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Introduction

Since the beginning, the United States has been the global leader in developing biotechnology. This dominance has been attributed, in part, to commercially relevant protections offered to biotechnology under US patent law. Indeed, in 1998, to stimulate its biotechnology industry, the European Union issued Directive 98/44/EC on the protection of biotechnical inventions, in part because the then patent system provided insufficient incentives for developing biotechnology. Upon incorporation into the European Patent Convention (EPC), the Directive provided broader protections for biotechnology inventions, stimulating the European biotechnology industry.

Recently, US courts have restricted the protections afforded to biotechnology by expanding the written description requirements. Regardless of whether this is intended to curb the perceived effect of patents on healthcare costs or to harmonize US patent law across technologies, the effect may be decreased investment in US biotechnology.

Recent US written description cases

Under US law, description of a claimed genus requires disclosure of either a representative number of species within that genus or structural features common to it. Consistent with those rubrics, US courts tended to find that biotech genera were sufficiently described. For example, in *Noelle v Lederman*, the Federal Circuit held that characterizing a new antigen sufficiently described a genus of antibodies binding it.

Recently, the Federal Circuit has applied a heightened written description standard for biotechnology genera. For example, in *AbbVie Deutschland GmbH v Janssen Biotech, Inc*, disclosure of over 300 antibodies was insufficient to support an anti-IL-12 antibody genus. While those antibodies were structurally related and derived from the same VH segment, the genus encompassed structurally dissimilar antibodies, derived from different VH segments. In *Amgen Inc v Sanofi*, the Federal Circuit held that *Noelle*'s "'newly characterized antigen' test flouts basic legal principles of the written description requirement" because it "allows patentees to claim antibodies by describing something that is not the invention." In *Idenix Pharmaceuticals LLC v Gilead Sciences Inc*, the Federal Circuit found that the specification insufficiently described methods for treating a hepatitis C viral infection with a genus of pharmaceutical compounds, because it did not distinguish effective from ineffective compounds. Over the past year, the Federal Circuit has applied an even stricter written description standard to biotechnology inventions.

Juno Therapeutics, Inc v Kite Pharma, Inc

In *Juno*, the Federal Circuit reversed the district court decision and found that Juno's patent insufficiently described a genus of polynucleotides encoding T-cell receptors (TCRs) comprising (1) the intracellular domain of human CD3 zeta chain; (2) a co-stimulatory region comprising a specific amino acid sequence; and (3) a single-chain antibody (scFv).

Focusing solely on the scFv element, the *Juno* panel found that the specification contained neither a representative number of scFvs nor a common structure linking them. Regarding the former, the panel viewed the claims as encompassing "millions of billions" of scFvs capable of binding limitless targets, yet the specification described only two scFvs. The panel criticized the specification for providing insufficient "details about which scFvs bind to which target", discounting the undisputed well-known use of scFvs in TCRs years before the priority date because "testimony that scFvs were generally known in the field is insufficient to satisfy the written description requirement."

Regarding the latter, the panel, looking to *Idenix* and *AbbVie Deutschland*, found that the patent insufficiently described structural features common to the claimed scFvs. While acknowledging the common general structure of scFvs, the panel noted that scFvs with different amino acid sequences recognized different antigens. Thus, the panel found that the patent failed to distinguish binding from non-binding scFvs and that Juno's claims, reciting a problem-to-be-solved and all solutions to it, including later-invented compounds, failed owing to insufficient written description.

Juno represents a troubling written description requirement for biotechnology patents. It focuses only on a portion of the claim, not the entire claim, which recited polynucleotides with three elements, two of which were structurally defined: the human CD3 zeta chain intracellular domain and the co-stimulatory signalling region.

While the scFv-encoding portion of the polynucleotides was variable, scFvs had undisputedly long been used in TCRs. Thus, it was these other elements, or their combination with scFvs, that provided the non-obvious improvement over the prior art. *Juno*'s focus on the scFVs ignored the inventive contribution, which was based on common structural features, and addressed the written description of the known element.

Further, *Juno* appears inconsistent with earlier decisions. While *Idenix* found that method-of-treatment claims lacked written description, it noted that the compound genus was sufficiently described. By contrast, the *Juno* claims were directed at compositions of matter, not function, and the panel's focus on "which scFvs bind to which target" mistakenly treated the polynucleotide claims like *Idenix*'s method-of-treatment claims, and addressed a function not recited in claims.

Juno is also inconsistent with *Ajinomoto Co, Inc v ITC*, decided contemporaneously with *Idenix*, where four "more potent promoters" were found to be representative of a similarly limitless genus because more potent promoters were long well known. Here, the *Juno* panel discounted the well-known use of scFvs in TCRs, ignoring *Ariad Pharm, Inc v Eli Lilly & Co*'s seminal holding that written description "will necessarily vary depending on context", including "the existing knowledge in the particular field, the extent and content of the prior art, [and] the maturity of the science or technology".

Accordingly, *Juno* significantly expanded the written description requirement for biotechnology inventions. More recent case law reinforces this trend.

Indivior UK Ltd v Dr Reddy's Laboratories SA: claimed ranges

In *Indivior*, a divided Federal Circuit panel applied a strict written description requirement to ranges in formulation claims. The majority affirmed that claims to a mucoadhesive film lacked written description for the terms "about 40 wt% to about 60 wt%" and "about 48.2 wt% to about 58.6 wt%" of a polymeric matrix.

The majority noted that the specification said "any desired level" of polymer may be used and provided examples of "at least 25%" and "at least 50%", which was inconsistent with the claimed "closed" concentration ranges (eg, "about 40-60%"). The majority acknowledged that Tables 1 and 5 included formulations comprising total polymer concentrations of 48.2% and 58.6%, respectively, but asserted that the values did not constitute the limits of a range and required a skilled artisan to add up the individual values of four polymers, determine aggregate percentages and combine those percentages to obtain an unrecited range. The majority held that written description requires more clarity.

Disagreeing with the patentee that, based on *In re Wertheim* and *Nalpropion Pharms, Inc v Actavis Labs FL, Inc*, the concentrations in Tables 1 and 5 sufficiently supported the claimed ranges, the majority responded that written description is fact-intensive and *Wertheim* had not created "a rule applicable to all description requirement cases involving ranges."

In dissent, Judge Linn criticized the majority's failure to follow precedent and its overly demanding written description standard for ranges. He argued that the majority took "any desired level" out of context, ignoring the part of the sentence that tied the specific percentages to the claimed characteristics: mucoadhesion and dissolution rate. He opined that the specification was consistent with closed ranges because "at least 25%" and "at least 50%" were bound by upper limits of 100%.

Judge Linn criticized the majority's lack of authority for its assertion that a closed range requires the disclosure of that specific range rather than the disclosure of the discrete endpoints. He also stated that the calculation of aggregate percentages was simple maths, well within ordinary skill level, demonstrated by the majority's acknowledgment that a specific concentration, derived from Table 1, was sufficiently described.

Specifically, Judge Linn characterized *Wertheim* and *Nalprion* as directly on point. He argued that Indivior's disclosed range of "at least 25% (25-100%)" and specific embodiments of 48.2% and 58.6% was sufficient written description – exactly as the disclosure of a 25 to 60% range and specific embodiments of 36% and 50% being sufficient for the *Wertheim* 35 to 60% range.

Judge Linn pointed out that the *Nalpropion* facts were substantially identical to *Indivior*: *Nalpropion* held that disclosure of "less than about 80% or less than about 70%" for one hour and "less than about 90% or less than about 80%" for two hours and the discrete values of 39% and 67% (one hour) and 62% and 85% (two hours) included in two tables was sufficient written description for claims reciting 39 to 70% (one hour) and 62 to 90% (two hours). Accordingly, he criticized the majority's failure to address *Nalpropion*.

Biogen Int'l GmbH v Mylan Pharmaceuticals Inc: dosing regimens

In *Biogen*, a divided Federal Circuit panel affirmed that claims for treating multiple sclerosis (MS) by administering 480mg/day of dimethyl fumarate (DMF) lacked written description, despite each claim element being explicitly recited in the specification.

The majority noted that the specification disclosed Nrf2's protective role in three dozen neurological disorders, including MS, but was focused primarily on drug discovery. Indeed, while the specification exemplified three screening methods, it described only a single relevant treatment method, which advised administering DMF but did not identify any specific disorder.

The majority noted that the "one and only" reference to 480mg/day was in a paragraph relating to potential DMF dosages, again unlinked from disorders, and in the range 480 to 720mg/day and contrasted the specific disclosure of 720 mg/day. The majority also contended that the specification's "therapeutically effective dose" included both clinical and therapeutic efficacy.

The majority noted the art-recognized link between DMF-mediated activation of Nrf2 and therapeutic effects and acknowledged that the specification may provide adequate description for methods of treating MS with DMF. The majority contended, however, that the single reference to 480mg/day "constitutes a significant fact that cuts against Biogen's case, particularly because it appears at the end of one range among a series of ranges."

Because the clinical efficacy of the 480mg/day dose was not demonstrated until after the filing date, the majority found that the alleged earlier conception of that dose was "mere theoretical research without more" and not patentable. The majority found insufficient written description because:

> a skilled artisan would not have recognised, based on the single passing reference to a [480mg/day] dose in the disclosure, that [480mg/day] would have been efficacious in the treatment of MS, particularly because the specification's only reference to [480mg/day] was part of a wide DMF-dosage range and not listed as an independent therapeutically efficacious dose.

Judge O'Malley dissented, citing the majority's failure to distinguish between clinical and therapeutic effects. In her view, "this threshold error impacted the . . . entire written description analysis". As she noted, clinical efficacy at the Food and Drug Administration (FDA) requires a therapy to outperform the standard-of-care treatment, whereas patent law is not as rigorous. She also considered that the patent's *in vivo* experiments sufficiently demonstrated that

DMF “would be expected to be therapeutically effective for the treatment of . . . MS” and criticized the majority for not providing any authority for its assertion that written description requires repeated recitations of an element.

The Federal Circuit denied Biogen’s petition for rehearing *en banc*. Judge Lourie (joined by Chief Judge Moore and Judge Newman) dissented, characterizing the case as an outlier in written description jurisprudence because every claim limitation was expressly stated in the specification. He identified four alleged errors in the decision.

First, he faulted the majority’s focus on the number of neurological disorders, despite the specification explicitly identifying MS and its reliance on the single disclosure of the 480mg/day dose, noting the absurd result that a court should determine written description sufficiency by comparing the number of times claimed elements and unclaimed elements are described.

Second, he said proving efficacy is the FDA’s province, not the patent office’s, and precedent establishes that “it is unnecessary to prove that a claimed pharmaceutical compound actually achieves a certain result” (quoting *Nuvo Pharms (Ir) Designated Activity Co v Dr Reddy’s Lab’ys Inc*). He emphasized that the Biogen specification expressly discloses that 480mg/day is an effective amount, leaving nothing for the skilled artisan to deduce.

Third, he asserted that the majority’s focus on efficacy conflated written description and enablement and erroneously imported operability into the written description analysis.

Finally, he pointed to written description precedent, which “requires an objective inquiry into the four corners of the specification”, and criticized the majority for going beyond those confines, including analysis of clinical trials, later-filed applications and *inter partes* review arguments. He opined that none was relevant to written description and that when a patent explicitly describes what is claimed, extrinsic evidence should not be used to challenge that description.

Sufficiency under EPO law

At the European Patent Office (EPO), written description is usually assessed under Article 83 EPC, sufficiency of disclosure, which states, in a deceptively simple manner, that “[t]he European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.” The Guidelines for Examination in the European Patent Office: Part F, Chapter III.1 provide that a detailed description of at least one way of carrying out the invention must be given and that details of common general knowledge need not be included.

Like in the United States, narrowing claim scope in response to lack of sufficiency objections in the EPO has become more common. Unlike *Juno*, however, the skilled artisan’s knowledge is, generally, considered, although the extent of that knowledge is often disputed, particularly in oppositions.

At the EPO, the line between sufficiency and inventive step is often blurred for biotechnology claims. For example, a claim to an antibody defined by its six complementarity-determining regions may not meet EPC requirements unless several such antibodies are exemplified. Such an objection may be raised under sufficiency (the skilled artisan cannot be expected to repeat the invention beyond the one exemplified antibody) or inventive step (the problem has not been solved across the claim’s full scope). It could be to the applicant’s advantage to try and have it considered under inventive step, so that additional data may be provided, if available, to support the claim. However, the ability to use post-filed data may be limited, given the recent referral (G2/21) to the Enlarged Board of Appeal.

Plausibility is also a concept that frequently arises during assessment of sufficiency in relation to medical use claims (the EPO equivalent of US method-of-treatment claims). The scope of plausibility is now before the Enlarged Board of Appeal, along with the question of whether post-filing data can support inventive step, if it is plausibly based on the

original application. The ultimate decision is likely to impact sufficiency of disclosure, given that plausibility remains an aspect of that assessment.

Conclusion

Whereas the United States once incentivized investment in biotechnology by providing broad patent protections to such inventions, recent case law has swung the pendulum towards narrow claims to the point where even a specification that explicitly discloses every element of a claim can be found to lack written description. Unless and until the courts reverse this trend, patentees may be dissuaded from investing in technology where ultimate patent protection is of little commercial benefit.

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