UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner

Case No. IPR2017-01987
U.S. Patent No.: 8,911,737
Issue Date: Dec. 16, 2014
Title: Methods of Administering Anti-TNFα Antibodies

PETITIONER SANDOZ INC.'S MOTION FOR REHEARING UNDER 37 C.F.R. § 42.71(d)

Before SUSAN L. C. MITCHELL, MICHELLE N. ANKENBRAND, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

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Petitioner Sandoz Inc. ("Sandoz" or "Petitioner"), pursuant to 37 C.F.R. § 42.71(d), respectfully requests rehearing of the March 9, 2018, Decision Denying *Inter Partes* Review of claims 1-6 of Patent No. 8,911,737 ("the '737 patent").

I. INTRODUCTION

The Board's rejection of the Petition in IPR2017-01987 was in error. The Board erroneously concluded that Sandborn 2001 (Ex. 2015) – an abstract describing a single study of the fusion protein etanercept to treat Crohn's disease ("CD") – negated the reasonable expectation of success of a person of ordinary skill in the art ("POSA") in arriving at the claimed invention of the '737 patent, namely, methods of treating CD by administering an anti-TNFα ***antibody***.

The Board's decision was procedurally flawed because it improperly relied on the Board's own inferences in lieu of evidence to decide what a POSA would understand from Sandborn 2001. As a result, the Board effectively required Petitioner to have anticipated and preemptively countered Patent Owner's attorney arguments concerning Sandborn 2001, despite the facts that (1) neither that reference nor those arguments were in the record prior to the filing of Patent Owner's Preliminary Response ("POPR") and (2) the Petition did not rely on any contradictory data. Ironically, had Patent Owner relied on expert evidence regarding a POSA's understanding of Sandborn 2001, as opposed to just attorney argument, any genuine issue of material fact raised would have been viewed in the

light most favorable to Petitioner, trial would have been instituted, and Petitioner would have had the opportunity to cross-examine Patent Owner's expert and develop rebuttal evidence during trial. Instead, however, because Sandborn 2001 was raised for the first time in the POPR ***without*** supporting evidence, Petitioner was deprived both of notice of Patent Owner's reliance on this reference and of an opportunity to respond.

The injustice caused by the Board's errors is particularly stinging here because Petitioner could readily have rebutted Patent Owner's contentions (and the Board's conclusion) regarding Sandborn 2001, if given the opportunity. In reaching its erroneous conclusion, the Board overlooked or misapprehended key facts. Specifically, the Board overlooked or misapprehended (1) that etanercept is not an antibody drug, (2) that Petitioner and its expert relied on data from antibody drugs – not etanercept – and (3) that there is no inconsistency between the Sandborn 1999 paper (Ex. 1005) relied upon by Petitioner (which contained no data on the use of etanercept in CD) and Sandborn 2001.

Patent Owner argued, and the Board apparently agreed, that Sandborn 2001 taught away from using the rheumatoid arthritis ("RA") dose of ***any*** biologic TNF-α inhibitor to treat CD. But it is an equally (or even more) plausible alternative that, faced with multiple successful antibody studies and a single "failed" study of etanercept, a POSA would conclude that etanercept's results in CD could be due to

the fact that it is a fusion protein, not an antibody – *i.e.*, that etanercept would not work to treat CD at ***any*** dose. This conclusion was ultimately proven true. Moreover, Patent Owner's argument (and the Board's conclusion) on Sandborn 2001 is belied by published literature showing that POSAs did not stop testing the RA dose of etanercept (let alone the RA doses of anti-TNFα antibodies) for efficacy in CD after the publication of Sandborn 2001. For example, in September 2001, another team of researchers, led by D'Haens et al.[1], described a study treating CD using the exact same dosing regimen of etanercept used in Sandborn 2001. Accordingly, Sandborn 2001 did not negate the reasonable expectation of success in using even etanercept at its RA dose to treat CD, let alone the reasonable expectation of success in using an anti-TNFα ***antibody*** to treat CD as claimed by the '737 patent.

The Board further erred in its analysis of reasonable expectation of success by failing to consider the appropriate scope of the '737 patent's claimed invention. The Board failed to consider, for example, that the claims of the '737 patent are directed to methods of treating CD by administering an anti-TNFα ***antibody***. The Board also failed to consider that the '737 patent claims do not require any particular therapeutic or clinical efficacy. Had the Board properly considered the

[1] Geert D'Haens et al., *Etanercept in the Treatment of Active Refractory Crohn's Disease: A Single Center Pilot Trial*, 96 AM. J. GASTROENTEROLOGY 2564 (2001) ("D'Haens") ("Ex. 1115").

scope of the claimed invention in its reasonable expectation of success analysis, it would not have accorded more weight to Sandborn 2001 – an abstract reporting a single study of the fusion protein etanercept to treat CD, in which patients did not achieve the specific clinical responses measured – than to the multiple studies described in Sandborn 1999, which show successful treatment of CD with prior art anti-TNFα ***antibodies*** (infliximab and CDP571).

II. BACKGROUND

The ’737 patent claims methods of treating CD by subcutaneously administering 40 mg of an anti-TNFα antibody having the known amino acid sequences of adalimumab, every other week. This is exactly the same dosing regimen that Patent Owner also claimed to treat RA in an earlier-issued patent, U.S. Patent No. 8,889,135 (“the ’135 patent”).[2] Sandoz filed its Petition in IPR2017-01987 on August 21, 2017, challenging the patentability of all claims of the ’737 patent as obvious over the prior art. In relevant part, Petitioner and its expert, Dr. Bjarnason, relied on a 1999 article by Sandborn and colleagues that describes multiple prior art studies in which the anti-TNFα antibodies infliximab and CDP571 were shown to treat RA and CD using the same doses and dosing regimens for both conditions. Ex. 1005. Specifically, Petitioner and its expert submitted that the prior art antibody studies described in Sandborn 1999 supported

[2] The Board found all claims of the ’135 patent to be unpatentable as obvious in three previous IPRs brought by other petitioners. Petition at 2.

the POSA's reasonable expectation of success in treating CD according to the methods claimed in the '737 patent, *i.e.*, by administering the same dosing regimen of adalimumab that would also treat RA.[3]

Patent Owner filed its POPR in due course on December 13, 2017. In its POPR, Patent Owner introduced Sandborn 2001 – a later abstract that was not previously in the record, and that reported a study evaluating the anti-TNFα fusion protein etanercept to treat CD. Patent Owner argued, *inter alia*, that Sandborn 2001 "refute[s] Petitioner's position that one would have had an expectation of success in using the same fixed dose of an anti-TNFα drug to treat both RA and Crohn's disease." POPR at 15, 37. Patent Owner did not submit any testimonial evidence in support of its proffered interpretation of Sandborn 2001, and instead relied solely on attorney argument. Patent Owner also never explained why a POSA would interpret the fusion protein etanercept results in Sandborn 2001 as outweighing or negating the teaching and suggestion in Sandborn 1999 regarding dosing regimen based on experience with two prior art anti-TNFα antibodies.

On March 9, 2018, the Board issued a decision denying institution of IPR2017-01987 on the sole basis that "the etanercept study failure Sandborn 2001 reports" would, in the Board's view, negate a POSA's reasonable expectation of

[3] Notably, this is the same premise upon which Patent Owner relied to obtain the '737 patent – the only working examples in the '737 patent relate to the treatment of RA (not CD), and the specification contains no information on any dosing regimen specific to CD.

success that "the same TNFα inhibitor could be administered at the same dose and dose frequency to treat both RA and Crohn's disease." Paper 15 at 20, 22.

III. ARGUMENT

A. Legal Standard for Rehearing

A party may request rehearing of a decision by the Board whether to institute a trial pursuant to 37 C.F.R. § 42.71(d). When rehearing a decision on petition, a panel will review the decision for an abuse of discretion. *Id*. at § 42.71(c). "An abuse of discretion occurs where the decision is based on an erroneous interpretation of the law, on factual findings that are not supported by substantial evidence, or represents an unreasonable judgment in weighing relevant factors." *Star Fruits S.N.C. v. United States*, 393 F.3d 1277, 1281 (Fed. Cir. 2005).

B. The Board improperly relied on its own inferences in lieu of evidence to decide what a POSA would understand

Patent Owner raised Sandborn 2001 for the first time in its POPR, and offered no accompanying evidence of what a POSA would have understood from that abstract about a dosing regimen for CD. Instead, Patent Owner's assertions with respect to a POSA's take-away from Sandborn 2001 relied purely on attorney argument. Notwithstanding the fact that no expert had actually weighed in on the matter, the Board accepted without question Patent Owner's assertion that Sandborn 2001 negated a POSA's reasonable expectation that a dosing regimen for an anti-TNFα ***antibody*** that was effective in treating RA also would have been

effective in treating CD. Paper 15 at 20, 22. But the Board's unsupported conclusion is not the only plausible interpretation of Sandborn 2001. It is equally plausible (or even more plausible) that a POSA would have viewed fusion protein efficacy in treating CD as different in kind given the prior art evidence on treating CD with antibodies. In fact, etanercept to date is not approved for CD.

Ironically, had Patent Owner's arguments been supported by expert testimony, any genuine issue of material fact raised by Sandborn 2001 would have been viewed in the light most favorable to the Petitioner for purposes of institution (37 C.F.R. § 42.108(c)). Trial would have been instituted and Petitioner would have been given the opportunity to cross-examine Patent Owner's expert and develop rebuttal evidence during trial. It is illogical and unfair that Patent Owner's attorney argument surrounding Sandborn 2001 should create a higher barrier to institution than would testimonial evidence from an expert.

Moreover, Sandborn 2001 was raised for the first time in the POPR. By adopting Patent Owner's attorney arguments on Sandborn 2001 as the basis for denying institution, the Board effectively required Petitioner to have anticipated and preemptively countered these arguments. But Sandborn 2001 was not of record before the filing of the POPR, and the Petition did not rely on contradictory etanercept data – or on any fusion protein data whatsoever – such that Petitioner had reason to seek it out. The Board's Decision overlooks these facts, and instead

incorrectly implies that Sandborn 1999 and Sandborn 2001 – separate references, from different journals, published years apart – should be treated as a single continuous disclosure simply because they share a lead author. This implication is both incorrect and unjust.

As a result of these procedural errors, Petitioner has been deprived of the opportunity to respond to Patent Owner's attorney arguments on Sandborn 2001 with actual evidence. This result is particularly unjust here where, if given the opportunity, Petitioner could readily have rebutted Patent Owner's contentions.

C. The Board Misapprehended or Overlooked Key Facts

The Board overlooked and/or misapprehended key facts when it reached its conclusions on the import of Sandborn 2001.

First, in relying so heavily on Sandborn 2001, the Board overlooked the fact that etanercept is a fusion protein, not an antibody (as required by the claims of the '737 patent). Nor did the Board treat all "biologic" TNFα inhibitors as fungible – rather the Board accorded ***more*** weight to a single CD study of the fusion protein etanercept than it did to the numerous prior art studies of TNFα antibodies cited by Petitioner. The Board's apparent conclusion on the heightened relevance of etanercept CD data as compared to antibody data, however, is unsupported by any evidence of record. Petitioner did not address this issue because the Petition did not rely on any etanercept data. Tellingly, Patent Owner, in its attorney argument

surrounding Sandborn 2001, did not even acknowledge that etanercept is not an antibody, let alone attempt to explain why Sandborn 2001 – a single study of a fusion protein in the treatment of CD – should be given ***greater*** weight than the multiple prior art studies showing that TNFα antibodies (infliximab and CDP571) treated CD and RA at the same doses.

Second, at Patent Owner's behest, the Board misapprehended that Petitioner and its expert "rel[ied]" on any information (or lack of information) regarding etanercept. *See* Paper 15 at 21 (faulting Petitioner and its expert for not addressing Sandborn 2001, and "relying instead on statements in Sandborn (from May 1999) that there had been no published clinical trials of etanercept for IBD."[4]). This conclusion is inaccurate. Petitioner and Dr. Bjarnason relied on Sandborn 1999's report of numerous clinical studies of prior art TNFα ***antibodies*** (infliximab and CDP571) in which those antibodies were shown to treat both RA and IBD at the same doses. In contrast, Petitioner did not present any arguments or draw any conclusions based on etanercept. In fact, the only mention of etanercept in the Petition is in a single footnote that simply stated, "Sandborn [1999] described clinical trials for the TNF-α inhibitor etanercept, a human fusion protein now marketed as Enbrel®, but reported that there had been no published clinical trials of etanercept for Crohn's or UC." Petition at 22, n. 17. Dr. Bjarnason likewise did

[4] CD and ulcerative colitis ("UC") are both types of inflammatory bowel disease, or "IBD."

not offer any opinion based on Sandborn 1999's report of no previous clinical trials of etanercept in IBD, and confined his mention of this report to a footnote. *See* ex. 1008 at 15, n. 2.

Additionally, the Board appears to have misapprehended an inconsistency between Sandborn 1999 and Sandborn 2001 where in fact none exists. In its Decision Denying Institution, the Board effectively treated Sandborn 1999 and Sandborn 2001 as a single reference, and implied that Petitioner cherry-picked data on etanercept. This implication is incorrect and misplaced. As a preliminary matter, Sandborn 1999 and Sandborn 2001 are separate references, from different journals, published years apart, and have multiple different authors. That the two references happen to share a lead author does not change these facts. More importantly, and contrary to the Board's apparent conclusion, this is not a case where Petitioner relied on helpful data for etanercept and ignored contradictory data. Petitioner did not rely on any etanercept IBD data at all, and none was presented in Sandborn 1999 – the data presented in Sandborn 2001 is therefore not inconsistent with the disclosure of Sandborn 1999.

D. The Board failed to consider the proper scope of the patent's *claimed invention* in its reasonable expectation of success analysis

1. The '737 recites anti-TNFα *antibodies*

The Board denied institution based on its conclusion that the etanercept study failure reported in Sandborn 2001 negated a POSA's reasonable expectation

that "the same TNFα inhibitor could be administered at the same dose and dose frequency to treat both RA and Crohn's disease." Paper 15 at 20. However, the '737 patent claims are not directed to any "TNFα inhibitor" as suggested by the Board's conclusion. Rather, the claims of the '737 patent recite "anti-TNFα antibod[ies]." Thus, in reaching its conclusion, the Board erred by failing to consider the proper scope of the patent's ***claimed invention.*** "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). As the Federal Circuit has explained, "[f]ailure to consider the appropriate scope of the … patent's *claimed invention* in evaluating the reasonable expectation of success … constitutes legal error that [is] review[ed] without deference." *Id.* (emphasis in original) (citation omitted) (internal quotation marks omitted).

Here, the Board erred in its analysis on reasonable expectation of success by failing to appreciate that the claims of the '737 patent are directed to methods of treating CD with an anti-TNFα ***antibody***. This failure is evident from the fact that the Board accorded more weight to the single fusion protein study described in Sandborn 2001 than it did to the many anti-TNFα ***antibody*** studies described in Sandborn 1999.

To be clear, Petitioner does not propose that information on etanercept or other non-antibody drugs is irrelevant. Indeed, as explained by Petitioner and Dr. Bjarnason, the long prior art history of treating IBD and RA with the same (non-antibody) drugs at the same doses would inform a POSA's overall knowledge. Petition at 18; Ex. 1008 at ¶¶ 81-98. However, in forming a reasonable expectation of success in arriving at the claimed invention – *i.e.*, treating CD with an anti-TNFα ***antibody*** – a POSA would not discount the data from numerous successful studies of the prior art anti-TNFα antibodies infliximab and CDP571 (described in Sandborn 1999) because of a single abstract (Sandborn 2001) showing a "failure" of the fusion protein etanercept.[5] Paper 15 at 22. If given the opportunity, Dr. Bjarnason will explain the relative significance of Sandborn 2001.

2. The '737 has no particular therapeutic efficacy requirement

The Board's heavy reliance on Sandborn 2001 also demonstrates a failure to apprehend that the '737 patent claims do not require a particular level of therapeutic efficacy. The "failure" of Sandborn 2001 does not bear on the operability or reasonable expectation of success of practicing the challenged claims, which require no particular level of efficacy, let alone the stringent level of

[5] Tellingly, Patent Owner selectively omitted from its Exhibit 2015 the abstract immediately following Sanborn 2001, which apparently documented successful treatment of CD with the anti-TNFα antibody infliximab. *See* ex. 2015 at 5 (program listing Hanauer et al., "Maintenance Infliximab (Remicade) Is Safe, Effective and Steroid-Sparing in Crohn's Disease: Preliminary Results from the Accent I Trial.").

efficacy demanded by the authors in Sandborn 2001.

Sandborn 2001 describes an 8-week, placebo-controlled study in which 23 patients with moderate to severe CD were given 25 mg of the fusion protein etanercept twice weekly – the same etanercept dose that is FDA approved to treat RA. Ex. 2015 at 6. At weeks 4 and 8 of the study, patients were assessed to see if they reached either of two specific, pre-determined clinical endpoints. *Id.* The primary clinical outcome assessed by Sandborn 2001 was a decrease in the baseline Crohn's Disease Activity Index ("CDAI") score of $\geq$ 70 points. *Id.* The secondary clinical outcome assessed was "clinical remission," defined as a CDAI score <150. *Id.* Sandborn 2001 reported that the etanercept-treated patients in that study did not achieve the pre-determined clinical endpoints any more frequently than did placebo-treated patients. *Id.* Based on these results, Sandborn 2001 concluded, "[s]ubcutaneous etanercept at a dose of 25 mg twice weekly is not an effective therapy for patients with moderate to severe CD." *Id.*

Importantly, Sandborn 2001 measured only two specific clinical endpoints. The abstract's conclusion that etanercept was "not an effective therapy" for CD was based on the failure of the drug to elicit achievement of those specific clinical endpoints. But the claims of the '737 patent do not require any particular level of therapeutic efficacy, let alone achievement of the clinical endpoints measured by Sandborn 2001. Accordingly, "it is of no moment" that the CD patients treated

with etanercept as described by Sandborn 2001 failed to achieve the measured clinical endpoints. *Intelligent Bio-Systems*, 821 F. 3d at 1367 (finding error in the Board's reliance on the absence of a reasonable expectation of success where the Board improperly imposed a non-existent claim requirement).

The case relied on by the Board in its Decision[6] – *In re Cyclobenzaprine Hydrochloride Extended Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012) ("*In re Cyclobenzaprine"*) – does not instruct otherwise, and is distinguishable from the present record. The prior art failure at issue in *In re Cyclobenzaprine* was the failure of others to make ***the patented invention*** – *i.e.*, an extended release cyclobenzaprine hydrochloride formulation which "provides [a] ***therapeutically effective*** plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions…" *Id.* at 1066. (emphasis added). Here, in contrast to *In re Cyclobenzaprine*, the cited prior art failure in Sandborn 2001 is not a failure to treat CD with an anti-TNFα antibody, let alone with adalimumab. Additionally, unlike the claims at issue in *In re Cyclobenzaprine* the claims of the '737 patent have no requirement for any particular level of clinical efficacy. Sandborn 2001's reported failure of etanercept to achieve specified levels of clinical efficacy therefore would not negate the POSA's reasonable expectation of success in achieving the claimed invention. *See*

[6] Paper 15 at 21.

Mylan Labs. Ltd. v. Aventis Pharma S.A., 2017 WL 4221400 at *12 (P.T.A.B. Sept. 21, 2017) (distinguishing *In re Cyclobenzaprine*, and noting that, absent a "therapeutically effective amount" limitation in the disputed patent claims, "Petitioner . . . need not establish a POSA reasonably would have expected . . . [clinical success] to demonstrate obviousness of [the claims].").

3. Later publications demonstrate that the Board's "reasonable expectation of success" analysis was flawed

That the Board's "reasonable expectation of success" analysis was flawed is also demonstrated by the fact that POSAs did not stop testing the RA dose of etanercept (let alone the RA doses of TNFα ***antibodies***) for efficacy in CD even after the publication of Sandborn 2001. For example, a September 2001 publication by D'Haens et al. described a study using the same RA dose of etanercept to treat CD. *See generally* ex. 1115. There, using additional and different efficacy measures, the authors concluded "[e]tanercept may be effective in Crohn's disease refractory to standard therapy." Ex. 1115 at 1. Had Sandborn 2001 truly resulted in the chilling effect ascribed by the Board, subsequent studies like the one described by D'Haens would not have been conducted.

IV. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that the Board institute *inter partes* review of claims 1-6 of the '737 patent on the grounds that the claims are obvious over the prior art combinations asserted in the Petition.

Dated: April 6, 2018

Respectfully Submitted,
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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing document PETITIONER SANDOZ INC.'S MOTION FOR REHEARING UNDER 37 C.F.R. § 42.71(d) is being served on April 6, 2018 via electronic mail upon the following counsel of record for Patent Owner AbbVie Biotechnology Ltd.:

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