

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.,
Petitioner,

v.

NOVARTIS AG,
Patent Owner.

Case IPR2016-00078
Patent 6,455,518

Before LORA M. GREEN, CHRISTOPHER L. CRUMBLEY, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

CRUMBLEY, *Administrative Patent Judge*.

DECISION

Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a) and 37 C.F.R. § 42.108

I. INTRODUCTION

Par Pharmaceutical Inc. (“Par”) filed a Petition requesting an *inter partes* review of claim 7 of U.S. Patent No. 6,455,518 (Ex. 1001, “the ’518 patent”). Paper 1 (“Pet.”). Novartis AG, the assignee of the ’518 patent, filed a Preliminary Response to the Petition. Paper 7 (“Prelim. Resp.”).

Pursuant to 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless the information presented in the Petition and any Preliminary Response shows “there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” Taking into account the information presented, we conclude that the record does not establish that there is a reasonable likelihood that Par will prevail in challenging claim 7 of the ’518 patent as unpatentable. Accordingly, we do not institute trial.

A. Related Matters

We are informed that the ’518 patent has been asserted in several actions captioned *Novartis Pharm. Corp. et al. v. Breckenridge Pharm., Inc.*, No. 14-1043-RGA (D. Del.); *Novartis Pharm. Corp. et al. v. Roxane Labs., Inc.*, No. 14-1196-RGA (D. Del.); and *Novartis Pharm. Corp. et al. v. Par Pharm., Inc.*, No. 14-1289-RGA (D. Del.). Pet. 3; Paper 5, 1. Related U.S. Patent No. 5,665,772 has been challenged in IPR2016-00084, currently pending before the Board.

B. The '518 Patent

The '518 patent, titled “Pharmaceutical Compositions for the Treatment of Transplant Rejection, Autoimmune or Inflammatory Conditions Comprising Cyclosporin A and 40-O-(2-Hydroxyethyl)-Rapamycin,” issued September 24, 2002, from U.S. Patent Application No. 09/758,301, filed on January 11, 2001. Ex. 1001, (54), (45), (21), (22). The patent is directed to a “synergistic combination of an IL-2 transcription inhibitor (e.g., cyclosporin A or FK506) and 40-O-(2-hydroxyethyl)-rapamycin,” which is said to be “useful in the treatment and prevention of transplant rejection and also certain autoimmune and inflammatory diseases.” *Id.*, Abstract.

According to the '518 patent, the compound rapamycin is known to be an immunosuppressant, but is difficult to formulate, is poorly soluble, and has poor oral bioavailability. *Id.* at 1:51–55. Its derivative, 40-O-(2-hydroxyethyl)-rapamycin (“everolimus”¹), is said to have improved formulation and pharmacokinetic properties. *Id.* at 1:55–57. Both rapamycin and everolimus are acknowledged to exhibit side effects at higher dosages, however. *Id.* at 1:57–59.

The '518 patent also discusses other immunosuppressants, called IL-2 transcription inhibitors, which derive their activity from inhibition of IL-2 gene transcription. *Id.* at 2:30–37. Examples of such compounds include

¹ Novartis refers to 40-O-(2-hydroxyethyl)-rapamycin as “everolimus,” terminology we adopt for the purposes of this Decision.

cyclosporin A and FK506, each of which have their own disadvantages. *Id.* at 1:60–2:29.

According to the '518 patent, it was surprisingly discovered that the combination of everolimus and IL-2 transcription inhibitors, in particular cyclosporin A, act synergistically. *Id.* at 2:38–41. In other words, treatment with both drugs together results in effective immunosuppression at lower dosages than would be required if administering each drug individually. *Id.* at 2:41–44. The '518 patent states that treatment using a synergistically effective amount of each drug permits reduction of side effects while enhancing pharmaceutical utility of the treatment. *Id.* at 2:46–51.

C. Challenged Claim

Challenged claim 7 is independent, and is reproduced below:

7. A method of treating or preventing an autoimmune or inflammatory condition or transplant rejection in a subject suffering from or at risk for such condition or rejection, comprising co-administering synergistically effective amounts of (I) an IL-2 transcription inhibitor and (II) 40-O-(2-hydroxyethyl)-rapamycin in the weight ratio 2:1 to 180:1.

Ex. 1001, 15:25–31.

D. Asserted Ground of Unpatentability

Par challenges claim 7 on a single ground of unpatentability: that claim 7 is unpatentable under 35 U.S.C. § 103(a)² as having been obvious

² The relevant sections of the Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, took effect on March 16, 2013. Because the application from which the '518 patent issued was filed before that date, our citations to

over Cottens,³ Kimball,⁴ Kahan,⁵ and Morris.⁶ Pet. 5. Par asserts that all references are prior art to the '518 patent under 35 U.S.C. § 102(b). Pet. 29, 31, 32, 34. Novartis does not, at this stage of the proceeding, challenge the prior art status of any reference.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, “[a] claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears.” 37 C.F.R. § 42.100(b). Under this standard, we construe claim terms using “the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant’s specification.” *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir.

Title 35 are to its pre-AIA version.

³ WO 94/09010 to Cottens et al. (published Apr. 28, 1994) (Ex. 1006).

⁴ Pamela M. Kimball et al., *Production of Synergistic but Nonidentical Mechanisms of Immunosuppression by Rapamycin and Cyclosporine*, 51 TRANSPLANTATION 486 (1991) (Ex. 1007).

⁵ Barry D. Kahan, *Cyclosporin A, FK-506, Rapamycin: The Use of a Quantitative Analytic Tool to Discriminate Immunosuppressive Drug Interactions*, 2 J. OF THE AM. SOC’Y OF NEPHROLOGY S222 (1992) (Ex. 1008).

⁶ Randall Ellis Morris, *Rapamycins: Antifungal, Antitumor, Antiproliferative, and Immunosuppressive Macrolides*, 6 TRANSPLANTATION REVIEWS 39 (1992) (Ex. 1009).

1997). We presume that claim terms have their ordinary and customary meaning. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) (“The ordinary and customary meaning is the meaning that the term would have to a person of ordinary skill in the art in question.”) (internal quotation marks omitted). A patentee may rebut this presumption, however, by acting as his own lexicographer and providing a definition of the term in the specification with “reasonable clarity, deliberateness, and precision.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Par asks that we construe the claim term *synergistically effective amounts* (Pet. 14); Novartis proffers a construction for that term, as well as for *co-administering*. Prelim. Resp. 4–5. For the purposes of this Decision, only *co-administering* requires construction. *See, e.g. Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting that only claim terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy).

1. *co-administering*

The method of claim 7 requires *co-administering* synergistically effective amounts of two compounds. As Novartis points out, the term “co-administration” is explicitly defined in the specification of the ’518 patent, as follows:

By “co-administration” is meant administration of the 40-O-(2-hydroxyethyl)-rapamycin and the IL-2 transcription inhibitor, e.g., cyclosporin A, together or at substantially the same time (e.g., within fifteen minutes or less), either in the same vehicle or in separate vehicles, so that upon oral administration, for

example, both compounds are present simultaneously in the stomach.

Prelim. Resp. 4 (quoting Ex. 1001, 6:29–35) (emphasis omitted).

We agree with Novartis that the patentee acted as its own lexicographer, defining “co-administration” with reasonable clarity, deliberateness, and precision as “administration . . . together or at substantially the same time.” The specification also provides two guideposts for determining what is “at substantially the same time”: either within fifteen minutes or less, or so that both compounds are present simultaneously in the stomach. We, therefore, determine that the broadest reasonable interpretation of the claim term *co-administering* is “administering together or at substantially the same time.”

B. Obviousness Over Cottens, Kimball, Kahan, and Morris

Par contends that claim 7 is unpatentable under 35 U.S.C. § 103(a), as its subject matter would have been obvious over the combined disclosures of Cottens, Kimball, Kahan, and Morris. Pet. 38–56. Par explains how the combined references teach the subject matter of each challenged claim and asserts that a person of ordinary skill in the art would have had reason to combine or modify the references. *Id.* Par also relies upon the Declaration of Dr. Allan MacDonald (Ex. 1004) to support its positions.

Cottens discloses “[n]ovel O-alkylated derivatives of rapamycin . . . especially 40-O-alkylated derivatives.” Ex. 1006, Abstract. Among the specifically disclosed “preferred novel compounds” is everolimus (40-O-(2-hydroxyethyl)-rapamycin). *Id.* at 3. Cottens states that rapamycin is known to be a potent immunosuppressant, and that certain derivatives have “an

improved pharmacologic profile over rapamycin, exhibit greater stability and bioavailability, and allow for greater ease in producing galenic formulations.” *Id.* at 1–2.

According to Cottens, the disclosed rapamycin derivatives may be administered alone or with other drugs. *Id.* at 8. For example, in immunosuppressive applications, they “may be used in combination with Ciclosporin, FK-506, or their immunosuppressive derivatives.” *Id.* Par argues that Cottens thus discloses “co-administering an IL-2 transcription inhibitor and [everolimus] but does not specify that the doses . . . would be synergistically effective amounts.” Pet. 30.

Kimball explores the mechanisms of immunosuppression by rapamycin and cyclosporin A, and determines that they are synergistic, but nonidentical. Ex. 1007, 1. For example, “rapamycin and cyclosporine synergistically inhibit T lymphocyte proliferation because they differ in mechanism of action as well as cell cycle restriction,” meaning that “rapamycin may be a clinically useful adjunct to cyclosporine immunosuppression.” *Id.* at 488. According to Par, Kimball “discloses co-administering synergistically effective amounts of IL-2 transcription inhibitors and rapamycin, as opposed to the rapamycin derivative [everolimus].” Pet. 32.

Kahan proposes a quantitative method for assessing synergy—the median-effect analysis—and investigates the interactions of various immunosuppressive drugs including cyclosporin A, FK506, and rapamycin. Ex. 1008, Abstract. Kahan describes both *in vivo* and *in vitro* results of combined treatment with cyclosporin A and rapamycin. *Id.* at S223–S225.

In the *in vivo* study, Kahan reports that rats receiving a combination of cyclosporin A and rapamycin survived more than 50 days following implantation, compared to less than 12 days for rats receiving a single drug, “demonstrating pharmacologic synergism.” *Id.* at S224. Kahan also discloses that this synergy permits cyclosporin A dose reduction by 3.7-fold and rapamycin dose reduction by 8.9-fold. *Id.* at S225. Par argues that Kahan thus “discloses co-administering synergistically effective amounts of IL-2 transcription inhibitors and rapamycin, as opposed to the rapamycin derivative [everolimus].” Pet 33.

Morris is a review of the research into rapamycin, “written relatively early in the research life of [rapamycin].” Ex. 1009, 41. Rapamycin is “particularly intriguing because it inhibits the activation of immune cells by unique, relatively selective, and extremely potent and highly effective mechanisms.” *Id.* at 39. Morris reports that “multiple combinations of [rapamycin] plus [cyclosporin A] . . . cause prolongation of graft survival that is synergistic.” *Id.* at 63. Morris also notes the “increased nephrotoxicity and diabetogenic effect of combined high doses of” rapamycin and cyclosporin A, suggesting “possible synergistic toxicity,” but notes that it is “possible that the toxic effects of each drug are different.” *Id.* at 63–64. According to Par, Morris “discloses co-administering synergistically effective amounts of IL-2 transcription inhibitors and rapamycin, as opposed to [everolimus].” Pet. 37.

1. The Parties’ Contentions

According to Par, a person of ordinary skill in the art would have combined Cottens with Kimball, Kahan, and Morris when looking for ways

to reduce the toxic side effects of rapamycin and other immunosuppressants by reducing the dosages of those drugs while maintaining a therapeutic effect. Pet. 39. Par cites Kimball, Kahan, and Morris as evidence that the prior art “taught that combining immunosuppressants that included rapamycin would have synergistic effects while simultaneously reducing side effects caused by higher doses.” *Id.* Dr. MacDonald testifies that at the time of the invention, a person of ordinary skill in the art would have known that everolimus is structurally similar to rapamycin and also exerts an immunosuppressant effect, as disclosed in Cottens. Ex. 1004 ¶ 85. From Kahan and Morris, Dr. MacDonald states, the person of ordinary skill would obtain effective dosages of rapamycin and cyclosporin A, and apply those dosages to a combination of everolimus and cyclosporin A. *Id.* ¶¶ 87–88.

Novartis raises numerous arguments in response. Our analysis focuses on the arguments regarding *co-administering*, as we find them dispositive to Par’s Petition. First, Novartis contends that at the time of the invention, immunosuppressants such as cyclosporin A and rapamycin were known to be toxic and required careful administration. Prelim. Resp. 8. In particular, cyclosporin A and rapamycin were known to be metabolized by the same family of CYP3A enzymes, and that co-administration of drugs metabolized by CYP3A enzymes “could lead to excessive concentrations of these drugs in the blood with a concomitant risk of toxicities.” *Id.* at 8–10. Novartis argues that in view of this knowledge, a person of ordinary skill in the art “would not have been motivated to add everolimus to an existing [cyclosporin A] treatment protocol, absent a teaching that this would have been at least safe for patients.” *Id.* at 10.

Furthermore, Novartis contends that the prior art cited by Par in this proceeding fails to teach *co-administering*, as specifically defined in the specification. *Id.* at 22–25. For example, Novartis notes that while Morris uses the word “co-administration,” there is no disclosure of administration “together or at substantially the same time,” such as within 15 minutes. *Id.* at 23. Rather, Morris is said to teach away from *co-administering*: Novartis notes Morris’ speculation that “coadministration of [cyclosporin A] could elevate [rapamycin] levels.” *Id.* at 24 (citing Ex. 1009, 64).

2. Analysis

Upon review of the record, we are persuaded by Novartis’ arguments that the prior art insufficiently discloses *co-administering*, as explicitly defined in the specification of the ’518 patent. Par’s Petition simply states at various points that the references “disclose co-administering,” without specifically indicating what disclosure in the reference is being relied on, or why a person of ordinary skill in the art would have understood the disclosure to be administration “together or at substantially the same time.”

In its element-by-element analysis of the proposed ground of unpatentability, Par identifies where each prior art reference allegedly discloses element [7b], “co-administering synergistically effective amounts of.” Pet. 47–50. We address each in turn. First, Par states that Cottens “directs that the disclosed rapamycin derivatives . . . should be co-administered with cyclosporin A.” *Id.* at 47 (citing Ex. 1006, 8). This overstates the disclosure of Cottens, especially given the specific definition of *co-administering* in the ’518 patent. Cottens only states that its derivatives (including everolimus) “may be administered . . . *together* with

other drugs,” and “may be used *in combination with*” cyclosporin A. Ex. 1006, 8 (emphasis added). Par does not explain why use “in combination with” would be understood by those of skill in the art to mean “administering together or at substantially the same time.” To the contrary, Cottens’ disclosure could reasonably be read as simply referring to administering both drugs “together” as part of a single treatment regimen, but spaced apart in time to avoid possible toxic effects.

Next, Par identifies portions of Kahan and Morris that allegedly teach cyclosporin A and rapamycin “co-administered at doses of 1-4 mg/kg/day and 0.02-0.5 mg/kg/day, respectively.” Pet. 48 (citing Ex. 1008, S223–S225; Ex. 1009, 59). We discern no such disclosure in either reference. The cited portion of Kahan discusses *in vivo* tests of a cyclosporin A/rapamycin combination, but does not state that the drugs were administered together or at substantially the same time. Ex. 1008, S223–S225 (0.02 mg/kg of rapamycin administered intravenously, 2.0 mg/kg of cyclosporin A administered orally). Similarly, the cited portion of Morris contains Table 10, which discloses treatment with rapamycin (RPM) and cyclosporin A (CsA), but only states that rapamycin was dosed on a QOD (every other day) schedule while cyclosporin A was dosed either QOD or QD (every day). Ex. 1009, 59. Morris contains no disclosure about when during this schedule each drug was dosed.

Nor does Dr. MacDonald provide further explanation of how a person of ordinary skill in the art would have understood these prior art disclosures to teach *co-administering* everolimus and cyclosporin A. In the portions of his Declaration cited by Par, Dr. MacDonald primarily re-states the

discussion in the Petition we found unpersuasive above. See Ex. 1004 ¶¶ 94, 102 (cited at Pet. 47–48). Elsewhere, in a section entitled “The Prior Art Taught Co-Administering [Everolimus] with IL-2 Transcription Inhibitors to Treat or Prevent Transplant Rejection and Autoimmune Conditions,” Dr. MacDonald only cites Cottens’ disclosure that everolimus could be administered “in combination with” cyclosporin A. *Id.* ¶ 82 (citing Ex. 1006, 8).

Finally, we do not agree with Novartis that the disclosures of toxicity in the prior art rise to the level of “teaching away” from *co-administering*. See *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (“[I]n general, a reference will teach away if it suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant.”). We do find the knowledge of toxicity relevant, however, in assessing how a person of ordinary skill in the art would have interpreted the disclosures of references such as Cottens, Kahan, and Morris. In particular, to the extent that any of these references are ambiguous regarding the treatment protocols used, a person of ordinary skill in the art would be more likely to interpret them as disclosing serial dosing of rapamycin and cyclosporin A, rather than simultaneous dosing, given the risk of toxicity that was understood to accompany administration of these drugs.

As we have found that the combined disclosures of Cottens, Kimball, Kahan, and Morris fail to disclose *co-administering* either rapamycin or everolimus with cyclosporin A, we are unpersuaded that the record sufficiently establishes that Par would prevail in demonstrating the

unpatentability of claim 7 over these references. We, therefore, decline to institute trial on Par's proposed ground of unpatentability.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition and Preliminary Response does not establish that there is a reasonable likelihood that Par will prevail in challenging claim 7 of the '518 patent as unpatentable under § 103(a).

IV. ORDER

In consideration of the foregoing, it is hereby ordered that the Petition is *denied*.

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Patent 6,455,518

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