ANTIBODY PATENT PROTECTION IN AUSTRALIA

Is the inventive step threshold for antibodies in Australia designed to stifle innovation?

INTRODUCTION

Antibodies have become significant therapeutic treatments for a broad range of diseases including cancer, inflammatory conditions and infectious diseases. This antibody success story, which includes blockbuster drugs such as Humira (AbbVie) Keytruda (Merck) Opdivo (BMS/Ono Pharmaceutical, Infliximab (JnJ/Janssen) and Dupixent (Sanofi) has turbo-charged the development of a multitude of next-generation antibody therapeutics. However, the unique structure/function relationship of antibodies and how they are generated presents patenting challenges, including how the inventiveness of antibodies is determined.

BACKGROUND

In a previous article by Wrays titled 'Maximising Antibody Patent Protection in Australia', we reviewed the current situation that exists at IP Australia, which generally requires Australian antibody claims to define 6 specific CDR sequences.

In this article, we consider the inventiveness of antibody claims in light of IP Australia practice, which appears to be aligning to that currently employed at the European Patent Office (EPO).

Under EPO practice, a novel antibody that binds to the same antigen as a known antibody is not considered inventive unless a surprising technical effect beyond that of the known antibody is demonstrated. According to Chapter 6.2 of the Guidelines for Examination in the EPO, examples of surprising technical effects can include "unexpected improvement over prior-art antibodies in one or more properties, such as therapeutic activity, stability or immunogenicity or an unexpected property not exhibited by prior-art antibodies".

In our experience, antibody inventive step objections raised by Australian Examiners, may include the following:

> *"The claimed subject matter can be distinguished from D1, in that D1 does not disclose the recited CDRs. However, it is not apparent that this confers an inventive step. It cannot be considered inventive to produce a mere alternative to that already known in the art. As such, the claimed subject matter lacks an inventive step."*

This approach to antibody patentability evokes consideration of two key issues:

1. Is this practice consistent with Australia inventive step jurisprudence; an
2. Does it support sound innovation policy in Australia?

INVENTIVE STEP IN AUSTRALIA

The precedent law in relation to inventive step in Australia developed around the reformulated Cripps Question, namely:

"Would the notional research group at the relevant date, in all the circumstances, directly be led as a matter of course to try [the claimed invention] in the expectation that it might well produce [a solution to the problem]?". Aktiebolaget Hassle v Alphapharm Pty Ltd (2002) HCA 59; (2002) 212 CLR 411 and approved in *Olin Mathieson v Biorex (1970) RPC 157.*

The High Court in *Aktiebolaget Hassle* (AB Hassle) also considered an earlier decision from *Wellcome Foundation Ltd v VR Laboratories (Aust) Pty Ltd (1981)* 148 CLR 262, which stated that:

"*The test is whether the hypothetical addressee faced with the same problem would have taken as a matter of routine whatever steps might have led from the prior art to the invention, whether they be the steps of the inventor or not.";*

The Wellcome test focuses on whether the steps taken by the person skilled in the art (PSA) in the face of the same problem are routine, whereas the Cripps question focuses on whether the PSA would have been directly led to the invention with an expectation of success.

Ultimately the High Court found that the approach in the Wellcome decision was similar to the Cripps question and accepted that as the correct approach for the determining an inventive step. In other words, the High Court confirmed that the inventive step threshold under Australian law requires an expectation of success.

INVENTIVE STEP AND ANTIBODIES

Applying the inventive step threshold, in a general sense, to antibody claims that define new sequences means that a finding of lack of inventiveness should be found only if the skilled person is led directly as a matter of course to the claimed sequences in the expectation that they might well produce a useful alternative or a better product than the prior art.

In this regard, Australian law does not require an invention to be superior to what is already known for it to be inventive – it is sufficient that it is a "useful alternative". Thus, a different antibody with different CDR sequences should, as a first point, be considered a "useful alternative" even if it is not shown to be an improvement on existing antibodies.

Further and relevantly, the generation of antibodies is not conducted with CDR sequences in mind, because extrapolation of CDR sequences to antibody binding and function is not currently possible. Therefore, in defending an antibody claim that defines CDR sequences, a strong position can be advanced that the skilled person cannot be directly led to the "invention" (that being the specific CDR sequences claimed) with any expectation of success. This means that a useful alternative antibody to one that is already known should be considered inventive under Australian law. In other words, there should be no need for a new antibody that binds to a known antigen to exhibit an unexpected or surprising functional effect over an existing antibody for it to be considered inventive.

GENERATION OF ANTIBODIES: NOT ROUTINE

Even if it is acknowledged that known methodologies exist that produce antibodies, it is not routine that such methodologies will produce or are even likely to produce antibodies exhibiting characteristics that make them suitable as antigen binding clinical candidates. The reason for this is that generation of antibody CDR sequences in an immunised animal is an exceedingly complex process that includes consideration of, for example:

- the selected immunisation methodology;
- how the antigen may be presented, and the relevant region of the antigen to target;
- the type of animal used;
- whether humanisation is required, appropriate or functionally possible;
- suitable methodologies to initially screen potential clinical candidates; and
- suitable assays to test for relevant antibody functionality.

The antibody generation process is further complicated because the potential antibody diversity that exists in a mammal considerably exceeds the estimated number of circulating B cells in the blood. Moreover, there is a constant turnover of B cells in the circulation. This means that antibodies generated in a specific immunised animal will differ depending on when they are exposed to an antigen. In other words, exposing an animal to the same antigen at different times will inevitably lead to the generation of different antibody repertoires. As such, it is extremely unlikely that two antibodies exhibiting the same sequences will be produced even if identical antibody generation methods are employed on identical animals.

It is also relevant that antibodies generated by one immunisation experiment can result in antibodies exhibiting distinctly different functionalities. For example, antibodies can act as receptor agonists, antagonists or neither, and there is no way of predicting which types of these antibodies will be produced by the antibody generation process.

Thus, taking a position that an alternative antibody is not considered inventive unless it exhibits a surprising technical effect beyond that of a known antibody appears to be inconsistent with Australia inventive step jurisprudence, as well as the complex technical aspects of producing antibodies that may ultimately be suitable for pharmaceutical applications.

INNOVATION POLICY

If Australia proceeds with a practice that requires new antibodies that bind to known antigens to exhibit unexpected or surprising functional effects over known antibodies, it is likely to disincentivise others from investing in research programs to develop antibodies to the same target, because of the uncertainty about being able to obtain patent protection. This would in turn detrimentally impact the development and commercialisation of new alternative antibody treatments. This is a situation that is not in the best interest of innovation stakeholders including the general public.

CONCLUSIONS

Because antibody pharmaceuticals have become uniquely valuable as contemporary medicines for the treatment of diseases, it is critical that the development and commercialisation of new alternative antibody medicines be supported by a patent system that is consistent with the precedent law and designed to incentivise innovation. With this in mind, judicial consideration of antibody inventiveness is keenly anticipated in Australia.

Dr Grant Shoebridge

Principal

Bindhu Holavanahalli

Senior Associate