Paper No. _____
Filed: April 1, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS II LLC

PETITIONER

V.

SHIRE INC.

PATENT OWNER

CASE NO.: UNASSIGNED
PATENT NO. 6,773,720
FILED: JUNE 8, 2000
ISSUED: AUGUST 10, 2004
INVENTORS: ROBERTO VILLA, MASSIMO PEDRANI, MAURO AJANI, LORENZO FOSSATI

TITLE: MESALAZINE CONTROLLED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 6,773,720

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Exhibit 1044	European Patent Number 0 384 514 to Richard John Dansereau and Michael John Kane, filed on Feb. 12, 1990, and issued on Nov. 24, 1993 ("*Dansereau*")
Exhibit 1045	U.S. Patent No. 4,421,736 to Eugene L. Walters, filed on May 20, 1982, and issued on Dec. 20, 1983 ("*Walters*")

I. INTRODUCTION

Petitioner Coalition For Affordable Drugs II LLC ("CFAD II"), requests an *Inter Partes* Review ("IPR") of Claims 1–4 (collectively, the "Challenged Claims") of U.S. Patent No. 6,773,720 (Ex. 1001) in accordance with 35 U.S.C. §§ 311–19 and 37 C.F.R. § 42.100 *et seq*.

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '720 patent is available for IPR and that the Petitioner is not barred or estopped from requesting IPR challenging the Claims of the '720 patent on the grounds identified in this Petition.

III. MANDATORY NOTICES (37 C.F.R. § 42.8)

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Coalition For Affordable Drugs II LLC ("CFAD II"), Hayman Credes Master Fund, L.P. ("Credes"), Hayman Orange Fund SPC – Portfolio A ("HOF"), Hayman Capital Master Fund, L.P. ("HCMF"), Hayman Capital Management, L.P. ("HCM"), Hayman Offshore Management, Inc. ("HOM"), Hayman Investments, L.L.C. ("HI"), nXn Partners, LLC ("nXnP"), IP Navigation Group, LLC ("IPNav"), J. Kyle Bass, and Erich Spangenberg are the real parties in interest (collectively, "RPI"). The RPI hereby certify the following information: CFAD II is a wholly owned subsidiary of Credes. Credes is a limited partnership. HOF is a segregated portfolio company.

HCMF is a limited partnership. HCM is the general partner and investment manager of Credes and HCMF. HCM is the investment manager of HOF. HOM is the administrative general partner of Credes and HCMF. HI is the general partner of HCM. J. Kyle Bass is the sole member of HI and sole shareholder of HOM. CFAD II, Credes, HOF and HCMF act, directly or indirectly, through HCM as the general partner and/or investment manager of Credes, HOF and HCMF. nXnP is a paid consultant to HCM. Erich Spangenberg is 98.5% member of nXnP. IPNav is a paid consultant to nXnP. Erich Spangenberg is the 98.5% member of IPNav. Other than HCM and J. Kyle Bass in his capacity as the Chief Investment Officer of HCM and nXnP and Erich Spangenberg in his capacity as the Manager/CEO of nXnP, no other person (including any investor, limited partner, or member or any other person in any of CFAD II, Credes, HOF, HCMF, HCM, HOM, HI, nXnP or IPNav) has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All of the costs associated with this Petition will be borne by HCM, CFAD II, Credes, HOF and/or HCMF.

B. Related Judicial and Administrative Matters (37 C.F.R. § 42.8(b)(2))

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that the '720 patent has been the subject of the following lawsuits: *Shire Development LLC et al v. Mylan Pharmaceuticals, Inc. et al.*, FLMD-8-12-cv-01190 (filed May 25, 2012); *Shire Development*

LLC et al. v. Watson Pharmaceuticals, Inc. et al., FLSD-0-12-60862 (filed May 8, 2012); *Shire Development LLC et al. v. Osmotical Pharmaceutical Corp.*, GAND-1-12-cv-00904 (filed March 16, 2012); *Shire Development LLC, et. al. v. Cadila Healthcare Limited, et. al.*, DED-1-10-cv-00581 (filed July 7, 2010). 37 C.F.R. § 42.8(b)(2).

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

Lead counsel is Sarah E. Spires, Reg. No. 61,501, sarah.spires@skiermontpuckett.com. Back-up counsel are Ki O, Reg. No. 68,952, ki.o@skiermontpuckett.com; Dr. Parvathi Kota, Reg. No. 65,122, parvathi.kota@skiermontpuckett.com; and Paul J. Skiermont (*pro hac vice* requested), paul.skiermont@skiermontpuckett.com—all of Skiermont Puckett LLP, 2200 Ross Ave. Ste. 4800W, Dallas, Texas 75201, P: 214-978-6600/F: 214-978-6601. Petitioner consents to electronic service.

IV. PAYMENT OF FEES (37 C.F.R. § 42.15(a) and § 42.103)

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 506293. Any overpayment or refund of fees may also be deposited in this Deposit Account.

V. IDENTIFICATION OF CHALLENGE

A. Overview of U.S. Patent No. 6,773,720

1. The '720 Patent Specification

The '720 patent is a § 371 National Stage Entry of PCT Application No. PCT/EP00/05321, filed June 8, 2000, which claims the benefit of Italian Application No. MI99A1316, filed June 14, 1999. (Ex. 1001 at Front Cover.)

The '720 patent is titled "Mesalazine Controlled Release Oral Pharmaceutical Compositions," and claims controlled-release oral pharmaceutical compositions for treating inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis. (Ex. 1001 at 1:9–13.) The active pharmaceutical ingredient ("API") in these compositions is 5-amino-salicylic acid (Ex. 1001 at 2:36–38), which "is also known as 5-ASA, 5-amino-salicylate, mesalazine, or mesalamine." (Ex. 1037, Palmieri Decl. ¶ 67.) 5-ASA "treats inflamed areas in the bowel by direct contact with the intestinal mucosal tissue." (Ex. 1006 at 3.) Thus, 5-ASA "must pass through the stomach and small intestine without being absorbed into the bloodstream." (*Id.*) Additionally, 5-ASA "must be administered throughout the entire length of the colon so that the mesalamine contacts all affected tissues." (*Id.*) To satisfy these requirements, the claimed oral composition contains a high percentage, by weight, of 5-ASA. (*See* Ex. 1001 at 3:52–56.)

The '720 specification describes these oral compositions as comprising: "(a) an inner lipophilic matrix consisting of substances with melting point below 90°C. in

which the active ingredient is at least partially inglobated; (b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed; [and] (c) optionally other excipients." (Ex. 1001 at 2:36–44.) Additionally, the '720 patent purports to demonstrate "effectively control[led] dissolution" using a matrix containing high levels of 5-ASA as an active ingredient. (*Id.* at 4:26–31, 3:52–56.)

The background section of the '720 specification acknowledges that controlled-release formulations of 5-ASA were known in the art at the time of filing. (Ex. 1001 at 1:11–13 (citing Ex. 1039 at 2:29–33, and Ex. 1040 at 2:10–11, 8:3–14).) The background section further admits that the use of lipophilic and hydrophilic matrices was a conventional technique in the preparation of sustained, controlled, delayed, or modified-release formulations. (*Id.* at 1:14–29.)

The '720 patent teaches a three-step process to arrive at the claimed oral composition:

> The compositions of the invention can be obtained with a method comprising the following steps:
>
> [Step 1] a) the active ingredient is first inglobated in a low melting excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion.
>
> [Step 2] After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain matrix granules containing the active ingredient particles.

> [Step 3] b) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients.

(Ex. 1001 at 2:48–59; *see also* Ex. 1006 at 4–5.)

The '720 patent contains five examples illustrating this process. (Ex. 1001 at 4:8–6:5 (Examples 1–5).) In each example, 5-ASA is added with a lipophilic substance until a homogeneous dispersion is obtained, and then granulated. (*Id.*) This granulation step exemplifies formation of the claimed "inner lipophilic matrix." Next, the lipophilic matrix is mixed with a hydrophilic compound or compounds to achieve a final homogeneity, which exemplifies the "outer hydrophilic matrix wherein the lipophilic matrix is dispersed." (*Id.*) Finally, the matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix is tabletted and optionally coated with a gastro-resistant (enteric) film. (*Id.* at 3:40–51.) Each of the five examples includes various conventional excipients in the tablets together with the lipophilic and hydrophilic compounds. (*Id.* at 4:8–6:5.)

Notably, the '720 patent does not disclose any examples that teach any step where 5-ASA is *first* mixed with a hydrophilic substance and *then* added to a lipophilic compound. Each claim of the '720 patent requires the 5-ASA composition to be "dispersed both in the lipophilic matrix and in the hydrophilic matrix," (Ex. 1001 at 6:30–31), and the support for this claim limitation is found in the following section of the specification:

> Part of mesalazine can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said com[p]ositions being preferably in the form of tablets, capsules and/or minitablets.

(*Id.* at 3:34–39.)

2. The '720 Claims

Claim 1, the only independent claim in the '720 patent, claims:

> Controlled-release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid, comprising:
> a) an inner lipophilic matrix consisting of substances selected from the group consisting of unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglycerid[e]s, waxes, ceramides, and cholesterol derivatives with melting points below 90° C., and wherein the active ingredient is dispersed both in said the lipophilic matrix and in the hydrophilic matrix;
> b) an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of compounds selected from the group consisting of polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, and natural or synthetic gums;
> c) optionally other excipients; wherein the active ingredient is present in an amount of 80 to 95% by weight of the total composition, and wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.

(Ex. 1001 at 6:7–31.)

Claim 2 depends from **Claim 1**, and requires that the "5-aminosalicylic acid is dispersed in a molten lipophilic matrix by kneading, extrusion and/or granulation." (Ex. 1001 at 6:32–34.)

Claim 3 depends from **Claim 1** and requires that the compositions be "in the form of tablets, capsules, or mintablets (sic)." (Ex. 1001 at 6:35–36.)

Claim 4 depends from **Claim 1** and is a process for the preparation of the compositions of **Claim 1**, which comprises: "a) melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90° C.; b) mixing the granules from step a) with the hydrophilic excipients and subsequent tabletting or compression." (Ex. 1001 at 6:37–43.)

3. The '720 Prosecution History

During prosecution of U.S. Application No. 10/009,491, which led to the '720 patent, the examiner initially rejected the applicants' claims as obvious in view of Ex. 1009 ("*Franco*"); obvious and anticipated in view of Ex. 1036 ("*Akiyama*"); and obvious in view of the combination of Ex. 1041 ("*Sanghvi*") and Ex. 1042 ("*Straub*"). (Ex. 1002 at 41–42, 58–60.) The examiner explained that *Franco* taught a pharmaceutical composition with an active core, a lipophilic coating, and a hydrophilic film. (Ex. 1002 at 41–42, 58–59.)

The applicants responded that *Franco* disclosed a reservoir system where "the active ingredient is confined within a core which acts as a reservoir from which the active ingredient is released via the erosion of the outer coating. However, as to the

present invention, the active ingredient is dispersed in a lipophilic matrix, not in an isolated core." (Ex. 1002 at 49–50.)

The applicants then distinguished *Akiyama* based on the claimed invention's two matrices and high active ingredient concentration. Specifically, the applicants argued that *Akiyama* "fail[s] to disclose or suggest the two matrices and the arrangement of the matrices as set forth in the claimed invention. The arrangement of the matrices in the present invention aid[s] in the combined release of an active ingredient via diffusion from a lipophilic matrix." (Ex. 1002 at 48.) The applicants also argued that *Akiyama*'s composition contained the "active ingredient ... in an amount much lower than that according to the claimed invention." (Ex. 1002 at 48.)

In the next office action, the examiner maintained her rejection of the pending claims as obvious in view of *Franco*. (Ex. 1002 at 42–43.) The examiner also rejected the claims because "the feature upon which applicant relies (i.e., the active ingredient is dispersed in a lipophilic matrix) is not recited in the rejected claims." (Ex. 1002 at 43.) Further, the examiner explained that the then-existing relevant claim limitation—"active ingredient is at least partly inglobated"—"does not limit the claim to 'active ingredient is dispersed in a lipophilic matrix' as alleged by the applicant." (Ex. 1002 at 43.)

In response, the applicants maintained that *Franco* taught a reservoir system, but that the claimed invention "relates to a 'multimatrix system' and not to a reservoir system." (Ex. 1002 at 31.) The applicants also amended their claims to state that the

active ingredient is dispersed in the lipophilic matrix and added a Markush group for both the inner lipophilic matrix and the outer hydrophilic matrix. (Ex. 1002 at 27.) Following an interview with the examiner, the claims were amended to require the 5-ASA to be dispersed in *both* the outer hydrophilic matrix and the lipophilic matrix. (Ex. 1002 at 8.) The claims were allowed and the '720 patent issued. (Ex. 1002 at 7.)

B. Claim Construction of Challenged Claims

A claim subject to IPR receives the "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b); *see In re Cuozzo Speed Techs., LLC*, No. 2014-1301, 2015 U.S. App. LEXIS 1699, at *21 (Fed. Cir. Feb. 4, 2015) ("We conclude that Congress implicitly adopted the broadest reasonable interpretation standard in enacting the AIA."). Unless otherwise noted below, Petitioner accepts, for purposes of IPR only, that the claim terms of the '720 patent are presumed to take on the ordinary and customary meaning that they would have to one of ordinary skill in the art.

1. "Controlled release"

The term "controlled release" means: "an oral pharmaceutical composition whereby the dissolution of active ingredient is not immediate." (Ex. 1037, Palmieri Decl. ¶ 20.)

2. "Matrix"

The term "matrix" means: "a macroscopically homogeneous structure in all its volume." (Ex. 1037, Palmieri Decl. ¶ 21; Ex. 1001 at 3:42–45.)

3. "Lipophilic"

The term "lipophilic" means: "having a poor affinity toward aqueous fluids." (Ex. 1037, Palmieri Decl. ¶ 22; *see* Ex. 1001 at 1:19–20; Ex. 1006 at 10.)

4. "Hydrophilic"

The term "hydrophilic" means: "having an affinity for water." (Ex. 1037, Palmieri Decl. ¶ 23; *see* Ex. 1001 at 1:17–26, 32–36; Ex. 1006 at 3, n.1.)

5. "Inner lipophilic matrix"

The term "inner lipophilic matrix" means: "a matrix with a matrix structure that exhibits lipophilic characteristics and is separate from the outer hydrophilic matrix." (Ex. 1001 at 1:17–20; Ex. 1037, Palmieri Decl. ¶ 24; *see* Ex. 1006 at 10–14.)

6. "Outer hydrophilic matrix"

The term "outer hydrophilic matrix" means: "a matrix with a matrix structure that exhibits hydrophilic characteristics and is separate from the inner lipophilic matrix." (Ex. 1001 at 1:21–26; Ex. 1037, Palmieri Decl. ¶ 25; *see* Ex. 1006 at 10–14.)

7. "Dispersed"

The term "dispersed" means: "sufficiently mixed to incorporate one substance with another." (Ex. 1037, Palmieri Decl. ¶ 26.)

8. "Wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix"

The term "wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix" means: "wherein the active ingredient is

sufficiently mixed in the matrices so as to be incorporated into both matrices." (Ex. 1037, Palmieri Decl. ¶ 27.)

9. "Consisting of substances selected from the group consisting of unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglycerid[e]s, waxes, ceramides, and cholesterol derivatives with melting points below 90° C." / "consists of compounds selected from the group consisting of polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, and nature or synthetic gums"

The terms "consisting of substances selected from the group consisting of …" and "consists of compounds selected from the group consisting of …" mean: "one or more" of the substances or compounds. (Ex. 1037, Palmieri Decl. ¶ 28.) Although "substances" and "compounds" are written in the plural form, the broadest reasonable interpretation of the terms also includes the singular form where, as here, the plural merely refers to a group of objects. *See, e.g.*, *Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286, 1307 (Fed. Cir. 2014) (holding that "the plural 'actions' may be reasonably read as at least one action per structure"); *Dayco Prods. v. Total Containment, Inc.*, 258 F.3d 1317, 1328 (Fed. Cir. 2001) (holding that "[i]n the phrase 'projections with recesses therebetweeen,' the use of the term 'recesses' can be understood to mean a single recess"); *Versa Corp. v. Ag-Bag Int'l Ltd.*, 392 F.3d 1325, 1330 (Fed. Cir. 2004) (holding that, "in context, the plural can describe a universe ranging from one to some higher number, rather than requiring more than one item" such that "the recitation of 'channels' does not mean a plurality of channel forming structures is

required."); *Allergan Sales, LLC v. Lupin Ltd.*, No. 2:11-cv-530, 2013 U.S. Dist. LEXIS 118433, at *45–47 (E.D. Tex. Aug. 20, 2013)("While the term 'effects' is undoubtedly a plural, here it refers to a group of possible side effects that might occur in a patient population. Nothing in the patent claims or specification requires that an individual experience a lessening of two or more side effects … The fact that the word 'effects' is plural does not require that there be a reduction in 'at least two' of these effects in a particular patient.").

C. Statement of Precise Relief Requested for Each Claim Challenged

1. Claims for Which Review is Requested

Petitioners request IPR under 35 U.S.C. § 311 of Claims 1–4 of the '720 patent, and cancellation of these four claims as unpatentable.

2. Statutory Grounds of Challenge

Petitioners request IPR of Claims 1–4 of the '720 patent in view of the following references, each of which is prior art to the '720 patent under 35 U.S.C. §§ 102(a) and (b) or 103. The Examiner did not reference any of the prior art listed in the following chart in any office action. Claims 1–4 are unpatentable under 35 U.S.C. § 103:

Ground	Proposed Rejections for the '720 Patent	Exhibit Number(s)
1	Claims 1–4 are obvious under 35 U.S.C. § 103(a) in view of U.S. Patent No. 3,965,256 to *Leslie et al.* (Ex. 1003) and the knowledge of a person of ordinary	1003

	skill in the art.	
2	Claims 1–4 are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 3,965,256 to *Leslie et al.* (Ex. 1003) in view of U.S. Patent No. 5,541,170 to *Rhodes et al.* (Ex. 1004).	1003, 1004
3	Claims 1–4 are obvious under 35 U.S.C. § 103(a) over EP 0 375 063 to *Groenendaal* (Ex. 1005) in view of U.S. Patent No. 3,965,256 to *Leslie et al.* (Ex. 1003).	1003, 1005

D. Overview of the State of the Art and Motivation to Combine

The introduction of sulfasalazine ("SASP") by Svartz in 1942 greatly facilitated the successful management of ulcerative colitis and other colonic and rectal ailments. (Ex. 1010 at 580–81, 589, 595–98.) Of SASP's two metabolites, 5-ASA was found to be the therapeutically active component, while the sulfapyridine moiety was linked to adverse side effects. (Ex. 1011 at 892–95; Ex. 1012 at 1499–502.) Administration of unbound or uncoated 5-ASA showed that it was readily absorbed in the upper intestine (jejunum), however, it was unable to reach the colon in therapeutic concentrations. (Ex. 1013 at 65; Ex. 1014 at 1–2.) This 5-ASA administration challenge spawned an ongoing research effort aimed at finding alternative 5-ASA delivery systems. (Ex. 1013 at 65–66.)

Prior to the '720 patent's July 14, 1999 foreign priority date, researchers had described several controlled-release pharmaceutical compositions comprising 5-ASA, many of which the FDA approved. One such composition—Asacol (Proctor & Gamble)—consists of a pellet of 5-ASA coated with Eudragit-S, a resin that dissolves at a pH >7, designed for release in the terminal ileum or colon. (Ex. 1015 at 407.) Three other similar delayed-release 5-ASA pellets—Claversa/Mesasal (Smith, Kline and French), Salofalk (Axcan Pharma, Falk Foundation), and Rowasa (Reid-Rowell)—were coated with Eudragit L100, a resin that dissolves at a pH >6 (the approximate pH of the ileum). (Ex. 1016 at 275.) Yet another 5-ASA composition—Pentasa (Marion-Merrell-Dow)—is a microsphere formulation consisting of 5-ASA microgranules enclosed within a semipermeable membrane of ethylcellulose. (Ex. 1017 at 1062–63; Ex. 1018 at 5:35–7:20.) Pentasa was designed for controlled release that begins in the duodenum and continues into the affected regions of the lower bowel. (Ex. 1017 at 1069–70; Ex. 1018 at 5:12–16, 11:23–12:3.) Additional 5-ASA controlled-release formulations are disclosed, for example, in Ex. 1014 at 1, 4–5, 11–13; Ex. 1039 at 1, 3–5; Ex. 1040 at 3; and Ex. 1018 at 2:4–25. (*See also* Ex. 1001 at 1:11–13.)

Patents and publications prior to the '720 patent priority date additionally acknowledged the disadvantages with the then-existing controlled release 5-ASA formulations, which included high production costs and required large amounts of excipients. (Ex. 1019 at 3:59–4:5.) Notably, the pH-dependent and time-dependent

drug delivery approaches disclosed in the prior art resulted in inconsistent delivery of 5-ASA to the colon, due to inter-patient variability in both pH and gastrointestinal tract length. (Ex. 1020 at 2:56–3:8, 3:44–46; Ex. 1004 at 1:16–19, 2:16–21.) Ordinarily skilled artisans would therefore have been motivated to create new 5-ASA controlled-release formulations to avoid these prior art disadvantages. (Ex. 1037, Palmieri Decl. ¶ 42.) *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007) (holding that "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed").

The use of matrices to formulate such controlled-release compositions was also well known before the '720 patent priority date. (Ex. 1021 at 1529; Ex. 1037, Palmieri Decl. ¶ 37.) Matrices were favored as controlled-release mechanisms because, *inter alia*, matrix-based compositions were inexpensive to manufacture. (Ex. 1021 at 1529; Ex. 1037, Palmieri Decl. ¶ 122.) Compositions utilizing lipophilic or hydrophilic matrices to control the release of 5-ASA were likewise described before the '720 patent priority date (*see, e.g.*, Ex. 1014 at 6–13; Ex. 1023 at 2:4–3:5, 3:36–4:58; Ex. 1024 at 2:18–4:10.), including compositions using more than one matrix (e.g., "dual matrix" compositions). (Ex. 1025 at 3:6–8 (using both a lipophilic and hydrophilic matrix); Ex. 1026 at 4:42–5:45, 7:4–10:23; Ex. 1037, Palmieri Decl. ¶¶ 39–40.) Some of these prior art "dual matrix" compositions included API in each matrix in order to control the release of an API in a two-stage progression. (Ex. 1023 at 2:4–15, 3:24–34; Ex. 1024 at 2:52–3:3; Ex. 1027 at 1:36–59.) In light of these disclosures, one of ordinary

skill in the art would have reasonably expected that the prior art matrices (lipophilic, hydrophilic, or both) could have been successfully utilized to control the delivery of 5-ASA. (Ex. 1037, Palmieri Decl. ¶ 41.) *See KSR Int'l Co.*, 550 U.S. at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

Before the '720 patent priority date, researchers understood that 5-ASA treats inflamed areas in the bowel by direct contact with the intestinal mucosal tissue. (Ex. 1014 at 1–2.) Consequently, it was also well known at the time that, to be effective in light of this mechanism of action, a 5-ASA oral composition must contain a high percentage, by weight, of API. (Ex. 1001 at 3:52–56; Ex. 1028 at 761–62.) The ordinarily skilled artisan would therefore have been "motivated to increase the content of 5-ASA" in such "formulations in order to improve the therapeutic activity of the composition." (Ex. 1037, Palmieri Decl. ¶ 142.) *See Commonwealth Sci. & Indus. Research Organisation v. Buffalo Tech. (USA), Inc.*, 542 F.3d 1363, 1375–76 (Fed. Cir. 2008) ("motivation to combine 'may also come from the nature of a problem to be solved, leading inventors to look to references relating to possible solutions to that problem'") (quoting *Pro-Mold Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996)).

In fact, researchers had already described compositions comprising a high content of 5-ASA before the '720 patent priority date. (*See, e.g.*, Ex. 1004 at 5:56–6:12;

Ex. 1019 at 5:53–57, 11:53–56, 16:5–27.) These successful formulations would have provided a skilled artisan with reasonable expectations that 5-ASA could have been successfully formulated at high dosage levels. (Ex. 1037, Palmieri Decl. ¶ 117.) *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 976 (Fed. Cir. 2014) (affirming invalidity for obviousness, and holding that "the expected properties of a claimed compound may be sufficient to lead to a reasonable expectation of success in modifying a prior art compound to make that claimed compound").

E. Level of Ordinary Skill in the Art

The level of ordinary skill in the art is apparent from the cited art. Further, a person having ordinary skill in the art (*also* "POSA") would "have either a Pharm. D. or a Ph.D. in pharmacy, pharmacology, or a related discipline; an M.D. with experience in using 5-amino salicylic acid (5-ASA);" "a BS in pharmacy with at least two years of experience formulating active pharmaceutical ingredients;" or "a Ph.D. in Pharmaceutics, Chemistry or a related field with 2–3 years of experience formulating active pharmaceutical ingredients, including controlled release formulations." (Ex. 1037, Palmieri Decl. ¶ 15.) A person of ordinary skill in the art "may work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others on the team, to solve a given problem. For example, a formulator, dissolution expert and a clinician may be part of the team." (*Id.*)

VI. DETAILED EXPLANATION OF THE CHALLENGE

A. Ground 1: Claims 1–4 of U.S. Patent No. 6,773,720 to Villa *et al.* are obvious under 35 U.S.C. § 103(a) in view of U.S. Patent No. 3,965,256 to Leslie *et al.*

The *Leslie* patent (Ex. 1003) issued in 1976, and thus is prior art to the '720 patent under 35 U.S.C. § 103(b). The Examiner did not consider *Leslie* during the '720 patent prosecution.

As discussed, one of ordinary skill in the art, aware of the deficiencies in the controlled-release 5-ASA compositions available before the '720 patent priority date, would have been motivated to formulate new 5-ASA compositions that remedied the prior art deficiencies discussed above. (*See* Part V-D, *infra*.) *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) ("'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.'") (quoting *KSR Int'l Co.*, 550 U.S. at 421). In the quest to formulate these new controlled-release 5-ASA compositions, it would have been obvious to one of ordinary skill in the art that producing 5-ASA according to the processes disclosed in U.S. Patent No. 3,965,256 (Ex. 1003, *Leslie*), could reasonably have been expected to produce the improved 5-ASA formulation of the '720 patent. *See Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1192 (Fed. Cir. 2014) ("A party asserting that a

patent is obvious must demonstrate…that the skilled artisan would have had a reasonable expectation of success from doing so.") (quotation omitted).

First, one of ordinary skill in the art would have looked to *Leslie* when seeking to improve 5-ASA formulations. *Leslie* discloses pharmaceutical compositions providing a "controlled slow release of one or more therapeutically active compounds." (Ex. 1003 at 1:9–10.) Because *Leslie* sought the same release control objectives that an ordinarily skilled artisan would have been motivated to achieve with respect to 5-ASA, one of ordinary skill in the art would have naturally looked to *Leslie* when seeking to improve 5-ASA formulations. *See In re Icon Health & Fitness, Inc.*, 496 F.3d 1374, 1380 (Fed. Cir. 2007) ("One skilled in the art would naturally look to prior art addressing the same problem as the invention at hand, and in this case would find an appropriate solution."). Additionally, *Leslie* expressly names the genus of "salicylate and acetyl-salicylate compounds" as preferred APIs for use according to the disclosed formulations. (Ex. 1003 at 8:42–43, 13:67.) One of ordinary skill in the art would have recognized that 5-ASA is a species of this preferred API genus, and thus would have had a reasonable expectation of success in applying the teachings from *Leslie* in the quest to formulate improved 5-ASA compositions. (*See, e.g.*, Ex. 1029 at 1298–300, 1301; Ex. 1030 at 7:12–16; Ex. 1037, Palmieri Decl. ¶¶ 62–70.) *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (finding obviousness where "the skilled artisan would have had that reasonable expectation of success that [application of the prior art technique] would work for its intended purpose.").

Leslie's teachings, applied to 5-ASA, disclose every element of the '720 patent claims. Specifically, the compositions disclosed in *Leslie* generally comprise an **API** and an **inner lipophilic matrix**—specifically a higher aliphatic alcohol such as **cetyl alcohol**, which is a "wax" (Ex. 1003 at 4:58)—combined with an **outer hydrophilic matrix** such as **hydroxyl-alkyl cellulose**. (*Id.* at 4:42.) *Leslie* teaches that the **API can be present in both the inner and the outer matrices**. (*Id.* at 4:63–5:8.) Additionally, *Leslie* discloses that these compositions are preferably **formulated into tablets** or capsules, and **optionally comprise other excipients such as diluents, binders, granulating aides**, colors, and flavoring materials. (*Id.* at 8:60–9:2.)

1. *Leslie* discloses an "inner lipophilic matrix," just as in Claim 1(a) of the '720 patent.

In *Leslie*, Examples 4 and 6 disclose compositions prepared using a nearly identical three-step procedure to those procedures disclosed in the '720 patent. As a first step, Examples 4 and 6 disclose melting cetyl alcohol—the lipophilic substance required by the '720 patent's Claim 1(a)—and mixing the API (Ex. 4: aminophylline; Ex. 6: papaverine hydrochloride) by stirring. (Ex. 1003 at 12:30–35, 13:28–31.) Higher aliphatic alcohols, such as cetyl alcohol, were well known at the time as lipophilic substances. (*See, e.g.*, Ex. 1031 at 5:49–60; Ex. 1037, Palmieri Decl. ¶ 77.) Claim 1 of the '720 patent requires that the lipophilic matrix comprise a substance selected from certain classes of chemical compounds, including waxes, with a melting point lower than 90°C. (Ex. 1001 at 6:10–15.) Cetyl alcohol is described in leading pharmaceutical

treatises as "waxy, white flakes, granules, cubes, or castings" with a melting point of 49°C. (Ex. 1032 at 99, 102; *see* Ex. 1037, Palmieri Decl. ¶¶ 78–80.) One of ordinary skill in the art also would have interpreted the term "waxes" to encompass cetyl alcohol. (*See* Ex. 1037, Palmieri Decl. ¶¶ 78–79; *see also* Part V-B, *infra*.) Patents and publications in the field of pharmaceutical formulation confirm that cetyl alcohol and other higher alcohols are considered a "wax" by others of skill in this field. (*See, e.g.*, Ex. 1034 at 2:46–56; Ex. 1035 at 3:50–57.) Because cetyl alcohol is a wax with a melting point of 49°C, it is a lipophilic substance within the Markush group of the '720 patent's Claim 1(a). (*See* Ex. 1037, Palmieri Decl. ¶¶ 77–79.)

"Leslie's disclosure of a wax—cetyl alcohol—meets Claim 1(a)'s properly-construed requirement of one or more lipophilic substances." (Ex. 1037, Palmieri Decl. ¶ 82.) However, even under a construction requiring at least two lipophilic substances, "it was both within the knowledge of and obvious to one of ordinary skill in the art at the time to combine multiple lipophilic delayed-release substances to achieve the target delayed-release profile." (Ex. 1037, Palmieri Decl. ¶ 83.) This is evident from a review of the relevant prior art. (Ex. 1037, Palmieri Decl. ¶ 84.) For example, Ex. 1023 (utilizing two waxes—castor wax and stearic acid—in Example 3), Ex. 1045 (utilizing two waxes—paraffin and castor oil—"to form a wax matrix" in Example 1), and Ex. 1027 (utilizing two waxes—glycerol monostearate or glycerol monopalmitate and beeswax—in Examples 3 and 4 and three waxes—cetyl alcohol, stearic acid, and glyceryl trilaurate—in Example 6) demonstrate the combination of

multiple lipophilic elements to achieve the target delayed-release profile.[1] (Ex. 1023 at 4:1–6; Ex. 1045 at 3:35–63; Ex. 1027 at 4:25–48, 4:66–5:14; 6:1–26; Ex. 1037, Palmieri Decl. ¶¶ 85, 88, 90.)

Leslie's Examples 4 and 6 further disclose as a second step, granulating the mixture of lipophilic substance and API, just as in the '720 patent's Claim 1(a). (Ex. 1003 at 12:30–35, 13:28–31.) Because neither example includes any additional excipients, "the matrix formed when the API is mixed with cetyl alcohol" and granulated as in Examples 4 and 6 would be "highly lipophilic." (Ex. 1003 at 12:30–35, 13:28–31; Ex. 1037, Palmieri Decl. ¶ 81.) Thus, *Leslie*'s Examples 4 and 6 teach the

[1] All lipophilic substances disclosed here have a melting point below 90°C , as required by Claim 1(a). "Castor wax, also known as hydrogenated castor oil, melts at 85–88°C." (Ex. 1037, Palmieri Decl. ¶ 86; Ex. 1032 at 82.) "Stearic acid has a melting point of approximately 54°C." (Ex. 1037, Palmieri Decl. ¶ 87; Ex. 1032 at 495.) "Paraffin congeals at 50–57°C, and typically melts by 68°C." (*See* Ex. 1032 at 327; Ex. 1037, Palmieri Decl. ¶ 89.) "Glycerol monostearate has a melting point of 55–60°C." (Ex. 1037, Palmieri Decl. ¶ 91; Ex. 1032 at 209.) "Beeswax, also known as white wax or yellow wax, has a melting point of 61–65°C." (Ex. 1037, Palmieri Decl. ¶ 92; Ex. 1032 at 558, 560.) "Glyceryl trilaurate has a melting point of 46.5°C." (Ex. 1037, Palmieri Decl. ¶ 93.)

"inner lipophilic matrix" according to '720 patent Claim 1(a). (Ex. 1037, Palmieri Decl. ¶¶ 94–95.)

2. *Leslie* discloses an "outer hydrophilic matrix," just as in Claim 1(b) of the '720 patent.

The next step in the '720 patent formulation procedure is mixing the 5-ASA-containing lipophilic matrix granules with a hydrophilic compound until homogenously dispersed. (Ex. 1001 at 4:17, 5:18, 5:41.) After sufficient homogenous mixing of the lipophilic matrix granules with the hydrophilic substance, the lipophilic matrix becomes dispersed within the hydrophilic matrix, thus forming the "outer hydrophilic matrix wherein the lipophilic matrix is dispersed" as in Claim 1(b). (*See, e.g.*, Ex. 1001 at 4:17, 5:18, 5:41; Ex. 1037, Palmieri Decl. ¶ 111.)

Leslie's Examples 4 and 6 similarly disclose as a next step, mixing the API-containing lipophilic matrix granules with a hydrophilic substance (hydroxy ethyl cellulose) until homogenously dispersed. (Ex. 1003 at 12:40–41, 13:34–36.) Hydroxy ethyl cellulose is a member of the "hydroxyalkyl celluloses" class of compounds contained in Claim 1(b)'s Markush group limitation. (*See* Ex. 1032 at 219; Ex. 1037, Palmieri Decl. ¶ 98.) *Leslie* further discloses several other hydroxyl alkyl celluloses for use in its compositions. (Ex. 1003 at 14:65–68.)

"*Leslie*'s disclosure of a hydroxyalkyl cellulose—hydroxyl ethyl cellulose—meets Claim 1(b)'s properly-construed requirement of one or more hydrophilic substances." (Ex. 1037, Palmieri Decl. ¶ 99.) However, even under a construction requiring at least

two hydrophilic substances, "[i]t was both within the knowledge of and obvious to one of ordinary skill in the art at the time to combine multiple hydrophilic delayed-release substances to achieve the target delayed-release profile." (Ex. 1037, Palmieri Decl. ¶ 100.) Specifically, an ordinarily skilled artisan "would have known to look to the Handbook of Pharmaceutical Excipients in determining which substances to use to achieve the target delayed-release profile." (Ex. 1037, Palmieri Decl. ¶ 101; *see* Ex. 1032.) This is evident from a review of the relevant prior art. (Ex. 1037, Palmieri Decl. ¶ 102.)

For example, Ex. 1043 discloses a "matrix tablet" for "colonic delivery" of APIs including "5-aminosalicylic acid," and cites the "*Handbook of [P]harmaceutical Excipients*" for the delayed-release matrix materials. (Ex. 1043 at 8:42, 52–53, 12:40, 53; Ex. 1037, Palmieri Decl. ¶¶ 103, 106.) Ex. 1043 further discloses utilizing numerous Claim 1(b) and other hydrophilic substances, including "*combinations of* pectin, calcium pectinate, microcrystalline starch, hydroxypropylmethylcellulose, lactose, starch, polyvinylpyrrolidone, microcrystalline cellulose, calcium phosphate, guar gum, and normal pharmaceutical additives and excipients," and also "teaches release profiles for numerous examples including *both* Eudragit—a polymer of methacrylic acid—and pectins." (Ex. 1043 at 8:47–52, 12:40, 12:53, 14:65–15:31, 18:24–51 (emphasis added); Ex. 1037, Palmieri Decl. ¶¶ 104–05 (emphasis added); *see also* Ex. 1032 at 61–62, 84–87, 215–16, 229–32, 252–61, 362–66, 392–99, 483–88.) As another example, Ex. 1044 discloses a targeted-release profile "outer tablet comprising

a first dose of active ingredient … dispersed in a pH independent hydrophilic polymer matrix" where "[p]olymer materials, lubricants and optional materials among those useful in the matrix are described in Handbook of Pharmaceutical Excipients (1986), incorporated by reference herein." (Ex. 1044 at pg. 3:22–23, pg. 4:18–19; Ex. 1037, Palmieri Decl. ¶¶ 107, 109.) Ex. 1044 further discloses utilizing numerous Claim 1(b) and other hydrophilic substances, including "cellulose ethers, polyvinylpyrrolidone, mixtures of natural hydrophilic gums (such as guar gum, gum Karaya, gum tragacanth, and xanthan gum), *and mixtures thereof*. Preferred are hydroxypropylmethylcellulose and *mixtures of two or more* cellulose ethers selected from the group consisting of methylcellulose, carboxypropylcellulose, hydroxypropylcellulose, and sodium carboxymethylcellulose and mixtures thereof." (Ex. 1044 at pg. 4:20–24 (emphasis added); Ex. 1037, Palmieri Decl. ¶ 108.)

Like the '720 patent, *Leslie* teaches mixing to yield a lipophilic matrix "dispersed" within the hydrophilic matrix. For instance, *Leslie*'s Example 4 teaches to "incorporate" the lipophilic granules in the hydrophilic substance by blending for three hours. (Ex. 1003 at 12:40–41.) *Leslie*'s Example 6 instructs to blend the lipophilic granules with the hydrophilic substance and "mix well." (Ex. 1003 at 13:34–36.) Other examples from *Leslie* confirm homogeneous dispersal of a lipophilic matrix (e.g., Ex. 1: "well blended"; Ex. 2: "uniform granular mass"; Ex. 5: "uniform granule blend"). (Ex. 1003 at 10:42, 11:27, 12:63.) Thus, as in the '720 patent, *Leslie* teaches forming an "outer hydrophilic matrix wherein the lipophilic matrix is dispersed" by

thoroughly mixing the API-containing lipophilic matrix granules with a hydrophilic substance. As a result, the compositions formed in at least *Leslie*'s Examples 4 and 6 disclose an "outer hydrophilic matrix" that meets all limitations of the '720 patent's Claim 1(b).

3. *Leslie* discloses oral pharmaceutical compositions comprising "optionally other excipients," just as in Claim 1(c) of the '720 patent.

Although the addition of "other excipients" to a pharmaceutical composition—as the '720 patent requires—was conventional and well known by those of ordinary skill in the art, *Leslie* also discloses several oral pharmaceutical compositions comprising "optionally other excipients." (Ex. 1037, Palmieri Decl. ¶¶ 112–13.) For instance, Example 4 discloses a composition comprising tablet lubricant excipients, and Example 6 discloses a composition comprising talc as an excipient. (Ex. 1003 at 12:26, 12:45–47, 13:24.) *Leslie*'s specification also generally teaches preparation of tablets using inert diluents, tablet binders, granulating aides, colors, and flavoring materials in the finished formulation. (*Id.* at 8:60–9:6.) Thus *Leslie* expressly discloses "optionally other excipients" as required by Claim 1(c) of the '720 patent.

4. *Leslie* discloses oral pharmaceutical compositions comprising API in the amount of 80 to 95% by weight of the total composition, just as in Claim 1(d) of the '720 patent.

Leslie discloses compositions comprising API "present in an amount of 80 to 95% by weight of the total composition," as the '720 patent's Claim 1 requires. (Ex. 1001 at 6:27–28.) For example, *Leslie* discloses a composition comprising 82% by

weight of API potassium chloride. (Ex. 1003 at 12:50–54.) *Leslie* additionally discloses as a typical composition produced according to its disclosure, "Formula A," which has a potassium chloride content of 80% by weight. (*Id.* at 5:15–19.) *Leslie* also discloses compositions that comprise other API at high dosages, including highly insoluble APIs such as papaverine hydrochloride at 75% by weight of the total composition. (*Id.* at 13:20–40; *see* Ex. 1022 at 1679.) *Leslie* further discloses that neither the API nor the dosage to be incorporated into the disclosed compositions is critical to the invention. (Ex. 1003 at 8:37–40, 8:53–59.) As such, one of ordinary skill in the art would have expected that the compositions taught in *Leslie* would be suitable for API formulations that required high dosage amounts. (Ex. 1037, Palmieri Decl. ¶ 114.) Indeed, one of ordinary skill in the art would have particularly expected 5-ASA, as a member of the preferred API genus of "salicylate and acetyl-salicylate compounds" disclosed in *Leslie*, could have been successfully formulated according to *Leslie*'s disclosure with API amounts between 80 and 95% by weight of the total composition. (*See* Ex. 1037, Palmieri Decl. ¶¶ 114–21.) *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.")

5. *Leslie* discloses oral pharmaceutical compositions comprising API dispersed in both the lipophilic matrix and the hydrophilic matrix, just as in elements (a) and (e) of the '720 patent's Claim 1.

The '720 patent does not provide an example of a composition comprising an active ingredient that is separately "dispersed both in the lipophilic matrix and in the

hydrophilic matrix." (Ex. 1001 at 6:28–31.) The specification states that "[p]art of mesalazine can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix." (Ex. 1001 at 3:34–39.)

Examples 4 and 6 of *Leslie*, as previously discussed, disclose a composition comprising an inner lipophilic matrix and an outer hydrophilic matrix that meet the limitations of the '720 patent's Claim 1. *Leslie*'s Examples 4 and 6 introduce API into the lipophilic matrix portion of the composition, as do all of examples of the '720 patent. Although Examples 4 and 6 do not require mixing an API with hydrophilic substances such that the API is dispersed in both matrices, the specification of *Leslie* teaches this variation:

> The active therapeutic compound intended for therapy may be incorporated in the higher alcohol before this is blended with the hydrated hydroxy-alkyl cellulose, or it may be incorporated in the hydrated hydroxy-alkyl cellulose, before it is incorporated with the higher alcohol ***or divided among both agents***. The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend. Each method of adding the active ingredient has its own particular advantages for use in the manufacture of a particular dosage form.

(Ex. 1003 at 4:63–5:8 (emphasis added).)

Thus, *Leslie* explicitly teaches compositions where the API is incorporated with the higher alcohol lipophilic matrix, the hydrated hydroxy-alkyl cellulose hydrophilic matrix, or divided among both matrices, as the '720 patent's Claim 1 requires. *Leslie*'s Example 7 expressly teaches that the API of Example 1 can be "added to the alcohol component or the cellulose component or divided between the two." (Ex. 1003 at 13:43–50.) *Leslie* also provides working examples of compositions formulated by blending an API directly with a hydrophilic substance. (*See, e.g.*, Ex. 1003 at 5:20–28.)

Viewing *Leslie*'s teachings as a whole, one of ordinary skill in the art would have appreciated that all of the compositions taught in *Leslie* could have been readily formulated to include a salicylate API in either or both matrices. (Ex. 1037, Palmieri Decl. ¶ 94.) In particular, one of ordinary skill in the art would have recognized that *Leslie*'s Examples 4 and 6 could have been easily formulated (as taught in Example 7) to include API blending with the hydrophilic substance directly, thus producing a composition in which the API is dispersed in both the lipophilic and the hydrophilic matrices. (Ex. 1037, Palmieri Decl. ¶¶ 94–98, 110–11.) *See Boston Sci. Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 991 (Fed. Cir. 2009) (reversing jury verdict of nonobviousness based on a reference where "all of the limitations are found in two separate embodiments pictured side by side in the patent, not in one embodiment," because "'[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.' … Combining two embodiments disclosed adjacent to each other in a prior art patent does not require a leap of inventiveness.") (quoting

KSR, 550 U.S. at 417). Thus, in light of the teachings of *Leslie* as a whole, it would have been obvious to formulate a composition having a salicylate dispersed in both the lipophilic and hydrophilic matrices. (Ex. 1037, Palmieri Decl. ¶¶ 94–98, 110–11.)

6. Dependent Claims 2–4 introduce claim limitations previously disclosed in *Leslie*.

The '720 patent Claim 1 pharmaceutical composition would have been obvious to one of ordinary skill in the art over the teachings of *Leslie*, as discussed. Claims 2–4 depend on this obvious Claim 1 pharmaceutical composition. None of dependent Claims 2–4 introduce claim limitations sufficient to distinguish *Leslie*, so Claims 2–4 of the '720 patent would also have been obvious to one of ordinary skill in the art.

Claim 2 of the '720 patent discloses the compositions of Claim 1 with the added limitation that the 5-ASA is dispersed in a molten lipophilic matrix by kneading, extrusion and/or granulation. (Ex. 1001 at 6:31–33.) This limitation is insufficient to distinguish the compositions of *Leslie* from the compositions of the '720 patent's Claim 2. Specifically, Examples 4 and 6 of *Leslie* similarly disclose formation of a lipophilic matrix by granulating the mixture of an API and molten cetyl alcohol. (Ex. 1003 at 12:30–35, 13:28–31.) Therefore, *Leslie* teaches all of the added limitations of Claim 2, such that Claim 2 is obvious for the same reasons as for Claim 1, discussed above.

Claim 3 of the '720 patent discloses the compositions of Claim 1 with the added limitation that the compositions are "in the form of tablets, capsules, [or]

mintablets (sic)." (Ex. 1001 at 6:35–36.) This limitation is insufficient to distinguish the compositions of *Leslie* from the compositions of the '720 patent's Claim 3. Specifically, Examples 4 and 6 of *Leslie* similarly disclose compositions formed by a final step of compressing into tablets or filling gelatin capsules. (Ex. 1003 at 12:45–47, 13:39–40.) Therefore, *Leslie* teaches all of the added limitations of Claim 3, such that Claim 3 is obvious for the same reasons as for Claim 1, discussed above.

Claim 4 of the '720 patent discloses a process for preparing the compositions of Claim 1. The claimed process steps include (1) melt granulation of a portion of the API with lipophilic excipients having melting points lower than 90°C, (2) mixing these granules with hydrophilic excipients, and (3) tabletting or compression. (Ex. 1001 at 6:39–43.) As explained with respect to Claims 1–3 above, the compositions described in Examples 4 and 6 of *Leslie* are also prepared using these process steps. Specifically, *Leslie* first melts cetyl alcohol—having a melting point of 49°C—with the API, and then granulates the mixture. (Ex. 1003 at 12:30–35, 13:28–31.) The granules formed from this step are then mixed with hydrated ethyl cellulose in both Examples 4 and 6. (*Id.* at 12:36–39, 13:34–36.) Finally, this mixture is dried and compressed into tablets. (*Id.* at 12:45–47, 13:39–40.) Therefore, the process disclosed in Claim 4 of the '720 patent is also obvious to one of ordinary skill in the art over the teachings of *Leslie*.

7. Claim Chart for Ground 1 showing exemplary citations in *Leslie*.

Element	Prior Art of US 3,965,256 to Leslie *et al.*
Claim 1 pre. Controlled-release	*Leslie* teaches controlled-release oral pharmaceutical

oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid	compositions: Ex. 1003 at 1:9–10 ("controlled slow release of one or more therapeutically active compounds"); *see also* *Id.* at Abstract, 1:17–18 ("pharmaceutical dosage forms intended for oral administration"); *see also* *Id.* at 3:37–42 ("According to the present invention, when a higher aliphatic alcohol is combined with an hydrated hydroxy-alkyl cellulose compound in critical proportions of one to the other, a particularly advantageous composition is formed which delays the release of a therapeutically active compound therefrom."); *see also* *Id.* at 3:9–13 ("The presence of varying amounts of water" in the digestive system "has been demonstrated to be the basis for virtually all of the inherent limitations of the conventional sustained acting tablet and capsule dosage forms."); *see also* *Id.* at 15:10 ("A slow release pharmaceutical tablet"). *Leslie* teaches active ingredients "salicylate and acetyl salicylate compounds": Ex. 1003 at 8:37–43 ("Both the pharmacologic nature of the active therapeutic ingredient and the dosage to be incorporated into the present sustained slow release composition, are not critical to the present invention. Examples of such pharmacologically active ingredients are … salicylate and acetyl-salicylate compounds"); *see also* *Id.* at 13:62–67 ("The following examples of pharmacologically active compounds are particularly suitable for administration to human and animals in the form of slow release medications: … salicylate and acetyl-salicylate compounds"); *see also* Ex. 1037, Palmieri Decl. ¶¶ 61–73.
1a. an inner lipophilic matrix consisting of substances selected from the group consisting of	*Leslie* teaches an inner lipophilic matrix consisting of at least a wax with a melting point below 90° C: Ex. 1003 at 12:30–35 ("Step 1: Melt the cetyl alcohol in a water jacketed tank. Hold the cetyl alcohol melt at 60°–70°C and incorporate with stirring the aminophylline. Granulate the resultant mass through a No. 16 standard mesh sieve. Harden

unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglyceride[e]s, waxes, ceramides, and cholesterol derivatives with melting points below 90° C., and wherein the active ingredient is dispersed both in said the lipophilic matrix and in the hydrophilic matrix;	the granules by drying at room temperature."); *see also* *Id.* at 13:28–31 ("Step 1: Melt the cetyl alcohol in a jacketed vessel and incorporate the papaverine hydrochloride, blend well and granulate through a No. 16 standard mesh sieve. Dry at room temperature."); *see also* Ex. 1037, Palmieri Decl. ¶¶ 77–93. *Leslie* also teaches the active ingredient is dispersed both in said the lipophilic matrix and in the hydrophilic matrix: Ex. 1003 at 4:63–5:7 ("The active therapeutic compound intended for therapy may be incorporated in the higher alcohol before this is blended with the hydrated hydroxy-alkyl cellulose, or it may be incorporated in the hydrated hydroxy-alkyl cellulose, before it is incorporated with the higher alcohol or divided among both agents. The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend. Each method of adding the active ingredient has its own particular advantages for use in the manufacture of a particular dosage form."); *see also* *Id.* at 13:43–50 ("When it is desired to incorporate a pharmacologically active compound with the slow release composition of Example 1 above, then said active agent may be added to the alcohol component or the cellulose component or divided between the two."); *see also* Ex. 1037, Palmieri Decl. ¶¶ 94–98, 110–11.
1b. an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of compounds selected from the group consisting of polymers or	*Leslie* teaches an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of at least a hydroxyalkyl cellulose: Ex. 1003 at 1:12–19 ("a combination of a higher aliphatic alcohol and a hydrated hydroxy-alkyl cellulose … in pharmaceutical dosage forms intended for oral administration, to provide a slow release of a therapeutically active compound"); *see also* *Id.* at 4:41–44 ("The hydroxy-alkyl cellulose preferred in practice is hydroxyethyl cellulose although the analogous, methyl and

copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, and natural or synthetic gums;	propyl cellulose derivatives are satisfactory."); *see also* *Id.* at 12:36–41 ("Step 2: Hydrate the hydroxy ethyl cellulose in a suitable vessel fitted with a mixer using two and one half volumes of water for each part by weight of hydroxy ethyl cellulose. Step 3: Incorporate the blend from Step 1. Total blending time three hours"); *see also* *Id.* at 13:32–36 ("Step 2: Hydrate the hydroxy ethyl cellulose with 15 gm of water. Step 3: Blend the granules obtained as a result of Step 1 with the hydrated cellulose component of Step 2 and mix well"); *see also* Ex. 1037, Palmieri Decl. ¶¶ 98–111.
1c. optionally other excipients;	*Leslie* teaches optionally other excipients: Ex. 1003 at 4:68–5:4 ("The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend."); *see also* *Id.* at 12:45–47 ("Step 5: Add tablet lubricant and compress into tablets of suitable size and shape or fill into appropriate gelatin capsules"); *see also* *Id.* at 4:68–5:4 ("The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend."); *see also* *Id.* at 8:62–66 ("When it is desired to prepare tablets containing the slow release composition, then it is preferred to utilize an inert diluent such as lactose or talc, to achieve the appropriate concentration of slow release composition within said unit dosage form."); *see also* *Id.* at 12:53 ("EXAMPLE 5" lists "Talc 1.50 gms.").
1d. wherein the active ingredient is present in an amount of 80 to	*Leslie* teaches an active ingredient is present in an amount of 80 to 95% by weight of the total composition: Ex. 1003 at 12:46–54 (listing the material for Example 5 as:

95% by weight of the total composition, and	Cetyl Alcohol 14.00 gms. Potassium Chloride 82.00 gms. Hydroxy Ethyl Cellulose 4.50 gms. Talc 1.50 gms.); *see also* *Id.* at 14:13, 23–36 ("To prepare the appropriate slow release unit dosage form containing the above described pharmacologically active ingredient [including at least one salicylate], any member of the classes of therapeutically active compounds and the particular pharmacologically active compound set forth above may be blended with an appropriate quantity of the composition of Claim 1. To this mixture is added an appropriate quantity of diluent to provide the predetermined concentration of from 20 percent to 30 percent by weight of the weight of the slow release composition… The manufacturing procedures described in Examples 1 through 6 may be utilized."); *see also* *Id.* at 13:21–24 (Example 6 lists ingredients as follows: Cetyl Alcohol 10 gm. Hydroxy Ethyl Cellulose 5 gm. Papaverine Hydrochloride 75 gm. Talc 10 gm.); *see also* Ex. 1037, Palmieri Decl. ¶¶ 114–21.
1e. wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.	*Leslie* teaches the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix: Ex. 1003 at 4:63–5:7 ("The active therapeutic compound intended for therapy may be incorporated in the higher alcohol before this is blended with the hydrated hydroxy-alkyl cellulose, or it may be incorporated in the hydrated hydroxy-alkyl cellulose, before it is incorporated with the higher alcohol or divided among both agents. The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend. Each method of adding the active ingredient has its own particular advantages for use in the manufacture of a particular dosage form."); *see also* *Id.* at 13:43–50 ("When it is desired to incorporate a

	pharmacologically active compound with the slow release composition of Example 1 above, then said active agent may be added to the alcohol component or the cellulose component or divided between the two.").
Claim 2. Compositions as claimed in claim 1, wherein 5-aminosalicylic acid is dispersed in a molten lipophilic matrix by kneading, extrusion and/or granulation.	*Leslie* teaches the compositions of Claim 1, wherein 5-amino salicylic acid is dispersed in a molten lipophilic matrix by at least granulation: Ex. 1003 at 12:30–35 ("Melt the cetyl alcohol in a water jacketed tank. Hold the cetyl alcohol melt at 60°–70°C and incorporate with stirring the aminophylline. Granulate the resultant mass through a No. 16 standard mesh sieve. Harden the granules by drying at room temperature."); *see also* *Id.* at 13:28–31 ("Melt the cetyl alcohol in a jacketed vessel and incorporate the papaverine hydrochloride, blend well and granulate through a No. 16 standard mesh sieve. Dry at room temperature.").
Claim 3. Compositions as claimed in claim 1, in the form of tablets, capsules, mintablets.	*Leslie* teaches the compositions of Claim 1 in the form of at least tablets and capsules: Ex. 1003 at 12:45–47 ("Add tablet lubricant and compress into tablets of suitable size and shape or fill into appropriate gelatin capsules."); *see also* *Id.* at 13:39–40 ("Compress into tablets of suitable size and shape.").
Claim 4a. A process for the preparation of the compositions of claim 1, which comprises: melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower	*Leslie* teaches a process for the preparation of the compositions of Claim 1 which comprises melt granulation of at least one portion of the active ingredient with the lipophilic excipients with a melting point lower than 90° C: Ex. 1003 at 12:30–35 ("Melt the cetyl alcohol in a water jacketed tank. Hold the cetyl alcohol melt at 60°–70°C and incorporate with stirring the aminophylline. Granulate the resultant mass through a No. 16 standard mesh sieve. Harden the granules by drying at room temperature."); *see also* *Id.* at 13:28–31 ("Melt the cetyl alcohol in a jacketed vessel and incorporate the papaverine hydrochloride, blend well and granulate through a No. 16 standard mesh sieve. Dry at room

than 90° C.;	temperature."); *see also* Ex. 1037, Palmieri Decl. ¶ 80.
4b. mixing the granules from step a) with the hydrophilic excipients and	*Leslie* teaches mixing the granules from step a) with the hydrophilic excipients: Ex. 1003 at 12:36–41 ("Step 2: Hydrate the hydroxy ethyl cellulose in a suitable vessel fitted with a mixer using two and one half volumes of water for each part by weight of hydroxy ethyl cellulose. Step 3: Incorporate the blend from Step 1. Total blending time three hours"); *see also* *Id.* at 13:32–36 ("Step 2: Hydrate the hydroxy ethyl cellulose with 15 gm of water. Step 3: Blend the granules obtained as a result of Step 1 with the hydrated cellulose component of Step 2 and mix well").
4c. subsequent tabletting or compression.	*Leslie* teaches subsequent tableting or compression: Ex. 1003 at 12:45–47 ("Add tablet lubricant and compress into tablets of suitable size and shape or fill into appropriate gelatin capsules."); *see also* *Id.* at 13:39–40 ("Compress into tablets of suitable size and shape.").

B. Ground 2: Claims 1–4 of U.S. Patent No. 6,773,720 to Villa *et al.* are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 3,965,256 to Leslie *et al.* in further view U.S. Patent No. 5,541,170 to Rhodes *et al.*

The *Rhodes* patent (Ex. 1004) issued in 1996, and thus is prior art to the '720 patent under 35 U.S.C. § 103(b). The Examiner did not consider *Rhodes* during the '720 patent prosecution.

Rhodes discloses successful clinical results from treating patients with high concentrations of 5-ASA. (*See* Ex. 1004 at Table I.) Specifically, *Rhodes* discloses compositions having a high content of 5-ASA, such as the composition in Example 5

containing just under 83% API by weight of the total composition. (Ex. 1004 at 5:56–6:12.)

As discussed previously, "[b]y the time of the '720 patent priority date, one of ordinary skill in the art would have recognized the deficiencies of pH-dependent controlled release compositions—which included inconsistent delivery to the colon due to intra-patient intestinal pH variability." (*See, e.g.,* Ex. 1020 at 2:56–3:8, 3:44–46; Ex. 1037, Palmieri Decl. ¶ 129.) Thus, one of ordinary skill in the art would have been motivated to create compositions with the high 5-ASA content of *Rhodes*' demonstrated successful clinical results, with the formulation of *Leslie* which is not dependent on pH for efficient delivery to the colon. (Ex. 1037, Palmieri Decl. ¶¶ 127, 129.) *See Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006) ("The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.").

In looking to so improve the *Rhodes* 5-ASA compositions, one of ordinary skill in the art would have been motivated to look to *Leslie*. (Ex. 1037, Palmieri Decl. ¶ 130.) *Leslie* teaches a matrix system that efficiently controls release of high-dose API compositions, including APIs with low solubility such as papaverine hydrochloride. (*See, e.g.* Ex. 1003 at 13:20–40; Ex. 1022 at 1679; Ex. 1037, Palmieri Decl. ¶¶ 118–19, 130.) *Leslie* further sought to overcome inherent deficiencies in the uniform release of APIs over an extended period of time due to unpredictable pH levels encountered in

the digestive system because of "[t]he presence of varying amounts of water" in the digestive system which "has been demonstrated to be the basis for virtually all of the inherent limitations of the conventional sustained acting tablet and capsule dosage forms." (Ex. 1003 at 3:9–13; Ex. 1037, Palmieri Decl. ¶ 131.)

"[B]ecause both *Rhodes* and *Leslie* sought the same release control objectives that one of ordinary skill in the art would have been motivated to achieve with respect to high-dose 5-ASA, one of ordinary skill in the art would have naturally looked to both *Rhodes* and *Leslie* when seeking to improve 5-ASA formulations." (Ex. 1037, Palmieri Decl. ¶ 132.) *See In re Icon Health & Fitness, Inc.*, 496 F.3d at 1380; *KSR Int'l Co.*, 550 U.S. at 417; *In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007) (holding that "[i]t was not unreasonable for one skilled in the art of snake venom to consider that a Fab fragment of a whole antibody that neutralizes one type of venom might be used to neutralize the venom of another species.").

Finally, *Leslie* expressly names the genus of "salicylate and acetyl-salicylate compounds" as preferred APIs for use according to its disclosed formulations. (Ex. 1003 at 8:42–43, 13:67.) "One of ordinary skill in the art would have recognized that the 5-ASA of *Rhodes* was a species of the preferred API genus, and thus would have been further motivated to apply *Leslie*'s teachings to formulate high dose 5-ASA compositions" that are pH-independent. (Ex. 1037, Palmieri Decl. ¶ 133; *see, e.g.*, Ex. 1029 at 1298–300, 1301; Ex. 1030 at 7:12–16.)

As previously discussed in part VI-A, it would have been obvious to one of ordinary skill in the art to combine the knowledge of the skill in the art with the teachings of *Leslie* to arrive at the composition of Claim 1. (Ex. 1037, Palmieri Decl. ¶¶ 59, 134.) Further combining the matrix formulations disclosed in *Leslie* with the high-dose compositions of 5-ASA disclosed in *Rhodes* explicitly teaches each element of the '720 patent's Claims 1–4. "[S]ince one of ordinary skill in the art would have been motivated to combine *Rhodes* and *Leslie* before the '720 patent priority date, and further would have had a reasonable expectation of success in doing so, Claims 1–4 of the '720 patent would have been obvious to one of ordinary skill in the art." (Ex. 1037, Palmieri Decl. ¶ 135.) *See Osram Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706 (Fed. Cir. 2012) ("Generally, a party seeking to invalidate a patent as obvious must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.") (quotation omitted).

1. Claim Chart for Ground 2 showing exemplary citations in *Leslie* and *Rhodes*.

Element	Prior Art of US 3,965,256 to Leslie *et al.* and U.S. Patent 5,541,170 to Rhodes *et al.*
Claim 1 pre. Controlled-release oral pharmaceutical compositions containing as an active ingredient 5-	*Leslie* teaches controlled-release oral pharmaceutical compositions: Ex. 1003 at 1:9–10. ("controlled slow release of one or more therapeutically active compounds"); *see also* *Id.* at Abstract, 1:17–18 ("pharmaceutical dosage forms intended

amino-salicylic acid	for oral administration"); *see also* *Id.* at 3:37–42 ("According to the present invention, when a higher aliphatic alcohol is combined with an hydrated hydroxy-alkyl cellulose compound in critical proportions of one to the other, a particularly advantageous composition is formed which delays the release of a therapeutically active compound therefrom."); *see also* *Id.* at 3:9–13 ("The presence of varying amounts of water" in the digestive system "has been demonstrated to be the basis for virtually all of the inherent limitations of the conventional sustained acting tablet and capsule dosage forms."); *see also* *Id.* at 15:10 ("A slow release pharmaceutical tablet"). *Leslie* also teaches active ingredients of "salicylate and acetyl salicylate compounds": Ex. 1003 at 8:37–43 ("Both the pharmacologic nature of the active therapeutic ingredient and the dosage to be incorporated into the present sustained slow release composition, are not critical to the present invention. Examples of such pharmacologically active ingredients are … salicylate and acetyl-salicylate compounds"); *see also* *Id.* at 3:9–13 ("The presence of varying amounts of water" in the digestive system "has been demonstrated to be the basis for virtually all of the inherent limitations of the conventional sustained acting tablet and capsule dosage forms."); *see also* *Id.* at 13:62–67 ("The following examples of pharmacologically active compounds are particularly suitable for administration to human and animals in the form of slow release medications: … salicylate and acetyl-salicylate compounds"); *see also* Ex. 1037, Palmieri Decl. ¶¶ 61–73. *Rhodes* also teaches controlled release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid: Ex. 1004 at Abstract ("A solid dosage form, such as a capsule or tablet, containing a pharmacologically active agent … in a

	sufficient amount that the oral dosage form remains intact until it reaches the colon. … The invention has particular application to dosage forms of … especially, 5-amino-salicylic acid,"); *see also* *Id.* at 1:11–17 ("The present invention relates to the administration of pharmacologically active agents to the large intestine and provides an orally administrable pharmaceutical composition for said purpose. It has particular, but not exclusive, application to the administration of 5-amino-salicylic acid (hereinafter referred to as 5-ASA) for the treatment of colonic or rectal disorders.").
1a. an inner lipophilic matrix consisting of substances selected from the group consisting of unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglyceride[e]s, waxes, ceramides, and cholesterol derivatives with melting points below 90° C., and wherein the active ingredient is dispersed both in said the lipophilic matrix and in the hydrophilic matrix;	*Leslie* teaches an inner lipophilic matrix consisting of at least a wax with a melting point below 90° C: Ex. 1003 at 12:30–35 ("Step 1: Melt the cetyl alcohol in a water jacketed tank. Hold the cetyl alcohol melt at 60°–70°C and incorporate with stirring the aminophylline. Granulate the resultant mass through a No. 16 standard mesh sieve. Harden the granules by drying at room temperature"); *see also* *Id.* at 13:28–31 ("Step 1: Melt the cetyl alcohol in a jacketed vessel and incorporate the papaverine hydrochloride, blend well and granulate through a No. 16 standard mesh sieve. Dry at room temperature"); *see also* Ex. 1037, Palmieri Decl. ¶¶ 77–93. *Leslie* also teaches the active ingredient may be dispersed both in said the lipophilic matrix and in the hydrophilic matrix: Ex. 1003 at 4:63–5:7 ("The active therapeutic compound intended for therapy may be incorporated in the higher alcohol before this is blended with the hydrated hydroxy-alkyl cellulose, or it may be incorporated in the hydrated hydroxy-alkyl cellulose, before it is incorporated with the higher alcohol or divided among both agents. The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend. Each method of adding the active ingredient has its own particular advantages for use in the manufacture of a particular

	dosage form."); *see also* *Id.* at 13:43–50 ("When it is desired to incorporate a pharmacologically active compound with the slow release composition of Example 1 above, then said active agent may be added to the alcohol component or the cellulose component or divided between the two."); *see also* Ex. 1037, Palmieri Decl. ¶¶ 94–98, 110–11.
1b. an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of compounds selected from the group consisting of polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, and natural or synthetic gums;	*Leslie* teaches an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of at least a hydroxyalkyl cellulose: Ex. 1003 at 1:12–19 ("a combination of a higher aliphatic alcohol and a hydrated hydroxy-alkyl cellulose … in pharmaceutical dosage forms intended for oral administration, to provide a slow release of a therapeutically active compound"); *see also* *Id.* at 4:41–44 ("The hydroxy-alkyl cellulose preferred in practice is hydroxyethyl cellulose although the analogous, methyl and propyl cellulose derivatives are satisfactory."); *see also* *Id.* at 12:36–41 ("Step 2: Hydrate the hydroxy ethyl cellulose in a suitable vessel fitted with a mixer using two and one half volumes of water for each part by weight of hydroxy ethyl cellulose. Step 3: Incorporate the blend from Step 1. Total blending time three hours"); *see also* *Id.* at 13:32–36 ("Step 2: Hydrate the hydroxy ethyl cellulose with 15 gm of water. Step 3: Blend the granules obtained as a result of Step 1 with the hydrated cellulose component of Step 2 and mix well"); *see also* Ex. 1037, Palmieri Decl. ¶¶ 98–111.
1c. optionally other excipients;	*Leslie* teaches optionally other excipients: Ex. 1003 at 4:68–5:4 ("The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the

	blend."); *see also* *Id.* at 12:45–47 ("Step 5: Add tablet lubricant and compress into tablets of suitable size and shape or fill into appropriate gelatin capsules"); *see also* *Id.* at 4:68–5:4 ("The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend."); *see also* *Id.* at 8:62–66 ("When it is desired to prepare tablets containing the slow release composition, then it is preferred to utilize an inert diluent such as lactose or talc, to achieve the appropriate concentration of slow release composition within said unit dosage form."); *see also* *Id.* at 12:53 ("EXAMPLE 5" lists "Talc 1.50 gms.").
1d. wherein the active ingredient is present in an amount of 80 to 95% by weight of the total composition, and	*Leslie* teaches an active ingredient is present in an amount of 80 to 95% by weight of the total composition: Ex. 1003 at 12:46–54 (listing the material for Example 5 as: Cetyl Alcohol 14.00 gms. Potassium Chloride 82.00 gms. Hydroxy Ethyl Cellulose 4.50 gms. Talc 1.50 gms.); *see also* *Id.* at 14:13, 23–36 ("To prepare the appropriate slow release unit dosage form containing the above described pharmacologically active ingredient [including at least one salicylate], any member of the classes of therapeutically active compounds and the particular pharmacologically active compound set forth above may be blended with an appropriate quantity of the composition of Claim 1. To this mixture is added an appropriate quantity of diluent to provide the predetermined concentration of from 20 percent to 30 percent by weight of the weight of the slow release composition… The manufacturing procedures described in Examples 1 through 6 may be utilized."); *see also* Ex. 1037, Palmieri Decl. ¶¶ 114–21.

	Rhodes also teaches the active ingredient is present in an amount of 80 to 95% by weight of the total composition: Ex. 1004 at 6:1–8 ("composition []…. each containing: 5-ASA 400 mg Lactose 46 mg Polyrinylpyrolidone 20 mg Magnesium stearate 4 mg Alginic acid 10 mg"); *see also* *Id.* at 7:65–66 ("The tablets of 5-ASA contained 400 mg").
1e. wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.	*Leslie* teaches the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix: Ex. 1003 at 4:63–5:7 ("The active therapeutic compound intended for therapy may be incorporated in the higher alcohol before this is blended with the hydrated hydroxy-alkyl cellulose, or it may be incorporated in the hydrated hydroxy-alkyl cellulose, before it is incorporated with the higher alcohol or divided among both agents. The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend. Each method of adding the active ingredient has its own particular advantages for use in the manufacture of a particular dosage form."); *see also* *Id.* at 13:43–50 ("When it is desired to incorporate a pharmacologically active compound with the slow release composition of Example 1 above, then said active agent may be added to the alcohol component or the cellulose component or divided between the two.").
Claim 2. Compositions as claimed in claim 1, wherein 5-aminosalicylic acid is dispersed in a molten lipophilic matrix by kneading,	*Leslie* teaches the compositions of Claim 1, wherein 5-amino salicylic acid is dispersed in a molten lipophilic matrix by at least granulation: Ex. 1003 at 12:30–35 ("Melt the cetyl alcohol in a water jacketed tank. Hold the cetyl alcohol melt at 60°–70°C and incorporate with stirring the aminophylline. Granulate the resultant mass through a No. 16 standard mesh sieve. Harden the granules by

extrusion and/or granulation.	drying at room temperature."); *see also* *Id.* at 13:28–31 ("Melt the cetyl alcohol in a jacketed vessel and incorporate the papaverine hydrochloride, blend well and granulate through a No. 16 standard mesh sieve. Dry at room temperature.").
Claim 3. Compositions as claimed in claim 1, in the form of tablets, capsules, mintablets.	*Leslie* teaches the compositions of Claim 1 in the form of at least tablets and capsules: Ex. 1003 at 12:45–47 ("Add tablet lubricant and compress into tablets of suitable size and shape or fill into appropriate gelatin capsules."); *see also* *Id.* at 13:39–40 ("Compress into tablets of suitable size and shape."). *Rhodes* also teaches the compositions of Claim 1 in the form of at least tablets and capsules: Ex. 1004 at Abstract ("A solid dosage form, such as a capsule or tablet"); *see also* *Id.* at 5:8–9 ("the dosage form will be a conventional tablet or a capsule"); *see also* *Id.* at 7:65–66 ("The tablets of 5-ASA contained 400 mg…").
Claim 4a. A process for the preparation of the compositions of claim 1, which comprises: melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90° C.;	*Leslie* teaches a process for the preparation of the compositions of Claim 1 which comprises melt granulation of at least one portion of the active ingredient with the lipophilic excipients with a melting point lower than 90° C: Ex. 1003 at 12:30–35 ("Melt the cetyl alcohol in a water jacketed tank. Hold the cetyl alcohol melt at 60°–70°C and incorporate with stirring the aminophylline. Granulate the resultant mass through a No. 16 standard mesh sieve. Harden the granules by drying at room temperature."); *see also* *Id.* at 13:28–31 ("Melt the cetyl alcohol in a jacketed vessel and incorporate the papaverine hydrochloride, blend well and granulate through a No. 16 standard mesh sieve. Dry at room temperature."); *see also* Ex. 1037, Palmieri Decl. ¶ 80.

4b. mixing the granules from step a) with the hydrophilic excipients and	*Leslie* teaches mixing the granules from step a) with the hydrophilic excipients: Ex. 1003 at 12:36–41 ("Step 2: Hydrate the hydroxy ethyl cellulose in a suitable vessel fitted with a mixer using two and one half volumes of water for each part by weight of hydroxy ethyl cellulose. Step 3: Incorporate the blend from Step 1. Total blending time three hours"); *see also* *Id.* at 13:32–36 ("Step 2: Hydrate the hydroxy ethyl cellulose with 15 gm of water. Step 3: Blend the granules obtained as a result of Step 1 with the hydrated cellulose component of Step 2 and mix well").
4c. subsequent tabletting or compression.	*Leslie* teaches subsequent tableting or compression: Ex. 1003 at 12:45–47 ("Add tablet lubricant and compress into tablets of suitable size and shape or fill into appropriate gelatin capsules."); *see also* *Id.* at 13:39–40 ("Compress into tablets of suitable size and shape."). *Rhodes* also teaches subsequent tableting or compression: Ex. 1004 at 9:3 ("Tablets were manufactured to the following formula….").

C. Ground 3: Claims 1–4 of U.S. Patent No. 6,773,720 to Villa *et al.* are rendered obvious under 35 U.S.C. § 103(a) by EP 0 375 063 to Groenendaal in view of U.S. Patent No. 3,965,256 to Leslie *et al.*

The *Groenendaal* patent application (Ex. 1005) was published in 1990, and thus is prior art to the '720 patent under 35 U.S.C. § 103(b). The Examiner did not consider *Groenendaal* during the '720 patent prosecution.

One of ordinary skill in the art would have been motivated to combine the formulations taught in *Leslie* with the high-dose of 5-ASA from *Groenendaal* with a

reasonable expectation of success in formulating the composition disclosed in the Claims.

Ground 3 is not redundant with Ground 2. For example, although both *Rhodes* and *Groenendaal* disclose 5-ASA weight of composition within the claimed range, the weight range disclosed in *Groenendaal*—from 20–90%—approaches the top of the '720 patent's claimed range of 80–95%, while *Rhodes* discloses a 5-ASA weight of nearly 83% of the total composition—falling at the lower end of the '720 patent's claimed range. (*Compare* Ex. 1005 at 3:35–36 *with* Ex. 1004 at 5:56–6:12.) In addition, while *Groenendaal* does not disclose the successful high dose 5-ASA clinical results disclosed in *Rhodes*, *Groenendaal* discloses valuable dissolution curves for high 5-ASA concentrations, which do not appear in *Rhodes*. (*See* Ex. 1004 at Table I; Ex. 1005 at Figure 3; 1 Ex. 1037, Palmieri Decl. ¶¶ 127, 139.)

Specifically, *Groenendaal* discloses compositions having a high 5-ASA content, as exemplified in a composition where the "solid dispersion is preferably 20–90%, more preferably 50–80%." (Ex. 1005 at 3:35–36.) Specifically, *Groenendaal* discloses actual dissolution curves for high concentrations of 5-ASA. (*See* Ex. 1005 at Figure 3.) Additionally, *Groenendaal* discloses orally administrable pharmaceutical compositions of 5-ASA which reach their therapeutic target in the lower intestines by:

> preparing a granulate for a multiparticulate oral composition based on the concept of solid dispersion, whereby a biologically active substance is dispersed in an acid-resistant or release-limiting substance using the

> melting, the solvent or the melting-solvent method, characterized in that before the dispersion is solidified it is mixed with water-insoluble carrier particles whereafter the complete mixture is further processed according to granulation methods known in the art.

(Ex. 1005 at 3:1–6.)

As discussed previously, by the time of the '720 patent priority date, those of ordinary skill in the art were motivated to increase the content of 5-ASA drug formulations in order to improve the therapeutic activity of the composition, since the 5-ASA mechanism of action requires that an oral composition must contain a high percentage, by weight, of API. (Ex. 1001 at 3:52–56; Ex. 1028 at 761–62.) *See Dystar Textilfarben GmbH*, 464 F.3d at 1361. Finally, "[t]hose of ordinary skill in the art also recognized the benefits of delaying release of 5-ASA to the lower intestines so that the entire quantity of therapeutic agent can reach its destination." (Ex. 1037, Palmieri Decl. ¶ 143.)

In looking to so improve the *Groenendaal* 5-ASA compositions, one of ordinary skill in the art would have been motivated to look to *Leslie*. (Ex. 1037, Palmieri Decl. ¶ 144.) *Leslie* teaches a matrix system that efficiently delays release of high-dose API compositions, including APIs with low solubility such as papaverine hydrochloride, until the APIs reach the lower-intestinal targets. (*See, e.g.,* Ex. 1003 at 13:20–40.) Because both *Groenendaal* and *Leslie* sought the same release control objectives that one of ordinary skill in the art would have been motivated to achieve with respect to 5-ASA, one of ordinary skill in the art would have naturally looked to both *Groenendaal*

and *Leslie* when seeking to improve 5-ASA formulations. *See In re Icon Health & Fitness, Inc.*, 496 F.3d at 1380. Additionally, in light of the successful, high-dose API working examples disclosed in *Leslie*, one of ordinary skill in the art would have reasonably expected, in light of the 5-ASA dissolution curves disclosed in *Groenendaal*, that the even higher-dose 5-ASA disclosed in *Groenendaal* could be formulated as an improved high-dose composition according to *Leslie*'s teachings. (Ex. 1037, Palmieri Decl. ¶¶ 139, 145.) *See KSR Int'l Co.*, 550 U.S. at 417; *In re Sullivan*, 498 F.3d at 1351.

Further, *Leslie* expressly names the genus of "salicylate and acetyl-salicylate compounds" as preferred APIs for use according to the disclosed formulations. (Ex. 1003 at 8:42–43, 13:67.) "One of ordinary skill in the art would have recognized the *Groenendaal* 5-ASA as a species of this preferred API genus, and thus would have been further motivated to apply *Leslie*'s teachings to formulate high dose 5-ASA compositions that delay API release until their lower intestine target is reached." (Ex. 1037, Palmieri Decl. ¶ 146*; see, e.g.*, Ex. 1029 at 1298–300, 1301; Ex. 1030 at 7:12–16.)

As previously discussed in part VI-A, "it would have been obvious to one of ordinary skill in the art to combine the knowledge of the skill in the art with the teachings of *Leslie* to arrive at the composition of Claim 1." (Ex. 1037, Palmieri Decl. ¶ 147.) Further combining the matrix formulations disclosed in *Leslie* with the high-dose compositions of 5-ASA disclosed in *Groenendaal* explicitly teaches each element of the '720 patent's Claims 1–4. "[S]ince one of ordinary skill in the art would have

been motivated to combine *Groenendaal* and *Leslie* before the '720 patent priority date, and further would have had a reasonable expectation of success in doing so, Claims 1–4 of the '720 patent would have been obvious to one of ordinary skill in the art." (Ex. 1037, Palmieri Decl. ¶ 148.) *See Osram Sylvania, Inc.*, 701 F.3d at 706.

1. Claim Chart for Ground 3 showing exemplary citations in *Groenendaal* and *Leslie*.

Element	Prior Art of EP 0 375 063 to Groenendaal *et al.* and U.S. 3,965,256 to Leslie *et al.*
Claim 1 pre. Controlled-release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid	*Groenendaal* teaches controlled release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid: Ex. 1005 at pg. 1:1–3 ("This invention relates to granulates for multiparticulate controlled-release oral compositions comprising biologically active substances, targeted to predetermined parts of the intestine and especially to the lower part thereof, and to oral compositions, containing such granulates."); *see also* *Id.* at pg. 3:10–16 ("It will be appreciated that in principle any biologically active compound can be incorporated in the granulates for multiparticulate oral compositions of this invention, and in particular those compounds, e.g. the therapeutic (poly) peptides, which are sensitive to acid or to digestive enzymes and those which are disagreeable to the stomach, but that the main application of this invention lies with compounds which are meant to act locally in the intestine. Examples of the latter are corticosteroids and non-steroidal anti- 75 inflammatory compounds, especially beclomethasone 17,21-dipropionate and 5- or 4-amino-salicylic acid or their derivatives."); *see also* *Id.* at pg. 3:32–36 ("Examples of the latter are corticosteroids and non-steroidal anti- 75 inflammatory compounds, especially beclomethasone 17,21-dipropionate and 5- or 4-amino-salicylic acid or their derivatives."); *see also* *Id.* at Claim 6 ("A granulate according to claim 5, characterized

	in that the anti-inflammatory drug is 5 or 4-amino- salicylic acid, or a derivative thereof."). *Leslie* also teaches controlled-release oral pharmaceutical compositions: Ex. 1003 at 1:9–10 ("controlled slow release of one or more therapeutically active compounds"); *see also* *Id.* at Abstract, 1:17–18 ("pharmaceutical dosage forms intended for oral administration"); *see also* *Id.* at 3:37–42 ("According to the present invention, when a higher aliphatic alcohol is combined with an hydrated hydroxy-alkyl cellulose compound in critical proportions of one to the other, a particularly advantageous composition is formed which delays the release of a therapeutically active compound therefrom."); *see also* *Id.* at 3:9–13 ("The presence of varying amounts of water" in the digestive system "has been demonstrated to be the basis for virtually all of the inherent limitations of the conventional sustained acting tablet and capsule dosage forms."); *see also* *Id.* at 15:10 ("A slow release pharmaceutical tablet"). *Leslie* also teaches active ingredients "salicylate and acetyl salicylate compounds": Ex. 1003 at 8:37–43 ("Both the pharmacologic nature of the active therapeutic ingredient and the dosage to be incorporated into the present sustained slow release composition, are not critical to the present invention. Examples of such pharmacologically active ingredients are … salicylate and acetyl-salicylate compounds"); *see also* *Id.* at 13:62–67 ("The following examples of pharmacologically active compounds are particularly suitable for administration to human and animals in the form of slow release medications: … salicylate and acetyl-salicylate compounds"); *see also* Ex. 1037, Palmieri Decl. ¶¶ 61–73.
1a. an inner lipophilic matrix consisting of	*Groenendaal* teaches an inner lipophilic matrix consisting of at least a wax with a melting point below 90° C:

substances selected from the group consisting of unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglyceride[e]s, waxes, ceramides, and cholesterol derivatives with melting points below 90° C., and wherein the active ingredient is dispersed both in said the lipophilic matrix and in the hydrophilic matrix;	Ex. 1005 at pg. 3:26–30 ("Examples of known release-limiting compounds are…. fatty acids such as stearic acid, fatty acid esters such as PRECIROL, long chain aliphatic alcohols such as cetyl, stearyl, cetostearyl and myristyl alcohol, hydrogenated vegetable oils such as hydrogenated castor oil and hydrogenated cottonseed oil, waxes such as bees wax…"). *Leslie* also teaches an inner lipophilic matrix consisting of at least a wax with a melting point below 90° C: Ex. 1003 at 12:30–35 ("Step 1: Melt the cetyl alcohol in a water jacketed tank. Hold the cetyl alcohol melt at 60°–70°C and incorporate with stirring the aminophylline. Granulate the resultant mass through a No. 16 standard mesh sieve. Harden the granules by drying at room temperature."); *see also* *Id.* at 13:28–31 ("Step 1: Melt the cetyl alcohol in a jacketed vessel and incorporate the papaverine hydrochloride, blend well and granulate through a No. 16 standard mesh sieve. Dry at room temperature."); *see also* Ex. 1037, Palmieri Decl. ¶¶ 77–93. *Leslie* also teaches the active ingredient is dispersed both in said the lipophilic matrix and in the hydrophilic matrix: Ex. 1003 at 4:63–5:7 ("The active therapeutic compound intended for therapy may be incorporated in the higher alcohol before this is blended with the hydrated hydroxy-alkyl cellulose, or it may be incorporated in the hydrated hydroxy-alkyl cellulose, before it is incorporated with the higher alcohol or divided among both agents. The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend. Each method of adding the active ingredient has its own particular advantages for use in the manufacture of a particular dosage form."); *see also* *Id.* at 13:43–50 ("When it is desired to incorporate a pharmacologically active compound with the slow release composition of Example 1 above, then said active agent may be added to the alcohol component or the cellulose component or

	divided between the two."); *see also* Ex. 1037, Palmieri Decl. ¶¶ 94–98, 110–11.
1b. an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of compounds selected from the group consisting of polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, and natural or synthetic gums;	*Leslie* teaches an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of at least a hydroxyalkyl cellulose: Ex. 1003 at 1:12–19 ("a combination of a higher aliphatic alcohol and a hydrated hydroxy-alkyl cellulose … in pharmaceutical dosage forms intended for oral administration, to provide a slow release of a therapeutically active compound"); *see also* *Id.* at 4:41–44 ("The hydroxy-alkyl cellulose preferred in practice is hydroxyethyl cellulose although the analogous, methyl and propyl cellulose derivatives are satisfactory."); *see also* *Id.* at 12:36–41 ("Step 2: Hydrate the hydroxy ethyl cellulose in a suitable vessel fitted with a mixer using two and one half volumes of water for each part by weight of hydroxy ethyl cellulose. Step 3: Incorporate the blend from Step 1. Total blending time three hours"); *see also* *Id.* at 13:32–36 ("Step 2: Hydrate the hydroxy ethyl cellulose with 15 gm of water. Step 3: Blend the granules obtained as a result of Step 1 with the hydrated cellulose component of Step 2 and mix well"); *see also* Ex. 1037, Palmieri Decl. ¶¶ 98–11.
1c. optionally other excipients;	*Groenendaal* teaches optionally other excipients: Ex. 1005 at pg. 3:56–59 ("The granulates according to the invention can be incorporated in any of the preparations for oral application known in the art, such as sachets, capsules and, preferably, tablets, optionally also containing pharmaceutically acceptable excipients."). *Leslie* also teaches optionally other excipients: Ex. 1003 at 4:68–5:4 ("The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the

	excipient such as lactose or talc, and incorporated in the blend."); *see also* *Id.* at 12:45–47 ("Step 5: Add tablet lubricant and compress into tablets of suitable size and shape or fill into appropriate gelatin capsules"); *see also* *Id.* at 4:68–5:4 ("The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend."); *see also* *Id.* at 8:62–66 ("When it is desired to prepare tablets containing the slow release composition, then it is preferred to utilize an inert diluent such as lactose or talc, to achieve the appropriate concentration of slow release composition within said unit dosage form."); *see also* *Id.* at 12:53 ("EXAMPLE 5" lists "Talc 1.50 gms.").
1d. wherein the active ingredient is present in an amount of 80 to 95% by weight of the total composition, and	*Groenendaal* also teaches an active ingredient is present in an amount of 80 to 95% by weight of the total composition: Ex. 1005 at pg. 3:34–36 ("When the biologically active compound is a non-steroidal anti inflammatory compound such as 5- or 4-amino-salicylic acid its percentage (w/w) in the solid dispersion is preferably 20–90%"). *Leslie* teaches an active ingredient is present in an amount of 80 to 95% by weight of the total composition: Ex. 1003 at 12:46–54 (listing the material for Example 5 as: Cetyl Alcohol 14.00 gms. Potassium Chloride 82.00 gms. Hydroxy Ethyl Cellulose 4.50 gms. Talc 1.50 gms.); *see also* *Id.* at 14:13, 23–36 ("To prepare the appropriate slow release unit dosage form containing the above described pharmacologically active ingredient [including at least one salicylate], any member of the classes of therapeutically active compounds and the particular pharmacologically active compound set forth above may be blended with an appropriate

	quantity of the composition of Claim 1. To this mixture is added an appropriate quantity of diluent to provide the predetermined concentration of from 20 percent to 30 percent by weight of the weight of the slow release composition… The manufacturing procedures described in Examples 1 through 6 may be utilized."); *see also* Ex. 1037, Palmieri Decl. ¶¶ 114–21.
1e. wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.	*Leslie* teaches the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix: Ex. 1003 at 4:63–5:7 ("The active therapeutic compound intended for therapy may be incorporated in the higher alcohol before this is blended with the hydrated hydroxy-alkyl cellulose, or it may be incorporated in the hydrated hydroxy-alkyl cellulose, before it is incorporated with the higher alcohol or divided among both agents. The active ingredient may be incorporated in the partially, or totally pre-formed blend of the two components, or finally, it may be included with the excipient such as lactose or talc, and incorporated in the blend. Each method of adding the active ingredient has its own particular advantages for use in the manufacture of a particular dosage form."); *see also* *Id.* at 13:43–50 ("When it is desired to incorporate a pharmacologically active compound with the slow release composition of Example 1 above, then said active agent may be added to the alcohol component or the cellulose component or divided between the two.").
Claim 2. Compositions as claimed in claim 1, wherein 5-aminosalicylic acid is dispersed in a molten lipophilic matrix by kneading, extrusion and/or granulation.	*Leslie* teaches the compositions of Claim 1, wherein 5-amino salicylic acid is dispersed in a molten lipophilic matrix by at least granulation: Ex. 1003 at 12:30–35 ("Melt the cetyl alcohol in a water jacketed tank. Hold the cetyl alcohol melt at 60°–70°C and incorporate with stirring the aminophylline. Granulate the resultant mass through a No. 16 standard mesh sieve. Harden the granules by drying at room temperature."); *see also* *Id.* at 13:28–31 ("Melt the cetyl alcohol in a jacketed vessel and incorporate the papaverine hydrochloride, blend well and

	granulate through a No. 16 standard mesh sieve. Dry at room temperature.").
Claim 3. Compositions as claimed in claim 1, in the form of tablets, capsules, mintablets.	*Groenendaal* teaches the compositions of Claim 1 in the form of at least tablets and capsules: Ex. 1005 at pg. 3:56–59 ("The granulates according to the invention can be incorporated in any of the preparations for oral application known in the art, such as sachets, capsules and, preferably, tablets, optionally also containing pharmaceutically acceptable excipients."); *see also* *Id.* at pg. 2:52–56 ("The process according to the invention is very versatile since it is applicable to both acid-resistant and release-limiting preparations. The process is also very efficient since no special apparatus is required for the simple step of mixing the water-insoluble carrier particles with the dispersion, and since due to the granules being irregular in shape and porous they can be immediately compressed into tablets."); *see also* *Id.* at pg. 2:57–59 ("The granulates according to the invention can be incorporated in any of the preparations for oral application known in the art, such as sachets, capsules and, preferably, tablets, optionally also containing pharmaceutically acceptable excipients."); *see also* *Id.* at pg. 4:1–5 ("Tablets containing the granulates according to the invention have the practical advantages which are inherent to tablets in general, and additionally they have the advantage of being multi-particulate compositions, in that they disintegrate in the stomach, releasing the granules, which are small enough to leave the stomach rapidly and reliably. Alternatively, tablets containing the granulates according to the invention can be left to disintegrate in a small amount of water, rendering a homogeneous, drinkable dispersion."); *see also* *Id.* at Claim 14 ("A multiparticulate controlled-release oral composition according to claim 13, characterized in that it is a tablet."). *Leslie* also teaches the compositions of Claim 1 in the form of at least tablets and capsules:

	Ex. 1003 at 12:45–47 ("Add tablet lubricant and compress into tablets of suitable size and shape or fill into appropriate gelatin capsules."); *see also* *Id.* at 13:39–40 ("Compress into tablets of suitable size and shape.").
Claim 4a. A process for the preparation of the compositions of claim 1, which comprises: melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90° C.;	*Leslie* teaches a process for the preparation of the compositions of Claim 1 which comprises melt granulation of at least one portion of the active ingredient with the lipophilic excipients with a melting point lower than 90° C: Ex. 1003 at 12:30–35 ("Melt the cetyl alcohol in a water jacketed tank. Hold the cetyl alcohol melt at 60°–70°C and incorporate with stirring the aminophylline. Granulate the resultant mass through a No. 16 standard mesh sieve. Harden the granules by drying at room temperature."); *see also* *Id.* at 13:28–31 ("Melt the cetyl alcohol in a jacketed vessel and incorporate the papaverine hydrochloride, blend well and granulate through a No. 16 standard mesh sieve. Dry at room temperature."); *see also* Ex. 1037, Palmieri Decl. ¶ 80.
4b. mixing the granules from step a) with the hydrophilic excipients and	*Leslie* teaches mixing the granules from step a) with the hydrophilic excipients: Ex. 1003 at 12:36–41 ("Step 2: Hydrate the hydroxy ethyl cellulose in a suitable vessel fitted with a mixer using two and one half volumes of water for each part by weight of hydroxy ethyl cellulose. Step 3: Incorporate the blend from Step 1. Total blending time three hours"); *see also* *Id.* at 13:32–36 ("Step 2: Hydrate the hydroxy ethyl cellulose with 15 gm of water. Step 3: Blend the granules obtained as a result of Step 1 with the hydrated cellulose component of Step 2 and mix well").
4c. subsequent tabletting or compression.	*Groenendaal* also teaches subsequent tableting or compression: Ex. 1005 at pg. 2:52–56 ("The process according to the invention is very versatile since it is applicable to both acid-resistant and release-limiting preparations. The process is also very efficient since no special apparatus is required for the

	simple step of mixing the water-insoluble carrier particles with the dispersion, and since due to the granules being irregular in shape and porous they can be immediately compressed into tablets"); *see also* *Id.* at pg. 4:55–56 ("The mass was then fed to an excenter press tabletting machine."). *Leslie* teaches subsequent tableting or compression: Ex. 1003 at 12:45–47 ("Add tablet lubricant and compress into tablets of suitable size and shape or fill into appropriate gelatin capsules."); *see also* *Id.* at 13:39–40 ("Compress into tablets of suitable size and shape.").

VII. CONCLUSION

Thus, Petitioners respectfully request *inter partes* review of Claims 1–4 of U.S. Patent No. 6,773,720.

Respectfully submitted, April 1, 2015

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CERTIFICATE OF SERVICE

I hereby certify that on April 1, 2015, a copy of this Petition for *Inter Partes* Review of U.S. Patent No. 6,773,720, including all exhibits, was served via FEDEX, overnight delivery, upon the following:

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