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

_____

Inter Partes Review No. IPR2016-___

U.S. Patent No. 6,881,745

Title:

Pharmaceutical Compositions for Poorly Soluble Drugs

PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 6,881,745

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TABLE OF CONTENTS

EXHIBIT LIST

Exhibit	Reference
1001	U.S. Patent No. 6,881,745 ("'745 Patent")
1002	File History of International Patent Application No. PCT/AU00/01592 ("the PCT application file history")
1003	File History of U.S. Patent Application No. 10/175,883 ("the '883 file history")
1004	File History of U.S. Patent Application No. 10/461,503, subsequently granted as U.S. Patent No. 6,881,745 ("the '745 file history")
1005	Declaration of David W. **Grainger**, Ph.D. in Support of the Petition for *Inter Partes* Review of U.S. Patent No. 6,881,745 ("Grainger Decl.")
1006	Declaration of Terrence F. **Blaschke**, M.D. in Support of the Petition for *Inter Partes* Review of U.S. Patent No. 6,881,745 ("Blaschke Decl.")
1007	Kai, et al., *Oral Absorption Improvement of Poorly Soluble Drug Using Solid Dispersion Technique*, Chemical and Pharmaceutical Bulletin, 44(3): 568-571 (1996) ("Kai")
1008	Sheehan, et al., *Current and Emerging Azole Antifungal Agents*, Clinical Microbiology Reviews, 12(1): 40-79 (1999) ("Sheehan")
1009	European Patent Office Publication 1 027 886 A2 ("Babcock")
1010	Kondo, et al., *Improved Oral Absorption of Enteric Coprecipitates of a Poorly Soluble Drug*, Journal of Pharmaceutical Sciences, 83(4): 566-570 (1994) ("Kondo")
1011	Yamaguchi, et al., *Improvement of Pharmaceutical Properties of 4''-O-(4-methoxyphenyl)acetyltylosin Using Solid Dispersion with Carboxymethylethylcellulose*, Yakuzaigaku, 53(4): 221-228 (1993) ("Yamaguchi")
1012	U.S. Patent No. 5,340,591 ("Nakano")
1013	Simoni, et al., *Bioavailability Study of a New, Sinking, Enteric-Coated Ursodeoxycholic Acid Formulation*, Pharmaceutical Research, 31(2): 115-119 (1995) ("Simoni")
1014	PCT Publication No. WO00/40220 ("Yuk")
1015	PCT Publication No. WO98/00113 ("Sangekar")
1016	PCT Publication No. WO98/42318 ("Vandecruys")
1017	Kohri, et al., *Improving the Oral Bioavailability of Albendazole in*

Exhibit	Reference
	Rabbits by the Solid Dispersion Technique, Journal of Pharmacy and Pharmacology, 51: 159-164 (1999) ("Kohri")
1018	U.S. Patent No. 6,509,038 ("Baert")
1019	Lin, et al., *Pharmacokinetics and Metabolism of Genaconazole, a Potent Antifungal Drug, in Men*, Antimicrobial Agents and Chemotherapy, 40(1): 92-96 (1996) ("Lin")
1020	Thorpe, et al., *Effect of Oral Antacid Administration of the Pharmacokinetics of Oral Fluconazole*, Antimicrobial Agents and Chemotherapy, 34(10): 2032-2033 (1990) ("Thorpe")
1021	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*, Antimicrobial Agents and Chemotherapy, 39(8): 1835-1841 (1995) ("Tett")
1022	Curriculum Vitae of Terrence F. Blaschke, M.D. ("Blaschke CV")
1023	Curriculum Vitae of David W. Grainger, Ph.D. ("Grainger CV")
1024	Durden and Elewski, *Fungal infections in HIV-Infected Patients*, Seminars in Cutaneous Medicine and Surgery, 16(3): 200-212 (1997) ("Durden")
1025	ALBENDAZOLE MONOGRAPH, THE MERCK INDEX, 12th Edition (1996), *available at* https://www.rsc.org/Merck-Index
1026	Lipinski, et al., *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings*, Advanced Drug Delivery Reviews, 23: 3-25 (1997) ("Lipinski")
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1028	Oh, et al., *Estimating the Fraction Dose Absorbed from Suspensions of Poorly Soluble Substances in Humans: A Mathematical Model*, Pharmaceutical Research, 10(2): 264-270 (1993) ("Oh")
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1030	Hörter and Dressman, *Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract*, Advanced Drug Delivery Reviews, 25(1): 3-14 (1997) ("Hörter")
1031	Amidon, et al., *A Theoretical Basis for a Biopharmaceutic Drug*

Exhibit	Reference
	Classification: The Correlation of in Vitro *Drug Product Dissolution and* in Vivo *Bioavailability*, Pharmaceutical Research, 12(3): 413-420 (1995) ("Amidon")
1032	Serajuddin, *Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs*, Journal of Pharmaceutical Sciences, 88(10): 1058-1066 (1999) ("Serajuddin")
1033	Löbenberg, et al., *Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards*, European Journal of Pharmaceutics and Biopharmaceutics, Vol. 50: 3-12 (2000) ("Löbenberg")
1034	Williams, et al., *Strategies to Address Low Drug Solubility in Discovery and Development*, Pharmacological Reviews, 65: 315-499 (2013) ("Williams")
1035	Diflucan ® (Fluconazole) Label, Pfizer (March 2013) ("Diflucan Label")
1036	Gordon, et al., *In vivo and in vitro evaluation of four different aqueous polymeric dispersions for producing an enteric coated tablet*, International Journal of Pharmaceutics, 11: 29-34 (1995) ("Gordon")
1037	Hasegawa, et al., *Application of Solid Dispersions with Enteric Coating Agents to Overcome Some Pharmaceutical Problems*, Chemical and Pharmaceutical Bulletin, 34(5): 2183-1290 (1986) ("Hasegawa")
1038	Hostetler, et al., *Effect of Cyclodextrin on the Pharmacology of Antifungal Oral Azoles*, Antimicrobial Agents and Chemotherapy, 36(2): 477-480 (1992) ("Hostetler")
1039	Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, 2nd Edition (1997)
1040	PCT Publication No. WO94/05263 ("Gilis")
1041	Augsburger, *Hard and Soft Gelatin Capsules*, *in* Modern Pharmaceutics, 4th Edition (2002) ("Augsburger")
1042	U.S. Patent No. 4,198,391 ("Grainger Patent")
1043	Patel, et al., *Advances in softgel formulation technology*, Manufacturing Chemist, 60: 26-28 (1989).
1044	Saano, et al., *Relative pharmacokinetics of three oral 400 mg ibuprofen dosage forms in healthy volunteers*, International Journal

Exhibit	Reference
	of Clinical Pharmacology, Therapy, and Toxicology, 29(10): 381-385 (1991) ("Saano")
1045	Salonen et al., *A comparison of the soft gelatin capsule and the tablet form of temazepam*, Acta pharmacologica et toxica, 58(1): 49-54 (1986) ("Salonen")
1046	U.S. Patent Application No. 10/572,984 ("Podili")
1047	Stegemann, Hard gelatin capsules today – and tomorrow, 2nd Edition (2002) ("Stegemann")
1048	U.S. Pharmacopeia, USP Pharmacists' Pharmacopeia, 2nd Edition (3rd Supp. 2009) ("Pharmacopeia")
1049	BASF, Kollicoat® MAE grades (November 2010) ("BASF")
1050	Ashland, AquaSolve™ Hypromellose Acetate Succinate (HPMCAS) ("Ashland")
1051	Brass, et al., *Disposition of Ketoconazole, an Oral Antifungal, in Humans*, Antimicrobial Agents and Chemotherapy, 21(1): 151-158 (1982) ("Brass")
1052	Chiou and Reigelman, *Pharmaceutical Applications of Solid Dispersion Systems*, Journal of Pharmaceutical Sciences, 60(9): 1281-1302 (1971) ("Chiou")
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1054	Bodey, *Azole Antifungal Agents*, Clinical Infectious Diseases, 14 (Supp. 1): S161-S169 (1992) ("Bodey")
1055	Handbook of Pharmaceutical Excipients, 6th Edition (2009)
1056	Hardin, et al., *Discrepancy between in vitro and in vivo antifungal activity of albendazole*, Journal of Medical and Veterinary Mycology, 35: 153-158 (1997) ("Hardin")
1057	Mayne Pharma International Pty Ltd.'s Complaint against Merck & Co., Inc., Merck Sharp & Dohme Corp, and N.V. Organon, dated May 29, 2015 in the District of Delaware, C.A. No. 15cv-438.
1058	Proof of Service on Merck & Co., Inc. and Merck Sharpe & Dohme Corp., dated June 12, 2016 in connection with C.A. No. 15-cv-438 (D. Del.)

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

Regulations

INTRODUCTION

This petition seeks *inter partes* review of U.S. Patent No. 6,881,745. (Ex. 1001.) The Examiner allowed the '745 patent's claims after only a brief examination before recognizing on-point prior art that he later relied on to rightly reject far narrower claims in the parent application as obvious. The Board should correct that oversight and cancel the '745 patent claims at issue here.

The '745 patent broadly claims a pharmaceutical composition consisting essentially of 100 mg of an "azole" type compound with antifungal properties and polymers containing "acidic functional groups." This combination seeks to enhance the azole's bioavailability—that is, its ability to be absorbed into the body. Such compositions had been in the art for many years before Patent Owner Mayne Pharma filed the '745 patent application in December 1999.

Since the mid-1980s, researchers had focused intently on improving azole antifungal bioavailability in response to the AIDS epidemic. HIV infection resulted in opportunistic and rampant, often fatal, fungal infections in AIDS patients. Multiple references before 1999 accordingly discussed how to improve bioavailability, including by mixing azoles with acid-resistant polymers. The '745 patent specification acknowledged much of this art, and the parent application accordingly claimed only a narrower azole-polymer "solid dispersion" made with special mixing techniques.

Despite these narrow claims, and further amendments, the Examiner rejected the parent claims as obvious over a journal article by Kai, et al. and a patent publication by Sangekar, each of which had already disclosed exactly such compositions. (Exs. 1007 ("Kai") and 1015 ("Sangekar").) Mayne spent five years trying to persuade the Examiner otherwise, but ultimately abandoned the parent. Early in those five years, however, Mayne filed a child application. The child had the identical specification focused on solid dispersions, but presented new, broader claims that eliminated the solid dispersion idea. The child thus laid sweeping claim to any composition consisting essentially of about 100 mg of any antifungal azole and any polymer having acidic functional groups—notwithstanding that Kai, Sangekar and many other references had already disclosed such compositions years earlier.

Long before December 1999, pharmaceutical chemists had learned how to improve the bioavailability of poorly soluble drugs like certain azoles by mixing them with polymers. Multiple references showed how these mixtures kept the drug particles small enough to be absorbed by a body. Acid-resistant polymers could further protect sensitive active ingredients from stomach acid before reaching the small intestine. Numerous published reports showed how such compositions could improve bioavailability as measured by standard metrics called "C_{MAX}" and the "Area Under the Curve" (or "AUC").

The Examiner unfortunately does not appear to have considered Kai, Sangekar or other on-point references before quickly allowing the broad claims in the child application. The Examiner first applied these references only afterward during the longer examination of the parent application. He then rightly found that Kai and Sangekar had already disclosed the putative invention and repeatedly rejected the narrower solid dispersion claims. The Board should correct the Examiner's oversight. Kai and Sangekar are but two of many references that invalidate the claims challenged here.

Nine references below either anticipate the '745 patent claims, or render the claims obvious to a skilled pharmaceutical chemist before December 1999. Merck thus seeks institution of an *inter partes* review to cancel claims 1–3, 5–7, and 9–14 of the '745 patent (none of which is specific to any azole), on the following grounds:

- **Grounds 1-6: Section 102 Anticipation (Kai, Sangekar, Kohri, Babcock, Baert and/or Vandecruys)**: Each of these references describes compositions consisting essentially of 100 mg of an azole plus acid-resistant polymers, exactly the invention claimed in the '745 patent.
- **Grounds 7-9: Section 102 Anticipation (Thorpe, Tett, and/or Lin)**: Each of these references anticipates claims 1, 3, 5 and 7 by disclosing 100 mg of an azole alone. These particular claims make an acid-resistant

polymer "optional"; as a result, prior art showing a 100 mg dose of an azole anticipates.

- **Ground 10: Section 103 Obviousness (Kai plus Sangekar and Babcock)**: These references together would have made the composition here blindingly obvious to a pharmaceutical chemist in late 1999. All three focus on azole antifungal compositions with polymers to improve bioavailability.
- **Ground 11: Section 103 Obviousness (Kohri plus Baert and Vandecruys)**: Likewise, these references show pharmaceutical chemists knew how to mix poorly soluble azoles with acid-resistant polymers to improve bioavailability, and that such mixtures would work.

In several claims, Mayne injected "wherein" clauses purporting to require the compositions to meet certain C_{MAX} or AUC benchmarks or ranges *in vivo*. These clauses, however, are legal nullities. They add nothing to the chemical structure of the composition. Indeed, most claims set the benchmark so low that the limit is illusory for many azoles. In any event, even if deemed limiting, many references report results that easily satisfy the benchmarks.

There is a reasonable likelihood that claims 1–3, 5–7, and 9–14 of the '745 patent are invalid, and the Board should institute an *inter partes* review, and cancel the challenged claims.

FACTS

A. The State of the Art in Azole Compositions as of December 1999

In the midst of the 1980's AIDS epidemic, aggressive fungal infections killed many AIDS patients. Fungal infections were also becoming more common as the side effects of increasingly frequent medical treatments, such as cancer chemotherapy and long-term catheter use. (Ex. 1005, at ¶ 12.)

Researchers accordingly focused intently on improving antifungal treatments. Their attention turned to antifungal compounds containing an "azole" ring that had existed since the 1940s. Some azoles, however, tend to be poorly soluble, clumping together and resist absorption into the body. This problem was not unique to azoles, and pharmaceutical chemists had published multiple techniques for solving this problem. (Ex. 1005, at ¶ 17-20.)

Most pertinent here, researchers had discovered that mixing poorly soluble drugs with various polymers could reduce clumping and enhance bioavailability. These techniques are discussed in many prior art references, such as Babcock (Ex. 1009, pub. 1999), Kondo (Ex. 1010, pub. 1999), Yamaguchi (Ex. 1011, pub. 1993), Nakano (Ex. 1012, pub. 1994), Simoni (Ex. 1013, pub. 1994), and Yuk (Ex. 1014, pub. 1999). Researchers had successfully implemented these techniques with azoles in reported experiments well before December 1999. (*See, e.g.*, Ex. 1005, at ¶¶ 18-23.)

The ’745 patent specification acknowledges this prior art, pointing to patent applications by Janssen, the Kai reference, and other sources. (*See* Ex. 1001, at 1:25-2:25.) For instance, the specification admits that Kai discloses an azole with “HP-55” (a polymer with acidic functional groups), resulting in the drug being “fully dissolved (supersaturated)” and thus bioavailable at pH 6.8 (the pH of the small intestine). (Ex. 1001, at 1:63-2:11.) Many other publications also described how to mix azoles with acid-resistant polymers well before Mayne filed the application for the ’745 patent. Kohri (Ex. 1017, pub. 1999), Sangekar (Ex. 1015, pub. 1996), Baert (Ex. 1018, pub. 1997), and Vandecruys (Ex. 1016, pub. 1998) all described such compositions before Mayne’s December 1999 priority date, as shown further below.

B. Mayne Applies for a Solid Dispersion Composition Patent in December 1999

Mayne filed two Australian priority patent applications, its first on December 23, 1999. (Ex.1001, at 1:4-13.) Mayne combined those two into a PCT application PCT/AU00/01592 filed in December 2000, which in turn led to a U.S. continuation, Serial No. 10/175,883. (*Id*.) That ’883 parent application led to two child applications: U.S. Serial Nos. 10/461,503 (Ex. 1004 (“the ’745 file history”)) and 11/763,578. The ’503 application ultimately yielded the ’745 patent. (*Id*.)

From the outset, Mayne admitted that the prior art disclosed azole-polymer compositions, as they set out the Background art. (Ex. 1002, at 2-3.) The

specification goes on to emphasize a solid dispersion as the invention's essence, featured presumably to distinguish the prior art. The '745 patent specification is essentially identical to the PCT. The Summary of Invention describes various processes that a skilled chemist could use to make a solid dispersion. (*See, e.g.*, Ex. 1001, at 5:51-6:24.) Every example similarly focuses on a solid dispersion. Examples 1 and 2 describe how to "produce a solid dispersion," and Example 3 just elaborates on Example 2. Nearly every mention of the "present invention" in the specification includes the phrases "solid dispersion…that may form a suspension in vitro." (*See, e.g.*, Ex. 1001, at Abstract; 2:53-55; 2:64-3:2; 3:58-3:64; 5:19-24; 7:35-41; 7:45-51.)

In both the PCT and the first or parent U.S. application, Mayne presented claims to a solid dispersion composition and methods for making such a solid dispersion. For example, claim 1 recited "[a] pharmaceutical composition in the form of a solid dispersion of a practically insoluble drug and a polymer having acidic functional groups, wherein *in vitro* the composition forms a suspension." (Ex. 1002, at 22.) Even as to the putatively narrow solid dispersion claims, an International Search Report for the PCT identified five "X references," *i.e.*, references that were "novelty destroying." (Ex. 1002, at 31-32.) Among these were Kai (Ex. 1007) and Sangekar (Ex. 1015). Notwithstanding the Search

Report, Mayne did not amend any claims, and prosecution entered the U.S. national stage.

Like the PCT, the U.S. '883 parent application claimed solid dispersion compositions of an azole and a polymer having acidic functional groups. (*See, e.g.*, Ex. 1003 ("the '883 file history"), at 37.) In spite of Mayne's effort to tailor its claims narrowly, the Examiner repeatedly rejected them as obvious in light of Kai and Sangekar, each of which discloses an azole-polymer mix in a solid dispersion. For instance, in the Office Action dated May 20, 2005, the Examiner found that Kai taught to add "a polymer (hydroxypropyl methyl cellulose phthalate) to [a] solvent (methylene chloride, ethanol)[,]" then to "add[] triazole to the polymer-solvent mixture," and then to "spray dry[] to form [a] solid dispersion of triazole in [a] hydroxylpropylmethyl celulose phthalate polymer." (*See* Ex. 1003, at 454-60.)

Mayne repeatedly tried to amend its claims and persuade the Examiner the invention could overcome the rejections based on Kai and Sangekar. (*See, e.g.*, September 13, 2006 Applicant Remarks, Ex. 1003, at 553-64.) In doing so, however, Mayne tellingly never tried to distinguish Kai or Sangekar as not disclosing azoles or polymers with acidic functional groups. Nor did Mayne ever disagree that Kai and Sangekar disclosed a solid dispersion. Instead, Mayne argued its invention constituted a new way of making a solid dispersion that

resulted in a composition with different physical properties than the prior art compositions.

For example, Mayne argued that "[t]he pharmaceutical composition of the ['883 application] is prepared in a fundamentally different manner to that of the composition disclosed in Kai, and as such the prior art composition would not have the physical properties of forming into a suspension *in vitro*[.]" (Ex. 1003, at 468.) Mayne argued further that, whereas Kai teaches preparing a solid dispersion by dissolving an azole into a solvent and then adding a polymer, Mayne's claimed composition dispersed "a polymer … in an organic solvent… and then add[ed] the practically insoluble drug (itraconazole) to the polymer dispersed in the solvent." (Ex. 1003, at 468.)

After six rejections over five years, Mayne ultimately abandoned the '883 application in July 2007. (Ex. 1003, at 595-597.)

C. The '745 Patent Issues with Broad Claims not Limited to Solid Dispersions

However, less than a year after filing the '883 application—and well before the Examiner first rejected the claims there as obvious in light of Kai and Sangekar—Mayne had filed the '503 child application that ultimately became the '745 patent. (Ex. 1004, at 1.) In the child application, Mayne dropped the solid dispersion limitation and instead sweepingly claimed a composition consisting essentially of *any* azole and *any* polymer with acidic functional groups, regardless

how the mix is prepared. In some claims, the polymer is even optional, pursuant to an Examiner's amendment. (*See, e.g.*, Ex. 1004, at 112.)

Unlike the parent application's five-year odyssey, the '503 application had only one office action, a rejection citing neither Kai nor Sangekar. Mayne overcame that rejection with a brief response. Less than a year after filing the application, Mayne was awarded the '745 patent. (Ex. 1004, at 107-108, 128-129.)

The '745 patent has 16 claims each directed to a pharmaceutical composition "consisting essentially" of an antifungal azole and at least one polymer (sometimes optional) with "acidic functional groups." Several "wherein" clauses recite the composition's *in vivo* C_{MAX} and AUC bioavailability benchmarks. The claims are challenged here not limited to any particular azole, composition dosage form (such as liquid or solid), subject to which the composition is administered (such as a human or an animal), or polymer. (Ex. 1001, at 10:54-12:48.)

Although Mayne had disclosed both Kai and Sangekar, the Examiner never substantively addressed either reference before allowing the '503 application's claims. The first record of the Examiner focusing on these references in assessing the parent claims is not until well after allowing the '503 application's claims.[1]

[1] The '503 application was allowed on August 12, 2004 (Ex. 1004, at 110-111), whereas Kai and Sangekar were first substantively addressed in a '883 application Office Action on May 20, 2005 (Ex. 1003, at 454-459).

ANALYSIS AND GROUNDS

The Board should institute an IPR as there is more than "a reasonable likelihood" that "at least 1 of the claims challenged" is invalid. 35 U.S.C. § 314(a). The Board should cancel claims 1-3, 5-7, and 9-14 of the '745 patent because the "preponderance of the evidence" shows these claims to be invalid 35 U.S.C. § 316(e).

In the remainder of this analysis, Part I defines a person of ordinary skill in the art for purposes of evaluating the '745 patent, and identifies proposed constructions for four claim terms. Part II then sets forth anticipation Grounds 1-9, and Part III sets forth obviousness Grounds 10 and 11.

THE PERSON OF SKILL IN THE ART AND CLAIM CONSTRUCTION

Pending the Supreme Court's review in *In re Cuozzo Speed Techs., LLC.*, 793 F.3d 1268 (Fed. Cir. 2015), *cert. granted*, 136 S.Ct. 890 (2016),[2] expired patents "'are to be given their broadest reasonable interpretation consistent with the specification, and … claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art.'" *In re Academy of*

[2] The Supreme Court heard oral arguments in *Cuozzo* on April 25, 2015, but has not yet handed down a decision as of the date of this filing. Because the claim construction standard here is broader than in U.S. district court, Merck reserves the right to argue a different claim construction in district court proceedings for any term of the '745 Patent.

Science Tech Center, 367 F.3d 1359, 1364 (Fed. Cir. 2004) (quoting *In re Bond*, 910 F.2d 831 (Fed. Cir. 1990).); *see also* 37 C.F.R. § 42.100(b).

Here, a person of ordinary skill would have been a pharmaceutical chemist as of December 1999, as defined below; and Merck construes four terms: (1) "consisting essentially of"; (2) "azole antifungal drug"; (3) "polymer having acidic functional groups"; and (4) "wherein in vivo the composition provides [a certain C_{MAX} or AUC level], after administration in the fasted state."

D. Person of Skill in the Art—the Skilled Pharmaceutical Chemist

Factors relevant to the "level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (internal citations omitted). "These factors are not exhaustive but are merely a guide to determining the level of ordinary skill in the art." *Id*.

Expert chemist Dr. David Grainger, Ph.D., submits a declaration with this Petition that describes the qualifications of a person of ordinary skill in December 1999. Such person would have been a pharmaceutical chemist with (1) an advanced scientific degree such as a Ph.D., M.D., Pharm D., or a Master's degree in chemistry, biochemistry, pharmacology, pharmaceutics, or a related field; or (2)

equivalent experience in chemistry, biochemistry, pharmacology, pharmaceutics, or a related field with experience in developing pharmaceutical formulations, optionally with a focus on formulations of poorly soluble drugs. (Ex. 1005, at ¶¶ 28-29.)

These qualifications are not rigid. Greater education or a specific skill may make up for less experience, and vice-versa. Moreover, one individual need not have every qualification. A multidisciplinary with the necessary expertise in its ranks would suffice. Such a team could include—and a physical chemist would draw upon the skills of—a clinician having experience in treating antifungal infections. (Ex. 1005, at ¶ 29.)

E. Claim Construction

In considering claim construction, the Board should give the words of the claim their plain meaning, unless such meaning is inconsistent with the specification and prosecution history. *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). The PTAB may also refer to extrinsic evidence to support its claim constructions, including expert testimony. *Game Show Network, LLC v. John H. Stephenson,* IPR2013-00289, Paper 51 at 10 (PTAB Nov. 7, 2014) (Board reviewed expert testimony regarding how POSA would interpret specification, giving more weight to expert testimony that was "consistent with the words from the specification).

"consisting essentially of"

The term "consisting essentially of" occurs in each independent claim (1, 5, 9, and 12). This term is typically a transitional phrase that limits a claim's scope to the specified materials or steps and permits inclusion of other element that would not materially affect the basic and novel characteristics of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, (CCPA 1976). Where the specification fails to define the basic and novel characteristics of the invention, however, "consisting essentially of" shall be construed as the open-ended term "comprising." *See, e.g.*, *Ex parte Miller*, 2015 WL 1871396, at *2 (PTAB Apr. 21,. 2015).

Here, the specification focuses on a different invention than what the '745 patent actually claims. The specification is about a "solid dispersion," but the '745 patent does not claim a solid dispersion. In focusing on a different invention, the specification never discloses the allegedly novel characteristics of the claimed invention. Without that description or other definition—and the specification has none, as it does not even mention the term "consisting essentially of"—the Board should construe "consisting essentially of" as coextensive with the open-ended term "comprising."

Alternatively, the Board should construe the term at the very least to encompass compounds specifically identified in the claims and specification as possible ingredients, including traditional excipients such as "disintegrants,

diluents, fillers, lubricants, glidants, colourants and flavours [*sic*]" (Ex. 1001, at 6:37-7:7; *see also* Claims 9, 12, 15, 16), as well as solvents, such as "methylene chloride, chloroform, ethanol, methanol, propan-2-ol, ethylacetate, acetone, water or mixtures thereof." (Ex. 1001, at 5:61-64; *see also* Claims 9, 12, 15, 16.)

"azole antifungal drug"

The term "azole antifungal drug" is in claims 1, 3, 5, 7, 9, and 12. As Dr. Grainger shows (at ¶ 14), a skilled pharmaceutical chemist would understand the term to mean "a five-membered heterocyclic compound containing at least one nitrogen atom and at least one other non-carbon atom having antifungal properties." The '745 patent recites only two species of such drugs: itraconazole and saperconazole. (*E.g.*, Ex. 1001, at 5:1-2.) The patent's claims, however, are not limited to these azoles and instead sweep broadly to include *any* azole antifungal. Dr. Grainger identifies examples of other azole antifungals in the prior art. (Ex. 1005, at ¶ 13.)

"polymer having acidic functional groups"

The term "polymer having acidic functional groups" is in each independent claim (1, 5, 9, and 12). As Dr. Grainger shows (at ¶ 19), a skilled pharmaceutical chemist would understand that term as follows:

- "polymer": "a chemical compound that is made of small molecules arranged in repeating structure, bonding together to form a larger molecule";
- "having": "possessing or forming in the body after administration at least one"; and
- "acidic functional groups": "a specific group of atoms or arrangement of bonds in a molecule that when exposed to aqueous milieu produce acidic behavior."

Claims 15 and 16, as well as the specification, identify examples (including preferred examples) of polymers with acidic functional groups, such as hydroxypropyl methylcellulose phthalate (also known as HP-55), carboxymethyl cellulose, cellulose acetate phthalate, and cellulose acetate trimellitate, among others. (*E.g.*, Ex. 1001, at 5:24-44.)

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

The term "wherein in vivo the composition provides [a certain C_{MAX} or AUC level], after administration in the fasted state" is in each independent claim (1, 5, 9, and 12). In the context of a composition patent like this one, these terms are essentially meaningless—they provide no limitation on the scope of the invention. The Board accordingly should construe this term as non-limiting here.

"A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim." *Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165. 1172 (Fed. Cir. 1993). "In the same manner as a claim preamble, whether a 'whereby' or a 'wherein' clause provides additional limitations to a claim depends on the context of its use; a fact-specific inquiry." ROBERT A. MATTHEWS, JR., 1 ANNOTATED PATENT DIGEST § 5:29.. In particular, such clauses are generally not limiting "'where a patentee defines a structurally complete invention in the claim body[.]'" *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)). This law is long-settled. *See Application of Gardiner*, 171 F.2d 313 (CCPA 1948) (in construing a whereby clause, "[i]t is trite to state that the patentability of apparatus claims must be shown in the structure claimed and not merely upon a use, function, or result thereof").

So it is here. The body of each '745 patent claim with a "wherein" clause 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[.]" (Ex. 1001, at 10:54-12:48.) The claimed compositions are structurally complete. The addition of C_{MAX} and AUC benchmarks adds nothing to the structure of this putative invention. With or

without those benchmarks, the claimed composition would still "consist essentially of" the claimed azole and either an optional or required polymer.

Nor is there anything in the claims or specification to suggest that the clauses have any practical significance. To the contrary, Mayne recites the exact same C_{MAX} and AUC benchmarks regardless of whether the azole is actually mixed with a polymer—the clauses apply with equal force to the claims where a polymer is "optional" as to the claims where a polymer is required. Put differently, the benchmarks add essentially nothing to the core composition invention of an azole plus an acid-resistant polymer.

Multiple prior art references in fact reported experiments with some azoles alone—*not* mixed with polymers to improve absorption—showing C_{MAX} and AUC results far exceeding the patent's low thresholds. (*See* Exs. 1019-21.) That is not surprising. As the accompanying declaration from Dr. Blashcke shows (*See* at ¶ 15-16), the benchmarks are set so low as to be almost illusory for many azoles—they could be triggered by even extremely low dosages in many cases.

The specification accordingly never once explains why the C_{MAX} and AUC terms might matter to the claimed invention's novelty. Just the opposite: the specification is limited to discussing a different putative invention for a "solid dispersion." Nor were the "wherein" terms ever argued to the Examiner as a basis for distinguishing prior art. The Examiner's reasons for allowance accordinglysay

nothing about these clauses. In these circumstances, only one construction is possible: the wherein clauses do not limit the claims and thus have no bearing on the claims' validity.

MULTIPLE REFERENCES ANTICIPATED THE '745 PATENT CLAIMS AT ISSUE

F. Anticipation Standards

Under 35 U.S.C. § 102, if a single prior art reference discloses each and every limitation of the claimed invention, the patent is anticipated and invalid. *Schering Corp. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (internal citation omitted). Applying these standards, multiple prior art references plainly anticipated the '745 patent claims challenged here, in whole or in part. First, six individual references—Kai, Sangekar, Kohri, Babcock, Baert and Vandecruys—each alone contains all of the limiting elements for nearly every claim. Second, three other individual references—Thorpe, Tett and Lin—each alone contains the limiting elements of the claims for which the addition of a polymer to the azole is "optional"—claims 1, 3, 5 and 7.

G. Anticipation Grounds

Grounds 1-6: Kai, Sangekar, Kohri, Babcock, Baert and Vandecruys each Anticipate the Challenged Claims

Kai (Ground 1), Sangekar (Ground 2), Kohri (Ground 3) Babcock (Ground 4), Baert (Ground 5), and Vandecruys (Ground 6) are each prior art references that anticipate the '745 patent.

Each reference discloses the '745 patent's basic composition, about 100 mg of an azole plus a polymer having acidic functional groups:

- **Kai (Ground 1)** is a 1996 article. (Ex. 1007, at 568.) Kai employs 100 mg of the triazole MFB-1041, which Dr. Gainger confirms is an azole antifungal drug covered by the '745 patent (Ex. 1005 at ¶ 38). Kai combines MFB-1041 with either hydroxypropyl methylcellulose phthalate ("HP-55") or carboxymethyl cellulose ("CMEC") (Ex. 1007, at 568), each of which the '745 patent identifies as a qualifying polymer (Ex. 1001, at 5:24-44); HP-55 is even "particularly preferred" in the '745 patent (*Id*. at 5:37-44).
- **Sangekar (Ground 2)** is a patent application published under the Patent Cooperation Treaty ("PCT application"), filed in 1997 and published in 1998. (Ex. 1015, at 1.) Sangekar employs 100 mg dosage forms of an azole called "Formula 1" or a "tetrahydrofuran azole antifungal," which

Dr. Grainger confirms is an azole antifungal drug covered by the '745 patent. (Ex. 1005, at ¶ 38.) Sangekar further identifies several polymers (at 3:2-10) to mix with the azole that are also identified in the '745 patent as containing acidic functional groups, such as methacrylic acid copolymer, cellulose acetate phthalate, and hydroxypropyl methylcellulose phthalate. (Exhibit 1001 5:24-36.).

- **Kohri (Ground 3)** Kohri is a February 1999 journal article (Ex. 1018). Kohri identifies 100 mg of an azole called "albendazole," which Dr. Grainger confirms is an antifungal azole covered by the '745 patent (at ¶ 38). Kohri further discloses mixing this azole with hydroxypropyl methyl cellulose phthalate, a "preferred" polymer under the '745 patent. (Ex. 1005, at ¶ 38.)
- **Babcock (Ground 4)** is a European Patent Application filed in February 1999, making it prior art under 35 U.S.C. § 102(e) and *Hazeltine Research, Inc. v. Brenner*, 382 U.S. 252, 255-56 (1965) (filed patent application constituted prior art under 35 U.S.C. § 102(e)). Babcock identifies 100 mg of an active ingredient (Ex. 1009, at ¶ 0041), and further identifies fluconazole as an ingredient appropriate for its composition (Ex. 1009, at ¶ 0067). Dr. Grainger confirms fluconazole is an azole covered by the '745 patent. (Ex. 1005, at ¶ 38.) Babcock

further describes mixing an active ingredient with "cellulose acetate phthalate (CAP) and cellulose acetate trimellitate (CAT)" (Ex. 1005, at ¶ 38), both of which the '745 patent identifies as qualifying polymers (Ex. 1001, at 5:24-36).

- **Baert (Ground 5)** is a U.S. Patent that claims priority to a May 1997 PCT application. (Ex. 1018, at 1:6-9.) Baert employs 100 mg dosage forms of itraconazole (Ex. 1018, at 2:44-45), an azole the '745 patent identifies as a practically insoluble and thus poorly bioavailable azole antifungal drug (Ex. 1001, at 4:55-5:12). Baert identifies (at 5:29-63) polymers to mix with itraconazole including carboxyalkylalkyl celluloses such as carboxymethylethyl cellulose, carboxyalkyl cellulose esters, polyacrylic acids polymethacrylic acids, and methacrylate copolymers, which Dr. Grainger confirms (at ¶ 38) are polymers having acidic functional groups as called for in the '745 patent.
- **Vandecruys (Ground 6)** is a PCT patent application filed in 1997 and published in 1998. (Ex. 1016, at 1.) Like Baert, Vandecruys similarly employs 100 mg itraconazole dosage forms. (Ex. 1016, at 2:23-26.) Vandecruys identifies as polymers to mix with itraconazole such as carboxyalkylalkyl celluloses like carboxymethylethyl cellulose, carboxyalkyl cellulose esters, polyacrylic acids, polymethacrylic acids

and methacrylate copolymers, which Dr. Grainger again confirms (Ex. 1005, at ¶ 38) are polymers having acidic groups under the '745 patent. (*See* Ex. 1049; Ex. 1057.)

Given these facts, Kai, Sangekar, Kohri, Babcock, Baert, and Vandecruys each anticipate every limiting element in the challenged claims, with a few minor exceptions noted below. Except for Kai, however, these references do not describe C_{MAX} or AUC results for 100 mg azole doses *in vivo*, though some describe such results for other doses. But that is irrelevant. As shown above, the "wherein" C_{MAX} and AUC terms cannot limit the claimed composition—though even those terms if they were limiting, Kai would still anticipate, as shown below.

The following tables for Kai and Sangekar (table 1), Kohri and Babcock (table 2), and Baert and Vandecruys (table 3) summarize how each reference anticipates each claim's elements:

Table 1: Kai and Sangekar Anticipate

Claim	Element	Kai (Ex. 1007)	Sangekar (Ex. 1015)
1	"**pharmaceutical composition**" (at 10:54)	Kai's compositions are a "pharmaceutical application of [a] solid dispersion system" (at 568, col. 1), as well as "formulations" (id)	Sangekar discloses a "pharmaceutical composition comprising a substantially amorphous solid solution, said solid solution comprising: (a) a compound of the formula I…; and (b) a polymer

			selected from the group" (2:24-3:10)
1 (cont' d)	"**consisting essentially of**" (at 10:54)	The only other ingredients were solvents dichloromethane (also known as methylene chloride) and ethanol (at 568, col. 2); the '745 patent recognizes these solvents explicitly (at 5:58-64)); no excipients required that are expected to significantly affect bioavailability	Sangekar discloses a "pharmaceutical composition comprising a substantially amorphous solid solution, said solid solution comprising: (a) a compound of the formula I…; and (b) a polymer selected from the group" (2:24-3:10); no excipients required that are expected to significantly affect bioavailability
1 (cont' d)	"**about 100 mg**" (at 10:55)	MFB-1041 at a dose of 10 mg/kg to 10-12 kg dogs (at 568, col. 2)	Sangekar discloses 100 mg capsules or tablets (at 10:24-27); see also Examples 19 and 20 (at 20:5-8, 21:6-13)
1 (cont' d)	"**an azole antifungal drug**" (at 10:55)	"(+)-2-(2,4-Difluorophenyl)-3-methyl-1-(1H-1,2,4-triazol-1-yl)-3-[6-(1H-1,2,4-triazol-1-yl)pyridazin-3-y1-thio]butan-2-ol (MFB-1041) is an orally active triazole antifungal agent which may have therapeutic benefits in aspergillus treatment." (at 568, col. 1)	"This invention relates to pharmaceutical compositions in the form of a substantially amorphous composition of matter comprising a tetrahydrofuran azole antifungal" (2:27-30) "The compound of Formula I is a tetrahydrofuran antifungal compound"

		Dr. Grainger (Ex. 1005) identifies MFB-1041 as an azole antifungal drug (at ¶ 38)	(4:12-13) Dr. Grainger (Ex. 1005) identifies the compound of Formula I as an azole antifungal drug (at ¶¶ 15, 38)
1 (cont' d)	"**optionally at least one polymer having acidic functional groups**" (at 10:55-56)	The polymer optional and not limiting; in any event, polymer meets element (*see infra* re claim 2 in chart)	polymer optional and not limiting; in any event, polymer meets element (*see infra* re claim 2 in chart)
1 (cont' d)	"**wherein in vivo the composition provides a mean C_{MAX} of at least 100 ng/mL, after administration in the fasted state**" (at 10:56-58)	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35); in any event, data presented meets element (*see* Ex. 1005, at 40)	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35)
2	claim depends from claim 1, plus "**at least one polymer having acidic functional group**s"	solid dispersions of MFB-1041 with carboxymethyl ethylcellulose (CMEC), and with hydroxypropyl methyl cellulose phthalate (HP-55) (at 586, abstract, col 1-2) both in '745 patent as qualifying polymers (at 5:24-44) Both identified by Dr. Grainger (Ex.1005) as qualifying polymers (at ¶ 38)	"(b) a polymer selected from the group consisting of: … carboxymethyl cellulose, … methacrylic acid and methacrylate copolymers, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate" (at 3:2-10) Dr. Grainger identifies each (Ex.1005) as qualifying polymers (at ¶ 38)
3	claim depends from claim 1,	non-limiting wherein clause (*see supra* at p.	non-limiting wherein clause (*see supra* at p.

	changing minimum C_{MAX} from "**at least 100 ng/mL" to "at least 150 to 250 ng/mL**"	16; Ex. 1005, at ¶¶ 34-35); in any event, data presented meets element (*see* Ex. 1005, at ¶ 40)	16; Ex. 1005, at ¶¶ 34-35)
5	claim is identical to claim 1, except it substitutes C_{MAX} element with "**wherein**" clause requiring "**a mean AUC of at least 800 ng h/mL, after administration in the fasted state**"	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35); in any event, data presented meets element (*see* Ex. 1005, at 40)	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35)
6	claim depends from claim 5, adding only a required "**polymer having acidic functional groups**"	see above re claim 2 for polymer	see above re claim 2 for polymer
7	claim depends from claim 5, changing only the required mean AUC from "**at least 800 ng h/mL in the fasted state" to a mean AUC of "1300 to 2300 ng h/mL in the fasted state**"	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35)
9	claim is identical to claim 2 (see above), except claim 9 adds that certain excipients may "**optionally**"	excipients optional and not limiting	excipients optional and not limiting

	be added to the composition		
10	claim depends from claim 9, only additionally requiring that the pharmaceutical composition is a "**capsule**"	Kai does not anticipate this claim	"A pharmaceutical composition of the above antifungal compounds that can be manufactured in a tablet or capsule form that has greater bioavailability than a suspension would also be a contribution to the art. This invention provides these contributions to the art" (at 2:13-18)
11	claim depends from claim 9, only additionally requiring that the pharmaceutical composition is a "**powder**"	Kai discloses compositions in the form of a "solid dispersion powder" (at 568)	"The solvent was evaporated under a hood, and then the residue was dried under a vacuum. The residue was then reduced to fine particles by grinding. The residue was then passed through a 30 mesh screen." (at 12:14-18)
12	claim is identical to claim 6 (see above), except claim 12 adds that certain excipients may "**optionally**" be added to the composition	excipients optional and not limiting	excipients optional and not limiting
13	claim depends from claim 12, only additionally requiring that the pharmaceutical composition is a	Kai does not anticipate this claim	see above claim 10

	"**capsule**"		
14	claim depends from claim 12, only additionally requiring that the pharmaceutical composition is a "**powder**"	see above for claim 11	see above for claim 11

Table 2: Kohri and Babcock Anticipate

Claim	**Element**	**Kohri** (Ex. 1017)	**Babcock** (Ex. 1009)
1	"**pharmaceutical composition**" (at 10:54)	"compositions of preparations" of albendazole (at 161)	"composition comprising a solid dispersion comprising a low-solubility drug and at least one polymer" (¶ 0027)
1 (cont'd)	"**consisting essentially of**" (at 10:54)	only other ingredient was solvent mixture of dichloromethane-ethanol (at 160); the '745 patent recognizes these solvents explicitly (at 5:58-64)	"present invention provides a composition comprising a solid dispersion comprising a low-solubility drug and at least one polymer" (¶ 0027); additional excipients are optional (e.g., ¶ 0090)
1 (cont'd)	"**about 100 mg**" (at 10:55)	preparations containing 0.1 g of albendazole (Ex. 1017, at Table 1.)	"for example, a drug with a therapeutic dose of 100 mg" (¶ 0041); comparative examples of drugs with dosages ranging from 30-300

Claim	**Element**	**Kohri** (Ex. 1017)	**Babcock** (Ex. 1009)
			mg. (Table 1)
1 (cont' d)	"**an azole antifungal drug**" (at 10:55)	albendazole (at Kohri 159); Dr. Grainger (Ex. 1005) identifies albendazole as an azole antifungal drug (at ¶ 38)	"examples of drugs deliverable by the invention are … the anti-fungal fluconazole" (¶ 0067); specific examples of antifungals include econazole, terconazole…" (¶ 0066); Dr. Grainger (Ex. 1005) identifies fluconazole as an azole antifungal drug (at ¶ 38)
1 (cont' d)	"**optionally at least one polymer having acidic functional groups**" (at 10:55-56)	polymer optional and not limiting; in any event, polymer meets element (see below in chart)	polymer optional and not limiting; in any event, polymer meets element (see below in chart)
1 (cont' d)	"**wherein in vivo the composition provides a mean C_{MAX} of at least 100 ng/mL, after administration in the fasted state**" (at 10:56-58)	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35); in any event, data presented meets element (*see* Ex. 1006, at ¶¶ 21-22)	non-limiting wherein clause (*see* Ex. 1005, at ¶¶34-35)
2	claim depends from claim 1, plus "**at least one polymer having acidic functional group**s"	Hydroxypropyl methylcellulose phthalate ("HP-55") (at 160, Table 1); in patent as qualifying polymer (at 5:24-44), and identified by Dr. Grainger (Ex. 1005) as a qualifying polymer (at	polymers " include cellulose acetate phthalate (CAP) and cellulose acetate trimellitate (CAT)." (¶ 0067); both in '745 patent as qualifying polymers (at 5:24-36), both identified by Dr.

Claim	**Element**	**Kohri** (Ex. 1017)	**Babcock** (Ex. 1009)
		¶ 38)	Grainger (Ex. 1005) as qualifying polymers (at ¶ 38)
3	claim depends from claim 1, changing minimum C_{MAX} from "**at least 100 ng/mL" to "at least 150 to 250 ng/mL**"	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35); in any event, data presented meets element (*see* Ex. 1016, at ¶¶ 21-22)	non-limiting wherein clause (*see* Ex. 1005, at ¶¶34-35)
5	claim is identical to claim 1, except it substitutes C_{MAX} element with "**wherein**" clause requiring "**a mean AUC of at least 800 ng h/mL, after administration in the fasted state**"	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35); in any event, data presented meets element (*see* Ex. 1016, at ¶¶ 21-22)	non-limiting wherein clause (*see* Ex. 1005, at ¶¶34-35)
6	claim depends from claim 5, adding only a required "**polymer having acidic functional groups**"	see above re claim 2 for polymer	see above re claim 2 for polymer
7	claim depends from claim 5, changing only the required mean AUC from "**at least 800 ng h/mL in the fasted state" to a mean**	non-limiting wherein clause (*see supra* at p. 16; Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (*see* Ex. 1005, at ¶¶34-35)

Claim	**Element**	**Kohri** (Ex. 1017)	**Babcock** (Ex. 1009)
	AUC of "1300 to 2300 ng h/mL in the fasted state"		
9	claim is identical to claim 2 (see above), except claim 9 adds that certain excipients may "**optionally**" be added to the composition	excipients optional and not limiting	excipients optional and not limiting
10	claim depends from claim 9, only additionally requiring that the pharmaceutical composition is a "**capsule**"	Kohri does not anticipate this claim	"[Exemplary dosage forms are powders or granules that may be taken orally either dry or reconstituted by addition of water to form a paste. slurry, suspension or solution; tablets, capsules……" (¶ 0090)
11	claim depends from claim 9, only additionally requiring that the pharmaceutical composition is a "**powder**"	dispersions " prepared by use of a solvent method…[t]he residue was dried for 12 h under vacuum and passed through a 100-mesh sieve." (at 160), as Dr. Grainger shows (Ex.1005 at Table 2), solid dispersions are in the form of a powder	"[e]xemplary dosage forms are powders or granules ..." (¶ 0090)
12	claim is identical to claim 6 (see above), except claim 12 adds that certain excipients	excipients optional and not limiting	excipients optional and not limiting

Claim	**Element**	**Kohri** (Ex. 1017)	**Babcock** (Ex. 1009)
	may "**optionally**" be added to the composition		
13	claim depends from claim 12, only additionally requiring that the pharmaceutical composition is a "**capsule**"	Kohri does not anticipate this claim	see above for claim 10
14	claim depends from claim 12, only additionally requiring that the pharmaceutical composition is a "**powder**"	see above for claim 11	see above for claim 11

Table 3: Baert and Vandecruys Anticipate

Claim	**Element**	**Baert** (Ex. 1018)	**Vandecruys** (Ex. 1016)
1	"**pharmaceutical composition**" (at 10:54)	"present invention is concerned with novel pharmaceutical compositions of itraconazole…" (at 1:10-11)	"present invention provides pharmaceutical compositions of itraconazole ..." (4:1-4)
1 (cont' d)	"**consisting essentially of**" (at 10:54)	compositions consist essentially of the drug and polymer, but may also further include pharmaceutically acceptable excipients (at	The compositions disclosed in Vandecruys consist essentially of the drug and polymer, but may also further include pharmaceutically

Claim	**Element**	**Baert** (Ex. 1018)	**Vandecruys** (Ex. 1016)
		7:25-31) No excipients are required that are expected to significantly affect bioavailability.	acceptable excipients. (at 7:20-24, 12:10-12) No excipients are required that are expected to significantly affect bioavailability.
1 (cont'd)	"**about 100 mg**" (at 10:55)	100 mg capsules of itraconazole. (at 2:44-47)	"pellets are filled in hard-gelatin capsules such that an amount of, for example, 100 or 200 mg of the active ingredient ..." (at 8:22-24)
1 (cont'd)	"**an azole antifungal drug**" (at 10:55)	"present invention is concerned with novel pharmaceutical compositions of itraconazole which can be administered to a mammal suffering from a fungal infection" (at 1:10-12); itraconazole is an azole antifungal drug according to the '745 patent, (at 1:38-46), and according to Dr. Grainger (at ¶ 38)	"present invention provides pharmaceutical compositions of itraconazole (or saperconazole) and a water-soluble polymer" (4:1-4); itraconazole is an azole antifungal drug according to the '745 patent (at 1:38-46), and according to Dr. Grainger (at ¶ 38)
1 (cont'd)	"**optionally at least one polymer having acidic functional groups**"	polymer optional and not limiting; in any event, polymer meets element (see below in chart)	polymer optional and not limiting; in any event, polymer meets element (see below in chart)

Claim	**Element**	**Baert** (Ex. 1018)	**Vandecruys** (Ex. 1016)
	(at 10:55-56)		
1 (cont' d)	"**wherein in vivo the composition provides a mean C_{MAX} of at least 100 ng/mL, after administration in the fasted state**" (at 10:56-58)	non-limiting wherein clause (*see* Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (*see* Ex. 1005, at ¶¶ 34-35)
2	claim depends from claim 1, plus "**at least one polymer having acidic functional groups**"	disclosed polymers include many with acidic functional groups: carboxyalkylcelluloses such as carboxymethylcellulose, carboxyalkylalkylcelluloses such as carboxymethylethylcellulose, carboxyalkylcellulose esters, polyacrylic acids polymethacrylic acids, and methacrylate copolymers. (at 5:29-63); each identified by Dr. Grainger (Ex. 1005) as a qualifying polymer (at ¶ 38)	disclosed water-soluble polymers include many with acidic functional groups: carboxyalkylcelluloses such as carboxymethylcellulose, carboxyalkylalkylcelluloses such as carboxymethylethylcellulose, carboxyalkylcellulose esters, polyacrylic acids, polymethacrylic acids and methacrylate copolymers. (at 5:9-33); each identified by Dr. Grainger (Ex. 1005) as a qualifying polymer (at ¶ 38)
3	claim depends from claim 1, changing minimum C_{MAX} from "**at least 100 ng/mL"**	non-limiting wherein clause (*see* Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (*see* Ex. 1005, at ¶¶ 34-35)

Claim	**Element**	**Baert** (Ex. 1018)	**Vandecruys** (Ex. 1016)
	to "at least 150 to 250 ng/mL"		
5	claim is identical to claim 1, except it substitutes C_{MAX} element with "**wherein**" clause requiring "**a mean AUC of at least 800 ng h/mL, after administration in the fasted state**"	non-limiting wherein clause (*see* Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (*see* Ex. 1005, at ¶¶ 34-35)
6	claim depends from claim 5, adding only a required "**polymer having acidic functional groups**"	see above for polymer	see above for polymer
7	claim depends from claim 5, changing only the required mean AUC from "**at least 800 ng h/mL in the fasted state" to a mean AUC of "1300 to 2300 ng h/mL in the fasted state**"	non-limiting wherein clause (*see* Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (*see* Ex. 1005, at ¶¶ 34-35)
9	claim is identical to claim 2 (see above), except claim 9 adds that certain excipients	excipients optional and not limiting	excipients optional and not limiting

Claim	**Element**	**Baert** (Ex. 1018)	**Vandecruys** (Ex. 1016)
	may "**optionally**" be added to the composition		
10	claim depends from claim 9, only additionally requiring that the pharmaceutical composition is a "**capsule**"	compositions can be formulated into a capsule (at 6:53-55.)	"drug coated and seal coated pellets may be filled in hard-gelatin capsules using standard automatic capsule filling machines" (at 11:1-2)
11	claim depends from claim 9, only additionally requiring that the pharmaceutical composition is a "**powder**"	compositions can be milled or ground into a powder (at 4:64-66)	Vandecruys does not anticipate this claim
12	claim is identical to claim 6 (see above), except claim 12 adds that certain excipients may "**optionally**" be added to the composition	excipients optional and not limiting	excipients optional and not limiting
13	claim depends from claim 12, only additionally requiring that the pharmaceutical composition is a "**capsule**"	see above for claim 10	see above for claim 10
14	claim depends from claim 12, only additionally requiring that the	see above for claim 11	Vandecruys does not anticipate this claim

Claim	**Element**	**Baert** (Ex. 1018)	**Vandecruys** (Ex. 1016)
	pharmaceutical composition is a "**powder**"		

As noted, even if the "wherein" bioavailability benchmarks were to be construed as actual limitations, Kai still discloses data that meets most of those claimed benchmarks. In Table 1, Kai reports CMAX 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. 1007, at 570, Table 1.)

In short, the '745 patent claims challenged here are all anticipated by not just one, but by multiple references. Nothing could more forcefully show the utter lack of novelty in these claims.

Grounds 7-9: Thorpe, Tett, and/or Lin Anticipate Claims 1, 3, 5 and 7

Thorpe (Ground 7, published 1990), Tett (Ground 8, published 1995), and Lin (Ground 9, published 1996) each anticipate claims 1, 3, 5 and 7.

Each of Thorpe, Tett, and Lin disclose a 100 mg dose of an azole antifungal drug alone without a polymer. (Ex. 1020, at 2032; Ex. 1021, at 1835; Ex. 1019, at 92.) Claims 1, 3, 5 and 7 each recite "about 100 mg of an azole antifungal drug," plus "optionally" a polymer having acidic functional groups as well as C_{MAX} (for

claims 1 and 3) and AUC (for claims 5 and 7) thresholds. As shown above (at p. 16), the "optional" polymer claims are not limiting and thus irrelevant here. Thorpe, Tett and Lin accordingly anticipate these claims:

Table 4: Thorpe, Tett, and Lin Anticipate

Claim	Element	Thorpe (Ex. 1020)	Tett (Ex. 1021)	Lin (Ex. 1019)
1	"**pharmaceutical composition**"	"subject received a single oral 100-mg capsule of fluconazole" (at 2032) Dr. Grainger confirms that fluconazole is an antifungal azole compound (Ex. 1005, at Table 4)	"[f]luconazole, a bis-triazole drug, is useful for the treatment and prophylaxis of superficial and systematic fungal infections" (1835) Dr. Grainger confirms that fluconazole is an antifungal azole compound (Ex. 1005, at Table 4)	"[g]enaconazole is a potent triazole antifungal agent that is superior to ketoconazole in an in vivo candida infection model, as well as in an immunocompromised animal model" (at 92) Dr. Grainger confirms that genaconazole is an antifungal azole compound (Ex. 1005, at Table 4)
1 (cont'd)	"**consisting essentially of**"	inactive ingredients include lactose monohydrate, maize starch, sodium laurilsulfate, colloidal	inactive ingredients include microcrystalline cellulose, dibasic calcium phosphate anhydrous,	methylcellulose solution (at 92); Dr. Grainger shows (Ex. 1005 at ¶ 33) that this is a common excipient and thus fits within

		anhydrous silica and magnesium stearate (Ex. 1035, at 1 "Diflucan"); these are common excipients and thus fit within the claim construction (*see Ex*. 1005, at ¶ 33) No excipients are required that are expected to significantly affect bioavailability.	povidone, croscarmellose sodium, FD&C Red No. 40 aluminum lake dye, and magnesium stearate (Ex. 1021, at 1836; Ex. 1035, at 1); These are common excipients and thus fit within the claim construction (*see* Ex. 1005, at ¶ 33) No excipients are required that are expected to significantly affect bioavailability	the claim construction (*see* Ex. 1005 at ¶ 33)
1 (cont'd)	"**[a]bout 100 mg**"	"subject received a single oral 100-mg capsule of fluconazole" (at 2032)	"[f]luconazole, a bis-triazole drug, is useful for the treatment and prophylaxis of superficial and systematic fungal infections" (1835)	"pharmacokinetics of the RR enantiomer were also evaluated in healthy male volunteers after a single oral dose of 100 or 200 mg" (at 92)
1 (cont'd)	"**an azole antifungal drug**"	"[f]luconazole is a new bis-triazole which has shown	fluconazole (at 1835); Dr. Grainger (Ex.	"…genaconazole, a racemic triazole

		good antifungal activity" (at 2032); Dr. Grainger (Ex.1005) identifies fluconazole as an azole antifungal drug (at ¶ 38)	1005) identifies fluconazole as an azole antifungal drug (at ¶ 38)	antifungal agent…" (at 92); Dr. Grainger (Ex. 1005) identifies fluconazole as an azole antifungal drug (at ¶ 38)
1 (cont' d)	"**optionally at least one polymer having acidic functional groups**"	polymer optional and not limiting	polymer optional and not limiting	polymer optional and not limiting
1 (cont' d)	"**wherein in vivo the composition provides a mean C_{MAX} of at least 100 ng/mL, after administration in the fasted state**"	non-limiting wherein clause (see Ex. 1005, at ¶¶ 34-35); in any event, data presented meets element (at ¶ 42)	non-limiting wherein clause (see Ex. 1005, at ¶¶ 34-35); in any event, data presented meets element (at ¶ 42)	non-limiting wherein clause (see Ex. 1005, at ¶¶ 34-35); in any event, data presented meets element (at ¶ 42)
3	claim depends from claim 1, changing minimum C_{MAX} from "at least 100 ng/mL" to "**at least 150 to 250 ng/mL**"	non-limiting wherein clause (see Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (see Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (see Ex. 1005, at ¶¶ 34-35)
5	claim is identical to claim 1, except	non-limiting wherein clause (see Ex. 1005, at	non-limiting wherein clause (see Ex. 1005, at	non-limiting wherein clause (see Ex. 1005, at

	it substitutes C_{MAX} element with "**wherein**" clause requiring "**a mean AUC of at least 800 ng h/mL, after administration in the fasted state**"	¶¶ 34-35)	¶¶ 34-35)	¶¶ 34-35)
7	claim depends from claim 5, changing only the required mean AUC from "at least 800 ng h/mL in the fasted state" to a mean AUC of "**1300 to 2300 ng h/mL in the fasted state**"	non-limiting wherein clause (see Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (see Ex. 1005, at ¶¶ 34-35)	non-limiting wherein clause (see Ex. 1005, at ¶¶ 34-35)

Thorpe, Tett and Lin accordingly anticipate claims 1, 3, 5 and 7, the "polymer optional" claims. Moreover, even if the "wherein" clause C_{MAX} and AUC were deemed limiting, these references would still anticipate the benchmarks in claims 1 and 5. Each reference discloses C_{MAX} and AUC scores far exceeding those benchmarks.

- **Thorpe** reports that a 100 mg capsule of fluconazole yielded a "C_{MAX} (μg/mL)" of "1.70± 0.22," equal to 1700 ng/mL—more than 10 times the threshold in claim 1. (Ex. 1020, at 2033, Table 1.) Thorpe reported that a 100 mg capsule of fluconazole yielded an "$AUC_{0->\infty}$ (μg·h/mL)" of "93.00 ± 13.82," equal to 93000 ng/mL h—again more than 10 times the threshold in claim 5. (Ex. 1020, at 2033, Table 1.)
- **Tett** shows that 100 mg dosages yielded a C_{MAX} of at least 1 mg/L, equivalent to 1000 ng/mL and is thus over 10 times the threshold in claim 1. (Ex. 1021, at 1838, Fig. 2.) Tett also reports intravenous and oral 100 mg doses all resulted in a fluconazole AUC of at least 40 mg/L hr, equivalent to 40000 ng/mL h and is thus over 50 times the threshold in claim 5. (Ex. 1021, at 1838, Fig. 1.)
- **Lin** reports a C_{MAX} of 1,700 ng/mL and AUC of 186,000 ng.h/mL (Ex. 1019, at Table 2) after administration of 100 mg of genaconazole in a fasted state (Ex. 1019, at 92.) These values are far in excess of claims 1 and 5, thus anticipating these elements too if they are deemed limiting.

MULTIPLE REFERENCES AND COMBINATIONS RENDER THE CHALLENGED '745 PATENT CLAIMS OBVIOUS

H. Obviousness Standards

Obviousness depends on: (1) the scope and content of prior art, (2) differences between the challenged claims and prior art, (3) the level of ordinary

skill in the pertinent art, and (4) secondary considerations such as commercial success and satisfaction of a long-felt need. *Graham v. John Deere Co.,* 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). Further, for an invention to be obvious, a person of ordinary skill must be "motivated to combine the teachings of the prior art references to achieve the claimed invention," and have "a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (internal citation omitted).

The Supreme Court has emphasized that "caution" should be exercised ""in granting a patent based on the combination of elements found in the prior art[.]" *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 401 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. In that analysis, the Board should look to common sense and "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418; *Astrazeneca AB v. Mylan Labs, Inc.*, 2007 U.S. Dist. LEXIS 39670, * 397-97 (Fed. Cir., May 31, 2007).

Here, the '745 patent claims recite elements that were previously found—together or separately—in the prior art: azoles plus acid-resistant polymers to improve azole bioavailability. Moreover, a pharmaceutical chemist would have

known that combining azoles and polymers with acidic functional groups would improve azole bioavailability with reasonable predictability. (*See, e.g.*, Ex. 1007; 1005 at ¶¶ 48-49.) Thus, each claim in the '745 patent is rendered obvious by the prior art.

I. Obviousness Grounds

Ground 10: Kai plus Sangekar and Babcock

Three anticipatory references above—Kai, Sangekar, and Babcock—would, taken together, have made the '745 patent's composition blindingly obvious to a skilled pharmaceutical chemist in December 1999. The Examiner indeed found that Kai or Sangekar alone rendered even narrower claims in the parent '883 application obvious. (Ex. 1003, at 576-582.) All the more so for the '745 patent's sweeping claims of about 100 mg of any azole plus any polymer with acidic functional groups.

The Scope and Content of the Prior Art: As shown above and in the accompanying declaration from Dr. Grainger, researchers by December 1999 had long ago recognized that certain polymers could render practically insoluble drugs more soluble and thus better absorbed by the body. Numerous references describe that insight, including Babcock (Ex. 1009, 1999), Kondo (Ex. 1010, 1994), Yamaguchi (Ex. 1011, 1993), Nakano (Ex. 1012, 1993), Simoni (Ex. 1013, 1994), and Yuk (Ex. 1014, 1999). While not confined to azoles, Babcock does use

fluconazole as an example. So scientists at the time would have been able to apply the insight to azoles in particular.

Scientists did just that throughout the 1990s. Kohri (Ex.1017, 1999), Baert (Ex. 1018, 1997), and Vandecruys (Ex. 1016, 1998) all reflect exactly such work, and provide additional context for the work in Kai, Sangekar, and Babcock. Moreover, while the "wherein" clauses with C_{MAX} and AUC are not limiting (*see supra* at p. 16), even if they were then Kai and Kohri reveal results far in excess of the minimum benchmarks in the patent. The scientific literature was replete with references identical to or within a hair's breadth of these claims.

Differences between the Prior Art and the '745 Patent: The 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.

First, every claim in the '745 patent has a composition with "about 100 mg" of active ingredient. Each of Kai, Sangekar, and Babcock recite the 100 mg amount, and Kai and Sagekar in particular show that amount mixed with appropriate polymers achieving good bioavailability. (*See, e.g.,* Ex. 1007, at Table 2; Ex. 1015, at Example 12; Ex. 1009, at ¶ 0041.) Moreover, Thorpe, Tett, and Lin similarly show azoles in 100 mg amounts, and a pharmaceutical chemist would have considered these references as background art. (Ex. 1005, at ¶ 44.)

Second, every claim in the '745 patent contains an azole antifungal drug. Each of Kai, Sangekar, and Babcock disclose such an azole. In light of the pressing societal need for effective antifungals (Ex. 1005, at ¶ 45), a pharmaceutical chemist would have been motivated to use such a drug because azoles had proven effective in the art. (*Id.*) The same art would have provided a reasonable expectation of success.

Third, every claim in the '745 patent consists essentially of an azole plus a polymer containing acidic functional groups, either as an optional or required component. Insofar as the polymer is optional, the claim is non-limiting; but insofar as the polymer is required, each of Kai, Sangekar, and Babcock describe mixing a qualifying polymer with an azole, as shown above (at Tables 1 and 2). Thus, again, the difference between the prior art and the '745 patent combination is nil.

Moreover, a motivation to combine an azole and a polymer in December 1999 would have been manifest. (Ex. 1005, at ¶ 47.) The AIDS crisis and other factors had made fungal infections increasingly common, creating a need for effective anti-fungal agents. Certain azoles, however, are practically insoluble, and even those that are not may benefit from being more soluble than otherwise. In addition, certain azoles break down in the stomach's acidic environment, and are thus better absorbed in the more neutral pH environment of the small intestine.

As Dr. Grainger explains (at ¶¶ 48-49), pharmaceutical chemists had long understood that insoluble drugs like azoles could be made more soluble in combination with certain polymers. Moreover, the right polymers could also protect acid-sensitive drugs from stomach acid, allowing those drugs to be absorbed in the small intestine. For azoles that would benefit from these steps, the prior art thus provided ample motivation to combine.

The same art further provided a reasonable expectation of success that the combination would work. Using polymers to improve solubility and thus bioavailability was well-known long before December 1999, and had proven an effective strategy for many drugs besides azoles. Researchers had thus applied those strategies to multiple azoles before December 1999, including in Kai, Sangekar, and Babcock, as well as in Kohri, Baert, and Vandecruys. As Dr. Grainger explains (at ¶ 50), a pharmaceutical chemist accordingly would have expected such a combination to improve bioavailability.

Fourth, every claim contains C_{MAX} or AUC benchmarks, expressed either as minimum requirements (in independent claims 1, 5, 9 and 12), or as a target range (in dependent claims 3 and 7). As shown above (at p. 16), these "wherein" terms are non-limiting, and thus irrelevant for purposes of an obviousness analysis. But even if these claims were construed as limiting, they still would be obvious.

As shown above, Kai discloses C_{MAX} and AUC data far in excess of the minimum thresholds required in the independent claims. That alone establishes the obviousness of those claims. Sangekar too shows the ease with which the C_{MAX} and AUC benchmarks could be achieved, as Drs. Grainger and Blaschke explain (at ¶ 51 and ¶ 23, respectively). Similarly, Babcock shows that a POSA would reasonably expect that an antifungal azole, such as fluconazole in Babcock, would satisfy the C_{MAX} and AUC values of the '745 patent, in view of, for example, Thorpe or Tett, which disclose that administration of fluconazole without a polymer results in C_{MAX} and AUC values that exceed those in the claims.

Dr. Blaschke shows also (at ¶¶ 23-26) that a skilled pharmaceutical chemist would have known how to easily manipulate the publicly-disclosed compositions to achieve the target ranges in dependent claims 3 and 5. To do so, a pharmaceutical chemist need only adjust the relative polymer-to-azole ratio, or the particular polymer or azole being used to achieve the desired range. Adjusting the polymer to azole ratio is merely routine.

Kai itself in fact teaches how to vary the parameters of an azole-polymer mix, such that it would have been a matter of routine work to achieve the claimed ranges. (Ex. 1006, ("Blaschke Decl."), at ¶ 26.) Kai shows that higher polymer-azole ratios resulted in higher CMAX and AUC levels—a 1:3 ratio of azole:HP-55 provided a CMAX of 1900 ng/mL and AUC of 11,800 ng/mL h, while a 1:5 ratio

provided a CMAX of 2590 ng/mL and AUC of 16,900 ng/mL h. (Ex. 1007, at 570, Table 1.) In contrast, administering the azole in Kai without a polymer resulted in CMAX and AUC scores close to zero. (Id.) A pharmaceutical chemist accordingly could vary the azole to polymer ratio to achieve the claimed ranges.

Dr. Blaschke explains (at ¶ 15) that a pharmaceutical chemist would have been motivated to achieve at least the C_{MAX} and AUC benchmarks in the independent claims to ensure azole bioavailability. The prior art showed that compositions with higher C_{MAX} and AUC readings were effective at treating fungal infections. That same art would have provided a pharmaceutical chemist with a reasonable expectation of success.

Fifth, various claims in the patent have miscellaneous features, including requiring the composition to be in a "powder" (claims 11 and 14) or a "capsule" (claims 10 and 13); or optionally contain certain excipients (claim 12) or specified polymers with acidic functional groups (claim 14). Kai and Sangkar describe powder compositions, as Dr. Grainger shows (at ¶ 56). Babcock describes a capsule (Ex. 1009 at ¶ 0090), which in any event would have been an obvious dosage form to any pharmaceutical chemist as Dr. Grainger confirms (at ¶ 56). The excipients in claim 12 are "optional" and thus not limiting, but Dr. Grainger nonetheless explains (at ¶ 57) why these ingredients would have been obvious to a pharmaceutical chemist. And Kai, Kohri, and Babcock indeed identify specific

polymers from those listed in claim 14. Accordingly, every one of the miscellaneous elements would have been obvious to a skilled pharmaceutical chemist.

Secondary Indicia: At this stage of these proceedings, Merck has no burden to identify and rebut secondary considerations. Rather, Mayne must first present a *prima facie* case for such consideration, which Merck would then have the chance to rebut. *Sega of Am., Inc. v. Uniloc USA, Inc.*, IPR2015-01453, 2015 WL 1090311, at *10 (PTAB Mar. 10, 2015) (declining to deny institution of *inter partes* review "based on the obviousness challenges solely because Petitioner does not address all arguments presented by Patent Owner during proceedings other than the current proceeding"). "Once a *prima facie* case of obviousness is established, it is Patent Owner's burden to introduce evidence supporting such objective indicia." *Id.* (citing *In re Huang*, 100 F.3d 135, 139 (Fed. cir. 1996)). For that reason, the Board typically rejects arguments against institution based on objective indicia, so that the Petitioner can have a fair opportunity to address any secondary indicia evidence on reply. *See, e.g.*, *Petroleum Geo-Services Inc. v. WesternGeco LLC*, IPR2015-01478, 2015 WL 1276718, at *22 (PTAB Mar. 17, 2015) (declining to deny institution of *inter partes* review, finding patent owner's arguments regarding secondary considerations premature where evidence had not been developed in instant proceeding).

Nonetheless, given that azole-polymer combinations within the '745 patent's claims were readily available before December 1999, it is clear that no secondary considerations support patentability. Petitioner is not aware of, and the specification does not disclose, any supposedly unexpected results from the combination claimed in the '745 patent. The specification is addressed to a wholly different invention, a solid dispersion. With respect to other possible secondary considerations such as long-felt need, commercial success, and the like, Mayne cannot possibly show a "nexus" to the putative invention, because azole-polymer compositions existed in the prior art and were known to enhance azole bioavailability. *See Tokai Corp. v. Easton Enter., Inc.*, 632 F.3d 1358, 1369-70 (Fed. Cir. 2011) (finding that no nexus existed between secondary consideration of commercial success and claimed invention where allegedly inventive utility lighters existed in prior art); *see also Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829 (Fed. Cir. 2015) ("If commercial success is due to an element in the prior art, no nexus exists.").

The '745 patent's composition could have met no long-felt need because there was no such need—the same composition was already available. Similarly, any commercial success cannot be attributed to the '745 patent's composition, because that composition was already available. Nor was there "failure by others"—just the opposite, others had succeeded before the '745 patent was

awarded. And Merck is aware of no praise by others for the '745 patent or the composition it claims. Simply put, no objective indicia apply here.

Ground 11: Kohri plus Baert and Vandecruys

The final ground advanced here is obviousness in view of Kohri, Baert and Vandecruys, in light of the background state of the art.

The Scope and Content of the Prior Art: The prior art for this obviousness combination is the same as for Ground 10, except with Kai, Sandgekar and Babcock acting as "background" art and Kohri, Baert, and Vandecruys acting as primary references here.

As shown above, Kohri (Ex. 1017, 1999), Baert (Ex. 1018, 1997), and Vandecruys (Ex. 1016, 1998) each disclose azole antifungal compositions of about 100 mg. (Ex. 1005, at ¶¶ 59-60.) Each also discloses mixing an azole with a polymer having acidic functional groups. (Ex. 1005, at ¶ 61.)

Finally, Kohri and Baert (but not Vandecruys) each report C_{MAX} and AUC bioavailability scores, albeit at different doses than in the '745 patent's "wherein" clauses. (Ex. 1017, at Table 2; Ex. 1018, at Example 3.) As Drs. Grainger explains (at ¶ 59), those dosing differences would not have led a skilled pharmaceutical chemist away from the combination in the '745 patent. (Ex. 1005, at ¶ 59.)

Differences between the Prior Art and the '745 Patent: As with Ground 10, the differences between the prior art in Ground 11 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.

First, every claim in the '745 patent has a composition with "about 100 mg" of active ingredient. Kohri, Baert, and Vandecruys identify such amounts. (*See supra* above at Tables 2, 3.) As Dr. Grainger explains, 100 mg doses are common in many contexts, including in azoles generally—as confirmed by the 100 mg doses used in Kai, Sangekar, Babcock, Thorpe, Tett and Lin. (Ex. 1007, at 568; Ex. 1015, at Example 12; Ex. 1020, at) A skilled pharmaceutical chemist accordingly would have been motivated to use such an amount.

Second, every claim in the '745 patent contains an azole antifungal drug. Kohri, Baert, Vandecruys, and Babcock all disclose such a drug. (*See supra* at pp. 21-23.) Baert and Vandecruys specifically disclose a poorly soluble azole, itraconazole. In light of the pressing societal need for effective antifungals (*see supra* at pp. 22-23), a pharmaceutical chemist would have been motivated to use an azole that had proven effective in the art. (Ex. 1008, at 41.) The same art would have provided a reasonable expectation of success.

Third, every claim in the '745 patent consists essentially of an azole plus a polymer containing acidic functional groups, either as an optional or required

component. Insofar as the polymer is optional, the claim is non-limiting; but insofar as the polymer is required, each of Kohri, Baert, and Vandecruys describe mixing a qualifying polymer with an azole, as shown above (at pp. 21-23). Thus, again, the difference between the prior art and the '745 patent combination is nil. The same motivation to combine azoles and relevant polymers and the same expectation of success apply to Ground 10 and applied to Ground 11. (*See supra*. at p. 45.)

Fourth, every claim contains C_{MAX} or AUC benchmarks, expressed either as minimum requirements (in independent claims 1, 5, 9 and 12), or as a target range (in dependent claims 3 and 7). As shown above (at p. 16), these "wherein" terms are non-limiting, and thus irrelevant for purposes of an obviousness analysis. But even if these claims were construed as limiting, they still would be obvious.

Kohri and Baert disclose C_{MAX} and AUC levels far exceeding the low benchmarks in independent claims 1, 5, 9 and 12, despite using different doses. Drs. Grainger and Blaschke show that a skilled pharmaceutical chemist would have reasonably expected C_{MAX} and AUC levels above those required in the '745 patent claims even with a 100 mg dose for at least some azoles, such as fluconazole, in view of the state of the art, which is exemplified, *inter alia*, by Thorpe, Tett, and Lin. (Ex. 1020; Ex. 1021; Ex. 1019). In addition and as shown above (at p. 48), Dr. Blaschke shows that a pharmaceutical chemist would have

been motivated to achieve at least these results, and would reasonably have expected to do so given the information in the prior art. (Ex. 1006, at ¶ 15.)

Fifth, various claims in the patent have miscellaneous features, including requiring the composition to be in a "powder" (claims 11 and 14) or a "capsule" (claims 10 and 13); or optionally contain certain excipients (claim 12) or specified polymers with acidic functional groups (claim 14). Kohri discloses compositions in the form of powder. (Ex. 1005, at Table 2.) The excipients in claim 12 are "optional" and thus not limiting, but Dr. Grainger nonetheless explains (at ¶ 57) why these ingredients would have been obvious to a pharmaceutical chemist. And Kohri, Baert, and Vandecruys each disclose polymers listed in claim 14. (Ex. 1005, at Table 2, 3.)

Secondary Indicia: For the same reasons as in Ground 7, secondary indicia cannot help Mayne save the '745 patent's claims.

MANDATORY DISCLOSURES

1. Grounds for Standing (37 C.F.R. § 42.104(a))

Merck certifies that the '745 patent is available for *inter partes* review and Merck is not barred or estopped from requesting an *inter partes* review challenging the patent on the grounds identified in this Petition.

2. Identification of Challenge (37 C.F.R. § 42.104(b))

In accordance with 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq.*, Merck petitions the Board to institute *inter partes* review of claims 1–3, 5–7, and 9–14 of U.S. Patent No. 6,881,745 (Ex. 1001), owned by Mayne Pharma International Pty Ltd.

3. Mandatory Notices (37 C.F.R. § 42.8(A)(1))

Merck is the real party-in-interest.

Merck has been charged with infringement of the '745 Patent in the parallel litigation *Mayne Pharma International Pty Ltd. v. Merck &Co., Inc.*, Case No. 15-cv-00438 (D. Del.), filed May 29, 2015. Petitioner was served with the complaint in that litigation on June 12, 2015. (*See* Ex. 1057, 1058.)

A Power of Attorney per 37 C.F.R. § 42.10(b) is filed herewith. Service via hand-delivery may be made at the postal mailing address below. Merck consents to electronic service by e-mail. Merck designates the following Lead and Back-up Counsel:

Lead counsel: Jane M. Love, Ph.D., Reg. No. 42,812;

Back-up Counsel: Robert W. Trenchard, pro hac filed subsequently.

CONCLUSION

For the foregoing reasons, the prior art references cited herein show that claims 1–3, 5–7, and 9–14 of the '745 Patent are unpatentable on grounds of

anticipation and obviousness. Accordingly, the PTAB should grant this Petition and institute *inter partes* review of claims 1–3, 5–7, and 9–14 of the '745 Patent .

The Patent Trial and Appeal Board is hereby authorized to charge any fees or credit any overpayment to Deposit Account No. 05-1408. Please refer to reference number 65240-00012.

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned attorney for the Petitioner, Petitioner declares that the argument section of this Petition (Sections II–XI) has a total of 12,177 words, according to the word count tool in Microsoft Word™.

Respectfully submitted,

Dated: June 11, 2016 /Jane M. Love PhD/

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Certificate of Service

The undersigned certifies she did cause to be served true and correct copies of the following:

- Petition for *Inter Partes* Review of U.S. Patent No. 6,881,745;
- Declaration of Dr. Grainger;
- Declaration of Dr. Blaschke;
- Exhibit List;
- Exhibits 1001-1058; and
- Power of Attorney

upon patent owner's counsel of record:

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by electronic mail and secure file transfer pursuant to agreement of the parties, on this 11th day of June, 2016.

Dated: June 11, 2016

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