Patenting genetic scissors: the global landscape and an Indian perspective

Manisha Singh, Partner, and Neha Ruhela, Senior Associate, of LexOrbis evaluate the use and patentability of the CRISPR-Cas system in India compared to the global landscape.

Genome editing is a group of technologies that provide the ability to change an organism's DNA. It allows genetic material to be added, removed, or altered at particular locations in the genome. The 2012 discovery of a new genome-editing method, widely known as CRISPR-Cas system, has triggered a revolutionary wave in the field of biotechnology. The 2020 Nobel Prize in Chemistry was awarded for CRISPR genome-editing. CRISPR technology has enormously higher precision, efficiency, strong specificity and effectiveness when compared to previously known genome-editing methods. In a very short span, CRISPR technology has demonstrated its near-unlimited potential and solution for therapeutics, diagnostics, medicine, and agriculture.

CRISPR-Cas editing

The acronym CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats, which are the hallmark of a bacterial defense system that forms the basis for CRISPR-Cas genome-editing technology. The CRISPR-Cas system, often described as 'genetic scissors', makes it possible to search, cut, remove and even replace a mutation in the genome – analogous to 'find-delete-replace' functions in computer word processors. The CRISPR system consists of two parts – a tailor-made guide-RNA and a Cas (CRISPR-associated) protein. Guide-RNA shepherds the Cas protein to a particular region of the genome and then the Cas protein cuts the target DNA. After DNA is cut, the cellular auto-mechanism (an easier process) or alternatively, insertion of a new DNA (a more difficult process) repairs the break in the region of the cut.

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CRISPR patent map

Using appropriate search string[1], the WIPO database retrieved more than 6,300 patent families for published documents. The trend in worldwide patent numbers has increased from around a dozen filings per month in 2014 to a monthly average ranging from 100 to 150 filings in 2022. With the substantial domination by China and the US over other key players including South Korea, Japan, and European Union, the global CRISPR patent landscape shows strong geographical biases.

Although China outnumbers the US for filings, the foundational patents of the CVC group (University of California, University of Vienna & Nobel co-laureate Emmanuel Charpentier) filed in 2012, as well as the Broad group (Broad Institute, University of Harvard & Massachusetts Institute of Technology) filed a few months later in 2013, have truly revolutionized the whole patent landscape. Globally, the top five positions are predominantly held by the Broad and CVC group and its spinoff. The next five rankings include three agricultural & one medical university of China and another Broad's spinoff. It is interesting to note that all the top 10 applicants/assignees are universities/institutes or their spinoffs. Big Pharma, such as Pfizer and Bayer, are also entering into the gene-editing space

through collaboration with successful CRISPR start-ups. Such partnerships could be a point of inflection for the gene-editing industry.

Under Indian jurisdiction, so far more than two hundred CRISPR patent documents have been published which include a lesser number of domestic filers. The evolving patent landscape of CRISPR is yet to be developed fully in India. Considering its promising demographic dividend and huge market, India has immense potential for use of CRISPR-based applications, particularly in affordable healthcare, agriculture & allied sector, and bio-energy. The grant of a few CRISPR-Cas9 patents brings significant advancement for the Indian patent regime and underlines India's ambition for gene-editing.

Crossing the patentability barrier

In February 2022, in *CVC v Broad*[2], the US Patent Trial and Appeal Board (PTAB) decided the long-running, complex, and intriguing IP dispute – 'who first invented the foundational patent for CRISPR-Cas9 editing in eukaryotic cells' in favor of the Broad Institute. PTAB ruling held that the Broad group was the first to prove the CRISPR-Cas9 technology worked in plants and animals including humans. However, CVC's appeal against the PTAB decision is likely on the way. *Per contra*, the game is playing out on a different footing at the European Patent Office (EPO) where the Opposition Division and Boards of Appeal ruled that the CVC group held the first-generation CRISPR-Cas9 patents. These IP wars on various fronts are *per se* sufficient to underscore the commercial prospects of CRISPR.

The major hurdles the CRISPR technology may face in the Indian Patent Office (IPO) are exclusions under clause (b), (i) and (j) of section 3 of the Patents Act, 1970 as below:

1. Ordre public doctrine [section 3(b)]

The public order and moral aspect as well as apprehension over commercial exploitation of germline-editing can be traced into Article 27.2 of the TRIPRS agreement and its statutory doppelganger viz. section 3(b) of the Indian Patents Act which bars patentability of *"an invention the primary or intended use or commercial exploitation of which could be contrary public order or morality or which causes serious prejudice to human, animal or plant life or health or to the environment"*. However, the application of this provision solely rests at the discretion of the Controller who often raises bald objections of public order or morality leading to the rejection of grant or deletion of certain claims. Hence, this

Résumés

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Manisha Singh is the Founder Partner of LexOrbis. Manisha is known and respected for her deep expertise in prosecution and enforcement of all forms of IP rights and for strategizing and managing global patents, trademarks, and design portfolios of large global and domestic companies. Her keen interest in using and deploying the latest technology tools and processes has immensely helped the firm develop efficient IP service delivery models and provide best-in-the-class services. She is also known for her sharp litigation and negotiation skills for both IP and non-IP litigations and dispute resolution. She is involved in a large number of intellectual property litigations with a focus on patent litigations covering all technical fields – particularly pharmaceuticals, telecommunications, and mechanics. She has been involved in and successfully resolved various trademarks, copyright, design infringement, and passing off cases in the shortest possible time and the most cost-efficient manner applying out-of-box strategies and thinking. She is an active member of many associations like INTA, APAA, AIPLA, AIPPI, LES, FICPI, and is actively involved in their committee work. She is an active writer and regularly authors articles and commentaries for some of the top IP publications.

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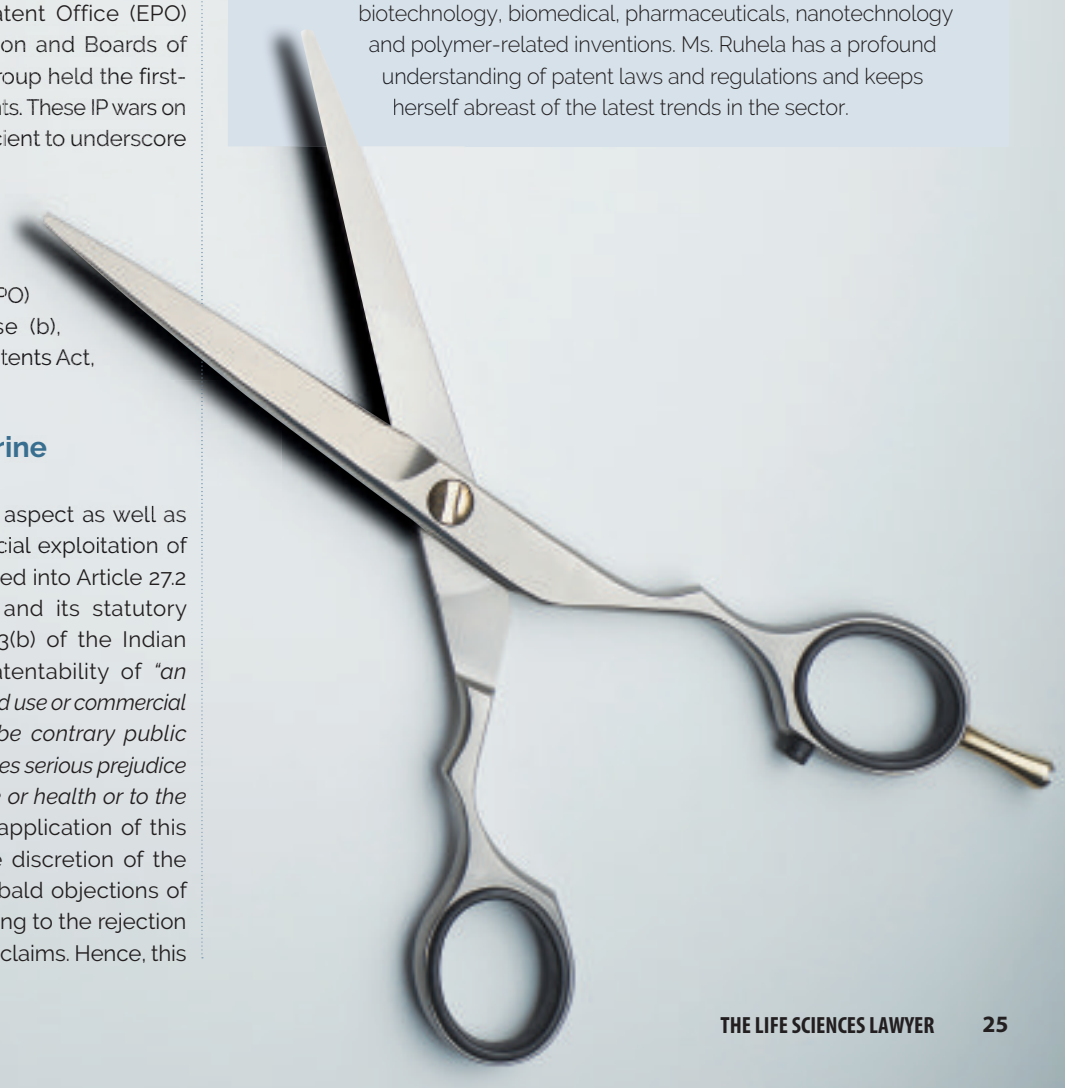

widely worded provision is without any sufficient guidance or safeguards against the arbitrary exercise of power by the Controller. To provide definiteness, the Indian Parliamentary Committee in its remarkable IPR review recommended that section 3(b) be amended to limit the exclusion to only those inventions which are barred under any law for the time being in force.

Concomitantly, the prevailing Indian Guidelines for *'Gene Therapy Product Development and Clinical Trials'* (2019) clearly prohibit germline gene therapy, due to ethical and social considerations. But it also suggests that somatic cell editing may be the more socially acceptable approach because it is not passed on to subsequent generations. Such regulatory flexibilities should also be considered while assessing the non-patentability through the lens of *ordre public*.

2. Method of medical treatment [section 3(i)]

This exclusion is embedded in Article 27.3(a) of the TRIPS agreement which states: *"Members may exclude from patentability diagnostic, therapeutic and surgical methods for the treatment of humans or animals"*. Most countries, including members of the European Patent Convention (EPC), Canada, New Zealand, China, Japan, and India exclude or limit the patentability of methods of medical treatment. Under such limitations, beneficial CRISPR-based therapy and diagnosis patents are likely to face challenges.

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TRIPS flexibility for 'method of treatment' exclusions reflects variations in statutory approaches. For instance, India has taken extra care to prevent exclusivity over the commercial use of medical treatment. Section 3(i) of the Indian Patents Act forbids *"any process for the medicinal, surgical, curative, prophylactic diagnostic, therapeutic or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products."* Whereas the Article 53 (c) of EPC excludes *"methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body"*. The phraseology of Indian exclusion may seem close to that of EPC in letter, but in spirit and practice the scope of Indian provision is wider than that of the European counterpart.

As an example, IN Application No 201827014776, the Controller applied section 3(i) objected to claims by merely stating that *"said technology is a method of diagnosis which is not allowable as per above mentioned section"*, which resulted in the narrowing of claims to *"an in-vitro non-therapeutic, non-diagnostic method for detecting pyrogens"*.

IPO interprets 'method of medical treatment' exclusion in a broader manner, hence enlarging a lesser protection to such inventions. Most countries do not bar diagnostic methods that can be carried out separately *(in vitro, ex vivo)*

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from the body. However, IPO refuses these applications by stating that the section 3(i) does not mark any distinction between *in vitro* and *in vivo* methods. Applications No. 201621022807 and 201741015794 have been refused by IPO, wherein the claims recite *"an in vitro multiplex PCR assay"* and *"method for detecting at least one biomarker in a sample"*, respectively.

Also, the exclusory section 3(i) has not yet undergone judicial scrutiny by Indian courts. IPO should update its examination procedures and practices to take this patentability limitation into account and to publish guidance clearly explaining the ambit of exclusion for CRISPR therapeutics and diagnostics.

3. Plant & animal and their variety [section 3(j)]

Section 3(j) of the Patents Act blocks patenting plants and animals in whole or any part thereof including varieties. In particular, genome-edited plants cannot be patented in India. However, India has a *sui generis* system – Protection of Plant Varieties and Farmers Rights Act (PPVFRA) granting IP rights to plant breeders who have developed any new plant varieties. Indian research groups are advancing on gene-editing applications in plants including high-yielding rice, high vitamin-A bananas, and improved mustard and papaya. In 2022, India also exempted genome-edited plants (which are free of exogenous introduced DNA) from stringent biosafety assessment[3]. Thus, the evaluation and release of a genome-edited plant as a new variety shall be governed as per other applicable laws including PPVFRA.

Parting comments

The global gene-editing market size was valued at USD 5.2 billion in 2020 and it is expected to reach USD 18.5 billion in 2028 with a forecasted CAGR of 17.2%. CRISPR breakthrough innovations are shaping the future of biotech. It offers unparalleled promises of curing the genetic and complex diseases. Institute of Genomics and Integrated Biology is exploring the possibility of CRISPR-mediated genetic correction of sickle cell disease through a clinical trial. During the pandemic, India launched a CRISPR-based test (FELUDA) for rapid and sensitive Covid-19 diagnostics. India is progressing towards unlocking gene-editing powers which can lead to swelling in patent numbers as well.

Despite few patentability limitations as outlined above, prudent drafting of claims for gene-editing inventions can be achieved with the assistance of a skilled service provider with legal knowledge and sound technical proficiency in the subject matter. Experts having acquaintance with genetic engineering techniques, gene therapy, spectrum of Cas proteins, sectoral regulations, and patent practices can guide the applicants to reap the benefits and obtain maximal possible protection of their inventions under the Indian patent regime. Besides, patent advisors abreast of nuances of patentability across the global gene-editing landscape would facilitate the patenting process more efficiently.

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