MOUSETRAP: INSUFFICIENCY TRAPS TWO 'GROUND BREAKING' PATENTS IN *REGENERON v KYMAB*

ANGUS MILNE AND DR BRIAN WHITEHEAD
Haseltine Lake Kempner LLP

Overview

The Supreme Court has set out a definitive assessment of the sufficiency requirement for UK patents in its recent judgment in *Regeneron v Kymab*.[1] In doing so, the Supreme Court held two of Regeneron's '*ground-breaking*' patents to be invalid on grounds of insufficiency.[2] The decision marks a dramatic reversal of the Court of Appeal's decision in the same case, which found both of Regeneron's patents to be valid and infringed by Kymab.[3]

The Supreme Court's decision emphasises the strict sufficiency requirement in the United Kingdom. Specifically, the decision makes it clear that any patent claim which is not able to be substantially performed across its scope by a skilled person/team at the patent's priority date is at risk of a validity challenge. This has particular implications for industries such as biotech, where technology is advancing rapidly, and a patent claim confined only to what is enabled may quickly become worthless.

In this article, the authors provide a brief summary of the Supreme Court's decision, set out how the decision impacts UK patent protection and, crucially, explain how decisions made at the patent drafting stage can avoid similar invalidity issues – and thereby safeguard R&D investment.

Technological Background

The case concerned two of Regeneron's patents related to transgenic mice capable of producing antibodies suitable for use in humans. The patents were European Patent (UK) No 1 360 287 ('EP287') and its divisional, European Patent (UK) No 2 264 163 ('EP163') (together, 'the patents').

The subject matter of the patents is highly complex and the authors do not propose to provide an exhaustive account here.[4] However, a short summary of the technology is helpful to illustrate the court's reasoning and conclusion. The summary below is simplified for expediency.

By the priority date, 16 February 2001, it was well recognised that antibodies (immunoglobulins) could be used for treatment of disease in humans. Further, mice had been identified as suitable platforms for the development of such antibodies.

There were, however, two known problems with using mice for this purpose. The first was that the human body tended to reject murine (mouse) antibodies. The second was that if human antibody genes were genetically implanted in mice, so that the mice then produced human antibodies coded from those genes, then the mice suffered from a reduced immune response (termed 'immunological sickness'). This 'sickness' reduced the development of suitable antibodies in response to antigens.

1) [2020] UKSC 27.

2) The Supreme Court allowed Kymab's appeal by a majority of four to one, holding that the patents were invalid. Lord Briggs gave the majority judgment. Lady Black gave a dissenting judgment.

3) For consideration of the previous decisions of the High Court and Court of Appeal in this long-running litigation, see the previous articles by Brian Whitehead published in this journal at 15(3) BSLR 119–122 and 16(5) BSLR 242–246.

4) Detailed summaries of the technological background are provided in the judgments of the Hight Court at [2016] EWHC 87 (Pat) and by the Court of Appeal at [2018] EWCA Civ 671.

The patents proposed to solve these two problems by creating a hybrid antibody gene structure, consisting in part of human and in part of murine elements, within the genome of the mice which would operate as the code to produce hybrid antibodies.

Antibodies share a characteristic structure consisting of four polypeptide chains (Figure 1): two identical 'heavy chains' and two identical 'light chains' bonded in a Y formation. Each chain has a constant region, so named because it does not vary in its segments, called C segments, and a variable region, in which the segments vary between different antibodies. The variable regions consist, in the light chains, of V (variable) and J (joining) segments and, in the heavy chains, of V, D (diversity) and J segments.

The patents proposed to create a hybrid antibody gene structure by replacing murine variable regions of the genome of the mice (that is, the regions coding for the V and J segments of the light chain and the V, D and J segments of the heavy chain) with human counterparts while maintaining the murine constant region of the genome.

The proposed hybrid antibody gene structure was known as the 'reverse chimeric locus'. Once created in the mouse genome, it operated as the code for the production of a variety of hybrid antibodies (Figure 2). The hybrid antibodies, once isolated and removed from the mice, could then have the murine constant regions removed and replaced with human equivalents before mass production and use in humans for therapy.

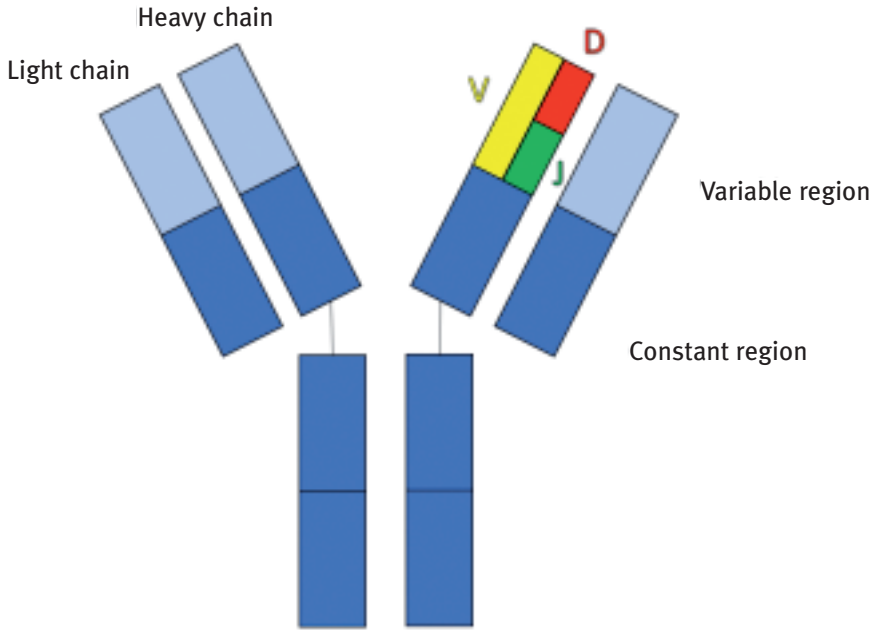
Regeneron's Patents

Regeneron argued that Kymab had infringed three claims of the patents which conferred a monopoly over mice '*fitted with*' (in the words of Lord Briggs) a reverse chimeric locus.[5] Kymab challenged the validity of each asserted claim on the basis of insufficiency.

It was common ground before the court that the outcome of all of the validity challenges turned on the validity of claim 1 of EP163, which read as follows:

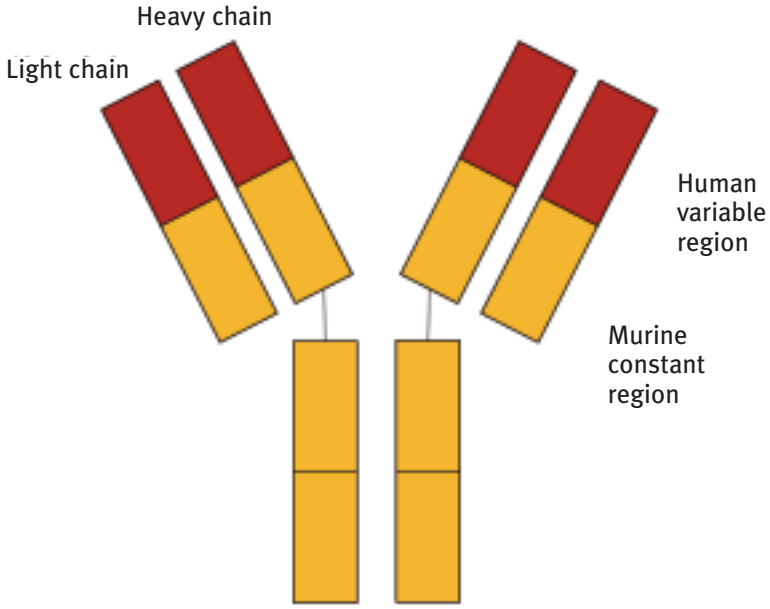
> *A transgenic mouse that produces hybrid antibodies containing human variable regions and mouse constant regions, wherein said mouse comprises an in situ replacement of mouse VDJ regions with human VDJ regions at a murine chromosomal immunoglobulin heavy chain locus and an in situ replacement of mouse VJ regions with human VJ regions at a murine chromosomal immunoglobulin light chain locus.*

Figure 1



5) Specifically, Regeneron asserted infringement of claims 5 and 6 of EP287 and claim 1 of EP163.

Figure 2



It was also common ground that claim 1 of EP163 extended to mice '*fitted with*' either partial or complete replacements of mouse VDJ/VJ regions with human counterparts. This construction of the claim, which is key to understanding the Supreme Court's judgment, meant that the claim extended to a range of qualifying types of mice (rather than to a single type of mouse). That range comprised both mice in which only a small part of the variable regions of the genome had been replaced with human counterparts, and mice in which all the variable regions of the genome had been replaced with human counterparts.

Sufficiency

General Requirements of Sufficiency

The Supreme Court's assessment of the validity of claim 1 of EP163 began with a restatement of the law of sufficiency.

First, the general rule. The Supreme Court set out that it is a general requirement of patent law both in the United Kingdom and under the European Patent Convention that, in order to patent an inventive product, the patentee must be able to demonstrate (if challenged) that a skilled person (or team) could make the product by the use of the teaching disclosed in the patent coupled with the common general knowledge which is already available at the time of the priority date, without having to undertake an undue experimental burden or apply any inventiveness of their own. In other words, the making of the claimed product must have been enabled.

Second, the Supreme Court highlighted a specific sufficiency requirement for patent claims extending beyond a single product to a range of products. In these instances, the sufficiency requirement means that substantially the whole of the claimed range of products must be enabled.

Having set out the legal principles, the Supreme Court turned to consider how these were to be applied to claim 1 of EP163 and the facts of the case.

Given that claim 1 of EP163 extended to a range of qualifying mice (as explained above), the Supreme Court considered that the sufficiency requirement necessitated that substantially the whole of the claimed range of transgenic mice had to be enabled. Turning to the facts of the case, the Supreme Court considered whether the evidence showed that a skilled team would have been able to make substantially all of the products in the claimed range of transgenic mice at the priority date. Based on the factual findings of the lower courts, the answer was clearly 'no'.

The Court of Appeal had previously held, on the basis of expert evidence from the High Court proceedings, that the teaching in the patents, coupled with the available common general knowledge as at the priority date, did enable some types of mice within the claimed range to be made, but not substantially all types across the whole range.

Specifically, the problem which faced the skilled team at the priority date was that there was no known way, even using the teaching in the patents, to combine more than a very small part of the human variable region gene locus with the endogenous murine constant region gene locus, in the same hybrid gene structure. It had taken several years, and significant further inventive steps, before methods were developed sophisticated enough to accommodate the whole of the human variable and murine constant region genes in a single hybrid gene structure.

As claim 1 of EP163 extended to a range of transgenic mice '*fitted with*' either partial or complete replacements of mouse VDJ/VJ regions with human counterparts, the inability to carry out anything other than a quantitatively small partial replacement meant that the claim was not enabled across substantially the whole range.

Principle of General Application

Regeneron accepted the Court of Appeal's conclusion that the patents enabled some, but not all, types of mice within the claimed range to be made. Rather than contest this factual finding, Regeneron argued that claim 1 of EP163 (and each of the other asserted claims) met the sufficiency requirement because it disclosed and enabled a principle of general application (and therefore did not need to enable every individual embodiment of that general principle).

Regeneron's case rested on the argument that the reverse chimeric locus disclosed in the patents was a principle of general application. This was so, Regeneron argued, because any transgenic mouse which possessed a reverse chimeric locus, and so produced hybrid antibodies which reduced immunological sickness in mice, would benefit from the technical contribution the disclosure of the patents had made to the art. In other words, the contribution of the patents – the reverse chimeric locus – benefited all types of mice which fell within the claims and therefore the contribution was generally applicable to all such mice.

Further, Regeneron argued that the case law of the European Patent Office ('EPO') had previously established that, where a patent claim disclosed a principle of general application, that claim would be sufficiently enabled if at least one way was clearly indicated enabling the skilled person (or team) to carry out the invention. In this regard, Regeneron focused on the Court of Appeal's finding that the teaching in the patents, coupled with the available common general knowledge as at the priority date, did enable some types of mice within the claimed range to be made.

On this basis, Regeneron concluded, the reverse chimeric locus was a principle of general application which had been sufficiently enabled. Therefore the asserted claims of the patents were valid.

The question raised by Regeneron's case, and subsequently answered by the Supreme Court, can therefore be summarised as follows: does a product patent, the teaching of which enables the skilled person only to make some, but not all, of the types of product within the scope of the claim, pass the sufficiency test where the invention would contribute to the utility of all the products in the range, if and when they could be made?

Conclusion

To answer this question, the Supreme Court assessed the role which the sufficiency requirement plays in the formation of the 'patent bargain' between a patent owner and the public.

The Supreme Court set out that the requirement of sufficiency exists to ensure that the extent of the monopoly conferred by a patent corresponds with the extent of the contribution which it makes to the art. In the case of a product claim, the contribution to the art is the ability of the skilled person (or team) to make the product itself.

For this reason, the patentee is required to disclose such information as will, coupled with the common general knowledge existing as at the priority date, be sufficient to enable the skilled person to make substantially all the types or embodiments of products within the scope of the claim.

A patent owner may choose to disclose a principle of general application if it would appear reasonably likely to enable the whole range of products within the scope of the claim to be made. But the patent owner takes the risk, if challenged, that the supposed general principle will be proved not in fact to enable a significant, relevant part of the claimed range to be made.

Applying these principles, the Supreme Court decided that Regeneron's proposed principle of general application – the reverse chimeric locus – did not in fact enable a significant, relevant part of the claimed range of transgenic mice to be made. The patents enabled a quantitatively small partial replacement of the mouse variable region. But they failed to enable larger replacements which were both more useful and valuable (and hence constituted a significant and relevant part of the claimed range). Instead, it had taken several years, and significant further inventive steps, before methods were developed sophisticated enough to enable the wider range of transgenic mice to be produced.

In reaching this conclusion, Lord Briggs approved the following statement made by Henry Carr J in the High Court:

> *I do not accept that all embodiments within the claim are unified by a single principle of a reverse chimeric locus. This is not a principle that enables the method to be performed, rather it is the result of successfully carrying out the method.*[6]

Lord Briggs added:

> *He was speaking mainly of process rather than product claims at that point, but the principle is the same for both. In relation to Claim 1 he could equally have said that the Reverse Chimeric Locus was not a principle that enables the products to be made, rather it is the result of successfully making the products.*

The Supreme Court concluded that the reverse chimeric locus was not a principle of general application that enabled products to be made substantially across the scope of claim 1 of EP163 (or the other asserted claims). Therefore, it was not capable of sufficiently enabling the claims.

As the technical contribution claimed in the patents was found to be insufficiently enabled, Regeneron was not entitled to its claimed monopoly. The claims of the patents were therefore held to be invalid on grounds of insufficiency.

Impact on Patent Protection

The decision of the Supreme Court emphasises the strict sufficiency requirement for UK patents. The Supreme Court distinguished between the invention considered as a pure idea (that is, the idea of a reverse chimeric locus) and the reduction of that idea to practice (that is, the range of products claimed in the patents). The Supreme Court then affirmed that it is the latter form which is protected by patent law because patents are about products and processes, not pure ideas.

The Supreme Court's decision also confirms that the sufficiency requirement for UK patents may be met by the disclosure of a principle of general application by the patentee, but only if the disclosure provides a general principle which, without any further inventive step, would enable the skilled person (or team) to work the relevant invention across substantially the whole scope of the claim.

Another issue which arises from the Supreme Court's decision is the treatment of inventive improvements. If the requirement that a claim is enabled across its entire scope is implemented strictly, the consequence would be that a squeeze could be set up tension between establishing infringement and meeting the sufficiency requirement (if it was the case that the alleged infringement could not have been implemented, at the priority date, by the skilled person applying the patent's teachings and the common general knowledge). Such an outcome would be unfair on patentees, as the scope of protection would be overly limited.

The harshness of such a rule is mitigated to some extent in two ways. First, the claim must only be enabled across *substantially* its entire scope. Second, Lord Briggs introduced the concept of 'relevant'/'irrelevant' ranges. In essence, Lord Briggs explained that a patent cannot be deemed insufficient merely because it does not teach how to make variants falling within an 'irrelevant' range, stating:

> *One can imagine an obviously irrelevant range, such as mice which are large and small, of differing colours, or having tails of varying length. No-one would say that Claim 1 fails for insufficiency because it includes*

6) Paragraph [0038] of [2020] UKSC 27.

> *mice with very short tails (which it does) merely because it does not teach how to make such mice. The quality and diversity of the stream of antibodies which the mouse exists to produce is, so far as is known, wholly unaffected by the length of its tail.*[7]

The same concept will apply to inventive improvements – if the improvement lies within an 'irrelevant' range, the patent's scope will extend to encompass it. If, though, the inventive improvement is required to produce something falling within a 'relevant' range, the patent will be insufficient to the extent that the improvement is held to fall within its scope.

At paragraph 56(vii), Lord Briggs stated:

> *Put broadly, the range will be relevant if it is denominated by reference to a variable which significantly affects the value or utility of the product in achieving the purpose for which it is to be made.*

Clearly, therefore, the precise contours of 'relevant' and 'irrelevant' ranges will be highly patent specific. Lord Briggs pointed to the example of mice with very short tails. Although it is easy enough to think up, and dismiss as 'irrelevant', such examples, it is equally easy to think of more borderline cases. The authors expect that this will be the subject of further decisions, which will hopefully shed further light on where the line is drawn, and in a manner which provides a fair degree of protection for patentees.

Finally, to compare the extent to which the United Kingdom and EPO are aligned in their application of the sufficiency requirements, it is of interest that the EPO's Technical Board of Appeal is, at the time of writing, considering its decision relating to Regeneron's EP163 (in case no. T1043/18). The EPO's Opposition Division had previously upheld EP163.

Avoiding Insufficiency at the Patent Drafting Stage

The Supreme Court considered the reverse chimeric locus disclosed in the patents to be a '*ground-breaking*' invention. For that reason, it is likely that some will view the finding of invalidity as a harsh outcome for a genuine technical breakthrough. However, this outcome also highlights the importance of making decisions at the patent drafting stage which minimise the insufficiency risk (and thereby safeguard investment in R&D).

Where sufficiency is a concern, prospective patentees should carefully consider whether it is possible to delay filing of the patent application until further enabling evidence can be included. Of course, delay always introduces the risk of other parties filing first, particularly in the fast-moving world of biotech, and therefore the timing of filing a patent application is a difficult judgment call. Moreover, it is not always practical to delay. For instance, in this case, it was a decade before the technology was developed to enable the claims of the patent to be performed across their scope.

Where delay is not an option, an alternative approach is to file follow-up patent applications once further enabling evidence can be included. Although additional filings will invariably increase upfront costs, this can be a sound investment in the long-term to avoid insufficiency issues and therefore protect valuable intellectual property.

Finally, findings of patent insufficiency can generally be avoided by a patentee being willing and able to amend the claims of its patent and narrow the scope of protection (in order to mirror the technical contribution provided by the patent). Such amendments are made easier by the inclusion of narrower, dependent claims when drafting the patent. Therefore, the Supreme Court's decision is an important reminder to include such fall-back positions.

However, it is worth noting that such fall-back claims would not have assisted Regeneron in this case. If Regeneron had chosen to amend the claims of its patents, and narrow the scope of protection to include only partial replacement of mouse VDJ/VJ regions with human counterparts, then Kymab would no longer have infringed those claims (because Kymab's 'Kymouse' product was fitted with a complete replacement of mouse VDJ/VJ regions).

7) Paragraph [0021] of [2020] UKSC 27.