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Special Focus: Patenting Antibodies

Patenting antibodies in Europe

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Introduction

As a complement to the series of articles beginning in this issue on obtaining, maintaining and enforcing antibody patents in the United States, this article provides a comparison of the requirements for patenting antibodies in the United States and Europe and provides examples illustrating the application of European patent law to antibodies.

In Europe, an invention must be new, inventive (non-obvious), and enabled to be considered patentable subject-matter. Europe has no provisions equivalent to the "written description" or "best mode" requirements of the United States. While, the basic principles of inventiveness (non-obviousness) and enablement are similar in Europe and the United States, the wording of the statues and their application by the courts and administrative bodies differs between the two systems. As a consequence, the tests used for determining inventiveness (non-obviousness) and enablement, and ultimately the scope of the allowable patent claims, differ between the two jurisdictions.

Inventiveness (Non-Obviousness)

In Europe, the test for 'inventiveness' or non-obviousness of a biotechnology invention typically revolves around answering the following question: "considering the 'state of the art' (i.e., what has gone on before in the relevant field) would the steps needed to arrive at the invention be *obvious to try, with a reasonable expectation of success*?" (see, for example, Decisions of the Boards of Appeal of the European Patent Office T 60/89 and T 293/93).

This issue of inventiveness often arises in the patenting of antibodies in Europe because once a pioneering antibody technology, such as humanisation, is in the public domain; European law considers application of that technology to any other antibody obvious. While an antibody that binds to a new and previously unidentified antigen is considered non-obvious because the antigen was unknown, it is considered obvious to generate an antibody to a known antigen using standard techniques such as immunization or phage display.

If an antibody can be shown to have an advantage over known antibodies to the same target or antibodies produced by the same method, then this fact can often be used to establish that the antibody is inventive. An advantage can be any property that is useful, such as cross-reactivity, increased selectivity, increased affinity, new or improved downstream function or improved stability. To be useful in establishing an inventive step, the advantage should be unpredictable considering the state of the art. So, if a known technique such as in vitro evolution is used to improve the affinity of an antibody, then the improved affinity of the resultant antibody is not "unexpected." Using the test mentioned above, there is a "reasonable expectation of success" that an antibody with improved affinity would be generated, so the antibody is likely to be considered obvious.

If, on the other hand, an antibody to a known target is found to bind to a different epitope compared to other antibodies, or have an advantageous property such as the ability to block the binding of antigen to its receptor, then this advantageous property is unexpected. There would not be a "reasonable expectation of success" in generating such an antibody if the consequence of epitope binding had not been previously characterised.

Beyond a "reasonable expectation of success," the first part of the test for inventiveness, requires that the steps needed to arrive at the invention be "obvious to try." So, if there was prejudice that the approach would be unsuccessful, i.e., others skilled in the relevant field had given indications that such efforts would be unproductive, the technique might not be considered obvious to try. For example, if an antibody is generated by modification of one or more of the CDR residues believed to be essential for antigen binding, then the resulting antibody may be inventive because it would not be obvious to use such an approach to produce a functional antibody.

There are exceptions, but in general the bar is fairly low in Europe for (1) the amount of "advantage;" (2) its unexpectedness; and (3) the amount of proof needed to show that the antibody has such an advantage. This is illustrated by a recent Decision of the Boards of Appeal of the European Patent Office (T 0601/05) that concerned a patent related to a pharmaceutical composition containing a human mAb that binds to TNFα. A murine anti-TNFα antibody was known and was in a Phase 1 clinical study,

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but, according to the appellant, results had shown that it was not pharmaceutically effective.

In the Board's view, inventiveness of the human mAb hinged on whether the patent contained enough evidence that the human TNFα-binding mAbs would indeed have therapeutic value. The patent described an assay showing that one of the human antibodies was able to inhibit lipopolysaccharide-stimulated secretion of TNFα from a human monocyte cell line. According to the patent, TNFα is one of the factors secreted during septic shock and inflammatory diseases. This was held to be sufficient evidence to make the pharmaceutical usefulness of the antibody "plausible," and, accordingly, inventiveness was found.

There are two things to note from this decision. Firstly, the results obtained using the murine antibody were considered to prejudice against attempting to generate therapeutically useful human anti-TNFα antibodies, meaning that it was not "obvious to try with a reasonable expectation of success." Secondly, in vitro data was considered sufficient to establish that human antibodies could be therapeutically useful. No data indicated that the human antibody actually inhibited TNFα secretion in vivo, let alone whether this would be therapeutically useful.

Enablement/Sufficiency

According to European patent law, a patent application must "disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art" (Article 83, EPC 2000). This provision is sometimes referred to as "sufficiency" and is equivalent to the US "enablement" requirement.

The test commonly used for sufficiency in Europe is whether it would be an "undue burden" for a person skilled in the art to put the invention into effect, i.e., would it be an undue burden for a skilled person to fill in the gaps missing from the technical disclosure in order to carry out the invention?

The scope of protection provided by patents is determined by the wording of the claims. Various types of claim language are commonly used to define antibodies in patent terms, including:

(1) by sequence, e.g., An antibody having the sequence shown as SEQ ID No. 1 or at least 80% identity thereto;

(2) by deposit, e.g., The antibody produced by the hybridoma deposited under Accession No. 12345;

(3) by target, e.g., An antibody capable of binding X;

(4) by activity, e.g., An antibody capable of binding X and blocking the binding of X to X-receptor.

Claims that define an antibody by sequence generally fulfill the sufficiency requirement. As the sequence is given, sufficient information is provided to derive all sequences within the scope of the claim.

Where an antibody is defined by the target and the target is a new antigen, the antibody is generally considered to fulfill the sufficiency requirement, even if the patent application does not describe the actual generation of such an antibody, because it is possible to generate an antibody to a given antigen using standard techniques.

However, difficulties can arise where an antibody is defined in terms of its activity. The sufficiency requirement requires the patent application to provide sufficient information for the invention to be practiced over the whole claim breadth. Often, the requirement is satisfied when an antibody is defined by its function and at least one example is provided of an antibody having such a function. It is important that the example(s) provided are described in sufficient detail so that further embodiments could be generated within the scope of the claim.

This point is illustrated by a Decision of the Boards of Appeal (T1466/05) which related to a patent application in which the definition of the antibody included the following: "An antibody reactive with pyridinoline in peptide-linked pyridoline and not free pyridoline."

The application described one specific monoclonal antibody produced by a deposited hybridoma that was stated to have the claimed activity. However, the application did not provide any technical details on how the specific monoclonal antibody was prepared and did not provide any guidance on the preparation of further antibodies having the desired activity. In particular, the application provided no guidance with respect to an antigen suitable for raising antibodies with the desired specificity, or screening antibody-producing clones or antibody libraries.

The application was therefore considered to provide insufficient information for the invention to be put into effect over the whole scope of the claim. It was considered an "undue burden" for a person skilled in the art to make other antibodies within the scope of the claim, given the lack of detail of (1) the antigen required to raise the antibodies; and (2) the screening process for the specific selection of such antibodies.

General Strategy

The most commonly encountered objection during prosecution of antibody patent applications in Europe is lack of inventiveness. It is often possible to argue against this by providing evidence of an unexpected advantage of the antibody, or technical reasons why preparation of the antibody would not have been expected to be successful. It often advantageous to consider how one might counter an obviousness objection before the patent application is filed, so that the necessary data may be included and reference may be made to useful evidence. Another common stumbling block for antibody patents is sufficiency. In order to avoid provoking such an objection, the patent application should provide detailed technical information on the preparation of each antibody, together with all known details of structure-function relationships, such as epitope sequence or key CDR residues, in order to provide support for the broadest possible antibody definition.