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Current topics in biotechnology patent law: The written description requirement

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Abstract

Universities and medical research institutions are as interested in securing patent protection for their biotechnological inventions as pharmaceutical and biotechnology companies. Obtaining adequate patent protection by universities and research institutions has been hampered by the 'embryonic' nature of its inventions. This problem is particularly noticeable in the fields of biotechnology and molecular medicine. This paper focuses on recent court cases in US biotechnology patent law and analyses the effects of the legal decisions on the effort by universities and research institutions to secure meaningful legal protection for biotechnological inventions.

Keywords: *biotechnology, patent law, university, written description, patent specification*

INTRODUCTION

Over the past 20 years or so, the United States Patent and Trademark Office (US PTO) has applied the US patent laws unevenly, sometimes wielding one aspect of the patent laws more vigorously in an effort to limit the scope of claims in patent applications directed to biotechnological subject matter. For example, in the early 1990s, the US PTO applied 35 USC §101[1] (the 'utility' statute) stringently, requiring that biotechnological patent applicants disclose substantial animal model or *in vivo* data to justify the utility of the claimed invention. During the mid to late 1990s, the US PTO liberalised the amount and type of data required to satisfy the utility standard under 35 USC §101, but the US PTO began to apply more strictly the 35 USC §112[2] requirement that the patent specification adequately teach one how to make and/or use the claimed invention (the 'enablement' requirement). More recently, the US PTO has closely examined the specification of biotechnology patent applications to determine whether the specification meets another requirement of 35 USC §112,[3] ie that the specification adequately describes the claimed invention (the 'written description' requirement). This paper will analyse recent cases in US biotechnology patent law that have applied the 'written description' requirement and discuss how this specific requirement of the US patent law has affected universities seeking to protect its biotechnology inventions.

UNIVERSITY OF ROCHESTER V. SEARLE ET AL.

In the *University of Rochester v. Searle et al.*, 358 F.3d 916 (Fed. Cir. 2004), the US Court of Appeals for the Federal Circuit (CAFC), the US appellate court with exclusive jurisdiction over US patent matters, reviewed a US District Court grant of summary judgment that the University of Rochester's US Patent No. (USPN) 6,048,850 was invalid. By way of background, the University of Rochester scientists had developed a screening assay to determine whether a drug displayed selectivity to the enzyme prostaglandin H synthase-2 (PGHS-2, also known as 'COX2'). All the claims of USPN

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6,048,850 were directed to methods for selectively inhibiting prostaglandin H synthase-2 activity in a human host by administering a non-steroidal compound that selectively inhibits activity of the prostaglandin H synthase-2 gene product to or in a human host in need of such treatment.

The University of Rochester sued Searle, Monsanto, Pharmacia and Pfizer (collectively, 'Pfizer'), alleging that Pfizer's sale of Celebrex® and Bextra® for treatment of inflammation infringed the claims of USPN 6,048,850. Pfizer moved for summary judgment, arguing that USPN 6,048,850 was invalid because it failed to comply with the written description and enablement requirements of 35 USC §112, ¶1.

Specification must describe the claimed invention

In the District Court proceeding, the Court held that USPN 6,048,850 neither disclosed any compound nor provided any suggestion as to how such a compound could be made other than by trial-and-error research and that the inventors knew of no such compound at the time their patent application was filed. Consequently, the District Court concluded that USPN 6,048,850 was invalid for lack of an adequate written description.

On appeal, the CAFC noted that the claimed subject matter need not be described *in haec verba* in the specification to satisfy the written description requirement, but that the specification must describe the claimed invention so that a person skilled in the art can recognise what the patentee claimed. The CAFC explained that a description of a generic structural term that is functional, eg 'lessening inflammation of tissues', fails to distinguish that chemical from others. Furthermore, the disclosure must allow one skilled in the art to visualise or recognise the identity of the subject matter purportedly described. USPN 6,048,850 contained no language describing compounds that achieve the effect required by the patent claims.

University patent held to be invalid

The defendants, Pfizer *et al*., presented several arguments on appeal, none of which was received favourably by the CAFC. For example, the CAFC refused to restrict its interpretation of the written description requirement as being limited to cases involving priority, to cases involving genetic material, or to cases involving compound claims *per se*. The CAFC did note that the written description requirement need not be satisfied only by providing a description of an actual reduction to practice, but that the patent application must describe the claimed subject matter so as to demonstrate that the applicant was in possession of the claimed invention, including all of the elements and limitations of the claims. In an important sub-holding, the CAFC rejected the defendants' argument (supported by *amicus curiae* briefs submitted by the University of Texas and the University of California) that the Bayh–Dole Act[4] would be compromised if universities were not able to patent the early stage technologies it developed. In contrast, the CAFC agreed that the Bayh–Dole Act was intended to enable universities to profit from their federally funded research, but the CAFC maintained that the Bayh–Dole Act was not intended to relax the statutory requirements for patentability.

Accordingly, the CAFC held that USPN 6,048,850 did not provide any guidance to the skilled practitioner that would indicate specific compounds that could be used to carry out the claimed methods and did not provide evidence that any such compounds were otherwise within the knowledge of a person of ordinary skill in the art at the relevant time. Consequently, the district court's grant of Pfizer's motion for summary judgment was affirmed and USPN 6,048,850 was held to be invalid.

IN RE WALLACH

On 11th August, 2004, the CAFC rendered the decision *In re Wallach,* 378 F.3d 1330 (Fed. Cir. 2004) in which the CAFC affirmed a decision of the US PTO Board of Patent Appeals and

Interferences affirming the rejection of certain claims as not having been supported under 35 USC §112 by an adequate written description in the patent specification. In *Wallach*, the appellants discovered two proteins (termed 'TBP-I' and 'TBP-II') that selectively inhibit the cytotoxic effect of tumour necrosis factor (TNF) and obtained a partial amino acid sequence of the N-terminus of TBP-II. The appellants' application contained claims to DNA encoding proteins having that partial sequence and having the ability to inhibit the cytotoxic effect of TNF.

Complete nucleic/ amino acid sequences required

The US PTO patent examiner rejected the DNA claims in US patent application 08/485,129 (the '129 application) under 35 USC §112 arguing that the specification lacked an adequate written description of the claimed invention. The relevant sections of claim 11 of the '129 application recited:

> an isolated DNA molecule, comprising a contiguous nucleotide sequence coding for a protein consisting of naturally occurring human Tumor Necrosis Factor (TNF) Binding Protein II, designated TBP-II, said TBP-II including the amino acid sequence: Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis, said protein having the ability to inhibit the cytotoxic effect of TNF.

CAFC affirmed examiner's determination

The appellants asserted that their provision of an amino acid sequence encoded by the claimed DNA, and not simply the name of the protein and a statement that the DNA can be obtained by reverse transcription, satisfied the written description requirement of 35 USC §112. The appellants further argued that the claims did not recite DNA molecules encoding a plurality of unknown proteins from various species having no common features, but only those nucleic acids encoding the single protein sequence that was actually described in the patent specification. Finally, the appellants argued that, because there is a known correlation between the function (ie encoding a specified amino acid sequence) and structure, the appellants' claims were an example of the sort of functional description permitted by 35 USC §112 in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316 (Fed. Cir. 2002).

On appeal to the Board of Patent Appeals and Interferences, the Board affirmed the rejections by the patent examiner, noting that the applicant did not describe the genetic material sought to be patented with sufficient specificity in the specification and that the specification did not provide adequate, written descriptive support for the claimed subject matter. More specifically, the Board of Patent Appeals and Interferences found that the appellants' specification included neither any actual DNA sequence within the scope of the claims nor the complete amino acid sequence of the TBP-II protein, but instead contained only the sequence of ten out of the 185–192 amino acids that make up the TBP-II protein. The Board noted that the identity of the nucleic acid encoding a protein is not an inherent property of the protein.

The CAFC agreed with the appellants that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence. Nonetheless, noted the CAFC, the appellants did not claim the nucleic acid molecules that encode the simple protein sequence that they disclose, but claimed the nucleic acids encoding a protein for which they provided only a partial sequence. The appellants conceded that urinary TBP-II has a sequence of 185–192 amino acids. Without the approximately 95 per cent of the amino acid sequence that the appellants did not disclose, the CAFC found that the DNA

molecules claimed in the '129 application had not been described. The appellants' possession of the protein could not be considered equivalent to possession of protein's amino acid sequence. Accordingly, the CAFC affirmed the Board of Patent Appeals affirmation of the examiner's determination that the specification of the '129 application did not provide an adequate written description of the claims.

Improper descriptions can result in a new filing date

NOELLE V. LEDERMAN ET AL.

The 2004 case of *Noelle v. Lederman et al.*, 355 F.3d 1343 (Fed. Cir. 2004) involved an appeal from an interference – a US PTO proceeding to determine which party was first to invent claimed subject matter – and involved the claims of USSN 08/742,480 and USPN 5,474,771. Noelle was the inventor on the USSN 08/742,480 application. Lederman *et al.* were the inventors on USPN 5,474,771. Noelle appealed a decision of the Board of Patent Appeals and Interferences, finding no interference-in-fact between the 08/742,480 application and USPN 5,474,771 and rejecting the claims of the 08/742,480 application pursuant to 35 USC §102(b).[5]

Noelle described the mouse antigen but also claimed the human antigen

The interference involved competing claims to the CD40CR antibody that represses the cell-to-cell signalling interaction between helper T cells and B cells. The CD40CR antigen is found on activated helper T cells and, once the CD40CR antigen and CD40 bind, the B cell begins to differentiate, proliferate and produce antibodies. The CD40CR antibody binds to the CD40CR antigen located on the surface of T-cells, thereby inhibiting its ability to bind to the CD40 receptor located on the resting B cell. B-cell activation inhibition prevents the B cell from producing antibodies. CD40CR antibodies are useful for treating allergic reactions and autoimmune diseases.

Noelle's USSN 08/742,480 application was filed 1st November, 1996, but claimed priority to 14th February, 1992. Noelle's USSN 08/742,480 application was directed to the genus, murine, chimeric, humanised and human forms of the CD40CR monoclonal antibody, as well as hybridomal cell lines that produce the CD40CR antibody. Lederman's USPN 5,474,771 had an effective filing date of 15th November, 1991. USPN 5,474,771 described and claimed the human form of the CD40CR monoclonal antibody (the '5c8 antibody') and a hybridomal cell line created to produce the monoclonal antibody 5c8.

On 3rd September, 1999, an interference was declared between the issued claims of Lederman's USPN 5,474,771 and Noelle's USSN 08/742,480 patent application. The Board of Patent Appeals and Interferences found that Noelle's genus and human claims from the USSN 08/742,480 application lacked the necessary support of an adequate written description in Noelle's earlier filed application because Noelle failed to describe any structural features of the human or genus antibodies or antigens. For this reason, the Board denied the benefit of the filing date of Noelle's earlier filed patent application to the claims contained in the USSN 08/742,480 application. Without the benefit of the earlier filing date, the Board determined that the claims to the human and genus forms of CD40CR antibody in Noelle's application USSN 08/742,480 were anticipated by Lederman's USPN 5,474,771 or by patent USPN 5,961,974 issued to Armitage. According to the Board of Patent Appeals and Interferences, one skilled in the art would not have had a reasonable expectation of successfully isolating human CD40CR antibodies given that Noelle disclosed only the mouse form of CD40CR antigen. As a result, the Board found no interference-in-fact between Noelle's remaining murine CD40CR antibody claim and Lederman's claim to the human form of CD40CR antibody.

On appeal, the CAFC noted that the test to determine if an application is to receive the benefit of an earlier filed

application is whether a person of ordinary skill in the art would recognise that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application. An earlier application that describes later-claimed genetic material only by a statement of function or result may be insufficient to meet the written description requirement. According to the CAFC, if the applicant disclosed a *fully characterised* antigen, either by its structure, formula, chemical name or physical properties, or by depositing the protein in a public depository, the applicant could then claim an antibody by its binding affinity to that described antigen.

Chiron did not provide structure, function or molecular weight

The CAFC found that Noelle did not provide sufficient support for the claims to the human CD40CR antibody in the USSN 08/742,480 application because Noelle failed to disclose the structural elements of the human CD40CR antibody or antigen in the earlier application. Noelle described only the mouse antigen when he claimed the mouse, human and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. The CAFC remarked that Noelle cannot claim the genus form of CD40CR antibody by simply describing the mouse CD40CR antigen. The CAFC found that the Board was also correct in its determination that the human and genus claims were anticipated by Lederman's USPN 5,474,771. The CAFC concluded, therefore, that the Board's decision was supported by substantial evidence, and affirmed the decision of the Board of Patent Appeals and Interferences.

Subject matter did not exist at time of application

CHIRON V. GENENTECH

Chiron V. Genentech, 363 F.3d 1247 (Fed. Cir. 2004) involved Chiron's USPN 6,054,561 which claimed a monoclonal antibody that binds to the human c-erbB-2 (HER2) antigen (which is overexpressed in a certain type of breast cancer) and a monoclonal antibody that binds to a human breast cancer antigen that is also bound by monoclonal antibody 454C11 produced by the hybridoma and a monoclonal antibody that binds to a human breast cancer antigen that is also bound by monoclonal antibody 520C9. The Chiron inventors filed their first application in February 1984. Continuation-in-part patent applications were filed in January 1985, May 1986 and June 1995. When USPN 6,054,561 was issued, Chiron sued Genentech over sales of Herceptin®, a humanised antibody used to treat breast cancer. This appeal focused on USPN 6,054,561's claims to priority based on the applications filed in 1984, 1985 and 1986.

Chiron's 1984 application disclosed a murine monoclonal antibody that bound to the c-erbB-2 (HER2/neu) antigen but did not identify the structure, function or molecular weight of the antigen nor any disclosure of chimeric or humanised antibodies. Chiron's 1985 application disclosed six additional murine monoclonal antibodies that bound to HER2. Although Chiron's 1985 application did not specifically disclose chimeric or humanised antibodies, it added a definition of the term 'monoclonal antibody' as an antibody composition having a homogeneous antibody population. Chiron's 1986 application disclosed six additional murine antibodies that bound to the c-erbB-2 (HER2/neu) antigen and that the c-erbB-2 (HER2/neu) antigen had a molecular weight of 185 kilodaltons. There was, however, no specific mention in Chiron's 1986 application of chimeric or humanised antibodies.

The trial record showed that genetically engineered antibodies, specifically chimeric antibodies, were disclosed initially in the scientific literature as a successful technology in May 1984, four months after the filing date of the Chiron's first patent application. Because the first publication occurred after the filing of the 1984 application, the CAFC found that this new technology arose by definition,

Chiron's application did not enable the claims

outside the bounds of the enablement requirement. Chiron, by definition, could not have possession of, and disclose, the subject matter of chimeric antibodies that did not even exist at the time of their 1984 application. Thus, axiomatically, Chiron could not satisfy the written description requirement for the new matter appearing in USPN 6,054,561, namely chimeric antibodies.

Evidence presented showed that creation of genetically engineered antibodies, such as chimeric antibodies, required significant experimentation in 1985 and 1986 because those antibodies were unpredictable at that early stage of development. Chiron's 1985 and 1986 applications provided no disclosure of either how to make and use chimeric antibodies or working examples of chimeric antibodies within the scope of the claims in Chiron's USPN 6,054,561. That is, the scope of Chiron's claim included not only murine but also chimeric antibodies. While Chiron's applications enabled murine antibodies, they do not enable chimeric antibodies.

The CAFC found that substantial evidence supported the jury's finding that the technology was still nascent at the time of the 1986 application and, thus, would have required undue experimentation. The record supported the jury's conclusion that the 1985 and 1986 applications did not enable the claims of USPN 6,054,561 without undue experimentation. Accordingly, the CAFC held that substantial evidence supported the jury's verdict that USPN 6,054,561 cannot claim priority to any of the 1984, 1985 and 1986 applications and because the district court did not err in denying Chiron's motion for a new trial, the judgment of the district court was affirmed.

DISCUSSION

US PTO imposing restraints on the scope of the claims

Taken together, the cases discussed above illustrate the continuing restraint imposed by the US PTO on the scope of claims in biotechnology patent applications. Several lessons may be gleaned from these biotechnology patent legal decisions. For example, the *University of Rochester v. Searle* decision demonstrates that a patentee's method claims requiring a specific compound will not be considered valid without a corresponding description in the patent specification of a representative compound useful for such a method. Clearly, such 'reach through' claims will be held to a very high standard by the courts. It is possible that the University of Rochester could have claimed the general process by which one would identify a COX2 inhibitor by evaluating candidate compounds using established *in vitro* and *in vivo* preclinical models followed by a Food and Drug Administration application and release of the drug to the marketplace. Although not without problems, such claims represent an alternative claiming strategy for universities and research institutions attempting to secure patent coverage on very early stage pharmaceutical and biotechnology inventions.

In re Wallach demonstrates that patent applicants will continue to have difficulty obtaining claim coverage to nucleic acids without an accompanying description of the protein the nucleic acid encodes. Any attempt by the applicant to broaden the claims to include coverage of nucleic acids for unknown proteins will continue to fail. Similarly, applicants will continue to meet resistance from the US PTO when attempting to obtain coverage to claims to nucleic acids encoding proteins from species other than species disclosed in the specification.

Noelle v. Lederman et al. demonstrates that applicants may patent a monoclonal antibody provided that the corresponding antigen is sufficiently well characterised. Unlike the situation in the *University of Rochester v. Searle* decision, the applicant need not have actually constructed the monoclonal antibody. Similarly, *Chiron v. Genentech* requires the patent applicant to demonstrate that the claimed subject matter, in this instance, a chimeric antibody, could be made by a person having ordinary skill in the art.

Describe thoroughly all aspects of technology

In summary, patent applicants are advised to describe thoroughly all aspects of their technology, including how to make and use the claimed subject matter. As illustrated by the cases discussed above, failure to do so can result in an invalid patent.

In addition to their significance to patent, the biotechnology patent decisions discussed above also impact relations between universities and their industrial partners in the biotechnology and pharmaceutical sectors. The embryonic nature of some university research efforts results in legal difficulties securing adequate patent protection when the commercial embodiments of such research is considerably 'downstream' from the initial university invention. Consequently, universities will necessarily require increased collaborative efforts with biotechnology and pharmaceutical companies in order to commercial technology developed initially within universities.

Notes

1. 35 USC §101 states that 'whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of Title 35 of the United States Code'.
2. The enablement requirement of 35 USC §112, ¶1 requires that the specification of a patent application must enable any person skilled in the art to which the invention pertains, or with which it is most clearly connected, to make and use the invention. The specification also must contain the best mode contemplated by the inventor of carrying out the invention.
3. The written description requirement of 35 USC §112, ¶1 requires that the specification of a patent application contain a written description of the invention and of the manner and process of making and using it in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the invention.
4. The Bayh–Dole Act allows universities to retain ownership of intellectual property rights to technology that was developed at least in part using federal funding provided to the university investigator. Although by law, in providing such funding, the US Federal Government has certain rights to the technology, retention of ownership by the university allows the university to license the technology to profit therefrom.
5. 35 USC §102 in general identifies conditions of patentability as they pertain to novelty of the invention and loss of a right to a patent. Specifically, 35 USC §102(b) is a statutory bar that prevents an applicant from obtaining a patent if the public came into possession of the invention on a date before a 1-year grace period ending with the US filing date. Public possession of the invention has occurred if the applicant's invention was patented or described in a printed publication in the USA or in a foreign country or is in public use or on sale in the USA prior to the statutory bar date.