Monoclonal Antibodies and Sequence Identity: what's the EPO's Practice?

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Abstract

Since the first marketing authorization for a monoclonal antibody (Mab) in the 1980s, the patent system has never stopped adding the fuel of interest to the fire of ingenuity in the field of monoclonal antibodies (Mabs).
In view of the ever-increasing pace of technological progress in this highly competitive environment, patent applications are often filed at the stage of Mab "prototypes", before any product is available that could be further developed. Patent claims have naturally adapted to this practice in order to attempt to protect not only the Mab « prototypes » but also downstream developments, and in particular the lead antibody that will ultimately be put on the market, as well as Mabs inspired by and unreasonably close to the lead Mab.
In this context, claims based on sequence identity are often sought after by applicants although they may not be accepted by the European Patent Office (EPO). EPO practice concerning Mab sequence identity cases appears rather variable, all the more so given that there is no official guideline in this area. A journey through Board of Appeal decisions and examination files nonetheless enables certain conclusions to be drawn in order for Applicants to be in a better position to handle examination proceedings.

Introduction

The commercial development of monoclonal antibodies (Mabs) began in the 1980s, with the marketing authorization in 1986 of the first monoclonal antibody (Mab): Muromonab. It was only at the end of the 1990s, with the arrival of chimeric Mabs, such as the famous Rituximab in 1997, that the Mab market really took off, and in 2017 it was worth more than 100 billion dollars[1].
The success of Mab development is closely linked to the patent system because of the many innovations in this feld and the high expenditure on Research and Development (R&D) necessary to obtain marketing authorization for a Mab. Spending on R&D usually exceeds one billion dollars for each new Mab[2,3]. Patents play their full role in this context by stimulating funding in the field of Mabs and by providing investors with a return on their investment.

When the question of filing a patent application arises for a Mab, it is therefore important to know when to file, what is the best scope of protection and how to anticipate the evolution of the Mab (planned or not). The consequences of haphazard drafting can be catastrophic, to the point of deterring investors in the event that the claims no longer cover the product under development or if they cannot prevent a third party from developing a Mab unreasonably close or similar to the developed Mab.

How can we patent a Mab in Europe?

The European Patent Office (EPO) accepts two main ways to patent a Mab.

The first way consists in protecting the Mab via so-called « functional » claims. There claims are usually focused on the target and its interaction with the Mab. The scope of functional claims can be very broad since it extends to all Mabs having the claimed functional features. These claims are commonly sought and usually accepted by the EPO when a new target is identified (T735/00), or when the target is already known but the Mab was difficult to obtain (T0187/04) or when the Mab has an unexpected property.
Unexpected properties that can be found in the functional claims are often supported by a characterization of the target, such as the epitope recognized, or by the nature of the interaction between the Mab and its target, such as affinity (e.g. Kd/Ka) or the effect of the Mab on its target (e.g. agonistic/antagonistic effect). Functional claims can also be based on the property of a Mab to compete with a reference Mab, which amounts to indirectly characterizing the epitope recognized and affinity thereto.
Functional claims can be in the following forms:

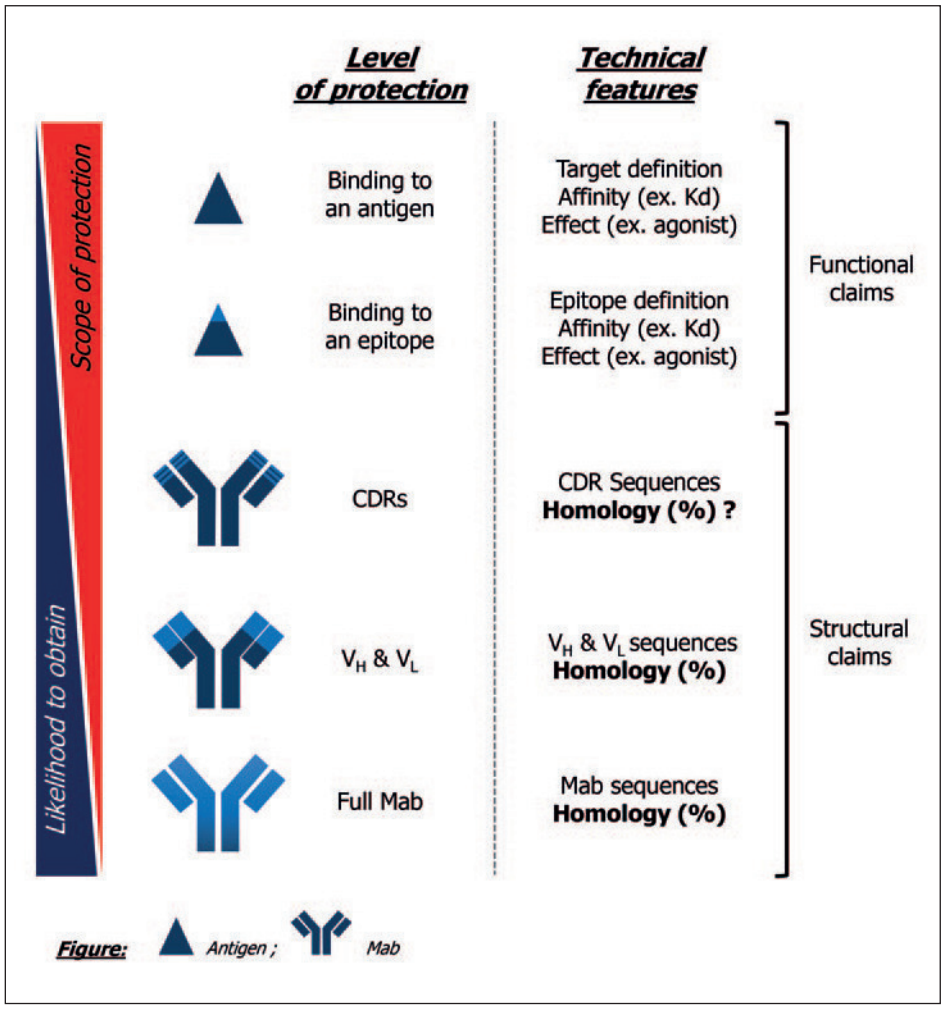
"Antibody that binds specifically to antigen X"
"Antibody that binds specifically to peptide Y within antigen X"
"Antibody that binds specifically to antigen X with a Kd < Z"

The second way to patent a Mab is based on so-called "structural" claims that seek to define the Mab as such, usually via its sequences. The EPO considers that the sequence claims must at least specify the sequence of the 6 CDRs (Complementarity-Determining Regions) involved in the interaction with the target. According to

1 Global Monoclonal Antibodies Market Hit $100 Billion in 2017: Report - https://www.prnewswire.com/news-releases/global-monoclonal-antibodies-market-hit-100-billion-in-2017-report-300599684.html
2 DiMasi et al., Innovation in the pharmaceutical industry : new estimated of R&D costs, Journal of Health Economics, 2016
3 DiMasi et al., The cost of biopharmaceutical R&D: is biotech different?, Manage. Decis. Econ., 2007

the EPO, the 6 CDRs are necessary to obtain the claimed technical effect for the entire Mab and so to meet the requirements of inventive step (Article 56 EPC). However, there are exceptions such as single domain antibodies "sdAb" for which inventive step can be acknowledged if experimental data are provided (T0617/07).
The scope of sequence claims is usually narrower than functional claims because they are limited to one Mab having specific sequences. Structural claims can be in the following forms:

"Antibody that binds specifically to antigen X comprising a heavy chain of SEQ ID NO : 1 and a light chain of SEQ ID NO : 2"



The Figure summarizes the main ways to patent a Mab in Europe.

The choice of the type of claims and the drafting thereof are of great importance.

It is essential to clearly delineate the scope of protection in order to strike the right balance between overly restrictive structural claims and overly broad functional claims. In this context, it may be wise to opt for claims based on sequence identities. However, this seemingly simple strategy is not infallible before the EPO.

Sequence identity

Although regularly used in claims by Applicants for decades, sequence identities are, in a growing number of cases, not accepted by the EPO as the appropriate defining feature of the claims. The reasons for refusing the application may be multiple but are usually based on Article 83 EPC (disclosure of the invention) or Article 56 EPC (inventive step). The Examiners can for example consider that any modification of the Mab sequences can change the specificity, and consequently that Mabs having homologous sequences may lose all recognition capability for the target.
Nevertheless, European examination files appear very heterogeneous and Mabs patents claiming sequence identity are regularly granted. It is sometimes difficult to explain this heterogeneity as the EPO has not published any official guideline on this subject. A journey through Board of Appeal decisions and examination files nonetheless enables us to have some ideas on how to proceed to protect Mabs with claims based on sequence identity.

Sequence identity *stricto sensu*

In general, the CDRs are intangible for the EPO, which considers that the slightest modification of the CDRs can affect the recognition of the target. Thus, a claim directed only at sequence identity of CDRs is usually not allowed in Europe. However, claims mentioning a degree of identity applied to a region broader than the CDRs, such as the variable region or the heavy/light chain, and specifying that the degree of identity does not apply to CDR sequences, are usually allowed by the EPO. Such claims may be drafted as follows:

"Antibody that binds specifically to antigen X comprising a heavy chain having at least 90% amino acid identity to SEQ ID NO : 1 and a light chain having at least 90% amino acid identity to SEQ ID NO : 2, wherein CDR1 of the heavy chain consisting of the amino acid sequence of SEQ ID NO : 3, CDR2 of the heavy chain consisting of the amino acid sequence of SEQ ID NO : 4, CDR3 of the heavy chain consisting of the amino acid sequence of SEQ ID NO : 5, CDR1 of the light chain consisting of the

amino acid sequence of SEQ ID NO : 6, CDR2 of the light chain consisting of the amino acid sequence of SEQ ID NO : 7 and CDR3 of the light chain consisting of the amino acid sequence of SEQ ID NO : 8."

This type of claim has been accepted in several examination files (ex. EP2630160, granted in 2016) but also by the Board of Appeal in the decision T 0516/11.

It is interesting to note that some Examiners have agreed to issue claims based on a sequence identity applied to a larger region than the CDRs without specifying that the identity does not apply to CDRs. This is the case, for example, of patent EP2320940 issued in 2015, drafted in the following form:

"Antibody that binds to antigen X, wherein the antibody comprises a heavy chain variable region sequence having at least 95% amino acid sequence identity to SEQ ID NO: 1 and a light chain variable region sequence having at least 95% amino acid sequence identity to SEQ ID NO: 2."

However, patents granted with this type of claim are uncommon because the Examiners have a tendency to challenge inventive step by considering that it is not guaranteed that Mabs presenting a CDR sequence homology are indeed able to bind to the target.

Sequence identity and functional features

In decision T2101/09, the Board of Appeal recognized that it might be necessary to further limit the scope of a claim referring to a functional feature.

Thus, many patents are granted with claims associating a certain degree of sequence identity with a Kd value (EP1639092, granted in 2016), epitope recognized (EP2219672, granted in 2016) and/or the effect of the Mab on its target (EP2418220 and EP2486941, granted in 2017).

This strategy is particularly relevant because the EPO requires that claimed Mabs have an "*unexpected property*" in order to recognize inventive step. Functional features that are linked to a degree of identity can therefore also be useful to defend inventive step. It should nevertheless be ensured that the application satisfies the requirements of Article 83 EPC so that the skilled person may achieve Mabs with the desired function on the basis of a particular known antibody and also weed out non-functional variants without undue burden (T617/07).

What degree of identity can be expected?

There is no guideline from the EPO regarding the acceptable degree of identity. In the decision T2101/09, the Board of Appeal observes that it is sometimes necessary to further limit the scope of a claim by increasing the degree of identity, but without specifying the criteria that must be taken into account in determining this degree of identity.

Thus, the degree of homology/identity accepted depends on the relevant prior art and the particular circumstances of each individual case (a general principle recalled in T2101/09). The lower the degree of identity claimed, the more likely it is that the EPO considers that the claim does not address the technical problem (Article 56 EPC) or that the skilled person cannot perform the invention over the whole area claimed without undue burden (Article 83 EPC).
In general, the sequence identity that is commonly observed in granted claims is at least equal to 90%.

Conclusion

The history of Mabs, which are the most fruitful medicinal products of the last decade for the biotech industry, is closely linked to the patent system since their emergence in the 1980s.

In the field of Mabs, the use of sequence identity is widespread when it comes to claiming Mab sequences. However, European practice for issuing sequence identity claims appears to be very heterogeneous and it is sometimes difficult to know what is acceptable or not for the EPO. A journey through Board of Appeal decisions and examination files provides some lessons in the practice of the EPO.

Firstly, CDRs are intangible for the EPO: a claim focused on a degree of identity of CDR sequences is generally not allowed in Europe. However, two main forms of claims seem to be accepted by the EPO. The first form consists in applying the degree of identity to a region broader than the CDRs while specifying that said degree of identity does not apply to CDR sequences. The second form consists in associating the degree of identity with a functional feature. This strategy can be particularly useful when the functional characteristic is a reflection of an "unexpected property" that justifies inventive step.

Thus, it is recommended to define the degree of identity in different ways and to provide fallback positions to combine degree of identity with functional features. It is nevertheless necessary to ensure that all the combinations contemplated have direct and unambiguous support in the original application to satisfy the requirements of Article 123(2) EPC.

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