claiming that their vaccine infringed on its patents relating to its mRNA technology filed during the period from 2010 to 2016.

It can be seen that the rules for patent protection of various countries share many things in common, and foreign theoretical practice is valuable as a beneficial reference for China. It is appropriate to take it as a reference to study and propose detailed rules for patent protection in China.

V. Exploration and practice of patent protection for nucleic acid drugs in China

In order to further expound the rules for patent protection of nucleic acid drugs, efforts have been made in a bid to analyze and explain, on the basis of actual cases, controversial issues such as the understanding of key terms in claims, reasonable summary of different hierarchical structures, judgment on teachings in the assessment of inventive step, and the application of the doctrine of equivalents in infringement determination.

1. Understanding of terms "comprising / including" or "having"

Nucleic acid drug molecules defined by nucleic acid sequences are in essence biological macromolecules, which can be comparable to drug compounds. The expression that the sense/antisense strand "comprising/having a nucleic acid sequence" should not be understood as the sense/antisense strand that can be added, at both ends, with any sequence. For instance, on the premise that the functional activity of the core sequence of the nucleic acid drug molecule has been verified, the addition of other sequence involving technical contributions not made by the invention to the core sequence structure usually requires no impact on the functional activity of the core structure of the nucleic acid drug. Hence, those skilled in the art can understand that "comprising/having" in the claims is premised on no impairment to the complementarity between the core sequence and the target RNA sequence.

[Case 1][6] Claim 1 relates to a double stranded RNAi agent for inhibiting expression of hepatitis B virus (HBV) in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises a core sequence indicated by SEQ ID NO:1 composed of 19 nucleotides and having no more than 21 nucleotides in length, and the antisense strand comprises a core sequence indicated by SEQ ID NO:2 composed of 21 nucleo-

<table>
<tr><th>Is the Target Known ?</th><th>Is There at Least One Oligonucleotide against This Target ?</th><th colspan="2">Novelty ?</th><th colspan="2">Inventive Step ?</th></tr>
<tr><td rowspan="3">No</td><td rowspan="3">No</td><td>USPTO</td><td rowspan="3">Yes, because the target is new (functional definition possible; however, in the US the oligonucleotide must have a modification to be eligible).</td><td>USPTO</td><td>Yes, but the USPTO could refuse a patent on the target.</td></tr>
<tr><td>EPO</td><td>EPO</td><td>Yes, because the target is new.</td></tr>
<tr><td>JPO</td><td>JPO</td><td>Yes, but the means-plus-function limitation renders the claim ambiguous.</td></tr>
<tr><td rowspan="3">Yes</td><td rowspan="3">No</td><td>USPTO</td><td rowspan="3">Yes, because it is the first oligonucleotide used in therapy (however, in the US, the oligonucleotide must have a modification to be eligible and a functional definition is not possible)</td><td>USPTO</td><td rowspan="2">Yes, if the oligonucleotide has a particular functional characteristic.</td></tr>
<tr><td>EPO</td><td>EPO</td></tr>
<tr><td>JPO</td><td>JPO</td><td>Yes, if the oligonucleotide targets a particular region.</td></tr>
<tr><td rowspan="3">Yes</td><td rowspan="3">Yes</td><td>USPTO</td><td rowspan="3">Yes, if the oligonucleotide has a different sequence/structure (e.g., with modifications) than oligonucleotides of the prior art (However, in the US, the oligonucleotide must have a modification to be eligible and a functional definition is not possible).</td><td>USPTO</td><td rowspan="3">No, unless the oligonucleotide has an unexpected or new property compared to the oligonucleotides disclosed in the prior art (e.g., addition of a new modification, surprising effect) or if the oligonucleotide targets a particular region (e.g., a particular region of a gene).</td></tr>
<tr><td>EPO</td><td>EPO</td></tr>
<tr><td>JPO</td><td>JPO</td></tr>
</table>

Table 2 Comparison of standards for assessing novelty and inventive step in the USPTO, EPO[5] and JPO

tides ad having no more than 23 nucleotides in length. The description fully describes the technical information about adding one or two nucleotides respectively to the core sequence to form a protruding end structure, and verifies the functional activity of two representative nucleic acid molecules based on such a design, thereby confirming that the double stranded RNAi agent of this kind can effectively inhibit HBV expression.

In this case, the sense and antisense strands of the nucleic acid molecule are defined in the claims by means of "a core sequence" and a length. From the perspective of those skilled in the art, such a drafting manner should be understood as the sense and antisense strands with at least one or two nucleotides added at both ends respectively on the basis of the core sequence, and the double stranded RNA (dsRNA) formed thereby still maintains the sequence complementarity between the core sequence and the target RNA so as to ensure its basic functional activity.

2. Understanding of terms "hybridize" and "complementarity"

The limitation of the antisense strand "capable of hybridizing/complementing a certain nucleic acid sequence" in a claim indicates that the nucleotide sequence not only corresponds to the target sequence that it acts on, but also has been extended to many sequences having a high degree of sequence identity with the target sequence. It can be seen that the actual scope of protection of such a limitation manner is much greater than that of the subject matter defined by the target sequence.

[Case 2][7] Claim 1 relates to use, in the manufacture of a medicament for glaucoma, of a composition comprising an effective amount of interfering RNA having a length of 19 to 49 nucleotides, and defines that the interfering RNA comprises a sense sequence, an antisense sequence and a region of at least 80% contiguous complementarity of 19 nucleotides between the sense and antisense sequences; wherein the antisense sequence hybridizes under physiological conditions to a particular mRNA target sequence, and has a region of at least 80% contiguous complementarity of 19 nucleotides with the hybridizing portion of mRNA.

In this case, the expression "at least 80% contiguous complementarity of 19 nucleotides" means that there are at least 16 contiguously complementary nucleotides, the expression "an effective amount of interfering RNA having a length of 19 to 49 nucleotides" means that 3 to 33 nucleotides may be further added, and the expressions "contiguous complementarity" and "hybridize…a portion of" further cover many nucleic acid sequences that are complementary to the target sequence, the scope of which is much greater than the scope of protection defined by the original particular mRNA target sequence.

3. Reasonable generalization of target genes/target sequences

The claims in relation to nucleic acid drugs defined by long target gene sequences cover a great number of optional target sequences. If the description only recites the effect data about nucleic acid drugs concerning one or two particular target sequences, and the structure-activity relationship of the nucleic acid drug molecules has not been clear yet, it is difficult for those skilled in the art to expect that all the nucleic acid drugs within said scope have similar technical effects and can solve the corresponding technical problems. Such a generalization cannot be supported by the description.

[Case 3][8] Claim 6 relates to the application of siRNA for down-regulating PRMT2 gene expression in the preparation of medicaments inhibiting the natural immune TLR4/IRF3 signaling pathway. The description devises three siRNA molecules for human PRMT2, and the effect experiments verify that only one siRNA molecule has inhibitory activity, while the other two demonstrate no activity at all. It is known in the prior art that down-regulating PRMT2 gene expression can effectively inhibit the TLR4/IRF3 signaling pathway, but the exact way to design the siRNA sequence of this gene is not clear.

In this case, the target gene PRMT2 has 22 transcripts with a length of about 1000 to 6000bp, which covers a huge number of optional target sequences; however, the rules for selecting a suitable target sequences are recited in neither the description nor the prior art, and only a portion of exemplary siRNA molecules for specific target sequences have inhibitory activity. Therefore, in the absence of clear guidance, the inhibitory effect of the claimed siRNA molecules on the target genes and/or the therapeutic effect thereof on the diseases still need to be selected and verified through undue experiments, thereby rendering the technical solution of the claim unsupported by the description.

4. Reasonable generalization of delivery system

The sense strand and delivery ligand of siRNA are connected by a covalent chemical bond, and are relatively independent, i.e., they are likely to be collaborated and replaced mutually. If the improvement of the invention over

the prior art lies in the selection of nucleic acid sequences and/or the chemical modifications thereof and those skilled in the art can fully expect, based on the particular ligand verified in the description, the delivery ligand of the same kind also have similar properties and achieve a similar technical effect, it is generally allowed to make reasonable generalization about the type of such delivery ligands.

[Case 4] [9] Claim 1 relates to a double stranded RNAi, and defines the core sequence structure, chain length and chemical modifications, as well as that the sense strand is conjugated to one or more GalNAc ligands. The description discloses hundreds of related RNAi agents, and verifies the functional activity thereof, wherein the sense strands thereof are all conjugated to the particular ligand L96, which is one of the examples of the GalNAc ligands.

In this case, the dispute focuses on whether the generalization of the types of GalNAc delivery ligands in the claims is reasonable. According to the description, the improvements of the siRNA sequences over the prior art lie in the selection and modification thereof. L96 is merely an exemplary GalNAc ligand that functions to select siRNA sequences and modifications with high functional activity. Meanwhile, the description of the present application and the prior art both teach other types of GalNAc ligands suitable for RNAi agent. Although the specific selection of ligands may have a certain impact on the *in vivo* functional activity of nucleic acid drugs, those skilled in the art are capable of selecting a suitable ligand to be conjugated to the sense strand in the claims so as to form the RNAi agent that can inhibit the target gene expression. The technical solution of the claim can be supported by the description.

5. Judgment on teachings in the inventive step assessment

For an invention involving a nucleic acid drug, if there is no improvement on the selection of the modification or delivery ligand, the distance on the target gene between the claimed target sequence and the known target sequence in the closest prior art exceeds the conventional length scope of the target sequence of the nucleic acid drugs so that they obviously do not belong to the same target, and the invention has achieved good technical effects with respect to the prior art in terms of activity, chemical stability or long-term effect, then the invention involves an inventive step.

[Case 5] [10] The invention relates to a recombinant adenovirus aiming at a c-Met gene RNA interference, which has a human c-Met gene siRNA expression sequence, and comprises sequences of both sense strand and antisense strand of the siRNA; the description recites that the target sequences of the siRNA are located in the 242 to 260 regions downstream of the start codon, and the inhibition efficiency reaches up to 70%. The closest prior art discloses a recombinant adenovirus inhibiting a c-Met gene expression, wherein the target sequences of the siRNA are located in the 349 to 369 regions downstream of the start codon, and the inhibition efficiency is merely about 50%.

In this case, the target sequences of the invention are far away from those in the closest prior art, from which it can be known that they do not belong to the same target. Furthermore, different innovative entities in the prior art induced complicated and contradictory sequence design rules through their self-created statistical methods, which fail to provide clear and pertinent technical guidance for the selection of the c-Met gene target sequences, thereby rendering the technical effects unexpectable. Meanwhile, the recombinant adenovirus product of the invention has the functional activity for medicinal purposes. Hence, the invention is found to involve an inventive step. If the target sequences of the nucleic acid drug invention partially overlap with or are close in position to the target sequences in the closest prior art, an overall analysis shall be conducted in consideration of the technical problem actually solved by the invention and on the basis of the functional activities of the nucleic acid drug molecules corresponding to respective potential target points near the known target sequences in the specification and relevant evidence so as to determine whether it is easy to determine the partially overlapping or positionally close target sequences by the technical means of "walking", thereby obtaining the claimed nucleic acid drug molecules.

[Case 6] [11] The claim relates to the use of an siRNA molecule that inhibits TRPV1 in the manufacture of a medicament for the treatment of an eye disease, and defines the entire nucleotide sequence of the siRNA molecule; and the description verifies the inhibitory activity and therapeutic effect. Reference 1 discloses the above-mentioned use of another siRNA molecule that inhibits TPRV1. The present application is identical to Reference 1 in terms of the length of siRNA, namely, 19 nucleotides in length. The nucleotides 3-19 of the siRNA of the present application are the same as the nucleotides 1-17 of Reference 1, which means the target sequences of the present application and Reference 1 partially overlap with each other. With respect to said Refer-

ence, the present application is only different in two nucleotides moving forward in parallel (namely, "walking") on the target gene sequence. The comparative experiment submitted by the applicant proves that the siRNA molecule of the present application has a significantly higher inhibition rate and a longer-lasting inhibition effect than the siRNA in the reference document and other siRNAs obtained by means of "walking".

In the present case, it is a conventional technical means to obtain a target sequence, which is similar to the target sequence in the prior art in terms of position and activity, by means of "walking". However, where the comparative experimental results demonstrate a greatly improved effect, the technical problem actually solved by the invention is not to "obtain an siRNA molecule having a similar structure and activity", but to "make a significant improvement in functional activity". Since the prior art does not teach the law of siRNA activity change, those skilled in the art, without clear guidance, cannot reasonably expect that the siRNA molecule with significantly improved functional activity at the existing target sequence can be successfully obtained by means of "walking". Therefore, it can be determined that the prior art fails to provide sufficient teaching, and the invention involves an inventive step.

6. The application of the doctrine of equivalents in patent infringement determination

The effective link-up between the patent infringement determination procedures and the patent grant and invalidation proceedings can promote the innovation and protection of patented technologies with authentic potential application value. The patent grant and invalidation proceedings are aimed to weigh up the scope of protection proposed by an applicant and make it compatible with the contribution objectively made by the invention. The utmost concern is about the legal certainty of the scope of protection of the invention after the grant and invalidation proceedings. The relevant patent examination standards shall be reasonably adjusted in the hope of adapting to the rapid development of the current biopharmaceutical technologies. However, the infringement determination procedures are conducted on the basis of the scope of protection of the invention determined in the patent grant and invalidation proceedings. Consideration shall be given to how to determine a reasonable scope of protection of invention in the event that the claim terms have been fixed, so that the accused infringers cannot easily evade patent infringement by means of altering patented technologies in an obvious manner while the public interest remains not impaired. As for claim construction in invalidation proceedings under the current stringent grant and invalidation rules, account shall be taken of the technical characteristics of nucleic acid drugs and the substantive contribution of the invention to expand the scope of protection of claims moderately.

For instance, reference can be made to the existing approach for determining biological sequence infringement.[12] Even though the granted patent claims are required to be drafted in a close-ended format and the sequence in the allegedly infringing product differs from the claimed sequence in terms of the expansion of a few residues, if the extended sequence has no impact on the realization of the final product function, infringement under the doctrine of equivalents may be found. Such a rule will be helpful in preventing others from evading infringement liability through minor modifications and protecting the patentees' innovative achievements in a reasonable and legal manner.

VI. Conclusion

Nucleic acid drugs are typical representatives in new fields and new forms, and also a hot research and development direction for innovative drugs. Compared with biological macromolecules such as monoclonal antibodies and polysaccharides, nucleic acid drugs are easier to be reversely analyzed. After determining the sequence structure, people can also imitate them using conventional chemical synthesis methods. These technical characteristics of the nucleic acid drugs determine that only strengthened patent protection for them can provide innovation entities with reasonable motivation and appropriate encouragement for innovation. Establishing patent protection policies for nucleic acid drugs that can not only stimulate the innovation vitality of market entities through intellectual property protection, but also avoid overly broad and inappropriate patent rights from hindering the overall development of the industry will give play to the "two-way transmission" function of patent grant and invalidation proceedings, which encourages innovation and promotes application, and promote the high-quality development of the biopharmaceutical industry in the form of creative quality-driven productive forces.

In recent years, with the advent of the new era of biopharmaceuticals and precision medicine, the research, development, and industrialization of nucleic acid drugs have

been booming. They are hailed as the "third wave of pharmaceutical manufacturing" after small molecule drugs and antibody drugs, and have become a highlight of innovative development. The drug patent protection policies also need to evolve rapidly together with the development of medical technology and industrial needs. This article has systematically reviewed the exploration and practice of rules for protecting nucleic acid drug patents in the hope of providing a guidance for a large number of innovation entities in the industry. At the same time, taking nucleic acid drug patents as an example to probe into patent protection in new fields and new formats will gradually improve patent protection methods and examination standards in practice, clarify the application of laws for hot issues, and strengthen intellectual property protection in new fields and new formats. ■

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[7] The Reexamination Decision No. 89100 (Patent Application No. 201110035346.1).

[8] The Reexamination Decision No. 1600294 (Patent Application No. 202111044203.7).

[9] The Invalidation Decision No. 563156 (Patent Application No. 201810143112.0).

[10] The Reexamination Decision No. 89185 (Patent Application No. 201110105532.8).

[11] Patent Application No. 201180026298.8.

[12] The Civil Judgment No. Yueminzhong 1094/2016.

AI Action Summit Opens in Paris

The Artificial Intelligence (AI) Action Summit opened in February in Paris, France, focusing on the discussion of global AI governance.

"It is high time that we move from science fiction to the real world of application of AI," Anne Bouverot, France's special envoy for AI, said at the opening ceremony.

She stressed that digital transformation, including AI development, should align with ecological transition efforts. She also urged participants to focus on AI applications that serve the public interest.

Many participants agreed that China's open-source AI models play a significant role in advancing open and inclusive AI development. Capgemini CEO Aiman Ezzat praised China's AI company DeepSeek for its model's openness and energy efficiency.

In recent years, with the accelerated convergence of innovative elements, China's AI technology has developed rapidly. The Patent Landscape Report on Generative Artificial Intelligence, published by the World Intellectual Property Organization (WIPO) in 2024, showed that from 2014 to 2023, China's patent applications for generative AI exceeded 38,000, ranking the first in the world.

Sources: Xinhua and China IP News