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Navigating Key Differences in Therapeutic Antibody Patent Protection Strategies Between the United States and Europe

By Yifan Mao, MS,* Glyn Truscott,** and Andrew T. Serafini, PhD*

Many of today's top-selling drugs worldwide are therapeutic antibodies thus antibody-related inventions can be extremely valuable. Developing antibody therapeutics requires significant resources and time, so it is paramount to develop a robust patent strategy to protect that investment, prevent reverse-engineering, and minimize design-arounds.

The World Intellectual Property Organization (WIPO) created The Standing Committee on the Law of Patents (SCP) in 1998 to focus on substantive patent law harmonization.[1] In November 2000, the SCP began focusing their efforts on a Substantive Patent Law Treaty (SPLT). The ultimate goal of the SPLT is global harmonization of issues relating to the grant of patents in order to improve global patent quality. Although the SPLT negotiations were put on hold in 2006,[2] the SCP continues their work on patent law harmonization, holding the SCP's 32nd session in December 2020 in Geneva, Switzerland. [3]

Applicants typically file antibody-related patent applications in many jurisdictions including the United States Patent and Trademark Office (USPTO) and the European Patent Office (EPO). The USPTO and EPO examine antibody claims for patent-eligibility, clarity, support and enablement, novelty and inventive step. However, despite the efforts of WIPO's SCP, the USPTO and EPO significantly differ during examination of antibody patent applications in their determination whether or not an antibody claim meets these requirements. For companies developing antibody products for both the United States (U.S.) and European markets, it is important to avoid Office-specific pitfalls when drafting and prosecuting antibody claims.

Recent case law in the U.S. creates a significant hurdle for applicants seeking broad protection for their antibodies. Through a series of court cases since 2014, the U.S. has gradually dismantled the old rule under which a claim reciting a newly characterized antigen would be considered to have met written description requirements.[4] The U.S. courts no longer consider that the relationship between antibody and antigen is analogous to the one-to-one relationship of a lock and key,[5] but insist that the relationship is akin to a lock and "a ring with a million keys on it." [6] Under the new 2018 written description guidance,[7] the application must "reasonably convey to the artisan that the inventor had possession at that time of the later claimed subject matter."[8] Applicants may show possession of a claimed genus through a disclosure of a representative number of species by actual reduction to practice, by disclosure of relevant, identifying characteristics (*i.e.*, structure or other physical and/or chemical properties), by functional characteristics coupled with a known or disclosed

correlation between function and structure, or by a combination of such identifying characteristics.[9]

The U.S. enablement requirement has become more restrictive. A claim is enabled if the specification provides sufficient guidance to enable a person of ordinary skill in the art ("POSA") to practice the claimed invention without undue experimentation. Because generating and screening antibodies against specific antigens were considered "well-known" and "routine," [10] enablement has not been a significant issue for antibody claims until recent years. In *MorphoSys AG v. Janssen Biotech, Inc.*, the court held that the claims are not enabled because "a POSA would require substantial time and effort to discover antibodies within the claims that are not conservative variants of the disclosed antibodies."[11] More recently on February 11, 2021, in *Amgen Inc. v. Sanofi*, the Federal Circuit affirmed the grant of Judgment as a Matter of Law ("JMOL") of lack of enablement of Amgen's antibody claims. These claims were directed to a genus of therapeutic antibodies that bind specified amino acid residues of PCSK9 and block binding of PCSK9 to LDL receptors.[12] The Federal Circuit held that "even assuming that the patent's 'roadmap' provided guidance for making antibodies with binding properties similar to those of the working examples, no reasonable factfinder could conclude that there was adequate guidance beyond the narrow scope of the working examples that the patent's 'roadmap' produced." [13] These court decisions highlight the difficulty of obtaining broad claim scope for antibody innovations in the U.S.

In contrast to the U.S., the main challenge for applicants in Europe is usually to show that the claimed antibodies are not obvious. In particular, the EPO considers that an antibody to a known target, made by standard techniques and defined by its sequence (typically at least all six CDRs), is deemed obvious unless "unexpected properties" are demonstrated for that antibody. Unlike its usual approach to small molecules, the EPO does not apply structural non obviousness to antibodies but takes the general view that generating multiple antibodies to a known target is routine. Therefore, it can be more challenging to obtain claims to the specific lead clinical antibody at the EPO than in the USPTO. However, the corollary of this approach is that broader antibody genus claims (*e.g.*, function or target-defined), once clear of the art, can be easier to obtain in the EPO than in the USPTO. This is because the rationale that it is routine to generate multiple antibodies to a target means that enablement and support are less of an issue for broader antibody claims, at least once the target and function are described and at least one antibody having the claimed features is described in the specification.

As compared to its U.S. counterpart, the EPO's antibody practice is remarkably settled. In March 2021, for the first time, the EPO published the influential "Guidelines for Examination" [14] highlighting some key features of its antibody practice.

In the following sections, we discuss some of the main formats in which antibodies can be claimed and strategic considerations to ensure that claims will grant despite very different approaches used by the EPO and USPTO.

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1. Claiming Structure

Antibodies have unique structures. A conventional antibody molecule has two heavy chains and two light chains, with each chain having a constant region and a variable region. Each variable region has three complementary determining regions (CDRs), which are highly variable and primarily responsible for binding target antigens. Interspersed with the three CDRs are the less variable framework regions.

U.S.

As the USPTO and U.S. courts tighten the written description and enablement requirements for antibody claims, claiming sequence identity (for example, to CDRs or the variable regions) is unlikely to be patentable unless the application discloses a sufficient number of examples that can support the breadth of the claims. In one exemplary case, the U.S. Patent Trial and Appeal Board (PTAB) reversed the examiner's written description rejection of claims directed to antibodies having a heavy chain variable region and a light chain variable region, each being 95% identical to respective reference sequences. The PTAB determined that the claims met the written description requirement because the application discloses seventy-three (73) different amino acid substitutions and stated that an "antibody having any of these substitutions should neutralize TNFα activity as antibodies with all of these substitutions have been shown to neutralize TNFα activity."[15]

Instead of sequence similarity, the USPTO favors claims reciting all six CDRs sequences. In some instances, applicants may be required to claim antibodies by describing the sequences of heavy chain and light chain variable regions. In other instances, claims drawn to having certain substitutions or consensus sequences within the CDR regions may be found allowable if these claims are supported by appropriate disclosure and data.

In some cases, the antibody is a naturally-occurring antibody, one example of which is an antibody isolated from a patient. Applicants must consider the patent-eligibility issues when drafting claims for naturally-occurring antibodies. Naturally-occurring antibodies are not patentable, but claims directed to expression vectors encoding these antibodies, host cells and methods of producing the antibodies, antibody-drug conjugates, and pharmaceutical compositions are all eligible for a patent. Patent-eligible claims can also be crafted to cover antibody variants that have structural changes compared to the corresponding naturally-occurring antibody. For example, claims can be drafted to cover antibody variants in which CDRs have been grafted to a different scaffold or the Fc domains have been modified to contain non-natural amino acid sequences.

Examples:
An isolated monoclonal antibody that binds to antigen X, wherein the antibody comprises the VH as set forth in SEQ ID NO:1 and the VL as set forth in SEQ ID NO: 2.

An isolated monoclonal antibody that binds to antigen X wherein the antibody comprises a VH comprising the

CDRs as set forth in SEQ ID NO: 1-3 and a VL comprising the CDRs as set forth in SEQ ID NO: 4-6.

EPO

To claim a monoclonal antibody by its sequence, the EPO will usually first require that at least all six CDRs are recited in the main claim. The reason for this is that the EPO considers the CDRs to be essential technical features that must be claimed to comply with the requirement for clarity under Article 84 EPC. In relatively rare instances, some variation of the CDRs may be allowed when the facts of the case support the variation. In such circumstances, a functional definition in the claim can be very useful (for example, to define that the antibody must retain a certain binding affinity or biological function). This is discussed further below.

For a new antibody to a known target that was generated by standard techniques, the EPO's approach to the assessment of obviousness is summarized by the Boards of Appeal in T0735/00:

The case law in this field acknowledges inventive step if and when there is evidence that a claimed monoclonal antibody prepared by routine methods shows unexpected properties (cf decision T 645/02 of 16 July 2003). If, however, there are no unexpected effects achieved with a further monoclonal antibody compared with a monoclonal antibody with essentially the same properties as desired the case law denies inventive step (cf decision T 512/94 of 23 June 1998)[16].

The "unexpected effect" that can be relied upon is not limited and will depend on the facts of the specific case. It may have been enough some years ago to simply assert a high level of affinity (e.g., at least nanomolar binding of the antibody to a target) as an unexpected effect, but as antibody technology has developed, this approach will not be enough in many cases.

The requirement for the claimed antibody to provide unexpected properties is to some extent related to the clarity requirement for all essential features to be recited in the claim. The more granular the unexpected effect, the more structural features are likely to be needed in the claim to make it plausible that substantially all antibodies will provide the asserted unexpected effect. In a crowded technical field with many prior art antibodies, the claim will likely need to recite at least the CDR and framework sequences that are essential to provide the effects observed for the exemplified antibody. Likewise, if effector functions are asserted as being unexpected when arguing inventive step, then the hinge and/or Fc region sequence or antibody isotype may also need to be included in the claim.

Finally, it is important to note that the EPO's requirement for unexpected properties only applies to new monoclonal antibodies to a known target prepared by standard techniques. Therefore, if a claimed antibody was not prepared by a standard technique, evidence of unexpected properties may not be required and non-obviousness could instead be established based on the difficulty of producing the antibody.

Furthermore, the EPO's requirement for unexpected properties will in some instances not apply to engineered

antibodies, in circumstances where the choices of modifying specific residues to achieve a desired result is an unpredictable task of human engineering rather than inevitable biology. For example, a claim to the sequence of a particular humanized antibody sometimes can be considered inventive: difficult and unexpected choices are needed to choose a suitable human acceptor sequence and identify back-mutated residues to retain the binding characteristics of the non-human parent antibody.[17]

2. Claiming Targets

Claiming antibodies by their novel targets is increasingly rare as most antigens are already known. Even if the target is previously unknown, broadly claiming antibodies by the target they recognize is no longer possible in the U.S. today—the newly characterized antigen written description rule has been abolished.[18] Claims directed to a genus of antibodies by an epitope, without a disclosure of the structure of antibodies responsible for binding the epitope and a sufficient number of representative antibody species for support[19], would also likely be rejected for lacking written description. Disclosure of the antibody-antigen complex that is common to a representative number of antibodies may be used to support a claimed genus of antibodies. These data can be generated using methods such as, X-ray crystallography, cryo-electron microscopy and computer aided protein homology modeling.

It is common for applicants to claim antibodies by the target they recognize in combination with other structural/functional features. Claims drafted this way will likely be found allowable.

At the EPO, it is possible to claim an antibody defined by its target binding—either by defining the target *per se* or by defining a newly-identified (linear or conformational) epitope on a known target. Defining an antibody by a newly-identified epitope is more likely to be found allowable. A more common claim type is to claim an antibody that competes with a reference antibody. If this approach is used, the method and technique for determining competition (and any relevant binding threshold), should be described in the specification. These features also may be required in the claims.

Examples of claim types:

- An antibody to protein X.
- An antibody that binds specifically to protein X.
- An antibody that binds specifically to an epitope within residues 95-110 of protein X.
- An antibody that binds specifically to protein X and competes with reference antibody Y for binding to protein X.

Provided that it is technically reasonable that antibodies across the claim scope can be produced without an undue burden, then it is unlikely that the EPO will find significant enablement or support objections. To avoid the

undue burden issue, antibody claim scope should be supported in the specification by at least one (and more ideally, several) exemplified antibodies. The main issues at the EPO will be establishing novelty by showing that no prior art antibody falls within the scope of the claim, and establishing inventive step by showing that any technical effect relied upon is plausibly provided across the entire claim scope (not just a single exemplified antibody).

3. Claiming Functional Features

Claims reciting only functional features are vulnerable to attack for lacking written description and enablement in the USPTO. Similar to defining antibodies by their targets, it is advisable to claim functional features in combination with some structural features to offer alternative and/or broader protection than claiming more specific structures. For example, a claim can be drafted to describe functional features associated with important residues and variability in CDRs.

An isolated antibody or antigen-binding portion thereof comprising: (a) an HCDR1 comprising an amino acid sequence of SEQ ID NO:1; (b) an HCDR2 comprising an amino acid sequence with amino acid substitutions at the 9th, 11th, or both the 9th and 11th amino acids of SEQ ID NO:2; (c) an HCDR3 comprising an amino acid sequence with amino acid substitutions at the 2nd or 12th amino acids of SEQ ID NO:3; (d) an LCDR1 comprising an amino acid sequence with amino acid substitutions at the 5th, 7th, 8th, 9th or all of these amino acids of SEQ ID NO:4, (e) an LCDR2 comprising an amino acid sequence of SEQ ID NO:5; and (f) an LCDR3 comprising an amino acid sequence with amino acid substitutions at the 3rd, 8th, or both the 3rd and 8th amino acids of SEQ ID NO:6; and wherein said antibody or antigen-binding portion thereof binds to the X polypeptide with a K_D of 100 nM or less and inhibits X activity with an IC_{50} around 10 nM or less.

Such functional limitations are also very useful at the EPO and can be helpful to limit the claim scope to those antibodies that do provide the asserted technical effect, *i.e.*, to exclude non working embodiments. Such functional features can be added to any other "definition" of the antibody, *e.g.*, an antibody defined by its sequence or by its target.

A further type of functional limitation at the EPO, is the medical use or second medical use claim available under Articles 54(4) and 54(5) EPC, for example:

- Antibody X for use in therapy
- Antibody X for use in a method of treating disease Y.

These purpose-limited product claims can be very useful to maintain the breadth of an antibody definition while excluding from the claim non-therapeutic prior art. These non-therapeutic prior art antibodies may include, for example, antibodies used in pre-clinical research, described in the materials and method section of a research paper, or available from an antibody catalogue or supplier for research purposes.

4. Claiming Production Process and Hybridomas

Antibodies can be claimed by the hybridomas from which the antibodies are produced. Since it is often not possible to describe hybridomas in structural terms, applicants can meet the written description and enablement requirement by depositing the hybridomas with an appropriate Depository Authority (*e.g.*, American Type Culture Collection, ATCC). Claims that rely on hybridoma deposits have more narrow claim scope.

Hybridoma-focused antibody claims are permitted at both the USPTO and the EPO. However, a critical difference exists because, unlike the USPTO, the EPO requires that the deposit is made by the applicant *before* the filing (or priority) date. It is not possible to file an application at the EPO then make the deposit at a later date.

Examples:

- A method of making an antibody comprising administering a peptide consisting of SEQ ID NO: 1 to a mammal, and purifying the resultant antibodies.
- An antibody raised against peptide having a sequence set forth in SEQ ID NO:1 and produced by a hybridoma cell line from hybridoma cell lines having ATCC accession number OTA-XXXX.
- An antibody produced by the hybridoma having ATCC accession number OTA-XXXX.
- A humanized version of the non-human antibody produced by the hybridoma having ATCC accession number OTA-XXXX.

5. Practice Tips

Antibody claims face different challenges in USPTO and EPO as the patent practices of these two major jurisdictions are diverging (rather than harmonizing). Applicants seeking patent protection in both regions should consider using multiple claiming strategies to protect the same asset. Applicants are advised to draft claims (with the necessary support in patent specifications) that comply with country/region-specific laws. Critically, the EPO takes a strict view when assessing whether an amendment during prosecution adds matter, so care should be taken when drafting the application to ensure that there is direct and unambiguous basis for EPO claim types and possible amendments (*e.g.*, functional limitations), and that unexpected effects are described ideally supported by data in the application as filed.

It is important to know what type of antibody invention is being described and pursued, both when drafting the application and when prosecuting it before the respective Patent Office. Drafting a specification for the EPO should include statements to address the issues discussed above, for example, explicitly linking sequence/structure to function, connecting key features from the Examples to particular structural features, and highlighting unexpected or unusual results shown in the Examples or difficulties faced when preparing the

antibody.

As with many other types of inventions, data are often crucial on the determination whether an applicant can obtain claims with the desired scope and features. Data covering representative working examples can be used to support a broader claim scope in the USPTO, and data showing surprising and unexpected properties are often required to show non-obviousness in the EPO. More data will typically be required at the USPTO and the EPO if applicants are trying to obtain broad claim scope. The potential use of post-filing data to support an application was discussed in the authors' recent KT MEMO blog article which can be found here.

After an application has been filed and patent prosecution has started, a practitioner must use the appropriate jurisdictional tests and apply the correct jurisdictional case law. As noted above, these tests and case law in the antibody space differ significantly between the USPTO and EPO.

Time and money will be wasted without careful attention to the key differences in these jurisdictions, and conversely, application drafting strategies tailored to take advantage of these differences can lead to success on both fronts.

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*Yifan Mao is a senior associate at Kilpatrick Townsend & Stockton, LLP, and she can be reached at ymao@kilpatricktownsend.com; 650-324-6311.
**Glyn Truscott is a partner at Elkington & Fife LLP, and he can be reached at Glyn.Truscott@elkfife.com; +44 20 7936 8817.
*Andrew T. Serafini is a partner at Kilpatrick Townsend & Stockton, LLP, and he can be reached at atserafini@kilpatricktownsend.com; 206 626 7769.

Footnotes

[1] *Standing Committee on the Law of Patents (SCP)*, WIPO, https://www.wipo.int/policy/en/scp/ (last visited Apr. 22, 2021).
[2] *Draft Substantive Patent Law Treaty*, WIPO, https://www.wipo.int/patent-law/en/draft_splt.htm (last visited Apr. 22, 2021).
[3] *Standing Committee on the Law of Patents: Thirty-Second Session*, WIPO, https://www.wipo.int/meetings/en/details.jsp?meeting_id=55611 (last visited Apr. 22, 2021).

[4] U.S. PAT. & TRADEMARK OFF., WRITTEN DESCRIPTION TRAINING MATERIALS 47 (2008), https://www.uspto.gov/sites/default/files/web/menu/written.pdf.

[5] Noelle v. Lederman, 355 F.3d 1343, 1350 (Fed. Cir. 2004).

[6] Amgen Inc. v. Sanofi, 872 F.3d 1367 (Fed. Cir. 2017).

[7] Memorandum from Robert W. Bahr, Deputy Comm'r, Pat. Examination Pol'y, to Pat. Examining Corps, Clarification of Written Description Guidance for Claims Drawn to Antibodies and Status of 2008 Training Materials (Feb. 22, 2018), https://www.uspto.gov/sites/default/files/documents/amgen_22feb2018.pdf.

[8] MPEP § 2163.02 (citations omitted).

[9] MPEP § 2163(II)(A)(3)(a)(ii).

[10] Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986); *In re* Wands, 858 F.2d 731, 736 (Fed. Cir. 1988).

[11] 358 F. Supp. 3d 354, 370-72 (D. Del. 2019).

[12] 987 F.3d 1080, 1082 (Fed. Cir. 2021).

[13] *Id*. at 1088.

[14] EUR. PAT. OFF., GUIDELINES FOR THE EXAMINATION IN THE EUROPEAN PATENT OFFICE pt. G, ch. II, § 5.6 (2021),

[15] Ex parte Yaohuang Ke, No. 2013-009436, at 8 (P.T.A.B. Feb. 10, 2016) (finding the claims of US9365644 meet the written description requirement because the application discloses 73 different amino acid substitutions and stated that an "antibody having any of these substitutions should neutralize TNF α activity as antibodies with all of these substitutions have been shown to neutralize TNFα activity").

[16] Case T 0735/00, Iatron Lab'ys, Inc. v. Dade Behring Marburg GmbH, ECLI:EP:BA:2004:T073500.20040323, ¶ 26 (Mar. 23, 2004).

[17] *See* Case T 0067/11, *In re* Centro de Inmunologia Molecular, ECLI:EP:BA:2014:T006711.20140526, ¶¶ 20-22 (May 26, 2014).

[18] Amgen Inc. v. Sanofi, 872 F.3d 1367 (Fed. Cir. 2017); Memorandum from Robert W. Bahr, *supra* note 7.

[19] So far U.S. courts have not issued clear guidance as to what constitute a sufficient number of representative species.