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. However, the high volume of applications in this area means that examiners have developed standardised approaches to assessing "antibody-specific" issues and these have been formalised in a dedicated section of the EPO's Guidelines for Examination (G, 11, 5.6 ; issued March 2021 and revised March 2022). 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. This briefing is intended to develop those Basic Principles into a guide to the drafting and prosecution of patent applications for antibody inventions.

We have focussed on therapeutic antibodies, but similar considerations apply to antibodies used in other applications, such as diagnostics. We have also generally assumed that the antibody molecule presents its binding domains in a traditional format comprising two heavy and two light chains. An increasing number of alternative formats are now known, but in practice we find that this does not make a significant difference to prosecution because the EPO takes the view that the underlying techniques required to generate those formats are also routine. Thus, while references to human or humanised antibodies, or to an antibody fragment or other format such as scFV, heavy chain only, bispecific, CAR or BiTE are common, these are seldom decisive for patentability unless there is an invention in the format per se.

Bearing the above in mind, this 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, our discussions with EPO examiners and the corresponding EPO Guidelines. Despite the large number of antibody applications filed and granted at the EPO, the quantity of Board of Appeal decisions concerned with "antibody inventions" remains relatively low.

In our opinion part of the reason for this is because the most common antibody applications have focussed narrowly on a lead molecule or molecules of the applicant. Such cases are less likely to present a freedom to operate risk for an innovator competitor and some innovators even prefer that a patent is granted and in force since this may reduce the likelihood of generic competition. For the generic / biosimilar competitor, the 9 month opposition term after grant of a European patent may come too early in product development, or other barriers to market entry (e.g. regulatory data exclusivity) may be viewed as more significant. Hence, narrow antibody patents are less likely to be opposed, which means comparatively fewer cases reach the Boards of Appeal.

For more detail on the most recent developments in EPO case law, please see our regular Review of EPO Antibody Decisions. We generally find that the approach taken by the Boards of Appeal matches our experience of ongoing EPO prosecution.

Unexpected Technical Effect

As is explained 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

- 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;data:
- Functional data to show that the antibody specifically binds to the target and has some functional effect(s) as a consequence; and
- Functional data to show that (in addition to the above) 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.

The current EPO Guidelines state that an antibody needs to be defined by the number of CDRs required for its binding. However, fewer than six CDRs will be only be allowed if it is experimentally shown that one or more of the six CDRs do not interact with the target epitope or if the claim concerns a specific antibody format allowing for epitope recognition by fewer CDRs. Examples of this might be a single domain (VHH/camelid) antibody that has only three CDRs in any event and an antibody comprising a so-called common light chain that does not contribute to specificity.

There are two common approaches to defining an antibody by CDRs:

i. "An antibody binding to <target>, which comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 sequences of <SEQ ID NOs>"; or

ii. "An antibody binding to <target>, which comprises the heavy and light chain CDRs of a heavy and light chain variable region pair of <SEQ ID NOs> or [less frequently] which comprises the heavy and light chain CDRs of the antibody of <deposited hybridoma>".

Approach (ii) seeks to use the entire variable regions to define the CDRs without the framework regions, but without explicitly reciting the CDRs as in (i). In our experience, EPO examiners have generally objected to such claims as unclear, because the precise location of a CDR can be dependent on the techniques used to identify it. This general practice has now been adopted in the EPO Guidelines, which explicitly state that CDRs must be defined according to a specific numbering scheme, for example, chosen from that of Kabat, Chothia or IMGT. Even if the claims will pursue approach (i) it is recommended that the application discloses the numbering scheme and definitions used to identify the CDRs. It is currently 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.

In the absence of a precise disclosure of the CDR numbering scheme used, it can still be worth the attempt to pursue approach (ii). This may apply particularly for applications with earlier filing dates, where there may be some doubt as to the exact location of the CDRs and/or no or only incomplete sequence information. A variation of this approach may seek to claim "a humanised variant" of a disclosed non-human antibody or heavy/light chain sequence pair.

Applicants should be prepared to go beyond approach (i) or (ii) and to recite in the claims a definition requiring the entire heavy and light variable region sequences. Although not yet a routine requirement, examiners may insist upon it if there is reason to believe that the unexpected technical effect relied upon for inventive step is in some way also dependent on the framework regions. That is, if the effect cannot be attributed solely to the CDRs. In some instances, a combination of CDR sequences with a functional definition linked to the technical effect may be allowable (see below). Applications should therefore also be drafted to provide basis for this combination of structural and functional features.

Where there are multiple candidate antibodies in an application, applicants should ensure that each molecule is defined by reference to as much structural information as is available at the time. Ideally this will include all six CDRs and both entire 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. Claims using this approach are likely to fail for lack of inventive step or sufficiency or support, and the "mix and match" language does not itself provide explicit basis for amendment to claim the specific combination of six CDRs in an individual molecule. Instead, the specific combinations of target-binding region sequences that make up each of the candidates should be individually disclosed.

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, usually human IgG and especially IgG1 and IgG4, 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.

Especially where an actual candidate molecule has been identified and its constant region is known, 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. This can be the case if the effector function of the constant region is relevant and/or the constant region contains any modifications. 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.

Structural information – sequence variability

In general, the EPO will not allow claims referring to substitutions/variability in the CDR sequences, unless the application provides evidence that such changes would not affect the properties of the antibody. Claims referring to substitutions/variability in the CDR sequences and/or framework regions may though be allowed where a functional definition is included, provided that the functional definition is clear and reflects the unexpected technical effect (GL G, II, 5.6.1.4).

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 (preferably at a stated temperature) 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. It is often not necessary to write a measurement technique into the claims but it can be useful to have the language available to enable this in case the closest prior art antibodies have very similar properties.

However, if a numerically defined 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 to support an unexpected technical effect available will, of course, be highly dependent upon the nature of a given antibody project. Examples cited in the Guidelines (G, 11, 5.6.2) are improved affinity, improved therapeutic activity, reduced toxicity or immunogenicity or an unexpected species cross-reactivity. However, in practice examiners often do not consider improved affinity alone to be sufficient to acknowledge an inventive step, especially where other high-affinity antibodies are already known. Improved affinity is therefore often combined with another characteristic.

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, as well as disclosing the sequences of potential backup candidates that may not be protected by the claims that ultimately grant. 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. Therefore, even if data on less preferred molecules is released into the public domain in this way, it can help to support patentability of a lead candidate or candidates.

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 representing unsuccessful attempts will help to show that successful attempts were not predictable in advance, and thus are unexpected. This kind of data is relevant where multiple, unrelated antibodies have been raised via immunisation or identified from a library but can be particularly useful for humanised antibodies, where several different humanised sequences were made and some are superior to others.

Applicants therefore need to weigh up the positive benefits of disclosing multiple antibodies in an application, versus the possible downsides of making these less preferred antibodies available to the public.

Multiple candidate antibodies – unity of invention

Under EPO practice, all of the claimed subject-matter must share a common inventive concept. At the search stage, when there is a lack of unity, only the invention mentioned first in the claims will be automatically searched and examined. Additional search fees must be paid in order to pursue another invention of interest.

When a claim set refers to multiple candidate antibodies, the EPO's starting position is usually that there is no common inventive concept linking the different antibodies. In case a lack of unity is raised, the subject-matter relating to the most important candidate antibody should generally be presented first in the claims (in order to avoid the need for payment of additional search fees). Where a specification defines a "family" of antibodies, for example different humanisations of the same rodent antibody or a set of antibodies identified by phage display in which some have heavy or light chains in common, these may be unitary. Antibodies that do not have common CDRs or chains are however almost always non-unitary. Even prima facie arguable objections of lack of unity are often difficult to overturn once raised, and in many cases the most practical approach is to elect a preferred antibody for examination and file a divisional application if resources permit.

Epitopes

The EPO may allow claims which define antibodies in terms of the epitope to which they bind. However, such claims are often the subject of detailed scrutiny. Patents with epitope claims are more likely to be opposed due to the freedom to operate risk presented to third parties.

Novelty can be an important issue; it will typically be up to the applicant to prove that prior art antibodies binding the same target and having the same properties as the reference antibody do not bind to the same epitope region. 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.

Inventive step is also likely to be very important; the EPO will need to be persuaded that the invention truly lies in the epitope and not in the sequence of the antibody. Examiners will typically consider whether it was obvious to target a particular region of a protein, and whether there were any technical hurdles in doing so.

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. The EPO's Guidelines now explicitly state that "linear epitopes" need to be defined using closed wording, i.e. "epitope consisting of <sequence>". For non-linear epitopes, the method of determining the epitope must be clearly identified (GL G, II, 5.6.1.6).

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 that 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. For example, for an epitope determined by crystallography, the number of Å should be included.

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.

The subject of this briefing is of course antibodies at the European Patent Office. However, it is also worth noting that there is recent USPTO case law rejecting epitope claims for lack of written description and lack of enablement. The USPTO will in essence only allow claims defining an antibody by a minimum of 6 CDR sequences.

A related concept is that of claims to antibodies that compete for binding with a reference antibody. Applicants sometimes try to use such claims in similar ways to those reciting epitopes and are usually unsuccessful. The EPO objects that antibodies may compete for other (e.g. steric) reasons without necessarily binding to the same epitope, and hence without necessarily sharing the technical effect.

Pharmaceutical composition claims

If there is an invention in the antibody as a product per se, then it is usually possible also to claim a pharmaceutical composition comprising that antibody. However, if the invention lies in the formulation of an existing, known antibody, this is more of a challenge. The EPO will generally assume that formulating a known molecule is obvious unless some particular unexpected technical effect is shown.

Given that composition cases are often filed to protect an optimised formulation, e.g. that will enter clinical trials, data in support of technical effects may be available. However, the EPO will treat each antibody or other biopharmaceutical protein as a separate formulation challenge. Therefore, if there is an invention in a formulation, that invention is usually confined to at most a small group of closely-related molecules, and often only a single molecule. For antibodies, this almost invariably means specifying both variable and constant region sequences. Once again it is important to include these sequences in the specification.

Claims to nucleic acid sequences / antibody production methods

As with other proteins, and unlike small molecule pharmaceuticals, an antibody invention can also be claimed by reference to nucleic acid sequences encoding the polypeptide sequences. However, it is important to remember that a nucleic acid encoding either the heavy or the light chain may not benefit from the arguments for inventive step that reside in the combination of the two.

To mitigate this problem, applicants are advised to include nucleic acid claims in formats that capture the antibody as a whole as opposed to just one of its chains. For example, claims to a DNA construct comprising the coding sequences of both chains can be useful, as can those to cells transformed with both coding sequences and method claims to expressing both chains at once. Cell claims now normally relate to transgenic "production" cell lines but claims to deposited hybridomas may also still be useful where the antibody coding genes have not yet been cloned out and sequenced. In these cases, it is vital that the hybridoma is deposited under the Budapest Treaty before filing, as the EPO will not accept as enabling a paper description of the hybridoma or allow a deposit to be made during examination.

Method claims can also be useful as protection against importation of antibodies produced elsewhere. Article 64(2) EPC and corresponding provisions of national law state that importation of the direct product of a patented process is an infringement. For this reason, applicants are advised to ensure that method claims recite the steps that lead up to the production of the antibody in the form it is likely to be imported. In particular, it is desirable to present claims that include any recombinant manipulations steps that may be required to arrive at the construct from which antibody heavy/light chains are expressed, and also downstream steps of isolating and/or purifying the antibody, and its formulation into a pharmaceutical composition. Similarly, If the antibody is going to be used in a more complex final product, such as in a chimeric antigen receptor (CAR) format, often the strongest claim will be to the CAR-T cell in which the antibody actually exerts its effect.

Multiple specificities

It is now very common for an application to contain at least some

claims relating to binding more than one target. Such claims may, especially in oncology applications, be to bispecific antibodies that simultaneously bind two targets via their two arms. In other areas claims to medical uses of different combinations of individual antibodies are more common. In these cases, it is important to distinguish whether the two (or more) antibodies have to be co-formulated into one composition as a so-called "cocktail" or if they can be delivered separately at different sites, times or dosages.

In all of these situations, however, there will need to be either an invention in one specificity or the other, or in the combination of the two, i.e. relating to the targets being bound, or to the properties of the multi-specific format of whichever type is applicable. Similar principles apply to combinations of an antibody with a small molecule or other different type of pharmaceutical, including antibody-drug conjugates (ADCs).

Supplementary Protection Certificates (SPCs)

The currently applicable EU 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. However, a good basic approach for antibodies is to make sure that at least some claims are presented to at least the full heavy/light chain variable region sequences, and preferably that of the constant region as well.

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, the application should include as much structural and functional information as is available. For the latter, it is helpful to include at least information regarding target- binding specificity and affinity, as well as any other functional properties that are likely to be recited in the future summary of product characteristics.

For more information, please contact:

Vicki Allen — vallen@jakemp.com
Patrick Campbell — pcampbell@jakemp.com
Andrew Bentham — abentham@jakemp.com
Graham Lewis — glewis@jakemp.com