Trials@uspto.gov
571-272-7822

Paper 10
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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MERCK SHARP & DOHME CORP.,
Petitioner,

v.

MAYNE PHARMA INTERNATIONAL PTY LTD.,
Patent Owner.

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Case IPR2016-01186
Patent 6,881,745 B2

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Before TONI R. SCHEINER, ERICA A. FRANKLIN, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

# I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") filed a Petition (Paper 1, "Pet.") on June 11, 2016, requesting an *inter partes* review of claims 1–3, 5–7, and 9–14 of U.S. Patent No. 6,881,745 B2 (Ex. 1001, "the '745 patent"). Mayne Pharma International Pty Ltd. ("Patent Owner") filed a Preliminary Response (Paper 8, "Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Upon consideration of the arguments and evidence presented in the Petition and the Preliminary Response, we are persuaded that Petitioner has established a reasonable likelihood that it would prevail in its challenges to claims 1–3, 5–7, and 9–14 of the '745 patent. Accordingly, we institute an *inter partes* review of claims 1–3, 5–7, and 9–14.

## *A. Related Proceedings*

The '745 patent has been asserted against Petitioner in *Mayne Pharma International Pty Ltd. v. Merck & Co., Inc. and Merck Sharp & Dohme Corp.*, Civil Action No. 15-438 (LPS) (CJB) (D. Del.), filed May 29, 2015. Pet. 56; Paper 5, 2; Prelim. Resp. 54. Petitioner was served with the complaint in that litigation on June 12, 2015. Pet. 56 (citing Ex. 1057, 1058).

*B. The Asserted Grounds of Unpatentability*

Petitioner asserts that the challenged claims are unpatentable on the following grounds:

| **References** | **Basis** | **Claims Challenged** |
|---|---|---|
| Kai[1] | § 102 | 1–3, 5–7, 9, 11, 12, 14 |
| Sangekar[2] | § 102 | 1–3, 5–7, 9–14 |
| Kohri[3] | § 102 | 1–3, 5–7, 9, 11, 12, 14 |
| Babcock[4] | § 102 | 1–3, 5–7, 9–14 |
| Baert[5] | § 102 | 1–3, 5–7, 9–14 |

[1] Toshiya Kai et al, *Oral Absorption Improvement of Poorly Soluble Drug Using Solid Dispersion Technique*, 44 CHEM. PHARM. BULL. 568–571 (1996) ("Kai") (Ex. 1007).

[2] WO 98/00113 A1, Surendra Sangekar et al., published January 8, 1998 ("Sangekar") (Ex. 1015).

[3] Naonori Kohri et al., *Improving the Oral Bioavailability of Albendazole in Rabbits by the Solid Dispersion Technique*, 51 J. PHARM. PHARMACOL. 159-164 (1999) ("Kohri") (Ex. 1017).

[4] EP 1 027 886 A2, Walter Christian Babcock et al., published August 16, 2000 ("Babcock") (Ex. 1009).

[5] U.S. Patent No. 6,509,038 B2, issued January 21, 2003 to Lieveb Elvire Colette Baert et al. ("Baert") (Ex. 1018).

| References | Basis | Claims Challenged |
|---|---|---|
| Vandecruys[6] | § 102 | 1–3, 5–7, 9, 10, 12, 13 |
| Thorpe[7] | § 102 | 1, 3, 5, 7 |
| Tett[8] | § 102 | 1, 3, 5, 7 |
| Lin[9] | § 102 | 1, 3, 5, 7 |
| Kai, Sangekar, and Babcock | § 103 | 1–3, 5–7, 9–14 |
| Kohri, Baert, and Vandecruys | § 103 | 1–3, 5–7, 9–14 |

Petitioner supports its challenges with the Declaration of David W. Grainger, Ph.D., dated June 10, 2016 (Ex. 1005, "Grainger Declaration"),

[6] WO 98/42318 A1, Roger Vandecruys et al., published October 1, 1998 ("Vandecruys") (Ex. 1016).

[7] John E. Thorpe et al., *Effect of Oral Antacid Administration on the Pharmacokinetics of Oral Fluconazole*, 34 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 2032–2033 (1990) ("Thorpe") (Ex. 1020).

[8] Susan Tett et al., *Pharmacokinetics and Bioavailability of Fluconazole in Two Groups of Males with Human Immunodeficiency Virus (HIV) Infection Compared with Those in a Group of Males without HIV Infection*, 39 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 1835–1841 (1995) ("Tett") (Ex. 1021).

[9] C. Lin et al., *Pharmacokinetics and Metabolism of Genaconazole, a Potent Antifungal Drug, in Men*, 40 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 92–96 (1996) ("Lin") (Ex. 1019).

and the Declaration of Terrence F. Blaschke, M.D, dated June 10, 2016 (Ex. 1006, "Blaschke Declaration"). Patent Owner supports its position with the Declaration of Robert A. Bellantone, Ph.D., executed September 19, 2016 (Ex. 2001, "Bellantone Declaration").

*C. The '745 Patent (Ex. 1001)*

The '745 patent, titled "PHARMACEUTICAL COMPOSITIONS FOR POORLY SOLUBLE DRUGS," issued April 19, 2005 to David Hayes and Angelo Mario Morella. The specification describes "pharmaceutical compositions of drugs that are practically insoluble in aqueous media" (Ex. 1001, 1:17–19), e.g., azole antifungal drugs (*id.* at 4:66–5:15). According to the specification, "[b]y utilizing compositions in accordance with the present invention . . . drugs previously considered to present bioavailability problems may be presented in dosage forms with superior bioavailability." *Id.* at 7:22–25.

The specification teaches that "the composition may be in the form of a solid dispersion of the practically insoluble drug and a polymer having acidic functional groups, and the composition may in vitro form a suspension." *Id.* at 2:52–55. "[T]he ratio of drug to polymer may be in the range of from 3:1 to 1:20 . . . [but] ratios in the narrower range of 3:1 to 1:5" or "1:1 to 1:3" or "1:1.5" are preferred. *Id.* at 5:46–50. Further, a particularly preferred polymer is "a polycarboxylic acid such as a hydroxypropyl methylcellulose phthalate such as . . . HP-50, HP-55 or HP-55S." *Id.* at 5:36–40.

Preferably, the "solid dispersion is formed by dispersing or dissolving the drug and the polymer in a suitable solvent, and subsequently spray drying to form the solid dispersion in the form of a powder" (*id.* at 5:58–61) "suitable for use in dosage forms such as tablets or capsules" (*id.* at 5:66).

According to the specification, "where the drug is itraconazole the inventive compositions have produced formulations that . . . have at least twice the bioavailability of, a commercially available itraconazole product (Sporanox™)." *Id.* at 7:27–30. For instance, in a randomized two-way crossover study, eight male volunteers were alternately dosed with a solid dispersion comprising 98 to 102 mg itraconazole and HP-50, and with "100 mg itraconazole as a marketed capsule (Sporanox™)," after an intervening washout period. *Id.* at 9:17–45. The pharmacokinetic performance of the two formulations is shown in the table below:

| Parameter | Example capsule | Sporanox ™ capsule (Lot 98P0800E) | Ratio |
|---|---|---|---|
| $C_{max}$ (ng/ml) | 182.6 | 56.0 | 326% |
| $T_{max}$ (h) | 2.94 | 3.44 | 85.5% |
| AUC (ng.h/ml) | 1776 | 622 | 285% |
| $AUC_{inf}$ (ng.h/ml) | 1875 | 664 | 282% |

*Id.* at 9:50–57. According to the specification, "it can be seen from these results that significantly higher plasma itraconazole levels are obtained from the [test] formulation described in the example than the marketed capsule form under these conditions." *Id.* at 9:59–62.

*D. Illustrative Claims*

Petitioner challenges claims 1–3, 5–7, and 9–14 of the '745 patent, of which claims 1, 5, 9, and 12 are independent claims. Claims 1, 2, and 5, reproduced below, are illustrative.

> 1. A pharmaceutical composition consisting essentially of about 100 mg of an azole antifungal drug and optionally at least one polymer having acidic functional groups wherein in vivo the composition provides a mean $C_{MAX}$ of at least 100 ng/ml, after administration in the fasted state.
>
> 2. A pharmaceutical composition according to claim 1, wherein said at least one polymer having acidic functional groups is present.

Ex. 1001, 10:54–61.

> 5. A pharmaceutical composition consisting essentially of about 100 mg of an azole antifungal drug and optionally at least one polymer having acidic functional groups wherein in vivo the composition provides a mean AUC of at least 800 ng.h/ml, after administration in the fasted state.

*Id.* at 11:1–5.

II. ANALYSIS

*A. Claim Construction*

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b). Under this standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*,

504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Finally, only terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g. Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

For purposes of this Decision, and on this record, only the following terms require explicit construction.

*1. "wherein in vivo the composition provides [a certain $C_{MAX}$ or AUC level], after administration in the fasted state"*

Two issues are raised with respect to the "wherein" clauses of the challenged claims. First, Petitioner and Patent Owner disagree as to whether the wherein clauses are entitled to patentable weight. Pet. 16–19; Prelim. Resp. 18–21. Second, Patent Owner contends that the wherein clauses "relate only to human $C_{MAX}$ and AUC levels." Prelim. Resp. 22.

*a. Patentable Weight*

Petitioner contends that the wherein clauses "are essentially meaningless" and "provide no limitation on the scope of the invention" (Pet. 16) because each of the challenged claims "defines the structure of the invention as 'consisting essentially of 100 mg of an azole antifungal drug

and'—'optionally' or required—'at least one polymer having acidic functional groups'" (*id.* at 17). Petitioner contends that "the claimed compositions are structurally complete" and, therefore, "[t]he addition of $C_{MAX}$ and AUC benchmarks adds nothing to the structure of this putative invention." *Id.*

We do not agree with Petitioner that the claimed compositions are structurally complete without the wherein clauses. A wherein clause is not given patentable weight if it merely expresses the intended result of a process—or in this case, the intended result of administration of the claimed pharmaceutical composition. *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005). But, when the clause states a condition that is material to patentability, it cannot be ignored. *Id.*

Here, each of the challenged claims requires that the pharmaceutical composition include about 100 mg of an unspecified azole antifungal drug (certain claims require at least one polymer with acidic functional groups as well), and the claimed composition must be capable of providing a certain $C_{MAX}$ and AUC level—e.g., at least 100 ng/ml or at least 800 ng.h/ml, respectively. Petitioner does not contend that all compositions containing about 100 mg of an azole antifungal drug would provide the $C_{MAX}$ or AUC profile recited in the wherein clauses. Moreover, there is evidence of record that not all such formulations necessarily provide the $C_{MAX}$ or AUC profile recited. For instance, as shown in Example 2 of the '745 patent, a composition containing 92 to 102 mg of itraconazole in a solid dispersion

with HP-50 provided a $C_{MAX}$ of 182.6 ng/ml and an AUC of 1776 ng.h/ml, while "100 mg itraconazole as a marketed capsule (Sporanox™)" provided a $C_{MAX}$ of only 56.0 ng/ml and an AUC of 622 ng.h/ml. *See* Ex. 1001, 9:17–62.

As a necessary property of the claimed composition, the $C_{MAX}$ and AUC parameters recited in the claims give meaning and purpose to the claims. *See Griffin v. Bertina*, 285 F.3d 1029, 1033–34 (Fed. Cir. 2002). We conclude that the wherein clauses meaningfully limit the claims, and are entitled to patentable weight.

*b. Scope of the Wherein Clauses*

According to Patent Owner, "[t]he $C_{MAX}$ and AUC levels recited in the 'wherein' clauses must be in humans." Prelim. Resp. 21. Patent Owner contends that "the *in vivo* data provided in the patent specification is obtained exclusively from humans" (*id.*), and one of ordinary skill in the art "would understand that these pharmacokinetic limitations are directed to measurements obtained after the inventive compositions are administered to humans" (*id.* (citing Ex. 2001 ¶¶ 70–72)). Patent Owner, supported by the testimony of Dr. Bellantone, further contends that one of ordinary skill in the art "would not consider the human $C_{MAX}$ and AUC levels described in the Challenged Claims to extend to any other animal species, because of the known inter-species variability in pharmacokinetics of a drug, and the recognition in the art . . . that human pharmacokinetics are 'unique.'" *Id.* at 21–22 (citing Ex. 2001 ¶¶ 70–72, 89).

> On the record before us, we are not persuaded.
>
> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment.

*Superguide Corp. v. DirecTV Enterprises, Inc.,* 358 F.3d 870, 875 (Fed. Cir. 2004); *see also Liebel-Flarsheim Co. v. Medrad Inc.,* 358 F.3d 898, 906 (Fed. Cir. 2004) (discussing recent cases where the court expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002) (Even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using "words or expressions of manifest exclusion or restriction.").

Here, although the specification discloses the results of a specific trial involving administration of a particular azole, itraconazole, to humans, the claims do not recite expressly that the pharmacokinetic parameters are in humans, nor, for that matter, do the claims require the particular azole used in the trial. Moreover, in a somewhat different, but related context, the specification states that "[t]he term 'in vivo' in general means in the living body of a plant or animal," and the term "drug" "denotes a compound having beneficial prophylactic and/or therapeutic properties when

administered to, *for example*, humans." Ex. 1001, 3:20–22, 36–37 (emphasis added).

Accordingly, although we agree that the wherein clauses *encompass* pharmacokinetic parameters in humans, we do not agree with Patent Owner that the broadest reasonable interpretation of the wherein clauses limits the claims to pharmacokinetic parameters in humans.

*2. "pharmaceutical composition," "drug," and "azole antifungal drug"*

These meanings of these terms are, to some extent, interrelated, and are discussed below in the context in which they arise. *See* Section II.D.2.

### *B. Admissibility of the Grainger and Blaschke Declarations (Exhibits 1005, 1006)*

Patent Owner contends that "Petitioner's expert declarations are unattested and unsworn, in violation of the Board's Rules" and "are therefore nothing more than inadmissible hearsay." Prelim. Resp. 47. Patent Owner contends that the Grainger and Blaschke Declarations "should be stricken or given no weight." *Id.* at 48.

"Evidence consists of affidavits, transcripts of depositions, documents, and things." 37 C.F.R. § 42.63(a). In particular, "*Affidavit* means affidavit or declaration under § 1.68 of this chapter." 37 C.F.R. § 42.2.

According to 37 C.F.R. § 1.68 (emphasis added):

> Any document to be filed in the Patent and Trademark Office and which is required by any law, rule, or other regulation to be under oath may be subscribed by a written declaration.

> *Such declaration may be used in lieu of the oath otherwise required, if, and only if, the declarant is on the same document, warned that willful false statements and the like are punishable by fine or imprisonment, or both* (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon. The declarant must set forth in the body of the declaration that all statements made of the declarant's own knowledge are true and that all statements made on information or belief are believed to be true.

We agree with Patent Owner that the Grainger and Blaschke Declarations fail to comply with § 1.68—nevertheless, we decline to exclude Exhibits 1005 and 1006 on that basis at this stage of the proceeding. Under 37 C.F.R. § 42.64(b)(1),

> Any objection to evidence submitted during a preliminary proceeding must be filed within ten business days of the institution of the trial. Once a trial has been instituted, any objection must be filed within five business days of service of evidence to which the objection is directed. The objection must identify the grounds for the objection with sufficient particularity to allow correction in the form of supplemental evidence.

And as set forth under 37 C.F.R. § 42.64(B)(2), "[t]he party relying on evidence to which an objection is timely served may respond to the objection by serving supplemental evidence within ten business days of service of the objection."

In this case, we will treat Patent Owner's argument, made in the Preliminary Response, as an objection to Exhibits 1005 and 1006. Inasmuch as Patent Owner's objections were made prior to institution, Petitioner will be afforded ten business days from the date of mailing of this Decision on

Institution to serve supplemental evidence in accordance with 37 C.F.R. § 42.64(b)(2). Assuming the evidence consists of the sworn Declarations of Dr. Grainger and Dr. Blaschke, Petitioner should also file that evidence as exhibits in the proceeding, along with an updated exhibit list.

*C. Admissibility of Kohri, Thorpe, Tett, and Lin (Exhibits 1017, 1020, 1021, and 1019)*

Patent Owner contends that Petitioner has not carried its "burden of demonstrating that the references on which it relies are 'printed publications' within the meaning of 35 U.S.C. §§ 102(b) and 311(b)." Prelim. Resp. 50. Patent Owner contends "[o]ther than baldly reciting the dates printed on the references themselves, Petitioner has provided no evidence regarding the dates Kohri, Thorpe, Tett and Lin were made available to the interested public." *Id.* at 51. According to Patent Owner, the "[t]he printed dates are, however, inadmissible hearsay and cannot establish public accessibility or the date on which the reference was publicly available." *Id.*

Kohri (Ex. 1017) appears to be a duplicate of a journal article published in the periodical "JOURNAL OF PHARMACY AND PHARMACOLOGY," while Thorpe (Ex. 1020), Tett (Ex. 1021), and Lin (Ex. 1019) appear to be duplicates of journal articles published in the periodical "ANTIMICROBIAL AGENTS AND CHEMOTHERAPY." These journal articles appear to fall under at least one, and in some cases two exceptions to the hearsay rule. Thorpe, Tett, and Lin qualify as exceptions to the hearsay rule as they are ancient documents subject to Fed. R. Evid. 803 (C)(16), which applies to documents

at least 20 years old whose authenticity has been established—and, as Thorpe, Tett, and Lin appear to be articles reproduced from periodical journals (*see* Section I.B. above), they are self-authenticating under Fed. R. Evid. 902 (6). In addition, all four exhibits appear to meet the circumstances outlined in Fed. R. Evid. 807, the residual exception to hearsay. For example, the masthead on the first page of each journal article, which includes the name of the journal, the volume number, publication date, and other indicia, provides circumstantial guarantees of trustworthiness. Moreover, the date printed on the first page of each journal article is offered as evidence of a material fact: the date of publication. Additionally, under the circumstances, we are persuaded that admitting the statements as evidence of the date of publication at this stage of the proceeding serves the interests of justice. *See also* Fed. R. Evid. 1001(e); 1003 (defining duplicates and the admissibility of duplicates).

Accordingly, we do not find that Exhibits 1017, 1019, 1020, and 2021 represent impermissible hearsay at this stage of the proceeding, and therefore, decline to exclude them.

*D. Asserted Anticipation by Kai (Ex. 1007)*

Petitioner contends that claims 1–3, 5–7, 9, 11, 12, and 14 are anticipated by Kai. Pet. 20, 23–28. Patent Owner disagrees. Prelim. Resp. 23, 26–32.

*1. Kai (Ex. 1007)*

Kai discloses a solid dispersion technique for improving the oral absorption of the poorly soluble triazole antifungal agent, MFB-1041. Ex. 1007, 568. According to Kai, MFB-1041 "may have therapeutic benefits in aspergillus treatment" (*id.*), but "has low solubility and potentially poor oral absorption characteristics" (*id.*). Kai prepared a "solid dispersion" of MFB-1041 by dissolving the drug in a mixed solvent; adding a polymer to the solution (e.g., HP-55, a preferred polymer of the '745 patent) at a drug-to-polymer ratio of 1:1–1:5; and spray-drying the mixture to obtain a "solid dispersion powder." *Id.* The solid dispersion powder was administered to beagle dogs (10–12 kg each) "*per os* with 20 ml of water under a fasted condition at a dose of 10 mg/kg body weight." *Id.* The pharmacokinetic properties of several different formulations of MFB-1041 are shown in Table 1 below.

Table 1. Pharmacokinetic Parameters of MFB-1041 after Oral Administration to Beagle Dogs

| Dosage forms | $C_{max}$ (μg/ml) | $T_{max}$ (h) | *AUC* (μg/ml h) |
|---|---|---|---|
| Crystal (MC suspension) | — | 0.5 | 1.0 |
| Metolose solid dispersion (1:5) | 0.95 | 4 | 6.0 |
| CMEC solid dispersion (1:5) | 1.73 | 3 | 11.8 |
| HP-55 solid dispersion (1:3) | 1.90 | 2 | 11.8 |
| HP-55 solid dispersion (1:5) | 2.59 | 4 | 16.9 |

Ex. 1007, 570.

*2. Analysis*

*Claims 1–3, 5–7, 9, and 12*

Petitioner contends that Kai discloses administration of 100 mg of MFB-1041, an azole antifungal drug, to dogs (i.e., administration of 10 mg/kg to 10–12 kg dogs), in solid dispersion with hydroxypropyl methylcellulose phthalate ("HP-55") or carboxymethyl cellulose ("CMEC"). Pet. 20, 24 (citing Ex. 1007, 568; Ex. 1005 ¶38). According to Petitioner's declarant, Dr. Grainger, *in vivo* administration of "a composition consisting essentially of 100 mg of an azole antifungal [MFB-1041] and a polymer having acidic functional groups" resulted in "$C_{max}$ values from 1730 ng/ml (1.73 μg/ml) to 2590 ng/ml (2.59 μg/ml), and AUC values from 11800 ng h/ml (11.8 μg h/ml) to 16900 ng/ml (16.9 μg h/ml)—all more than 10 times the minimum benchmarks in claims 1, 5, 9, and 12." Ex. 1005 ¶ 40 (citing Ex. 1007, 570).

Patent Owner contends that "Kai does not disclose a 'pharmaceutical composition' that consists essentially of a 'drug.'" Prelim. Resp. 26. According to Patent Owner, Miyoshi[10] "demonstrates that the MFB-1041 agent of Kai produces clonic convulsions" which "present a serious toxicity that involves repeated violent muscle contractions." *Id.* at 27 (citing Ex. 2009, 1; Ex. 2001 ¶¶ 79–81). Given this purported toxicity, Patent Owner

[10] Toshimi Miyoshi et al., *Effect of Maltosyl-β-cyclodextrin on Drug Binding to Serum Albumin*, 57 J. PHARM SCI. & TECH., JAPAN 174–180 (1997) ("Miyoshi") (Ex. 2009) (English language abstract only).

contends "that MFB-1041 is not a 'drug' that can be used in a 'pharmaceutical composition,'" as those claim terms should be construed. *Id.*

Patent Owner, relying the specification of the '745 patent, and the testimony of Dr. Bellantone, contends that "[t]he plain and ordinary meaning of 'pharmaceutical' is a 'medicinal drug'" (Prelim. Resp. 11 (citing Ex. 2001 ¶¶ 47–48; Ex. 2005, 3)), and "[t]he term 'drug' . . . denotes a compound having beneficial prophylactic and/or therapeutic properties when administered" "which is 'suitable for use as a medication'" (*id.* at 16, 17 (citing Ex. 1001, 3:21–23; Ex. 2001 ¶ 61)). Thus, according to Dr. Bellantone, "the person of ordinary skill in the art would understand that 'azole antifungal drug' in the challenged claims means a compound that is suitable for use as an antifungal medication" (Ex. 2001 ¶ 61), and does not "include compounds without clinically beneficial antifungal properties [or] azole compounds that are unsuitable for administration to patients" (*id.* ¶ 64).

Nevertheless, on the record as it presently stands, we are persuaded that Petitioner shows sufficiently that Kai discloses a pharmaceutical composition consisting essentially of an azole antifungal drug. First, on the present record, we do not agree that the claim terms "drug" and "pharmaceutical composition" should be construed as narrowly as Patent Owner proposes—i.e., we are not persuaded that the broadest reasonable interpretation of "pharmaceutical compositions" and "drugs" excludes

agents with both adverse and beneficial effects. Second, to the extent Miyoshi discloses that MFB-1041 is associated with clonic convulsions in the absence of the solubilizing agent G 2-*β*-CyD, we note that Kai administers MFB-1041 as a solid dispersion with HP-55 or CMEC, and moreover, administers it orally, rather than intravenously. Ex. 1007, 568. On this record, Dr. Bellantone has not addressed the relevance or possible impact of these differences.

Patent Owner further contends that Kai administered MFB-1041 at a dose of 10 mg/kg to 10–12 kg dogs, and thus the dogs "would on average have received a dose exceeding 100 mg."' Prelim. Resp. 27–28. Patent Owner contends, therefore, that Kai does not disclose "about 100 mg" of an azole antifungal drug correlated with $C_{MAX}$ and AUC results. *Id.* at 27. We are not persuaded by this argument. The issue is whether Petitioner has provided evidence sufficient to show that about 100 mg of MFB-1041, administered as the solid dispersion disclosed by Kai, provides a mean $C_{MAX}$ of at least 100 ng/ml and a mean AUC of at least 800 ng.h/ml (or a mean $C_{MAX}$ of at least 150 to 250 ng/ml, and a mean AUC of at least 1300 to 2300 ng.h/ml, in the case of claims 3 and 7) after administration in the fasted state. As noted by Dr. Grainger, administration of a solid dispersion of MFB-1041 in all cases resulted in $C_{MAX}$ and AUC values that exceeded the required levels by more than ten times. Ex. 1005 ¶ 40 (citing Ex. 1007, 570). As at least one of the dogs weighed 10 kg (and therefore received about 100 mg of MFB-1041), we are persuaded that Petitioner has shown sufficiently that Kai

discloses a composition consisting essentially of an azole antifungal drug that meets the requirements of the claims with respect to $C_{MAX}$ and AUC values.

Patent Owner also contends that "Kai does not disclose an 'about 100 mg' dose when Kai's methodology is applied to humans" (Prelim. Resp. 29), "notwithstanding that, as properly construed, the $C_{MAX}$ and AUC limitations of the '745 patent recite human $C_{MAX}$ and AUC values" (*id.* at 31). As discussed above in Section II.A.1.b, however, we do not agree with Patent Owner that the broadest reasonable interpretation of the "wherein" clauses limits the claims to $C_{MAX}$ and AUC values in humans.

Finally, Patent Owner contends that the challenged claims require that the composition provide "a certain $C_{MAX}$ or AUC after administration '***in the fasted state***," but "the Petition never addresses this limitation." Prelim. Resp. 43. This argument is not persuasive. Petitioner's claim chart cites page 568 of Kai, and as discussed above in Section II.D.1, Kai teaches on page 568 that MFB-1041 was administered to beagle dogs (10–12 kg each) "*per os* with 20 ml of water under a fasted condition at a dose of 10 mg/kg body weight."

*Claims 11 and 14*

These claims depend from claims 9 and 12, respectively, and additionally require that the pharmaceutical composition is in the form of a powder. Petitioner notes that Kai discloses that its compositions are in the form of a solid dispersion powder (Pet. 27, 28 (citing Ex. 1007, 568)), and

we are satisfied that Petitioner has shown sufficiently that Kai discloses its pharmaceutical composition in the form of a powder.

In conclusion, on this record, we are persuaded that Petitioner has shown a reasonable likelihood of prevailing in its challenge to claims 1–3, 5–7, 9, 11, 12, and 14 as anticipated by Kai.

*E. Asserted Anticipation by Sangekar (Ex. 1015), Babcock (Ex. 1009), Baert (Ex. 1018), and Vandecruys (Ex. 1016)*

Petitioner contends that each of Sangekar, Babcock, and Baert anticipates claims 1–3, 5–7, and 9–14, and that Vandecruys anticipates claims 1–3, 5–7, 9, 10, 12, and 13. Petitioner acknowledges that "these references do not describe $C_{MAX}$ or AUC results for 100 mg azole doses *in vivo*," but contends that "the 'wherein' $C_{MAX}$ and AUC terms cannot limit the claimed composition." Pet. 23.

As discussed above in Section II.A.1.a, however, we are persuaded that the wherein clauses meaningfully limit the claims, and are entitled to patentable weight. Accordingly, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenges to the claims on the basis of anticipation by Sangekar, Babcock, Baert, or Vandecruys.

*F. Asserted Anticipation by Kohri (Ex. 1017)*

Petitioner contends that claims 1–3, 5–7, 9, 11, 12, and 14 are anticipated by Kohri. Pet. 21, 28–32. Patent Owner disagrees. Prelim. Resp. 24, 33–34.

*1. Kohri*

Kohri discloses administration to rabbits of albendazole in the form of a solid dispersion with certain polymers, e.g., HP-55. Ex. 1017, 159–160. According to Kohri, albendazole "has a wide-spectrum anthelminthic effect" and is "used for treating echinococcosis in man." *Id.* at 159, Abstract.

*2. Analysis*

Petitioner, supported by the testimony of Dr. Grainger and Dr. Blaschke, contends that albendazole is an azole antifungal drug (Pet. 29 (citing Ex. 1005 ¶ 38)), and that Kohri discloses a composition consisting essentially of "about 100 mg" of albendazole (*id.* at 28 (citing Ex. 1017, Table 1)) that meets the "wherein" clauses of the claims with respect to $C_{MAX}$ and AUC (*id.* at 29 (citing Ex. 1006 ¶¶ 21–22)).

Patent Owner contends, among other things, that albendazole is not an azole antifungal drug, but "is 'used for treating echinococcosis in man' and has a 'wide-spectrum anthelminthic effect.'" Prelim. Resp. 33–34 (citing Ex. 1017, 1). According to Patent Owner, echinococcosis "is an infection by parasitic tapeworms" and "[a]n 'anthelminthic effect' is 'destructive to worms.'" *Id.* at 34 (citing Ex. 2001 ¶ 91; Ex. 2011, 3, 5–6).

Having considered the evidence of record, we agree with Patent Owner on this point. As discussed above, Kohri describes albendazole as having a wide-spectrum anthelminthic effect. Dr. Grainger cites Hardin[11] as evidence that albendazole also is an antifungal drug. Ex. 1005 ¶ 38 (citing Ex. 1056). Hardin, however, teaches that albendazole, although exhibiting antifungal activity *in vitro*, is completely lacking in antifungal activity *in vivo*. Hardin suggests that this discrepancy is due to rapid conversion *in vivo* of albendazole to albendazole sulphoxide, which has significant antiparasitic activity, but no antifungal activity. Ex. 1056, 157–158. Given this evidence, we determine that Petitioner has not shown sufficiently that Kohri discloses a composition consisting essentially of an azole antifungal drug.

Accordingly, we determine that Petitioner has not established a reasonable likelihood of prevailing in its challenge to claims 1–3, 5–7, 9, 11, 12, and 14 as anticipated by Kohri.

*G. Asserted Anticipation by Thorpe (Ex. 1020)*

Petitioner contends that claims 1, 3, 5, and 7 are anticipated by Thorpe. Pet. 37–41. Patent Owner disagrees. Prelim. Resp. 24, 33–34.

[11] T.C. Hardin et al., *Discrepancy between in vitro and in vivo antifungal activity of albendazole*, 35 JOURNAL OF MEDICAL & VETERINARY MYCOLOGY 153-158 (1997) ("Hardin") (Ex. 1056).

*1. Thorpe*

Thorpe discloses administration of "a single oral 100-mg capsule of fluconazole," a "bis-triazole which has shown good antifungal activity" in various clinical studies, to healthy male subjects "after an overnight fast," with or without an antacid. Ex. 1020, 2032. The pharmacokinetic parameters for fluconazole with and without an antacid are shown below in Table 1.

TABLE 1. Pharmacokinetic parameters for fluconazole with and without an antacid[a]

| Regimen | $C_{max}$ (μg/ml) | $T_{max}$ (h) | $AUC_{0-\infty}$ (μg · h/ml)[b] | $k_{el}$ ($h^{-1}$) |
|---|---|---|---|---|
| Fluconazole without antacid | 1.70 ± 0.26 (1.41–2.16) | 4.29 ± 2.59 (2–12) | 93.00 ± 13.82 (74–115) | 0.01957 ± 0.0025 (0.0175–0.0258) |
| Fluconazole with antacid | 1.71 ± 0.22 (1.38–2.12) | 5.14 ± 1.88 (2–8) | 92.43 ± 14.57 (75–116) | 0.01964 ± 0.0027 (0.0153–0.0254) |

[a] Values are expressed as means ± standard deviations. Differences between parameters were not statistically significant (see text). Ranges for individual subjects are shown in parentheses ($n$ = 14).
[b] The maximum contributions due to extrapolation from 144 h to infinity were 8.2 and 9.0% for fluconazole without and with the antacid, respectively.

*Id.* at 2033.

*2. Analysis*

Claims 1, 3, 5, and 7 recite that the "polymer having acidic functional groups" is an optional component of the claimed composition. Petitioner contends that Thorpe discloses "a 100 mg dose of an azole antifungal drug alone without a polymer." Pet. 37 (citing Ex. 1020, 2032). Petitioner, relying on the testimony of Dr. Grainger, contends that "Thorpe reports that a 100 mg capsule of fluconazole yielded a 'CMAX (μg/mL)' of '1.70± 0.22,' equal to 1700 ng/mL—more than 10 times the threshold in claim 1" and an 'AUC0->∞ (μg·h/mL)' of '93.00 ± 13.82,' equal to 93000 ng.h/mL—again more than 10 times the threshold in claim 5." Pet. 40, 42 (citing Ex. 1020, 233, Table 1; Ex. 1005 ¶ 42).

Patent Owner does not address Petitioner's contentions, but argues that Petitioner has failed to meet its burden of presenting evidence that Thorpe is a "'printed publication[]' within the meaning of 35 U.S.C. §§ 102(b) and 311(b), and hence prior art." Prelim. Resp. 50.

As discussed above in Section II.C., however, we are not persuaded that Thorpe should be excluded at this stage of the proceeding. Moreover, we have reviewed Petitioner's contentions regarding Thorpe's disclosures, and find them to be supported by the record as it presently stands.

Accordingly, on this record, we are persuaded that Petitioner has shown a reasonable likelihood of prevailing in its challenge to claims 1, 3, 5, and 7 as anticipated by Thorpe.

*H. Asserted Anticipation by Tett (Ex. 1021) and Lin (Ex. 1019)*

Petitioner contends that claims 1, 3, 5, and 7 also are anticipated by each of Tett and Lin. Inasmuch as we already have determined that Petitioner has established a reasonable likelihood of prevailing in its challenge to claims 1, 3, 5, and 7 as anticipated by Thorpe, and we institute review of these claims on that basis, we decline to consider the patentability of claims 1, 3, 5, and 7 on the grounds of anticipation by Tett or Lin. *See* 37 C.F.R. § 42.108(a).

*I. Asserted Obviousness over Kai, Sangekar, and Babcock*

Petitioner contends that the subject matter of claims 1–3, 5–7, and 9–14 would have been obvious over Kai, Sangekar, and Babcock—together

with Kohri, Baert, Vandecruys, Thorpe, Tett, and Lin (with these latter references cited here as "background art"). Pet. 44–50. Patent Owner disagrees. Prelim. Resp. 35–36.

In this challenge, Petitioner contends essentially that the "[t]he differences between the prior art and the '745 patent are non-existent, or at most so small as to be an obvious step for a skilled pharmaceutical chemist to take." Pet. 45. Petitioner notes, however, that "various claims in the ['745] patent have miscellaneous features, including requiring the composition to be in . . . a 'capsule' (claims 10 and 13)" (*id.* at 49), but these "miscellaneous features" are taught by several of the references, and "would have been obvious to a skilled pharmaceutical chemist" (*id.* at 49–50).

Patent Owner contends that "Kai fails to teach or suggest (1) 'a pharmaceutical composition,' (2) 'an azole antifungal drug' and (3) '100 mg.'" Prelim. Resp. 36. Patent Owner contends that "neither Sangekar nor Babcock cure these deficiencies in Kai and Petitioner never claims that they do." *Id.* Patent Owner further contends that "Petitioner also fails to provide sufficient rationales for combining the base and secondary references to arrive at the claimed inventions." *Id.* at 37.

As discussed above, however, on this record, we are persuaded that Petitioner has established a reasonable likelihood of showing that claims 1–3, 5–7, 9, 11, 12, and 14, which require all three of these elements, as well as certain $C_{MAX}$ and AUC parameters, are anticipated by Kai. Moreover, although Kai does not disclose that its pharmaceutical composition "is

present in a capsule," as required by claims 10 and 13, we agree with Petitioner that it would have been obvious for one of ordinary skill in the art to place Kai's solid dispersion powder into a capsule, as Petitioner notes that Sangekar, for example, teaches that a comparable composition comprising a solid solution of a tetrahydrofuran azole antifungal in a polymer matrix "can be manufactured in a tablet or capsule form." Pet. 23–24, 27 (citing Ex. 1015, 2:13–18, 2:24–3:10).

Accordingly, on this record, we are persuaded that Petitioner has shown a reasonable likelihood of prevailing in its challenge to claims 1–3, 5–7, and 9–14 as unpatentable over Kai, Sangekar, and Babcock.

*J. Asserted Obviousness over Kohri, Baert, and Vandecruys*

Petitioner contends that the subject matter of claims 1–3, 5–7, and 9–14 would have been obvious over Kohri, Baert, and Vandecruys—together with Kai, Sangekar, and Babcock as "background art." Pet. 52–55. Patent Owner disagrees. Prelim. Resp. 35–36.

Inasmuch as we already have determined that Petitioner has established a reasonable likelihood of prevailing in its challenge to claims 1–3, 5–7, and 9–14 as unpatentable over Kai, Sangekar and Babcock, and we institute review of these claims on that basis, we decline to consider the patentability of claims 1–3, 5–7, and 9–14 on the ground of obviousness over Kohri, Baert, and Vandecruys. *See* 37 C.F.R. § 42.108(a).

*K. Alleged Failure to Identify All Real Parties-in-Interest*

Patent Owner contends that "the Petition is incurably incomplete because it fails to identify MCI [Merck & Co., Inc.] as a real party-in-interest and is therefore not entitled to the filing date accorded to it in this proceeding." Prelim. Resp. 66.

Patent Owner contends that "Petitioner and MCI share the same corporate identity" (*id.* at 56 (citing Ex. 2043, 2–3)); that "Petitioner 'is a wholly owned subsidiary of [MCI]'" (*id.* at 53 (citing Ex. 2021, 1)); that MCI "executed the Power of Attorney for this Petition" (*id.* (citing Paper 2, 2)); and that "'Merck' lawyers interchangeably represent both petitioner and MCI in legal proceedings before the Board and U.S. Federal Courts" (*id.* at 54, some capitalization omitted (citing Ex. 2030, 1)). Patent Owner notes that it filed "Litigation asserting claims 9 and 12 of the '745 patent against Petitioner and its parent, MCI" (*id.* at 54 (citing Exs. [2]057; 2026; 2027)), and "Petitioner and MCI both jointly filed the same answer to [Patent Owner's] Second Amended Complaint asserting the exact same affirmative defense of patent invalidity" (*id.* (citing Ex. 2028)), and "served the same set of invalidity contentions asserting the same prior art and the exact same grounds of invalidity presented in the Petitioner" (*id.* (citing Ex. 2029)). Accordingly, Patent Owner asserts that "MCI controls Petitioner and maintains the ability to control the Petition." *Id.* at 52.

The Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,759 (Aug. 14, 2014), makes clear that an important factor in determining

whether a party is a real party-in-interest is control or the ability to control the proceeding. At this stage of the proceeding, Patent Owner's assertions and evidence, as yet untested, are insufficient proof of control, and therefore insufficient to establish that MCI is a real party-in-interest.[12]

Accordingly, we are not persuaded that the Petition should be denied on the basis of Patent Owner's assertions and the evidence as it stands thus far.

## III. CONCLUSION

For the foregoing reasons, on this record, we are persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1–3, 5–7, and 9–14 of the '745 patent are unpatentable.

We emphasize that at this stage of the proceeding, we have not made a final determination as to the admissibility of any evidence, the patentability of any challenged claim, or the construction of any claim term.

[12] We suggest that the parties be prepared to address this issue during the initial conference call with the panel (see the Scheduling Order accompanying this Decision).

## IV. ORDER

Accordingly, it is

ORDERED that that pursuant to 35 U.S.C. § 314 an *inter partes* review of claims 1–3, 5–7, and 9–14 of U.S. Patent No. 6,881,745 B2 is hereby instituted on the following grounds:

Claims 1–3, 5–7, 9, 11, 12, and 14 under 35 U.S.C. § 102 as anticipated by Kai;

Claims 1, 3, 5, and 7 under 35 U.S.C. § 102 as anticipated by Thorpe; and

Claims 1–3, 5–7, and 9-14 under 35 U.S.C. § 103 as obvious over Kai, Sangekar, and Babcock; and

FURTHER ORDERED that the trial is limited to the grounds identified above and no other ground is authorized; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the ’745 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of trial.

For PETITIONER:

Jane M. Love
GIBSON, DUNN & CRUTCHER LLP
jlove@gibsondunn.com

For PATENT OWNER:

Jeremy Lowe
Jonathan Harris
AXINN, VELTROP & HARKRIDER LLP
jlowe@axinn.com
jharris@axinn.com