In the United States Patent and Trademark Office

---

Before the Patent Trial and Appeal Board

FOHILL CAPITAL PARTNERS
MYCONOVO, INC.,
Petitioner

v.

DR. FALK PHARMA GmbH,
Patent Owner

---

U.S. Patent No. 8,865,688
Issue Date: October 21, 2014
Inventor: William Forbes

Title: COMPOSITIONS AND METHODS FOR TREATMENT OF BOWEL DISEASES WITH GRANULATED MESALAMINE

---

*Inter Partes* Review No.: Unassigned

---

Petition for *Inter Partes* Review of U.S. Patent No. 8,865,688 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-42.80, 42.100-42.123

**Page**

# TABLE OF CONTENTS

## LISTING OF EXHIBITS PURSUANT TO 37 C.F.R. § 42.63(e)

| Exhibit | Description |
|---|---|
| 1001 | U.S. Patent No. 8,865,688 ("the '688 Patent") |
| 1002 | Declaration of George A. Digenis, Ph.D. ("Digenis Decl.") |
| 1003 | U.S. Patent No. 6,004,581 ("the '581 Patent") |
| 1004 | Stephen Hanauer et al., *Mesalamine Capsules for Treatment of Active Ulcerative Colitis: Results of A Controlled Trial*, 88 AMERICAN J. GASTROENTEROLOGY 1188 (1993) ("Hanauer") |
| 1005 | J. N. C. Healey, *Gastrointestinal Transit and Release of Mesalazine Tablets in Patients with Inflammatory Bowel Disease*, 25 SCAND J. GASTROENTEROLOGY 47 (Supp. 127 1990) ("Healey") |
| 1006 | L. M. L. Stolk et al., *Dissolution Profiles of Mesalazine Formulations in Vitro*, 12 PHARMACEUTISCH WEEKBLAD SCIENTIFIC EDITION 200 (1990) ("Stolk") |
| 1007 | European Patent Application No. 0 671 168 A1 ("EP168") |
| 1008 | PCT Publication No. WO 91/07949 ("PCT949") |
| 1009 | S. S. Davis, *The Design and Evaluation of Controlled Release Systems for the Gastrointestinal Tract*, 2 J. CONTROLLED RELEASE 27 (1985) ("Davis-1985") |
| 1010 | S. S. Davis et al., *Transit of Pharmaceutical Dosage Forms Through the Small Intestine*, 27 GUT 886 (1986) ("Davis-1986") |
| 1011 | U.S. Patent No. 6,551,620 ("the '620 Patent") |

| | |
|---|---|
| 1012 | Salix Announces Statistically Significant Top-Line Results of a Unique Granulated Mesalamine Product Registration Study in Ulcerative Colitis (September 2007), available at http://www.sec.gov/Archives/edgar/containers/fix021/1009356/000119312507195530/dex992.htm ("Sept. 2007 Press Release") |
| 1013 | U.S. Patent Application Publication No. 2010/0035850 A1 ("Meyeroff") |
| 1014 | XIFAXAN Trials Initiated in C. difficile-Associated Diarrhea, Irritable Bowel Syndrome and Hepatic Encephalopathy. New Article [online] EndoNurse, 12 January 2006 ("Endonurse") |
| 1015 | European Patent Application No. 0 040 590 A2 ("EP590") |
| 1016 | '688 Patent File History ("FH688"), Amendment 5/9/2014 |
| 1017 | '688 Patent File History ("FH688"), Amendment 6/20/2014 |
| 1018 | '688 Patent File History ("FH688"), Amendment to the Claims |
| 1019 | '688 Patent File History ("FH688"), Notice of Allowance |
| 1020 | '688 Patent File History ("FH688"), Amendment 10/8/2013 |
| 1021 | '688 Patent File History ("FH688"), Amendment 4/24/2013 |
| 1022 | European Patent Application No. 0 453 001 A1 ("EP001") |
| 1023 | P.J. Watts et al., *Encapsulation of 5-aminosalicylic Acid into Eudragit RS Microspheres and Modulation of Their Release Characteristics by Use of Surfactants*, 16 J. CONTROLLED RELEASE 311 (1991) ("Watts") |
| 1024 | Marakhouski et al., "*A Double-blind Dose-escalating Trial Comparing Novel Mesalazine Pellets with Mesalazine Tablets in Active Ulcerative Colitis*," Aliment Pharmacol. Ther. 21:133-140 (2005) ("Marakhouski") |

| | |
|---|---|
| 1025 | Brunner et al., "*Gastrointestinal Transit and Release of 5-Aminosalicylic Acid from $^{153}$Sm-labelled Mesalazine Pellets vs. Tablets in Male Healthy Volunteers*," Aliment. Pharmacol. Ther. 17:1163-1169 (2003) ("Brunner") |
| 1026 | Brouwers, J.R.B.J. "*Advanced and controlled drug delivery systems in clinical disease management*," Pharmacy World & Science: (1996) 18(5), 153-162 ("Brouwers") |

MycoNovo, Inc. and Foxhill Opportunity Fund, L.P. ("Petitioner") requests that the Board institute *inter partes* review ("IPR") of claims 1 and 16 of U.S. Patent No. 8,865,688 ("the '688 Patent") issued to William Forbes (Ex. 1001), and that these claims be canceled as unpatentable over the prior art. *Inter partes* review of claims 1 and 16 of the '688 Patent was instituted in IPR2016-00297 on June 10, 2016, based on a petition filed by Generico, LLC and Flat Line Capital, LLC (collectively, "Generico"). For the sake of completeness and efficiency, the present Petition is a practical copy of the petition in IPR2016-00297. Petitioner is requesting however, that the Board institute only on the Grounds instituted in IPR2016-00297, *i.e.*, Grounds 3 and 4 (which the Board determined subsumed Ground 1), as to claims 1 and 16, and not on Grounds 1 and 2. A Motion for Joinder with IPR2016-00297 is being filed concurrently with this Petition.

## I. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

Petitioner provides the following mandatory notices under 37 C.F.R. §§ 42.8(a)(1) and 42.8(b).

### A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner hereby certifies that the following persons or entities are the only real parties in interest for this IPR petition: MycoNovo, Inc., ("MycoNovo"), Foxhill Opportunity Fund, L.P. ("Foxhill"); Foxhill Capital Partners, LLC; Foxhill Capital (GP), LLC; Neil

Anthony Weiner; Laura Pollack Weiner; and William D. Hare. No other entities or persons other than Petitioners have authority to direct or control Petitioners' actions or decisions relating to this petition. Petitioners are collectively funding all of the fees and costs of this petition for inter partes review.

### B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner identifies the following related matters:

District Court and C.A.F.C. Matters: *Salix Pharmaceuticals, Inc. et al. v. Novel Laboratories, Inc.*, 1-15-cv-00027 (DED); *Salix Pharmaceuticals, Inc. et al. v. Novel Laboratories, Inc.*, 1-15-cv-00213 (DED); *Salix Pharmaceuticals, Inc et al v. Mylan Pharmaceuticals, Inc. et al*, 1-15-cv-00109 (N.D.W.V.).

USPTO Matters:

GeneriCo, LLC and Flat Line Capital, LLC v. Dr. Falk Pharma GmbH, Case IPR2016-00297 (instituted); and Mylan Pharmaceuticals, Inc. v. Dr. Falk Pharma GmbH, Case IPR2016-01386.

### C. Lead And Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

| Lead Counsel | Back-Up Counsel |
|---|---|
| William Hare (Reg. No. 44,739)<br>McNeely Hare & War LLP<br>12 Roszel Road, Suite C104,<br>Princeton, NJ 08540<br>Telephone: (202) 640-1801<br>Fax: (202) 478-1813<br>bill@miplaw.com | Gabriela Materassi (Reg. No. 47,774)<br>McNeely Hare & War LLP<br>12 Roszel Road, Suite C104,<br>Princeton, NJ 08540<br>Telephone: (347) 684-4154<br>Fax: (202) 478-1813<br>materassi@miplaw.com |

### D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Pursuant to 37 C.F.R. 42.10(b), a Power of Attorney has been filed with this Petition. Documents may be delivered by hand to the addresses of lead and back-up counsel above. Petitioner consents to electronic service by e-mail at the above listed email addresses of Lead and Back-Up Counsel (bill@miplaw.com and materassi@miplaw.com).

## II. GROUNDS FOR STANDING (37 C.F.R. §§ 42.101 and 42.104)

Petitioner hereby certifies that IPR is available for the '688 Patent and that Petitioner is not barred or estopped from requesting an IPR challenging the patent claims on the instituted grounds identified in this Petition because a motion for joinder has been filed to join IPR2016-00297 no later than one month after institution in accordance with 37 C.F.R. § 42.122(b) and 35 U.S.C. §315(c).

## III. PAYMENT OF FEES (37 C.F.R. § 42.103)

The required fee for this petition are submitted herewith via online payment. The Office is authorized to charge any fee deficiencies and credit overpayments to Deposit Acct. No. 502923, Customer ID No. 32687.

## IV. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22(a))

Petitioner requests *inter partes* review and cancellation of claims 1 and 16.

Petitioner's full statement of the reasons for the relief requested is set forth in detail below.

## V. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Petitioner respectfully requests *inter partes* review and cancellation of claims 1 and 16 of the '688 Patent based on the grounds set forth in the table below:

| Ground | Challenged Claims | Statutory Basis | References |
|---|---|---|---|
| 1 | 1 and 16 | § 103 | Sept. 2007 Press Release in view of Endonurse and Davis-1985 |
| 2 | 1 and 16 | § 103 | Sept. 2007 Press Release in view of Endonurse, Davis-1985 and EP590 |
| 3 | 1 and 16 | § 103 | Sept. 2007 Press Release in view of Endonurse, Davis-1985 and Marakhouski |
| 4 | 1 and 16 | § 103 | Sept. 2007 Press Release in view of Endonurse, Davis-1985 and Brunner |

Grounds 1-4 are practical copies of the grounds presented in the petition in IPR2016-00297, including Grounds 3 and 4 that were instituted by the Board, challenging the same claims over the same prior art and using the same arguments and expert testimony.

Petitioner supports its challenges with the Declaration of George A. Digenis, Ph.D. ("Digenis Decl.") (Ex. 1002). The Digenis Declaration is an exact copy of Dr. Digenis' declaration from IPR2016-00297, which was relied upon by the Board in that proceeding. Dr. Digenis' IPR2016-00297 Declaration is cited in this Petition to avoid unnecessary cost and to advance efficiency in this instance. As mentioned above, this Petition is presented along with a motion to join IPR2016-00297, and, by using the same Declaration, Petitioner has eliminated the need for analysis of another declaration or the addition of a new expert.

## VI. BACKGROUND

### A. The '688 Patent

The '688 Patent is directed to methods for "maintaining the remission of ulcerative colitis" through a "granulated mesalamine formulation." (Ex. 1001, '688 Patent col. 34:11-35:17). The '688 Patent acknowledges that, at the time it was filed, numerous prior art formulations containing mesalamine existed for treating ulcerative colitis. For instance, the patent identifies prior art formulations that are "related to delivery of the intact molecule to the colonic mucosa without breakdown during digestion." (Ex. 1001, '688 Patent col. 1:60-63). This includes "oral mesalamine treatments [that] are based on 3 types of delivery systems" including "azo-bonded to release drug in the colon once the drug is exposed to colonic bacteria," polymer-coated "delayed release tables" for "release of drug

when the pH in the digestive tract reaches the desired value," and "time-dependent release mechanisms." (Ex. 1001, '688 Patent col. 1:61-2:3).

The '688 Patent, however, claims the following problems purportedly existed with prior art mesalamine formulations for treating UC: "variation within formulations in the release of mesalamine, including premature release, the possibility of dose dumping, and sensitivity to conditions that increase gastric pH and cause premature release of mesalamine (e.g., ingestion of a meal)." (Ex. 1001, '688 Patent col. 2:3-8).

The '688 Patent, however, is not directed to a novel formulation of mesalamine. Rather, the claims are directed to a method of "maintaining the remission of ulcerative colitis" that comprises administration of "a granulated mesalamine formulation." (Ex. 1001, '688 Patent col. 34:10-13). The '688 Patent expressly incorporates embodiments of granulated mesalamine formulations taught in prior patents (to which the '688 Patent does not claim priority). (Ex. 1001, '688 Patent col. 10:47-53).

The '688 Patent purports to solve the alleged prior-art problems with the claimed methods for maintaining the remission of ulcerative colitis. (Ex. 1001, '688 Patent col. 34:10-35:17). During prosecution, the Applicant identified his "discovery that the oral mesalamine formulation was equally effective when administered with or without food." (Ex. 1017, FH688, Amendment 6/20/14 at 5-

6). After a tortured prosecution history, including seven office action rejections and amendment to independent claim 1 on six separate occasions, the issued claims require that administration of the granulated mesalamine is "**without food**." (Ex. 1001, '688 Patent col. 34:15).

### B. Prosecution History of the '688 Patent

The '688 Patent issued from U.S. Patent Application No. 12/573,081, filed October 9, 2009, which was purportedly related to U.S. Provisional Application Nos. 61/102,807 and 61/109,708, filed October 3, 2008 and October 30, 2008, respectively. Accordingly, the priority date for the '688 Patent is not earlier than October 30, 2008.

The '688 Patent underwent a tortured prosecution history before allowance. The claim that eventually issued as claim 1 (claim 14 during prosecution) was amended at least six times. Applicant submitted two additional office-action responses that included unsuccessful attempts to persuade the Examiner to allow the claim without amendment. (*See* Ex. 1018, FH688 Amendments to the Claims).

Independent claims 1 and 16 (which recite substantively similar requirements) were both finally allowed upon Applicant's amendment that the claimed methods for "maintaining the remission of ulcerative colitis" were "without food." In support of this amendment, Applicant stated: "unlike other 5-mesalamine drugs available at the time of the invention, Applicant has

demonstrated that the claimed methods are equally safe and effective when granulated mesalamine is administered to a subject without food." (Ex. 1017, FH688, Amendment 6/20/14 at 5).

Applicant further argued that, "[a]t the time of the invention, one of ordinary skill in the art would look to the teachings of the most similar formulation to determine if administration with food is required." (Ex. 1017, FH688, Amendment 6/20/14 at 6). Applicant distinguished two FDA-approved oral mesalamine formulations, Lialda® and Pentasa®. Applicant argued that Lialda® was, similar to the "pending claims [which] are directed to methods of administering a delayed and extended-release oral mesalamine formulation, Lialda®" is a "delayed and extended-release oral mesalamine tablet that was approved for inducing the remission of active, mild to moderate ulcerative colitis . . . ." (*Id*. at 6, emphasis in original). Citing prescribing information for Lialda®, Applicant argued that it is administered as "two to four 1.2 g tablets taken once daily **with food**." (*Id*., emphasis in original). With respect to Pentasa®, Applicant argued that it is "not a controlled and extended release formulation." (*Id*.) Finally, Applicant pointed to two examples in the '688 Patent's specification that purport to describe the results of a clinical trial showing that "there is no decrease in efficacy when granulated mesalamine is administered without food." (*Id*. at 7).

Upon allowing the application, the Examiner's "Reasons for Allowance"

stated:

> [t]he cited prior art is silent with respect to whether or not the mesalamine formulation is administered with or without food. One skilled in the art would reasonably expect the formulation to be administered with food, since similar mesalamine formulations are directed to be administered with food (see Lialda® information pamphlet, submitted by Applicants with response to filed 20 June 2014).

(Ex. 1019, FH688, Notice of Allowance at 3). The Examiner concluded that persons of skill in the art would have been motivated to administer mesalamine formulations *with food:*

> Additionally, one skilled in the art would be motivated to administer the mesalamine formulation with food, since 5-aminosalicylate compounds, including mesalamine, are known to have increased bioavailability when administered with food.

(Ex. 1019, FH688, Notice of Allowance at 3).

### C. Background of the Prior Art

#### 1. Ulcerative Colitis

Inflammatory bowel disease ("IBD") refers to inflammatory conditions of

the gastrointestinal tract, including ulcerative colitis ("UC"), Crohn's disease ("CD"), as well as other conditions. CD can affect any portion of the gastrointestinal tract, from the mouth to the anus. By contrast, UC is limited to the colon, and often limited to the colonic mucosa (which is the most inner surface of the lumen of the colon). (Ex. 1002, Digenis Decl. ¶ 26). The prevailing treatment for UC involves management of the symptoms. Management of UC symptoms includes two facets: *inducing* remission and *maintaining* remission. Inducement of remission controls an acute attack of UC, whereas maintenance of remission seeks to prevent relapses of acute attacks. (Ex. 1002, Digenis Decl. ¶ 26, citing Ex. 1001, '688 Patent col. 1:54-59).

**2. Mesalamine (5-Aminosalicylic Acid)**

Beginning in the 1950s, sulfasalazine became the "the most widely prescribed medication for treatment of inflammatory bowel disease, specifically ulcerative colitis (UC)." (Ex. 1004, Hanauer at 1188). Sulfasalazine is composed of sulfapyridine and 5-aminosalicylic acid (also known as *mesalamine* or 5-ASA) that is linked by an azo bond. (Ex. 1004, Hanauer at 1188). In the 1970s, it was discovered that 5-ASA was the therapeutically-active moiety of sulfasalazine. This led to the development of 5-ASA formulations for the treatment of IBD, UC and CD. (Ex. 1004, Hanauer at 1189).

Indeed, prior to filing of the '688 Patent, it was well-known among persons

of ordinary skill that aminosalicylic acid was therapeutically effective for treating UC. (Ex. 1002, Digenis Decl. ¶ 28). "The active compound aminosalicylic acid (in particular 5-ASA) or its derivatives have been used successfully for a relatively long time for the treatment of intestinal disorders, such as, for example, ulcerative colitis and Crohn's disease." (Ex. 1011, '620 Patent col. 1:15-18).

Persons of ordinary skill also knew that aminosalicylic acid works by locally administering the drug at the sites of the lesions within the colon. (Ex. 1002, Digenis Decl. ¶ 29, citing Ex. 1011, '620 Patent col. 1:32-39 ("The action of aminosalicylic acid in the treatment of intestinal disorders, or in the prevention of their recurrence . . . takes place by means of the contact of the active compound directly at the site of the disorder in the intestine, the action of aminosalicylic acid, or a derivative thereof, being directly related to its local concentration in the intestinal area to be treated."); *see also id*. citing Ex. 1005, Healey at 47 ("[t]he effectiveness of mesalazine in the treatment of inflammatory bowel disease is attributed mainly to a *topical action* on the intestinal mucosa." (emphasis added)).

Oral administration of aminosalicylic acid, however, requires the drug to travel through the stomach and the small intestine before reaching the colon. Accordingly, the principal challenge to administering aminosalicylic acid for treatment of UC and other IBD conditions affecting the large intestine is that aminosalicylic acid will be readily absorbed in the small intestine. "A problem in

the treatment with aminosalicylic acid is that the active compound is very easily absorbed and can be excreted via the kidney before its action can occur." (Ex. 1011, '620 Patent col. 1:45-48). (*See also* Ex. 1002, Digenis Decl. ¶ 30, citing Ex. 1006, Stolk at 200 ("Plain mesalazine is totally absorbed in the upper part of the intestine."); Ex. 1004, Hanauer at 1189 ("Oral administration of mesalamine is limited by absorption in the proximal small bowel, necessitating protected delivery systems for distribution to distal sites of enterocolonic inflammation."))

For this reason, oral administration of 5-ASA has for a long time focused delayed and controlled/sustained release of mesalamine. (Ex. 1002, Digenis Decl. ¶ 31, citing Ex. 1005, Healey at 47 ("Because mesalazine is readily absorbed from the small intestine, metabolized, and excreted in the urine, a delayed-release tablet preparation has been developed to prevent release until the drug has reached the terminal ileum and colon;" marketed as Claversal®); Ex. 1011, '620 Patent col. 1:49-51 ("[i]n the prior art, tablets and pellets are known which are coated with an enteric coating in order to thus prevent a premature release of the active compounds;" discussing numerous prior art references)). (*See also* Ex. 1002, Digenis Decl. ¶ 31, citing Ex. 1006, Stolk at 200 ("pharmaceutical formulations [of mesalazine] have been designed, which can transport mesalazine undisturbed through stomach, duodenum and proximal jejunum and deliver high concentrations of mesalazine selectively at the inflammatory sites of the distal small intestine and

colon").

In particular, the delayed/controlled release of mesalamine to the lower intestine has commonly been formulated as azo-bonded pro-drugs or non-linked agents. (Ex. 1002, Digenis Decl. ¶ 32, citing Ex. 1009, Hanauer at 1189). By the early 1990s, non-linked agents used two mechanisms: (1) *pH-dependent* enteric coatings (such as acrylic-based resins) that dissolve above pH of approximately 7, after the drug has left the stomach; and (2) *pH-independent* slow-release that delivers "active drug continuously to the small and large bowel, independent of intestinal pH"). (Ex. 1002, Digenis Decl. ¶ 32, citing Ex. 1009, Hanauer at 1189).

### 3. Enteric Coating

Enteric coating was a well-known means to delay the release of mesalamine prior to the filing of the '688 Patent. The stomach's pH is generally lower than the pH of the intestinal tract. (Ex. 1002, Digenis Decl. ¶ 33, citing Ex. 1007, EP168 col. 1:27-33 ("it is recognized that the value of pH in the stomach is usually 1.8 to 4.5 in a healthy human and that the value of pH in the intestines is 6.5 to 7.5 and the pH does not essentially differ between the small intestine and the large intestine").

Accordingly, a coating that is *insoluble* at the stomach's pH range, but *soluble* at the intestinal tract's pH range, can delay and control the release of mesalamine until it reaches the lower intestines. Indeed, this was well-known to

persons of ordinary skill prior to filing of the '688 Patent. (Ex. 1002, Digenis Decl. ¶ 34, citing Ex. 1008, PCT949 at 1:10-18 ("In a medical context, it is particularly advantageous to be able to administer orally a medicament which is coated so that it passes through the stomach and is released only when the coated material reaches the small intestine. Such coatings are called 'enteric' coatings and are relatively easy to formulate taking advantage of the fact that the stomach contents are acid and the intestinal contents are neutral to slightly alkaline.")).

Enteric coatings, including methacrylic acid copolymer, among others, were known to persons of ordinary skill prior to filing the '688 Patent. (Ex. 1002, Digenis Decl. ¶ 35, citing Ex. 1005, Healey at 47). Methacrylic acid copolymer is soluble above pH 6.0. Accordingly, prior to filing the '688 Patent, persons of ordinary skill knew to apply enteric coatings of methacrylic acid copolymer to aminosalicylic acid formulations to delay its release so that it was insoluble in the stomach, but soluble within the intestine. (Ex. 1002, Digenis Decl. ¶ 35, citing Ex. 1005, Healey at 47 (discussing mesalazine tablets "coated with the enteric-coating polymer methacrylic acid copolymer, type A (Eudragit L). This pH sensitive polymer is resistant to gastric conditions but soluble above pH 6.0 in the intestine … A relatively thick coating is applied to the tablets to delay any release of the drug until they reach the terminal ileum and proximal colon"); citing Ex. 1006, Stolk at 200 ("Asacol® tablets contain 400 mg mesalazine and the tablets are

coated with an acrylic resin (Eudragit® S), which dissolves above pH 7.0. Thus *in vivo* it should be transported intact until it reaches the ascending part of the colon where the intraluminal pH rises above 7 and mesalazine is liberated.").

Enteric coatings comprising methacrylic acid copolymer were sold before the filing of the '688 Patent under the brand names Eudragit S and Eudragit L, and were well-known among persons of skill in the art. (Ex. 1002, Digenis Decl. ¶ 36; Ex. 1022, EP001 at 3:17-18 ("Polymer types for forming pH-dependent membrane include . . . copolymers of methacrylic acid (Eudragit L, Eudragit S)"); Ex. 1005, Healey at 48 ("enteric-coating polymer, methacrylic acid copolymer, type A (Eudragit L)"); Ex. 1006, Stolk at 200 (mesalazine "tablets are coated with an acrylic resin (Eudragit® S)"); Ex. 1013, EP590 at 4:2-3 ("Suitable partly methyl esterified methacrylic acid polymers are sold under the names Eudragit L and Eudragit S."); Ex. 1007, EP 168 col. 6:3-13 ("poly(methacrylic acid, methyl methacrylate (Eudragit L and Endragit S [sic]) are preferably used as enteric polymer")).

#### 4. Polymer Matrix

Polymer matrices were also a well-known means to sustain the release of mesalamine, and treat IBD, long before the '688 Patent. (Ex. 1002, Digenis Decl. ¶ 37). For instance, in 1990, Watts disclosed an investigation regarding "the controlled delivery of drugs to the colon" that included the production of "Eudragit

RS microspheres containing 5-aminosalicylic acid (5-ASA), an agent active against inflammatory bowel disease." (Ex. 1023, Watts at 311). The Eudragit series of polymers "are a family of polymers based on acrylic and methacrylic acids suitable for use in orally-administered drug delivery systems." (Ex. 1023, Watts at 311). Two grades of the Eudragit series, "Eudragit RL and RS, are insoluble in aqueous media but permeable and as such have been shown to be suitable for use in sustained-release microencapsulated dosage forms." (Ex. 1023, Watts at 311). Watts explicitly disclosed a "drug polymer matrix" containing 5-ASA with Eudragit RS. (Ex. 1002, Digenis Decl. ¶ 37, citing Ex. 1023, Watts at 312, 317). Watts concluded, "[w]e have demonstrated that 5-ASA can be successfully encapsulated into Eudragit RS to produce microspheres for potential sustained-release oral drug-delivery applications." (Ex. 1023, Watts at 316-17). Importantly, the '620 Patent (which long preceded the '688 Patent) identifies Eudragit RS as a non-gel forming polymer, *i.e.*, one that is "insoluble in the intestinal tract and permeable to intestinal fluids." (Ex. 1011, '620 Patent at col. 3:47-55).

Similarly, EP477 disclosed combining mesalamine in a non gel-forming polymer matrix comprising Eudragit RS. (Ex. 1002, Digenis Decl. ¶ 38; Ex. 1015, EP477 at 8:1-14 (disclosing "[e]ncapsulation of 5-amino-salicylic acid in EUDRAGIT®RS" in a polymer matrix, including through stirring); EP477 at 2:14-

17 (disclosing "[t]he products [of encapsulation] may also be 'homogeneous microspheres', wherein the bioactive substance [5-ASA] is dispersed in the polymer [Eudragit RS].").

Watts further explained that the motivation for investigating controlled delivery of 5-ASA was the same as that of the '688 Patent: "[s]ince 5-ASA largely is absorbed from the upper intestine, selective delivery into the colon is required for it to be therapeutically effective." (Ex. 1023, Watts at 312).

**5. Combinations of Enteric Coatings and Polymer Matrices**

Delayed and controlled dosage formulations for treating IBD was not a quiet art before the '688 Patent. On the contrary, long before, persons of skill in the art had been actively investigating alternative dosage formulations to adequately delay/control/sustain release of mesalamine for the treatment of IBD. (Ex. 1002, Digenis Decl. ¶ 40, citing Ex. 1023, Watts at 312 ("colon-specific delivery of 5-ASA is currently receiving considerable research interest [as of 1990]," listing numerous existing approaches); *see* Ex. 1004, Hanauer at 1189).

Indeed, existing drugs before the '620 Patent (which long preceded the '688 Patent) employed variations of soluble enteric coatings as well as permeable polymers: Asacol® (enteric coating of Eudragit S), Claversal® (enteric coating of Eudragit L), Pentasa® (semi-permeable polymer coating). (*See* Ex. 1002, Digenis Decl. ¶ 41, citing Ex. 1006, Stolk at 200; Ex. 1005, Healey at 47; *see also* Ex.

1023, Watts at 312 (citing other approaches)).

Persons of skill also experimented with combinations of enteric coatings and insoluble permeable polymers. (Ex. 1002, Digenis Decl. ¶ 42). For instance, Salofalk® comprised an outer-coating of semi-permeable ethylcellulose, and an inner enteric coating of Eudragit L. (Ex. 1006, Stolk at 200). EP001 disclosed a pharmaceutical composition for "targeted controlled release . . . within the intestine" comprising "two membranes, one of pH-dependent solubility and the other insoluble but permeable to the intestinal fluids." (Ex. 1022, EP001 at 1). EP590 disclosed pharmaceutical formulations for treatment of IBD comprising a coating of both "acrylic polymer soluble only above pH 5.5" and a "water insoluble [sic] polymer" such as Eudragit RS/RL. (Ex. 1015, EP590 at 3:11-20).

Persons of ordinary skill also combined 5-ASA in a polymer matrix surrounded by an enteric coating. (Ex. 1002, Digenis Decl. ¶ 42). Marakhouski disclosed pellets "coated with Eudragit-L" that contained 5-ASA "located in the core embedded in a matrix polymer responsible for prolonged release of the drug." (Ex. 1024, Marakhouski at 135). Brunner (published in 2003-five years before the earliest priority date of the '688 Patent) disclosed pellets provided by Dr. Falk Pharma GmbH, the patent owner of the '688 Patent. (Ex. 1025, Brunner at 1164). The pellets contained 500 mg of mesalamine, "coated with Eudragit L" and "with an additional polymer in the pellet core providing prolonged release after removal

of the Eudragit L coating." (*Id.*)

### D. **Person of Ordinary Skill in the Art**

In view of the subject matter of the '688 Patent, a person of ordinary skill in the art as of the patent's filing date would typically hold an advanced degree in the chemical or pharmaceutical fields (such as chemistry, polymer chemistry, pharmaceutics or pharmacokinetics), or a bachelor's degree combined with several years of experience in these fields, or alternatively, an M.D. with several years specializing in the treatment of gastrointestinal disorders. (*See* Ex. 1002, Digenis Decl. ¶ 14).

## VII. CLAIM CONSTRUCTION (37 C.F.R. § 42.104(b)(3))

In accordance with the Trial Practice Guide, Petitioner hereby provides "a simple statement that the claim terms are to be given their broadest reasonable interpretation, as understood by one of ordinary skill in the art and consistent with the disclosure" (77 Fed. Reg. 48764), except as discussed below

### A. **Without Food**

The term "without food" should be construed to mean "without a meal."

The claim language recites a method of "administering to the subject a granulated mesalamine formulation . . . without food." (Ex. 1001, '688 Patent col. 34:10-15).

The specification supports this construction. The specification suggests that "without food" means "without a high-fat meal." The specification discloses examples that allegedly studied the "effect of food intake on 5-ASA absorption." (Ex. 1001, '688 Patent col. 16:53-55). Example 1 describes a study of the pharmacokinetics of 5-ASA and its metabolite (N—Ac-5-ASA) under "fasting conditions." (Ex. 1001, '688 Patent col. 14:10-15). Subjects received granulated mesalamine either following an "overnight fast or a high-fat meal." (Ex. 1001, '688 Patent col. 14:61-63). Similarly, Example 4 describes administration of granulated mesalamine to subjects either "following an overnight fast or a high-fat meal." (Ex. 1001, '688 Patent col. 16:54-55). *Bell Atlantic Network Services, Inc. v. Covad Communications, Inc.,* 262 F.3d 1258, 1271 (Fed Cir. 2001) ("when a patentee uses a claim term throughout the entire patent specification, in a manner consistent with only a single meaning, he has defined that term by implication") (citations omitted)). A person of ordinary skill at the time of the '688 Patent filing would understand "fasting conditions" to yield an empty stomach. (Ex. 1002, Digenis Decl. ¶ 44).

The prosecution history also supports this construction. During prosecution, the Applicant repeatedly distinguished a "meal" with the claimed requirement of administering granulated mesalamine "without food." For instance, after amending the claim to require that granulated mesalamine is taken "with or

without food," the Applicant distinguished over the prior art (including other 5-ASA prodrugs) on the ground that his invention can be "administered without regard to meals (i.e., with or without food)." (Ex. 1016, FH688, Amendment 5/9/14 at 7). The Applicant also distinguished over other 5-ASA prodrugs by equating "with food" with "at the same time as the subject has a meal." (Ex. 1017, FH688, Amendment 6/20/14 at 6-7). Subsequently, after amending the claim to require administration of granulated mesalamine "without food," the Applicant distinguished the invention from a prior art formulation (Lialda®) on the ground that Lialda® was prescribed to be taken "with food" or "with a meal." (Ex. 1017, FH688, Amendment 6/20/14 at 6).

Accordingly, a person ordinary skill would understand from both the '688 Patent's specification and prosecution history that, in the course of amending the challenged claims to require mesalamine administration "without food," the Applicant clearly and unmistakably disclaimed embodiments of "without food" that did not comprise, or amount to, a "meal." (Ex. 1002, Digenis Decl. ¶ 46).

Thus, in light of the foregoing statements during prosecution, Applicant unequivocally disavowed embodiments of "without food" that comprise less than "without a meal." *See Biogen Idec, Inc. v. GlaxoSmithKline LLC,* 713 F.3d 1090, 1095 (Fed. Cir. 2013) ("when the patentee unequivocally and unambiguously disavows a certain meaning to obtain a patent, the doctrine of prosecution history

disclaimer narrows the meaning of the claim consistent with the scope of the claim surrendered"). The fact that Applicant may have surrendered more than was necessary for allowance is beside the point; the statements nevertheless "shed light on what the applicant meant by its various terms." *Uship Intellectual Props., LLC v. United States,* 714 F.3d 1311, 1316 (Fed. Cir. 2013).

### B. **Granulated Mesalamine Formulation**

The term "granulated mesalamine formulation" should be construed to mean "a mesalamine formulation with a pH dependent enteric coating around a polymer matrix core."

During prosecution, Applicant repeatedly distinguished the claimed "granulated mesalamine formulation" over the prior art on the ground that it contained a pH dependent enteric coating around a polymer matrix core. For instance, Applicant specifically distinguished the claims over a cited prior art reference, NetDoctor. NetDoctor taught a prior art mesalamine formulation called Asacol®. Applicant pointed out to the Examiner that "the chemical makeup of both formulations [the claimed formulation and Asacol®], and consequently, as is evidenced by Applicants' specification, the pharmacokinetics and clinical properties are distinct from each other." (Ex. 1021, FH688, Amendment 4/24/13 at 9). To show this, Applicant pointed to disclosure in the '688 Patent's specification teaching that the "granulated mesalamine formulation" comprises "an inner

polymer matrix mesalamine core" and an *"inner enteric pH dependent (delayed) release coating" and the "inner coating dissolves, for example, at pH ~ 6, but resists dissolution in the stomach . . . ."* (*Id*. at 9-10, citing Ex. 1001, '688 Patent col. 9:37-45) (emphasis in original). Applicant next pointed to another portion of the '688 Patent's specification that also distinguished over Asacol®: "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."* (Ex. 1021, FH688, Amendment 4/24/13 at 10, citing Ex. 1001, '688 Patent col. 9:46-54) (emphasis in original).

Elsewhere during prosecution, Applicant expressly distinguished over another cited prior art reference (2007 Press Release) on the ground that, unlike the 2007 Press Release, the claimed granulated mesalamine formulation contained an enteric coating surrounding a polymer matrix. In particular, Applicant argued that whereas the claimed formulation has the feature that 85% to 90% of the mesalamine formulation reaches the terminal ileum and colon (which is a requirement of the claims challenged in this petition), the 2007 Press Release does not teach this feature. And the reason, according to Applicant, this feature is missing from the 2007 Press Release is because the granulated mesalamine formulation in the instant application differs from the 2007 Press Release.

Specifically, Applicant stated:

> the instant application discloses a granulated mesalamine composition with a pH-dependent coating that dissolves at pH 6 or greater and a polymer matrix core which distributes the mesalamine slowly and uniformly throughout the lumen of the terminal ileum and colon. The instant application also provides pharmacokinetic information and release profile information that support the recited feature that 85% to 90% of mesalamine reaches the terminal ileum and colon [citing embodiments from the specification].

(Ex. 1020, FH688, Amendment 10/8/13 at 6).

Following that, Applicant once again distinguished over Asacol® on the ground that, unlike Asacol®, the claimed "granulated mesalamine formulation" contained a pH dependent enteric coating and a polymer matrix core:

> While the Asacol tablets of NetDoctor and the formulation of the instant application both contain mesalamine, the release profile of the instant application is distinct from that of Asacol tablets due to its polymer matrix core, which provides a mechanism by which mesalamine is uniformly and slowly released and distributed in the lumen of the colon. In contrast, NetDoctor merely discloses that the Asacol tablets have an enteric coating; however, there is nothing

further in NetDoctor to indicate that extended release of mesalamine takes place throughout the colon.

(Ex. 1020, Amendment 10/8/13 at 7-8).

This construction is consistent with the specification. The disclosed embodiments of the granulated mesalamine formulation contain a pH-dependent coating and a polymer matrix core. (*See e.g.*, Ex. 1001, '688 Patent col. 9:40-45 ("a granulated mesalamine formulation which comprises, for example, an inner polymer matrix mesalamine core that is surrounded by an outer flavor coating, a middle coating, and an inner enteric pH dependent (delayed) release coating. The inner coating dissolves, for example, at pH≥6, but resists dissolution in the stomach"). Indeed, this is true for every disclosed embodiment of the granulated mesalamine formulation. (*See* Ex. 1001, '688 Patent col. 9:46-54 ("following dissolution of the inner coating, the polymer matrix core of the granulated mesalamine . . ."); col. 10:47-53 and col. 13:5-10 (incorporating by reference patents and patent applications disclosing granulated mesalamine formulations with pH-dependent enteric coatings and polymer matrix cores); col. 10:63-67 ("granules composed of mesalamine in a polymer matrix with an enteric coating that dissolves at pH 6 and above"); col. 11:25-38 ("a pH dependent coating that dissolves at pH 6 or greater, reached in the terminal ileum and colon, and a polymer matrix core which distributes the mesalamine slowly and uniformly

throughout the lumen of the terminal ileum and colon")).

Further, this is consistent with the claim language. *All* claims of the '688 Patent require that "85% to 90% of the mesalamine reaches the terminal ileum and colon." (Ex. 1001, '688 Patent (claims 1-16)). As described in more detail above (*see supra* pp. 10-11), plain mesalamine that is orally administered will be absorbed in the stomach and upper intestine. (Ex. 1002, Digenis Decl. ¶ 53, citing (Ex. 1011, '620 Patent col. 1:45-48 ("A problem in the treatment with aminosalicylic acid is that the active compound is very easily absorbed and can be excreted via the kidney before its action can occur."); citing Ex. 1006, Stolk at 200 ("Plain mesalazine is totally absorbed in the upper part of the intestine."); Ex. 1004, Hanauer at 1189 ("Oral administration of mesalamine is limited by absorption in the proximal small bowel, necessitating protected delivery systems for distribution to distal sites of enterocolonic inflammation.")).

Thus, for "85% to 90% of the mesalamine [to] reach[] the terminal ileum and colon," as required by the claims, then a delay/control mechanism must be applied, such as a pH-dependent enteric coating and a polymer matrix core. Indeed, this is precisely how the '688 Patent explains that "85% to 90% of the mesalamine reaches the terminal ileum and colon." The only embodiment describing that "that 85% to 90% of drug reaches the diseased area" has an "inner enteric pH dependent (delayed) release coating" and a "polymer matrix core of the

granulated mesalamine [that] provides a mechanisms by which mesalamine, the active therapeutic agent, is uniformly and slowly released and distributed in the lumen of the colon." (Ex. 1001, '688 Patent col. 9:37-55).

## VIII. ANALYSIS

### A. GROUND 1: Claims 1 and 16 are rendered obvious under 35 U.S.C. § 103 over September 2007 Press Release in view of Endonurse and Davis-1985.

Sept. 2007 Press Release was published on September 5, 2007, and is therefore prior art under 35 U.S.C. § 102(b). The Sept. 2007 Press Release discloses the successful outcome of Phase III registration trials for Salix Pharmaceutical, Inc.'s "granulated mesalamine product," which is indicated for "maintenance of remission in patients with ulcerative colitis." (Ex. 1012, Sept. 2007 Press Release).

Endonurse was published on January 12, 2006, and is therefore prior art under 35 U.S.C. § 102(b). Endonurse discloses a report on a late-stage trial evaluating granulated mesalamine for treatment of ulcerative colitis, including dosing "four 375 mg tablets once daily." (Ex. 1014, Endonurse at 2).

Davis-1985 was published in 1985, and is therefore prior art under 35 U.S.C. § 102(b). More description of Davis-1985 relevant to this analysis is available below.

**1. A method of maintaining the remission of ulcerative colitis in a subject comprising administering to the subject a granulated mesalamine formulation comprising**

Sept. 2007 Press Release discloses a method of maintaining the remission of ulcerative colitis in a subject comprising administering to the subject a granulated mesalamine formulation: the press release announces successful completion of Phase III registration trials for a "granulated mesalamine product" that is indicated for "maintenance of remission in patients with ulcerative colitis." (Ex. 1012, Sept. 2007 Press Release). The formulation disclosed in Sept. 2007 Press Release includes granulated mesalamine that "combines an enteric pH-dependent coating, which provides for delayed release, and a polymer matrix core, which provides for an extended release." (Ex. 1012, Sept. 2007 Press Release). This meets the construction of "granulated mesalamine formulation," as properly construed above. (*See supra* Sec. VII.B).

**four capsules each comprising 0.375 g of granulated mesalamine once per day in the morning,**

Sept. 2007 Press Release discloses "[r]esults from the study indicate that 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." (Ex. 1012, Sept. 2007 Press Release).

Endonurse discloses "four 375 mg tablets once daily" of granulated mesalamine. (Ex. 1014, Endonurse at 2). This dosage regime is for the same

purpose disclosed in Sept. 2007 Press Release. (*Compare* Ex. 1012, Sept. 2007 Press Release ("successfully maintain remission in ulcerative colitis patients") *with* Ex. 1014, Endonurse at 2 ("for the maintenance of remission of ulcerative colitis"); *compare* Ex. 1012, Sept. 2007 Press Release ("delayed and extended release formulation of mesalamine . . . designed to provide for the distribution of the active ingredient beginning in the small bowel and continuing throughout the colon") *with* Ex. 1014, Endonurse at 2 ("formulated to deliver mesalamine by means of dual-release granules to the distal ileum and colon")).

Accordingly, a person of ordinary skill at the time of the '688 Patent would have had reason to dose the 1.5 g of daily granulated mesalamine, as disclosed in Sept. 2007 Press Release, in four 375 mg doses once per day, as disclosed in Endonurse, and as required by the challenged claims. (Ex. 1002, Digenis Decl. ¶ 61).

Indeed, this conclusion is bolstered because the '688 Patent itself teaches that "effective dosage levels" can vary, and "can be accomplished by one skilled in the art using routine pharmacological methods." The '688 Patent specifically states:

> As will be readily apparent to one skilled in the art, the useful in vivo dosage to be administered and the particular mode of administration will vary depending upon the age, weight and mammalian species

> treated, the particular compounds employed, and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine pharmacological methods. Typically, human clinical applications of products are commenced at lower dosage levels, with dosage level being increased until the desired effect is achieved.

(Ex. 1001, '688 Patent col. 8:14-25).

Indeed, the '688 Patent acknowledges that there is nothing critical about the claimed four 375 mg dosage units. (Ex. 1002, Digenis Decl. ¶ 63). The patent discloses numerous varying "effective" dosage amounts of granulated mesalamine: 0.5g and 4g per day (col. 2:40-42); 1.5 g per day (col. 2:43-44); 3 g per day (col. 2:45-46); 0.75 g to "about" 4 g (col. 3:21-22). (Ex. 1001, '688 Patent). The patent also acknowledges that the "effective amount" will vary from patient to patient: an "effective amount of a granulated mesalamine formulation may vary according to factors such as the disease state, age, and weight of the subject, and the ability of a granulated mesalamine formulation to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response." (Ex. 1001, '688 Patent col. 8:46-53).

Moreover, the '688 Patent defines an "effective amount" to include "an

amount effective, at dosages and for periods of time necessary, to achieve the desired result, e.g., sufficient to treat or *prevent* UC or other mesalamine related disorders in a patient or subject." (Ex. 1001, '688 Patent col. 8:43-46, emphasis added). Accordingly, an "effective amount" is defined to include an amount sufficient to satisfy the purpose of the challenged claims, *i.e.*, "maintain[] the remission of ulcerative colitis." (Ex. 1001, '688 Patent col. 34:10-11; col 35:4-5).

Further, a person of ordinary skill at the time of the '688 Patent would have had reason to administer the claimed dosage regime "in the morning." This is because this is the time when the patient is most likely to be on an empty stomach. Further, there is nothing in the '688 Patent that discloses, teaches or suggests that administration of the claimed dosage range in the morning, versus at other periods of the day (when the patient has not had a meal, or is on an empty stomach) is critical to maintaining remission of ulcerative colitis. On the contrary, the '688 Patent alternately discloses embodiments where the claimed granulated mesalamine is administered "in the morning, afternoon or evening" (col. 3:64), where the claimed four dosages are administered "in the morning, in the afternoon, in the evening or in the night" (col. 13:29-30). Indeed, the '688 Patent goes so far as to teach that the "morning" can comprise half the day—anytime from 3:00 a.m. until noon (col. 13:31-32). (Ex. 1002, Digenis Decl. ¶ 65).

**without food, wherein:**

Based on the '688 Patent's prosecution history, the purported point of novelty of the challenged claims is administration of a granulated mesalamine formulation *without food*. (*See supra* Sec. VI.B). The claims of the '688 Patent were finally allowed based on the Examiner's understanding that persons of ordinary skill "would be motivated to administer the mesalamine formulation with food, since 5-aminosalicylate compounds, including mesalamine, are known to have increased bioavailability when administered *with food*." (Ex. 1019, FH688, Notice of Allowance at 3) (emphasis added).

However, higher bioavailability translates to lesser amounts of mesalamine available to be deposited on the distal ileum and colon. The claimed "granulated mesalamine formulation," as properly construed above, (*see supra* Sec. VII.B), requires a pH dependent enteric coating around a polymer matrix core. Given this, persons of ordinary skill knew that it would be preferable to administer mesalamine *without food,* on an empty stomach, so that its bioavailability would be kept to a minimum. In this way, the greatest portion of the mesalamine dose would be deposited on the linings of the distal ileum and colon. Indeed, the challenged claims expressly require that "85% to 90% of the mesalamine reaches the terminal ileum and colon." (Ex. 1001, '688 Patent claims 1-16). (*See* Ex. 1002, Digenis Decl. ¶ 68).

This conclusion is supported by express understandings of persons of skill in

the art prior to the '688 Patent. In 1985, Davis reported that the efficacy of drug delivery systems **intended for the colon** can likely *increase* when administered *without food*. Specifically, Davis found that "gastric emptying" is affected by the "quantity and nature of food in the stomach a well as the size and the digestibility of the administered material." (Ex. 1009, Davis-1985 at 34). Importantly, small particles—such as granulated particles or small pellets—empty rapidly from the stomach because they do not have to be "reduced in size by the normal digestive process" or wait until the end of the digestive phase to be emptied by the "so-called interdigestive housekeeper wave." (*Id*.) Likewise, granulated particles can be emptied during the digestive phase. (*Id*.) Based on this, Davis concluded in 1985:

> [d]elivery 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.**

(Ex. 1009, Davis-1985 at 34) (citations omitted) (emphasis added).

The important absorption sites for treatment of ulcerative colitis are *not* the upper small intestine. Rather, they are the lower intestine and colon. This is

because ulcerative colitis specifically afflicts the large intestine, including the colon. (Ex. 1002, Digenis Decl. ¶ 70). Thus, the foregoing teaching from Davis-1985 suggests that the efficacy for ulcerative-colitis drugs would *increase* when administered to a fasted stomach. (Ex. 1002, Digenis Decl. ¶ 70).

Davis further concluded that, "[d]osage 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." (Ex. 1009, Davis-1985 at 36). Yet, Davis' view of a "non-optimal site" is the colon. Davis previously stated, "[a]s a general rule, therefore, drugs should be formulated so that they can be largely absorbed from the small intestine," because the "main site for the absorption of drugs in man is considered to be the small intestine, with its high effective surface area." (Ex. 1010, Davis-1986 at 886). Yet, for patients receiving treatment of ulcerative colitis, the optimal site is the colon. (Ex. 1002, Digenis Decl. ¶ 71).

Persons of ordinary skill also knew that food increases the pH of the stomach. Embodiments of the granulated mesalamine disclosed in the '688 Patent include a polymer matrix with a pH-dependent enteric coating (incorporated by reference via, *inter alia,* the '620 Patent). (Ex. 1001, '688 Patent col. 10:48-52). The '620 Patent discloses, the "enteric coating should only dissolve after the formulation has left the stomach." (Ex. 1011, '620 Patent col. 4:15-18). Preferred

embodiments include enteric coatings that "dissolve in digestive juices above pH 5.5-7." (*Id*. col. 4:18-26). The '688 Patent separately discloses an embodiment of the recited granulated mesalamine that has an "inner enteric pH dependent (delayed) release coating." (Ex. 1001, '688 Patent col. 9:37-46).

Yet, at the time of the '688 Patent, persons of ordinary skill already knew that food can increase the pH of the stomach from about 2.0 to about 5.0-6.0. (Ex. 1002, Digenis Decl. ¶ 73, citing Ex. 1009, Davis-1985 at 34 ("[t]he generally accepted value for the pH of the resting stomach is about 2.0 . . . . The presence of food will raise the pH to 5 or 6 . . . ."). Indeed, the '688 Patent expressly recognized that food can increase the pH of the stomach. In one embodiment, the inner pH-dependent coating of the granulated mesalamine "dissolves at pH≥6, but resists dissolution in the stomach, where gastric fluid is pH 1 during fasting and *approximately pH 4 during a meal*." (Ex. 1001, '688 Patent col. 9:43-46) (emphasis added).

Likewise, a person of ordinary skill at the time of the '688 Patent would have had reason to administer the granulated mesalamine formulation disclosed in the '688 patent *without food*. If food increases the stomach's pH to 5.0-6.0, but the enteric coating of the '688 Patent's granulated mesalamine dissolves at 5.5, that would motivate a person of ordinary skill to administer granulated mesalamine *without food* so that it does not do exactly what the granulated mesalamine is not

supposed to do—namely, dissolve until "after the formulation has left the stomach." (Ex. 1002, Digenis Decl. ¶ 74, citing Ex. 1011, '620 Patent col. 4:15–18).

**said method maintains remission of ulcerative colitis in a subject for a period of at least 6 months of treatment;**

Sept. 2007 Press Release discloses a method that maintains remission of ulcerative colitis in a subject for a period of at least 6 months of treatment: "[r]esults from the study indicate that 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." (Ex. 1012, Sept. 2007 Press Release).

**remission is defined as a DAI score of 0 or 1;**

Sept. 2007 Press Release discloses "remission is defined as a DAI score of 0 or 1": results from the study indicate patients "remained relapse-free." (Ex. 1012, Sept. 2007 Press Release). A person of skill in the art would recognize that remaining "relapse-free", *i.e.*, in remission, would be defined by a DAI score of 0 to 1. (Ex. 1002, Digenis Decl. ¶ 78, citing Ex. 1013, Meyeroff at ¶ 20 ("remission refers to application of the customary markers utilized in clinical practices to assess IBD. For example, a patient is considered to be in remission for UC if a UC-DAI score of [≤] is obtained . . .")).

**the granulated mesalamine formulation is not administered with antacids; and**

The '688 Patent discloses that the only active ingredient in the recited methods is mesalamine. (*See generally* Ex. 1001, '688 Patent and claims 1 and 16). And the Sept. 2007 Press Release discloses that the "300-subject, multicenter, 6-month, double-blind, randomized, placebo-controlled study demonstrates the utility of this delayed and extended release formulation of mesalamine." (Ex. 1012, Sept. 2007 Press Release).

It would have been obvious to a person of ordinary skill at the time of the '688 Patent to *avoid* co-administering granulated mesalamine with antacids for the treatment of ulcerative colitis. One embodiment of the granulated mesalamine disclosed in the '688 Patent includes an enteric coating that dissolves at pH 6 and above. (Ex. 1001, '688 Patent col. 10:63-65). Persons of ordinary skill generally knew that the stomach's pH is lower than the pH of the intestinal tract. (Ex. 1002, Digenis Decl. ¶ 81, citing Ex. 1007, EP168 col. 1:27-33 ("it is recognized that the value of pH in the stomach is usually 1.8 to 4.5 in a healthy human and that the value of pH in the intestines is 6.5 to 7.5 and the pH does not essentially differ between the small intestine and the large intestine"). Accordingly, because indigestion remedies, such as antacids, generally increase the pH value of the stomach, then co-administering an enteric-coated mesalamine with an antacid would cause the coating (which is pH-sensitive) to dissolve in the stomach, which

would cause release of the mesalamine in the stomach or upper portions of the small intestines. That, in turn, would prevent the delivery of the active mesalamine to the lower intestines, which is the site of the ulcerative colitis lesions. Thus, the amount of mesalamine reaching the distal ileum and colon would be significantly decreased. (Ex. 1002, Digenis Decl. ¶ 81, citing Ex. 1009, Davis-1985 at 34 (stating that the presence of antacids will raise the pH of the stomach); citing Ex. 1026, Brouwers at 156 (identifying 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").

Further, the '688 Patent does not disclose, teach or suggest that avoiding co-administration of granulated mesalamine along with antacids was somehow surprising or inventive. The '688 Patent simply discloses that granulated mesalamine is not administered with antacids "because it could affect the way granulated mesalamine formulation dissolves." (Ex. 1001, '688 Patent col. 5:40–41; col. 13:50-51). This is consistent with the general understanding of persons of ordinary skill at the time of the '688 Patent's filing (Oct. 2009) that antacids would increase the stomach's pH, and result in early dissolution of the mesalamine's enteric coating. (Ex. 1002, Digenis Decl. ¶ 82, citing Ex. 1009, Davis-1985 at 34 (stating that the presence of antacids will raise the pH of the stomach); citing Ex. 1026, Brouwers at 156 (identifying 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")).

**wherein 85% to 90% of the mesalamine reaches the terminal ileum and colon.**

Sept. 2007 Press Release discloses 85% to 90% of the mesalamine reaches the terminal ileum and colon: "[t]his formulation is designed to provide for the distribution of the active ingredient beginning in the small bowel and continuing throughout the colon." (Ex. 1012, Sept. 2007 Press Release). A person of ordinary skill would understand that the small bowel includes the terminal ileum. (Ex. 1002, Digenis Decl. ¶ 84).

During prosecution, Applicant claimed that the Sept. 2007 Press Release "provides no information for how the drug is distributed throughout the targeted region." (Ex. 1020, FH688, Amendment 10/8/13 at 6). This is wrong. The formulation disclosed in the Sept. 2007 Press Release is clearly the same as that disclosed in the '688 Patent. The formulation disclosed in Sept. 2007 Press Release includes granulated mesalamine that "combines an enteric pH-dependent coating, which provides for delayed release, and a polymer matrix core, which provides for an extended release." (Ex. 1012, Sept. 2007 Press Release). This mirrors the description of the claimed mesalamine formulation by the Applicant during prosecution: "the instant application discloses a granulated mesalamine composition with a pH-dependent coating that dissolves at pH 6 or greater and a

polymer matrix core which distributes the mesalamine slowly and uniformly throughout the lumen of the terminal ileum and colon." (Ex. 1020, FH688, Amendment 10/8/13 at 6; *see also* Ex. 1021, FH688, Amendment 4/24/13 at 10 ("the claimed formulation has a specific pH dependent release profile whereby the inner coating of the claimed formulation resists dissolution at lower pH ranges (e.g., 1 to 4), thus allowing for dissolution and delivery of the granulated mesalamine in the lumen of colon")).

Thus, based on the foregoing, a person of ordinary skill would expect that the formulation disclosed in Sept. 2007 Press Release would have the same release profile as the challenged claims of the '688 Patent, namely "85% to 90% of the mesalamine reaches the terminal ileum and colon," because they are the same formulations. (Ex. 1002, Digenis Decl. ¶ 86).

**16. A method of maintaining the remission of ulcerative colitis in a subject comprising**

This element is obvious for the same reasons discussed in connection with Claim 1.

**advising the subject that granulated mesalamine should not be taken with antacids and**

This element is obvious for the same reasons discussed in connection with Claim 1.

**administering to the subject granulated mesalamine formulation comprising four capsules each comprising 0.375 g of granulated mesalamine once per day in the morning,**

This element is obvious for the same reasons discussed in connection with Claim 1.

**without food, wherein:**

This element is obvious for the same reasons discussed in connection with Claim 1.

**said method maintains remission of ulcerative colitis in a subject for a period of at least 6 months of treatment;**

This element is obvious for the same reasons discussed in connection with Claim 1.

**remission is defined as a DAI score of 0 or 1;**

This element is obvious for the same reasons discussed in connection with Claim 1.

**the granulated mesalamine formulation is not administered with antacids; and**

This element is obvious for the same reasons discussed in connection with Claim 1.

**wherein 85% to 90% of the mesalamine reaches the terminal ileum and colon.**

This element is obvious for the same reasons discussed in connection with Claim 1.

### B. GROUND 2: Claims 1 and 16 are rendered obvious under 35 U.S.C. § 103 over September 2007 Press Release in view of Endonurse, Davis-1985 and EP590.

A description of September 2007 Press Release, Endonurse and Davis-1985 is set forth under Ground 1. EP590 was published November 25, 1985, and is therefore prior art under 35 U.S.C. § 102(b). EP590 is directed to a "pharmaceutical preparation for oral administration, having improved release properties" that "releases a major part of its drug contents in the lower part of the intestinal system." (Ex. 1015, EP590 at 1:5-14). EP590 contemplates treatment of for ulcerative colitis, and the preferred therapeutic agent is granulated mesalamine (5-aminosalicylic acid). (Ex. 1015, EP590 at 1:28-2:6; 4:12-16; 6:8-34 ("granules" of salicylazo-sulfapyridine (SASP, which comprises 5-ASA)). EP590 discloses administering "granulated" drug containing 5-ASA after 10 hours of fasting, with results showing increased absorption of active ingredients in the large intestine over the small intestine. (Ex. 1015, EP590 at 6:5-9:35).

For those claim elements not expressly discussed in this Ground 2, the corresponding discussion in connection with those elements in Ground 1 are hereby incorporated in this ground.

**four capsules each comprising 0.375 g of granulated mesalamine once per day in the morning,**

The discussion of this element from Ground 1 is incorporated herein by reference. EP590 discloses a method of administering granulated mesalamine in

the morning. In particular, EP590 discloses administering "granular preparations" of the "invention" (including 2 g salicylazo-sulfapyridine (SASP, which comprises 5-ASA) to test persons). (Ex. 1015, EP590 at 8:24-31). The test persons were fasted before and after administration of the granulated mesalamine: "[a]fter at least 10 hours fasting the test preparation was ingested with 200 ml water. Three hours later restrictions on feeding were lifted." (Ex. 1015, EP590 at 8:33-35). Because the patients were fasted for at least 10 hours before administration, a person of ordinary skill would understand that administration would occur in the morning. This way the 10 hour fasting would coincide with sleep. Otherwise, a 10 hour fast before administration, followed by three hour fast after administration, would mean the patients would be going to sleep without eating. (Ex. 1002, Digenis Decl. ¶ 102).

**without food, wherein:**

EP590 discloses a method of administering granulated mesalamine without food. In particular, EP590 discloses administering "granular preparations" of the "invention" (including 2000 g salicylazo-sulfapyridine (SASP, which comprises 5-ASA) to test persons). (Ex. 1015, EP590 at 8:24-31). The test persons were fasted before and after administration of the granulated mesalamine: "[a]fter at least 10 hours fasting the test preparation was ingested with 200 ml water. Three hours later restrictions on feeding were lifted." (Ex. 1015, EP590 at 8:33-35). This

meets the construction of the phrase, "without food," as being limited to "without a meal," because a person of ordinary skill would understand that 200 ml of water is not a meal. (*See supra,* Sec. VII.A; *see* Ex. 1002, Digenis Decl. ¶ 105).

EP590 further discloses that testing of SASP and acetyl-5-ASA excreted in urine was performed, with the conclusion that the "preparations of the invention [including granulated SASP] gave a significantly *lowered* amount of excreted SASP . . . ." (Ex. 1015, EP590 at 9:27-35) (emphasis added). The *lowered* excretion in urine was concluded to suggest drug release in the colon (favorable for treatment of ulcerative colitis), whereas higher excretion in urine suggested "absorption in the small intestine" (not favorable for treatment of ulcerative colitis). (Ex. 1015, EP590 at 6:15-21).

This is the same reasoning taught by the '688 Patent for why granulated mesalamine can be taken *without* food. Example 1 in the '688 Patent describes a study where granulated mesalamine was administered to patients either "following an overnight fast or a high-fat meal." (Ex. 1001, '688 Patent col. 14:61-63). This study showed "a 27% increase in the cumulative urinary excretion of 5-ASA was observed with a high fat meal." (Ex. 1001, '688 Patent col. 14:66-67). Based in part on this finding, the '688 Patent concludes "granulated mesalamine formulation can be taken without regard to food." (Ex. 1001, '688 Patent col. 15:3-5).

In other words, a high-fat meal increased excretion of 5-ASA in the urine,

which indicates higher absorption in the small intestine, which is *not* favorable for treatment of ulcerative colitis. Accordingly, EP590 teaches administration of granulated preparations of mesalamine "without food," or without a meal, and it also teaches that doing so lowered the excretion of 5-ASA in the urine, thereby increasing the application in the large intestine. For these reasons, persons of skill would have been motivated to combine the mesalamine formulation disclosed in the September 2007 Press Release *without food,* as disclosed in EP590, because doing so would reduce absorption of the drug in the small intestine, and increase its application in the large intestine, *i.e.*, at the sites of the ulcerative colitis condition, which would therefore increase the therapeutic efficacy of treating ulcerative colitis. (Ex. 1002, Digenis Decl. ¶ 106).

Further, a person of ordinary skill at the time of the '688 Patent would understand that a high-fat meal raises the pH in the stomach and suppresses gastric emptying. The longer tenure of a formulation coated with a pH-sensitive coating at a higher than pH 1-2 results in the greater release of mesalamine at the upper portion of the small intestines where higher absorption of the drug occurs. (Ex. 1002, Digenis Decl. ¶ 107, citing Ex. 1007, EP168 col. 1:27-33; citing Ex. 1008, PCT949 at 1:10-18). Higher absorption results in higher bioavailability of the drug, and hence a 27% increase in its cumulative urinary excretion is recorded in Example 1 of the '688 Patent. (Ex. 1002, Digenis Decl. ¶ 107). However, higher

bioavailability translates to lesser amounts of mesalamine available to be deposited on the distal ileum and colon. (*See* Ex. 1009, Davis-1985 at 34). Since the known mechanisms of action of mesalamine for treatment of ulcerative colitis involves topical deposition in the inflicted areas of the large bowel (Ex. 1001, '688 Patent col. 1:60-63), it would have been obvious to a person of skill in view of September 2007 Press Release in view of EP590 to administer granulated mesalamine formulations without a meal. (Ex. 1002, Digenis Decl. ¶ 107).

Accordingly, a person of ordinary skill at the time the '688 Patent would understand, based on EP590, that ingesting granulated mesalamine in connection with fasting—*i.e.*, "without food" or "without a meal"—yields increased application in the large intestine (favorable for treating ulcerative colitis) rather than the small intestine (not favorable for treating ulcerative colitis). (Ex. 1002, Digenis Decl. ¶ 108). Thus, a person of ordinary skill would have a reason to try administering granulated mesalamine without food to increase the therapeutic efficacy of maintaining remission of ulcerative colitis. (Ex. 1002, Digenis Decl. ¶ 108).

### C. GROUND 3: Claims 1 and 16 are rendered obvious under 35 U.S.C. § 103 over September 2007 Press Release in view of Endonurse, Davis-1985 and Marakhouski.

A description of September 2007 Press Release, Endonurse and Davis-1985 is set forth under Ground 1. Marakhouski was published in 2005, and is therefore

prior art under 35 U.S.C. § 102(b). Marakhouski discloses clinical study results regarding a formulation of 5-ASA pellets. (Ex. 1024, Marakhouski at 133).

For those claim elements not expressly discussed in this Ground 3, the corresponding discussion in connection with those elements in Ground 1 are hereby incorporated in this ground.

**without food, wherein:**

The pellets disclosed in Marakhouski were "coated with Eudragit-L" and contained 5-ASA "located in the core embedded in a matrix polymer responsible for prolonged release of the drug." (Ex. 1024, Marakhouski at 135). This meets the construction of "granulated mesalamine formulation," as properly construed above. (*See supra* Sec. VII.B).

Marakhouski teaches that the pellets can be taken without food:

> The size of the pellets guarantees their continuous transit through the stomach into the intestine. Because of their small size (approximately 1 mm), the pellets pass the pylorus continuously and not only during an interdigestive phase, thus preventing the so-called dose-dumping effect. **Hence, the pellets can be taken independent of meals.**

(*Id*. at 134) (emphasis added). This meets the construction of the phrase, "without food," as being limited to "without a meal." (*See supra,* Sec. VII.A).

Marakhouski also discloses that the patients took the pellets "three times a

day in the morning, at midday and in the evening 1 h before meals." (Ex. 1024, Marakhouski at 135). This also meets the construction of the phrase, "without food," as being limited to "without a meal." (*See supra,* Sec. VII.A).

A person of ordinary skill at the time of the earliest priority date of the '688 Patent would have been motivated to combine Marakhouski's teaching administering a granulated mesalamine formulation without food—*i.e.*, "independent of meals" and "before meals"—with the other cited references. This is because Marakhouski discloses the administration of the same "granulated mesalamine formulation" that alleviates the exact problem identified by the '688 Patent as allegedly existing in the prior art. The '688 Patent claims the following problems purportedly existed with prior art mesalamine formulations for treating UC: "variation within formulations in the release of mesalamine, including premature release, **the possibility of dose dumping,** and sensitivity to conditions that increase gastric pH and cause premature release of mesalamine (e.g., ingestion of a meal)." (Ex. 1001, '688 Patent col. 2:3-8). As shown above, Marakhouski teaches the disclosed pellet "prevent[s] the so-called dose-dumping effect [and] [h]ence, the pellets can be taken independent of meals." (Ex. 1024, Marakhouski at 134). (*See also* Ex. 1002, Digenis Decl. ¶ 112).

**the granulated mesalamine formulation is not administered with antacids; and**

The discussion of this element from Ground 1 is incorporated herein by

reference. Specifically, persons of ordinary skill knew that the goal of 5-ASA was administration to the colon, and yet pH-dependent delivery systems "can be prone to the possibility of dose dumping when combined with antacids." (Ex. 1002, Digenis Decl. ¶ ¶ 81-82, quoting Ex. 1026, Brouwers at 156). Marakhouski specifically discloses that the Eudragit-L coating on the 5-ASA pellets begin dissolving at pH ≥ 6.0. (Ex. 1024, Marakhouski at 135). The '688 Patent specifically identifies "the possibility of dose dumping" as an alleged drawback of prior art mesalamine formulations. (Ex. 1002, '688 Patent col. 2:3-8). Thus, a person of ordinary skill would have had reason not to administer the "granulated mesalamine formulation" with antacids to prevent dose-dumping. (Ex. 1002, Digenis Decl. ¶ 113).

### D. GROUND 4: Claims 1 and 16 are rendered obvious under 35 U.S.C. § 103 over September 2007 Press Release in view of Endonurse, Davis-1985 and Brunner.

A description of September 2007 Press Release, Endonurse and Davis-1985 is set forth under Ground 1. Brunner was published in 2003, and is therefore prior art under 35 U.S.C. § 102(b). Brunner discloses a scintigraphy study of mesalamine pellets. (Ex. 1025, Brunner).

For those claim elements not expressly discussed in this Ground 4, the corresponding discussion in connection with those elements in Ground 1 are hereby incorporated in this ground.

**four capsules each comprising 0.375 g of granulated mesalamine once per day in the morning,**

The discussion of this element from Ground 1 is incorporated herein by reference. The pellets disclosed in Brunner were provided by Dr. Falk Pharma GmbH, the patent owner of the '688 Patent. (Ex. 1025, Brunner at 1164). The pellets contained 500 mg of mesalamine, "coated with Eudragit L" and "with an additional polymer in the pellet core providing prolonged release after removal of the Eudragit L coating." (*Id.*) This meets the construction of "granulated mesalamine formulation," as properly construed above. (*See supra* Sec. VII.B).

Brunner teaches that the pellets are taken once per day in the morning, as required by claim 1, because it teaches the pellets "were taken orally with 200 mL of water **in the morning** after an overnight fast." (Ex. 1025, Brunner at 1164) (emphasis added).

**without food, wherein:**

Brunner teaches that the pellets can be taken without food because it teaches the pellets "were taken orally with 200 mL of water in the morning after an overnight fast." (Ex. 1025, Brunner at 1164). This meets the construction of the phrase, "without food," as being limited to "without a meal," because a person of ordinary skill would understand that 200 mL of water following an overnight fast is not a meal. (*See supra,* Sec. VII.A; *see* Ex. 1002, Digenis Decl. ¶ 120).

A person of ordinary skill at the time of the earliest priority date of the '688 Patent would have been motivated to combine Brunner's teaching administering a granulated mesalamine formulation without food—*i.e.*, after an overnight fast with 200 mL of water—with the other cited references. (Ex. 1002, Digenis Decl. ¶ 121). This is because Brunner discloses the administration of the same "granulated mesalamine formulation" that can be taken "independent" of food intake. Specifically, Brunner teaches the disclosed pellets could be effective independent of whether food was ingested or not. Brunner teaches:

> Pellets with the same Eudragit L coating, but with a matrix polymer in the pellet core to provide prolonged release, could show some advantages compared with tablets, such as passage through the stomach **independent of concomitant food** intake or facilitated passage through strictures in the upper gastrointestinal tract.

(Ex. 1025, Brunner at 1167) (emphasis added).

The '688 Patent claims that the efficacy of prior art mesalamine formulations were sensitive to co-administration with food because they purportedly had "sensitivity to conditions that increase gastric pH and cause premature release of mesalamine (e.g., ingestion of a meal)." (Ex. 1001, '688 Patent col. 2:3-8). Yet, Brunner taught the same granulated mesalamine formulation could be efficaciously taken "independent of concomitant food," and

indeed disclosed an embodiment disclosed "after an overnight fast"—*i.e.*, "without food." (Ex. 1025, Brunner at 1164). Thus, a person of ordinary skill at the time of the '688 Patent's priority date would have had reason to, and been motivated to, combine Brunner's teaching administering a granulated mesalamine formulation without food—*i.e.*, after an overnight fast with 200 mL of water—with the other cited references. (*See also* Ex. 1002, Digenis Decl. ¶ 122).

## IX. CONCLUSION

For the foregoing reasons, the Petitioner respectfully requests that trial be instituted and that claims 1 and 16 of the '688 Patent be cancelled.

Respectfully submitted,

/William D. Hare/
William D. Hare
Reg. No. 44,739
Lead Counsel for Petitioner MycoNovo, Inc. and Foxhill Opportunity Fund, L.P.

Dated: July 11, 2016

McNEELY, HARE & WAR LLP
12 Roszel Road, Suite C104
Princeton, NJ 08540

## CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on July 11, 2016, I caused to be served true and correct copies of the foregoing:

- Petition for *Inter Partes* Review of U.S. Patent No. 8,865,688
- Exhibits 1001-1026
- Power of Attorney of MycoNovo, Inc.
- Power of Attorney of Foxhill Opportunity Fund, L.P.

by overnight courier on the Patent Owner at the correspondence address of the Patent Owner, as follows:

Mary W. Bourke (Registration No. 30,982)
Womble Carlyle Sandridge & Rice LLP
222 Delaware Ave., Suite 1501
Wilmington, DE 19801
T: (302) 252-4333
mbourke@wcsr.com

Tryn Stimart
Womble Carlyle Sandridge & Rice LLP
8065 Leesburg Pike, 4th Floor
Tysons Corner, VA 22182-2738
T: (703) 790-7924
tstimart@wcsr.com

Preston H. Heard (Registration No. 64,675)
Womble Carlyle Sandridge & Rice LLP
271 17th St. N.W., Suite 2400
Atlanta, GA 30363
T: (404) 888-7366
pheard@wcsr.com

And to counsel for Petitioners Generico, LLC and Flat Line Capital, LLC in IPR2016-00297, as follows:

Zachary D. Silbersher (Registration No. 62,090)
Gaston Kroub (Registration No. 51,903)
Kroub, Silbersher & Kolmykov PLLC
305 Broadway 7th Fl.
New York, NY 10007
Tel: (212) 323-7442
zsilbersher@kskiplaw.com
gkroub@kskiplaw.com

Dated: July 11, 2016

/William D. Hare/
William D. Hare, Reg. No. 44,739