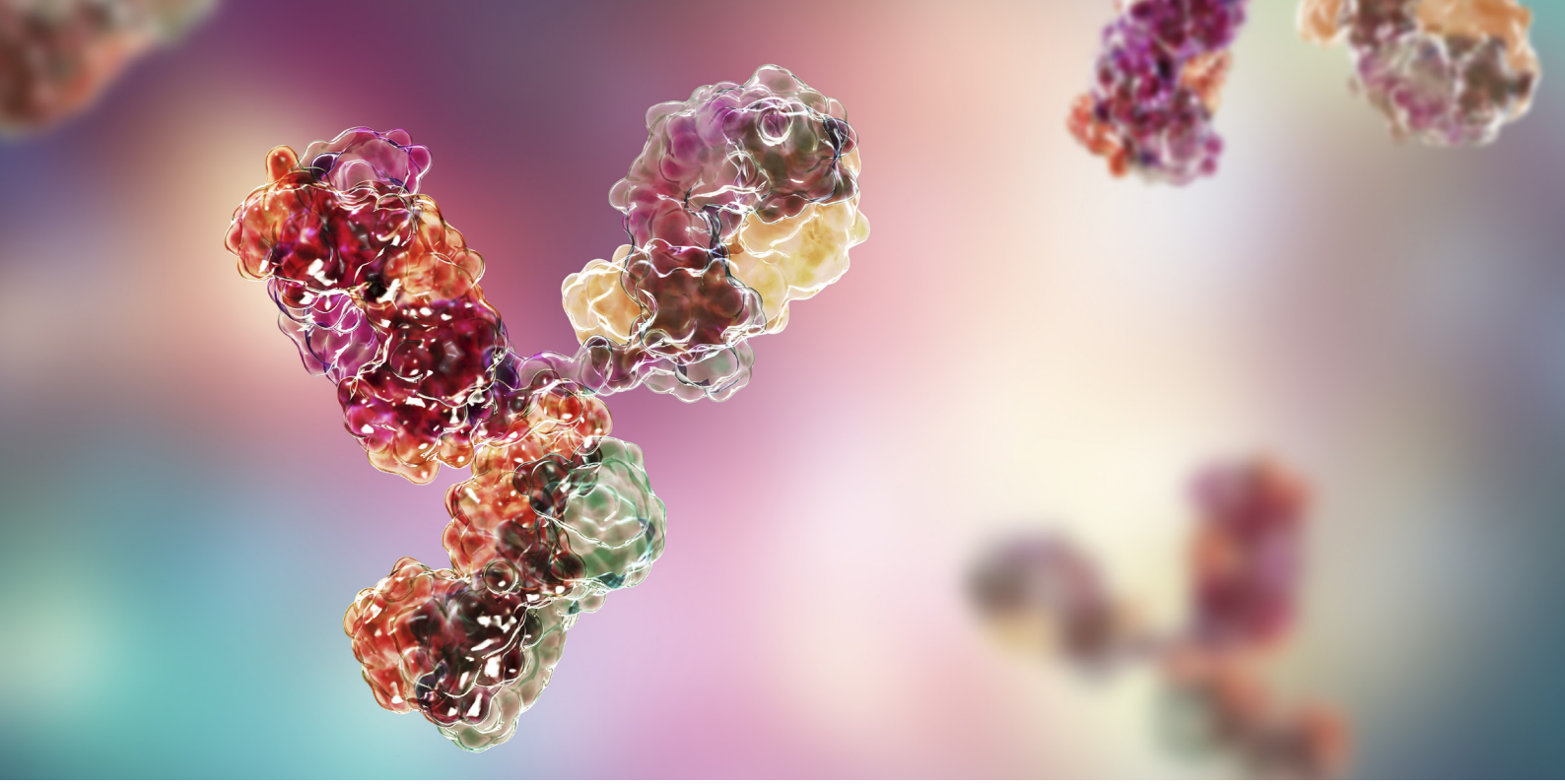

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A New Focus on Antibodies in 2021 Update to EPO Guidelines

The European Patent Office (EPO) makes annual updates to the Guidelines for Examination in the European Patent Office (Guidelines) in view of recent case law or other changes and where the EPO considers further clarification is needed. Today, 1 March 2021, a whole new Guidelines section focusing on antibodies will enter into force, which the EPO indicates has been added because this is an area of practice deemed in need of "further clarification"[1]. In this article we explore what this means for seeking patent protection for antibody technologies.

Significant importance but problematic?

Of the top 10 blockbuster drugs by global sales[2], at least six are antibodies - Humira (adalimumab), Keytruda (pembrolizumab), Opdivo (nivolumab), Avastin (bevacizumab), Stelara (ustekinumab), and Rituxan (rituximab). **There is no doubt that antibody-based therapies are of significant importance to human health and of significant commercial importance.** Vast research efforts are underway around the world to develop further antibody-based therapies and wherever there is notable research effort in human healthcare, there are corresponding patent filings. The introduction of a section to guide Applicants and Examiners concerned with antibody technologies is an indication that challenges are frequently encountered.

The new section of the Guidelines deals with two issues that we know from experience can cause problems, and that we can infer have also been causing problems during antibody patent

[1] Notice from the European Patent Office dated 25 January 2021 concerning the updating of the Guidelines for Examination in the European Patent Office. https://www.epo.org/law-practice/legal-texts/official-journal/2021/01/a6.html

[2] The top 20 drugs by global sales in 2019, from Fierce Pharma 27 Jul 2020. https://www.fiercepharma.com/special-report/top-20-drugs-by-global-sales-2019

prosecution for Examiners at the EPO. A first issue discussed (G-II, 5.6.1)[3] is that of how to properly define the antibodies for which protection is sought. These paragraphs also point out various ways in which definitions used in patent claims can fall short and so lack clarity or embrace too much so that a claim lacks novelty. A second issue discussed (G-II, 5.6.2)[3] is inventive step and what may be needed to show a patentable step forward in antibody technology. On the one hand it is good to see that nothing in this section suggests a departure from existing EPO practice for this technology area. On the other hand, the need to introduce this new section of the Guidelines emphasises that directly transferring patent practice from other technology areas or jurisdictions is not always successful for antibody technologies before the EPO.

How to demonstrate inventive step?

Of note is that **the new Guidelines section says (twice, just to be sure) that "structural non-obviousness" does not equate with inventive step**. In other words, the fact that the amino acid sequence of a new antibody to a known antigen could not be predicted from existing antibodies to the same antigen, does not mean that the new antibody is considered inventive.

This is a misconception that we regularly encounter, and understandably so, because patent practice in other jurisdictions (e.g. in the US) would appear to recognise structural non-obviousness, and because an argument that an altered chemical structure for a small molecule pharmaceutical could not be predicted to retain the same therapeutic effect can be persuasive. EPO practice does not acknowledge an inventive step solely on the basis that a novel antibody is structurally different from known antibodies binding to the same antigen because it is considered merely common practice for a person skilled in the art to create alternative antibodies using known techniques. This view of antibodies arises from the way patent practice developed in this area.

It is necessary to show that the new antibody has either a surprising technical effect, or that there were technical difficulties to overcome in producing the new antibody.

For the surprising technical effect, the new Guidelines offers some examples of acceptable properties that could be demonstrated. These include an improved affinity, an improved therapeutic activity, a reduced toxicity or immunogenicity, an unexpected species cross-reactivity or a new type of antibody format with proven binding activity. Furthermore, the Guidelines also explains that if inventive step relies on an improved property versus the enabled antibodies of the prior art, the main characteristics of the method for determining the property must also be indicated in the claim or indicated by reference to the description. Unfortunately, that is end of the guidance provided about demonstrating the surprising technical effect. The is probably because one set of Guidelines cannot provide all the answers for all situations. Nevertheless, in our experience an improved binding affinity may need to be a significant improvement, such as an order of magnitude greater, for inventive step to be recognized and this is not readily apparent from the new Guidelines in their current format.

How to define a new antibody?

The new Guidelines section offers Applicants various ways in which antibodies may be successfully defined, but then sounds a note of caution for each type of definition. We note that the new Guidelines appear to focus on conventional antibodies. No guidance is given for whether additional or different considerations apply to unusual antibody constructs such as the immunotherapeutics based on multi-specific constructs which are a key focus for cancer immunotherapy[4].

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[3] Unedited English version of the amended Guidelines for Examination, which will enter into force on 1 March 2021. https://www.epo.org/law-practice/legal-texts/guidelines/guidelines-preview.html

[4] TriKEs and BiKEs join CARs on the cancer immunotherapy highway. Tay et al (2016) Human vaccines & Immunotherapeutics, vol 12, no. 11 pp2790-2796. TriKEs and BiKEs join CARs on the cancer immunotherapy highway - PubMed (nih.gov)

An easy way to define an antibody is by reference to its amino acid sequence. To obtain commercially meaningful patent protection, it is common for patent claims to be drafted to embrace a number of possible antibodies, rather than just a single antibody and so we frequently see claims that aim to use only the CDRs on one of the heavy or light chains, or referencing a percentage sequence homology to the CDRs or the variable domain sequences. Our experience that such claims can attract objections is reflected in the section on defining antibodies. Generally, all six CDRs should be defined for a conventional antibody unless there is a reason that fewer than six CDRs are needed for that antibody to specifically bind its antigen. However, this may not be the end of the requirements for a structural definition. If the inventive step is to be based on an improved binding affinity, the EPO consider that the structural requirements for conventional antibodies inherently reflecting this affinity must comprise the six CDRs and the framework regions because the framework regions also can influence the affinity.

An antibody can be functionally defined. One option is to define the antibody by the antigen to which it binds, as long as the antigen is clearly defined in the claims. Unless the antigen itself is novel, which is rare these days, the key to such a definition will be in defining the antigen so specifically that the claim does not embrace known antibodies binding to another epitope on the same antigen. Alternatively, the antibody could be defined by a combination the antigen to which it binds and further functional features. Caution is sounded however; firstly, because any known antibodies produced by the same techniques to the same antigen will be considered to inherently have the same properties, and secondly, because it has to be carefully assessed whether the application provides an enabling disclosure across the whole scope claimed and whether the functional definition allows the skilled person to clearly determine the limits of the claim.

A frequently used approach to define antibodies that is specifically endorsed by the new Guidelines section is a combination of structural and functional features. This allows an antibody to be characterised by the sequences of both variable domains or by the CDRs with less than 100% sequence identity when combined with a clear functional feature.

It is possible to define antibodies by the process of their production. However, such a product-by-process definition, based on immunisation by an antigen would need to accurately define the antigen sequence used. If the definition of the antigen allows any variation from a defined sequence, objections can be expected because the use of variants renders the scope of the antibodies obtained by the immunisation process unclear.

An antibody can be defined by its epitope. For either linear or non-linear (discontinuous) epitopes, the amino acids of the epitope need to be clearly defined using closed language. If this type of definition is used then it is also important to ensure distinguishing over known antibodies binding the same antigen, that the application provides an enabling disclosure across the whole scope claimed, and that the functional definition allows the skilled person to clearly determine the limits of the claim. Also, for a definition relying on a non-linear or discontinuous epitope the Guidelines indicate that the method for determining this discontinuous epitope must also be indicated in the claim and the application must provide an enabling disclosure allowing the skilled person to determine whether further antibodies bind this epitope. The application must also enable the production without undue burden of additional antibodies binding to the same epitope.

Antibodies may also be defined through a deposited hybridoma cell producing the antibodies. Again caution is needed and the advice of a European Patent Attorney should be sought before the initial priority founding patent application is filed because the EPO have specific requirements concerning biological deposits which are strictly applied and these requirements are different from those of other jurisdictions.

What can we take away from this?

In conclusion, it is helpful for Applicants to have a consolidated source of information on how

to claim antibodies and how to show inventiveness before the EPO. The fact that this is being introduced in 2021 may be a reflection of the importance of antibody technologies combined with the some of the challenges Applicants experience in obtaining desirable patent protection.

About the author

Isobel Finnie leads the life sciences and biotechnology team at Haseltine Lake Kempner, where her practice embraces a wide variety of life science technologies, especially in the fields of biotechnology and biochemistry. She has considerable experience in patenting antibody-based therapeutics.