

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ENDO PHARMACEUTICALS INC.,
Petitioner,

v.

DEPOMED, INC.,
Patent Owner.

Case IPR2014-00656
Patent 6,635,280 B2

Before ERICA A. FRANKLIN, GRACE KARAFFA OBERMANN, and
TINA E. HULSE, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Endo Pharmaceuticals Inc. (“Petitioner”) filed a Corrected Petition requesting an *inter partes* review of claims 1, 2, 8–15, 43, 45, and 46 of U.S. Patent No. 6,635,280 B2 (Ex. 1001, “the ’280 patent”). Paper 5 (“Pet.”). Depomed, Inc. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 8 (“Prelim. Resp.”). On September 29, 2014, we instituted an *inter partes* review of claims 1, 2, 8, 9, 13–15, 43, 45, and 46 on certain grounds of unpatentability alleged in the Petition. Paper 12 (“Dec. Inst.”), 22–23. Patent Owner timely filed a Response to the Petition. Paper 24 (confidential) (“PO Resp.”); Paper 25 (public). Petitioner timely filed a Reply to Patent Owner’s Response. Paper 38 (confidential) (“Pet. Reply”); Paper 39 (public).

Both parties filed motions to exclude certain exhibits and testimony. Paper 49 (Petitioner); Paper 51 (Patent Owner). Both parties opposed the other’s motion to exclude. Paper 54 (Patent Owner Opposition); Paper 52 (Petitioner Opposition). And both parties filed reply briefs in support of their motions to exclude. Paper 56 (Petitioner Reply); Paper 57 (Patent Owner Reply).

Patent Owner also filed a Motion for Observation (Paper 50) on certain cross-examination testimony of Petitioner’s declarant, Dr. Clive Wilson, and Petitioner filed a Response (Paper 53).

A consolidated oral hearing for this proceeding and Cases IPR2014-00652 and IPR2014-00654 was held on June 15, 2015, a transcript of which has been entered in the record.¹ Paper 65 (“Tr.”)

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1, 2, 8, 9, 13–15, 43, 45, and 46 of the ’280 patent are unpatentable.

A. Related Proceedings

Petitioner and Patent Owner identify various district court actions involving the ’280 patent, including an action involving the parties titled *Depomed, Inc. v. Endo Pharmaceuticals Inc., L.P.*, No. 3:13-cv-02467-JAP-TJB (D.N.J.). Pet. 1; Paper 8, 2–3.

The Board instituted *inter partes* review proceedings involving U.S. Patent No. 6,340,475 B2 (“the ’475 patent”), which is the parent of the ’280 patent (IPR2014-00654); and involving U.S. Patent No. 6,723,340 (IPR2014-00652).

The Board issued Final Written Decisions in *inter partes* review proceedings involving the ’280 patent (IPR2014-00377), and the ’475 patent (IPR2014-00378 and IPR2014-00379), which were initiated by Petitioner

¹ The parties filed joint Objections to Demonstrative Exhibits. Paper 62. Some of those objections were addressed during a conference call with the Board. Paper 63. In this Final Written Decision, we rely directly on the arguments presented properly in the parties’ briefs and the evidence of record. The demonstrative exhibits were only considered to the extent they are consistent with those arguments and evidence.

Purdue Pharma LP. In those Decisions, the Board found none of the challenged claims unpatentable.

B. The '280 Patent (Ex. 1001)

The '280 patent relates to drugs formulated as unit oral dosage forms by incorporating them into polymeric matrices comprising hydrophilic polymers that swell upon imbibition of water to a size large enough to promote gastric retention of the drug during the fed mode. Ex. 1001, Abstract. Drugs administered by conventional tablets generally become available to body fluids at a high rate initially, followed by a rapid decline. *Id.* at 1:31–33. To address that issue, controlled drug delivery systems were introduced in the 1970's. *Id.* at 1:35–37. Many of the controlled delivery systems utilize hydrophilic, polymeric matrices that provide controlled release of sparingly soluble drugs. According to the Specification, however, such matrices do not provide adequate control of drug release for highly soluble drugs. *Id.* at 1:45–50.

The claimed invention allows drugs that are highly soluble in water to be administered orally in a way that will prolong their release rate throughout the duration of the fed mode. *Id.* at 5:32–36. This prolonged release rate reduces the problem of transient overdosing, and controls the dosage to safer and more effective levels over an extended period of time. *Id.* at 5:36–41. Moreover, the Specification states that particles exceeding about 1 cm in size are larger than the pylorus and are retained in the stomach for approximately 4 to 6 hours. *Id.* at 11:66–12:2. The Specification states that these benefits are due, in part, to using a polymeric matrix that is water-swallowable rather than just hydrophilic, that has an erosion rate substantially slower than its swelling rate, and that releases the drug primarily by

diffusion rather than erosion. *Id.* at 5:57–62. Preferred polymeric matrices include water-swellaable polymers such as hydroxypropylmethylcellulose (“HPMC”) and poly(ethylene) oxide (“PEO”). *Id.* at 7:54–8:51.

C. Illustrative Claims

Independent claims 1 and 43 are illustrative and are reproduced below:

1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 15:85 to 80:20, said dosage form being one that when swollen in a dimensionally unrestricted manner as a result of imbibition of water is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode, that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid, that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug after such immersion, and that remains substantially intact until substantially all of said drug is released.

43. A method of administering to a subject a drug that is therapeutic to said subject when absorbed in the stomach where said drug has at least one ionized group in the pH range 5 through 8, said method comprising orally administering to said subject a dosage form of said drug while said subject is in a fed mode, said dosage form comprising one or more polymers forming a solid polymeric matrix with said drug incorporated therein at a weight ratio of drug to polymer of from 0.01:99.99 to 80:20, said polymeric matrix being one that:

(a) when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode,

(b) releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix,
(c) retains at least about 40% of said drug one hour after such immersion in gastric fluid, and
(d) releases substantially all of said drug within about ten hours after such immersion,
thereby extending the release rate of said drug with time during said fed mode while releasing substantially all of said drug within said stomach where said drug is maintained in an acidic environment.

D. Grounds of Unpatentability Instituted for Trial

We instituted trial based on the following grounds of unpatentability:

Claim(s)	Basis	References
1, 2, 8, 9, 13–15, 45, and 46	§ 103	Baveja, ² the '548 patent, ³ the Shell 1993 publication, ⁴ and the Shell '790 patent ⁵
43	§ 103	The Shell 1993 publication, Baveja, and Colombo ⁶

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light

² Baveja et al., *Zero-Order Release Hydrophilic Matrix Tablets of β -adrenergic Blockers*, 39 INT'L J. OF PHARM. 39–45 (1987) (Ex. 1008).

³ Edgren et al., US 4,871,548, issued Oct. 3, 1989 (Ex. 1006).

⁴ John W. Shell, WO 93/18755 A1, published Sept. 30, 1993 (Ex. 1007).

⁵ John W. Shell, US 5,007,790, issued Apr. 16, 1991 (Ex. 1005).

⁶ Colombo et al., *Drug Release Modulation by Physical Restrictions of Matrix Swelling*, 63 INT'L J. OF PHARM. 43–48 (1990) (Ex. 1009).

of the specification of the patent in which they appear. *See In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015); 37 C.F.R. § 42.100(b). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. *Prior Construed Claim Terms*

The parties do not contest the construction of the following claim terms set forth in the Decision to Institute:

Claim Term	Claim(s)	Construction
“gastric fluid”	1, 43	“both the fluid in the stomach and simulated or artificial fluids recognized by those skilled in the art as a suitable model for the fluid of the human stomach” (Dec. Inst. 6)
“releases substantially all of said drug after such immersion”	1	“at least 80% of the drug has been released” (Dec. Inst. 7)
“releases substantially all of said drug within about ten hours after such immersion”	43	“at least 80% of the drug has been released after ten hours of immersion in gastric fluid” (Dec. Inst. 7)

Claim Term	Claim(s)	Construction
“substantially intact”	1	“substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles” (Dec. Inst. 7)
“when swollen in a dimensionally unrestricted manner”	1, 43	“has increased in size in such a way that is not restricted in any dimension” (Dec. Inst. 7–8)

PO Resp. 14; Pet. Reply 2.

Because nothing in the full record developed during trial persuades us to deviate from our prior constructions, we continue to consider those constructions as the broadest reasonable constructions consistent with the Specification, and, on that basis, we adopt them for purposes of this Decision.

Patent Owner does, however, request reconsideration of our decision with respect to two claim terms: (1) “releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid” in independent claim 1 (i.e., the “dissolution and diffusion” limitation); and (2) “releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix” in independent claim 43 (i.e., the “erosion or diffusion” limitation). PO Resp. 14–19. In our Decision to Institute, we construed both terms according to their plain and ordinary meaning and declined to import any requirement that the drug release occur “primarily” by diffusion in claim 1, or by “rate-controlling” erosion or diffusion in claim 43. Dec. Inst. 9–10.

In its Response, Patent Owner proposes that the “dissolution and diffusion” limitation means “rapid dissolution of the drug out of the water-swollen matrix, such that the drug is released at a rate controlled by the rate of diffusion”; and that the “erosion or diffusion” limitation means “releases said drug into gastric fluid by either (a) rapid dissolution of the drug followed by slow rate-controlling diffusion of the drug out of said matrix or (b) rapid dissolution of the drug and rate-controlling erosion of said matrix.” PO Resp. 14–15. Petitioner opposes Patent Owner’s proposed construction, arguing that it is inconsistent with the broadest reasonable construction standard. Pet. Reply 2.

As an initial matter, we note that we construed the “dissolution and diffusion” limitation of the ’280 patent in the Final Written Decision entered in IPR2014-00377. There, we determined that the broadest reasonable interpretation of the limitation is “releases the drug by dissolution of the drug in the matrix followed by diffusion of the drug out of the matrix.” *Purdue Pharma L.P. v. Depomed, Inc.*, IPR2014-00377, slip op. at 8–12 (PTAB July 8, 2015) (Paper 72). With this construction as a backdrop, we proceed to consider Patent Owner’s arguments about its proposed alternate construction.

Patent Owner argues that the district courts and the parties previously agreed to its proposed constructions. PO Resp. 15. Given our different claim construction standard, however, we are not bound by the prior district court constructions or any alleged agreements between the parties made in district court.

Patent Owner then argues that the claim language supports its construction because the claim terms recite releasing the drug into gastric

fluid by a particular mechanism in the context of a controlled release dosage form. *Id.* at 16. Specifically, Patent Owner argues that a person of ordinary skill in the art would understand that a controlled release dosage form is characterized by its rate-controlling drug release mechanism. *Id.*

Even if a person of ordinary skill in the art would understand that a controlled release dosage form is characterized by its rate-controlling drug release mechanism, the claim language does not expressly require a particular rate-controlling drug release mechanism. For example, the claim language does not recite that diffusion is the rate-controlling drug release mechanism of claim 1. Rather, the language of claim 1 states simply that drug is released by “dissolution and diffusion.” And, as explained by the Banker & Rhodes reference—which Patent Owner’s declarant relies heavily on—systems can be “dissolution rate-limited or diffusion-controlled.” Ex. 1025,⁷ 589; *see also id.* at 581–82 (describing dissolution-controlled systems and diffusional-controlled systems); *see also* Ex. 2015 ¶ 44 (Dr. Hopfenberg discussing the Banker & Rhoades reference). Thus, based on the full record developed during trial, the broadest reasonable interpretation of the “dissolution and diffusion” term is not limited to diffusion-controlled drug release.

Similarly, claim 43 simply states that drug is released “by the dissolving of said drug by said gastric fluid and either erosion of said drug by said gastric fluid or diffusion of said dissolved drug out of said matrix.” Ex. 1001, claim 43. Nothing in this language dictates that the rate-

⁷ Gwen M. Jantzen & Joseph R. Robinson, *Sustained and Controlled-Release Drug Delivery Systems*, in MODERN PHARMACEUTICS 575 (Banker & Rhodes 3d ed., 1996) (Ex. 1025, “Banker & Rhodes”).

controlling mechanism of release is either by erosion or diffusion (as opposed to, for example, dissolution).

Moreover, we are not persuaded that the Specification requires Patent Owner's construction. Our reviewing court has warned that, "[a]bsent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification or prosecution history when those sources *expressly disclaim* the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004) (emphasis added). Here, the Specification does not expressly disclaim any mechanism of drug release. Indeed, most of the '280 patent claims are directed to drug dosage forms that release the drug by erosion or diffusion (as with claim 43), reciting that the dosage form "releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix or diffusion of said dissolved drug out of said matrix." Ex. 1001, claim 43; *see also* independent claims 19, 22, 24, 27, 28, 29, 30, 32, 33, 34, 37, 38, 39, 40, 42, 44 (reciting similar "erosion or diffusion" limitations). Thus, we do not find that Patent Owner has established persuasively that the Specification provides a basis for narrowing the claimed "dissolution and diffusion" limitation of claim 1.

Patent Owner then argues that we have conflated the different inventions of claim 1 and claim 43. PO Resp. 18. Patent Owner distinguishes the claims because claim 1 is directed to highly soluble drugs, whereas claim 43 is directed to any drug having at least one ionized group in the pH range 5 through 8. *Id.* But we remain unpersuaded to narrow our reading of claim 1 based upon Patent Owner's assertion that a person of ordinary skill in the art would understand that the release of a highly soluble

drug, as recited by claim 1, occurs only by a diffusion-controlled mechanism.

Indeed, the Specification describes, “[t]he invention is also of use with drugs that have been formulated to include additives that impart a small degree of hydrophobic character, to further retard the release rate of the drug into the gastric fluid.” Ex. 1001, 7:44–47. As Petitioner and its declarant assert, claim 1 of the ’280 patent does not preclude the use of an additive. Pet. Reply 9 (citing Ex. 1042 ¶¶ 33–34). Thus, if the use of such an additive results in dissolution-controlled drug release for a highly soluble drug, as Patent Owner asserts, we are not persuaded that the Specification limits the invention of claim 1 to diffusion-controlled drug release. *See, e.g.*, Ex. 2015 ¶ 154 (explaining that such an additive confers dissolution control to a highly soluble drug).

For similar reasons, we are not persuaded that claim 43 is limited to diffusion-controlled or erosion-controlled drug release. As with claim 1, claim 43 does not preclude the use of an additive to retard the release rate of a highly soluble drug and render it a dissolution-controlled drug release mechanism. Thus, we are not persuaded that the Specification expressly disclaims drug release mechanisms other than those controlled by diffusion or erosion.

Finally, Patent Owner argues that a person of ordinary skill in the art would have understood the plain and ordinary meaning of the claims to require that “dissolution of the drug triggers the ultimate drug release according to the claimed rate-controlling mechanism, which is diffusion for the Product Claims, and diffusion or erosion for the Method Claim.” PO Resp. 18–19; Ex. 2015 ¶¶ 71–72.

Petitioner's declarant, Dr. Wilson, testifies otherwise, explaining a person of ordinary skill in the art would understand the plain and ordinary meaning of the claims is simply that—at least both dissolution and diffusion contribute to drug release for claim 1 and at least dissolution and diffusion or dissolution and erosion contribute to drug release for claim 43. Ex. 1042 ¶¶ 9–10. Dr. Wilson also explained that Banker & Rhodes describes a system that utilizes a combination of diffusion and dissolution with a swelling-controlled matrix. *Id.* ¶¶ 18–19. In particular, Banker & Rhodes describes such a system as one where the polymer swells and “allows entrance of water, which causes dissolution of the drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on the polymer-swelling rate, drug solubility, and the amount of soluble fraction in the matrix.” Ex. 1025, 590. Thus, according to the Banker & Rhodes treatise, drug formulations using a “swelling-controlled” matrix may release drugs by “dissolution of the drug and diffusion out of the swollen matrix,” wherein variable factors may control the rate of release. *Id.* In other words, contrary to Patent Owner's assertions, claiming a “controlled release drug” and referring to drug release by “dissolution and diffusion” does not necessarily mean the drug release must be controlled by either dissolution or diffusion.

Upon considering the arguments and evidence, we determine that the broadest reasonable interpretation of (1) “releases said drug . . . by the dissolution and diffusion of said drug out of said matrix” is “releases the drug by dissolution of the drug in the matrix followed by diffusion of the drug out of the matrix”; and (2) “releases said drug into gastric fluid by the dissolving of said drug by said gastric fluid and either erosion of said matrix

or diffusion of said dissolved drug out of said matrix” is “releases the drug into gastric fluid by dissolving the drug by the gastric fluid followed by erosion of the matrix or diffusion of the dissolved drug out of the matrix.”

B. Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. “[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does.” *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

C. The Level of Ordinary Skill in the Art

In large part, the parties agree as to the level of ordinary skill in the art. Pet. 9; PO Resp. 13. Both agree that a person of ordinary skill in the art would be a person with at least a bachelor's degree in chemistry, chemical engineering, pharmaceutical science, and/or material science, as well as substantial experience in development of controlled release oral dosage forms involving polymeric materials. Pet. 9; PO Resp. 13. In light of the parties' general agreement, we adopt that description of the level of ordinary skill in the art for purposes of this proceeding. In our analysis, we consider the applied prior art as representative of the level of ordinary skill in the art.

D. Obviousness over Baveja, the '548 Patent, the Shell 1993 Publication, and the Shell '790 Patent

Petitioner asserts that claims 1, 2, 8, 9, 13–15, 45, and 46 of the '280 patent are unpatentable as obvious over Baveja, the '548 patent, the Shell 1993 publication, and the Shell '790 patent. Pet. 21–35; Pet. Reply 6–13. Petitioner also relies on the Declaration of Clive Wilson, Ph.D. Ex. 1011. Patent Owner disagrees with Petitioner's assertions (PO Resp. 21–40), relying on the Declaration of Harold Hopfenberg, Ph.D. (Ex. 2015).

1. Baveja (Ex. 1008)

Baveja discloses a dosage form comprised of a swellable hydrophilic matrix that exhibits zero-order (i.e., constant) release of a drug. Ex. 1008, Summary. Baveja uses β -adrenergic blockers propranolol hydrochloride, alprenolol hydrochloride, and metoprolol tartrate as model drugs. *Id.* at 40. Baveja describes tablets with different ratios of HPMC, sodium

carboxymethylcellulose (“Na CMC”), and drug, which are then subjected to an in vitro dissolution study. The in vitro dissolution study involves placing the tablets into a dissolution rate test apparatus with diluted HCl (pH 3.0) for three hours and then in 0.2 M phosphate buffer (pH 7.4) for another 9 hours. *Id.*

The results of the dissolution studies for tablets formed from just HPMC and drug are shown in Figures 1–3. For example, Figure 2 is reproduced below:

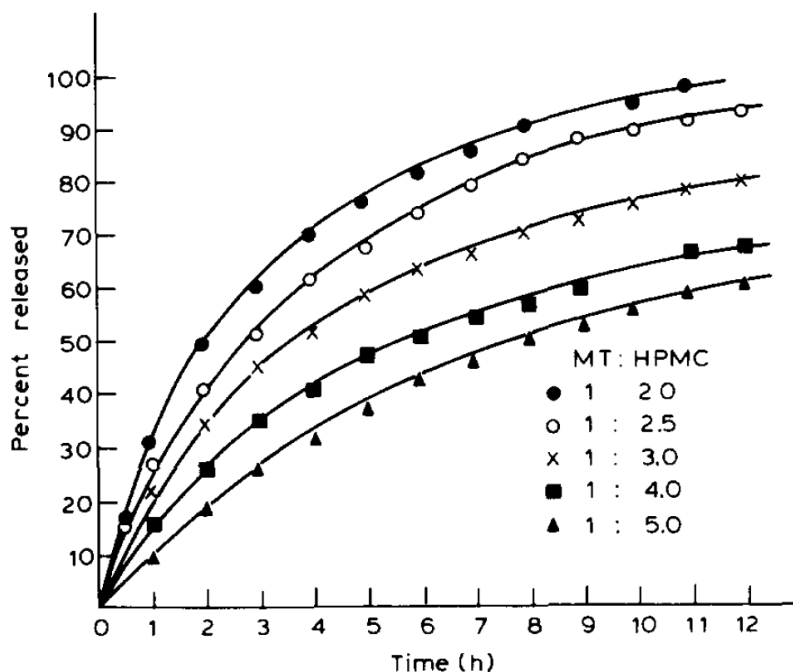


Fig. 2. Release of metoprolol tartrate (cumulative percent) as a function of time from tablets containing drug: HPMC in the ratios given.

Figure 2 illustrates the cumulative percent of metoprolol tartrate released as a function of time from tablets containing metoprolol tartrate and HPMC in the ratios shown. *Id.* at 41.

As explained by Baveja, the rate of release of the tablets made of drug and HPMC decreases with time, which may be due to “an increase in

diffusional path length for the drug[,] which in turn may be due to slower erosion rate of the rubbery layer and faster advancement of swelling front into the glassy polymer.” *Id.*

Baveja also describes tablets formed from HPMC, Na CMC, and drug in varying amounts that exhibit a nearly zero-order rate of release. *Id.*, Abstract.

2. *The '548 Patent (Ex. 1006)*

The '548 patent relates to a controlled release dosage form comprising a drug and at least two different cellulose ethers. Ex. 1006, 1:12–16. According to the '548 patent specification, “[an] object of the present invention is to provide a dosage form of delivering a drug in the gastrointestinal tract that substantially avoids a premature disintegration.” *Id.* at 3:1–4. The '548 patent specification also states that the disclosed invention “delivers a drug at a rate of dosage form release that corresponds to the rate of change of the integrity of the dosage form over a prolonged period of at least eight hours.” *Id.* at 3:4–7.

Moreover, the dosage form uses cellulose ethers, which swell extensively when hydrated and lessen direct drug contact with mucosal tissues. *Id.* at 11:23–26. The drug delivery matrix is suitable for gastric retention over the releasing lifetime of the dosage system. *Id.* at 10:65–68. Furthermore, “when all the drug is released, the system bioerodes into innocuous particles and dissolved polymers that pass from the gastrointestinal tract.” *Id.* at 10:68–11:3.

3. *The Shell 1993 Publication (Ex. 1007)*

The Shell 1993 publication discloses a sustained-release oral drug dosage form that releases a solution of a drug into the stomach and that

comprises a tablet or capsule of a plurality of particles of a solid-state drug dispersed in alkyl cellulose. Ex. 1007, 2:13–17. The alkyl cellulose “swells unrestricted dimensionally via imbibition of gastric fluid to increase the size of the particles . . . with consequent increase in gastric retention time of the particles.” *Id.* at 2:17–21. The dosage form also “permits dissolution of the dispersed drug by imbibed gastric fluid while the drug is within the particle and release of the resulting solution” and “maintains its physical integrity over at least a substantial portion of the time period during which the drug is released into the stomach and then dissolves.” *Id.* at 2:23–31.

4. *The Shell '790 Patent (Ex. 1005)*

The Shell '790 patent discloses a sustained-release oral dosage form that “is retained well in the stomach and releases drug as a solution into the stomach.” Ex. 1005, 1:6–9. The dosage form comprises a plurality of solid particles composed of a solid-state drug dispersed within a hydrophilic, water-swellaable polymer that swells in gastric fluid to increase the particle size to a level that promotes retention in the stomach over the time period. *Id.* at 1:54–60. The dosage form also “permits slow dissolution of the dispersed drug by gastric fluid and release of the resulting solution from the particles.” *Id.* at 1:60–62. Finally, the dosage form “maintains its physical integrity over at least a substantial portion of the time period and thereafter rapidly dissolves.” *Id.* at 1:65–67.

5. *Analysis*

Petitioner asserts that claims 1, 2, 8, 9, 13–15, 45, and 46 of the '280 patent are unpatentable as obvious over Baveja, the '548 patent, the Shell 1993 publication, and the Shell '790 patent. We have reviewed the arguments and evidence presented by both parties, and we are not persuaded

that Petitioner has shown by a preponderance of the evidence that the claims are unpatentable as obvious over the cited references.

Petitioner argues that each limitation of claim 1 is disclosed in at least one of the four cited references. Pet. 22–28. For example, Petitioner notes that each reference discloses controlled-release oral drug dosage forms comprising a polymeric matrix. *Id.* at 22; *see also* Ex. 1008, Summary; Ex. 1006, 1:12–19; Ex. 1007, 2:13–17; Ex. 1005, 1:54–58. Petitioner also asserts that the Shell 1993 publication discloses that the dosage form when swollen in a dimensionally unrestricted manner is of a size that promotes retention in the stomach. Pet. 23–24; *see also* Ex. 1007, 2:17–21 (stating the dosage form “swells unrestricted dimensionally via imbibition of gastric fluid to increase the size of the particles . . . with consequent increase in gastric retention time of the particles”). Petitioner further states that the Shell 1993 publication discloses that the release rate of the drug is by dissolution and diffusion. Pet. 24–25; *see also* Ex. 1007, 7:2–6 (“The release rate of the drug(s) from the particle is primarily dependent upon the rate at which the drug(s) is leached from the particles, which in turn is related to the dissolution rate of the drug, the particle size and drug concentration in the particle.”). Petitioner also states that Figures 1 and 2 of Baveja disclose drug release studies in which the dosage forms retained at least 40% of the drug after one hour and released at least 80% of the drug after immersion in gastric fluid. Pet. 25–26; *see also* Ex. 1008, Figs. 1–2. Finally, Petitioner notes that at least the Shell ’790 patent discloses a dosage form that remains substantially intact until substantially all of the drug is released. Pet. 27; Ex. 1005, 2:60–67 (stating “the polymer maintains its integrity (i.e., it does not significantly or appreciably dissolve, erode or

otherwise decompose or degrade) over at least a substantial portion (i.e., at least about 90% and preferably over 100%) of the intended dosing period”).

Based on the evidence presented above, we are persuaded that Petitioner has shown that each limitation of claim 1 is separately disclosed by at least one of the cited references. Our analysis, however, does not end there. A patent “is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. Petitioner must also show that there was a reason to combine those elements to achieve the claimed invention with a reasonable expectation of success. *See PAR Pharm.*, 773 F.3d at 1193. To make that determination, we can look to “interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art.” *KSR*, 550 U.S. at 418. We can also look to the nature of the problem to be solved. *In re Gartside*, 203 F.3d 1305, 1319 (Fed. Cir. 2000) (holding that suggestion to combine “may come from, *inter alia*, the teachings of the references themselves and, in some cases, from the nature of the problem to be solved”). After considering the parties’ arguments and evidence, however, we are not persuaded that Petitioner has shown by a preponderance of the evidence that a person of ordinary skill would have combined the teachings in the manner recited by the claims with a reasonable expectation of success.

Petitioner argues that a person of ordinary skill in the art with knowledge of Baveja, the ’548 patent, the Shell 1993 publication, and the Shell ’790 patent would have known how to make a dosage form containing all the elements of claim 1 of the ’280 patent. Pet. 21 (citing Ex. 1011

¶¶ 151–61). In particular, Petitioner contends that a person of ordinary skill in the art would have been motivated to combine the teachings of the cited art because all of the references “are intended to solve the same problem; that is, the controlled release of a drug.” *Id.*; Pet. Reply 12–13 (citing Ex. 1042 ¶¶ 8–20, 77–80, 81, 85). As such, Petitioner argues that a person of ordinary skill in the art reading Baveja would look to the other references “for further examples of formulations that would be compatible with the teachings of Baveja.” Pet. 21. According to Petitioner’s declarant, Dr. Wilson, a person of ordinary skill in the art would have understood that the matrices and release profiles disclosed in the ’548 patent and Shell 1993 publication were also appropriate for use in a sustained-release drug dosage form such as those disclosed in Baveja. Ex. 1011 ¶ 158. Finally, Petitioner argues that a person of ordinary skill in the art would have been motivated to combine the cited references because they have interrelated teachings. Pet. 22 (citing Ex. 1011 ¶ 159); Pet. Reply 13 (citing Ex. 1042 ¶¶ 82–83, 86). For example, Petitioner states that all of the references relate to controlled release oral drug dosage forms and each describes polymer matrices that swell when hydrated. Pet. 22; Pet. Reply 13.

Upon considering the full trial record, however, we find Petitioner’s arguments to be overly vague and nonspecific. Although it is true that our obviousness approach should be “expansive and flexible,” *KSR*, 550 U.S. at 415, “patents are not barred just because it was obvious ‘to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.’” *Procter &*

Gamble Co. v. Teva Pharms USA, Inc., 566 F.3d 989, 997 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

Thus, even though the references may have interrelated teachings and are intended to solve the same problem of controlled drug release, Petitioner has not explained persuasively *how or why* a person of ordinary skill in the art would have combined the various features of the cited prior art references in the manner recited by the claims. Indeed, Petitioner has not even explained what features of which references a person of ordinary skill in the art would have combined to derive the claimed invention and why that person would have done so.

Given the numerous possible combinations of references, during oral argument, the panel asked counsel for Petitioner which references Petitioner really needs for its obviousness challenge:

JUDGE HULSE: Do you really need all four of these references to make out your case?

[COUNSEL FOR PETITIONER]: No, Your Honor, we do not.

JUDGE HULSE: Which would you primarily rely on?

[COUNSEL FOR PETITIONER]: Shell '93, Your Honor. If we were asked that question, we think Shell '93, together with one or any of the – would render these claims obvious.

Tr. 28.

But even if we were to focus on the Shell 1993 publication, we are still not persuaded that Petitioner has met its burden. We agree with Patent Owner that the Shell 1993 publication does not teach a dosage form that “releases substantially all of said drug after [immersion in gastric fluid].”

PO Resp. 35 (citing Ex. 2015 ¶¶ 148–50). According to the broadest reasonable interpretation of this limitation, Petitioner must show that the Shell 1993 publication teaches a dosage form that releases “at least 80% of said drug” after immersion in gastric fluid. Petitioner has failed to do so. Petitioner relies on Example 1 and Figure 1 as disclosing this limitation. Pet. 26 (citing Ex. 1007, Example 1, Figure 1). Figure 1, which illustrates the results of Example 1, is reproduced below:

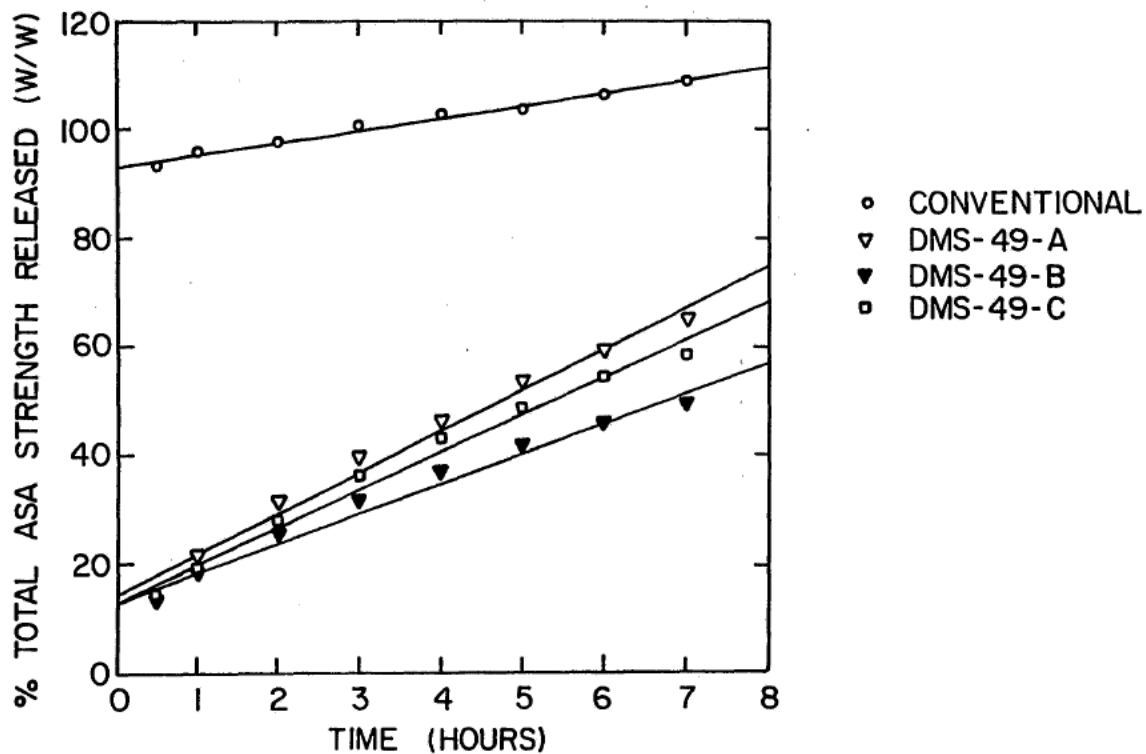


FIG. 1.

Figure 1 depicts the percentage of aspirin released over time for the various drug formulations tested, including conventional aspirin without hydroxypropylcellulose. Ex. 1007, 13–14.

As an initial matter, claim 1 requires that the dosage form release “substantially all of *said drug*” after immersion in gastric fluid. The “said

drug” of claim 1 is a drug “whose solubility in water is greater than one part by weight of said drug in ten parts by weight of water.” Petitioner has not shown that the aspirin tested in Example 1 of the Shell 1993 publication satisfies this solubility requirement. Moreover, even if aspirin were highly soluble, Figure 1 does not show that any of the dosage forms (other than conventional aspirin) released at least 80% of the drug over the course of the seven-hour experiment.⁸ Ex. 1007, Fig. 1, *see also id.* at 13–14. Thus, we find that the Shell 1993 publication does not teach a dosage form that “releases substantially all of said drug.”

We agree with Petitioner, however, that at least Baveja and the Shell ’790 patent teach a dosage form that does satisfy this limitation.⁹ Pet. 26–27 (citing Ex. 1008, Fig. 1; Ex. 1005, Example 2). Despite this determination, however, it is unclear which reference or combination of references Petitioner contends a person of ordinary skill in the art would rely on to modify the dosage form of the Shell 1993 publication. That is, Petitioner does not explain persuasively *why or how* a person of ordinary skill in the art would modify the drug formulation of the Shell 1993 publication in view of Baveja and/or the Shell ’790 patent to develop a drug formulation that releases at least 80% of a highly soluble drug. *See InTouch Techs., Inc. v. VGO Commc’ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014) (reversing

⁸ The “conventional” dosage form tested is a tablet of aspirin without hydroxypropylcellulose. Ex. 1007, 13–14.

⁹ Petitioner also argues that “Example 3 of the ’548 patent describes a dosage form that releases approximately 80% of its ibuprofen after eight hours.” Pet. 26 (citing Ex. 1006, Example 3, Fig. 6). We, however, are not persuaded that the ’548 patent teaches this limitation, because Petitioner has not directed us to evidence that ibuprofen is a highly soluble drug.

district court's judgment of invalidity where expert's testimony "was vague and did not articulate reasons why a person of ordinary skill in the art at the time of the invention would combine these references").

Nor are we persuaded that Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in combining the drug formulations of the cited references. As Patent Owner notes, Petitioner's declarant testified about several formulation considerations that impact drug release. PO Resp. 22. Such considerations include the drug to polymer ratio (Ex. 2023, 78:17–23), type of polymer used (*id.* at 79:24–80:5), and particle size (*id.* at 99:10–100:15). Dr. Wilson also testified that formulating a reliable gastric retentive controlled release dosage form is "very difficult." *Id.* at 101:10–15. Given this testimony from Petitioner's own declarant, we credit the testimony of Patent Owner's declarant, Dr. Hopfenberg, that "[m]atrices formulated with a given polymer in a dosage form can result in different release controlling mechanisms, depending on the details of the matrix formulation and drug solubility characteristics." Ex. 2015 ¶ 163. Accordingly, we find that Petitioner does not address sufficiently why a person of ordinary skill in the art would believe it could modify the formulation of the Shell 1993 publication to incorporate the drug release profile of Baveja and/or the Shell '790 patent without, for example, affecting the other desired properties of the Shell 1993 publication formulation (e.g., the swelling in a dimensionally unrestricted manner to a size that promotes gastric retention).

Furthermore, establishing persuasively a reasonable expectation of successfully combining elements known in the art first requires some clear

articulation of that combination, which, as explained above, is missing when examined through the lens of the full trial record. Petitioner has not identified any combinations of the cited references that would be most promising to try. Instead, Petitioner's declarant makes conclusory assertions that "it would be natural for a [person of ordinary skill in the art] to combine the teachings of these references" and that a person of ordinary skill in the art would have expected success in combining the references because that person "would be focused on the characteristics necessary to achieve those goals." Ex. 1042 ¶¶ 86–87.

In contrast, Patent Owner's declarant, Dr. Hopfenberg, credibly explains why a person of ordinary skill in the art would not have a reasonable expectation of success in combining the references. For example, Dr. Hopfenberg testifies that a person of ordinary skill in the art would expect the drug release characteristics of Baveja to change if the disclosed dosage forms were reformulated to remain substantially intact. Ex. 2015 ¶ 179. Dr. Hopfenberg also explains that a person of ordinary skill in the art reading the Shell 1993 publication would not modify that dosage form according to the Shell '790 patent. Ex. 2015 ¶ 165. Dr. Hopfenberg explains that the Shell 1993 publication is described as an "improvement" of the formulation of the Shell '790 patent. *Id.* (quoting Ex. 1007, 1:20–22). Specifically, Dr. Hopfenberg notes that, unlike the polymers in the '790 patent, the polymers described in the Shell 1993 publication are not crosslinked and are "inherently safer." *Id.* (quoting Ex. 1007, 1:30–32). Thus, we are persuaded that Petitioner has not established by a preponderance of the evidence that the prior art would have guided a person of ordinary skill in the art to combine prior art elements in a manner that

would have yielded the claimed invention. *See, e.g., In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1071 (Fed. Cir. 2012) (describing a proposed combination of known elements without direction or guidance regarding “which of many possible choices is likely to be successful” as involving impermissible hindsight) (quoting *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009)).

We agree with Patent Owner that Petitioner’s obviousness challenge amounts to picking and choosing certain preferred attributes of the various references and combining them to yield the claimed invention. PO Resp. 1–2. We are also persuaded by Dr. Hopfenberg’s testimony that such a piecemeal combination reflects impermissible hindsight. *See, e.g., Ex. 2015 ¶ 177* (“Only in hindsight can the preferred attributes of Baveja and the ’548 Patent be selectively retained and combined with the desired integrity of Shell 1993 Pub. and the Shell ’790 Patent dosage form.”); *see Cheese Sys., Inc. v. Tetra Pak Cheese and Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) (“Obviousness ‘cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.’”) (citation omitted).

Accordingly, after considering the parties’ arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1, 2, 8, 9, 13–15, 45, and 46 of the ’280 patent are unpatentable as obvious over Baveja, the ’548 patent, the Shell 1993 publication, and the Shell ’790 patent.

E. Obviousness of Claim 43 over the Shell 1993 Publication, Baveja, and Colombo

Petitioner asserts that claim 43 of the '280 patent is unpatentable as obvious over the Shell 1993 publication, Baveja, and Colombo. Pet. 42–45; Pet. Reply 6–13. Patent Owner disagrees with Petitioner's assertions. PO Resp. 40–49. We incorporate here our earlier findings and discussion regarding the disclosures of the Shell 1993 publication and Baveja.

1. Colombo (Ex. 1009)

Colombo relates to swellable matrix systems in the form of a tablet comprising a mixture of the drug diltiazem, HPMC, ethylcellulose, and mannitol. Ex. 1009, 44. Colombo discloses three different matrices: Case 0, the plain matrix; Case 1, the matrix coated with cellulose acetate propionate ("CAP") on one face; and Case 2, the matrix coated with CAP on both faces. *Id.* Colombo describes "[s]welling and release experiments" in which the matrices were swollen in deionized water for 120 minutes, and the drug release measurements were obtained concomitantly with the matrix swelling observations. *Id.*

Colombo describes and depicts the morphological changes in the matrices over time, observing that, in the uncoated system (Case 0), "[v]ery quickly (after 15 min) the swelling of the matrix moves both in axial and radial directions." *Id.* Colombo also discloses the drug release profiles of the systems. *Id.* at 45. Figure 5 of Colombo is reproduced below:

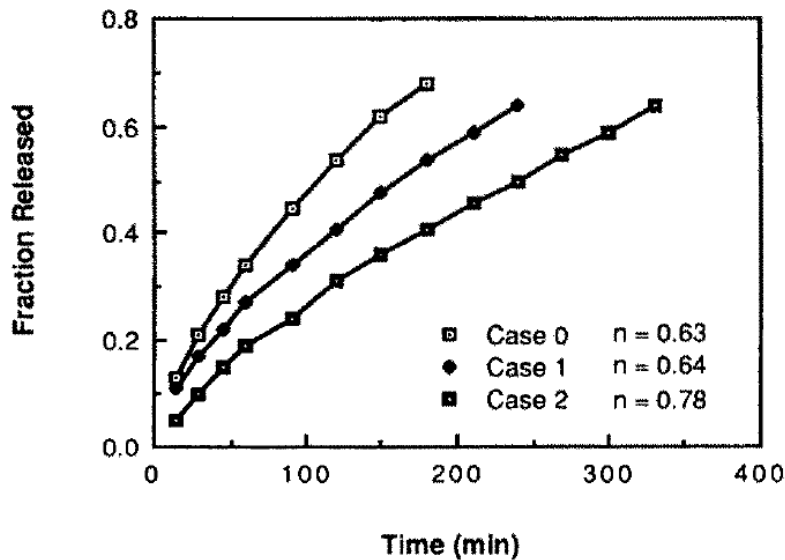


Fig. 5. Drug release profiles of the systems. Calculated values of exponent n of Eqn 2 are also shown.

Figure 5 depicts the fraction of diltiazem released over time for the Case 0, Case 1, and Case 2 matrices.

2. Analysis

Petitioner asserts that the subject matter of claim 43 of the '280 patent would have been obvious over the Shell 1993 publication, Baveja, and Colombo. Petitioner argues that Colombo and Baveja each “disclose the limitations set forth in claim 43, except for the method of administration, which . . . is expressly disclosed by . . . the Shell 1993 Publication.” Pet. 42–43. Petitioner also argues that the Shell 1993 publication expressly discloses all of the limitations set forth in claim 43. *Id.* at 43.

For the same reasons explained above, we are not persuaded that the Shell 1993 publication teaches a drug dosage form that “releases substantially all of said drug within about ten hours after [immersion in gastric fluid].” We are also not persuaded that Colombo teaches this limitation, as Figure 5 does not show any formulation that ever releases at least 80% of the drug, as required by the claims. Ex. 1009, Fig. 5.

Nevertheless, as explained above, we find that the Baveja reference discloses this limitation.

Baveja, however, fails to teach a dosage form that “when swollen in a dimensionally unrestricted manner as a result of imbibition of gastric fluid is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach said fed mode” (i.e., the “swelling” limitation). *See supra*. As explained above, the Shell 1993 publication teaches this limitation. Thus, we are persuaded that Petitioner has shown that each limitation of claim 43 was separately known in the art, as evidenced by the teachings of the Shell 1993 publication, Baveja, and Colombo.

Petitioner argues that a person of ordinary skill in the art would have been motivated to combine the references because they are intended to solve the same problem and would have understood that the dosage forms of Baveja and Colombo are also appropriate for administration, like those described in the Shell 1993 publication. Pet. 44 (citing Ex. 1011 ¶ 190). Petitioner also contends that the references have interrelated teachings and that it would, therefore, be “natural” for a person of ordinary skill in the art to combine the teachings of the references. *Id.* at 44–45 (citing Ex. 1011 ¶ 191).

For the same reasons stated above with respect to claim 1, however, we find that Petitioner has not shown sufficiently that a person of ordinary skill in the art would have had a reason to combine the references to achieve the claimed invention with a reasonable expectation of success. In other words, Petitioner has not articulated reasoning with rational underpinnings to support a motivation to combine the teachings of the prior art. *KSR*, 550

U.S. at 417–18 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

Accordingly, after considering the parties’ arguments and the supporting evidence, we determine that Petitioner has not shown by a preponderance of the evidence that claim 43 is unpatentable as obvious over the Shell 1993 publication, Baveja, and Colombo.

F. Secondary Considerations of Nonobviousness

In light of our determination that Petitioner has not shown by a preponderance of the evidence that any of the challenged claims are unpatentable as obvious, we need not reach the merits of Patent Owner’s evidence of secondary considerations of nonobviousness.

III. MOTIONS TO EXCLUDE EVIDENCE

Both parties filed motions to exclude evidence offered by the opposing side. The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence (“FRE”). See 37 C.F.R. §§ 42.20(c), 42.62(a). We address each party’s motion in turn.

1. Petitioner’s Motion to Exclude Evidence

Petitioner moves to exclude Exhibits 2163 and 2165, which are a textbook chapter and a journal article, under FRE 401, 402, and 403. Paper 49. Because we did not rely on either of these exhibits or any testimony associated with these exhibits in reaching our Decision here, we dismiss Petitioner’s motion to exclude as moot.

2. *Patent Owner's Motion to Exclude Evidence*

Patent Owner moves to exclude claim charts from the copending district court litigation (Ex. 1015) and corresponding testimony relying on the claim charts as irrelevant and prejudicial under FRE 401, 402, and 403. Paper 51, 2–4. We do not rely on Exhibit 1015 or any of the corresponding testimony in reaching our Decision here. Accordingly, we dismiss Patent Owner's motion to exclude this evidence as moot.

Patent Owner also moves to exclude (1) the declaration and report of Dr. Kinam Park (Exhibits 1019 and 1029), and corresponding testimony relying on those exhibits as unreliable expert opinion (Paper 51, 1–2); and (2) allegedly new opinions raised by Dr. Wilson in his Reply Declaration (Ex. 1042) (Paper 51, 4–10). Patent Owner's arguments, however, go to the weight of the evidence presented, and not to the admissibility. As explained above, we accorded Dr. Park's test results little to no weight. And as for the allegedly new opinions of Dr. Wilson, to the extent any evidence was improperly presented, we have declined to rely on it in reaching our Decision. Regardless, we need not reach the merits of Patent Owner's motion to exclude because, even considering the disputed evidence, Petitioner has not shown by a preponderance of the evidence that any of the claims are unpatentable as obvious. Accordingly, Patent Owner's motion to exclude this evidence is dismissed as moot.

IV. CONCLUSION

We conclude that Petitioner has not shown by a preponderance of the evidence that claims 1, 2, 8, 9, 13–15, 43, 45, and 46 of the '280 patent are unpatentable under 35 U.S.C. § 103.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1, 2, 8, 9, 13–15, 43, 45, and 46 of the '280 patent are not held unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is *dismissed*;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is *dismissed*; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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