Trials@uspto.gov
Tel: 571-272-7822

Paper 55
Entered: October 5, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS II LLC,
Petitioner,

v.

COSMO TECHNOLOGIES LTD.,
Patent Owner.

Case IPR2015-00988
Patent 6,773,720 B1

Before JACQUELINE WRIGHT BONILLA, SHERIDAN K. SNEDDEN, and SUSAN L. C. MITCHELL, *Administrative Patent Judges.*

BONILLA, *Administrative Patent Judge*.

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

I. INTRODUCTION

Coalition For Affordable Drugs II LLC ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–4 of U.S. Patent No. 6,773,720 B1 (Ex. 1001, "the '720 patent"). Paper 1 ("Petition" or "Pet."). Cosmo Technologies Ltd. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp."). Thereafter, we instituted *inter partes* review of claims 1–4 of the '720 patent based on a ground that those claims would have been obvious under 35 U.S.C. § 103(a). Paper 8 ("Dec. on Inst."), 3, 20.

After institution of trial, Patent Owner filed a Response to the Petition, Papers 17, 18 ("PO Resp."), and Petitioner filed a Reply to the Response, Papers 31, 32 ("Reply").[1] Patent Owner also filed a Motion for Observation on the Cross-Examination of Petitioner's Reply Witness, Christine S. Meyer, Ph.D. (Paper 43), and Petitioner filed a Response to that Motion (Paper 47).

In addition, Patent Owner filed a Motion to Exclude certain evidence submitted by Petitioner (Paper 42), Petitioner filed an Opposition to the Motion (Paper 46), and Patent Owner filed a Reply to the Opposition to its Motion to Exclude (Paper 49). Petitioner likewise filed a Motion to Exclude certain evidence submitted by Patent Owner (Paper 44), and Patent Owner filed an Opposition to that Motion (Paper 45).

An oral hearing was held on August 5, 2016. A transcript of the hearing has been entered into the record. Paper 54 ("Tr.").

[1] The two listed paper numbers correspond to confidential and public versions of the papers.

We have jurisdiction under 35 U.S.C. § 6. 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 1–4 of the '720 patent are unpatentable. We deny both parties' Motions to Exclude Evidence.

A. Ground of Unpatentability at Issue

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. § 103(a) on the ground that claims 1–4 would have been obvious over Groenendaal (Ex. 1005)[2] and Leslie (Ex. 1003).[3] Pet. 13–14, 48–60.

Petitioner supports its challenges to the claims in the Petition with a Declaration by Anthony Palmieri III, Ph.D. ("Palmieri Decl.") (Ex. 1037). With its Response, Patent Owner presents the Declarations by Gordon Rausser, Ph.D. ("Rausser Decl.") (Ex. 2016), Michael S. Epstein, M.D. ("Epstein Decl.") (Ex. 2157), and Robert K. Prud'homme, Ph.D. ("Prud'homme Decl.") (Ex. 2192). With its Reply, Petitioner presents a Declaration by Christine S. Meyer, Ph.D. ("Meyer Decl.") (Ex. 1059).

B. Related Proceedings

The parties identify the following as related district court proceedings regarding the '720 patent: *Shire Dev. LLC v. Mylan Pharm., Inc.*, FLMD-8-12-cv-01190 (M.D. Fla.) (filed May 25, 2012); *Shire Dev. LLC v. Watson Pharm., Inc.*, FLSD-0-12-60862 (S.D. Fla.) (filed May 8, 2012); *Shire Dev. LLC v. Osmotical Pharm. Corp.*, GAND-1-12-cv-00904 (N.D. Ga.) (filed

---

[2] Groenendaal et al., EP Appl. Publ. No. 0 375 063 A1, filed Dec. 18, 1989, published on June 27, 1990 ("Groenendaal") (Ex. 1005).

[3] Leslie, U.S. Patent No. 3,965,256, filed June 5, 1974, issued June 22, 1976 ("Leslie") (Ex. 1003).

March 16, 2012); *Shire Dev. LLC v. Cadila Healthcare Ltd.*, DED-1-10-cv-00581 (D. Del.) (filed July 7, 2010). Pet. 2–3; Paper 5, 2.

C. The '720 Patent

The '720 patent is directed to controlled release oral pharmaceutical compositions containing 5-amino salicylic acid, also known as mesalazine or 5-ASA, as an active ingredient. Ex. 1001, 1:4–6. Mesalazine is used to treat Crohn's disease and ulcerative colitis, which involve inflammation of the intestines. *Id*. at 1:9–11. The compositions comprise (1) "an inner lipophilic matrix consisting of substances with [a] melting point below 90° C. in which the active ingredient is at least partially inglobated," and (2) "an outer hydrophilic matrix in which the lipophilic matrix is dispersed." *Id*. at 2:36–44. The specification describes that "[p]art of mesalazine can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix." *Id*. at 3:34–39.

The specification states that the "lipophilic matrix consists of substances selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40 to 90° C." *Id*. at 3:1–5. In addition, the hydrophilic matrix "consists of excipients known as hydrogels," which include "compounds selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid." *Id*. at 3:18–30.

D. Claims

The '720 patent contains four claims. Independent claim 1 and dependent claim 4 are reproduced in their entirety below.

> 1. Controlled-release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid, comprising:
>
> a) an inner lipophilic matrix consisting of substances selected from the group consisting of unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglycerids, waxes, ceramides, and cholesterol derivatives with melting points below 90º C., and wherein the active ingredient is dispersed both in [] the lipophilic matrix and in the hydrophilic matrix;
>
> b) an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of compounds selected from the group consisting of polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, and natural or synthetic gums;
>
> c) optionally other excipients;
>
> wherein the active ingredient is present in an amount of 80 to 95% by weight of the total composition, and wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.
>
> 4. A process for the preparation of the compositions of claim 1, which comprises:
>
> a) melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90º C.;
>
> b) mixing the granules from step a) with the hydrophilic excipients and subsequent tabletting or compression.

Claim 2 depends from claim 1, and recites the "5-aminosalicylic acid is dispersed in a molten lipophilic matrix by kneading, extrusion and/or

granulation." Claim 3, which also depends from claim 1, recites that the composition is "in the form of tablets, capsules, mintablets."

II. ANALYSIS

A. Level of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the relevant art (hereafter "POSA" or "ordinary artisan") includes someone with "a Pharm. D. or a Ph.D. in pharmacy, pharmacology, or a related discipline; an M.D. with experience in using 5-amino salicylic acid (5-ASA)"; "a BS in pharmacy with at least two years of experience formulating active pharmaceutical ingredients"; or "a Ph.D. in Pharmaceutics, Chemistry or a related field with 2–3 years of experience formulating active pharmaceutical ingredients, including controlled release formulations." Pet. 18 (quoting Palmieri Decl., Ex. 1037 ¶ 15); Reply 2–5. According to Petitioner, a POSA "may work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others on the team, to solve a given problem. For example, a formulator, dissolution expert and a clinician may be part of the team." *Id*. (quoting Ex. 1037 ¶ 15).

Patent Owner contends that a POSA "as of July 14, 1999 would have had a formal education of at least a Bachelor's degree in the fields of pharmacy or chemical engineering, combined with a minimum of three years of experience in the field of drug delivery technology or similar technical field of study." PO Resp. 7 (citing Prud'homme Decl., Ex. 2192 ¶ 19).

The contentions by the two parties in this regard do not diverge dramatically. Reply 2–3 (citing Ex. 1125, 101:10–13). We adopt the level of ordinary skill in the art as described by Petitioner and its witness,

Dr. Palmieri, because it is consistent with the subject matter before us, the '720 patent, and prior art of record. We agree that a POSA, in the relevant time frame, would have included a person having a Bachelor's degree in pharmacy with at least two years of experience formulating active pharmaceutical ingredients or, alternatively, the other levels of experience indicated by the parties. Pet. 18; PO Resp. 7.

B. Claim Construction

In an *inter partes* review, we interpret claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). 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. *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. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In a section of the Petition entitled "Claim Construction of Challenged Claims," Petitioner provides proposed constructions of certain terms in the challenged claims. Pet. 10–13. For example, Petitioner argues that "matrix" means "a macroscopically homogeneous structure in all its volume." Pet. 10 (citing Ex. 1001, 3:42–45). Petitioner also construes "consisting of substances selected from the group consisting of" and "consists of compounds selected from the group consisting of" in claim 1 as relating to the recited inner lipophilic matrix and outer hydrophilic matrix, respectively. *Id*. at 12–13. Petitioner contends that "[a]lthough 'substances' and

'compounds' are written in the plural form, the broadest reasonable interpretation of the terms also includes the singular form where, as here, the plural merely refers to a group of objects." *Id*. at 12.

Patent Owner does not challenge the above-mentioned proposed constructions. *See* Prelim. Resp. 18–20 (discussing, but not disagreeing with, Petitioner's proposed claim construction of "matrix"); PO Resp. 8–13. We conclude that the proposed claim constructions asserted by Petitioner regarding the above-mentioned terms correspond to a broadest reasonable interpretation of those terms in view of the specification at issue.

Beyond those terms, a significant dispute exists between the parties regarding the term "waxes" in claim 1. "Waxes" are included in the recited Markush group in relation to the "inner lipophilic matrix" of the composition of claim 1. In its claim construction section, the Petition does not provide a construction for this term per se. Pet 10–13. The Petition indirectly offers a relevant construction of "waxes," however, in its arguments pertaining to Leslie at issue in the unpatentability ground before us. *Id*. at 21–23 (discussing Ex. 1003 in relation to the "inner lipophilc matrix" recited in claim 1). Specifically, Petitioner contends that "a higher aliphatic alcohol such as cetyl alcohol," which is disclosed in Leslie, is a "wax." *Id*. at 21 (citing Ex. 1003, 4:58 (disclosing cetyl alcohol as a preferred higher aliphatic alcohol), 12:30–35 (Example 4), 13:28–31 (Example 6) (disclosing the use of cetyl alcohol in when preparing slow release tablets)).

In support, relying on testimony by Dr. Palmieri, Petitioner argues that "aliphatic alcohols, such as cetyl alcohol, were well known at the time as lipophilic substances." *Id*. at 21 (citing Ex. 1037 ¶ 77; Ex. 1031, 5:49–60). Petitioner refers us to a "leading pharmaceutical treatise[]," which

describes cetyl alcohol as "'*waxy*, white flakes, granules, cubes, or castings' with a melting point of 49°C." *Id*. at 21–22 (citing Ex. 1032, 99, 102; Ex. 1037 ¶¶ 78–80) (emphasis added); Reply 7. Thus, according to Petitioner and Dr. Palmieri, a POSA would have interpreted the term "waxes" in claim 1 to encompass "cetyl alcohol and other higher alcohols." Pet. 22 (citing Ex. 1037 ¶¶ 78–79).

Petitioner also cites to two U.S. patents, one disclosing certain controlled release oral dosage forms (Ex. 1034, "the '189 patent") and another relating to methods of manufacturing wax matrices (Ex. 1035, "the '410 patent"). Pet. 22 (citing Ex. 1034, 2:46–56; Ex. 1035, 3:50–57); Reply 7. The '189 patent describes "at least one wax" as including cetyl alcohol. Ex. 1034, 2:46–56. The '410 patent refers to "waxes which are solid at room temperature such as higher fatty acids, higher fatty acid ester derivatives, higher alcohols and higher alcohol ester derivatives, among others," without mentioning cetyl alcohol in particular. Ex. 1035, 3:50–57.

By contrast, Patent Owner, relying on testimony of its expert, Dr. Prud'homme, argues that "waxes" should be defined chemically as "an ester of a high molecular weight monohydric alcohol and high molecular weight fatty acid," which does not include fatty alcohols, such as cetyl alcohol. PO Resp. 9–13 (citing Ex. 2192 ¶¶ 88–89). In support, Patent Owner and its expert cite numerous relevant treatises, textbooks, and dictionaries, all of which support the chemical definition of "waxes" as Patent Owner proposes, i.e., that "waxes" are esters. *Id*. at 9–11; Ex. 2192 ¶ 89; Ex. 2194, 388, 390, 1st col.; Ex. 2209, 964, 1st col.; Ex. 2210, 1467–68; Ex, 2211, 236, 121, 217 (contrasting definitions of "cetyl alcohol," "beeswax," and "carnauba wax"); Ex. 2212, 1100; Ex. 2220, 403–404

(contrasting definitions of "cetyl alcohol" (a "[f]atty alcohol") and "cetyl esters" (a "[s]ynthetic wax")).

Patent Owner also contends that Petitioner's definition of "waxes," which includes any substance that is "waxy" or has "wax-like" properties, is unreasonably broad, not least of which because "those properties fail to distinguish many substances that fall under the other Markush groups" in challenged claim 1. PO Resp. 11–13. Patent Owner further argues that patents are not reliable sources of extrinsic evidence regarding claim construction. *Id*. at 13.

In view of the record before us, we agree with Patent Owner's construction of "waxes" in claim 1, i.e., that the term "waxes" does not include cetyl alcohol or other higher alcohols that are not esters. That construction is consistent with the term's use in the challenged claims, the specification of the '720 patent, multiple treatises and dictionary definitions of the term, as well as extrinsic evidence definitions of "cetyl alcohol" and uses of that term in the prior art.

For example, certain prior art, as cited by Petitioner, refers to cetyl alcohol as "waxy," but not as a "wax" per se. Pet. 21–22; Ex. 1032, 99, 102; Reply 7. We are not persuaded that all "waxy" or "wax-like" substances are "waxes" as recited in claim 1. Patent Owner points to evidence indicating that, beyond "waxes," other members of the "inner lipophilic matrix" Markush group in claim 1 include many substances that are "waxy" or "wax-like." PO Resp. 12 (citing Ex. 2192 ¶ 95 (explaining, with citations to evidence, how other members of the recited group are "waxy" or "waxlike")).

In addition, the two U.S. patents listing cetyl alcohol or higher alcohols generally as "waxes" are outweighed significantly by non-patent extrinsic evidence in the form of relevant treatises, textbooks, and dictionaries that chemically define "waxes" as being esters. *See, e.g.*, Ex. 2210, 1467–68 (defining "wax" as including cetyl ester, but not cetyl alcohol); *see also* PO Resp. 9–12 (providing multiple citations to treatises, textbooks, and dictionaries).

Petitioner's contentions in its Reply do not persuade us otherwise. For example, Petitioner refers to a book entitled "Food Lipids," which discusses the "Chemistry of Waxes and Sterols." Ex. 1062, 89. This reference acknowledges that "[b]y a strict chemical definition, a wax is the ester of a long chain acid and a long chain alcohol." *Id*. The reference goes on to state that "this academic definition is much too narrow both for the wax chemist and for the requirements of the industry," indicating that a broader definition—one that includes an extensive list of substances, including any "hydrocarbons, wax esters, sterol esters, ketones, aldehydes, alcohols, and sterols" possessing certain wax properties—"better fits the reality." *Id*. This reference does not persuade us to construe "waxes" in claim 1 as Petitioner contends, however, because it relates to "Food Lipids" rather than controlled release oral pharmaceuticals, and the reference does not dispute that "wax" has a specific chemical definition that does not include cetyl alcohol.

Looking at the entire record before us, both intrinsic and extrinsic evidence indicate that the term "waxes" in claim 1 refers to a chemical definition of the term, and not to a significantly broader group of substances that happens to have wax properties. The construction offered by Petitioner

is unreasonably broad in light of the term's well understood chemical definition, the relevant Markush group in challenged claim 1 itself, which includes a number of different forms of fatty acids having wax properties (Ex. 2192 ¶ 95) in addition to waxes, and in light of the specification of the '720 patent, which only uses chemically defined waxes (i.e., carnauba wax or beeswax) in all five of its examples. Ex. 1001, 4:6–6:31.

In its Reply, Petitioner further argues that cetostearyl alcohol, also disclosed in Leslie, qualifies as a wax, and asserts that Patent Owner's expert, Dr. Prud'homme, admits as much. Reply 7–8 (citing Ex. 1003, 14:54–60, 15:15-17; Ex. 1125, 230:3–9, 233:12–16). In addition, Petitioner relies on a different patent by Leslie (Ex. 1031, "the '433 patent") and another reference, the "Handbook of Pharmaceutical Excipients," discussing emulsifying wax. Reply 7 (citing Ex. 1031, 2:45–53; Ex. 1057, 2).

The passage in the '433 patent cited by Petitioner, however, discloses that a lipophilic phase in a cream may contain a higher aliphatic alcohol, such as cetyl alcohol or cetostearyl alcohol. Ex. 1031, 2:45–53. This passage does not indicate that cetyl alcohol and/or cetostearyl alcohol correspond to "waxes." In addition, the Handbook of Pharmaceutical Excipients indicates that "emulsifying wax contains cetostearyl alcohol, purified water, and either sodium lauryl sulfate or a sodium salt of a similar higher primary aliphatic alcohol." Ex. 1057, 550; *see also* Ex. 1031, 12:11–14 (indicating that "Emulsifying Wax" is "a waxy solid prepared from cetostearyl alcohol and a polyoxyethylene derivative of a fatty acid ester of sorbitan").

Such evidence fails to indicate that cetostearyl alcohol, by itself, corresponds to a wax. We are not persuaded otherwise by elicited testimony

of Dr. Prud'homme, cited by Petitioner, when briefly asked about the Handbook of Pharmaceutical Excipients. Reply 7–8 (citing Ex. 1125, 230:3–9, 233:12–16); Tr. 15:1–16:7. The entirety of Dr. Prud'homme's testimony in the record supports Patent Owner's construction of "waxes," which excludes both cetyl alcohol and cetostearyl alcohol. *See, e.g.*, Ex. 2192 ¶¶ 88–98.

We conclude that the term "waxes" in challenged claim 1 refers to esters of alcohols and fatty acids, and does not include higher alcohols that are not in an ester form. Thus, the term "waxes" does not include either cetyl alcohol or cetostearyl alcohol by itself.

C. Asserted Obviousness of claims 1–4 over Groenendaal (Ex. 1005) and Leslie (Ex. 1003)

Petitioner contends that claims 1–4 of the '720 patent would have been obvious over Groenendaal in view of Leslie. Pet. 48–60. Petitioner contends that "[o]ne of ordinary skill in the art would have been motivated to combine the formulations taught in Leslie with the high-dose of 5-ASA from Groenendaal with a reasonable expectation of success in formulating the composition disclosed in the Claims." *Id*. at 48–49.

1. Leslie

Leslie discloses slow release oral compositions comprising a combination of a higher aliphatic alcohol and a hydrated hydroxy-alkyl cellulose. Ex. 1003, 1:8–21. That combination "in critical proportions of one to the other . . . delays the release of a therapeutically active compound." *Id*. at 3:37–51. Regarding the higher aliphatic alcohol, Leslie states that "a particularly preferred alcohol is cetyl alcohol," and that "cetostearyl alcohol is another alcohol which is preferred." *Id*. at 4:54–62. Leslie further discloses that "it is important that the alkyl cellulose component be

hydrated," and the "hydroxy-alkyl cellulose preferred in practice is hydroxyethyl cellulose." *Id*. at 4:30–53.

Leslie teaches that the "active therapeutic compound intended for therapy may be incorporated in the higher alcohol before this is blended with the hydrated hydroxy-alkyl cellulose, or it may be incorporated in the hydrated hydroxy-alkyl cellulose, before it is incorporated with the higher alcohol or divided among both agents." *Id*. at 4:63–68. Leslie further teaches that "[b]oth the pharmacologic nature of the active therapeutic ingredient and the dosage to be incorporated into the present sustained slow release composition, are not critical to the present invention," and that "[e]xamples of such pharmacologically active ingredients" include "salicylate and acetyl-salicylate compounds." *Id*. at 8:37–59; 13:62–67.

Leslie presents example formulations and methods for making the described compositions. Example 1 presents a general method for making such compositions. *Id*. at 10:30–68. Example 1 discloses hydrating hydroxy ethyl cellulose, melting cetyl alcohol and adding it to a diluent, such as lactose or talc, which is granulated. *Id*. at 10:30–38. "The granules of cetyl alcohol are added to the hydrated hydroxy ethyl cellulose" and the "whole is then well blended and to it is added the selected active ingredient as well as further diluents . . . to permit compression into tablets." *Id*. at 10:39–48.

In Example 4, Leslie discloses (1) melting cetyl alcohol at 60º–70ºC and incorporating it with aminophylline, an active ingredient, by stirring, (2) hydrating hydroxy ethyl cellulose, (3) incorporating the blend from (1) with a "[t]otal blending time [of] three hours," and (4) drying "the resultant granular mass," and passing it through a mesh sieve before making tablets. *Id*. at 12:21–47. The composition comprises "73.00 % w/w" of the active

ingredient aminophylline. *Id*. at 12:23–26. Example 6 in Leslie discloses a similar composition and manufacturing process, but includes 75 g of the active ingredient papaverine hydrochloride (out of 100 g total). *Id*. at 13:19–40.

Example 5 in Leslie discloses (1) hydrating hydroxy ethyl cellulose, (2) adding potassium chloride as an active ingredient to the hydrated cellulose "with constant stirring" "until a free-flowing uniform granule blend is obtained," (3) drying and granulating the cellulose-potassium chloride granules, (4) melting cetyl alcohol at 50º–60ºC, and incorporating the granules from (3), with "[c]ontinue[d] stirring until a free-flowing granular mass is obtained" before lubricating the granules and pressing them into "cores." *Id*. at 12:48–13:15. The composition includes 82 g of potassium chloride (out of 102 g total). *Id*. at 12:51–54.

Example 7 in Leslie states that when one desires to "incorporate a pharmacologically active compound with the slow release composition of Example 1 above, then said active agent may be added to the alcohol component or the cellulose component or divided between the two." *Id*. at 13:43–47. Example 9 discusses the use of cetostearyl alcohol instead of cetyl alcohol "as described in Examples 1 through 7." *Id*. at 14:54–64.

2. Groenendaal

Groenendaal discloses "controlled-release oral compositions comprising biologically active substances, targeted to predetermined parts of the intestine and especially to the lower part thereof." Ex. 1005, 2:1–3. The compositions are in the form of a "solid dispersion," which the reference defines "as a dispersion of one or more active ingredients in an inert

excipient at solid state prepared by the melting (fusion), solvent, or melting-solvent method." *Id*. at 2:14–18.

Groenendaal discloses mixing water-insoluble carrier particles "with the dispersion before it is solidified, without any need to actively deposit the solid on the carrier cores." *Id*. at 2:49–50. More specifically, Groenendaal teaches

> a method for preparing a granulate for a multiparticulate oral composition based on the concept of solid dispersion, whereby a biologically active substance is dispersed in an acid-resistant or release-limiting substance using the melting, the solvent or the melting-solvent method, characterized in that before the dispersion is solidified it is mixed with water-insoluble carrier particles whereafter the complete mixture is further processed according to granulation methods known in the art.

Id. at 3:1–6.

In addition, Groenendaal discloses that the "percentage of the biologically active compound (w/w) in the solid dispersion can vary between 0.01–99%," but teaches, in particular, that "[w]hen the biologically active compound is a non-steroidal anti-inflammatory compound such as 5- or 4-amino-salicylic acid its percentage (w/w) in the solid dispersion is preferably 20–90%, more preferably 50–80%." *Id*. at 3:31–36.

In Example 5, Groenendaal discloses a sustained release formulation of granules prepared from a mixture comprising 75 g ethylcellulose, 75 g hydrogenated castor oil, 1175 g methylene chloride, 500 g 5-amino salicylic acid (5-ASA), and 450 g water-insoluble carrier powdered cellulose, therefore comprising 22% 5-ASA (500 g 5-ASA out of 2275 g total weight of the composition). *Id*. at 6:1–9. Groenendaal states that Figure 3 shows

that those granules demonstrate sustained release of 5-ASA. *Id*. at 6:16, Fig. 3.

3. Analysis

Petitioner contends that both Leslie and Groenendaal teach controlled release oral pharmaceutical compositions comprising a lipophilic matrix, i.e., a wax (e.g., cetyl alcohol), with a melting point below 90° C, as recited in the challenged claims. Pet. 52–54. In support, Petitioner contends that cetyl alcohol, a higher aliphatic alcohol disclosed in both references, is a wax, and therefore qualifies as a lipophilic matrix, as recited in claim 1. Pet. 21–22 (citing Ex. 1032, 99, 102; Ex. 1031, 5:49–60). In its Reply, Petitioner also argues that cetostearyl alcohol, another higher aliphatic alcohol disclosed in Leslie, is a wax. Reply 6–7, 15.

Petitioner further contends that Leslie's composition comprises an inner lipophilic matrix, i.e., granules of cetyl alcohol (or cetostearyl alcohol), dispersed within an outer hydrophilic matrix, i.e., hydroxy-alkyl cellulose or hydroxy ethyl cellulose. Pet. 54–55 (citing Ex. 1003, Examples 4 and 6); Reply 17 (referring to "cetyl alcohol or cetostearyl alcohol as a lipophilic matrix"). Petitioner also points to where Leslie discloses that an "active therapeutic compound . . . may be . . . divided among both agents," i.e., the higher alcohol and the hydrated hydroxy-alkyl cellulose, to show that Leslie teaches that an active ingredient may be dispersed in both the inner lipophilic matrix and the outer hydrophilic matrix, as also recited in claim 1. Pet. 54–55, 57 (citing Ex. 1003, 4:63–5:7; 13:43–50).

As noted above, we construe "waxes" in independent claim 1 to refer to esters of alcohols and fatty acids, and to not include higher aliphatic alcohol that are not esters, such as cetyl alcohol or cetostearyl alcohol. By

pointing us to granules of cetyl alcohol (or cetostearyl alcohol or even "other higher alcohols") in Leslie's compositions, Petitioner does not establish sufficiently that Leslie discloses the "inner lipophilic matrix" as recited in claim 1. Pet. 21–25, 33–34, 53–55; Reply 17. Thus, even assuming a person of ordinary skill in the art "would have been motivated to combine the formulations taught in Leslie with the high-dose of 5-ASA from Groenendaal with a reasonable expectation of success" as Petitioner contends (Pet. 48–49), Petitioner does not establish sufficiently that the combination would result in the compositions recited in claim 1.

Beyond that issue, Patent Owner persuasively argues that "Petitioner fails to account for the extraordinary variety of pH-independent controlled-release compositions known at the time," and that "[b]eyond matrices, pH-independent controlled release approaches included reservoir dosage forms, osmotic dosage forms, and chemically-modified active ingredients." PO Resp. 16–18 (citing Ex. 2192 ¶¶ 44–48 (citing additional evidence in support)); Reply 10–11 (citing Ex. 1125, 179:9–15), Ex. 2204, 143, 145.

We agree with Patent Owner that Petitioner fails to provide a "compelling reason why a person of ordinary skill would have selected matrices," much less the specific formulation in Leslie, "over any other pH-independent approach." *Id*. at 18. Rather than picking "known options" from a "finite number of identified, predictable solutions," *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007), Petitioner's obviousness challenge is more akin to "merely throw[ing] metaphorical darts at a board filled with combinatorial prior art possibilities" when the prior art gave little or conflicting indications as to which parameters were critical or which of many possible choices were likely to be successful. *In re Kubin*, 561 F.3d

1351, 1359 (Fed. Cir. 2009); *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

Petitioner points out that Leslie lists "salicylate and acetyl-salicylate compounds," among a very large number of other possible active ingredients (Ex. 1003, 8:40–49, 13:66–14:5), and includes aspirin (acetylsalicylic acid) as an active ingredient in a list of possible active ingredients in an example (*id*. at 14:10–36 (listing twelve possible actives in a table)). Petitioner does not explain adequately, however, why one "would have been motivated to look to Leslie" in particular to "improve" the 5-ASA compositions disclosed in Groenendaal when one takes into account the crowded art of controlled release formulations generally. Pet. 48–52; *see also* Ex. 1001, 1:14–2:24 (disclosing a number of "different known techniques" for preparing controlled release formulations of 5-ASA, including those involving matrices and reservoir dosage forms); Pet. 15–16, 25–26 (discussing previously known controlled release formulations containing 5-ASA and previously known matrices used to formulate controlled release compositions); Reply 15.

We are not persuaded sufficiently by Petitioner's assertions regarding alleged manufacturing "costs" and issues with "pH-dependent and time-dependent drug delivery approaches," such as pH-dependent enteric coatings. Pet. 15–16, 20 (citing Ex. 1020, 2:56–3:8 (stating that "[u]sing pH as an indicator of colonic arrival of the dosage form presents some difficulties" and "the validity of the use of enteric coatings to attain colonic release has been questioned"), 3:44–46; Ex. 1004, 1:16–19, 2:16–21 (stating that a system involving "time dependency makes it impossible to limit administration of the agent to the colon"); Ex. 1037 ¶¶ 42, 129 (presenting

conclusory statements or citing Ex. 1020, 2:56–3:8, 3:44–46); Reply 12 (citing Pet. 15; Ex. 1037 ¶ 122 (stating that "matrix-based compositions are inexpensive to manufacture")).

As an initial matter, Patent Owner persuades us that, besides cost, a formulator would have considered many other factors, such as dose size, compressibility, flowability, aqueous solubility, partition coefficient, drug stability, interaction with excipients, and chemical structure and weight, when formulating controlled release compositions. PO Resp. 23–24 (citing testimony by Dr. Palmieri in this regard).

In addition, Petitioner does not argue that Groenendaal fails to disclose a pH-independent approach or that Groenendaal's approach is limited to pH- or time-dependent formulations. Pet. 48–60; Ex. 1037 ¶¶ 136–148; *see also* Ex. 1005, 3:1–6 (stating that "a biologically active substance is dispersed in an acid-resistant *or release-limiting substance*") (emphasis added). Again, Petitioner's assertions do not explain adequately why one would have looked to Leslie in particular to "improve" the 5-ASA compositions disclosed in Groenendaal, especially when many other options of pH-independent controlled release formulations existed. PO Resp. 16–18 (citing Ex. 2192 ¶¶ 44–48). We also agree with Patent Owner that Petitioner does not explain adequately "why lower cost would differentiate matrices from other pH-independent approaches, which also included low-cost manufacturing alternatives." *Id*. at 18–19 (citing Ex. 2192 ¶ 51 (citing additional evidence in support)).

Nor are we persuaded otherwise by Petitioner's contention that Patent Owner's argument "rests on the flawed assumption that having multiple options somehow teaches away from the claimed invention." Reply 9–12.

Even if other options did not "teach away" from the formulation of Leslie, Petitioner does not explain adequately why one would have looked to Leslie's formulations—among the many options available for controlled release formulations—in relation to compositions comprising high amounts of 5-ASA. Patent Owner's arguments in this regard are especially pointed when we take into account the fact that Leslie issued as a U.S. patent in 1976, while Groenendaal (which fails to mention Leslie) published as a European patent application in 1990, fourteen years later, and the priority date of the '720 patent is 1999, an additional nine years later. *Leo Pharm. Products, Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013) (indicating that significant "elapsed time between the prior art and the [relevant] patent's filing date evinces that the [] patent's claimed invention was not obvious to try").

Groenendaal discloses controlled release oral compositions where the "percentage of the biologically active compound (w/w) in the solid dispersion can vary between 0.01–99%," including compositions comprising "5- or 4-amino-salicylic acid its percentage (w/w) in the solid dispersion is preferably 20-90%, more preferably 50-80%." Ex. 1005, 3:31–36. Petitioner does not indicate adequately why an ordinary artisan would have looked to Leslie in particular for the purpose of preparing a composition having a high percentage (i.e., 80 to 95%) by weight of 5-ASA, especially when Groenendaal itself already disclosed relevant "compositions having a high 5-ASA content." Pet. 49.

Petitioner relies on the argument that "[b]ecause both Groenendaal and Leslie sought the same release control objectives," an ordinary artisan would have looked to the two references "when seeking to improve 5-ASA

formulations." Pet. 50–51. Petitioner points to where Leslie discloses compositions comprising potassium chloride or papaverine hydrochloride at percentages as high as 75 to 82% by weight,[4] and where Leslie states that "[b]oth the pharmacologic nature of the active therapeutic ingredient and the dosage to be incorporated into the present sustained slow release composition, are not critical to the present invention." Pet. 27–28 (citing Ex. 1003, 5:15–19, 8:37–59, 12:50–54; 13:20–40), 56–57 (citing Ex. 1003, 12:46–54, 14:13, 23–36). Petitioner does not suggest, however, that Leslie discloses a specific example composition comprising any "salicylate and acetyl-salicylate compounds," such as aspirin, at percentages as high as 80% by weight. Instead, Petitioner points to aspirin listed in a table in Example 7 of Leslie, where Leslie indicates that aspirin is incorporated "with the slow release composition of Example 1" comprising different components, as well as "20 percent to 30 percent by weight" of a diluent, such as talc or lactose. Pet. 51, 53; Ex. 1003, 13:42–14:36.

In view of teachings in Groenendaal of controlled release compositions having even higher percentages of 5-ASA than those described in Leslie in relation to any active ingredient, Petitioner does not explain adequately why one would have been motivated to use the formulations of Leslie when generating compositions having 80 to 95% of 5-ASA by weight, in particular, as recited in challenged claim 1.

---

[4] We recognize that Patent Owner contends that Groenendaal's compositions "actually account[] for much less than 80%" of 5-ASA. PO Resp. 34–38. We need not address this contention, as we are not persuaded that Petitioner meets its burden to establish obviousness, even assuming Groenendaal discloses or suggests a percentage of 5-ASA of 80% or higher by weight of the composition.

At best for Petitioner, the record before us indicates a close call, but certainly not a strong case, regarding a showing of obviousness by the preponderance of evidence based on our analysis of the prior art. To the extent that it is a close call, it is noteworthy that the burden of persuasion is on Petitioner. *In re Magnum Oil Tools Int'l, Ltd*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (quoting *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)) ("In an *inter partes* review, the burden of persuasion is on the petitioner to prove 'unpatentability by a preponderance of the evidence,' 35 U.S.C. § 316(e), and that burden never shifts to the patentee.").

Moreover, evidence of secondary considerations are not insubstantial here. Evidence of a long-felt but unsolved need, in particular, is compelling. Both parties persuade us that researchers had reasons, for many years, to try to develop controlled release oral formulations comprising very large amounts of 5-ASA, for example to create pills that provided effective treatment while minimizing the number of pills needed to be taken by a patient per day. PO Resp. 49–51; Pet. 19. The parties raise different points regarding the "once-daily" dosing aspect of Lialda, with Petitioner pointing out that the claims do not require such dosing. Reply 17–20. We agree with that point, but the claims require compositions containing 5-ASA "in an amount of 80 to 95% by weight of the total composition," which Patent Owner persuasively indicates leads to dosages that allow for fewer pills per day. PO Resp. 49–51.

Patent Owner also puts forth evidence of commercial success of Lialda (*id*. at 51–54)—albeit Petitioner disputes that such success is "tied to the invention of the '720 patent" (Reply 20–25)—and neither party disputes

that the challenged claims encompass this commercial product. *See, e.g.*, Tr. 67:8–15 (counsel for Petitioner agreeing that "Lialda does fall within the claims"). Patent Owner also points to evidence of widespread praise of Lialda. PO Resp. 54–55. For example, Patent Owner cites an "Expert Opinion" article from 2008 describing the development of Lialda, i.e., a "high-concentration, once-daily MMX mesalamine," as "a major advance in the history of 5-ASA therapy for UC [ulcerative colitis]." Ex. 2031, 1051, 1055. We find such evidence to be relevant and favorable to Patent Owner in our obviousness analysis, especially in conjunction with persuasive evidence of a long-felt but unsolved need.

Looking at the entire record before us, we conclude that Petitioner has not meet its burden of persuasion to establish unpatentability of the challenged claims.

III. MOTIONS TO EXCLUDE

A party moving to exclude evidence bears the burden of proof to establish that it is entitled to the relief requested, e.g., that the material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

Petitioner moves to exclude Patent Owner's Exhibits 2081 and 2082, which Petitioner contends that Patent Owner introduced for the first time during the deposition of Dr. Meyer (Ex. 2235, 118), who provided a declaration cited by Petitioner in its Reply regarding the commercial success of Lialda. Paper 44, 1–2: Reply 21–25. Because we do not rely on those exhibits in rendering our decision here, we dismiss Petitioner's motion as moot.

Patent Owner moves to exclude Petitioner's Exhibits 1048, 1052, 1057, 1058, 1062, 1069, 1072, 1078, 1079, 1090, 1100, and 1126. Paper 42. Patent Owner contends that Exhibits 1048, 1052, and 1062 constitute inadmissible hearsay because Petitioner relies on those articles or book chapter "without any expert confirmation" as to their "reliability." *Id*. at 1–4. Because we do not rely on Exhibit 1048 or 1052 in rendering our decision here, we dismiss Petitioner's motion in this regard as moot.

In relation to Exhibit 1062, which we discuss in our analysis above, this exhibit corresponds to a chapter in a published and peer-reviewed book. We do not consider it to be inadmissible hearsay in relation to what the chapter indicates regarding views of those of ordinary skill in the art, regardless of the truth of statements asserted therein. *See, e.g., Abbott Labs. v. Diamedix Corp.*, 969 F.Supp. 1064, 1066–67 n.1 (N.D. Ill. 1997) (The "relevance of [a reference] is its very existence and the effect its existence had on the knowledge base of those in the field of art. As such, it is not hearsay."). We deny Patent Owner's motion to exclude this exhibit, although we consider Patent Owner's contentions regarding reliability when weighing that evidence.

Patent Owner also asks to exclude, as not authenticated, Exhibits 1069, 1072, 1078, 1079, 1090, and 1100, cited in the declaration of Petitioner's expert, Dr. Meyer (Ex. 1059). Because we do not rely on those exhibits in rendering our decision, we dismiss Patent Owner's motion in this regard as moot.

IV. CONCLUSION

Taking account of the arguments and evidence presented during trial, we determine that Petitioner has not established by a preponderance of the

evidence that claims 1–4 of the ’720 patent would have been obvious over Groenendaal in view of Leslie.

V. ORDER

For the foregoing reasons, it is

ORDERED that claims 1–4 of the ’720 patent have not been shown to be unpatentable as obvious over Groenendaal in view of Leslie;

FURTHER ORDERED that Petitioner’s and Patent Owner’s Motions to Exclude are denied; and

FURTHER ORDERED that, because this is a Final Written Decision, 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.

For PETITIONER:

Sarah Spires
Skiermont Puckett LLP
sarah.spires@skiermontpuckett.com

Ki O
Skiermont Puckett LLP
ki.o@skiermontpuckett.com

Parvathi Kota
Skiermont Puckett LLP
parvathi.kota@skiermontpuckett.com

Paul Skiermont
Skiermont Puckett LLP
paul.skiermont@skiermontpuckett.com

For PATENT OWNER:

Edgar H. Haug
Frommer Lawrence & Haug LLP
ipr.cosmo@flhlaw.com

Andrew S. Wasson
Frommer Lawrence & Haug LLP
ipr.cosmo@flhlaw.com