Regeneron v Kymab: UK Supreme Court finds Regeneron's transgenic mouse patents insufficient

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Introduction

The Supreme Court[1] brought a lengthy dispute between Regeneron and Kymab to a close in the summer of 2020. Regeneron owned a family of patents with a claimed priority of 2001 which related to transgenic mice, and particularly transgenic mice which are suitable for use in the development of therapeutic antibodies. The patent family included EP (UK) 1 360 287 ("EP 287") and its divisional EP (UK) 2 264 163 ("EP 163"; together the "Regeneron Patents"). The two patents substantially share a specification, though have differing claim sets. The Regeneron Patents protected Regeneron's hugely successful VelocImmune® transgenic mouse, which is a core element of its business in the creation of therapeutic antibodies. In 2013, Regeneron sued Kymab[2] for infringement of EP 287, and in 2014 added EP 163 to the proceedings. Regeneron alleged that various strains of Kymab's "Kymouse®" transgenic mice infringed the Regeneron Patents either *per se* or by their method of creation. Kymab argued that it did not infringe the patents, and counterclaimed that the patents were invalid on various grounds. The case was characterised by enormous technical complexity, and resulted in two substantial judgments from the High Court and the Court of Appeal[3]. However, by the time the dispute reached the Supreme Court the only remaining challenge to the Regeneron Patents was one of insufficiency, and it was settled that if the Regeneron Patents were valid, then they were infringed. In a 4:1 majority decision (with Lady Black dissenting), the Lordships held the Regeneron Patents invalid and, in so doing, summarised the principles by which sufficiency should be assessed in the UK.

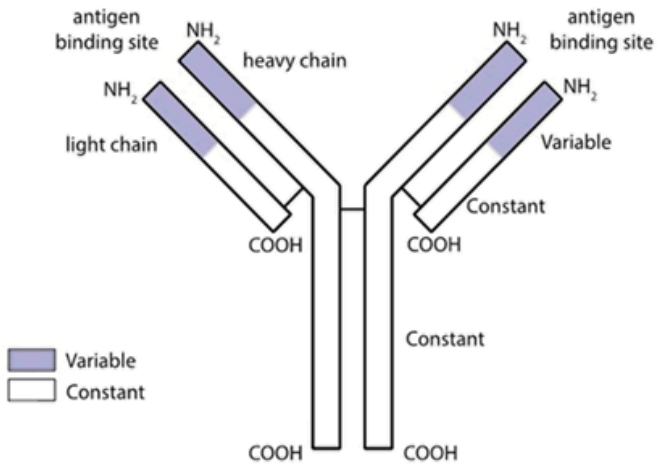
Technical Background

The production of therapeutic antibodies has been one of the great medical developments of the last thirty years. An antibody is a Y shaped protein, comprising four polypeptide chains linked by disulphide bonds. Each antibody contains two light chains and two heavy chains; each light chain has one variable region and one constant region, and each heavy chain has one variable region and three constant regions. The variable regions are responsible for the antibody's ability to bind to antigens, and within each variable region there are three small "hyper variable regions" (or "complementarity determining regions"), which are primarily responsible for the binding affinity and specificity of the antibody. The constant regions mediate downstream functions within the body. The sequence of a variable region differs from one antibody to the next (particularly in the hyper variable regions), whereas the sequence of the constant region is highly conserved between antibodies.

[1] [2020] UKSC 27

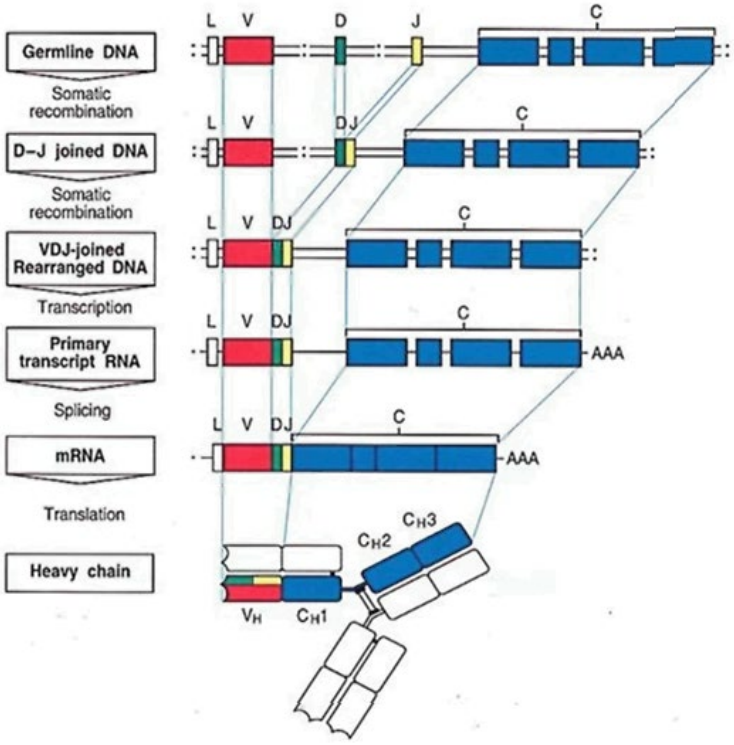
[2] Kymab had initially been a joint defendant with Novo Nordisk. However, Novo Nordisk's involvement had ended by the time the proceedings reached the Supreme Court.

[3] [2016] EWHC 87 (Pat) and [2018] EWCA Civ 671



Antibodies are “built” within B cells. To do so, a B cell selects from a number of discrete gene segments, known as variable (V), diversity (D) and joining (J) gene segments, and constant (C) gene segments. Heavy chains are built from V, D, J and C segments. Light chains are built from V, J and C segments. The human heavy chain gene locus contains 125 distinct V segments, 27 D segments and 9 J segments. When combined with the options for a light chain, the human gene loci provides combinations for approximately 1.5 million different antibodies. Further, when an antibody binds successfully with an antigen, the B cell producing it will undergo proliferation and subsequent mutation to “optimise” the antibodies it produces for the antigen, meaning the number of possible antibodies is near infinite. This process is known as affinity maturation, and results in gradual mutation towards an optimised antibody which binds the antigen very effectively.

The therapeutic possibilities of generating antibodies for use in humans was recognised in the 1980s; however, introducing antibodies produced in animals into humans caused significant immunogenicity issues with human’s producing human anti-mouse antibodies and becoming ill as a result (the “HAMA



response") when murine antibodies were used, meaning the antibodies were not suitable for therapeutic use. Some initial success was achieved with "chimeric" antibodies (whereby the variable regions from a mouse antibody are attached to a human constant region), though such antibodies still have immunogenicity issues. It was not until the laboratory of Greg Winter at the Medical Research Council in Cambridge developed a method of transplanting the complementarity determining regions from a mouse antibody (the portion of an antibody which is responsible for its ability to bind to the target antigen) into the variable regions of a human antibody, thereby reducing the immunogenicity issues, that the therapeutic capability of antibodies was realised.

However, the labour required to produce such a "humanised" antibody was significant, and although immune issues were reduced they were not wholly eliminated. The next step therefore was to develop a method of producing fully human antibodies. Two methods of doing so were developed throughout the 1990s. The first was phage display, a method of producing a multiplicity of antibodies by bacteriophage screening. The second was the development of transgenic mice, capable of producing human antibodies when immunised with the relevant antigen. In these mice, the sequence encoding for human antibody production is randomly inserted into the genome of the mouse (and the corresponding sequence coding for the production of the mouse's own antibodies disabled), such that the mice generate wholly human antibodies, which are then extracted and used as the basis for therapeutic development. Transgenic animals are responsible for the majority of therapeutic antibodies in use today.

Unfortunately, transgenic mice which are programmed to produce fully human antibodies suffer from immunological sickness. Further, for various technical reasons including limited B cell proliferation and affinity maturation, transgenic mice with randomly inserted human gene loci do not produce totally optimal human antibodies.

The Patents

The invention claimed in the Regeneron Patents is to a transgenic mouse with an *in situ* replacement of the mouse VDJ gene segments with the human VDJ segments. The consequence of such a targeted replacement is that the mouse produces antibodies with a human variable region and a mouse constant region – termed in the litigation a "reverse chimeric" antibody (though the term does not appear in the Regeneron Patents). The gene locus comprising the human VDJ segments and mouse C segments is termed a "reverse chimeric locus". The DNA coding for these antibodies can then be extracted, and the human variable region can be paired with the DNA sequence for a human constant region, making a fully human antibody.

The invention, described as "ground-breaking" by the Supreme Court, has the benefit that a mouse which produces reverse chimeric antibodies does not suffer from immunological sickness, and has good B cell proliferation and affinity maturation characteristics. Regeneron has put the invention into practice in its VelocImmune® transgenic mice, which are a very successful drug development platform for therapeutic antibodies. The Regeneron Patents disclose a method of *in situ* gene replacement, as well as the concept of a mouse with the reverse chimeric locus *per se*. Claim 1 of EP 163 claims:

> 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.

The claim is therefore to a range of products. At one end of the scale, the claimed range includes mice with only one human VDJ heavy chain region and one human VJ light chain region inserted as an *in situ* replacement (which can still make more than a single reverse-chimeric antibody, due to affinity maturation). At the other end of the range, the claim includes mice with all of the human VDJ heavy chain regions and all of the human VJ light chain regions inserted as an *in situ* replacement.

Technology in Dispute

The technical dispute between the parties at first instance was over the extent to which the skilled person was enabled to conduct the *in situ* genetic replacement at the priority date based upon the disclosure of the specification and their common general knowledge.

The parties also disputed the character of the invention itself. Regeneron contended that even if the reverse chimeric locus incorporates only one or two of the human V segments, the locus will solve the problems of mouse immunological sickness and poor affinity maturation, and the invention is therefore one of general applicability. In contrast, Kymab argued that a reverse chimeric locus which incorporates only a small number of human V, D and J segments will result in a mouse that can generate only a relatively small number of reverse chimeric antibodies, compared to a mouse which incorporates all of the human V, D and J segments – this second mouse would therefore be more valuable in drug discovery, because it would be able to raise a greater number of potentially useful antibodies. According to Kymab, the claims of the Regeneron Patents therefore covered products which they did not enable, and which were more valuable than the products that they did enable.

High Court and Court of Appeal decisions

The High Court had found that the Regeneron Patents were novel, inventive, and infringed. However, it also found that the skilled person was not enabled to create any of the mice with a reverse chimeric locus at the priority date, as in order to operate the methods disclosed in the patent the skilled person would need either to make a further inventive contribution, or face an undue burden of experimentation in order to arrive at a functioning method. This was because the technology needed to insert a large segment of DNA at a specified location in the target genome was not available to the skilled person at the relevant date. The Regeneron Patents were therefore held to be insufficient.

The Court of Appeal overturned the High Court's decision on insufficiency. Having argued that the skilled person would use their common general knowledge to modify the method in the Regeneron Patents to introduce a series of small DNA inserts into the mouse genome, the Court agreed with Regeneron that although it was not possible to make all of the mice within the claimed range, it was possible to make those with only a small subset of the V, D and J gene segments inserted.

In general, a patent claim which claims a range of products, but does not enable products across the breadth of the range to be made, is invalid because it is insufficient. However, the Court of Appeal held that the invention to which the claim related was the concept of the reverse chimeric locus. It considered that the reverse chimeric locus was a principle of general application, as any animal which made use of it would not suffer from immunological sickness. The Court reasoned that because any mouse (even those which could not yet be made at the priority date) would benefit from the principle, the principle itself was enabled across the range. This enablement, in conjunction with the teaching to make at least one embodiment within the range, meant that the Regeneron Patents were valid. In reaching this decision Lord Justice Kitchin noted at paragraph [260] of the Court of Appeal judgment that "were protection to be limited to only those embodiments which could have been made at the priority date without undue effort, the protection provided by the patent would have rapidly become ineffectual."

In summarising the Court of Appeal decision in paragraph [27] of the Supreme Court judgment, Lord Briggs set out the Court of Appeal's reasoning as follows:

> "The patent bargain requires that the reward given to the patentee should be commensurate with the contribution which the invention makes to the art […] To limit the patentee strictly to a monopoly over the products which can immediately be made would be to deprive the patentee of any reward for the public benefit which will be derived from the use of that same invention in future types of product. In a fast-moving field, where new products quickly outperform their predecessors so as to render them obsolete, the reward of a monopoly limited to those immediately capable of being made would be short lived and illusory."

The Legal Question before the Supreme Court

Kymab appealed the Court of Appeal's interpretation of the law of insufficiency to the Supreme Court. It was agreed between the parties that the skilled person was enabled to make some but not all of the mice within the range claimed by Regeneron. The question before the Supreme Court was phrased by Lord Briggs at paragraph [5]:

> "The question for this court is therefore whether 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, passes 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."

The Decision

The decision by the Supreme Court is unequivocal and relatively short. It held by a 4:1 majority that the Court of Appeal was wrong to consider that the reverse chimeric locus was a principle of general application, and that because the claims of the Regeneron Patents were not enabled across their range, they were insufficient.

Giving the leading judgment, Lord Briggs (with whom Lords Sales, Hodge and Reed agreed) acknowledged at paragraph [56(vii)] that it is not always the case that enablement must be shown across a range – rather, "[t]he requirement to show enablement across the whole scope of the claim applies only across a relevant range. 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." Going on to assess whether the quantity of human DNA capable of insertion into the mouse genome was a relevant range, Lord Briggs noted that at the priority date the skilled person's understanding was that the usefulness of a mouse in drug discovery was directly proportional to the amount of the human variable gene locus which had been inserted into it. The range as featured within the claims of the Regeneron Patents is therefore a relevant range, as the skilled person would consider it to be material to the value of the products made.

Lord Briggs also set out what he considered to be the proper definition of a principle of general application based upon the case law of the UK and the EPO. He noted that the concept derives from the EPO case *Genentech I/Polypeptide expression* (T 292/85), in which a principle of general application was sufficient because the principle could be worked by the skilled person irrespective of the inputs used. In *Polypeptide* the patent claimed processes and resulting products which produced a uniform stream of specified polypeptides. The claim was framed by the use of a range of bacteria, plasmids and regulons as input criteria, but the claim language was wide enough to claim input types (including unknown bacterial variants) which had not yet been made available in the art. Nonetheless the patent was held valid because although the claim contained functional definitions it was not disputed that when those as yet unknown bacterial variants were disclosed and used as inputs in the claimed process, the process would work.

Lord Briggs stated at paragraph [46] that such a principle of general application was not compatible with Regeneron's argument, because "the inventive shortfall at the priority date lay not in the range of possible inputs to which the invention could be applied, but in the inability to create Reverse Chimeric Locus involving the whole (or anything more than a very small part of) the human variable region." In effect, the range of potential inputs was known (i.e. the human VDJ segments), but could not all be worked, unlike in *Polypeptide*.

The *Polypeptide* and subsequent EPO cases are therefore consistent with the broader general principle of insufficiency because the skilled person is enabled to work all of the embodiments of the invention. The general principle of insufficiency is set out in the EPO case *Unilever/Detergents* (T 435/91):

> "[…] the criteria for determining the sufficiency of the disclosure are the same for all inventions, irrespective of the way in which they are defined, be it by way of structural terms of their technical features or by their function. In both cases the requirement of sufficient disclosure can only mean

> that the whole subject matter that is defined in the claims, and not only a part of it, must be capable of being carried out by the skilled person without the burden of an undue amount of experimentation or the application of inventive ingenuity"

As Lord Briggs acknowledged, this principle is also clearly expressed in English case law. In *Biogen v Medeva*[4], the House of Lords[5] described the enablement requirement of a patent as follows:

> "[…] there is more than one way in which the breadth of a claim may exceed the technical contribution to the art embodied in the invention. The patent may claim results which it does not enable, such as making a wide class of products when it enables only one of those products and discloses no principle which would enable others to be made."

The Supreme Court drew a distinction between the technical contribution of the Regeneron Patents and the invention they described. Lord Briggs explained that the teaching in the patent which allows the skilled person (in combination with their common general knowledge) to make what is claimed is called the technical contribution. In the Regeneron Patents the technical contribution enabled the skilled person to make a mouse with a portion of the human VDJ segments inserted into a reverse chimeric locus. Lord Briggs distinguished this from the invention of the reverse chimeric locus *per se* – the technical contribution of the Regeneron Patents did not allow the skilled person to work the invention of the reverse chimeric locus in substantially all of its embodiments[6], because the skilled person was not enabled to make a mouse with all or even most of the human VDJ segments inserted into a reverse chimeric locus. In order to have a valid claim, Regeneron would therefore have needed to limit the claim to match the scope of the technical teaching of the patent.

The Supreme Court acknowledged at paragraph [60] that this application of the law provided Regeneron with "scant and short lived reward for their efforts and ingenuity" but it was not sympathetic to the alternative approach that the Court of Appeal had taken, and issued a strong rebuke to the Court of Appeal at paragraph [58], saying:

> "It is now known that the type of mouse fitted with a reverse chimeric locus which actually does serve as the gold standard in the art has the whole of the human variable region gene locus as part of its hybrid antibody gene structure. Yet the Court of Appeal would have upheld a monopoly for its manufacture and exploitation when the disclosure in the patent, coupled with the common general knowledge, would not have enabled a skilled person to make such a mouse at all."

It further intimated at paragraph [59] that the Court of Appeal had overstepped its judicial power in making its decision:

> "To water down that requirement would tilt the careful balance thereby established in favour of patentees and against the public in a way which is not warranted by the EPC and which would exceed by a wide margin the scope for the development of the law by judicial decision-making in a particular Convention state."

Principles of Insufficiency

In making his judgment, at paragraph [56] Lord Briggs set out eight principles of insufficiency which he considered could be derived from the EPO and UK authorities. These principles are uncontroversial, and provide a convenient summary of the law of insufficiency in the UK. The authors expect to see them referred to and relied upon in judgments discussing insufficiency for many years ahead. Lord Briggs' principles are:

[4] [1997] RPC

[5] The House of Lords was replaced by the Supreme Court in 2009.

[6] It should be noted that Lord Briggs did not require that every possible embodiment should be enabled – if a *de minimis* proportion of the total embodiments are not enabled, a patent claim may still be sufficient.

i) The requirement of sufficiency imposed by article 83 of the EPC exists to ensure that the extent of the monopoly conferred by the patent corresponds with the extent of the contribution which it makes to the art.

ii) In the case of a product claim, the contribution to the art is the ability of the skilled person to make the product itself, rather than (if different) the invention.

iii) Patentees are free to choose how widely to frame the range of products for which they claim protection. But they need to ensure that they make no broader claim than is enabled by their disclosure.

iv) The disclosure required of the patentee is such 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. That is what, in the context of a product claim, enablement means.

v) A claim which seeks to protect products which cannot be made by the skilled person using the disclosure in the patent will, subject to de minimis or wholly irrelevant exceptions, be bound to exceed the contribution to the art made by the patent, measured as it must be at the priority date.

vi) This does not mean that the patentee has to demonstrate in the disclosure that every embodiment within the scope of the claim has been tried, tested and proved to have been enabled to be made. Patentees may rely, if they can, upon 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 they take the risk, if challenged, that the supposed general principle will be proved at trial not in fact to enable a significant, relevant, part of the claimed range to be made, as at the priority date.

vii) Nor will a claim which in substance passes the sufficiency test be defeated by dividing the product claim into a range denominated by some wholly irrelevant factor, such as the length of a mouse's tail. The requirement to show enablement across the whole scope of the claim applies only across a relevant range. 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.

viii) Enablement across the scope of a product claim is not established merely by showing that all products within the relevant range will, if and when they can be made, deliver the same general benefit intended to be generated by the invention, regardless how valuable and ground-breaking that invention may prove to be.

Lady Black

Lady Black made a brief dissenting judgment, in which she effectively agreed with the Court of Appeal that the reverse chimeric locus was a principle of general application. Lady Black agreed that a claim must be enabled across its breadth, but that the characterisation of a claim defined its breadth. In light of this she considered that the characterisation of the claim used by Lord Briggs was incorrect – Regeneron's claim was not to a range of products as defined by the characteristics of the reverse chimeric loci within them, rather it was to the use of a reverse chimeric locus in a mouse. The reverse chimeric loci might differ, but each chimeric locus worked as an input (even if not all of them had been enabled at the priority date). On the basis that the reverse chimeric locus was the contribution to the art, and could be inserted into a mouse with consistent effect in reducing immunological sickness, Lady Black considered that the reverse chimeric

locus was a principle of general application (and that the claim covering this principle was sufficient as a result).

Conclusion

Although the Supreme Court's decision deals with a case of staggering technical complexity, it is arguable that it has not effected any change in the law of sufficiency in the UK. Lord Briggs' list of the criteria by which sufficiency should be assessed is certainly a useful consolidation and summary of the law, but it does not move the law of sufficiency forward in any meaningful way.

However, as Lady Black persuasively argued, this case ultimately did not come down to a recalibration or resolution of a legal complexity. Indeed, the principles of law were generally agreed between the Court of Appeal and the Supreme Court, including the dissenting Lady Black. Rather, the dispute turned on the manner in which the claim was characterised, and the language used to frame the invention. If the claims of the Regeneron Patents had been framed in such a way that it was clear that the claims protected mice which did not suffer from immunological sickness as a result of the use of a reverse chimeric locus, and if the Regeneron Patents had enabled the making of one such reverse chimeric locus, it is arguable that the Regeneron Patents would have been upheld as disclosing a principle of general application (and been sufficient). This case may therefore ultimately prove to be of more interest and concern to those individuals who are tasked with drafting patents than those who are tasked with enforcing them. As grappled with by the Court of Appeal and the Supreme Court, the case raises important questions regarding how ground breaking inventions in fast-moving fields can and should be claimed so that the inventor's technical contribution can be properly rewarded.