Antibodies in the European Patent Office - Advanced Guide to Drafting and Prosecution

The European Patent Office (EPO) applies the same basic patentability criteria to antibodies as to other inventions, but it can sometimes appear that antibodies are treated as a special case. For an explanation of the basic approach adopted by the EPO, please see our related briefing Antibodies in the European Patent Office - Basic Principles or ask your usual J A Kemp contact. The present briefing is intended to develop those Basic Principles into a guide to the drafting and prosecution of patent applications for antibody inventions.

The briefing focuses on the most common type of antibody invention at the present time - namely monoclonal antibody products for which the target and any associated disease indications are already known. We also provide guidance on ensuring your antibody claims are appropriate to support future applications for Supplementary Protection Certificates (SPCs).

Where is the Case Law?

This Advanced Guide is drawn primarily from our experience prosecuting large numbers of antibody cases before the EPO and our discussions with EPO examiners. This may raise the question: Why is there so little supporting case law?

The main reason is that antibody case law at the EPO has been relatively slow to develop in recent years. In our opinion this is because the most common pending antibody applications during this period have focussed narrowly on a lead molecule or molecules of the applicant.

As a consequence, an innovator competitor is unlikely to have freedom to operate concerns for their own molecule, and could even prefer that a patent is granted and in force since this may reduce the likelihood of generic competition. On the other hand, the 9 month opposition term after grant of European patents may come too early in product development for a generic / biosimilar competitor, or they may take the view that their primary barrier for market entry will be regulatory data exclusivity rather than the patent. Again they may therefore prefer the patent to be granted and maintained in force in the meantime.

The net effect is that there are comparatively few oppositions filed against this type of invention, and thus comparatively few cases reach the Boards of Appeal. The EPO Examining Divisions have therefore developed their approach from the principles outlined in earlier
decisions, adapted by their exposure to high volumes of cases.

Unexpected Technical Effect

As is explained in more detail in our Basic Principles briefing, where the target and its relevance to a disease indication are known, the EPO generally assumes that any antibody with a unique amino acid sequence will be novel over prior art antibodies to the same target, but a demonstration of an unexpected (surprising) technical effect will be required to establish an inventive step. It must be at least plausible that the unexpected technical effect, usually a functional characteristic, is shared by substantially all antibodies falling within the scope of the claim.

The following sections provide our suggestions for how best to prepare a patent application to meet these requirements.

Guide to Drafting and Prosecution - How to Prepare for the Unexpected

A patent application for a new antibody to a known target having the necessary “unexpected technical effect” will typically require at least three forms of information or supporting data:

- Structural information for at least one exemplary antibody - typically the lead molecule or molecules in the project - desirably for both the target-binding region and the constant region;
- Functional data to show that the antibody specifically binds to the target; and
- Functional data to show that the antibody has an unexpected technical effect / functional characteristic that can be relied on for inventive step.

Structural information - target-binding region

The claims will typically need to incorporate a structural definition of the antibody, at least for the target-binding region. It can be assumed that a minimum of six CDRs will be required unless there is compelling data to show that target binding and other key characteristics are shared by antibodies defined less precisely. It is now relatively common for complete variable region sequences to be required.

Where there are multiple candidate antibodies in an application, it should be ensured that each molecule is defined by reference to as complete a set of structural information as possible, ideally all six CDRs and both complete variable region sequences. The use of “mix and match” language, which typically seeks to encompass any combination of CDRs and variable region sequences from multiple candidates should not be relied on. Instead, the specific combinations of target-binding region sequences that make up each of the candidates should be disclosed.

It is increasingly common for EPO examiners to object that references to CDRs in the claims are unclear unless the identification method used is also recited. Under strict EPO disclosure
requirements, it may only be possible to comply with a request to insert a definition of the identification method into a claim if there is an explicit reference to it in the application as filed.

The application as filed should therefore disclose how the structural information was determined. In particular, the numbering scheme and definitions used to identify CDRs should be specified (Kabat, Chothia, AbM etc). It is acceptable to list alternative CDR sequences for a given molecule based on the different available definitions, provided that each alternative is clearly identified alongside the definition used.

**Structural information - constant region**

Sequence information for the variable region is routinely included in applications, but there is often no indication of the constant region either by reference to an isotype class or a specific sequence. Desirably, at least one preferred isotype class should be recited, and ideally at least one exemplary constant region sequence should also be included. This information should be presented together with the target-binding region information, such that there is an explicit disclosure of the structure of the combined target-binding region and constant region for each complete antibody molecule.

It may be helpful to recite the sequence of a complete heavy chain and a complete light chain for each molecule, with an explicit statement that each heavy chain / light chain pair is combined to produce a complete molecule of the invention. Once again, “mix and match” language should not be relied upon.

In some cases it may be necessary to specify the isotype / constant region sequence in the claims, particularly if this is relevant to the unexpected characteristic relied upon for inventive step. Under strict EPO disclosure requirements, this will likely only be possible if there is an explicit reference to the constant region in the application as filed.

**Functional data relating to target binding**

A demonstration that an antibody binds to a target should not be difficult to provide, since any antibody development plan will likely include a significant quantity of data demonstrating target specificity and affinity/avidity.

There is no single preferred technique for measuring target binding for patent purposes, although surface plasmon resonance is increasingly regarded as the standard. Whichever technique is used, the patent application should ideally describe this in general terms (optionally by reference to standard texts) but should also include the specific experimental conditions that apply to the determinations of binding that were actually conducted for the exemplary antibodies of the application: temperature, ionic strength, nature of target etc. At least one individual experiment should be described in full in the Examples and the corresponding data provided in the application.

If a required level of affinity/avidity is recited in the claims, typically the EPO will now require
that the claims also include an indication of the technique used to determine this parameter. Under strict EPO disclosure requirements, it may only be possible to comply with a request to insert the technique if there is an explicit reference to it in the application as filed.

**Functional data relating to an unexpected technical effect**

The type of functional data available will, of course, be highly dependent upon the nature of a given antibody project. However, the EPO will be looking for evidence of a functional property of the claimed antibodies in the application. Therefore, although additional data in support of an inventive step may be filed during prosecution, it is important to at least include a description of the functional characteristics of the antibodies. The techniques used to demonstrate the functional characteristics should be described both in general and in more specific terms, and at least one individual experiment should be described in full in the Examples alongside the corresponding data.

If it is necessary or desirable to limit the claimed antibodies by reference to a functional feature in the claims, an EPO examiner may request that claims also include an indication of the technique used to determine the feature for the exemplary antibodies disclosed in the application. It may only be possible to comply with such a request if there is an explicit disclosure of the technique in the application as filed.

**Is comparative data necessary?**

EPO examiners often look for comparative data with prior art antibodies as evidence of an unexpected technical effect. A patent application does not necessarily need to include comparative data, and indeed it may not be possible to include comparisons to particular prior art antibodies - not least because these may only be identified in later Patent Office searches. However, if the applicant wishes to rely upon comparative data generated after filing to prove that a functional characteristic of the claimed antibodies represents an improvement over the prior art, the comparative data must relate to information about the claimed antibodies that is disclosed in the application as filed. It must be at least plausible from the application that the claimed antibodies possess the property relied upon.

As a consequence, the more information that is included in the application regarding the antibody of interest, the easier it is likely to be to rely upon comparative data that is only generated later in response to an objection based on a particular prior art antibody.

It can, in particular, be helpful to include comparative data from related antibodies produced in the course of the antibody development project which do not share the same characteristics as the lead antibody, or lead antibodies.

This may seem counter-intuitive, since such data may limit the extent to which the structural definition in the claims can be broadened to a class of molecules. However, comparative data of this type may help to illustrate or emphasise the unexpected nature of a characteristic relied upon for inventive step, since it can help to establish that anti-target antibodies (and hence prior art antibodies) cannot be assumed to share that characteristic.
Another situation where including data relating to a number of different anti-target antibodies can be helpful is where a panel of antibodies have been developed in an attempt to identify candidates which have one specific improved property - such as improved solubility, reduced isomerisation etc. Comparative data for antibodies for which such attempts were unsuccessful will help to show that the successful attempts were not predictable in advance, and thus are unexpected.

Epitopes

Although the EPO have historically allowed claims which define antibodies in terms of their epitope binding, such claims are coming under increasing scrutiny. Our understanding is that the EPO now require more detailed information concerning how the epitope was identified and how binding to it is to be assessed. The EPO may also require detailed information regarding any novel / inventive characteristics that are asserted as being conferred on an antibody by virtue of binding to a particular epitope, as well as evidence that prior art antibodies do not bind to the same epitope. This need not necessarily take the form of epitope-binding data for prior art antibodies. The EPO may accept a technical explanation as to why a prior art antibody would not bind to the same epitope.

Where an epitope is identified in an application, it should be considered whether it represents a sequence bound by an antibody only when present in the context of the target molecule as a whole, or whether it can also be bound as a short peptide fragment in isolated form. Care should be taken when drafting the specification so that it is clear exactly what properties are intended when referring to epitope binding. There are a variety of different methods can be used in establishing epitope binding, including analysis of binding to short fragments, mutagenesis studies, and crystallography analysis. It is desirable to include detailed information regarding the technique that has been used for the antibodies that are disclosed.

When drafting an application, consideration should be given to the techniques employed both for epitope determination and for assessment of the resulting characteristics. Sufficient information should be provided to ensure that the particular epitope is clearly defined, and that one of skill in the art could produce antibodies which can be identified as binding to it. The EPO may also require evidence to establish that it is at least plausible that all antibodies binding to the particular epitope can be expected to share the resulting properties.

Supplementary Protection Certificates (SPCs)

The SPC Regulation pre-dates the development of biological pharmaceuticals such as antibodies, and thus does not take into account the particular complexities of such molecules as compared to traditional small molecule pharmaceuticals. As a consequence, the basic requirements to obtain a valid SPC are the same for all types of pharmaceutical. One of these requirements is that the active ingredient of an authorised medicinal product must be “protected by the basic patent” (Article 3(a) of the SPC Regulation).

This requirement is not satisfied merely because the active ingredient is encompassed within a
claim of the patent for the purposes of infringement. Rather, the cumulative effect of multiple CJEU decisions is that the active ingredient must be “specified” in the claims at some higher degree of precision. For more detailed information, see our separate SPC briefing.

The key point to bear in mind is that it is desirable to include a claim (or language to support a claim) that defines the expected active ingredient of any medicinal product with as high a degree of precision as possible. Where possible, this should include as much structural information as is available regarding both target-binding and constant regions of an antibody.

[1] Board of Appeal decision T735/00

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