UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NOTICE OF DOCKETING

17-2312 - Dr. Falk Pharma GmbH v. GeneriCo, LLC

Date of docketing: July 18, 2017

Appeal from: Patent and Trademark Office - Patent Trial and Appeal Board in Inter Partes Review Nos. IPR2016-00297, IPR2016-01386, IPR2016-01409

Appellant(s): Dr. Falk Pharma GmbH

Critical dates include:

- Date of docketing. See Fed. Cir. R. 12 and 15.
- Certified list. See Fed. Cir. R. 17.
- Entry of appearance. (*Due within 14 days of the date of docketing*.) See Fed. Cir. R. 47.3.
- Certificate of interest. (*Due within 14 days of the date of docketing*.) See Fed. Cir. R. 47.4.
- Docketing Statement. (*Due within 14 days of the date of docketing, or within 30 days if the United States or its officer or agency is a party in the appeal*.) [Only in cases where all parties are represented by counsel. See Fed. Cir. R. 33.1 and the mediation guidelines available at www.cafc.uscourts.gov.]
- Requests for extensions of time. See Fed. Cir. R. 26 and 27. **N.B. Delayed requests are not favored by the court**.
- Briefs. See Fed. Cir. R. 31. **N.B. You will not receive a separate briefing schedule from the Clerk's Office**. However, in a case involving an appellant, a cross-appellant, and an appellee, a special briefing schedule is used. The appellant's opening brief is due within 60 days of the date of docketing. The cross-appellant's opening brief is due within 40 days of filing of the appellant's opening brief. The appellee's brief is due within 40 days of filing of the cross-appellant's brief. The appellant's response/reply brief is due within 40 days of filing of the appellee's brief. The cross-appellant's reply brief is due within 14 days of filing of the appellant's response/reply brief. The joint appendix is due within 10 days of filing of the cross-appellant's reply brief.
- Settlement discussions. See Fed. Cir. R. 33.
- **ORAL ARGUMENT SCHEDULE CONFLICTS:** Counsel should advise the clerk in writing within 30 days once briefing is completed of potential scheduling conflicts or as soon as they are known and should not wait until an actual conflict arises. Once scheduled, a case will not be postponed except on motion showing **compelling reasons**. See Practice Note following Fed. Cir. R. 34.

The official caption is reflected on the electronic docket under the listing of the parties and counsel. The Rules of Practice and required forms are available at www.cafc.uscourts.gov.

Peter R. Marksteiner
Clerk of Court

cc: Office of the Solicitor, US Patent and Trademark Office
Mary W. Bourke
Robert Florence
William Hare
Zachary David Silbersher

Date: July 18, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENERICO, LLC, FLAT LINE CAPITAL, LLC, MYLAN PHARMACEUTICALS INC., FOXHILL CAPITAL PARTNERS, and MYCONOVO, INC.,

Petitioners

v.

DR. FALK PHARMA GmbH,

Patent Owner.

Case IPR2016-00297[1]
U.S. Patent 8,865,688

PATENT OWNER'S NOTICE OF APPEAL TO THE U.S. COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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[1] Case IPR2016-01386 and Case IPR2016-01409 were joined with this proceeding.

Pursuant to 35 U.S.C. §§ 141(c), 142, and 319, 37 C.F.R. §§ 90.2(a) and 90.3(a), Patent Owner Dr. Falk Pharma GmbH ("Patent Owner") hereby appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision (Paper 55) entered May 19, 2017 (Attachment A) regarding U.S. Patent No. 8,865,688 ("the '688 patent"), and from all underlying orders, decisions, rulings and opinions that are adverse to Patent Owner related thereto and included therein, including those within the decision on Institution of *Inter Partes* Review, entered November 30, 2016 (Paper 33).

In particular, for the limited purpose of providing information under 37 C.F.R. § 90.2(a)(iii)(2), Patent Owner anticipates that the issues on appeal may include, but are not limited to the following:

1. The determination of unpatentability of claims 1 and 16 of the '688 patent under 35 U.S.C. § 103.
2. The construction of the claim term "remission is defined as a DAI score of 0 or 1."
3. The constitutionality of the *inter partes* review.
4. Any findings or determinations purportedly supporting or related to these issues, as well as procedural and substantive issues decided adverse to Patent Owner, in any order, decision, ruling or opinion by the Board in this proceeding.

Patent Owner is concurrently providing true and correct copies of this Notice of Appeal, along with the required fees, to the Director of the United States Patent and Trademark Office and the Clerk of the United States Court of Appeals for the Federal Circuit.

Respectfully submitted,

Dated: July 18, 2017

/Mary W. Bourke/

Mary W. Bourke
Registration No. 30,982
Lead Counsel for Patent Owner

Case IPR2016-00297
U.S. Patent 8,865,688

CERTIFICATE OF SERVICE

I hereby certify that the original of this **Notice of Appeal** was hand delivered on July 18, 2017 to the Director of the United States Patent and Trademark Office at the address below:

Director of the U.S. Patent & Trademark Office
c/o Office of the General Counsel
United States Patent and Trademark Office
Madison Building East, Room 10B20
600 Dulany Street
Alexandria, VA 22314

A copy of this Notice of Appeal is being filed and served on July 18, 2017 as follows:

Patent Trial and Appeal Board
Madison Building East
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Alexandria, VA 22313
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(via email pursuant to 37 C.F.R. § 42.6(e))

Dated: July 18, 2017

/Mary W. Bourke/
Mary W. Bourke
Registration No. 30,982
Lead Counsel for Patent Owner

ATTACHMENT A

Trials@uspto.gov
571-272-7822

Paper: 55
Entered: May 19, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENERICO, LLC, FLAT LINE CAPITAL LLC,
MYLAN PHARMACEUTICALS INC.,
FOXHILL CAPITAL PARTNERS, and MYCONOVO, INC.,
Petitioner,

v.

DR. FALK PHARMA GMBH,
Patent Owner.

Case IPR2016-00297[1]
Patent 8,865,688 B2

Before GRACE KARAFFA OBERMANN, *Vice Chief Administrative Patent Judge*, LORA M. GREEN and ELIZABETH M. ROESEL, *Administrative Patent Judges*.

ROESEL, *Administrative Patent Judge*.

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

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[1] Case IPR2016-01386 and Case IPR2016-01409 have been joined with this proceeding.

In this *inter partes* review, instituted pursuant to 35 U.S.C. § 314, GeneriCo, LLC ("GeneriCo"), Flat Line Capital, LLC ("Flat Line"), Mylan Pharmaceuticals Inc. ("Mylan"), Foxhill Capital Partners ("Foxhill"), and MycoNovo, Inc. ("MycoNovo") (collectively, "Petitioner") challenge the patentability of claims 1 and 16 of U.S. Patent No. 8,865,688 B2 (Ex. 1001, "the '688 patent"), owned by Dr. Falk Pharma GmbH ("Falk" or "Patent Owner").

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 shown by a preponderance of the evidence that claims 1 and 16 of the '688 Patent are unpatentable.

I. BACKGROUND

A. Procedural History

On December 8, 2015, GeneriCo and Flat Line filed a Petition requesting *inter partes* review of claims 1 and 16 of the '688 Patent. Paper 1 ("Pet."). On March 15, 2016, Patent Owner filed a Preliminary Response. Paper 11 ("Prelim. Resp.").

On June 10, 2016, we instituted *inter partes* review of the challenged claims. Paper 13 ("Decision to Institute" or "Dec.").

On September 14, 2016, Patent Owner filed a Patent Owner Response. Paper 24 ("PO Resp.").

On November 30, 2016, we granted motions for joinder filed by Mylan, Foxhill, and MycoNovo. Paper 33.

On December 23, 2016, Petitioner filed a Reply to Patent Owner's Response. Paper 36 ("Pet. Reply").

With the Petition, GeneriCo and Flat Line filed a Declaration of George A. Digenis, Ph.D. Ex. 1002. Patent Owner cross-examined Dr. Digenis on August 4, 2016, and filed a transcript of his deposition testimony as Exhibit 2032.

With the Patent Owner Response, Patent Owner filed a Declaration of Alan Victor Safdi, M.D. (Ex. 2035), a Declaration of Lorin Johnson, Ph.D. (Ex. 2036), and a Declaration of Roland H. Greinwald, Ph.D. (Ex. 2037). Petitioner cross-examined Dr. Safdi on November 16, 2016, and filed a transcript of his deposition testimony as Exhibit 1056. Petitioner cross-examined Dr. Johnson on December 16, 2016, and filed a transcript of his deposition testimony as Exhibit 1067.

With the Reply, Petitioner filed a Supplemental Declaration of George A. Digenis, Ph.D. Ex. 1059.

On January 11, 2017, Petitioner filed a motion to exclude Patent Owner's evidence. Paper 43 ("Pet. Mot."). Patent Owner filed an opposition to Petitioner's motion to exclude, and Petitioner filed a reply. Papers 49, 51.

On January 11, 2017, Patent Owner filed a motion to exclude Petitioner's evidence. Paper 45 ("PO Mot."). Petitioner filed an opposition to Patent Owner's motion to exclude, and Patent Owner filed a reply. Papers 48, 52.

An oral hearing was held February 15, 2017. A transcript of the hearing was entered in the record. Paper 54 ("Tr.").

B. Related Proceedings

Pursuant to 37 C.F.R. § 42.8(b)(2), the parties identify the following district court actions in which the '688 patent is being asserted: *Salix*

Pharmaceuticals, Inc. et al. v. Novel Laboratories, Inc., Nos. 1-15-cv-00027 and 1-15-cv-00213 (D. Del.) (consolidated) and *Salix Pharmaceuticals, Inc. et al v. Mylan Pharmaceuticals, Inc. et al.*, No. 1-15-cv-00109 (N.D. W.Va.). Pet. 1; Paper 32 (Patent Owner's updated mandatory notices). According to Patent Owner, Salix Pharmaceuticals, Inc. ("Salix") is the original assignee and the current exclusive licensee of the '688 patent and is a real party-in-interest. PO Resp. 5 n.1; Paper 6 (Patent Owner's mandatory notices).

C. The '688 Patent

The '688 patent relates to a method of maintaining the remission of ulcerative colitis.[2] Ex. 1001, Abstract, 1:15. The '688 patent explains that ulcerative colitis is an inflammatory disease of the colonic mucosa and that the goal of treatment is to induce and maintain remission of the disease. *Id.* at 1:15–17, 1:49–50. According to the '688 patent, maintenance medications must be taken for a prolonged period of time to enable subjects to stay in remission. *Id.* at 1:55–59.

The method described and claimed in the '688 patent includes administering a once-daily dose of granulated mesalamine.[3] The '688 patent acknowledges that oral mesalamine formulations are known in the art for treating ulcerative colitis. *Id.* at 1:60–2:3. The patent identifies problems with prior art delivery systems, including: "premature release, the

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[2] Ulcerative colitis is sometimes referred to in this record and in the art by the abbreviation "UC."

[3] Other names for mesalamine include 5-aminosalicylic acid, 5-ASA, and mesalazine. *See, e.g.*, Ex. 1001, 5:36, cols. 21–25 (Example 7, Tables 5–9); PO Resp. 18.

possibility of dose dumping, and sensitivity to conditions that increase gastric pH and cause premature release of mesalamine (e.g., ingestion of a meal)." *Id.* at 2:3–8. According to the '688 patent, bowel diseases, such as ulcerative colitis, are not adequately controlled using currently available formulations. *Id.* at 2:12–15.

For a description of the granulated mesalamine formulations, the '688 patent refers to three earlier patents or publications. *Id.* at 2:9–11, 10:47–52 (incorporating by reference U.S. Patent/Publication Nos. 6,277,412; 6,551,620; and 2003/0133983).

The '688 patent describes two Phase III clinical studies in which 562 subjects (study 1: 305 subjects; study 2: 257 subjects) were randomized 2:1 to receive either a 1.5 gram granulated mesalamine formulation or placebo once daily in the morning for six months. According to the '688 patent, in both studies, the proportion of subjects who remained relapse-free at six months was greater for the granulated mesalamine formulation than for placebo. *Id.* at 17:1–35 (Example 5, Table 2); *see also id.* at Figures 1–3 (patient disposition and results of study 1); 6:43–7:25 (summarizing results of phase 3 studies discussed in Examples); 16:1–25 (Example 2); 25:14–33:64 (Examples 8–11, Tables 10–14).

The '688 patent also describes pharmacokinetic studies comparing absorption of mesalamine granules: (1) administered once and twice daily, and (2) administered under fed and fasted conditions. *Id.* at 7:26–31; *id.* at 14:58–15:5 (Example 1—evaluation of effect of a high fat meal intake on absorption of mesalamine granules); *id.* at 16:47–67 (Example 4—Effect of Food on Absorption and Disposition of Granulated Mesalamine Formulations); *id.* at 17:38–21:15 (Example 6—comparison of once daily

(QD) to twice daily (BID) administration). Based on these studies, the '688 patent concludes that a granulated mesalamine formulation can be administered once- or twice-daily, *id.* at 7:26–28, "without regard to food," *id.* at 15:4–5, and that the rate and extent of absorption of mesalamine and its metabolite "were not affected by a high-fat meal," *id.* at 16:63–64.

D. Illustrative Claim

The '688 patent includes 16 claims. The Petition challenges claims 1 and 16, which are directed to a "method of maintaining the remission of ulcerative colitis in a subject." Ex. 1001, 34:10–22, 35:4–17.

Claim 1 is reproduced below, with paragraph breaks and bracketed lettering added for ease of reference:

> 1. A method of maintaining the remission of ulcerative colitis in a subject comprising
>
> [a] administering to the subject a granulated mesalamine formulation comprising four capsules each comprising 0.375 g of granulated mesalamine once per day in the morning, without food, wherein:
>
> [b] said method maintains remission of ulcerative colitis in a subject for a period of at least 6 months of treatment;
>
> [c] remission is defined as a DAI score of 0 or 1;
>
> [d] the granulated mesalamine formulation is not administered with antacids; and
>
> [e] wherein 85% to 90% of the mesalamine reaches the terminal ileum and colon.

Id. at 34:10–22. Claim 16 is identical to claim 1, except that claim 16 recites an additional step, "advising the subject that granulated mesalamine should not be taken with antacids," and claim 16 omits the indefinite article "a" in the phrase, "a granulated mesalamine formulation" in paragraph [a]. *Compare id.* (claim 1), *with id.* at 35:4–17 (claim 16). The parties present the same contentions for claim 16 as they present for claim 1. *See, e.g.*, Pet.

39; PO Resp. 36–68. Accordingly, it is not necessary to consider claim 16 separately from claim 1, and we generally confine our discussion to claim 1.

E. References

This Decision refers to the following references:

S. S. Davis, *The Design and Evaluation of Controlled Release Systems for the Gastrointestinal Tract*, 2 J. Controlled Release 27–38 (1985), Ex. 1009 ("Davis-1985");

Salix Announces Statistically Significant Top-Line Results of a Unique Granulated Mesalamine Product Registration Study in Ulcerative Colitis (September 2007), http://www.sec.gov/Archives/edgar/containers/fix021/1009356/0001 1931 2507195530/dex992.htm, Ex. 1012 ("Sept. 2007 Press Release");

XIFAXAN® Trials Initiated in C. difficile-Associated Diarrhea, Irritable Bowel Syndrome and Hepatic Encephalopathy. New Article [online] EndoNurse, 12 January 2006, Ex. 1014 ("Endonurse");

Y. Marakhouski et al., *A Double-blind Dose-escalating Trial Comparing Novel Mesalazine Pellets with Mesalazine Tablets in Active Ulcerative Colitis*, 21 Aliment Pharmacol. Ther. 133–140 (2005), Ex. 1024 ("Marakhouski"); and

M. Brunner et al., *Gastrointestinal Transit and Release of 5-aminosalicylic Acid from ^{153}Sm-labelled Mesalazine Pellets vs. Tablets in Male Healthy Volunteers*, 17 Aliment. Pharmacol. Ther. 1163–1169 (2003), Ex. 1025 ("Brunner").

F. Instituted Ground

We instituted *inter partes* review based on the following ground of unpatentability asserted in the Petition: claims 1 and 16 under 35 U.S.C. § 103(a) as obvious over the Sept. 2007 Press Release, Endonurse, and Davis-1985 in view of Marakhouski or Brunner.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142–46 (2016). Under that standard, claim terms are generally given their ordinary and customary meaning, as would have been understood by a person of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Although it is entirely proper to use the specification to interpret what the patentee meant by a word or phrase in the claim, this is not to be confused with adding an extraneous limitation appearing in the specification, which is improper. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

The parties dispute the meaning of the phrase, "remission is defined as a DAI score of 0 or 1," which we address below. No other claim term requires express construction for purposes of this Decision. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

"remission is defined as a DAI score of 0 or 1"

Patent Owner contends that the phrase, "remission is defined as a DAI score of 0 or 1," means "remission is defined as a rectal bleeding subscore of 0 and a mucosal appearance subscore of less than 2 using the DAI." PO Resp. 13. Petitioner contends that the '688 patent Specification defines DAI to include four subscores, not just two subscores, as set forth in Patent Owner's proposed construction. Pet. Reply 5 (citing Ex. 1001, 17:2–11).

Claim 1 is directed to a method of maintaining the remission of ulcerative colitis. Clauses [a] and [d] of claim 1 recite the steps of the method, and clauses [b], [c], and [e] recite the results of the method. Clause [b] recites that the method "maintains remission of ulcerative colitis in a subject for a period of at least 6 months," and clause [c] recites that "remission is defined as a DAI score of 0 or 1." Ex. 1001, 34:16–18.

In claim 1, the clause, "remission is defined as a DAI score of 0 or 1," is an express definition for the term "remission." In the Specification, the term, "DAI score," is expressly defined in the following passage:

> Ulcerative colitis disease activity was assessed using a modified Sutherland Disease Activity Index1 (DAI), which is a sum of four subscores based on stool frequency, rectal bleeding, mucosal appearance on endoscopy, and physician's rating of disease activity. Each subscore can range from 0 to 3, for a total possible DAI score of 12.

Ex. 1001, 17:7–12.[4] When the express definitions for "remission" and "DAI score" are read together, the claim 1 phrase "remission is defined as a DAI

[4] Petitioner contends that the word, "modified" or "revised," refers to the fact that the DAI used in the Examples includes only two subscores. Pet. Reply 5–6. Patent Owner disagrees, contending that "modified" or "revised" refers to the exclusion of friability as a component of the

score of 0 or 1" is properly interpreted as "remission is defined as a DAI score of 0 or 1, where the DAI score is a sum of four subscores."

Patent Owner does not dispute that the term "DAI," both as understood in the art and as used in the '688 patent, refers to a sum of four DAI subscores. *See* PO Resp. 16 (characterizing two of the DAI subscores as "objective" and the other two as "subjective"). Instead, Patent Owner contends that the Specification uses the term "remission" synonymously with "relapse-free" and defines both terms consistent with Patent Owner's proposed construction, which is based on two, rather than four, DAI subscores. PO Resp. 14–17 (citing Ex. 1001, 6:53–62, 17:15–23, 25:32–35, 26:21–24, 26:51–53, 26:56–58, 28:3–8, 28:60–62, 33:27–31).

Patent Owner is correct that the Specification describes clinical trials in which "remission" and "relapse-free" were defined based on two DAI subscores. *See, e.g.*, Ex. 1001, 6:54–56 ("documented UC remission (revised Sutherland Disease Activity Index [DAI] subscores: rectal bleeding 0; mucosal appearance <2)"); *id.* at 6:60–62 ("relapse defined as a rectal bleeding subscore ≥ 1 and a mucosal appearance subscore ≥ 2 per DAI"). The claim, however, provides its own definition of "remission." That is, claim 1 specifically recites: "remission is defined as a DAI score of 0 or 1." That express definitional language in the claim itself is complete and unambiguous, and it cannot be overridden by a description of exemplary

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sigmoidoscopic scoring system. PO Mot. 13 (citing Ex. 1067, 93:2–5). We find it unnecessary to resolve this dispute. Even accepting Patent Owner's contention regarding the meaning of "modified" or "revised" in the Specification, we agree with Petitioner that claim 1 is properly construed as requiring that the DAI score be based on four subscores.

embodiments in the Specification. *See Straight Path IP Grp., Inc. v. Sipnet EU S.R.O.*, 806 F.3d 1356, 1361 (Fed. Cir. 2015) ("When claim language has as plain a meaning on an issue as the language does here, leaving no genuine uncertainties on interpretive questions relevant to the case, it is particularly difficult to conclude that the specification reasonably supports a different meaning.").

We, therefore, reject Patent Owner's proposed construction for the phrase, "remission is defined as a DAI score of 0 or 1." Consistent with claim 1's express definitions of "remission" (Ex. 1001, 34:18) and the Specification's express definition of "DAI score" (*id.* at 17:7–12), we construe the phrase, "remission is defined as a DAI score of 0 or 1," as "remission is defined as a DAI score of 0 or 1, where the DAI score is a sum of four subscores."

B. Person of Ordinary Skill in the Art

The parties dispute the definition of a person of ordinary skill in the art ("POSITA") for the '688 patent. Petitioner contends that a POSITA would have at least a bachelor's degree and several years' experience in the chemical or pharmaceutical fields, or alternatively, would be a medical doctor specializing in the treatment of gastrointestinal disorders. Pet. 17 (citing Ex. 1002 ¶ 14). Patent Owner contends that a POSITA would be a physician with experience diagnosing and treating patients suffering from ulcerative colitis and similar diseases. PO Resp. 10 (citing Ex. 2035 ¶ 30). Patent Owner further contends that, if the physician does not have pharmacokinetics experience, a POSITA "may also include individuals who have an advanced degree in pharmacy or pharmaceutics with practical experience associated with ulcerative colitis." *Id.*

"Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (quoting *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983)).

The '688 patent relates to a method for administering granulated mesalamine to treat ulcerative colitis. The claimed method is the result of pharmacokinetic studies and clinical studies conducted by the inventors. Ex. 2036 ¶¶ 7, 10–12, 19, 21 (inventor declaration describing pharmacokinetic and clinical studies); Exs. 2029, 2045, 2048–2050 (reports and protocol for pharmacokinetic and clinical studies). Most of the written description of the '688 patent relates to these studies. Ex. 1001, 6:27–35, 6:43–7:25, 16:1–45, 17:1–35, 21:17–33:64, Figs. 1–3 (clinical studies); *id.* at 7:26–31, 14:5–15:67, 16:47–67, 17:38–21:15 (pharmacokinetic, *in vitro*, and animal studies).

According to Dr. Johnson's testimony, neither of the inventors is a medical doctor, and neither has experience treating patients. Ex. 1067, 16:23–17:8, 22:19–23:3. Co-inventor William Forbes has a doctorate in pharmacy ("Pharm.D.") and was Vice President of Research and Development for Salix at the relevant time. Ex. 1012, 1; Ex. 1067, 24:14–25:17. Co-inventor Lorin Johnson[5] has a Ph.D. in molecular biology and

[5] On July 31, 2015, Patent Owner filed a petition to correct inventorship pursuant to 37 C.F.R. § 1.324 to add Lorin Johnson as an inventor. Ex. 2041 (Petition to Correct Inventorship); Ex. 2036 ¶ 7; *see also* PO Resp. 5–6 n.1

was a founder and chief scientist for Salix at the relevant time. Ex. 2036 ¶ 3; Ex. 1067, 14:13–15:22.

Others working in the same field as the inventors have a similar educational background. For example, Dr. Roland Greinwald is the head of research and development at Falk, with responsibility for pharmaceutical development and clinical development. Ex. 2037 ¶¶ 2, 3. Dr. Greinwald has a doctorate in natural sciences with a focus on pharmaceutical biology, microbiology, biochemistry, and plant science. *Id.* ¶ 5. Dr. Greinwald is a co-author of Marakhouski (Ex. 1024) and Brunner (Ex. 1025), which report the results of a clinical, pharmaco-scintigraphic, and pharmacokinetic studies of a granulated mesalamine formulation.

The record demonstrates that pharmacokinetic and clinical studies—i.e., the types of investigations that led to the '688 patent—are not conducted exclusively by physicians. For example, "James D. Carlson, PharmD" is the investigator on two pharmacokinetic studies that are the basis for the '688 patent. Ex. 2029, 2; Ex. 2045, 2. The non-physician inventors, Forbes and Johnson, are the signatories on clinical studies that are the basis for the '688 patent. Exs. 2048–2051. Another report submitted by Patent Owner shows a clinical study conducted by a multi-disciplinary team, including two medical doctors (Wolfgang Kruis and Karin Dilger), a non-physician scientist (Ralph Müller), and a biostatistician (Reinhard Fisebitt). Ex. 2025, 1–2. In addition, Marakhouski (Ex. 1024) discloses a clinical study, and Brunner (Ex. 1025) discloses pharmaco-scintigraphic and pharmacokinetic

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(identifying William Forbes and Lorin Johnson as inventors of the subject matter of the '688 patent).

studies. As demonstrated by the author affiliations (Exs. 1024, 1025), these studies are the work of multi-disciplinary teams, including Dr. Greinwald—a doctor of natural sciences, but not a physician. Ex. 2037 ¶¶ 2, 3, 5.

After considering the parties' positions and the relevant evidence, we determine that a POSITA with respect to the '688 patent is a person having an advanced degree (master's degree, Ph.D., or doctorate) in pharmacy, pharmaceutical science, biology, microbiology, chemistry, biochemistry, or a related field, with experience in developing or evaluating pharmaceutical formulations for the treatment of ulcerative colitis or other gastrointestinal disorders, or alternatively, a medical doctor specializing in the treatment of ulcerative colitis or other gastrointestinal disorders.

Patent Owner contends that Petitioner's expert, Dr. Digenis, is not a POSITA and is not qualified to testify regarding the subject matter of the '688 patent because he is not a medical doctor and does not have experience diagnosing or treating patients suffering from ulcerative colitis or other gastroenterological conditions. PO Resp. 11; PO Mot. 1–5. Petitioner does not challenge Dr. Safdi's qualifications as a POSITA.[6]

Based upon their stated qualifications, we consider both Dr. Digenis and Dr. Safdi qualified to opine from the viewpoint of a POSITA regarding the subject matter of the '688 Patent. Ex. 1002 ¶¶ 2–10, Exhibit A (Digenis CV); Ex. 2035 ¶¶ 2–16, Exhibit A (Safdi CV). *See SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010), *aff'd sub nom. Glob.*-

[6] Although Petitioner argues that Dr. Safdi is not qualified to testify regarding the reliability and intended purpose of the Sept. 2007 Press Release and Endonurse (Pet. Mot. 2–4), Petitioner's argument is not based on a lack of scientific qualifications.

Tech Appliances, Inc. v. SEB S.A., 563 U.S. 754 (2011) (expert testimony admissible where testimony established an "adequate relationship" between witness's experience and the claimed invention).

Dr. Digenis meets our definition of a POSITA because, among other qualifications, he has bachelor's and master's degrees in Pharmacy, a Ph.D in Organic Pharmaceutical Chemistry, experience in teaching and research in medicinal chemistry and pharmaceutics, and is a Fellow of the American Association of Pharmaceutical Scientists (AAPS). Ex. 1002 ¶¶ 3–9, Ex. A. Dr. Digenis has experience associated with ulcerative colitis and similar conditions, including studies of drug formulations for delivery to the colon, Ex. 2032, 26:22–27:5, and studies of two mesalamine formulations (Asacol and a confidential drug), *id.* at 33:13–34:7, 181:14–183:23. Brunner cites a paper co-authored by Dr. Digenis relating to gastrointestinal behavior of orally administered drug formulation using gamma scintigraphy. Ex. 1025, 1169 (reference 9); *see also* Ex. 1002, Ex. A, 26 (reference 127).

Dr. Safdi meets our definition of a POSITA because, among other qualifications, he is a gastroenterologist with experience in clinical research, including studies of mesalamine formulations for the treatment for ulcerative colitis. Ex. 2035 ¶¶ 2–14.

C. Obviousness Analysis

Petitioner contends that claims 1 and 16 are unpatentable as obvious over the Sept. 2007 Press Release, Endonurse, and Davis-1985 in view of either Marakhouski or Brunner. Pet. 25–39, 44–50.

Patent Owner contends that a POSITA would not have relied on the Sept. 2007 Press Release, Endonurse, or Davis-1985, that the cited art does not teach or suggest a method of maintaining "remission" as defined in the

claims or a step of administering granulated mesalamine "without food," and that evidence of secondary considerations supports non-obviousness. PO Resp. 4–6, 36–68.

1. Legal Standard

A claim is unpatentable for obviousness, if the differences between the subject matter sought to be patented 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. 35 U.S.C. § 103(a). In applying section 103, we assess the scope and content of the prior art, the level of ordinary skill in the relevant art, the differences between the claimed invention and the prior art, and whether the claimed invention would have been obvious to a person of ordinary skill in the art in light of those differences. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). We also consider "secondary considerations," such as commercial success, long-felt but unsolved need, and failure of others. *Id.*

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). On the other hand, "the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a [factfinder] can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418.

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue

> the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Id. at 421.

Evidence of secondary considerations plays a critical role in the obviousness analysis because it serves as objective indicia of nonobviousness. *Nike, Inc. v. Adidas AG*, 812 F.3d 1326, 1339 (Fed. Cir. 2016). Objective indicia can be the most probative evidence in the record, and they enable the court to avert the trap of hindsight. *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Although it may not be dispositive, evidence of secondary considerations must always be considered as part of the obviousness analysis, when such evidence is present in the record. *Nike*, 812 F.3d at 1339; *In re Kao*, 639 F.3d 1057, 1067 (Fed. Cir. 2011).

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). The burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review). Furthermore, Petitioner cannot satisfy its burden of proving obviousness by employing "mere conclusory statements." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016).

2. Scope and Content of the Prior Art

The Sept. 2007 Press Release is Salix's[7] announcement of the successful completion of the first of two Phase III trials evaluating a granulated mesalamine formulation for the maintenance of remission of ulcerative colitis. Ex. 1012, 1. The press release discloses that a "greater proportion of subjects dosed once-a-day with 1.5 grams of granulated mesalamine remained relapse-free over 6 months of treatment than patients dosed with placebo." *Id.* The press release describes the evaluated formulation as having "an enteric pH-dependent coating, which provides for delayed release, and a polymer matrix core, which provides for extended release," where the drug "begins to release at a pH of 6.0." *Id.* According to the press release, this formulation "provide[s] for the distribution of the active ingredient beginning in the small bowel and continuing throughout the colon." *Id.* The Sept. 2007 Press Release discloses the top line results of one of the two Phase III clinical trials described in the '688 patent. *Compare* Ex. 1012, 1–2, *with* Ex. 1001, 6:43–7:25; *see also* Ex. 2036 ¶¶ 19–21 (describing Salix's Phase III clinical trials, stating "Salix's clinical studies . . . are described in the '688 patent specification").

Endonurse is a press release from Salix regarding various clinical trials, including "two late-stage trials designed to evaluate granulated mesalamine for the maintenance of remission of ulcerative colitis." Ex. 1014, 1. According to Endonurse, "these Phase III trials [are] designed to evaluate the efficacy and safety of granulated mesalamine, dosed four 375

[7] As noted above, Salix is the original assignee and current exclusive licensee of the '688 patent.

mg tablets once daily, for the maintenance of remission of ulcerative colitis." *Id*. at 2. Endonurse relates to the same two Phase III trials as described in the '688 patent, one of which is also disclosed in the Sept. 2007 Press Release. *Compare* Ex. 1014, 2, *with* Ex. 1001, 6:43–7:25 *and* Ex. 1012.

Davis-1985 is an academic paper discussing three factors relevant to the design and evaluation of control release delivery systems for orally administered medications: the drug, the delivery system, and the intended destination. Ex. 1009, 27 (Abstract, Introduction). Petitioner focuses on Davis-1985's discussion of the third factor: "Destination—Characteristics of the Gastrointestinal Tract." *Id.* at 34–37. In this section, Davis-1985 discusses the physiology of the gastrointestinal tract, including the effect of food on the pH of the stomach and on the process of gastric emptying. *Id*. at 34. Davis-1985 discusses observations of the transit of various pharmaceutical formulations through the gastrointestinal tract using gamma scintigraphy and the implications of these observations for controlled release systems. *Id*. at 34–36. Davis-1985 also discusses positioned release of drugs in the colon, using 5-aminosalicylic acid for the treatment of ulcerative colitis as an example. *Id.* at 36–37.

Marakhouski compares the clinical efficacy of a "new" pellet formulation of mesalazine (5-ASA) with a conventional tablet formulation for the treatment of mild to moderately active ulcerative colitis. Ex. 1024, 133 (Summary), 134-1.[8] According to Marakhouski, the pellet formulation has a "combination of delayed and prolonged release characteristics." *Id*. at

[8] Where appropriate, we use the suffix "-1" to refer to the first column and "-2" to refer to the second column.

134-1. Both formulations have a pH-dependent coating, Eudragit-L, which dissolves at pH ≥ 6.0 in the ileocaecal region (junction between the small intestine and the large intestine). *Id.* at 135-1. The pellets are small (< 2 mm) particles containing 5-ASA embedded in a matrix polymer core, which provides for prolonged release of the drug. *Id.* According to Marakhouski, the pellet formulation "prevent[s] the so-called dose-dumping effect" and "can be taken independent of meals." *Id.* at 134-1; *see also* 138-1 (same). Marakhouski concludes that the pellet formulation is "as effective and well tolerated as the standard tablet formulation for the therapy of mild to moderately active ulcerative colitis." *Id.* at 138-2.

Brunner compares the gastrointestinal transit and release of pellet and tablet formulations of mesalazine (5-ASA) using gamma scintigraphy and plasma pharmacokinetics in healthy volunteers. Ex. 1025, 1 (Title, Summary). According to Brunner, both formulations have a Eudragit L coating, which dissolves at pH ≥ 6.0, and the pellets additionally have a matrix polymer core that provides prolonged release. *Id.* at 1164-2, 1167-2. Brunner states that the pellet formulation "could show some advantages compared with tablets, such as passage through the stomach independent of concomitant food intake." *Id.* at 1167-2. Brunner concludes that both the pellets and tablets release 5-ASA in the same target region and pass through the gastrointestinal tract under fasting conditions in healthy volunteers in a comparable time. *Id.* at 1163-1, 1168-2–69-1.

3. Differences Between Claim 1 and the Prior Art

Preamble and Paragraph [a]

Petitioner contends that elements recited in the preamble and paragraph [a] of claim 1 are taught by the Sept. 2007 Press Release and Endonurse. Pet. 25–28.

We find that the Sept. 2007 Press Release and Endonurse each disclose a method of maintaining the remission of ulcerative colitis. Taken together, these references expressly disclose administering a granulated mesalamine formulation comprising four capsules each comprising 0.375 g of granulated mesalamine once per day. Ex. 1012, 1; Ex. 1014, 1–2. These facts are undisputed by Patent Owner and are sufficient to establish that the Sept. 2007 Press Release and Endonurse disclose the elements recited in the preamble and most of paragraph [a] of claim 1.

Paragraph [a]: "without food"

Petitioner relies on Davis-1985, Marakhouski, and Brunner to argue obviousness of administering a granulated mesalamine formulation "without food," as recited in claim 1, paragraph [a]. Pet. 29–33, 43–46, 48–50.

The Sept. 2007 Press Release and Endonurse do not expressly disclose administering a granulated mesalamine formulation "without food," as recited in claim 1, paragraph [a]. We find Petitioner has shown that this limitation is suggested by either Marakhouski or Brunner in view of Davis-1985. More specifically, we find that these references would have suggested to a POSITA that the method of the Sept. 2007 Press Release and Endonurse could be advantageously and successfully practiced by administering granulated mesalamine without food.

Our finding is supported by Marakhouski and Brunner, each of which discloses administration of granulated mesalamine without food. Ex. 1024, 135-1 (patients took pellets three times a day "1 h before meals"); Ex. 1025, 1164-2 (pellets were taken orally "after an overnight fast"). Marakhouski and Brunner also disclose that granulated mesalamine "can be taken independent of meals" or "independent of concomitant food intake." Ex. 1024, 134-1; Ex. 1025, 1167-2. This feature is described as an advantage of the pellet formulation. Ex. 1024, 134-1; Ex. 1025, 1167-2.

Accordingly, we find that the "without food" limitation is taught by Marakhouski or Brunner. As discussed in subsections II.C.4. and II.C.5. below, we find Petitioner has shown that a POSITA would have had a reason to combine the teachings of the Sept. 2007 Press Release, Endonurse, Davis-1985, and either Marakhouski or Brunner, and that a POSITA would have had a reasonable expectation of success of maintaining remission of ulcerative colitis in view of the combined teachings of these references.

Paragraph [a]: "in the morning"

Petitioner contends that a person of ordinary skill in the art would have had a reason to administer granulated mesalamine "in the morning" because that is the time when a patient's stomach is most likely to be empty. Pet. 29 (citing Ex. 1002 ¶ 65).

The Sept. 2007 Press Release and Endonurse do not expressly disclose administering a granulated mesalamine formulation "in the morning," as recited in claim 1, paragraph [a]. We find that this limitation is taught by either Marakhouski or Brunner, each of which discloses administration of granulated mesalamine in the morning. Ex. 1024, 135-1

(patients took pellets three times a day, including "in the morning"); Ex. 1025, 1164-2 (pellets were taken orally "in the morning").

Our finding is further supported by Dr. Digenis' testimony that a POSITA would have had reason to administer granulated mesalamine "in the morning" because "this is the time [of day] when the patient is most likely to be on an empty stomach." Ex. 1002 ¶ 65. We find that Petitioner's arguments and evidence establish a reason to combine and a reasonable expectation of success with respect to the "in the morning" limitation for the reasons as discussed in subsections II.C.4. and II.C.5. below.

Paragraphs [b] and [c]

Paragraphs [b] and [c] recite: "said method maintains remission of ulcerative colitis in a subject for a period of at least 6 months of treatment" where "remission is defined as a DAI score of 0 or 1." Petitioner contends that these claim limitations are disclosed by Sept. 2007 Press Release and Endonurse. Pet. 33–34.

Relevant to paragraph [b] of claim 1, the Sept. 2007 Press Release and Endonurse each discloses a method of maintaining remission of ulcerative colitis, including once-a-day dosing of granulated mesalamine. Ex. 1012, 1; Ex. 1014, 1–2. The Sept. 2007 Press Release discloses that "subjects dosed once-a-day with 1.5 grams of granulated mesalamine remained relapse-free over 6 months of treatment." Ex. 1012, 1. These facts are undisputed by Patent Owner and are sufficient to establish that the Sept. 2007 Press Release and Endonurse disclose the limitation of paragraph [b] of claim 1.

Claim 1, paragraph [c], recites: "remission is defined as a DAI score of 0 or 1." Ex. 1001, 34:18. As discussed above, we construe this phrase as

"remission is defined as a DAI score of 0 or 1, where the DAI score is a sum of four subscores."

We find that Petitioner has shown that that it would have been obvious to practice the method disclosed in the Sept. 2007 Press Release and Endonurse by defining "relapse-free" as a DAI score of 0 or 1, where the DAI score is based on a sum of four subscores.[9] Our finding is supported by Dr. Digenis' testimony that a POSITA would have recognized that "relapse-free," i.e., remission, would be defined by a DAI score of 0 to 1. Ex. 1002 ¶ 78 (citing Ex. 1013 ¶ 20).[10] Our finding is further supported by Meyeroff, which discloses: "a patient is considered to be in remission for UC if a UC-DAI score of ≤1 is obtained, with rectal bleeding and stool frequency scores of 0, and at least a 1-point reduction in sigmoidoscopy score from baseline." Ex. 1013 ¶ 20. Patent Owner does not dispute that Meyeroff's definition of remission meets the limitation of paragraph [c] under a claim construction requiring a sum of four DAI subscores.

Our finding is further supported by Cooney,[11] which Patent Owner relies upon to argue nonobviousness of claim 1's definition of "remission." PO Resp. 56–58. Cooney discloses twelve clinical activity indices for

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[9] We note that neither party argues that the selection of a definition of remission has any impact on whether there would have been a reasonable expectation of success for the claimed method.

[10] Meyeroff et al., US 2010/0035850 A1, published Feb. 11, 2010, Ex. 1013 ("Meyeroff").

[11] R. Cooney et al., *Outcome Measurement in Clinical Trials for Ulcerative Colitis: Towards Standardization*, 8:17 Trials 1–9 (2007), Ex. 2039 ("Cooney"). Cooney is cited and relied upon extensively by Patent Owner. PO Resp. 56–58.

scoring ulcerative colitis, including "the Mayo score, or Disease Activity Index (DAI)." Ex. 2039, 2 (second column and Table 1), 3 (Table 2). Cooney teaches that the DAI is currently favored by the Food and Drug Administration (FDA) for trial design in ulcerative colitis, *id.* at 2-2, and is one of the most widely used of the activity indices in clinical trials, *id.* at 6-1. Contrary to Patent Owner's argument (PO Resp. 56–58), we find that Cooney's teachings would have led a POSITA to practice the method of the Sept. 2007 Press Release and Endonurse using the DAI, rather than some other index, for assessing whether patients remain relapse-free or in remission. The Mayo score, or Disease Activity Index (DAI), as described by Cooney, uses the same four subscores as described in the '688 patent. *Compare* Ex. 2019 (Table 2, 1st & 4th columns), *with* Ex. 1001, 17:5–11.

Contrary to Patent Owner's argument (PO Resp. 56–58), we also find that Cooney would have led a POSITA to define remission as a DAI score of 0 or 1, where the DAI score is based on a sum of four subscores. Cooney discloses three remission endpoints that have been used in clinical trials: a DAI score of 0, ≤ 1, or ≤ 2. Ex. 2039, 6-1. Each of these endpoints is based on "the full DAI score," i.e., a sum of four subscores. Ex. 1056, 94:13–14. Thus, a POSITA would have had a reason to use any one of these three numerical definitions of remission in the method described in the Sept. 2007 Press Release and Endonurse. Because two out of the three definitions meet the limitation of claim 1[c], Cooney supports a conclusion of obviousness. *ACCO Brands Corp. v Fellowes, Inc.*, 813 F.3d 1361, 1367 (Fed. Cir. 2016) ("even if one possible obvious combination falls outside of the claims, it fails to undercut the fact that the other possible obvious combination lies within their scope").

Paragraph [d]

Paragraph [d] of claim 1 recites: "the granulated mesalamine formulation is not administered with antacids." Petitioner contends that a person of ordinary skill in the art would have known not to administer granulated mesalamine with antacids because antacids were known to increase stomach pH and cause dissolution of the pH-sensitive coating and release of mesalamine in the stomach and upper small intestine instead of the distal ileum and colon. Pet. 35–36 (citing Ex. 1002 ¶¶ 81, 82).

We find Petitioner has shown that the prior art would have led a POSITA to practice the method disclosed in the Sept. 2007 Press Release and Endonurse by administering the granulated mesalamine formulation without antacids.

Our finding is supported by the Sept. 2007 Press Release and Endonurse. The Sept. 2007 Press discloses a granulated mesalamine formulation having an enteric pH-dependent coating, which is designed to release the active ingredient beginning in the small bowel at a pH of 6.0. Ex. 1012, 1. Endonurse discloses that the granulated mesalamine is "formulated to deliver mesalamine by means of dual-release granules to the distal ileum and colon." Ex. 1014, 2. Based on these disclosures, a POSITA would have known that the granulated mesalamine formulation disclosed in the Sept. 2007 Press Release and Endonurse relies on pH differences between the stomach and the small bowel to achieve targeted delivery of mesalamine to the distal ileum and colon.

Our finding is further supported by Dr. Digenis' testimony. According to Dr. Digenis, a POSITA would have understood that the stomach's pH is generally lower than the pH of the intestinal tract and also

understood that antacids generally increase the pH of the stomach. Ex. 1002 ¶¶ 81, 82 (citing Ex. 1007, 1:27–33[12]; Ex. 1009, 34; and Ex. 1026, 156[13]). Dr. Digenis testifies that, because antacids were known to increase stomach pH, a POSITA would have understood that co-administering antacids with a granulated mesalamine formulation having an enteric pH-dependent coating (as disclosed in the Sept. 2007 Press Release) would cause the pH-sensitive coating to dissolve in the stomach, resulting in release of the mesalamine in the stomach or upper portions of the small intestines. *Id.* This, in turn, would have been understood to decrease the amount of mesalamine reaching the lower intestines—the target site for delivery of mesalamine according to the Sept. 2007 Press Release and Endonurse. *Id.* ¶ 81. We credit this testimony of Dr. Digenis, which is not contradicted by Patent Owner's declarants.

Our finding is further supported by the teachings of Davis-1985 and Brouwers. Davis-1985 teaches that administering antacids will raise the pH of the stomach. Ex. 1009, 34-1. Brouwers discusses site-specific delivery of 5-ASA (mesalamine), identifying a goal of "a high concentration of 5-ASA into the colon" and warning that "pH-dependent delivery systems can be prone to dose dumping when combined with antacids." Ex. 1026, 156. These prior art teachings reinforce Dr. Digenis' testimony that a POSITA would have known not to administer antacids with a granulated mesalamine

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[12] Hirakawa et al., EP 0 671 168 A1, published Sept. 13, 1995, Ex. 1007 ("EP '168").

[13] J.R.B.J. Brouwers, *Advanced and Controlled Drug Delivery Systems in Clinical Disease Management*, 18(5) Pharmacy World & Science 153–162 (1996), Ex. 1026 ("Brouwers").

formulation having an enteric pH-dependent coating, as disclosed in the Sept. 2007 Press Release.

Paragraph [e]

Paragraph [e] of claim 1 recites: "wherein 85% to 90% of the mesalamine reaches the terminal ileum and colon." Petitioner contends that a person of ordinary skill in the art would have expected that the formulation disclosed in the Sept. 2007 Press Release would have the recited release profile—85% to 90% of the mesalamine reaches the terminal ileum and colon—because the press release discloses the same formulation as the '688 patent. Pet. 37–38.

We find Petitioner has shown that the release profile recited in claim 1—85% to 90% of the mesalamine reaches the terminal ileum and colon—is an inherent property of the granulated mesalamine formulation disclosed in the Sept. 2007 Press Release and Endonurse. These references disclose a formulation that is designed to deliver mesalamine in a site-specific manner to the terminal ileum and colon. More specifically, the Sept. 2007 Press Release discloses a granulated mesalamine formulation that "is designed to provide for the distribution of the active ingredient beginning in the small bowel and continuing throughout the colon." Ex. 1012, 1.[14] Endonurse discloses that "[g]ranulated mesalamine is formulated to deliver mesalamine by means of dual-release granules to the distal ileum and colon." Ex. 1014, 2.

[14] According to Dr. Digenis, a person of ordinary skill would have understood that the small bowel includes the terminal ileum. Ex. 1002 ¶ 84.

There is no dispute that the granulated mesalamine formulation discussed in the Sept. 2007 Press Release and Endonurse is the same as the granulated mesalamine formulation described in the '688 patent. Although the trade name is not mentioned, all three publications disclose clinical trials of Salix's Apriso formulation. Ex. 1012; Ex. 1014, 2; Ex. 1001, 6:43–7:25; Ex. 2036 ¶¶ 16, 19, 21, 22. The Sept. 2007 Press Release provides essentially the same description of the granulated mesalamine formulation as the '688 patent. The Sept. 2007 Press Release states that the granulated mesalamine formulation "combines an enteric pH-dependent coating, which provides for delayed release, and a polymer matrix core, which provides for extended release . . . [where] granulated mesalamine . . . begins to release at a pH of 6.0." Ex. 1012, 1. Similarly, the '688 patent states that "each granulated mesalamine formulation capsule contains, for example, granules composed of mesalamine in a polymer matrix with an enteric coating that dissolves at pH 6 and above." Ex. 1001, 10:63–66; *see also id.* at 9:37–45.

The '688 patent demonstrates that the release profile recited in claim 1—85% to 90% of the mesalamine reaches the terminal ileum and colon—is an inherent property of the granulated mesalamine formulation. In the following passage, the '688 patent attributes this release profile to the dual-release formulation:

> In one embodiment, following dissolution of the inner coating, the polymer matrix core of the granulated mesalamine provides a mechanism by which mesalamine, the active therapeutic ingredient, is uniformly and slowly released and distributed in the lumen of the colon. The release profile and additional pharmacokinetic data show that the pellets of the granulated mesalamine formulation have a relatively low rate and extent of systemic absorption, and that 85% to 90% of drug reaches the diseased area.

Ex. 1001, 9:46–54; *see also id.* at 11:26–38 (formulation provides desired release profile); *id.* at 16:65–67 ("Approximately 80% of an administered oral dose of mesalamine is estimated to be available in the colon, sigmoid, and rectum when dosed as mesalamine granules.")

The '688 patent does not identify other factors, aside from the delayed and extended release formulation, that are responsible for achieving the release profile recited in claim 1. For example, we find no indication in the '688 patent that achieving the recited release profile requires that the drug be administered "in the morning," "without food," or without antacids—conditions recited in claim 1, but not disclosed in the Sept. 2007 Press Release or Endonurse. In fact, the '688 patent indicates that the rate and extent of absorption of mesalamine and its metabolite "were not affected by a high-fat meal." Ex. 1001, 16:63–64.

Our reliance on the '688 patent to show that the recited release profile is an inherent characteristic of the granulated mesalamine formulation is consistent with Federal Circuit precedent. *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (challenged patent itself defined the disputed limitation "as a property that is necessarily present" under conditions disclosed in the prior art); *In re Kao*, 639 F.3d at 1070 (relying on appellant's specification to confirm that the claimed "food effect" is an inherent property of the drug itself); *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) ("the [inventors'] application itself instructs that [recited binding property] is not an additional requirement imposed by the claims . . ., but rather a property necessarily present in [recited protein]").

Because the Sept. 2007 Press Release and Endonurse disclose the same granulated mesalamine formulation as described in the '688 patent, we

find that the formulation disclosed in the Sept. 2007 Press Release and Endonurse inherently has the same release profile as recited in claim 1. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("The initial blood serum concentration resulting from administering a [drug] dosage is an inherent property of the formulation"); *In re Kao*, 639 F.3d at 1070.

The record establishes that the release profile of a mesalamine formulation, including the amount of mesalamine that reaches the terminal ileum and colon, can be estimated empirically by orally administering the formulation to a group of patients and measuring the amounts of mesalamine and its metabolites in the blood, and urine over a period of days. In general, the lesser the amount of mesalamine and its metabolites in the blood and urine, the greater the amount of mesalamine that is estimated to reach the terminal ileum and colon. Ex. 2032, 77:11–78:16; Ex. 1056, 134:8–135:6; Ex. 1067, 54:14–57:1.

In *Santarus*, the Court explained that "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." 694 F.3d at 1354. "To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Id.* Blood levels were likewise at issue in *Kao*, where the appellant asserted that the prior art did not disclose a "food effect" limitation, i.e., a higher C_{max} under fed versus fasted conditions. 639 F.3d at 1070. The Court held that the prior art's "express teachings render the claimed . . . formulation obvious, and the claimed 'food effect' adds nothing of patentable consequence."

Here, as in *Santarus* and *Kao*, the method recited in the '688 patent claims does not become nonobvious simply by administering a known granulated mesalamine formulation to a group of patients and claiming the resulting release profile.

4. Reasons to Combine

Petitioner contends that the understandings of a POSITA regarding the effect of food on the efficacy of drug formulations intended for the colon, as evidenced by Davis-1985, would have led a POSITA to administer granulated mesalamine without food. Pet. 30–33, 43–44. Petitioner further contends that Marakhouski and Brunner each discloses that granulated mesalamine can be administered independent of food and that it would have been obvious to combine this teaching with the other cited references in order to obtain the advantages disclosed in these references. Pet. 45–46, 48–50.

We find Petitioner has shown that a POSITA would have had a reason to combine the teachings of the Sept. 2007 Press Release and Endonurse with the teachings of either Marakhouski or Brunner.

The evidence establishes that all four references pertain to a granulated mesalamine formulation that provides delayed and extended release of mesalamine. More specifically, all four references disclose a pellet or granulated formulation, where the pellets or granules have an enteric pH-dependent coating, which provides for delayed release and begins to release at a pH of 6.0, and a polymer matrix core, which provides for extended or prolonged release. Ex. 1012, 1; Ex. 1014, 2; Ex. 1024, 135-1, 138-1; Ex. 1025, 1164-2, 1167-2.

The evidence further establishes that all four references pertain to a granulated mesalamine formulation that was provided by or licensed from the same company—Falk (Patent Owner). The Sept. 2007 Press Release states: "Salix acquired rights to market granulated mesalamine in the U.S. from Dr. Falk Pharma GmbH of Freiburg, Germany." Ex. 1012, 2; *see also* Ex. 2036 ¶ 8 (co-inventor Johnson: "Salix in-licensed Falk's granulated mesalamine technology in 2002 . . . ."). Endonurse does not mention Falk, but plainly relates to the same granulated mesalamine formulation and Phase III clinical trials as the Sept. 2007 Press Release. *Compare* Ex. 1012, 1, *with* Ex. 1014, 1, 2 (both references discussing evaluation of granulated mesalamine for the maintenance of remission of ulcerative colitis in 300-subject, multicenter, placebo-controlled, double-blind, randomized Phase III trials).

Marakhouski and Brunner likewise relate to a granulated mesalamine formulation from Falk. Ex. 1025, 1164-2 (Brunner: "The study medication was provided by Dr[.] Falk Pharma GmbH, Freiburg, Germany"); Ex. 1024, 134-1, 138-2, 140-2 (Marakhouski cites Brunner (ref. 21) as disclosing how 5-ASA is released from pellets in the gastrointestinal tract). At the hearing, Patent Owner confirmed that Marakhouski and Brunner relate to Falk's Salofalk® Granu-Stix® formulation, which is similar to Salix's granulated mesalamine formulation discussed in the Sept. 2007 Press Release and Endonurse. Tr. 51:3–6, 51:18–52:11. Patent Owner represented that all four references—the Sept. 2007 Press Release, Endonurse, Marakhouski, and Brunner—relate to a granulated mesalamine formulation within the scope of the '688 patent claims. *Id.* at 52:12–13.

The evidence further establishes that all four references relate to the treatment of ulcerative colitis. The Sept. 2007 Press Release and Endonurse disclose a dosing regimen for maintaining remission of ulcerative colitis. Ex. 1012, 1; Ex. 1014, 1, 2. Marakhouski evaluates a granulated mesalamine formulation for the treatment of mild to moderately active ulcerative colitis. Ex. 1024, 1 (Summary). Brunner likewise discusses administering granulated mesalamine for the treatment of ulcerative colitis. Ex. 1025, 1163-2, 1167-2, 1168-2.

Because all four references pertain to the same or similar granulated mesalamine formulation for treatment of the same disease (ulcerative colitis), a POSITA seeking to practice the method disclosed in the Sept. 2007 Press Release and Endonurse would have had a reason to consult either Marakhouski or Brunner for information on whether granulated mesalamine should be administered with or without food.

Petitioner has shown that a POSITA would have been motivated to combine the teachings of the Sept. 2007 Press Release and Endonurse with the teachings of either Marakhouski or Brunner in order to obtain the advantages disclosed in either Marakhouski or Brunner. Ex. 1002 ¶¶ 111, 112, 121, 122. These advantages include the ability to administer the drug independent of food. Ex. 1024, 134-1 (pellet formulation "prevent[s] the so-called dose-dumping effect" and "[h]ence . . . can be taken independent of meals"); Ex. 1025, 1167-2 ("passage through the stomach independent of concomitant food intake" is one of the "advantages" of a pellet formulation).

Petitioner has also shown that a POSITA would have had a reason to combine the teachings of Davis-1985 with the teachings of the Sept. 2007 Press Release, Endonurse, and either Marakhouski or Brunner.

As already discussed, the Sept. 2007 Press Release and Endonurse disclose a method of maintaining the remission of ulcerative colitis, including oral administration of a granulated mesalamine formulation. Ex. 1012, 1; Ex. 1014, 2. The Sept. 2007 Press Release and Endonurse are silent on whether the granulated mesalamine should be administered with or without food. As discussed below, the evidence establishes that a POSITA would have considered the teachings Davis-1985 relevant in determining whether granulated mesalamine should be administered with or without food.

First, a POSITA's attention would have been drawn to Davis-1985 because it addresses the same drug—5-aminosalicylic acid (mesalamine)—for treatment of the same disease— ulcerative colitis—as discussed in the Sept. 2007 Press Release and Endonurse. More specifically, Davis-1985 addresses "positioned release of a drug in the various regions of the colon, following oral administration," using "5-aminosalicylic acid for the treatment of ulcerative colitis" as an example. Ex. 1009, 36.

Second, a POSITA would have considered the teachings of Davis-1985, comparing oral administration in fed and fasted states (*id*. at 34, 36), to be relevant in determining whether granulated mesalamine should be administered with or without food. More specifically, a POSITA would have considered the teachings of Davis-1985, regarding gastrointestinal transit times and bioavailability of orally administered drugs in fed and fasted states (*id*. at 34, 36), to be relevant in determining whether a drug, such as mesalamine, that is intended to be delivered to the lower intestine and colon (*see* Ex. 1012, 2; Ex. 1014, 2), should be administered with or without food. Our finding is supported by the testimony of Dr. Digenis, who

explains how Davis-1985's teachings regarding the effect of food on gastrointestinal transit times, bioavailability, stomach pH, and gastric emptying would have led a POSITA to conclude that a drug formulated with a pH-dependent coating and intended to be delivered to the colon should be administered without food. Ex. 1002 ¶¶ 69–71, 73–74.

Patent Owner argues that a POSITA would not have relied upon the Sept. 2007 Press Release or Endonurse because they are directed to investors, not clinicians, because pharmaceutical companies often overstate the impact of clinical data, and because the data is preliminary and not peer-reviewed. PO Resp. 39–42. We are not persuaded by Patent Owner's arguments.

The fact that the Sept. 2007 Press Release and Endonurse are directed to investors enhances, rather than detracts from, the reliability of these references. The evidence establishes that Salix's press releases—the Sept. 2007 Press Release and Endonurse—were included as exhibits to Form 8-K filings with the Securities and Exchange Commission ("SEC"). Exs. 1051, 1052. Section 18 of the Securities Exchange Act of 1934 imposes liability for false and misleading statements in documents filed with the SEC, and Section 10(b) and SEC Rule 10b-5 impose liability for untrue statements or omissions of material facts in connection with the purchase or sale of any security. 15 U.S.C. §§ 78j(b), 78r; 17 C.F.R. § 240.10b-5.

Reliability of the Sept. 2007 Press Release is further enhanced by the identification of the source of the information as "Bill Forbes, Pharm.D., Vice President, Research and Development, Salix Pharmaceuticals." Ex. 1012, 1. In fact, the entire second paragraph of the press release is a statement by Dr. Forbes set forth in quotation marks. *Id.* at 1–2. We find

that Dr. Forbes' statements in the Sept. 2007 Press Release would have been relied on by a POSITA to no lesser extent than his statements in the '688 patent.

Reliability of the Sept. 2007 Press Release is still further enhanced by the indication that the data discussed therein was for purposes of submission to the Food and Drug Administration ("FDA"). The press release announces "the successful completion and outcome of the first of two Phase III registration trials" and that a New Drug Application ("NDA") will be submitted within the next few months. Ex. 1012, 1–2. Although Patent Owner asserts that pharmaceutical companies often overstate the impact of clinical data, Patent Owner identifies no such overstatement in either the Sept. 2007 Press Release or Endonurse.

Patent Owner's argument that the data is preliminary and not peer-reviewed does not distinguish the data summarized in the Sept. 2007 Press Release from the data in the '688 patent—both were prepared prior to obtaining FDA approval. The Sept. 2007 Press Release and Endonurse are not unreliable merely because they are not published in peer-reviewed journals. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1374–75 (Fed. Cir. 2005) (error to distinguish prior art news article based on lack of peer review and author's academic credentials outside the relevant art).

Patent Owner argues that a clinician would not look to Davis-1985 for teachings regarding treatment of ulcerative colitis, that Davis-1985 is a general academic reference directed to the design and evaluation of controlled release systems, and that Davis-1985 focuses on absorption of drug in the small intestine for systemic absorption, not topical action in the

colon. PO Resp. 42–44. We are not persuaded by Patent Owner's arguments.

Petitioner has identified particular teachings of Davis-1985 relating to the effect of food on the gastrointestinal transit and absorption of an orally administered drug. Pet. 30–33. Petitioner's expert has explained how these teachings would have led a POSITA to conclude that a drug intended for the colon should be administered without food. Ex. 1002 ¶¶ 69–71, 73. Although Davis-1985 does not contain a specific instruction as to whether a delayed and extended release mesalamine formulation should be administered with or without food, we find that its teachings are nevertheless relevant to that question. For example, Davis-1985 discusses the effect of food on systemic absorption of orally administered drugs. Ex. 1009, 34-1 to 34-2.[15] That discussion is relevant to whether a drug intended for topical action in the colon should be administered with or without food. As Patent Owner concedes, a POSITA would have understood that, for an orally administered drug, there is a relationship between systemic absorption and the amount that is available to act topically on the colon: the higher the systemic absorption, the lower the amount available to act on the colon and vice-versa. PO Resp. 18, 49; Ex. 2035 ¶¶ 41, 77, 92.

5. Predictability and Reasonable Expectation of Success

"Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *In re Kubin*, 561 F.3d at 1360 (citing *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)).

[15] There is no dispute that "measured bioavailability," as discussed in Davis (Ex. 1009, 34-2), refers to systemic bioavailability, not bioavailability in the colon. Tr. 14:1–11, 48:5–17.

Obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). The requirement to show a reasonable expectation of success pertains to the subject matter of the claims. No greater or different measure of success is required. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (The "correct inquiry" is whether there is "a reasonable expectation of achieving what is claimed in the patent-at-issue.").

We find that Petitioner has shown that the prior art establishes a reasonable expectation of success for the method of claim 1. More specifically, we find that, based upon the combined teachings of the Sept. 2007 Press Release, Endonurse, Davis-1985, and either Marakhouski or Brunner, a POSITA would have had a reasonable probability of success in maintaining remission of ulcerative colitis by administering granulated mesalamine without food.

Our finding is supported by the Sept. 2007 Press Release, which announces "the successful completion and outcome" of a Phase III registration trial "to evaluate the safety and efficacy" of a delayed and extended release granulated mesalamine formulation. Ex. 1012, 1. The Sept. 2007 Press Release states: "a statistically significantly greater proportion of subjects dosed once-a-day with 1.5 grams of granulated mesalamine remained relapse-free over 6 months of treatment than patients dosed with placebo." *Id.* The Sept. 2007 Press Release quotes Dr. Forbes as stating that a "300-subject, multicenter, 6-month, double-blind, randomized, placebo-controlled study" demonstrates that granulated mesalamine dosed once a day "successfully maintain[s] remission in ulcerative colitis patients."

Id. There is no indication in the Sept. 2007 Press Release that the granulated mesalamine had to be administered with food in order to obtain the reported success in maintaining remission of ulcerative colitis.

Our finding is further supported by Marakhouski, which discloses the results of a 233-patient study in which granulated mesalamine was administered three times a day "1 h before meals." Ex. 1024, 133 (Summary), 135-1, 136-1. The treatment was shown to be effective for inducing remission of mild to moderately active ulcerative colitis over an eight-week treatment period. *Id.* at 133 (Summary), 136 (Fig. 1), 138-2.

Our finding is further supported by the teachings of Davis-1985 and the expert testimony regarding the impact of food on gastrointestinal transit times and bioavailability. Davis-1985 teaches that "[t]he process of gastric emptying is affected by the quantity and nature of food in the stomach." Ex. 1009, 34-1. Davis-1985 compares gastrointestinal transit in a fed and fasted state as follows:

> Delivery systems, administered to a fasted stomach, will empty rapidly from the stomach and can be transported through the small intestine to the terminal ileum in as little as 1.5—2 h by an interdigestive housekeeper wave. Thus, if the important absorption sites for the administered drug are in the upper small intestine, the measured bioavailability in the fasted state will be considerably different to that measured in the fed state.

Id. at 34-1–34-2. Based on scintigraphic studies of gastrointestinal transit of a pellet formulation, Davis-1985 teaches the following implications for controlled release delivery systems:

> Dosage on an empty stomach, or after a light meal, could result in the delivery system arriving at the colon after only 3 h. Consequently the greater proportion of the drug will be delivered to a non-optimal site.

Id. at 36-1.

According to Dr. Digenis, the foregoing teachings from Davis-1985 would have suggested to a POSITA that drugs intended to be absorbed in the lower intestine and colon, including drugs for treating ulcerative colitis, would have increased efficacy when administered to a fasted stomach, i.e., without food. Ex. 1002 ¶¶ 69–70. We credit this testimony, which is not contradicted by Patent Owner's declarants. In fact, Dr. Safdi agrees with Dr. Digenis' premise that higher bioavailability via absorption through the small intestine translates to lesser amounts of mesalamine available to be deposited on the distal ileum and colon. *Compare* Ex. 1002 ¶¶ 68, 106, *with* Ex. 2035 ¶ 77 ("the more mesalamine that is absorbed in the gastrointestinal tract, the less mesalamine there is to act topically to treat ulcerative colitis in the colon").

Our finding is further supported by prior art teachings and expert testimony regarding the impact of food on stomach pH, gastric emptying, and dissolution of pH-dependent coatings. Dr. Digenis testifies that a POSITA would have understood that food raises the pH in the stomach and suppresses gastric emptying. Ex. 1002 ¶¶ 73, 106. Dr. Digenis' testimony is supported by Davis-1985, which discloses that the pH of the resting stomach is about 2.0, and that the presence of food will raise the pH to 5 or 6. Ex. 1009, 34-1. Dr. Digenis' testimony is further supported by Davis-1985's teaching that "[t]he process of gastric emptying is affected by the quantity and nature of food in the stomach," and the presence of food in the stomach causes some dosage forms to be retained in the stomach until the end of the digestive phase. *Id.*

Dr. Digenis further testifies that a POSITA would have understood that, for a formulation having a pH-dependent coating, administration with food (as compared to without food) would result in a longer tenure of the formulation in the stomach at a higher pH and consequently a greater release of the drug in the upper portion of the small intestine, where higher absorption of the drug occurs. Ex. 1002 ¶ 106. According to Dr. Digenis, this understanding would have led a POSITA to administer granulated mesalamine having a pH-dependent coating without food, so as to avoid dissolution of the coating and release of the drug in the stomach and upper small intestine and to provide greater application of mesalamine to the inflicted areas of the colon. *Id.* ¶¶ 73–74, 106–107. Dr. Digenis' testimony is supported by prior art teachings regarding pH-dependent enteric coatings, which "tak[e] advantage of the fact that the stomach contents are acid and the intestinal contents are neutral to slightly alkaline." Ex. 1008, 1:14–18.[16] Such coatings allow a drug to pass through the stomach and be released only when the coated material reaches the small intestine. *Id.* at 1:10–14, Ex. 1011, 4:15–16; *see also* Ex. 1007, 1:27–33 (describing difference in pH values of stomach and intestines).

Patent Owner argues that, "contrary to Dr. Digenis' opinion, a rise in stomach pH caused by the ingestion of food as described in Davis-1985 does not suggest that an enteric coated granulated mesalamine formulation should be administered without food." PO Resp. 44. Patent Owner argues that it was well known that any rise in pH was short lived and could be easily

[16] Ring et al., WO 91/07949, published June 13, 1991, Ex. 1008 ("PCT '949").

counteracted with a thicker enteric coating and a polymer that dissolves at a higher pH threshold. *Id.* at 45 (citing Ex. 2032, 196:7–197:11; Ex. 2038, 575, 577).[17] We are not persuaded by Patent Owner's arguments, which are not supported by testimony from Patent Owner's expert, Dr. Safdi.

Even if Patent Owner is correct that a thicker enteric coating and/or higher pH threshold would have permitted administration of granulated mesalamine with food, it does not follow that there would have been no motivation or reasonable expectation of success in administering the drug without food. Patent Owner acknowledges that administration with food may be problematic due to a rise in stomach pH. PO Resp. 44. The existence of other known solutions to this problem (e.g., a thicker enteric coating) does not identify an insufficiency in Petitioner's evidence showing a motivation and reasonable expectation of success in pursuing the claimed solution, namely administering the drug without food.

Patent Owner argues that a POSITA would need to conduct a "food effect" study to determine whether a drug formulation should be administered with or without food, that neither Marakhouski nor Brunner discloses such a study, and that administering granulated mesalamine without food is neither predictable nor has a reasonable expectation of success absent a "food effect" study. PO Resp. 48–54; Tr. 37:4–15. We are not persuaded by Patent Owner's arguments.

As discussed above, the requirement to show a reasonable expectation of success pertains to the subject matter of the claims. *Intelligent Bio-*

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[17] G. McLauchlan et al., *Comparison of Gastric Body and Antral pH: A 24 Hour Ambulatory Study in Healthy Volunteers*, 30 Gut 573–578 (1989), Ex. 2038 ("McLauchlan").

Systems, 821 F.3d at 1367. Here, the claims do not recite any food effect. For example, there is no requirement that administration of granulated mesalamine without food is more effective, less effective, or equally effective, as compared to administration with food. There is also no requirement that food have any effect on any pharmacokinetic parameter, such as area under the curve (AUC), peak plasma concentration (C_{max}), or time to that peak (T_{max}). Nor is there any requirement that food have any effect on urinary excretion. *Cf.* Ex. 1001, 14:57–15:2 (Example 1: effect of high fat meal on absorption of mesalamine granules, as measured by T_{max}, C_{max}, and urinary excretion); *id.* at 16:47–64 (Example 4: effect of food on 5-ASA absorption, as measured by C_{max} and AUC).

The measure of success required by the claims is maintaining remission of ulcerative colitis for a period of at least 6 months of treatment, where remission is defined as a DAI score of 0 or 1. Ex. 1001, 34:16–18. For the reasons discussed above, the prior art, including the Sept. 2007 Press Release, shows a reasonable expectation of success for the claimed method. The prior art, including Davis-1985 and either Marakhouski or Brunner, also shows a reasonable expectation of success when granulated mesalamine is administered without food.

6. Secondary Considerations

Before reaching a conclusion on the question of obviousness, we consider Patent Owner's evidence and contentions that nonobviousness is supported by objective indicia, including long-felt but unmet need, failure of others, and unexpected results. PO Resp. 59–68.

Long-Felt Need and Failure of Others

Patent Owner contends that, at the time of the claimed invention, there was a long-felt but unmet need for improved methods of maintaining the remission of ulcerative colitis using an improved oral mesalamine formulation. PO Resp. 67. More specifically, Patent Owner contends that there was a need for a once-daily, low dose granulated mesalamine formulation administered without food for maintaining the remission of ulcerative colitis (versus treating or inducing remission) for at least 6 months. *Id.* at 68. Patent Owner contends that Falk tried but failed to demonstrate therapeutic equivalence of a low, 1.5 g of a granulated mesalamine formulation administered once a day versus three times a day to maintain the remission of ulcerative colitis. *Id.* at 61–62 (citing Ex. 2025, 102; Ex. 2037 ¶¶ 12–16). Patent Owner further contends that Falk failed to demonstrate that there was no adverse impact when administering granulated mesalamine without food. PO Resp. 62–63 (citing Ex. 2026, 3; Ex. 2035 ¶¶ 92–98; Ex. 2036 ¶ 14; Ex. 2037 ¶¶ 17–21).

Long-felt need is closely related to the failure of others. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1082 (Fed. Cir. 2012). To be probative of non-obviousness, the evidence must demonstrate "both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *Id.* Nonobviousness is suggested by the failure of others to find a solution to the problem which the patent in question purports to solve. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991). However, an unsolved problem in the art is not evidence of nonobviousness "unless it is shown . . . that the widespread efforts of skilled workers having

knowledge of the prior art had failed to find a solution to the problem." *In re Allen*, 324 F.2d 993, 997 (CCPA 1963).

Here, Patent Owner identifies two problems addressed by the '688 patent that others in the art allegedly failed to solve: (1) a once-daily, low dose of granulated mesalamine for maintaining remission of ulcerative colitis; and (2) administering granulated mesalamine without food. PO Resp. 61–62, 68. As support for a failure of others, Patent Owner cites Falk's studies, SAG-27 (comparing once daily dosing to three times daily dosing) and SAG-19 (comparing administration with and without food). *Id.* at 61–63 (citing Exs. 2025, 2026). As support for a long-felt need, Patent Owner cites the declaration testimony of Drs. Safdi and Johnson and two articles to show that complex dosing regimens impact patient compliance. PO Resp. 67–68 (citing Ex. 2035 ¶ 99; Ex. 2036 ¶ 9–10, 21; Exs. 2016, 1018).

Petitioner argues that SAG-27 and SAG-19 do not show a failure of others because they are Patent Owner's own studies, they were never made public, and SAG-27 showed efficacy for the claimed method. Pet. Reply 19–20 (citing Ex. 1067, 67:18–68:21; Ex. 2025, 126–127). Petitioner contends there was no long-felt but unmet need because it was known in the art that once-daily dosing would increase patient compliance. *Id.* at 21–22 (citing Ex. 2012, 2484; Ex. 2018, 582-1).[18]

[18] Petitioner cites Exhibit 1063 as disclosing "no compliance differences between once-daily and twice-daily" dosing of MMX mesalazine. Pet. Reply 22 (citing Ex. 1063, 899-2, 901-1). We do not rely on Exhibit 1063 to support this Decision.

We find that SAG-27 and SAG-19 are Patent Owner's own clinical studies. Patent Owner does not direct us to precedent supporting that Patent Owner's own work may be relied upon to show a failure of others. *Cf. In re Cyclobenzaprine*, 676 F.3d at 1081–82 (failure of "another pharmaceutical company" to develop an extended release formulation was evidence of nonobviousness).

Even if SAG-27 were treated as the work of others, we find that it does not show a failed attempt to demonstrate efficacy for the claimed method. At best, the study failed to prove "non-inferiority" of once daily dosing as compared to three times daily dosing. Ex. 2025, 129. However, there are numerous statements in SAG-27 supporting that a 1.5 g once daily dose is "efficacious for maintenance of remission in UC." *Id.* at 126; *see also id.* at 129 ("All treatment groups were highly efficacious in the maintenance treatment of ulcerative colitis.").

Evidence cited by both parties shows that it was known in the art that a simpler dosing regimen would improve patient compliance. *See, e.g.*, Ex. 2018, 582-2 ("once-daily oral formulations of 5-ASA are likely to become a viable therapeutic option due to their ability to offer comparable efficacy, improved adherence and long-term clinical outcomes"). Any lingering doubt about whether a 1.5 g once-daily dose of granulated mesalamine would be effective for maintaining remission of ulcerative colitis was resolved by the Sept. 2007 Press Release, which announces "the successful completion and outcome" of a Phase III clinical trial of this method. Ex. 1012, 1. Patent Owner does not identify any problem relating to once-daily dosing that was not solved by the method disclosed in the Sept. 2007 Press Release. Accordingly, we find that the preponderance of the evidence

does not support a long-felt but unmet need or failure of others to solve a problem of a once-daily, low dose of granulated mesalamine for maintaining remission of ulcerative colitis.

Even if SAG-19 were treated as the work of others, we find that this evidence is insufficient to show a long-felt need or failure of others to solve a problem relating to administration of granulated mesalamine without food. Patent Owner contends that "SAG-19 demonstrated a marked food effect . . . thus suggesting that mesalamine should be administered with food and not without food." PO Resp. 63 (citing Ex. 2026, 59–61, 64–66, 87, 97; Ex. 2035, ¶¶ 94–95; Ex. 2036, ¶ 14; Ex. 2037, ¶¶ 20–21). Patent Owner does not, however, direct us to evidence that SAG-19 led Falk to conclude that granulated mesalamine should be administered with food. On the contrary, the Falk dosing information submitted by Patent Owner includes no recommendation that granulated mesalamine be administered with food. Ex. 2008, 52 (Falk Brochure: "[n]o delay between the intake of Salofalk . . . granules and meals is required . . ."); Ex. 2009, 1–2 (Summary of Product Characteristics for Salofalk granules: Posology and method of administration).

We find that the preponderance of the evidence does not show that a method of administering granulated mesalamine without food was lacking in the prior art or that skilled artisans struggled to attain it. Ex. 1024, 1 (Summary), 135-1, 138-2 (Marakhouski: granulated mesalamine administered without food is effective for treating mild to moderately active ulcerative colitis); Ex. 1025, 1167-2 (Brunner: granulated mesalamine passes through the stomach "independent of concomitant food intake"). *Cf. In re Cyclobenzaprine*, 676 F.3d at 1082 (evidence showed "that a

therapeutically effective PK profile was lacking in the prior art and that skilled artisans struggled to attain it").

Unexpected Results

Patent Owner contends that the ability to administer granulated mesalamine without food was an unexpected result and a "significant advantage." PO Resp. 63, 66. More specifically, Patent Owner contends that, contrary to the results of Falk's food effect study (SAG-19) and Salix's hypothesis in its own food effect study (MPPK 1002), "Salix surprisingly discovered that for its granulated mesalamine formulation the absorption of mesalamine and its metabolite were not significantly affected by a high fat meal." *Id.* at 65 (citing Ex. 2029, 2–6, 19, 53–54; Ex. 2035 ¶¶ 96–98; Ex. 2036 ¶¶ 15, 16; Ex. 2047).

"Evidence of unexpected results can be used to rebut a prima facie case of obviousness." *Pfizer*, 480 F.3d at 1369. "[B]y definition, any superior property must be ***unexpected*** to be considered as evidence of non-obviousness." *Id.* (emphasis added). To be probative of non-obviousness, "evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

Here, Patent Owner contends that Salix's food effect study (MPPK 1002) showed a different and unexpected result, as compared with Falk's food effect study (SAG-19). PO Resp. 65; *see also* Ex. 2035 ¶ 98; Ex. 2036 ¶ 16. We find that Patent Owner's assertion of unexpected results is unpersuasive for several reasons.

First, Patent Owner does not disclose how Salix supposedly obtained a different or unexpected result, as compared with Falk. Patent Owner asserts that Salix made changes to Falk's granulated mesalamine formulation. Tr. 51:18–52:8. Yet nothing in the '688 patent or this record reveals how Salix changed the formulation or the method of administration in order to lessen the food effect. *Id.* at 52:5 (Patent Owner: "it's not in the record").

Second, Patent Owner's contention that the results of Salix's food effect study (MPPK 1002) were "surprising[]" (PO Resp. 65) does not square with their efforts to obtain patent protection. As already discussed, the patent claims, both as filed (Ex. 1018) and as issued (Ex. 1001, 34:10–35:17), do not recite the absence of a food effect.

Third, even if we credit Patent Owner's assertion that Salix's food effect study (MPPK 1002) provided a different result, as compared with Falk's (SAG-19), we are not convinced that the results were unexpected. Regarding systemic absorption, the result described in the '688 patent and SAG-19 does not differ from that described in Falk's product literature. *Compare* Ex. 1001, 7:29–31 ("the overall systemic absorption of mesalamine granules was low and essentially unaltered by a high-fat meal eaten before dosing") *and* Ex. 2029, 6 (same), *with* Ex. 2009, 6 (Summary of Product Characteristics for Salofalk granules: "Food intake delays absorption for 1 to 2 hours but does not change the rate and extent of absorption."). The preponderance of the evidence does not show that the ability to administer granulated mesalamine without food was an unexpected result, as compared with the prior art. Ex. 1024, 138-1 (pellet formulation

allows "transit through the stomach independent of food intake"); Ex. 1025, 1167-2 (same).

7. Conclusion Regarding Obviousness

Accordingly, after giving appropriate weight to Patent Owner's evidence of secondary considerations, we conclude that Petitioner has established by a preponderance of the evidence that the method of claims 1 and 16 would have been obvious in view of the Sept. 2007 Press Release, Endonurse, and Davis-1985 and either Marakhouski or Brunner.

D. Motions to Exclude

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).

Petitioner's Motion To Exclude

Petitioner moves to exclude paragraphs 68–72 of the Safdi Declaration (Ex. 2035) and paragraph 22 of the Johnson Declaration (Ex. 2036) for lack of foundation under FRE 702 on the grounds that neither Dr. Safdi nor Dr. Johnson is qualified to testify regarding the reliability and intended purpose of the Sept. 2007 Press Release and Endonurse. Pet. Mot. 2–4. We find it unnecessary to consider Petitioner's objections to the admissibility of paragraphs 68–72 of Exhibit 2035 and paragraph 22 of Exhibit 2036, since Patent Owner's argument that a POSITA would not have relied upon the Sept. 2007 Press Release or Endonurse is not persuasive for the reasons discussed above, even assuming that paragraphs 68–72 of Exhibit 2035 and paragraph 22 of Exhibit 2036 are admissible.

For this reason, we *dismiss as moot* Petitioner's Motion to Exclude, as it pertains to paragraphs 68–72 of Exhibit 2035 and paragraph 22 of Exhibit 2036.

Petitioner moves to exclude Exhibit 2051[19] under FRE 403 on the grounds that any probative value is outweighed by prejudice to Petitioner because the exhibit was not relied upon by Patent Owner, either in its Response or Preliminary Response and it "remains unclear" to Petitioner how Patent Owner will rely on the exhibit. Pet. Mot. 4–5. We are not persuaded by Petitioner's argument. Without objection from Petitioner, Exhibit 2051 was marked by Patent Owner during redirect examination of its witness, Dr. Johnson. Ex. 1067, 89:18–25; *see* 37 C.F.R. 42.64(a) ("An objection to the admissibility of deposition evidence must be made during the deposition."). Patent Owner's deposition questions revealed to Petitioner how Patent Owner relies on Exhibit 2051. Ex. 1067, 90:1–91:12. Moreover, Petitioner should have been aware of Ex. 2051 because it was cited during prosecution of the '688 patent to support the Examiner's finding that "5-aminosalicylate compounds, including mesalamine, are known to have increased bioavailability when administered with food"—a finding that Petitioner quoted and relied upon in the Petition. Pet. 7, 29–30 (quoting Ex. 1019, 3).

For these reasons, we *deny* Petitioner's Motion to Exclude, as it pertains to Ex. 2051.

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[19] Johnson, US 2007/0167416 A1, published July 19, 2007, Ex. 2051.

Patent Owner's Motion To Exclude

Patent Owner moves to exclude the testimony of Dr. Digenis, including paragraphs 16–122 of Ex. 1002, paragraphs 4–6 of Ex. 1059, and Ex. 2032, under FRE 702 and 703 on the grounds that Dr. Digenis is not qualified to testify regarding the '688 patent because he is not a medical doctor and does not have experience diagnosing or treating patients suffering from ulcerative colitis or other gastroenterological conditions. PO Mot. 1–5.

As discussed in section II.B. above, we find that Dr. Digenis is qualified to opine from the viewpoint of a POSITA regarding the subject matter of the '688 Patent. Therefore, for the reasons discussed in section II.B., we *deny* Patent Owner's motion, as it pertains to Exhibits 1002, 1059, and 2032.

Patent Owner moves to exclude Exhibits 1062, 1063, 1065, and 1066 on various grounds. PO Mot. 5–8.

Patent Owner contends that Exhibits 1062, 1065, and 1066 are irrelevant under FRE 401 and 402. PO Mot. 6. We disagree. Exhibits 1062, 1065, and 1066 are relevant to rebut Patent Owner's argument that a POSITA would not rely on Endonurse.

Patent Owner contends that Exhibits 1062, 1065, and 1066 are untimely supplemental evidence and unfairly prejudicial to Patent Owner under 37 C.F.R. § 42.64(b). PO Mot. 6–7. We disagree. Patent Owner argued in its Patent Owner Response that a POSITA would not rely on Endonurse. PO Resp. 39–42. Exhibits 1062, 1065, and 1066 are proper reply evidence responsive to Patent Owner's argument. As we stated in our July 15, 2016 procedural order, "if Patent Owner addresses the issues raised in its objections to evidence in a Patent Owner Response, then Petitioner will

have an opportunity to file a Reply to the Patent Owner Response, including a reply declaration or other reply evidence responsive to issues raised in the Patent Owner Response." Paper 15, 2.

Patent Owner contends that Exhibits 1063, 1065, and 1066 are inadmissible hearsay under FRE 801 and 802 and that Exhibits 1065 and 1066 are unauthenticated and inadmissible under FRE 901 and 902. PO Mot. 7–8. Exhibits 1065 and 1066 are printouts of webpages. Exhibit 1065 appears to be pages from Salix's website, and Exhibit 1066 appears to be pages from the website of the Digestive Health Physicians Association (DHPA). Petitioner cites Exhibits 1065 and 1066 as evidence that Endonurse is relied upon by gastroenterologists. Accordingly, Exhibits 1065 and 1066 are not hearsay because they are not offered to prove the truth of matters asserted in the web pages, but only to show that Endonurse is referenced therein. On this record, there is no indication that Exhibits 1065 and 1066 are anything other than what Petitioner represents they are, and the exhibits are adequately authenticated under FRE 901.

For these reasons, we *deny* Patent Owner's motion, as it pertains to Exhibits 1062, 1065, and 1066. We have not relied on Exhibit 1063 as support for this Decision. For this reason, we *dismiss as moot* Patent Owner's motion, as it pertains to Exhibit 1063.

Patent Owner moves to exclude various portions of the deposition testimony of Dr. Safdi (Ex. 1056) under FRE 106, 401, 402, and/or 403 on the grounds that Petitioner mischaracterizes and ignores Dr. Safdi's full testimony on various issues. Patent Owner's arguments go to the weight to be given Dr. Safdi's testimony, not its admissibility. The Board, sitting as a non-jury tribunal with administrative expertise, is well-positioned to

determine and assign appropriate weight to evidence presented. Patent Owner's request that the Board consider additional portions of Dr. Safdi's testimony under FRE 106 is not properly the subject of a motion to exclude evidence. The entire deposition transcript is already in the record as Exhibit 1056.

For these reasons, we *deny* Patent Owner's motion, as it pertains to portions of Exhibit 1056.

III. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that claims 1 and 16 of the '688 patent are unpatentable under 35 U.S.C. § 103(a) as obvious over the Sept. 2007 Press Release, Endonurse, and Davis-1985 in view of either Marakhouski or Brunner.

IV. ORDER

Accordingly, in consideration of the foregoing, it is hereby:

ORDERED that claims 1 and 16 of the '688 patent are held unpatentable under 35 U.S.C. § 103(a);

FURTHER ORDERED that Petitioner's motion to exclude is *dismissed as moot*, as it pertains to Exhibits 2035 and 2036, and *denied*, as it pertains to Exhibit 2051;

FURTHER ORDERED that Patent Owner's motion to exclude is *dismissed as moot*, as it pertains to Exhibit 1063, and *denied*, as it pertains to Exhibits 1002, 1056, 1059, 1062, 1065, 1066, and 2032;

FURTHER ORDERED that, because this is a final written decision, any party 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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