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REVIEW

Patent disclosure requirements for therapeutic antibody patents

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ABSTRACT

Introduction: Therapeutic antibodies have grown to become an important product class within the biopharmaceutical market. A prerequisite to their commercialization is adequate patent protection. Disclosure requirements and the types of claims available in different jurisdictions can impact the scope of protection available for antibodies.

Areas covered: A comparative review of statutory bases, patent office practices and selected decisions in Canada, the United States and the United Kingdom related to disclosure requirements is provided.

Expert opinion: Differences in disclosure requirements exist in different jurisdictions which can impact the type of claims obtained and their survival when attacked in litigation. Including a wide variety of claim types is a key strategy to ensuring therapeutic antibodies are adequately protected. Method of use claims may provide advantages and broader protection in some circumstances and should also be considered.

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United Kingdom

1. Introduction

Since the first monoclonal antibody, Muromonab-CD3 (ORTHOCLONE® OKT3), was approved for marketing in the United States (US) 30 years ago for preventing kidney transplant rejection [1], therapeutic antibodies have grown to become an important product class within the biopharmaceutical market. As the cost of bringing a biologic to market has been estimated to average \$2.6 billion [2], a prerequisite for their commercialization is sufficient patent protection. There are important jurisdictional differences regarding what is required to patent an antibody which can impact patent strategy. Monoclonal antibodies and their therapeutic potential have been well known for decades. What is necessary to meet the inventive step requirement for a novel antibody to a known target can vary by jurisdiction. Some jurisdictions view the production of a subsequent therapeutic antibody to a known target without some unexpected property to be not patentable for lack of inventiveness. The inventive step requirements of different jurisdictions have been reviewed elsewhere [3]. In addition, the interpretation of disclosure requirements and the types of claims available in different jurisdictions can impact the scope of protection available for antibodies [4,5].

This article provides a comparative review of statutory bases, patent office practices and selected decisions in Canada, the United States, and the United Kingdom (UK) related to disclosure requirements as they apply to therapeutic antibodies. The term 'disclosure' is used to encompass the somewhat different jurisdictional usages of 'written description' and 'enablement' which in some jurisdictions are separate and in others intertwined and also including 'literal support,' as well as 'support' in different jurisdictions. As will

become evident in subsequent sections describing the statutory requirements, the disclosure provisions are on their face similar. However, their interpretation by the requisite patent offices and the courts can result in differing scope of protection.

It should be noted that the material discussed here is intended to provide only general information and comment and should not be considered, or relied upon, as legal advice.

2. Canada

In Canada, the disclosure requirements are outlined in Section 27(3) of the *Patent Act* [6] and Section 84 of the *Patent Rules* [7].

2.1. Section 27(3) of the Patent Act

Particularly relevant to antibody patents are paragraphs (a) and (b) of Section 27(3) of the *Patent Act*, which require that the specification:

- (a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;
- (b) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it pertains, or with which it is mostly closely connected, to make, construct, compound or use it [6]...

These requirements have been interpreted as requiring that

[t]he description must be correct ... both clear and accurate ... It must not contain erroneous or misleading statements calculated to deceive or mislead the persons to whom the specification is

Article highlights

- A comparative review of statutory bases, patent office practices and selected decisions in Canada, the United States and the United Kingdom related to disclosure requirements is provided.
- Jurisdictional differences exist in the framing and application of disclosure requirements.
- In the Canadian trial *AbbVie v. Janssen* [17], use claims of functionally claimed antibodies were found valid. This decision suggests that a single antibody class can, in at least some cases, be sufficient to meet the disclosure requirements of claims directed to the use of functionally claimed antibodies.
- In contrast, in the corresponding US litigation of *AbbVie v. Janssen* [19], antibody claims functionally claimed were ultimately found invalid, for among other reasons, lacking 'written description support', suggesting that a single antibody class may not be sufficient for broad product claims.
- The UK may provide an intermediate position — patent claims that include embodiments that are clearly not supported by the data in the application will not meet the disclosure requirements. However, claims may properly encompass embodiments which may be provided or invented in the future, if such embodiments demonstrate the technical contribution made by the invention.

This box summarizes key points contained in the article.

addressed and render it difficult for them without trial and experiment to comprehend in what manner the invention is to be performed... The description of the invention must also be full ... for nothing that has not been described may be validly claimed. The description must also give all information that is necessary for successful operation or use of the invention, without leaving such result to the chance of successful experiment, and if warnings are required in order to avert failure such warnings must be given [8, pp .111–112; 9, pp. 225–226; 10, pp. 39–40]...

As such, Subsection 27(3) comprises both elements of a written description requirement (paragraph a) and an enablement requirement (paragraph b).

2.2. Section 84 of the Patent Rules

Section 84 of the *Patent Rules* requires that the 'claims shall be clear and concise and shall be fully supported by the description independently of any document referred to in the description' [7]. Hence, the characteristics of the invention set out in the claims must also be set out in the description. Since the claims included in the application at the time of filing are considered part of the specification, any matter in the originally filed claims not included in the description can be added to the description. On its face, Section 84 would seem to be related to the US written description requirement or the European support requirement. However, Section 84 has been suggested to bring into play Section 27(3) of the *Patent Act* and thereby operates to import both the written description and enablement requirements of Section 27(3) [see 11].

2.3. Canadian Patent Office practice

Section 84 is the primary section used by the Canadian Intellectual Property Office (CIPO) to ensure disclosure requirements are met and objections under Section 84 are typically

raised when the scope of the claims is considered to be broader than what is enabled or soundly predicted by the description. For example, an objection under this section will be raised if the examiner feels that an 'essential element' is missing and/or the entire claimed subject matter does not have the promised utility. Objections under Section 27(3) typically accompany objections under Section 84 as a matter of course and addressing the objection under Section 84 usually also addresses the objection under Section 27(3).

Like the United States and Europe, claims to an antibody specific for a novel antigen can be obtained even in the absence of working examples if the antigen is sufficiently described. Until recently however, the written description and enablement requirements applied to claims for monoclonal antibodies were interpreted as requiring working examples describing the making of the monoclonal antibodies. This changed in 2009, when the biotechnology examination guidelines in CIPO's Manual of Patent Office Practice [12] were amended to acknowledge that the general procedures for making monoclonal antibodies were known in the art and detailed explanations of these procedures and working examples were not strictly required to provide an enabling description, bringing Canada in line with US and European jurisdictions. A recent Patent Appeal Board decision confirmed that claims to hybridoma cells are similarly available without working examples [13]. However, if a working example or biological deposit is not provided, the applicant typically has to include structural description of the particular epitope to which the monoclonal antibody would bind to satisfy disclosure requirements.

If the epitope has not been demonstrated but is predicted, for example by computer modeling, a specification must, in addition to disclosing a structural description of the epitope, provide a factual basis and sound line of reasoning to support the prediction of the putative antibody-binding site to satisfy the legal requirements of nonexemplified subject matter.

For new antibodies to known antigens, disclosure of a specifically recognized novel epitope or structural features of the antibody such as the set of complementarity determining region (CDR) sequences may be required, although functional limitations are also possible [14]. Including CDR sequences for a number of related or unrelated antibodies that share a functional limitation may also support broad claims to an antibody functionally limited.

Until recently, examiners had taken the rigid position that CDR sequences must be disclosed when nonexemplified humanized antibodies are claimed. This approach has been adopted after the Patent Appeal Board in *Re Sloan-Kettering* (CD 1296) [15] held that claims to a humanized antibody were not adequately described or enabled, emphasizing the absence of CDR sequence information, among other factual considerations. However, the Commissioner of Patents in *Re Chugai Seiyaku and Kabushiki Kaisha* (CD 1398), hereinafter 'Kaisha' [16], reversed the *Re Sloan-Kettering* (CD 1296) [15] decision and held that a specification does not need to disclose working examples of humanized antibodies or sequence information of CDRs, in an instance where the humanized antibodies were directed to fully characterized antigen and

the counterpart mouse monoclonal antibodies were exemplified. The Patent Appeal Board noted that the production of humanized monoclonal antibodies has become routine and ‘that the same rationale that permits monoclonal antibodies to be adequately described through reference to the fully characterized antigen to which they specifically bind’ [16, para.48] should be applied to satisfy the description requirement for humanized antibodies.

As discussed in the next section on Canadian case law the case *AbbVie v. Janssen* [17] has confirmed that functional limitations are valid and a single antibody class can, in at least some cases, be sufficient to meet the disclosure and enablement requirements of claims directed to the use of functionally claimed antibodies. Moreover, as the case exemplifies, use claims can be desirable. CIPO often requires some cell and/or some animal data to support and enable therapeutic ‘use’ claims although exemplary data are not strictly required if utility is soundly predicted. Unexpected or surprising results, for example, surprising therapeutic results, can be particularly helpful if broadly claiming a group of antibodies that share the disclosed properties.

2.4. Canadian case law

In Canada, patenting requirements for therapeutic antibodies were recently canvassed in the case of *AbbVie v. Janssen* [17]. The case is Canada’s first guidance from the Federal Court on validity and infringement issues of patents covering therapeutic antibodies. AbbVie Corporation Deutschland GmbH & Co. KG, AbbVie Biotechnology Ltd., and AbbVie Corporation (hereinafter AbbVie) commenced a patent infringement action against Janssen Inc. (hereinafter Janssen) alleging Janssen’s human anti-interleukin-12 (IL-12) antibody, ustekinumab, approved in Canada for treatment of psoriasis, infringed Canadian Patent No. 2,365,281 (the ‘281 Patent).

After considering the validity, including sufficiency and enablement, and infringement issues the trial court of first instance held that the ‘281 Patent was valid and infringed.

The ‘281 Patent at issue, entitled ‘Human Antibodies that Bind Human IL-12 and Methods for Producing’, disclosed isolated human antibodies that bind IL-12, which is a cytokine that functions in regulation of immune reactions in the body [18]. In particular, the ‘281 Patent disclosed the amino acid sequences of numerous antibodies having a range of IL-12 binding affinities. These antibodies were developed using phage display technology. AbbVie initially identified a lead antibody, which they called ‘Joe-9’ that had low affinity for IL-12 [18]. To improve the IL-12 affinity of Joe-9, mutations were introduced into antibody regions responsible for binding IL-12, and a large library was generated. Screening this library, AbbVie identified an antibody with improved affinity for IL-12, ‘Y61’. Further modifications led to the identification of J695, which showed a significant increase in IL-12 binding affinity and neutralizing activity [18]. All of the antibodies disclosed in the ‘281 Patent were derived from Joe-9 and hence shared much of the same amino acid sequences. The ‘281 Patent further disclosed that *in vivo* administration of J695 antibody was particularly useful in the treatment of psoriasis.

In contrast, Janssen’s ustekinumab antibody had been developed using transgenic mouse technology. It had different antibody heavy chain and light chain sequences and

bound to human IL-12 at a different epitope than J695. The structural differences between ustekinumab and J695 were discussed in detail in the US decision [19, p.5], which dealt with the corresponding US patents, discussed in more detail later in the paper.

Although the ‘281 Patent had 223 claims, only two claims were at issue in the trial, claims 143 and 222. These read:

143. The use of a neutralizing isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a Koff rate constant of $1 \times 10^{-4} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance and which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC₅₀ of $1 \times 10^{-9} \text{ M}$ or less, to treat psoriasis [18].

222. The use of an isolated human antibody, or antigen-binding portion thereof, which binds to a human interleukin comprising a p40 subunit and dissociates from the human interleukin with a Koff rate constant of $1 \times 10^{-2} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance, and which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC₅₀ of $1 \times 10^{-9} \text{ M}$ or less, which neutralizes the activity of the interleukin, to treat psoriasis [18].

Justice Hughes, as he then was, construed these claims as directed to the use of human antibodies (however created), which bind and dissociate from IL-12 at an affinity of at least $1 \times 10^{-4} \text{ s}^{-1}$ (claim 143) or at least $1 \times 10^{-2} \text{ s}^{-1}$ (claim 222); and which ‘have a potency of at least $1 \times 10^{-9} \text{ M}$ to treat psoriasis [17, para.101]. Potency was described as the ‘ability of the antibody to inhibit the functional activity of the antigen’ [17, para.24].

The Court considered whether the claims in question were broader than the invention disclosed and whether the claims met the disclosure requirement because only one type of antibody that bound IL-12 within the class was disclosed. In his decision, Justice Hughes suggested that it is possible to patent an antibody that targets a particular biological mediator with particular claimed properties which can extend to other antibodies that target the same mediator and contain the claimed properties, regardless of how it was made or its degree of structural similarity [17]. The mere fact that the scope of an antibody claim was defined by its function did not render it invalid. He stated that:

[168] Janssen argues, as a policy issue, whether “functional claiming” should be allowable. It argues that, having discovered one antibody that binds to IL-12 so as to treat psoriasis, can AbbVie claim any antibody that binds to IL-12 and treats psoriasis? ... AbbVie was the first to confirm that, if you want to treat psoriasis, you must get an antibody that binds to IL-12 and it must have at least a certain level of stickiness and potency. That is very different from saying – we have a particular antibody (J695), and we put it into people, and it treats their psoriasis; therefore, we want a patent claiming any antibody that does that. There may be many ways to treat psoriasis, but AbbVie’s way is to have an antibody that does so by binding to IL-12 with at least a certain level of [affinity] and potency. That is the difference [17, para.168].

Importantly, the decision upheld the validity of functional claim limitations. In reaching his decision in *Janssen Inc v. AbbVie Corp*, Justice Hughes considered the law in Europe (including the United Kingdom) regarding the validity of ‘functional claiming’ for biologics. He concluded that like in the United Kingdom, in Canada, the question of sufficiency or overbreadth is to be considered on a case-by-case basis. Specifically,

[t]here is no simple principle that can be universally applied that would say, for example, that you have shown only one or two antibodies in your disclosure; you cannot claim all that will do the particular trick that you have in mind [17, para.178].

Justice Hughes also acknowledged that the parties (and their privies) engaged in a similar litigation in the United States and the pending appeal before the Federal Circuit (discussed later), but noted that the claims at issue in that case were different from the claims at issue in the Canadian case.

Janssen appealed and the Federal Court of Appeal set aside the lower court's decision for technical reasons and remitted the matter back to trial for a rehearing before another judge [20]. It should be noted that the appeal was allowed in relation to a pre-trial order that prevented Janssen from pleading further prior art references. As such, the issues of validity and infringement required reconsideration. The Federal Court of Appeal did not overturn the trial judge's decision on substantive issues.

At the beginning of 2015, the parties settled out of court [21]. Notwithstanding, the Federal Court's decision remains binding on the patent office with respect to the issue of functional claim limitations and disclosure and enablement requirements of claims directed to the use of functionally claimed antibodies. The decision, although the first pertaining to therapeutic antibodies, is not inconsistent with the recent PAB *Kaisha* decision described earlier, which stated that structural limitations are not required for claiming humanized antibodies.

The out of court resolution of this dispute could have been impacted by the US Federal Circuit's 1 July 2014 decision [19] which affirmed the jury verdict decision that found AbbVie's claims obvious [22, pp. 185–186] in light of art that may not have been considered in the Canadian case. Furthermore, the European counterpart of the '281 Patent, European Patent No. 2,168,984 [23], was opposed by Janssen and revoked by the Opposition Division of the European Patent Office (EPO) on 19 September 2014 [24]. Although, AbbVie filed an appeal, it never provided any documents that contained 'anything that could be regarded as a statement of grounds' [24]. As such, the Technical Board of Appeal rejected AbbVie's appeal due to inadmissibility. The revocation decision became final on 22 September 2015.

3. United States

3.1. 35 USC §112 (a)

Written description, enablement and best mode provisions are provided by 35 USC §112 (a). Under 35 USC §112 (a), the specification must contain a written description of the invention, and of the manner and process of making and using it, 'in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...' [25].

3.2. United States Patent Office practice

The United States Patent and Trademark Office (USPTO) which summarizes the statutory disclosure requirements and related case law in its guidelines states that to satisfy the written description requirement, 'a patent specification must describe

the claimed invention in sufficient detail that a person skilled in the art can conclude that the inventor had possession of the claimed invention' [26; 27, p.1438]. With regard to antibodies, it is possible to meet the written description requirement for a claim to an antibody for a novel antigen if the antigen is sufficiently described by its structure, formula, chemical name, physical properties, or deposit in a public depository for an antibody claimed by its binding affinity to that antigen if generating the claimed antibody is routine [26,28]. Reminiscent of CIPO's previous stance on monoclonal antibodies, the USPTO currently typically refuses to issue claims to human antibodies unless exemplified, alleging their manufacture is not routine as held in *Centocor v. Abbott* discussed later.

Further, for antibodies to a known antigen it is necessary to produce several different antibodies within the scope of claims to show possession of a class of antibodies [29,30].

3.3. US case law

Like in Canada, AbbVie and Janssen engaged in a similar litigation over the antibody ustekinumab in the United States. Unlike in Canada, the contested claims in AbbVie's patents were ultimately found to be invalid. AbbVie's patents 6,914,128 (the '128 Patent) [31] and 7,504,485 (the '485 Patent) [32] were assessed with respect to infringement and validity. Five claims were at issue in the proceedings. The claims in question were directed to human antibodies that bind to and neutralize the activity of human IL-12. The scope of the claims at issue was different from the scope of the claims in the Canadian action, however similar to Canada the contested claims contained functional limitations rather than structural limitations.

In this instance, claims 29, 30, 32, and 64 of the Patent '128 and claim 11 of the Patent '485 were at issue. Claim 29 read:

'A neutralizing isolated human antibody, or antigen-binding portion thereof that binds to human IL-12 and disassociates from human IL-12 with a K_{off} rate constant of $1 \times 10^{-2} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance' [31].

Claim 30 read:

'The neutralizing isolated human antibody of claim 29, or an antigen-binding portion thereof, which dissociates from human IL-12 with a K_{off} rate constant of $1 \times 10^{-4} \text{ s}^{-1}$ or less' [31].

Claim 32 read:

'The neutralizing isolated human antibody of claim 29, or an antigen-binding portion thereof, which disassociates from human IL-12 with a K_{off} rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less' [31].

Claim 64 read:

'A pharmaceutical composition comprising the antibody or an antigen binding portion thereof of claims 1, 16, 21, 27, 29, 41, 44, 45, 48, 50, 51, and a pharmaceutically acceptable carrier' [31].

Claim 11 read:

The composition of any one of claims 1–4, wherein the antibody, or antigen binding portion thereof, dissociates from the p40 subunit of IL-12 with a K_d of $1 \times 10^{-10} \text{ M}$ or less or a K_{off} rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance [32].

Following claim construction, the District Court granted summary judgment to AbbVie and found that its five asserted

claims were infringed. However, after a trial on validity, all of AbbVie's asserted claims were found to be invalid on the grounds of written description, enablement, and obviousness [33]. AbbVie appealed to the Federal Circuit. In upholding, the District Court's decision the Federal Circuit held that the patents were invalid since AbbVie did not substantially challenge the obviousness finding [19]. However, the Court still went on to consider the written description question. In its decision, the Court was critical of functional claiming and stated that:

... When a patent claims a genus using functional language to define a desired result, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus [19, p.22]..."

The panel analogized the genus to a plot of land, where the species disclosed go only to a corner of the plot; they do not sufficiently describe all the boundaries. In this instance, AbbVie failed to demonstrate that it invented species sufficient to support a claim to the functionally defined genus [19, p.26]. All of the antibodies described in the patents were derived from Joe-9 and shared at least 90% amino acid sequence similarity in their variable regions, and that more than 200 of the antibodies differ from Y61 at a single amino acid residue [19, p.7]. In contrast, Centocor's antibody, which was encompassed by the scope of the claimed genus, had different heavy chains and light chains and shared only about 50% sequence similarity in the variable regions as compared to Joe-9 [19, p.8]. As such, the jury's verdict that AbbVie's patents were invalid for lack of adequate written description was affirmed. In view of its holding with respect to written description, the Court did not address AbbVie's argument regarding enablement [19, p.27].

Two key differences can be noted between the Canadian and US decisions. The first is the type of claims at issue. The claims at issue in the Canadian case were use claims for treating psoriasis, whereas the claims at issue before the US courts were antibody claims that were claimed by binding affinity. Accordingly, US courts were faced with the question of whether, having found one way of making such antibodies, AbbVie was entitled to claim all antibodies with said binding affinity. Interestingly, neither the '128 Patent nor the '485 Patent had any method of treatment-type claims (these claims were initially pursued but were canceled). A second key difference is that validity was assessed by a jury in the US litigation. The significant structural differences between the AbbVie and Janssen antibodies and their method of manufacture could have helped persuade a jury that AbbVie was not entitled to such broad claims.

The written description requirement had also been considered in the *Centocor v. Abbott* [28] case, where the Court of Appeals for the Federal Circuit vacated a \$1.67 billion jury verdict (the largest patent infringement award in US history). The case concerned Abbott's biologic drug, adalimumab and it was alleged to have infringed Centocor's US Patent No. 7,070,775 [34] (the '775 Patent) which provided protection for Centocor's biologic drug, infliximab. The technology in this

case involved antibodies to human tumor necrosis factor alpha (TNF- α), the overproduction of which can lead to arthritis. Both Centocor and Abbott sought to develop antibodies to human TNF- α with (1) high affinity, (2) neutralizing activity, and (3) reduced immunogenicity [28].

The opponents in this case had pursued very different strategies. Centocor identified a mouse antibody to human TNF- α , which they called A2 mouse antibody that had high affinity and neutralizing activity. They also made a chimeric antibody which had reduced immunogenicity due to replacement of mouse constant regions with human constant regions. The constant region is identical in all antibodies of the same isotype but differs in antibodies of different isotypes as well as different species. The variable region is a portion of the antibody that recognizes an antigen and comprises the CDRs [35].

Centocor filed a patent application in 1991 claiming its A2 mouse antibody and chimeric antibody derived therefrom. Centocor then filed a series of continuation-in-part applications, and in 2002, Centocor added claims reciting human variable regions in the application. Abbott in contrast used phage display technology to create fully-human antibodies. Abbott filed its patent application in 1996. Both patents were granted. Centocor sued Abbott for patent infringement, arguing that adalimumab infringed Centocor's patent claims for human antibodies. Specifically, Centocor asserted claims 2, 3, 14, and 15 of the '775 Patent. At trial, the jury found that the '775 Patent was infringed by Abbott. On appeal, the Federal Circuit considered whether the '775 Patent provided adequate written description for the claimed human variable regions. In overturning the jury's decision, the Court confirmed that an antibody to a novel protein without describing the antibody will meet the written description requirement when: '(1) the applicant fully discloses the novel protein and (2) generating the claimed antibody is so routine that possessing the protein places the applicant in possession of an antibody' [28, p.1359]. The Court found that the asserted claims in the '775 Patent failed to satisfy both requirements.

First, human TNF- α was well known at the time of filing the patent application. Also, the claims in the '775 Patent recited a 'class of antibodies containing a human variable region that have particularly desirable therapeutic properties: high affinity, neutralizing activity and A2 specificity' [28, p.1352]. The Court went on to establish that claiming antibodies with specific properties (i.e. an antibody that binds to human TNF- α with A2 specificity) can result in a claim that does not meet written description requirements because antibodies with those properties have not been adequately described. Thus, Centocor failed to show that generating fully-human antibodies with the claimed properties would be routine for a person of ordinary skill in the art.

As such, the Court concluded that merely describing an antigen that the antibodies bind to was not enough to satisfy the written description requirement in this case. Although generating antibodies to a certain antigen was found to be routine, screening those antibodies for certain properties was not. Consequently, *Centocor v. Abbott* has been used by the USPTO for the proposition that making human antibodies is not routine. Although it is possible to obtain general antibody claims to a novel target, claims to human antibodies must usually be exemplified.

4. United Kingdom

Two patent offices and two patent statutes are relevant when considering antibody claims in the United Kingdom. The United Kingdom has its own patent office that grants patents [36], and patent protection is also available through the EPO if the patentee applies using the *European Patent Convention (EPC)* [37]. In the latter case, a patent application is processed as a single application at the EPO, but once granted, it becomes separate patent in the European member countries selected by the patentee. Although the case law discussed later is decided by UK courts, the relevant patents have been issued by the EPO and as such the practice guidelines (which are generally similar) of both offices are discussed.

4.1. EPC articles 83 and 84

Under Article 83 of the *EPC*, the applicant must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art [37]. Article 83 also relates to Article 84 of the *EPC*, which requires the applicant define the claims in such a way that they are supported by the description.

4.2. UK Patents Act 1977 Section 14

In the United Kingdom, the concept of sufficiency and disclosure are outlined in Sections 14(3) and 14(5)(c) of the 1977 *UK Patents Act* [38]. Section 14(3) states that: '[t]he specification of an application shall disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art' [38]. Section 14(5)(c) states that: '[t]he claim or claims shall – be supported by the description...' [38]. Although only Section 14(3) serves as basis for revoking a patent, cases have also incorporated the requirements of Section 14(5)(c) [see 39, pp. 535–536].

4.3. European and UK patent offices

European and UK patent practices differ from Canadian and US practices, in that a new antibody to a known target will generally not meet the inventive step requirement unless obtaining the antibody was unexpected and/or the antibody shows unexpected advantages [see 40, 41]. The UK Patent Office's guidelines explicitly specify that generation of

humanised antibodies against a known target is not likely to involve an inventive step if non-humanised antibodies against the same target are already known as such modifications are well known in the art and so it would be obvious to replace them.

The EPO has summarized the level of disclosure that is required for antibodies based on the case law from the Boards of Appeal [42].

4.4. UK case law

Two UK courts, the Intellectual Property Enterprise Court and the Patents Court of the Chancery Division of the High Court of Justice of England and Wales, have jurisdiction to determine

infringement and validity of UK national patents or the UK-validated part of a European patent.

A recent decision from the High Court of Justice of England and Wales, Patents Court, *Eli Lilly v. Janssen Alzheimer Immunotherapy* [43], (hereinafter 'Lilly' and 'Janssen') dealt with the validity of Janssen's European Patent (UK) No. 1,994,937 [44] (the '937 Patent) for an antibody as a treatment of Alzheimer's disease. The '937 Patent disclosed and claimed pharmaceutical compositions comprising an antibody to β -amyloid peptide (A β) for use in preventing or treating a disease characterized by amyloid deposit in a patient (e.g. Alzheimer's disease).

The claims at issue were claims 1 and 4–6. Claim 1 read:

[a] pharmaceutical composition comprising an antibody to A β and a pharmaceutically acceptable non-toxic carrier or diluent, for use in preventing or treating a disease characterised by amyloid deposit in a patient, wherein the isotype of the antibody is human IgG1 [44].

Claim 4 read:

[t]he pharmaceutical composition for use in preventing or treating a disease characterised by amyloid deposit in a patient of any preceding claim wherein the antibody binds specifically to the aggregated form of A β peptide without binding to the dissociated form [44].

Claim 5 read:

[t]he pharmaceutical composition for use in preventing or treating a disease characterised by amyloid deposit in a patient of any of claims 1–3 where the antibody binds specifically to the dissociated form of A β peptide without binding to the aggregated form [44].

Claim 6 read:

'[t]he pharmaceutical composition for use in preventing or treating a disease characterised by amyloid deposit in a patient of any of claims 1–3 where the antibody binds specifically to both aggregated and dissociated forms of A β peptide' [44].

Lilly sought an order of revocation of the '937 Patent and a declaration that its antibody called solanezumab did not infringe the '937 Patent, which Lilly at the time of the litigation had in Phase 3 development for the treatment of Alzheimer's disease. Lilly attacked the validity of the '937 Patent on the basis of lack of novelty, obviousness, and insufficiency. The Court dismissed Lilly's arguments with respect to novelty and obviousness but held that the Patent was invalid for insufficiency. It was further held that had the patent been valid Lilly's antibody would have infringed it.

Justice Arnold considered two types of insufficiency in his decision: (1) failure to enable the invention to be performed without undue burden and (2) failure to enable the invention to be performed over the whole scope of the claim [43]. It was found that the patent suffered from both types of insufficiency. The Court construed the broad independent claim of the '937 Patent as covering any antibody to A β when used for treating Alzheimer's or related disorders. The Court found that utility across the breadth of that claim had not been demonstrated. Rather, the teaching of the '937 Patent only made plausible that a particular subset of antibodies would be effective in treating Alzheimer's, not any antibody. Justice Arnold held that:

[310] The conclusion that I draw from the evidence as a whole is that it is not the case that all antibodies to A β are effective to reduce amyloid burden or to reduce total cortical A β levels even in the kind of tests performed in the Patent. On the contrary, at least some mid-region and C-terminal antibodies are ineffective at least in PDAPP mice. While there is some evidence to show that mid-region and C-terminal antibodies have an effect on A β plaques in PSAPP mice, which are not used in the examples in the Patent that would simply present the skilled team with the conundrum of which tests to rely on. Still less do all antibodies to A β produce cognitive benefits even in mice. Still less are all antibodies to A β effective to prevent or treat AD (or any other disease characterised by amyloid deposit) [43, para.310].

Interestingly, the Court reviewed post-filing evidence in concluding that the patent was insufficient. The Court noted that later clinical trial had demonstrated that despite a decade of work, the patentee had not succeeded in making a suitable therapeutic antibody. Further, and again by reference to post-patent publications, it was held that it was not possible for a person skilled in the art to perform the invention across the whole breadth of the claim without undue burden.

A further noteworthy aspect of the *Lilly v. Janssen* case is that the decision was rendered on 25 June 2013 after the Opposition Division of EPO had revoked the '937 Patent at Oral Proceedings [45]. Several opponents, including Lilly, filed oppositions against the patent. On 3 October 2013, Janssen filed a notice of appeal to the Boards of Appeal of the EPO. On 30 November 2016, the patent was declared invalid from the date of grant and revoked on 21 December 2016.

Corresponding patents have issued in the United States [46,47] and Canada [48] with much narrower claims. At the end of 2016, Lilly announced that the solanezumab antibody failed Phase 3 clinical trials in United States, and Lilly will not be pursuing a regulatory submission for the treatment of mild dementia due to Alzheimer's [49].

The issue of sufficiency was also considered in earlier decisions from the UK Court of Appeal. The decisions of *Regeneron Pharmaceuticals Inc v. Genentech Inc* [50] (hereinafter 'Regeneron') and *Eli Lilly & Co v. Human Genome Sciences Inc* (hereinafter 'HGS') [51] found relatively broad antibody claims to meet the sufficiency requirement. It should be noted in the latter case, the antibodies were directed to a novel protein, where broad claims could be expected. These two cases in conjunction with *Lilly v. Janssen* suggest that sufficiency of disclosure requirements can be met by limited exemplary data if it is predictable based on the data provided that the invention will work across the full scope of the claim. Further, as different claim types may also have different requirements for meeting sufficiency of disclosure, inclusion of several claim types may be beneficial.

In *Regeneron* the Court of Appeal upheld the decision of the court of first instance and indicated that the monopoly right claimed was not too broad as to render the claims at issue insufficient. The case concerned the validity of patent European Patent No 1,238,986 (the '986 Patent) owned by Genentech [52].

The main claim at issue was claim 1, which read:

Use of a hVEGF antagonist in the preparation of a medicament for the treatment of a non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation, wherein the hVEGF

antagonist is: (a) an anti-VEGF antibody or antibody fragment; (b) an anti-VEGF receptor antibody or antibody fragment; or (c) an isolated hVEGF receptor [52].

Although claim 14, which claimed a human vascular endothelial growth factor (hVEGF) antagonist for use in the treatment of the disease or disorder claimed in claim 1 [52], was also at issue, the Court found the two claims to be in substance the same and referred only to claim 1 throughout the decision. The Court of Appeal concluded that claim for an invention of broad application may properly encompass embodiments which may be provided or invented in the future, 'provided such embodiments embody the technical contribution made by the invention' [50, paras.173–174].

Interestingly, the Court dismissed Regeneron's and Bayer's (hereinafter 'the appellants') argument that the data in Example 6 of the patent did not demonstrate or prove that vascular endothelial growth factor (VEGF) played a causative role in rheumatoid arthritis or that its blocking would be in any way beneficial to patients [50, para.131]. The Court noted that:

[132] This is true but it does not take the appellants very far. It has never been suggested that VEGF causes [rheumatoid arthritis]. Nor does the data in the patent demonstrate or prove that blocking VEGF will be beneficial to patients. However, as Genentech correctly says, this is not the correct question. For the reasons I have elaborated, a patent is not insufficient merely because it does not demonstrate or prove efficacy. It is enough that it is possible to make a reasonable prediction based upon the data in the patent that the invention will work across the scope of the claim [50, para.132].

The appellants also argued that the presence of VEGF had not been demonstrated in the various other non-neoplastic diseases outlined in the specification at the date of filing [50,52] such that one skilled in the art would not be able to predict that anti-VEGF therapy would be effective. The Court of Appeal however concluded that there was enough evidence before the trial judge to establish that it was plausible that VEGF antagonism could be used to treat any nonneoplastic neovascular disease [50]. The patent did not

promise that all VEGF antagonists will pass clinical trials and achieve regulatory approval for the treatment of all neovascular diseases... But that does not mean to say that anti-VEGF therapy will not treat the disease by addressing its angiogenic component [50, para.141].

In *HGS*, the Court of Appeal decided outstanding issues of sufficiency of antibody claims that were remitted by the United Kingdom Supreme Court [53]. The case concerned the validity of patent European Patent No. 0,939,804 (the '804 Patent) owned by HGS [54]. At issue were claims 13, 18, and 19. Claim 13 read:

[a]n isolated antibody or portion thereof that binds specifically to:
(a) the full length Neutrokin-a polypeptide (amino acid sequence of residues 1 to 285 of SEQ ID NO: 2); or (b) the extracellular domain of the Neutrokin-a polypeptide (amino acid sequence of residues 73 to 285 of SEQ ID NO: 2) [54].

Claim 18 read:

'[a] pharmaceutical composition comprising the polypeptide of any one of claims 10 to 12 or the antibody or portion thereof of any one of claims 13 to 17 and optionally, a pharmaceutically acceptable carrier' [54].

Claim 19 read:

[a] diagnostic composition comprising the nucleic acid molecule of any one of claims 1 to 4, the polypeptide of any one of claims 10 to 12 or the antibody or portion thereof of any one of claims 13 to 17 [54].

Claims 13, 18, and 19 of the patent at issue claimed an isolated antibody specific for a particular polypeptide sequence defined by sequence, a ‘pharmaceutical composition’ and ‘diagnostic composition.’ The Court noted that

[t]he difficulty is in knowing which of the products would be worthwhile introducing into a human or animal body; and in what circumstances. But that, as I see it, is part of the question: is there a good enough chance that it will work? [53, para.73].

The Court held that neither the ‘pharmaceutical composition’ nor the ‘diagnostic composition’ promised any particular effect. Also, since the Supreme Court found claim 1 to be sufficient, ‘it would ...be extraordinary if the very same conclusion made claims 18 and 19 insufficient’ [53, para.73].

Interestingly, the patents in question were all EPO-granted patents validated in the United Kingdom. This is not surprising as most patents litigated in the United Kingdom are EPO-granted patents. According to a study by Cremers et al., between 2000 and 2008, only 16.2 % of patents litigated in the United Kingdom were domestic patents [55]. Interestingly, 35.4% of cases where validity was at issue and the validity challenge was not triggered by an infringement claim resulted in patent revocation in the United Kingdom. Where infringement was alleged, the revocation rate was 41.8%. Although the reason for the discrepancy is unknown, it is curious that revocation rates are higher in jurisdictions where the litigated patents are predominantly EPO-granted patents. This may suggest a different interpretation of patent criteria by the EPO and national courts.

5. Expert opinion

The jurisdictional differences in requirements for patenting antibodies can create challenges for those seeking to gain comprehensive international patent protection. This paper provides a brief overview of patent disclosure requirements and some key cases in Canada, United States, and United Kingdom relating to therapeutic antibodies. This overview is by no means exhaustive; the goal is rather to illustrate similarities and differences in the disclosure requirements and provide a window to their interpretation in the canvassed jurisdictions.

From the above discussion certain themes emerge. Nuances in the disclosure requirements of different jurisdictions may be relevant for what claims can be obtained and successfully defended. In addition, the disclosure requirements for different types of claims may be different. Accordingly, pursuing a variety of claim types is beneficial as different requirements to meet written description/support and enablement/sufficiency threshold may be applied. In comparing the Canadian and US *AbbVie v. Janssen* decisions, it is noted that the use claims at issue in the Canadian case survived the validity challenge, whereas the antibody claims at issue in the US case did not. It is possible that the outcome of the US decision would have been different if ‘128 and ‘485 patents contained method of use-type claims (and if these claims were at issue in the proceedings). In addition to

jurisdictional differences in disclosure requirements, the disclosure requirements for claiming a genus of antibodies may be different than what is required for using a genus of antibodies – for treatment or making a medicament. Given that antibodies that bind the same target or that treat the same disease can be made using different methods – e.g. creating chimeric antibodies versus screening for fully human antibodies – patents claiming single antibodies may have little value for preventing competitors from marketing similarly efficacious yet chemically distinct antibodies. Given the cost of bringing a therapeutic antibody to market, providing sufficient protection (broader perhaps than the antibody exemplified) to prevent competitors from working around patents may be important for ensuring the antibody makes it to market and can incentivize the claiming of antibody genera. At the same time, use claims should be carefully crafted to be supported across the full scope of the claim as they can be invalidated on the basis of post-filing evidence. The contrasting outcomes of the UK decisions of *Lilly v. Janssen, Regeneron, and HGS*, clearly indicate that including different claim types could bolster a patentee’s chances of withstanding a validity challenge on the basis of insufficiency of disclosure.

The case law discussed in this paper also illustrates a patentee’s conundrum when determining how early in the research and development project they should file a patent application, especially in jurisdictions that do not afford patentees grace period before they file a patent. It is thus advantageous to consider a multipronged patent strategy with consideration of the disclosure requirements for each prong. For example, identifying sequence of novel epitopes of novel antibodies and/or adequately describing and exemplifying functional limitations that circumscribe the antibody class to be claimed with multiple antibodies could protect from sufficiency enablement challenges. Further, since different jurisdictions have different examination practices and case law, familiarity with these requirements can be beneficial when preparing international applications to be pursued in multiple jurisdictions.

Additional questions can also be asked. For example, do jurisdictional differences in the support requirements produce differing scopes of protection in different jurisdictions and/or are the support requirements universally less stringent for use patents allowing such claims to protect a broader scope of antibodies than composition claims? Striking the right balance between reward and incentivising improvements and competition may be particularly difficult for antibodies – any number of similar yet chemically distinct antibodies may perform equivalent functions. Given the importance of the therapeutic antibody market, it is expected that courts will continue to refine the boundaries of what disclosure is required for therapeutic antibodies.

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