

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DR. FALK PHARMA GMBH,

Petitioner,

v.

ELLODI PHARMACEUTICALS LP,

Patent Owner.

Case No. **

U.S. Patent No. 8,771,729

**DECLARATION OF ALAN F. PARR, PHARM.D, PH.D.,
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 8,771,729**

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LIST OF MATERIALS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 8,771,729 to Perrett et al.
1002	U.S. Publication No. 20070111978 to Dohil et al.
1003	EP2482822B1 that was revoked by the European Patent Office
1004	The Opposition Division of the European Patent Office decision revoking EP2484822B1 with auxiliary requested claims
1005	“Guidance for Industry: Orally Disintegrating Tablets,” U.S. Food & Drug Administration, Center for Drug Evaluation and Research (CDER), 2008.
1007	“DRAFT Guidance for Industry: Orally Disintegrating Tablets,” U.S. Food & Drug Administration, Center for Drug Evaluation and Research (CDER), 2007.
1008	International Publication No. WO2000044351 to Grother et al.
1009	Svoboda et al., “Oral formulations of budesonide: a novel treatment for inflammatory bowel disease,” <i>Drugs of Today</i> , 44:857-863 (2008) at 857.
1010	Tan et al., “Eosinophilic gastroenteritis treated with non-enteric-coated budesonide tablets,” <i>European Journal of Gastroenterology & Hepatology</i> , 13:425-427 (2001)
1011	Kolkman et al., “Evaluation of oral budesonide in the treatment of active distal ulcerative colitis,” <i>Drugs of Today</i> , 40:589-601 (2004)
1012	Siewert et al., “Eosinophilic gastroenteritis with severe protein-losing enteropathy: Successful treatment with budesonide,” <i>Digestive and Liver Disease</i> , 38:55-59 (2006)
1013	Elsing et al., “Budesonide for the treatment of obstructive eosinophilic jejunitis,” <i>Z. Gastroenterology</i> , 45:187-189 (2007).

Exhibit No.	Description
1014	Aceves et al., “Topical viscous budesonide suspension for treatment of eosinophilic esophagitis,” Journal of Allergy and Clinical Immunology 116:705-706 (2005)
1015	Aceves et al., “Oral Viscous Budesonide: A potential new therapy for eosinophilic esophagitis in children,” American Journal of Gastroenterology, 102:1-9 (2007)
1016	The United States Pharmacopeia, USP 32, 2009 at pages 262-263 “<701> Disintegration”
1017	Danckwerts, “Intraoral Drug Delivery: A Comparative Review,” American Journal of Drug Delivery, 1:171-186 (2003).
1018	Fu et al., “Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies,” Critical Reviews in Therapeutic Drug Carrier Systems, 21:433-475 (2004)
1019	Shukla et al., “Mouth Dissolving Tablets I: An overview of formulation technology,” Scientia Pharmaceutica, 77:309-326 (2009) (March 6, 2009)
1020	U.S. Publication No. 20050232988 to Venkatesh et al.
1025	Goodman & Gilman’s: The Pharmacological Basis of Therapeutics, 11th edition, eds. Brunton, Lazo, Parker, 2005
1026	Budenofalk® Brochure (2005)
1027	Budenofalk® Advertisement (2007)
1028	Dr. Falk Pharma Brochure (2008)
1033	Teitlebaum et al., Eosinophilic esophagitis in children: Immunopathological analysis and response to fluticasone propionate,” Gastroenterology 122:1216-1225 (2002)

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Exhibit No.	Description
1034	Noel et al., “Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis,” Clinical Gastroenterology and Hepatology 2:568-575 (2004)
1035	U.S. Patent No. 7,122,198 to Singh et al.
1036	U.S. Patent No. 7,229,641 Cherukuri et al.

1. I, Alan F. Parr, Pharm.D., Ph.D., have been retained by Knobbe, Martens, Olson & Bear, LLP, counsel for Dr. Falk Pharma GmbH. I understand that Dr. Falk Pharma is petitioning for inter partes review of U.S. Patent No. 8,771,729 (“the ’729 patent,” EX1001) and requests that the United States Patent and Trademark Office cancel all claims of the ’729 patent as unpatentable. The following discussion and analysis provides my opinion as to why all claims would have been obvious to a person of ordinary skill in the art in October of 2009.

**I. BACKGROUND AND QUALIFICATIONS, AND
PREVIOUS TESTIMONY**

A. Background and Qualifications

2. I am a pharmaceutical formulation scientist with more than 30 years of pharmaceutical experience.

3. I am currently the managing member for Bio Ceutics, LLC, based in Acworth, Georgia. In this capacity, I serve as a resource to pharmaceutical companies in the areas of biopharmaceutics, formulation development, general product development, and the design and implementation of novel *in vivo* pre-clinical studies.

4. I received my Pharm.D. in Pharmacy from the University of Nebraska College of Pharmacy in 1981 followed by a Ph.D. in Pharmaceutical Sciences from the University of Kentucky in the College of Pharmacy in 1986, where the topic of

my thesis related to radiolabeling of intact dosage forms for scintigraphic studies *in vivo*.

5. From 1986-87, I conducted post-doctoral research at the University of Kentucky, College of Pharmacy, where I designed and coordinated clinical bioavailability studies in animals and humans and investigated pharmaceutical dosage forms through *in vivo* scintigraphic studies, particularly in the area of gastrointestinal transit.

6. Prior to, during, and following my post-doctoral training and various staff pharmacist positions between 1981 and 2015, I spent the majority of my scientific career working for GlaxoSmithKline (“GSK”) and its predecessor corporations in North Carolina.

7. During my career, I worked on a variety of drug products, including orally disintegrating tablet dosage formulations. My experience in developing orally disintegrating tablet dosage formulations includes reviewing and giving guidance on the formulation development plan of the orally disintegrating formulation, reviewing details from executed experiments and data generated on orally disintegrating formulations, and making recommendations to improve the orally disintegrating formulation products being developed. My experience with disintegration testing is associated with the use of the disintegration apparatus referenced by the USP <701> Disintegration Test to monitor the in-process quality of numerous formulations of

various dosage forms that I manufactured. Additionally, I have used this apparatus to determine the impact of formulation changes on the gelling of drugs. In this application it allowed me to screen a larger number of formulation changes in less time and with less resources. The USP <701> Disintegration Test was a test that I routinely used (and is commonly used) during formulation development activities and commercial manufacture of drug products. The USP <701> Disintegration Test is easy to run, it does not require sophisticated analytical equipment, and it can reduce the resources needed for product development.

8. Also, during my time at GSK, I worked on eleven commercialized drug products, four of which were sustained release formulations. I have also consulted on a variety of other products, including sustained release dosage forms. My experience in developing sustained release formulations spans decades. Over that time I have worked on five matrix formulations and three drug products involving enteric coating technology, and I have employed lipophilic and amphiphilic agents to control solubility of the drug active for at least six drug products.

9. From 1987 through 1995, I was a Research Investigator at Glaxo, Inc. in the Pharmaceuticals Department. From there, I was appointed Senior Group Leader, then Department Head of the GlaxoWellcome Pharmaceutical Sciences Department, a position I served in until 2001. Between 2001 and 2005, I directed the Product Line Extensions Group at GSK in the Pharmaceutical Development Division, where I

managed a group of eight Ph.D. and ten non-Ph.D. scientists and led the development of new product line extensions.

10. In 2005, I was appointed Director of Biopharmaceutics in the GSK Pharmaceutical Development Division, where I identified and implemented process improvements on GSK compounds. I was also charged with designing and developing novel pharmacokinetics studies and methods to evaluate the *in vivo* behavior of dosage forms. I retired from GSK in 2015.

11. I have served on the committees of various professional societies. For example, I was appointed Chairperson of the Product Quality Research Institute (“PQRI”) Biopharmaceutics Technical Committee (2001-2012), Chairperson of the PQRI Sequential Design Working Group (2001-2012), Member of the U.S. Pharmacopeial Convention (“USP”) Biopharmaceutics Expert Committee (2005-2010), Member of the USP Dosage Form Expert Committee (2010-2015), Member of the USP Extemporaneous Compounding Committee (2010-2015 and 2015-2020), Member of the American Association of Pharmaceutical Scientists (1983-Present). I have also been appointed as an Adjunct Faculty Member of the University of North Carolina School of Pharmacy numerous times over the last twenty years.

12. I have published 44 papers and 2 book chapters in medical and scientific journals and have authored or co-authored 40 presentations as an expert in my field.

13. I am a named inventor on three patents and two PCT publications.

14. In formulating my opinions, I have relied upon my training, knowledge, and experience in the relevant art and documents cited herein. A copy of my current *curriculum vitae* is provided as Exhibit 1029 (EX1029), and it provides a comprehensive description of my academic and employment history.

B. Compensation

15. I am being compensated for my time spent working on this case at my standard hourly consulting rate. My compensation is not dependent on the substance of my opinions or testimony, or on the outcome of the case.

C. Previous Testimony

16. I previously served as an expert witness in the following matters:

- *Bayer Inc. v. Apotex Inc.*, Canada [T-1468-13; T-1368-14];
- *Cosmo Technologies v. Actavis Labs. Fl, Inc.*, No. 1:15-cv-00164-LPS (D. Del.);
- *Cosmo Technologies v. Alvogen Pine Brook, Inc.*, No. 1:15-cv-00193-LPS (D. Del.);
- *Cosmo Technologies v. Lupin Ltd.*, No. 1:15-cv-00669-LPS (D. Del.);
- *Cosmo Technologies v. Mylan Pharmaceuticals Inc.*, No. 1:15-cv-00152-LPS (D. Del.);
- *Apotex Inc. v. AstraZeneca Canada Inc.*, Canada [T-389-11];

- *AstraZeneca Canada Inc. v. Apotex Inc.*, Canada [T-1670-17];
- *Pfizer Canada Inc. v. Apotex Inc.*, Canada [T-402-16];
- *Bayer Intellectual Property GmbH v. Taro Pharmaceutical Industries Ltd.*, No. 1:17-cv-00462-RGA (D. Del);
- *Bristol-Myers Squibb Co. v. Apotex Inc.*, Canada [T-351-18]; and
- *Bayer Inc v. Apotex Inc.*, Canada [T-2019-83].

II. MATERIALS CONSIDERED

17. Documents that I have considered and reviewed in connection with providing this declaration are included as exhibits in the List of Documents Considered, above. In forming my opinions, I have also relied on my knowledge, education and training as reflected in my qualifications and credentials set forth above and in my *curriculum vitae*.

III. LEGAL STANDARDS

18. I am not a patent attorney nor have I independently researched the law on patentability. I have been informed by counsel of general principles concerning patent law and the analysis of whether a patent claim is valid. I have followed these principles in arriving at my conclusions in this declaration.

19. I understand that a patent claim is presumed valid. I also understand that the patent challenger (here, Dr. Falk Pharma) has the burden of proving unpatentability by the preponderance of the evidence. The sections below set forth

my understanding of the legal principles that are relevant to my opinions in this declaration.

A. CLAIM CONSTRUCTION

20. I understand that the claims of a patent define the scope of the inventions that are protected by the patent. I understand that the language of the claims is construed as it would be understood by a hypothetical person having ordinary skill in the art at the time of the invention.

21. I understand that words in a claim will be given their ordinary (or customary) meaning unless it appears that the patentee used them differently.

22. I also understand that, in construing patent claims, courts seek to determine what a person skilled in the art would have understood the claims to mean primarily in light of the intrinsic evidence of record, which includes the language of the claim itself and other issued claims, the specification, the art cited during prosecution, and the prosecution history.

23. Unless otherwise specified, I have applied the ordinary meaning of each term recited by the claims in reaching the opinions described in this declaration.

B. OBVIOUSNESS

24. I understand that 35 U.S.C. § 103 governs the determination of obviousness. I understand that 35 U.S.C. § 103 states:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the

differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art to which the subject matter pertains.

25. I further understand that the four factors to be considered in an obviousness inquiry are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations including long-felt need, commercial success, and unexpected results.

26. I also understand that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In such a circumstance, when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious.

27. I understand that for the subject matter of a patent claim to be obvious, the prior art must create a reasonable expectation of success in producing the claimed subject matter. I understand that a reasonable expectation of success does not require a certainty of success. I further understand that a claim may be proven obvious by

a single prior art reference or by a combination of prior art references. I have been informed that when prior art references are combined to show that claimed subject matter would have been obvious to a person of ordinary skill in the art, there must be some teaching, suggestion or motivation to combine the prior art teachings. I understand that such teaching, suggestion or motivation to combine prior art teachings can come from any source, including common knowledge, the prior art as a whole, any need or problem known in the field, the inferences a person of ordinary skill in the art would ordinarily make, and the ordinary creativity of a person of ordinary skill in the art.

IV. THE PERSON OF ORDINARY SKILL IN THE ART

28. I understand that obviousness is analyzed from the perspective of a hypothetical person of ordinary skill in the art. I understand that the hypothetical person of ordinary skill in the art is presumed to have knowledge of all of the prior art relevant to the claimed subject matter, and may have the combined understanding of those of ordinary skill in various fields pertinent to the subject matter of a patent.

29. I understand that October 2009 is the relevant time frame for analyzing the obviousness of the '729 patent. A person of ordinary skill in the art related to the '729 patent would have a Ph.D., another advanced degree, or its equivalent, in areas related to pharmaceuticals, chemistry, biology, medicine, or a related discipline, and 2-3 years of experience in formulation development. Alternatively, a person of

ordinary skill in the art would have a lesser degree in those fields, with at least five or more years of experience in formulation development. The experience in formulation development would include, for example, experience formulating orally disintegrating tablets, immediate release tablets or capsules, or sustained release tablets or capsules. The person of ordinary skill in the art would also have had access to a medical doctor with a specialty in gastroenterology, and other individuals with expertise related to the above subjects.

30. My opinions concerning the obviousness of the '729 patent claims, as set forth herein, are from the perspective of a person of ordinary skill in the art, as set forth above.

V. BACKGROUND REGARDING DR. FALK PHARMA

31. Dr. Herbert Falk founded Dr. Falk Pharma in 1960 within his family's pharmacy in Freiburg, Germany. *See* EX1028 (Dr. Falk Brochure) at 5 ("From the outset, Herbert Falk specialized in research and development in the fields of gastroenterology and hepatology. Guided by the conviction that a specialist working in his or her chosen area will deliver better results, the company went on to develop innovative drugs for the treatment of chronic diseases."); *id.* at 7 ("1960 Founding of Dr. Falk Pharma in the family pharmacy in Freiburg, Germany."). Also in 1960, he developed the company's first hepatological formulation, Hepatofalk®. *Id.* at 7 ("1960 Development of the first hepatological preparation, Hepatofalk®"). In 1974,

Dr. Falk Pharma launched the world’s first bile acid preparation for the dissolution of gallstones, Chenofalk®. *Id.* (“1974. . . Chenofalk® is launched as the world’s first ever bile acid preparation for the dissolution of gallstones.”). In 1979, Dr. Falk Pharma released Ursofalk® for the treatment of cholestatic liver disease. *Id.* (“1979 Launch of Ursofalk®, which is still the leading medication for the treatment of cholestatic liver diseases.”). In 1984, Dr. Falk Pharma released Salofalk® for treating inflammatory bowel diseases. *Id.* (“1984 Salofalk® becomes the world’s first mesalazine preparation for treating inflammatory bowel diseases; it still leads the market in many countries.”). In 1998, Dr. Falk Pharma released Budenofalk®, which contains budesonide as a topical corticosteroid for the treatment of inflammatory bowel diseases.” *Id.* (“1998 Launch of Budenofalk®, a topical corticosteroid for the treatment of inflammatory bowel diseases.”).

32. By 2008, Dr. Falk Pharma had grown into an medium-sized family-owned company focused on designing pharmaceutical formulations for gastroenterological and hepatological indications with over 100 employees and operating in 63 countries. *See* EX1028 (Dr. Falk Brochure) at 3 (“As an innovative, medium-sized family firm we concentrate on medicines for indications in gastroenterology and hepatology.”), *see also id.* at 9 (“Dr. Falk Pharma operates nationally and internationally, manufacturing and selling mainly prescription drugs in a variety of formulations for gastroenterological and hepatological indications.”),

see also id. at 11 (see graph of number of full-time employee equivalents), *see also id.* at 17 (“Dr. Falk Pharma markets its products in 63 countries around the world.”).

33. By 2008, “Dr. Falk Pharma ha[d] acquired an outstanding reputation for the development of novel formulations with a topical effect and delayed-release formulations,” and was regarded as “one of the world’s specialists in the field.” *See* EX1028 (Dr. Falk Brochure) at 13 (“In particular, Dr. Falk Pharma has acquired an outstanding reputation for the development of novel formulations with a topical effect and delayed-release formulations, and is currently regarded as one of the world’s specialists in the field.”).

34. As can be seen in the table below, by 2008 Dr. Falk Pharma was invested “not only in developing drugs with new active ingredients, but also in finding new drug delivery systems and in expanding the range of conditions treated by [their] medication.” EX1028 (Dr. Falk Brochure) at 13 (“Our research and development departments concentrate not only on the development and licensing of new preparations and drug delivery systems, but also on researching new applications for existing drugs.”).

Präparatenamen Brand names	Wirkstoff Active substance	Darreichungsformen Pharmaceutical forms	Indikationen Indications
Salofalk® Colitofalk®	Mesalazin Mesalazine	Tabletten, Granulat, Suppositorien, Rektalschaum, Klysmen Tablets, granules, suppositories, rectal foam, enemas	Colitis ulcerosa, Morbus Crohn Ulcerative colitis, Crohn's disease
Budenofalk®	Budesonid Budesonide	Hartkapseln, Rektalschaum Capsules, rectal foam	Morbus Crohn, kollagene Colitis, distale Colitis ulcerosa (Rektalschaum) Crohn's disease, collagenous colitis, distal ulcerative colitis (rectal foam)
Ursofalk®	Ursodeoxycholsäure Ursodeoxycholic acid	Hartkapseln, Filmtabletten, Suspension Capsules, film-coated tablets, suspension	Primär biliäre Zirrhose, Auflösung von Gallensteinen, biliäre Refluxgastritis Primary biliary cirrhosis, dissolution of gallstones, biliary reflux gastritis
Endofalk® Classic Endofalk® Tropic	Macrogol 3350 PEG 3350	Pulver zur Herstellung einer Lösung zum Einnehmen Powder for the preparation of an oral solution	Darmreinigung vor Koloskopie Bowel cleansing prior to colonoscopy
Falkamin®	Verzweigt-kettige Aminosäuren Branched-chain amino acids	Pellets Pellets	Hepatische Enzephalopathie Hepatic encephalopathy
Mucofalk® Apple/Orange	Flohsamenschalen Plantago ovata seed shells	Granulat Granules	Chronische Obstipation, Durchfälle, Reizdarmsyndrom, Analfissuren, Hämorrhoiden Chronic constipation, diarrhoea, irritable bowel syndrome, anal fissures, haemorrhoids
Laxofalk®	Macrogol 4000 PEG 4000	Pulver zur Herstellung einer Lösung zum Einnehmen Powder for the preparation of an oral solution	Chronische Obstipation Chronic constipation
Zinkamin-Falk®	Zink-Histidin-Verbindung Zinc-histidine complex	Hartkapseln Capsules	Zinkmangel bei verschiedenen Erkrankungen Zinc deficiency in different indications
Azafalk®	Azathioprin Azathioprine	Filmtabletten Film-coated tablets	Immunsuppression Immunosuppression

EX1028 (Dr. Falk Brochure) at 9.

35. Since 1967, Dr. Falk Pharma has “arranged internationally recognized scientific congresses, the Falk Symposia and Workshops.” EX1028 (Dr. Falk Brochure) at 2. The Falk Symposia and Workshops “provide independent forums for intensive scientific exchange,” that educate clinicians and researchers regarding new results and best practices, which helps to ensure “the timely and consistent

transfer of new information and allowing it to form the basis of practical therapeutic progress.” *Id.* at 19. By 2008, Dr. Falk Pharma had conducted “more than 200 events” that were “attended by some 100,000 participants from over 100 countries.” *Id.* at 2. In addition, Dr. Falk Pharma organizes and sponsors continuing medical education events. By 2008, it had conducted “over 13,000 seminars” that were “attended by over one million physicians and patients in Germany alone.” *Id.* at 2; *see also id.* at 19 (also describing the Falk Symposia and Workshops).

36. Today, Dr. Falk Pharma remains a family-owned company, yet it has a global reach. Dr. Falk Pharma’s products are available to patients in over 65 countries (which is two more countries than it had in the 2008 timeframe). “For over 60 years, Dr. Falk Pharma has been developing products, forms of therapy and the field of gastroenterology and hepatology as a whole” with a focus “[t]o enable relief, well-being, more ease of movement and confidence in everyday situations” for people “with inflammatory bowel disease as well as digestive and metabolic problems.” *See* <https://drfalkpharma.com/en/about-us/now-into-the-future/>

VI. THE ’729 PATENT

37. The ’729 patent (EX1001) is directed to “Orally administered corticosteroid compositions.” EX1001 (“the ’729 patent”) at Title.

38. The ’729 patent has 40 claims, with claims 1 and 27 being independent claims. *See* EX1001 (“the ’729 patent”) at Claims.

A. Independent claim 1 and its dependent claims

39. Independent claim 1 of the '729 patent recites:

Claim 1. An orally disintegrating solid pharmaceutical composition comprising

[i] less than or equal to about 20 mg of a topically administrable corticosteroid and

[ii] at least one disintegrant,

[iii] wherein the solid pharmaceutical composition has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration,

[iv] wherein the solid pharmaceutical composition disintegrates within 60 seconds when tested using the USP <701> Disintegration Test, and

[v] wherein upon administration the corticosteroid is deposited topically in the upper gastrointestinal tract.¹

EX1001 (“the '729 patent”) at Claim 1.

40. Claims 2-26, 29-37, and 39-40 depend, either directly or indirectly through another claim, from independent claim 1. These claims are reproduced below.

Claim 2. The solid pharmaceutical composition of claim 1, wherein said solid pharmaceutical composition disintegrates within 30 seconds.

¹ Bracketed labels, e.g., “[i]” and “[ii],” have been added for convenient referencing to the claim limitations.

Claim 3. The solid pharmaceutical composition of claim 1, wherein said corticosteroid is selected from the group consisting of budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, and salts, solvates and esters thereof.

Claim 4. The solid pharmaceutical composition of claim 1, further comprising an adhesive agent.

Claim 5. The solid pharmaceutical composition of claim 4, wherein the adhesive agent is selected from the group consisting of sucrose aluminum sulfate complex, chitosan and derivatives thereof, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, cross-linked or uncross-linked polyacrylates, cross-linked polyacrylates, acidic cross-linked or uncross-linked polyacrylates, polyacrylic acid homopolymers or copolymers, aminoalkyl methacrylate copolymers, methacrylic acid/methylmethacrylate copolymer, alkylacrylate/alkylmethacrylate copolymers, ammoniomethacrylate copolymers, carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof.

Claim 6. The solid pharmaceutical composition of claim 1, wherein the at least one disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, low-substituted hydroxylpropylcellulose, mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

Claim 7. The solid pharmaceutical composition of claim 1, further comprising an excipient selected from the group consisting of mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, cyclodextrin, and combinations thereof.

Claim 8. The solid pharmaceutical composition of claim 1, which is substantially free of lubricant.

Claim 9. The solid pharmaceutical composition of claim 1, further comprising at least one antifungal agent.

Claim 10. The solid pharmaceutical composition of claim 9, wherein the antifungal agent is selected from the group consisting of mitotic inhibitor antifungals, pyrimidine analog antifungals, polyene antifungals, benzimidazole antifungals, imidazole antifungals, polyene antifungals, triazole antifungals, thiazole antifungals, allylamine antifungals, echinocandin antifungals, and uncategorized antifungals.

Claim 11. The solid pharmaceutical composition of claim 10, wherein the antifungal agent is selected from the group consisting of anidulafungin, caspofungin, clotrimazole, fluconazole, itraconazole, micafungin, nystatin, posaconazole, and voriconazole.

Claim 12. The solid pharmaceutical composition of claim 1, further comprising at least one antiviral agent..

Claim 13. The solid pharmaceutical composition of claim 12, wherein the antiviral agent is selected from the group consisting of interferons, nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors,

integrase inhibitors, fusion inhibitors, maturation inhibitors, purine analogs, pyrimidine analogs, and uncategorized antiviral drugs.

Claim 14. The solid pharmaceutical composition of claim 12, wherein the antiviral agent selected from the group consisting of aciclovir, brivudine, docosanol, famciclovir, ganciclovir, idoxuridine, penciclovir, trifluridine, tromantadine, valaciclovir, and valganciclovir.

Claim 15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of an orally disintegrating tablet (ODT).

Claim 16. The pharmaceutical composition of claim 15, wherein the ODT comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid, and the rapidly dispersing granules comprise the disintegrant and a sugar alcohol and/or saccharide.

Claim 17. The pharmaceutical composition of claim 16, wherein the drug particles have an average particle size of less than about 400 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm , and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 μm .

Claim 18. The pharmaceutical composition of claim 16, wherein the drug particles have an average particle size of less than about 4 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm .

Claim 19. The pharmaceutical composition of claim 16, wherein the corticosteroid is disposed over the surface of an excipient, the

rapidly dispersing granules have an average particle size of less than about 300 μm .

Claim 20. The pharmaceutical composition of claim 4, wherein the adhesive agent and the corticosteroid are intimately associated.

Claim 21. The pharmaceutical composition of claim 20, wherein said corticosteroid is surrounded or encapsulated by the adhesive agent.

Claim 22. The pharmaceutical composition of claim 20, wherein the corticosteroid is disposed on the surface of said adhesive agent.

Claim 23. The pharmaceutical composition of claim 16, wherein the ODT comprises a lyophilized matrix, wherein the lyophilized matrix comprises the corticosteroid in combination with at least one excipient.

Claim 24. The pharmaceutical composition of claim 23, wherein the excipient is selected from the group consisting of mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

Claim 25. The pharmaceutical composition of claim 23, wherein the ODT is in the form of a wafer or film.

Claim 26. The pharmaceutical composition of claim 16, wherein the ODT is in the form of a wafer or film.

Claim 29. A method for treating an inflammatory condition of the gastrointestinal tract comprising administering to an individual in need thereof a pharmaceutical composition according to claim 1.

Claim 30. The method of claim 29, wherein said inflammation of the gastrointestinal tract comprises inflammation of the esophagus.

Claim 31. The method of claim 29, wherein said condition is eosinophilic esophagitis.

Claim 32. The method of claim 29, wherein said inflammation comprises inflammation of the glottis, epiglottis, tonsils, or oropharynx.

Claim 33. The method of claim 29, wherein said condition is viral or bacterial pharyngitis.

Claim 34. The method of claim 29, wherein said condition is gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD) or erosive esophagitis.

Claim 35. The solid composition of claim 1, formulated for topical administration to the upper gastrointestinal tract.

Claim 36. The solid composition of claim 35, wherein the upper gastrointestinal tract is further defined as the esophagus.

Claim 37. The pharmaceutical composition of claim 16, wherein the ODT further comprises a sugar alcohol, a disintegrant, and microcrystalline cellulose, wherein the drug particles comprise fluticasone, and the rapidly dispersing granules comprise a disintegrant and a sugar alcohol or saccharide or a mixture thereof.

Claim 39. The solid pharmaceutical composition of claim 1, that comprises from about 0.01 mg and about 20 mg fluticasone.

Claim 40. The solid pharmaceutical composition of claim 1, that comprises from about 2 to about 10 mg fluticasone.

EX1001 (“the ’729 patent”) at Claims 2-26, 29-37, and 39-40.

B. Independent claim 27 and its dependent claims

41. Independent claim 27 of the '729 patent recites:

Claim 27. An orally disintegrating tablet comprising
[i] less than or equal to about 20 mg of a corticosteroid selected from
the group consisting of fluticasone, budesonide, mometasone, and salts,
solvates and esters thereof, and
[ii] at least one disintegrant, wherein
[iii] the orally disintegrating tablet disintegrates within 60 seconds
when tested using the USP <701> Disintegration Test.²

EX1001 (“the '729 patent”) at Claim 27.

42. Claims 28 and 38 depend from independent claim 27. These claims are reproduced below.

Claim 28. The orally disintegrating tablet of claim 27, that
comprises from about 2 to about 10 mg fluticasone.

Claim 38. The orally disintegrating tablet of claim 27, that
comprises from about 0.01 mg and about 20 mg fluticasone.

EX1001 (“the '729 patent”) at Claims 28 and 38.

VII. SCOPE AND CONTENT OF THE PRIOR ART

43. In this section of my declaration, I provide an overview of knowledge
that a person of ordinary skill in the art would have possessed based on the scope

² Bracketed labels have been added for convenient referencing to the claim limitations.

and content of the prior art as of October 2009. I begin with a discussion of budesonide, followed by a discussion of solid orally disintegrating pharmaceutical compositions, and FDA Guidance regarding in vitro testing of such compositions.

A. **Budesonide Was A Known Corticosteroid With Desirable Anti-Inflammatory Activity**

44. Glucocorticoids were known to be an important class of drugs that were used by clinicians due to their anti-inflammatory and immunosuppressive effects by October of 2009. *See* EX1025 (Goodman & Gillman’s) at 1014-1015 (“The effects of glucocorticoids on the inflammatory response are numerous and well documented.”). Budesonide was known to be a potent anti-inflammatory glucocorticoid before October of 2009. For example, Goodman & Gillman’s explains that budesonide “is proposed to deliver adequate steroid therapy to a specific portion of inflamed gut while minimizing systemic side effects owing to extensive first pass hepatic metabolism to inactive derivatives. Topical therapy (e.g., enemas and suppositories) also is effective in treating colitis limited to the left side of the colon. While the topical potency of budesonide is 200 times higher than hydrocortisone, its oral systemic bioavailability is only 10%.” *Id.* As another example, Svoboda explains that budesonide has a “unique local mechanism of delivery and efficient first-pass metabolism, [which] result[s] in fewer systemic adverse effects than with conventional glucocorticoids.” Svoboda et al., “Oral formulations of budesonide: a novel treatment for inflammatory bowel disease,”

Drugs of Today, 44:857-863 (2008) (EX1009) at 857 (“Budesonide is a promising drug for a variety of documented applications and has potential in gastroenterology. Its unique local mechanism of delivery and efficient first-pass metabolism, resulting in fewer systemic adverse effects than with conventional glucocorticoids, makes this a desirable drug for clinical practice.”). Svoboda explains that these properties made budesonide a desirable drug for clinical practice to treat a wide spectrum of inflammatory diseases as follows:

Summary

Budesonide is a promising drug for a variety of documented applications and has potential in gastroenterology. Its unique local mechanism of delivery and efficient first-pass metabolism, resulting in fewer systemic adverse effects than with conventional glucocorticoids, makes this a desirable drug for clinical practice. This drug has shown promise in treating a wide spectrum of inflammatory diseases from inflammatory bowel disease and other colitides to autoimmune liver diseases. Future research should focus on ways to increase delivery methods to promote long-term usage for maintenance therapy for the disease entities listed above, as well as for other potential nongastrointestinal conditions.

EX1009 (Svoboda) at 857.

45. As another example, Tan teaches that budesonide was selected to treat eosinophilic gastroenteritis because it is “a locally acting corticosteroid with a high first-pass effect, which minimizes systemic side effects.” Tan et al., “Eosinophilic

gastroenteritis treated with non-enteric-coated budesonide tablets,” European Journal of Gastroenterology & Hepatology, 13:425-427 (2001) (EX1010) at 425 (“Based on a surgical full-thickness biopsy of the antrum, the diagnosis of eosinophilic gastroenteritis was made. Treatment with prednisone resulted in a clinical response, but the prednisone dose could not be lowered below 5 mg. *We preferred to treat the patient with corticosteroids with minimal systemic side effects.* As there was gastric involvement, we could not give entericcoated budesonide capsules. *Therefore, we treated the patient with budesonide tablets,* which were designed originally for use as a clyisma but now are given orally. With this treatment regimen, the patient has been in remission for more than 2 years.”) (emphasis added). Tan teaches that eosinophilic gastroenteritis is a disorder “that can involve any area of the gastrointestinal tract.” *Id.* at page 425 (“Eosinophilic gastroenteritis is an uncommon disorder that may involve any area of the gastrointestinal tract. Treatment consists of corticosteroids, which induce a quick response.”). A person of ordinary skill in the art would have considered budesonide to be a desirable drug for treating inflammation of the gastrointestinal tract.

46. Before October of 2009, Dr. Falk Pharma had developed an orally administered gastro-resistant capsule formulation of budesonide known as Budenofalk®. EX1028 (Dr. Falk Pharma Brochure) at 7 (“1998 Launch of Budenofalk®, a topical corticosteroid for the treatment of inflammatory bowel

diseases.”). Budenofalk[®] was also used for treatment of patients suffering from Crohn’s Disease. *Id.*

47. In addition, Dr. Falk Pharma’s Budenofalk[®] formulation had been used to successfully treat ulcerative colitis, eosinophilic gastroenteritis, and obstructive eosinophilic jejunitis. For example, Kolkman studied Budenofalk[®] in 16 patients having distal ulcerative colitis and reported that “Budenofalk[®] is effective in distal [ulcerative] colitis and side effects are rare.” Kolkman et al., “Evaluation of oral budesonide in the treatment of active distal ulcerative colitis,” *Drugs of Today*, 40:589-601 (2004) (EX1011) at 589-590 (“This limited study suggests that Budenofalk[®] is effective in distal colitis and side effects are rare.”). Kolkman encouraged persons of ordinary skill in the art to conduct “a large clinical trial” to confirm “efficacy and assess further possible side effects.” *Id.* at 590 (“Based on these observations a large clinical trial using 9 mg o.d. is indicated to confirm efficacy and assess further possible side effects.”).

48. Siewert reported that Budenofalk[®] was used to successfully treat eosinophilic gastroenteritis. *See* Siewert et al., “Eosinophilic gastroenteritis with severe protein-losing enteropathy: Successful treatment with budesonide,” *Digestive and Liver Disease*, 38:55-59 (2006) (EX1012) at 55 (“Both the inflammatory alterations and the severe intestinal protein loss [of a patient diagnosed with eosinophilic gastroenteritis] were successfully treated with budesonide

[formulated as Budenofalk[®]], a topically active corticosteroid preparation with controlled small bowel release.”).

49. Elsing reported that Budenofalk[®] was used to successfully treat eosinophilic jejunitis. *See* Elsing et al., “Budesonide for the treatment of obstructive eosinophilic jejunitis,” *Z. Gastroenterology*, 45:187-189 (2007) (EX1013) at 187 (“Our subject is a male patient in whom the disease involves the muscular layer causing obstructive jejunitis. The diagnosis was made after surgical resection. A relapse was subsequently treated with short-term intravenous steroids followed by oral budesonide for three months. Treatment [with Budenofalk[®]] was effective with no apparent side effects.”).

50. In 2005, Aceves reported that a viscous suspension of budesonide was orally administered as a topical formulation to successfully treat eosinophilic esophagitis (EOE or EE). *See* Aceves et al., “Topical viscous budesonide suspension for treatment of eosinophilic esophagitis,” *Journal of Allergy and Clinical Immunology* 116:705-706 (2005) (EX1014, hereafter “Aceves 2005”) at 706. Aceves 2005 explains that the clinicians conducting the study opted for the topical viscous suspension formulation of budesonide because it was easier to administer and avoided long-term systemic therapy as follows:

Because long-term systemic steroid therapy can result in significant secondary side effects on growth and bone development, we opted for a topical steroid formulation that is easier to use in young or

developmentally delayed children and does not require the use of a MDI inhaler.

EX1014 (Aceves 2005) at 706. Aceves 2005 explained that “viscous oral suspension of budesonide improved symptoms, resolved endoscopic abnormalities, and markedly reduced or eliminated esophageal eosinophils in 2 patients unable to use a MDI inhaler with a puff and swallow technique.” *Id.* (“In our experience, a viscous oral suspension of budesonide improved symptoms, resolved endoscopic abnormalities, and markedly reduced or eliminated esophageal eosinophils in 2 patients unable to use an MDI inhaler with a puff and swallow technique.”). Aceves 2005 concluded that “oral budesonide suspension warrants further investigation for the treatment of patients with EE.” *Id.* (“As such, oral budesonide suspension warrants further investigation for the treatment of patients with EE.”).

51. Following the success reported by Aceves 2005, the Aceves team of researchers expanded their trial in 2007 to 20 patients and “described the efficacy and safety of once daily oral viscous budesonide (OVB) in inducing and maintaining remission of disease activity in children with EE.” Aceves et al., “Oral Viscous Budesonide: A potential new therapy for eosinophilic esophagitis in children,” *American Journal of Gastroenterology*, 102:1-9 (2007) (EX1015, hereinafter “Aceves 2007”) at 1 (“This is a retrospective analysis of symptoms, endoscopic and histological findings, efficacy, and safety of treatment in children with EE receiving oral viscous budesonide.”). Aceves 2007 reported that “[e]ighteen (90%) of our

patients, including the partial responder and one nonresponder, had improved endoscopy scores and all symptomatic children had improved symptom scores.” *See Id.* at 6 (“Eighteen (90%) of our patients, including the partial responder and one nonresponder, had improved endoscopy scores and all symptomatic children had improved symptom scores.”). Aceves 2007 explained that the oral viscous budesonide formulation was likely to provide clinical advantages because it was palatable, provided topical administration through pan-esophageal mucosa, and requires only once daily administration as follows:

Our data suggest that OVB is an effective and safe treatment for young children with proven EE. It may have advantages over other therapies in that it is palatable, its volume (8–12 Ml) provides pan-esophageal mucosal coverage, and it requires only once daily administration.

Aceves 2007 at 8. Aceves 2007 concluded that “[t]opical viscous budesonide is a safe and effective therapy for EE in young children.” *Id.* at Abstract; *see also id.* at 8 (under the “STUDY HIGHLIGHTS” heading stating “Oral viscous budesonide (OVB) is safe, effective therapy for EE in children.”).

52. The Aceves team of clinicians filed a provisional patent application on November 12, 2005, and a non-provisional patent application on November 9, 2006. *See* US2007/0111978 (EX1002, hereinafter “Dohil”) at title page items (22) and (60):

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(54) **VISCOUS BUDESONIDE FOR THE
TREATMENT OF INFLAMMATORY
DISEASES OF THE GASTROINTESTINAL
TRACT**

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(57) **ABSTRACT**

Provided herein are methods for preventing or alleviating
the symptoms of and inflammation associated with inflam-
matory diseases and conditions of the gastrointestinal tract,
for example, those involving the esophagus. Also provided
herein are pharmaceutical compositions useful for the meth-
ods of the present invention.

53. Dohil summarizes the data from Aceves 2005 in Examples 1 and 2. *See* EX1002 (Dohil) at ¶¶[0046]-[0047]. Dohil also summarizes the data from Aceves 2007 in Example 3. *See id.* at ¶¶[0048]-[0070]. Dohil's abstract states that the patent application discloses pharmaceutical compositions for preventing or alleviating the symptoms of inflammatory diseases and conditions of the gastrointestinal tract, such as the esophagus, as follows:

Provided herein are methods for preventing or alleviating the symptoms of and inflammation associated with inflammatory diseases and conditions of the gastrointestinal tract, for example, those involving the esophagus. Also provided herein are pharmaceutical compositions useful for the methods of the present invention.

EX1002 (Dohil) at Abstract; *see also id.* at ¶[0002] ("The invention is in general directed to methods and pharmaceutical compositions for preventing or alleviating

the symptoms of and inflammation associated with inflammatory diseases involving the esophagus.”).

54. Dohil discloses that “[l]ong term systemic steroid therapy can result in significant secondary side effects on growth and bone development, therefore topical steroid formulations are often used to treat EE and potentially other inflammatory gastrointestinal diseases and conditions involving the esophagus.” EX1002 (Dohil) at ¶[0005]. Dohil emphasizes that topical steroid formulations are advantageous for treating the upper gastrointestinal tract. *Id.* at ¶[0010] (“The present methods are also useful for preventing or alleviating symptoms and inflammation associated with other diseases or conditions of the gastrointestinal tract, for example, the upper gastrointestinal tract, where it is beneficial to target a particular target site, rather than provide systemic therapy”).

55. Dohil explains that previous methods of administering topical steroids to the esophagus through a metered-dose inhaler had drawbacks of being difficult to administer as follows:

Systemic corticosteroids and swallowed topical steroids, such as fluticasone propionate (Flovent™) administered through metered-dose inhaler (MDI), have been shown to induce and maintain low esophageal eosinophil levels (25-30). In one method, for example, a fluticasone metered dose inhaler (MDI) is puffed into the oropharynx and swallowed (Teitelbaum, J E, Fox, V L, Twarog F J, Nurko S, Ntonioli D, Gleich G, Badizadegan K, Furuta G T. Eosinophilic esophagitis in

children: immunopathological analysis and response to fluticasone propionate. Gastroenterology. 2002;122:1216-25.). This puff and swallow technique is often difficult for patients, especially smaller children, and especially children with developmental delays, to perform efficiently. This results in a less than effective dose of the topical steroid being delivered to the esophagus.

EX1002 (Dohil) at ¶[0006].

56. Dohil teaches that the budesonide is the preferred topically administered corticosteroid for its compositions as indicated by the following six quotations from Dohil:

- “In certain aspects, the corticosteroid is a topical corticosteroid, such as, for example, Budesonide.” EX1002 (Dohil) at ¶[0011];
- “Also provided are pharmaceutical compositions comprising a corticosteroid, for example a topical corticosteroid, such as, for example, Budesonide, in the form of a dissolving tablet, a dissolving wafer, a capsule, or a gel capsule.” EX1002 (Dohil) at ¶[0013];
- “Compounds useful in the present invention include topical steroids that may be used to treat inflammatory gastrointestinal conditions, including, for example, Budesonide.” EX1002 (Dohil) at ¶[0026];

- “In other illustrative embodiments of the invention, the Budesonide is provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus.” EX1002 (Dohil) at ¶[0032];
- “5. The method of claim 1, wherein said corticosteroid is Budesonide.” EX1002 (Dohil) at 12, claim 5; and
- “17. The pharmaceutical composition of claim 15, wherein said corticosteroid is Budesonide.” EX1002 (Dohil) at 12, claim 17.

57. Dohil discloses at least two types of formulations of budesonide:

- (1) a viscous oral suspension of budesonide (*see, e.g.*, Dohil at ¶¶[0021], [0030], [0046]-[0070]); and
- (2) a solid oral lozenge formulation that dissolves rapidly in the mouth or esophagus (*see, e.g.*, Dohil at ¶¶[0032], [0013], [0037], claims 19 and 20).

58. With respect to the solid oral lozenge formulation, Dohil discloses that “Budesonide is provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus. The lozenge or other similar tablet, capsule, or other solid, wo[u]ld dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.” EX1002 (Dohil) at ¶[0032] (“In other illustrative embodiments of the invention, the Budesonide is provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and

coating the esophagus. The lozenge or other similar tablet, capsule, or other solid, [would] dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.”). Dohil discloses budesonide in the form of a dissolving tablet and a dissolving wafer. *See id.* at ¶[0013] (“Also provided are pharmaceutical compositions comprising a corticosteroid, for example a topical corticosteroid, such as, for example, Budesonide, in the form of a dissolving tablet, a dissolving wafer, a capsule, or a gel capsule.”). Dohil discloses that “disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.” *Id.* at ¶[0037] (“If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.”). Dohil’s claims 19 and 20 recite dissolving tablets and wafers. EX1002 (Dohil) at 12 (“19. The pharmaceutical composition of claims 15-17, wherein said composition is a dissolving tablet. 20. The pharmaceutical composition of claims 15-17, wherein said composition is a dissolving wafer.”).

59. Based on at least the foregoing, the desirability of using budesonide to treat inflammation of the upper gastrointestinal tract was well known in the prior art. A person of ordinary skill in the art would have been motivated to make a solid orally disintegrating pharmaceutical composition containing budesonide based on at least, for example, Dohil and additional references discussed herein. By 2009, methods

for formulating orally disintegrating compositions containing pharmaceutically active ingredients were well known in the prior art for reasons discussed, for example, in the next section of my declaration.

B. Orally disintegrating pharmaceutical compositions

60. Orally disintegrating pharmaceutical compositions were well-known in the prior art by October of 2009. Orally disintegrating pharmaceutical compositions dissolve or disintegrate in a patient's mouth in the absence of additional water. The patient's saliva causes the orally disintegrating pharmaceutical composition to disintegrate, and this allows the active ingredient contained in the composition to dissolve or disperse in the saliva. Thereafter, the active ingredient may be absorbed through the mucosa of the mouth, esophagus, or other sections of the gastrointestinal track.

61. Several review articles describing orally disintegrating pharmaceutical compositions were available by 2009. These reviews included:

- Fu et al., "Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies," Critical Reviews in Therapeutic Drug Carrier Systems, 21:433-475 (2004) (EX1018);
- Danckwerts, "Intraoral Drug Delivery: A Comparative Review," American Journal of Drug Delivery, 1:171-186 (2003) (EX1017); and

- Shukla et al., “Mouth Dissolving Tablets I: An overview of formulation technology,” *Scientia Pharmaceutica*, 77:309-326 (2009) (EX1019).³

62. In the following paragraphs, I discuss (1) synonyms used to refer to orally disintegrating pharmaceutical compositions in the prior art literature, (2) the desirability of orally disintegrating pharmaceutical compositions to dissolve rapidly in saliva for the improvement of patient compliance with taking medication, (3) the desirability of solid formulations for oral administration and delivery of active ingredients, and (4) commercially available orally disintegrating pharmaceutical compositions that existed by the year 2009.

1. Synonyms for orally disintegrating pharmaceutical compositions

63. The prior art uses several terms to refer to orally disintegrating pharmaceutical compositions. For example, Fu refers to these compositions as “fast disintegrating tablets (FDTs).” *See* EX1018 (Fu) at Abstract (“Fast disintegrating

³ Shulka was published on March 6, 2009. *See* EX1019 (Shulka) at 309. Thus, Shulka was published nearly 7 months before the October 1, 2009 date on which the priority founding provisional application was filed for the ’729 patent. *See* EX1001 (the ’729 patent) at title page, item (60) (“Provisional Application No. 61/247,642, filed Oct. 1, 2009”). I understand that Shulka therefore qualifies as prior art to the ’729 patent.

tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients.”). Danckwerts refers to these compositions as “quick-disintegrating/dissolving tablet[s].” *See* EX1017 (Danckwerts) at 178 (“Quick-disintegrating/dissolving tablet drug delivery is now a well-accepted and important new class of drug delivery system.”). Shukla refers to these compositions as “mouth dissolving drug delivery systems (MDDS).” *See* EX1019 (Shukla) at Abstract (“MDDDS [mouth dissolving drug delivery systems] have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration.”).

64. A person of ordinary skill would have recognized that such terms were used relatively interchangeably in the literature to refer to solid orally disintegrating pharmaceutical compositions. For example, Fu explains that “[t]he FDT [fast disintegrating tablet] is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and/or quick disintegrating tablet.” EX1018 (Fu) at 434. Danckwerts similarly explains that “[t]oday the drug delivery systems are known as fast-dissolve, quick-dissolve, rapid melt, quick-disintegrating, etc., all representing the same type

of drug delivery systems, which is referred to in this review as the quick-disintegrating intraoral drug delivery system.” EX1017 (Danckwerts) at 178. Shukla explains that mouth dissolving tablets (MDTs) “are known by various names such as ‘fast-melting, fast-dissolving, oral disintegrating or orodisperse’.” EX1019 (Shukla) at 310 (“MDTs are known by various names such as ‘fast-melting, fast-dissolving, oral disintegrating, or orodisperse’.”).

65. Fu acknowledges that many orally disintegrating pharmaceutical compositions qualify as “orally disintegrating tablets” under the FDA’s definition of that term. *See* EX1018 (Fu) at 434 (“All FDTs [fast disintegrating tablets] approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets.”). In particular, the FDA defines “orally disintegrating tablets” as “[a] solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.” *See* FDA’s “Guidance for Industry: Orally Disintegrating Tablets,” U.S. Food & Drug Administration, Center for Drug Evaluation and Research (CDER), 2008 (EX1005, hereinafter “FDA Guidance”) at 2 (“A solid dosage form containing medical substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”).

2. Rapid disintegration/dissolving in saliva can improve patient compliance

66. A desirable feature of orally disintegrating pharmaceutical compositions is rapid disintegration and/or rapid dissolution in saliva. For example, Shukla teaches that “MDTs [mouth dissolving tablets] disintegrate and/or dissolve rapidly in saliva; therefore, water is not required during administration.” EX1019 (Shukla) at 310 (“These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatric and geriatric patients.”). Fu similarly teaches that “[t]he disintegration time for good FDTs [fast disintegrating tablets] varies from several seconds to about a minute.” EX1018 (Fu) at 434. As mentioned above, the FDA Guidance defines orally disintegrating tablets as a solid dosage form that “disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.” EX1005 (FDA Guidance) at page 2 (“A solid dosage form containing medical substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”).

67. Orally disintegrating pharmaceutical compositions were often developed to improve patient compliance with taking medication. It was known that many patients have difficulty swallowing tablets and gelatin capsules. For example, Fu teaches that “[d]ysphagia, or difficulty in swallowing, is common among all age

groups.” EX1018 (Fu) at 433 (“Dysphagia, or difficulty swallowing, is common among all age groups”). Fu further teaches that “dysphagia is common in about 35% of the general population, as well as an additional 30-40% of elderly institutionalized patients and 18-22% of all persons in long-term care facilities.” EX1018 (Fu) at 433-34 (“According to a study by Sastry et al., dysphagia is common in about 35% of the general population, as well as an additional 30-40% of elderly institutionalized patients and 18-22% of all persons in long-term care facilities.”). Fu teaches that “[a]nother study shows that an estimated 50% of the population suffers from this problem.” EX1018 (Fu) at 434. Shulka references yet another study, which “showed that 26% out of 1576 patients experienced difficulty in swallowing tablets due to their large size, followed by their surface, shape and taste.” EX1019 (Shulka) at 310 (“One study showed that 26% out of 1576 patients experienced difficulty in swallowing tablets due to their large size, followed by their surface, shape and taste.”).

68. Patients who have difficulty swallowing medications may have a high incidence of noncompliance with taking their medications, which can result in ineffective therapy. Danckwerts explains that “[l]ack of patient compliance is probably the most important factor that results in suboptimal therapeutic outcome for patients.” EX1017 (Danckwerts) at 172. Danckwerts explains that, “[t]o achieve optimal drug therapy, one must ensure that patients receive the correct medication,

at the right dosage, and at the most convenient dosing interval.” EX1017 (Danckwerts) at 172. Difficulties with patient compliance can be significantly improved by formulating active ingredients in an orally disintegrating pharmaceutical composition. For example, Fu explains that “[s]olid dosage forms that can be dissolved or suspended with water in the mouth for easy swallowing are highly desirable for the pediatric and geriatric population, as well as other patients who prefer the convenience of readily administered dosage forms.” EX1018 (Fu) at 434.

69. As discussed above, it was desirable for orally disintegrating pharmaceutical compositions to disintegrate rapidly in the mouth of a patient upon contact with saliva. For example, Fu explains that “[t]he key to FDT [fast disintegrating tablet] formulations is fast disintegration, dissolution, or melting in the mouth, and this can be achieved by producing the porous structure of the tablet matrix or adding superdisintegrant and/or effervescent excipients.” EX1018 (Fu) at 469. Fu further explains that “[t]he ‘fast disintegration’ usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible.” EX1018 (Fu) at 435. Danckwerts similarly discloses that “[w]hatever mechanism is used, the drug delivery systems all disintegrate in the patient’s mouth within a minute without the need of water or chewing.” EX1017 (Danckwerts) at 178. Danckwerts teaches that the rapid disintegration “is clearly why there is such

good patient compliance with these systems, and also why they are receiving so much interest from manufacturers.” EX1017 (Danckwerts) at 178.

70. The patient’s saliva provides an important role in dissolving and dispersing the active ingredient from an orally disintegrating pharmaceutical composition. For example, Danckwerts teaches that “[a] major feature of the environment of the oral cavity that plays a vital role in quick-disintegrating drug delivery systems is the presence of saliva, produced by the salivary glands.” EX1017 (Danckwerts) at 173. Danckwerts explains that “[t]he volume of saliva produced daily ranges between 0.5 and 2L, and it is this amount of fluid that is available to help disintegrate quick-disintegrating oral mucosal drug delivery systems.” EX1017 (Danckwerts) at 173-174.

3. Desirability of solid formulations for oral administration and delivery

71. Solid orally disintegrating pharmaceutical compositions were known to have several desirable properties as compared with liquid compositions. For example, Shulka teaches that a solid mouth-dissolving tablet formulation can provide “[c]onvenience of administration and accurate dosing as compared to liquid formulations.” EX1019 (Shulka) at 311. Dosing accuracy can be improved when a solid pharmaceutical composition is formulated for a single-unit dose as compared with a liquid formulation that is not premeasured (for example, inaccurate measuring during dosing or reconstitution of liquid formulations can lead to under- or over-

dosing). Also, solid pharmaceutical compositions can provide greater pharmaceutical stability, improved transportability, be easier to manufacture, be easier to store, lower the risk of contamination, and be lower in cost than a liquid formulation. For example, Fu teaches that “FDTs [fast disintegrating tablets] have all the advantages of solid dosage forms, such as good stability, accurate dosing, easy manufacturing, small packaging size, and easy handling by patients.” EX1018 (Fu) at 434. As another example, some liquid formulations require refrigeration during storage, which is less commonly required for solid formulations.

72. Another advantage of solid orally disintegrating pharmaceutical compositions is that they can be administered orally (through the mouth). For example, Danckwerts discloses that the oral cavity is an ideal route of administration to assist with patient compliance and safety as follows:

The oral cavity, however, does not have the same problems as other mucosal routes of drug delivery. Patient compliance is not a problem and there is no adverse physiological effect, such as mucociliary damage, that could possibly prohibit its use as a site for drug delivery. In addition, the oral mucosa is less vulnerable to damage or irritation than nasal mucosa. Another major advantage of oral mucosa as a site for drug delivery is that it facilitates removal in cases of emergency.

EX1017 (Danckwerts) at 172.

73. Another advantage of solid orally disintegrating pharmaceutical compositions is that they can promote absorption of active ingredients through the

oral mucosa, pharynx, and esophagus. For example, Shulka teaches that a solid mouth-dissolving tablet formulation can provide “[m]ore rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.” EX1019 (Shukla) at 311. Danckwerts teaches that transmucosal delivery through oral or esophageal mucosa can beneficially “avoid long-term parenteral therapy.” EX1017 (Danckwerts) at 172 (“To avoid long-term parenteral therapy, current research is focused mainly on the transmucosal and transdermal routes of drug delivery. Transmucosal routes available include the nasal passage, oral mucosa, vaginal passage or rectal mucosa as sites for possible drug application.”). Fu similarly discloses that bioavailability can be increased with a solid orally disintegrating pharmaceutical composition. *See* EX1018 (Fu) at 466 (“It has been found that FDTs [fast disintegrating tablets] can promote pregastric absorption of the active ingredients through buccal, sublingual, oropharyngeal, and esophageal membranes.”); *id.* at 467 (“Increased bioavailability and side-effect reduction were observed when the drugs with marketed first-pass hepatic metabolism were absorbed through the buccal and esophageal mucosa.”).

74. Danckwerts contrasts solid orally disintegrating pharmaceutical compositions with “intraoral mucoadhesive systems.” EX1017 (Danckwerts) at 174-178 (under heading “2.1 Intraoral Mucoadhesive Systems”). Intraoral mucoadhesive systems are designed to adhere to the oral mucosa. *Id.* at 174

(“Intraoral drug delivery systems designed to transfer drugs through the oral mucosa can be broadly categorized into four types: mucoadhesive buccal patches and tablets; quick-dissolving/disintegrating solid dosage forms; solid intraoral delivery systems; and aerosol intraoral drug delivery systems”). Danckwerts explains that few mucoadhesive drug delivery systems reached commercial production due to problems with effective bioadhesion and patient compliance. *See id.* at 174 (“Although much research has been conducted on mucoadhesive polymers, not many mucoadhesive drug delivery systems have reached commercial production. Effective bioadhesion and patient compliance still seem to be a problem.”). For example, a “mucoadhesive liquid” is one type of intraoral mucoadhesive formulations. *See* EX1017 (Danckwerts) at 178 (under heading “2.1.3 Mucoadhesive Liquid”). Mucoadhesive liquids can coat the oral mucosa to expose the oral cavity to pharmaceutically active ingredients over an extended period of time. *Id.* at 178 (“Most oral infections or diseases benefit from more prolonged contact with the mucosa, even those used as breath fresheners. To address this problem, Access Pharmaceuticals has developed their MucoAdhesive Liquid Technology, which provides an extended coating of the oral mucosa and can present pharmaceutically active ingredients to the entire oral cavity over an extended period.”). Unfortunately, such mucoadhesive liquid formulations can be undesirable because the extended contact time between the pharmaceutically active ingredients

and the oral mucosa can result in patients developing oral mucositis, which is “a painful ulcerative condition that is an adverse effect of the treatment.” *Id.* at 178. Development of oral mucositis can lead to patient noncompliance because it “can present as multiple ulcers appearing anywhere in the mouth.” *Id.* at 178 (“Patients exposed to long treatments of chemotherapy and radiation often develop oral mucositis, a painful ulcerative condition that is an adverse effect of the treatment”). Solid orally disintegrating pharmaceutical formulations were often more desirable than intraoral mucoadhesive formulations for at least these reasons.

4. Commercially available orally disintegrating pharmaceutical compositions

75. By 2009, there were several commercially available solid orally disintegrating pharmaceutical formulations available. Exemplary commercially available formulations included the Zydis[®] fast-dissolving wafer, the WOWTab[®] (With-Out-Water tablet), the Flash Dose[®] tablet, and OraSolv[®]. Each of these formulations are briefly described in the following paragraphs.

76. The Zydis[®] fast-dissolving wafer was developed in the late 1970s. *See* EX1017 (Danckwerts) at 178 (“Zydis[®] was the first quick-disintegrating intraoral drug delivery system to be commercialized on a large scale.”). It is a “freeze-dried structure [that] disintegrates within 2-3 seconds, releasing the drug.” *Id.* at 179 (“When Zydis[®] units are put into the mouth, the freeze-dried structure disintegrates within 2-3 seconds, releasing the drug.”). It is “suitable for drugs that are intended

for rapid absorption in the oral cavity.” *Id.* (“The quick disintegration is also suitable for drugs that are intended for rapid absorption in the oral cavity.”).

77. The WOWTab[®] (With-Out-Water tablet) accomplishes quick disintegration “by mixing a low-moldability saccharide with a high-moldability saccharide.” EX1017 (Danckwerts) at 179 (“Yamanouchi Pharmaceutical Co. found that when a raw material obtained by granulating a low moldability saccharide showing quick disintegration and dissolution was combined with a high moldability saccharide, and subjected to compression, the resulting tablet exhibited quick disintegration and dissolution in the buccal cavity.”). The WOWTab[®] was extensively studied, and by 1999 at least nine different formulations had been produced. *Id.* (“Until 1999, at least nine different formulations had been produced using the WOWTab[®] technology.”).

78. “The Flash Dose[®] tablet developed by Fuisz Technologies Ltd can dissolve in the mouth of the patient in less than 10 seconds.” EX1017 (Danckwerts) at 180. This tablet is made when a “blend of sugars is placed in a fast-spinning machine and subjected to flash heat to produce long, cotton candy-like fibers known as ‘floss.’” *Id.* (“The Shearform[™] technology used by Fuisz Technologies Ltd is a process in which a unique blend of sugars is placed in a fast-spinning machine and subjected to flash heat to produce long, cotton candy-like fibers known as ‘floss.’”).

79. OraSolv[®] is a saliva-activated effervescent tablet “for quick disintegration in the mouth [that] has been produced by Cima Labs Inc.” EX1017 (Danckwerts) at 181 (“Like normal oral effervescent tablets that disintegrate quickly in a glass of water, a saliva-activated effervescent tablet (OraSolv[®]) for quick disintegration in the mouth has been produced by Cima Labs Inc.”). “The effervescent sensation is not only pleasant to the patient but also tends to stimulate saliva production, thereby providing additional fluid to aid in further effervescent action.” *Id.* “Thus, once the tablet is placed in the patient’s mouth, it disintegrates rapidly and completely without any voluntary action by the patient.” *Id.*

80. Fu compiled several of the commercially available orally disintegrating pharmaceutical formulation technologies in Table 1, which is reproduced below:

Basis for Technology	Company	Technology
Lyophilization process	Cardinal Health	Zydis [®]
	Janssen Pharmaceutica	Quicksolv [®]
	Pharmalyoc	Lyoc [®]
	Elan	NanoCrystal [™]
Cotton candy process	Biovail (Fuisz)	FlashDose [®]
Tableting process	Cima Labs	OraSolv [®] /DuraSolv [®]
	Yamanouchi	WOWTAB [®]
	Elan Corp.	Fast Melt [®]
	Ethypharm	Flashtab [®]
	Eurand	AdvaTab [™] /Ziplets [®]
	KV Pharmaceutical	OraQuick [®]
	SPI Pharma	Pharmburst [™]
	Akina	Frosta [®]

EX1018 (Fu) at 437 (Table 1); *id.* at 436 (describing Table 1).

81. In addition, Fu discloses that “[t]here are about 40 drugs that have been formulated into marketed FDTs [fast disintegrating tablets] using various technologies (Table 2).” Table 2 from Fu is reproduced below:

Brand name	Active ingredient	Application	Company	Technology
Claritin® RediTabs®	Loratadine	Antihistamine	Schering Corporation	Zydis®
Feldene Melt®	Piroxicam	NSAID	Pfizer	
Maxalt®-MLT®	Rizatriptan benzoate	Migrane	Merck	
Pepcid® ODT	Famotidine	Anti-ulcer	Merck	
Zyprexa®	Olanzapine	Psychotic disorders	Eli Lilly	
Zofran® ODT®	Ondansetron	Anti-emetic	Glaxo Smith Kline	
Risperdal® M-Tab™	Risperidone	Schizophrenia	Janssen	
Zubrin™(pet drug)	Tepoxalin	Canine NSAID	Schering Corporation	
Zelapar™	Selegiline	Parkinson's disease	Elan / Amarin Corporation	
Klonopin® Wafers	Clonazepam	Sedation	Roche	
Children's Dimetapp® ND	Loratadine	Allergy	Wyeth Consumer Healthcare	
Imodium Instant Melts	Loperamide HCl	Anti-diarrheal	Janssen	
Propulsid® Quicksolv®	Cisapride monohydrate	Gastrointestinal prokinetic agent	Janssen	Quicksolv®
Tempra Quicklets Tempra FirsTabs	Acetaminophen	Analgesic	Bristol-Myers Squibb	OraSolv®
Remeron® SolTab®	Mirtazapine	Anti-depression	Organon Inc.	
Triaminic® Softchews®	Various combinations	Pediatric cold, cough and allergy	Novartis Consumer Health	

Zomig-ZMT® and Rapimelt®	Zolmitriptan	Anti-migraine	AstraZeneca	DuraSolv®
Alavert®	Loratadine	Allergy	Wyeth Consumer Healthcare	
NuLev®	Hyoscyamine sulfate	Anti-ulcer	Schwarz Pharma	
Kemstro™	Baclofen	Anti-spastic analgesic	Schwarz Pharma	
Benadryl® Fastmelt®	Diphenhydramine citrate	Allergy, sinus pressure relief	Pfizer	WOWTAB®
Nasea OD	Ramosetron HCl	Anti-emetic	Yamanouchi	
Gaster D	Famotidine	Anti-ulcer	Yamanouchi	
Excedrin® QuickTabs	Acetaminophen	Pain reliever	Bristol-Myers Squibb	QuickTabs™
Ralivia FlashDose®	Tramadol HCl	Analgesics	Biovail	FlashDose®
Zolpidem ODT	Zolpidem tartrate	Sleep disorders	Biovail	
Fluoxetine ODT	Fluoxetine	Anti-depression	Biovail	
Nurofen® Flashtab®	Ibuprofen	NSAID	Boots Healthcare	Flashtab®
Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	Anti-ulcer	ETHEX Corporation	OraQuick
Cibalginadue FAST	Ibuprofen	NSAID	Novartis Consumer Health	Ziplets™

EX1018 (Fu) at 438-439 (Table 2); *id.* at 436 (describing Table 2); *id.* at 469 (“There are about 40 drugs that have been formulated into marketed FDTs using various technologies (Table 2).”).

82. Ideally, a solid orally disintegrating pharmaceutical composition would be able to be formulated with a wide range of active ingredients. For example, Fu teaches that “[t]he FDT [fast disintegrating tablet] technology should be versatile enough to accommodate unique properties of each drug.” EX1018 (Fu) at 435; *see also id.* at 435 (“For the ideal FDT technology, the drug properties should not significantly affect the tablet property.”).

83. In sum, the prior art teaches that solid orally disintegrating pharmaceutical compositions were desirable to assist with patient compliance in taking medications and that many classes of drugs would benefit from being formulated into such compositions. For example, Danckwerts concludes that “[t]here is no doubt that the need for these systems is real, and many classes of drugs would benefit from this noninvasive type of drug delivery.” EX1017 (Danckwerts) at 183. Fu similarly explains that “[t]he popularity and usefulness of the formulation resulted in development of several FDT [fast disintegrating tablet] technologies” and they have “received ever-increasing demand” and “the field has become a rapidly growing area in the pharmaceutical industry.” EX1018 (Fu) at Abstract (“Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last

decade, and the field has become a rapidly growing area in the pharmaceutical industry.”). Fu concludes by stating that, “[c]onsidering the many benefits of FDTs [fast disintegrating tablets], it is only a matter of time until a majority of oral formulations are prepared in FDT forms.” EX1018 (Fu) at 469.

C. The Prior Art Discloses Solid Orally Disintegrating Compositions Of Budesonide

84. The formulation of budesonide as an orally disintegrating solid pharmaceutical composition that would dissolve rapidly was disclosed in at least the following four references by October of 2009:

- (1) U.S. Patent Publication No. 2007/0111978 to Dohil (EX1002);
- (2) WO2000/044351 to Grother (EX1008);
- (3) U.S. Patent No. 7,122,198 to Singh (EX1035); and
- (4) U.S. Patent No. 7,229,641 to Cherukuri (EX1036).

Dohil’s disclosure of orally disintegrating solid pharmaceutical compositions containing budesonide has been discussed above. Each of Grother, Singh, and Cherukuri are discussed below.

1. Grother

85. Grother discloses “fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.” EX1008 (Grother) at Abstract (“The present invention relates to fast dispersing solid dosage forms that preferably dissolve in the

oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.”). Grother defines fast dispersing dosage form (FDDF) as “compositions which disintegrate/disperse within 1 to 60 seconds, preferably 1 to 30 seconds, more preferably 1 to 10 seconds and particularly 2 to 8 seconds of being placed in the oral cavity.” *Id.* at 13:19-22 (“As used herein and in the claims, the term ‘fast dispersing dosage form (FDDF)’ refers to compositions which disintegrate/disperse within 1 to 60 seconds, preferably 1 to 30 seconds, more preferably 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity.”). Grother catalogues over 15 different fast dispersing dosage forms described in the prior art. *See id.* at 6:7-12:6, 13:22-14:6.

86. Grother discloses a fast dispersing dosage form comprising an active ingredient, a modified starch, and a matrix forming agent as follows:

There is disclosed a fast dispersing solid dosage form designed to release an active ingredient rapidly in the oral cavity characterized in that said dosage form is essentially free of mammalian gelatin and comprises:

- at least one active ingredient;
 - at least one modified starch at a concentration of from 20 to 90% by weight of said solid dosage form; and
 - at least one matrix forming agent;
- wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.

EX1008 (Grother) at 12:10-19. The fast dispersing dosage form is recited by Grother’s claim 1 as follows:

Claim 1. A fast dispersing solid dosage form designed to release an active ingredient rapidly in the oral cavity characterized in that said dosage form is essentially free of mammalian gelatin and comprises:

- a) at least one active ingredient;
- b) at least one modified starch at a concentration of from 20 to 90% by weight; and
- c) at least one matrix forming agent;

wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.

EX1008 (Grother) at page 12, claim 1.

87. Grother discloses that “[a]ny drug may be used as the active ingredient in the composition of the present invention.” EX1008 (Grother) at 15:19-20. Grother discloses that “[e]xamples of suitable drugs include but are not limited to those listed below:” EX1008 (Grother) at 15:20-21. Grother lists several types of suitable drugs. *See id.* at 16:1-21:15. Grother’s list of suitable drugs includes budesonide as follows:

Corticosteroids: beclomethasone, betamethasone, ***budesonide***, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.

EX1008 (Grother) at 18:15-18 (emphasis added).

2. Singh

88. Singh discloses that fast disintegrating tablets are particularly suitable for children or aged patients who have difficulty in chewing and/or swallowing an intact tablet/capsule as well as patients who have an upper gastrointestinal tract disease as follows:

However, in certain conditions there is a requirement of fast disintegrating or dissolving tablets which can be administered even without water. Such fast dissolving tablets disperse readily to form a suspension or solution of the drug after mixing with the saliva, which is easily swallowed by the patients. These are particularly suitable for children or aged patients who have difficulty in chewing and/or swallowing an intact tablet/capsule.

Fast mouth dissolving tablets are also suitable for those patients:—

- a) Who are suffering from nausea or vomiting;
- b) Who have an upper gastrointestinal tract disease e.g., injury in food pipe;
- c) Who have undergone upper GI surgery;
- d) Who are prostrate;
- e) Who are elderly and have frequent urination problems at night.
- f) Who are incapacitated elderly patients e.g. suffering from Parkinson's disease;
- g) Who are children;
- h) Who are in a situation where water is not available.

EX1035 (Singh) at 1:23-30.

89. Singh discloses that “fast dissolving tablets disperse readily to form a suspension or solution of the drug after mixing with the saliva, which is easily swallowed by the patients.” EX1035 (Singh) at 1:20-23. The fast dissolving tablet preferably “dissolves or disperses in the mouth within one minute.” *Id.* at 2:29-36 (“It is the object of the present invention to provide a pharmaceutical preparation in solid dosage form, preferably in the form of a compressed tablet which when orally administered dissolves or disperses in the mouth within one minute requiring very little amount of body fluids like saliva to produce a smooth solution or suspension of the drug with a prolonged sweet taste.”). Singh discloses a fast dissolving pharmaceutical composition in solid dosage form with a prolonged sweet taste comprising a pharmaceutically active reagent, a water soluble sugar, a non-sugar sweetener in a fast release form, and a non-sugar sweetener in a mucoadhesive slow release form as follows:

Accordingly the present invention relates to a novel fast dissolving pharmaceutical composition in solid dosage form with a prolonged sweet taste which comprises:

- a) at least one pharmaceutically active agent in an amount of from 0.1 to 99 weight % of the total dosage form;
- b) at least one water soluble sugar in an amount of from 5 to 95 weight % of the total dosage form;

- c) at least one non-sugar sweetener in a fast release form in an amount of from 0 to 10 weight % of the total dosage form; and
- d) at least one non-sugar sweetener in a mucoadhesive slow release form in an amount of from 0.5 to 20 weight % of the total dosage form.

EX1035 (Singh) at 2:37-49; *see also id* at 2:50-67 (disclosing “a process for the preparation of a fast dissolving pharmaceutical composition”).

90. Singh discloses that “[t]he drugs, pharmaceutically active agents or their salts to be employed for the fast dissolving buccal tablet in accordance with the present invention can be selected from the following group of drugs.” EX1035 (Singh) at 3:12-15. Singh lists several types of drugs that can be employed for the fast dissolving buccal tablet. *See id.* at 3:16-19:54. Singh’s list of drugs for use in the fast dissolving buccal tablet includes budesonide as follows:

GLUCOCORTICOID such as 21-Acetoxypregnenolone, Alclometasone, Algestone, Amcinonide, Beclomethasone, Betamethasone, Betamethasone dipropionate, **Budesonide**, Chloroprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Corticosterone, Cortisone, Cortivazol, Deflazacort, Desonide, Desoximetasone, Dexamethasone, Diflorasone, Diflucortolone, Difluprednate[,] Enoxolone, Fluazacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone acetonide, Fluocinonide, Fluocortin butyl, Fluocortolone, Fluorometholone, Fluperolone acetate, Fluprednidene acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halometasone, Halopredone Acetate, Hydrocotramate,

Hydrocortisone, Hydrocortisone Acetate, Hydrocortisone phosphate, Hydrocortisone 21-Sodium Succinate, Hydrocortisone Tebutate, Mazipredone, Medrysone, Meprednisone, Methylprednisolone, Mometasone furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 21-Diethylaminoacetate, Prednisolone Sodium Succinate, Prednisolone Sodium Phosphate, Prednisolone Sodium 21-mSulfobenzoate, Prednisolone 21-Stearoylglycolate, Prednisolone Tebutate[,] Prednisolone 21-Trimethylacetate, Prednisone, Prednival, Prednylidene, Prednylidene 21-Diethylaminoacetate, Tixocortal, Triamcinolone, Triamcinolone acetonide, Triamcinolone benetonide, Triamcinolone hexacetonide,

EX1035 (Singh) at 16:56-17:14 (emphasis added).

3. Cherukuri

91. Cherukuri discloses “a rapid-melt composition for delivery of prophylactic and therapeutic active materials,” that preferably is “a gastrointestinal therapeutic.” EX1036 (Cherukuri) at 1:15-20 (“The present invention relates to a rapid-melt composition for delivery of prophylactic and therapeutic active materials to a mammal, methods of making the same, and methods of using the same.”); *id.* 9:6-10 (“Still yet another preferred active material used in the composition of the present inventive matter is a gastrointestinal therapeutic. Gastrointestinal therapeutics are used to treat gastritis, nausea and vomiting, gastroesophageal reflux disease, colitis, Crohn's disease and diarrhea.”). Cherukuri discloses that “it is an important aspect of the present inventive subject matter that the compressed rapid-

melt product disintegrates quickly in the mouth of the mammal,” preferably “in less than 20 seconds of being placed in the mammal’s mouth.” *Id.* at 14:50-56 (“As stated previously, it is an important aspect of the present inventive subject matter that the compressed rapid-melt product disintegrates quickly in the mouth of the mammal. Preferably, the compressed rapid-melt product disintegrates in less than 20 seconds of being placed in the mammal's mouth, preferably within 10 seconds, and more preferably within 7 seconds.”). Cherukuri discloses that several classes of active ingredients can be formulated in the rapid-melt composition. *See id.* at 7:51-11:52. Cherukuri discloses the use of budesonide in the rapid-melt composition. *Id.* at 9:64-67 (“Other drugs which can also be used are fluticasone propionate, mometasone furoate, epinastine, beclomethasone dipropionate, triamcinolone acetonide, ***budesonide***,, and azelastine.”) (emphasis added).

34. Based on the foregoing, each of Dohil, Grother, Singh, and Cherukuri, disclose the formulation of budesonide as an orally disintegrating solid pharmaceutical composition.

D. FDA Guidance regarding in vitro testing of orally disintegrating compositions.

92. In December of 2008, the FDA published its guidance for the pharmaceutical industry regarding orally disintegrating tablets. *See* EX1005 (FDA Guidance). The documents relating to this guidance are available at this website: <https://www.regulations.gov/docket/FDA-2007-D-0365/document>. The FDA

published a draft of the guidance on April 8, 2007 in the Federal Register on April 9, 2007, and asked for comments and suggestions from the relevant public within 60 days of publication. *See* FDA’s “Guidance for Industry: Orally Disintegrating Tablets DRAFT GUIDANCE,” U.S. Food & Drug Administration, Center for Drug Evaluation and Research (CDER), 2007 (EX1007, hereinafter “FDA DRAFT Guidance”). There was virtually no change in the key technical content between the draft guidance published on April 8, 2007 and the final guidelines published in December of 2008.

93. The FDA Guidance explains that orally disintegrating tablets are designed to disintegrate or dissolve rapidly without the need to swallow or chew, which should benefit patients with impaired swallowing as follows:

In an effort to develop drug products that are more convenient to use and to address potential issues of patient compliance for certain product indications and patient populations, pharmaceutical manufacturers have developed products that can be ingested simply by placing them on the tongue. The products are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids. This mode of administration was initially expected to be beneficial to pediatric and geriatric patients, to people with conditions related to impaired swallowing, and for treatment of patients when compliance may be difficult (e.g., for psychiatric disorders).

EX1005 (FDA Guidance) at 1.

94. The FDA Guidance defines orally disintegrating tablets as “[a] solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.” EX1005 (FDA Guidance) at 2. The FDA Guidance further clarifies that orally disintegrating tablets are “solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative.” *Id.* at 2 (“Based on the original product rationale and Agency experience, we recommend that, in addition to the original definition, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative.”). The FDA Guidance explains that “[t]o provide both a standard for and consistency in disintegration testing, we recommend that applicants use the USP method for disintegration testing,” specifically “USP 29, <701> Disintegration, pp.2670-2672.” *Id.* at 3.

95. The USP <701> Disintegration Test “is provided to determine whether tablets or capsules disintegrate within the prescribed time when placed in a liquid medium.” *See* The United States Pharmacopeia 32, NF 27, Volume 1 (2009) (EX1016, hereinafter “USP”) at 262-63. The USP <701> Disintegration Test

involves immersing a tablet into an immersion fluid at $37\pm 2^{\circ}\text{C}$ for a specified time limit to observe if the tablet disintegrates. *Id.* at 262-263. “For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent.” *Id.* at 262. “Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core.” *Id.* A person of ordinary skill in the art would have been familiar with the USP <701> Disintegration Test in 2009.

VIII. INTRODUCTION TO OBVIOUSNESS GROUNDS

96. This section provides a summary of the obviousness grounds for claims 1-40 that are addressed in this declaration.

Ground	Reference(s)	Challenged Claims
1	Dohil in view of the knowledge of a POSA	1-7, 15, 20-21, 27, 29-36
2	Grother in view of the FDA Guidance	1-7, 9-15, 20, 27-28, 35-36, 38-40
3	Dohil and Venkatesh in view of the knowledge of a POSA	8, 16-18
4	Grother, the FDA Guidance, and Venkatesh	8, 16-26, 37

**IX. GROUND 1: DOHIL IN VIEW OF THE KNOWLEDGE OF A PERSON
OF ORDINARY SKILL IN THE ART**

97. Dohil discloses an orally disintegrating solid composition having the same ingredients claimed by the '729 patent. This section introduces Dohil, then explains how Dohil in view of the knowledge of a person of ordinary skill in the art renders obvious claims 1-7, 15, 20-21, 27, and 29-36 of the '729 patent.

A. Introduction to Dohil

98. Dohil discloses a budesonide formulation “provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus.” EX1002 (Dohil) ¶[0032] (“In other illustrative embodiments of the invention, the Budesonide is provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus.”). Dohil explains that the lozenge “or other similar tablet” will “dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.” *Id.* (“The lozenge or other similar tablet, capsule, or other solid, [would] dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.”). Exemplary dosage amounts of budesonide include “1-2 mg or 2-3 mg.” *Id.* at ¶[0015] (“In certain embodiments, 1-2 mg or 2-3 mg or corticosteroid per day is administered to said individual.”).

B. Claim 1

99. Dohil discloses orally disintegrating solid compositions that render obvious all limitations of claim 1.

1. Preamble

100. The preamble of claim 1 recites: “[a]n orally disintegrating solid pharmaceutical composition.”

101. Dohil discloses the recited orally disintegrating solid pharmaceutical composition. For example, Dohil discloses that “[b]udesonide is provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus. The lozenge or other similar tablet, capsule, or other solid, would dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.” EX1002 (Dohil) at ¶[0032]. Dohil discloses “[b]udesonide, in the form of a dissolving tablet.” *Id.* at ¶[0013] (“Also provided are pharmaceutical compositions comprising a corticosteroid, for example a topical corticosteroid, such as, for example, Budesonide, in the form of a dissolving tablet, a dissolving wafer, a capsule, or a gel capsule.”); *id.* at ¶[0037] (“Pharmaceutical preparations for oral use may be obtained by combining the corticosteroids with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.”).

102. Dohil’s lozenges and tablets are solid pharmaceutical compositions that dissolve rapidly in the mouth and meet the preamble.

2. Limitation 1[i]

103. Limitation 1[i] recites “less than or equal to about 20 mg of a topically administrable corticosteroid.”

104. Dohil discloses that “[b]udesonide is provided in the form of a lozenge which may be dissolved in the mouth.” EX1002 (Dohil) ¶[0032] (“In other illustrative embodiments of the invention, the Budesonide is provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus.”).

105. Budesonide is a topically administrable corticosteroid, as stated by the ’729 patent. EX1001 (the ’729 patent) 3:11-28 (“The term ‘having no significant systemic glucocorticoid or mineralocorticoid activity’, as used herein refers to corticosteroid compositions which do not provide a generalized effect in the body through absorption into the circulation, but do provide local effects through topical contact with a diseased tissue. Corticosteroids which have high systemic glucocorticoid potencies when administered orally include e.g., hydrocortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, etc.) or mineralocorticoid potencies (e.g., aldosterone). These corticosteroids may be suitable for use in the compositions of the present invention if they are used at a

sufficiently low dose, or are otherwise formulated such that they do not have significant systemic glucocorticoid or mineralcorticoid activity. Exemplary corticosteroids suitable for use in the compositions of the present invention include, but are not limited to budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone and tixocortol.”), 7:6-13 (“Suitable corticosteroids which may be included in the pharmaceutical compositions of the present invention include budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, tixocortol and salts, solvates, and esters thereof.”).

106. Dohil further discloses that “[i]n certain embodiments, 1-2 mg or 2-3 mg or corticosteroid per day is administered to said individual.” EX1002 (Dohil) ¶[0015] (“In certain embodiments, 1-2 mg or 2-3 mg or corticosteroid per day is administered to said individual.”); *id.* at ¶[0031] (“In general however, a suitable dose may be in the range of from about 10 to 400 ug/kg of body weight per day, or for example, in the range of 20 to 300 ug/kg per day, or for example in the range of 30 to 200 ug/kg per day, or for example in the range of 30 to 100 ug/kg per day, or for example in the range of 35 to 100 ug/kg per day, or for example in the range of 30-50 ug/kg per day, or for example in the range of 40-100 ug/kg/day, or for example in the range of 40-60 ug/kg/day, or in an illustrative embodiment in the range of 35-60 ug/kg/day.”), ¶[0058] (“In some embodiments of the invention, 0-1 mg/day, 1-2 mg/day, 2-3 mg/day, 3-4 mg/day, 4-5 mg/day, or 5-6 mg/day of corticosteroid, for

example topical corticosteroid, for example, Budesonide, are administered to a patient.”).

107. Dohil’s patients were actually dosed with budesonide at 0.5, 1, and 2 mg/day. *Id.* ¶[0058] (“Treatment. Patients received OVB for a mean of 3.6 months before repeat endoscopy. Fifteen patients received OVB 1 mg/day, four received 2 mg/day and one unintentionally received 0.5 mg/day [Table 1].”), ¶[0053] (“Treatment. Patients received OVB 0.5 to 2 mg daily and were instructed not to ingest any solids or liquids for 30 minutes afterwards.”), Table 1. Dohil discloses a lozenge or tablet containing a daily dose of budesonide. *Id.* [0031] (“In one illustrative example, the dose is provided once a day.”).

108. Dohil therefore discloses limitation 1[i].

3. Limitation 1[ii]

109. Limitation 1[ii] recites “at least one disintegrant.”

110. Dohil discloses that “[b]udesonide is provided in the form of a lozenge which may be dissolved in the mouth.” EX1002 (Dohil) ¶[0032] (“In other illustrative embodiments of the invention, the Budesonide is provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus.”). It was known to the person of ordinary skill in the art that the rapid dissolution of the lozenge is desirably aided by at least one disintegrating agent. For example, the Fu review article is representative of the person of ordinary skill in the

art's understanding and Fu describes several disintegrating agents used in orally disintegrating pharmaceutical compositions. *See* EX1018 (Fu) at 446-47 (heading “Disintegrants Used in FDTs”). Dohil teaches “[i]f desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate.” EX1002 (Dohil) at ¶[0037].

111. Dohil therefore discloses limitation 1[ii].

4. Limitation 1[iii]

112. Limitation 1[iii] recites “wherein the solid pharmaceutical composition has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration.”

113. **Claim construction:** The '729 patent defines “having no significant systemic glucocorticoid or mineralocorticoid activity” to refer “to corticosteroid compositions which do not provide a generalized effect in the body through absorption into the circulation, but do provide local effects through topical contact with a diseased tissue.” EX1001 (the '729 patent) at 3:11-16 (“The term ‘having no significant systemic glucocorticoid or mineralocorticoid activity’, as used herein refers to corticosteroid compositions which do not provide a generalized effect in the body through absorption into the circulation, but do provide local effects through topical contact with a diseased tissue.”). I have applied this definition.

114. The '729 patent states that budesonide has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration. EX1001 (the '729 patent) at 3:11-28 (“Exemplary corticosteroids suitable for use in the compositions of the present invention include, but are not limited to budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone and tixocortol.”). I understand that budesonide must have no significant systemic glucocorticoid or mineralocorticoid activity for dependent claim 3 (which recites “budesonide”) to properly depend from claim 1.

115. Dohil teaches the corticosteroid used in its formulations should “ha[ve] a low bioavailability” to “result in decreased systemic side effects and complications.” EX1002 (Dohil) at ¶[0041] (“In one illustrative embodiment, the corticosteroid of the composition has a low bioavailability, so that much of it will remain in the gastrointestinal tract, for example, in the esophagus. This may result in decreased systemic side effects and complications, allowing patients with chronic conditions to receive treatment for longer periods of time.”). Dohil teaches that budesonide undergoes “rapid hepatic metabolism.” EX1002 (Dohil) at ¶[0065] (“This may be because budesonide absorbed intestinally undergoes rapid hepatic metabolism.”). The rapid hepatic metabolism was a known property of budesonide that limits its systemic activity, as discussed above in the section of this report entitled “Budesonide Was A Known Corticosteroid With Desirable Anti-

Inflammatory Activity.” Thus, a person of ordinary skill in the art would have known that the rapid hepatic metabolism of budesonide would result in no significant systemic glucocorticoid or mineralocorticoid activity after oral administration in Dohil’s rapidly dissolving lozenges and tablets.

116. Dohil therefore discloses limitation 1[iii].

5. Limitation 1[iv]

117. Limitation 1[iv] recites “wherein the solid pharmaceutical composition disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.”

118. Dohil discloses that “[t]he lozenge or other similar tablet, capsule, or other solid, would dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.” EX1002 (Dohil) at ¶[0032]. A person of ordinary skill in the art would have understood that it was desirable for the disintegration time of Dohil’s rapidly dissolving lozenge or tablet to dissolve within, for example, several seconds to about a minute. For example, the Fu review article is representative of the person of ordinary skill in the art’s understanding and Fu teaches that orally disintegrating pharmaceutical compositions dissolve “from several seconds to about a minute.” EX1018 (Fu) at 434 (“The disintegration time for good FDTs varies from several seconds to about a minute.”).

119. It would have been obvious to formulate Dohil’s rapidly dissolving lozenge or tablet to disintegrate within 60 seconds when tested using the USP <701> Disintegration Test in view of the knowledge of the person of ordinary skill in the art. The knowledge of the person of ordinary skill in the art is represented by, for example, the FDA’s Guidance for Industry on orally disintegrating tablets. The FDA Guidance explains that orally disintegrating tablets “disintegrate rapidly, usually within a matter of seconds.” EX1005 (FDA Guidance) at 2 (“A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”). The FDA recommended that such compositions have “an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative (see Section IV).” *Id.* at 2 (“Based on the original product rationale and Agency experience, we recommend that, in addition to the original definition, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative”). The FDA Guidance “recommend[s] that applicants use the USP method for disintegration testing,” *id.* at 3 (“To provide both a standard for and consistency in disintegration testing, we recommend that applicants use the USP

method for disintegration testing.”), specifically “USP 29, <701> Disintegration,” *id.* at 3 n.3 (“USP 29, <701> Disintegration, pp. 2670-2672.”).⁴

120. A person of ordinary skill in the art would have been motivated to follow the FDA Guidance in formulating Dohil’s rapidly dissolving lozenge or tablet containing budesonide. The FDA Guidance provides the agency’s thinking and recommendations on the topic of orally disintegrating pharmaceutical compositions. *Id.* at 1 (“This guidance provides pharmaceutical manufacturers of new and generic drug products with an Agency perspective on the definition of an orally disintegrating tablet (ODT)—which is a different dosage form than, for example, a chewable tablet or a tablet that should be swallowed whole with liquid—and also provides recommendations to applicants who would like to designate proposed products as ODTs.”). The FDA regulates the use of pharmaceutical compositions in the United States. Dohil’s formulations were intended to “be used in therapy for human patients,” EX1002 (Dohil) at ¶[0028] (“While the compositions of the present invention will typically be used in therapy for human patients, they may also be used in veterinary medicine to treat similar or identical diseases.”), and the initial testing

⁴ Also, the FDA published draft guidance on April 8, 2007 that include the same key technical content as the final 2008 Guidance. *See* FDA DRAFT Guidance at page 1, 2, and 3.

of its formulations was conducted within the United States, *id.* at ¶[0049] (“This retrospective review was approved by Children’s Hospital, San Diego (CHSD) and University of California at San Diego (UCSD), Human Research Protection Program. Patients were referred from CHSD subspecialty clinics and other institutions to the EE clinic.”). A person of ordinary skill in the art seeking to formulate budesonide into an orally disintegrating pharmaceutical composition would be highly motivated to follow the FDA Guidance that such a composition should disintegrate within 30 seconds or less when tested using the USP <701> Disintegration Test.

121. A person of ordinary skill in the art would have had a reasonable expectation of success in formulating budesonide into a rapidly disintegrating lozenge or tablet that dissolved within 60 seconds using the USP <701> Disintegration Test based on Dohil’s description of how to formulate such rapidly disintegrating lozenges or tablets. See, e.g., ¶¶[0027]-[0041] (section entitled “Formulation”). Formulating orally disintegrating pharmaceutical compositions that dissolve within “several seconds to about a minute” would have been a routine exercise by 2009. EX1018 (Fu) at 434 (“During the last decade, fast disintegrating tablet (FDT) technologies that make tablets disintegrate in the mouth without chewing and additional water intake have drawn a great deal of attention.”); EX1005 (FDA Guidance) at 2 (“These products represented different manufacturing

technologies, a variety of tablet sizes and weights, and various disintegration strategies, thus demonstrating that relatively rapid disintegration is readily achievable across a variety of products.”). Based on the numerous commercially available orally disintegrating systems and products available by 2009, the person of ordinary skill in the art’s expectation of success would have been high. For example, the Danckwerts and Fu review articles are representative of the knowledge of the person of ordinary skill in the art. These references disclose several commercially available orally disintegrating systems and products. *See* EX1017 (Danckwerts) at 179-181; EX1018 (Fu) at 436-439. Thus, the development of an orally disintegrating dosage form would be readily achievable by 2009. Dohil in view of the knowledge of the person of ordinary skill in the art therefore renders obvious limitation 1[iv].

6. Limitation 1[v]

122. Limitation 1[v] recites “wherein upon administration the corticosteroid is deposited topically in the upper gastrointestinal tract.”

123. Upon administration of Dohil’s lozenge or tablet, it “dissolve[s] rapidly in the mouth or esophagus to produce a solution” of budesonide that is deposited topically in the upper gastrointestinal tract by “coat[ing] the esophagus.” EX1002 (Dohil) at ¶[0032] (“The lozenge or other similar tablet, capsule, or other solid, [would] dissolve rapidly in the mouth or esophagus to produce a solution that can

then coat the esophagus.”). Dohil repeatedly discloses that its formulations are designed to topically deposit budesonide in the “upper gastrointestinal tract,” *id.* at ¶[0010] (“The present methods are also useful for preventing or alleviating symptoms and inflammation associated with other diseases or conditions of the gastrointestinal tract, for example, the upper gastrointestinal tract, where it is beneficial to target a particular target site, rather than provide systemic therapy.”), such as “to the esophagus,” *id.* at ¶¶[0013] (“In certain embodiments, these tablets, wafers, and capsules are formulated with at least one excipient to deliver a viscous form of the corticosteroid to the esophagus.”), [0037] (“For dissolving tablets, appropriate excipients include those that increase the resulting liquid viscosity of the dissolved tablet, enabling it to reach the esophagus, for example, to coat the esophagus.”), [0041] (“In one illustrative embodiment, the corticosteroid of the composition has a low bioavailability, so that much of it will remain in the gastrointestinal tract, for example, in the esophagus”).

124. Dohil therefore discloses limitation 1[v]. Dohil in view of the knowledge of a person of ordinary skill in the art therefore renders obvious claim 1.

C. Claim 2

125. Claim 2 recites:

Claim 2. The solid pharmaceutical composition of claim 1, wherein said solid pharmaceutical composition disintegrates within 30 seconds.

126. Dohil discloses a budesonide lozenge or tablet that “dissolve[s] rapidly in the mouth.” EX1002 (Dohil) at ¶[0032] (“The lozenge or other similar tablet, capsule, or other solid, [would] dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.”). A person of ordinary skill in the art would have been motivated to formulate Dohil’s rapidly dissolving lozenge or tablet to disintegrate within 30 seconds with a reasonable expectation of success, as discussed above regarding limitation 1[iv]. Indeed, the FDA recommended that such compositions have “an in-vitro disintegration time of approximately 30 seconds or less,” EX1005 (FDA Guidance) at 2 (“Based on the original product rationale and Agency experience, we recommend that, in addition to the original definition, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative.”), using the “USP 29, <701> Disintegration” test. *Id.* 3 n.3 (“USP 29, <701> Disintegration, pp. 2670-2672.”).⁵ Dohil therefore renders obvious claim 2.

⁵ Also, the FDA published draft guidance on April 8, 2007 that include the same key technical content as the final 2008 Guidance. *See* FDA DRAFT Guidance at page 2 and 3.

D. Claim 3

127. Claim 3 recites:

Claim 3. The solid pharmaceutical composition of claim 1, wherein said corticosteroid is selected from the group consisting of budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, and salts, solvates and esters thereof.

128. Dohil discloses that “[b]udesonide is provided in the form of a lozenge which may be dissolved in the mouth.” EX1002 (Dohil) at ¶[0032] (“The lozenge or other similar tablet, capsule, or other solid, [would] dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.”), ¶[0013] (“Also provided are pharmaceutical compositions comprising a corticosteroid, for example a topical corticosteroid, such as, for example, Budesonide, in the form of a dissolving tablet, a dissolving wafer, a capsule, or a gel capsule.”). Dohil therefore renders obvious claim 3.

E. Claims 4 and 5

129. Claim 4 recites:

Claim 4. The solid pharmaceutical composition of claim 1, further comprising an adhesive agent.

130. Claim 5 recites:

Claim 5. The solid pharmaceutical composition of claim 4, wherein the adhesive agent is selected from the group consisting of sucrose aluminum sulfate complex, chitosan and derivatives thereof,

polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, cross-linked or uncross-linked polyacrylates, cross-linked polyacrylates, acidic cross-linked or uncross-linked polyacrylates, polyacrylic acid homopolymers or copolymers, aminoalkyl methacrylate copolymers, methacrylic acid/methylmethacrylate copolymer, alkylacrylate/alkylmethacrylate copolymers, ammoniomethacrylate copolymers, carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof.

131. **Claim construction:** The '729 patent defines “adhesive agent” to refer “to agents which promote adhesion of the corticosteroid to biological surfaces, and includes, but is not limited to bio-adhesive agents.” EX1001 (the '729 patent) at 2:66-3:2 (“The term ‘adhesive agent’, as used herein refers to agents which promote adhesion of the corticosteroid to biological surfaces, and includes, but is not limited to bio-adhesive agents.”). I have applied this definition. The '729 patent states that suitable adhesive agents include polyvinylpyrrolidone, sodium carboxymethylcellulose, and hydroxypropyl cellulose. *Id.* at 10:23-39 (“Suitable adhesive agents include sucrose aluminum sulfate complex, chitosan and derivatives thereof (e.g., trimethylchitosan, chitosan salts), polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, cross-linked or uncross-linked polyacrylates, cross-linked polyacrylates, acidic cross-

linked or uncross-linked polyacrylates, polyacrylic acid homopolymers or copolymers, aminoalkyl methacrylate copolymers, methacrylic acid/methylmethacrylate copolymer, alkylacrylate/alkylmethacrylate copolymers, ammoniomethacrylate copolymers, Eudragit® polymers (E, L, S, NE, RL, and RS grades), carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof[.]”).

132. Dohil discloses that its tablets are beneficially “formulated with at least one excipient to deliver a viscous form of the corticosteroid to the esophagus.” EX1002 (Dohil) at ¶[0013] (“In certain embodiments, these tablets, wafers, and capsules are formulated with at least one excipient to deliver a viscous form of the corticosteroid to the esophagus.”). Such excipients promote adhesion of the corticosteroid to the esophagus, which meets the claimed “adhesive agent.” “The excipient may be, for example, selected from the group consisting of... *hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and polyvinylpyrrolidone (PVP: povidone).*”) (emphasis added). *Id.* at ¶[0014] (“The excipient may be, for example, selected from the group consisting of lactose, sucrose, sucralose, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, *hydroxypropylmethyl-*

cellulose, sodium carboxymethyl-cellulose (CMC), and polyvinylpyrrolidone (PVP: povidone).”) (emphasis added); *id.* at ¶[0037] (“Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, sucralose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, *hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone).*”) (emphasis added). Dohil therefore renders obvious claims 4-5.

F. Claim 6

133. Claim 6 recites:

Claim 6. The solid pharmaceutical composition of claim 1, wherein the at least one disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, low-substituted hydroxypropylcellulose, mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

134. The '729 patent states that crospovidone is “cross-linked PVP [polyvinylpyrrolidone].” EX1001 (the '729 patent) at 8:50-51, 13:3-4 (“A non-limiting list of suitable disintegrants for the rapidly dispersing microgranules includes *crospovidone (cross-linked PVP)*, sodium starch glycolate, cross-linked sodium carboxymethylcellulose, calcium silicate, and low substituted hydroxypropyl cellulose.”).

135. Dohil teaches “[i]f desired, disintegrating agents may be added, such as the *cross-linked polyvinylpyrrolidone*, agar, or alginic acid or a salt thereof such as sodium alginate.” EX1002 (Dohil) at ¶[0037](emphasis added). Dohil therefore renders obvious claim 6.

G. Claim 7

136. Claim 7 recites:

Claim 7. The solid pharmaceutical composition of claim 1, further comprising an excipient selected from the group consisting of mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, cyclodextrin, and combinations thereof.

137. Dohil discloses that “[s]uitable excipients are, in particular, fillers such as sugars, including *lactose, sucrose... or sorbitol....*” EX1002 (Dohil) at ¶[0037] (“Suitable excipients are, in particular, fillers such as sugars, including *lactose, sucrose*, sucralose, mannitol, or *sorbitol*; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone).”(emphasis added); *id.* at ¶[0014] (“The excipient may be, for example, selected from the group consisting of *lactose, sucrose*, sucralose, mannitol, *sorbitol*, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-

cellulose, sodium carboxymethyl-cellulose (CMC), and polyvinylpyrrolidone (PVP: povidone).”) (emphasis added). Dohil therefore renders obvious claim 7.

H. Claim 15

138. Claim 15 recites:

Claim 15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of an orally disintegrating tablet (ODT).

139. **Claim construction:** The '729 patent defines “orally disintegrating tablet”, “orally dispersing tablet”, or “ODT” to refer “to a solid dosage form of the present invention, which disintegrates rapidly in the oral cavity of a patient after administration, without chewing.” EX1001 (the '729 patent) at 2:41-44 (“The terms “orally disintegrating tablet”, “orally dispersing tablet”, or “ODT” refer to a solid dosage form of the present invention, which disintegrates rapidly in the oral cavity of a patient after administration, without chewing.”). I have applied this definition. This definition is substantively the same as the definition of an orally disintegrating tablet adopted by the FDA. EX1005 (FDA Guidance) at 2 (“A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”).

140. Dohil discloses that budesonide formulated as a lozenge or tablet that “dissolve[s] rapidly in the mouth or esophagus.” EX1002 (Dohil) at ¶[0032] (“In other illustrative embodiments of the invention, the Budesonide is provided in the

form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus.”); *id.* at [0013] (“Also provided are pharmaceutical compositions comprising a corticosteroid, for example a topical corticosteroid, such as, for example, Budesonide, in the form of a dissolving tablet, a dissolving wafer, a capsule, or a gel capsule.”). A person of ordinary skill in the art would understand that Dohil’s lozenges and tablets dissolve rapidly in the oral cavity without chewing. Dohil therefore renders obvious claim 15.

I. Claims 20-21

141. Claim 20 recites:

Claim 20. The pharmaceutical composition of claim 4, wherein the adhesive agent and the corticosteroid are intimately associated.

142. Claim 21 recites:

Claim 21. The pharmaceutical composition of claim 20, wherein said corticosteroid is surrounded or encapsulated by the adhesive agent.

143. **Claim construction:** The ’729 patent defines “intimately associated” to “to describe the spatial relationship between two or more components of a composition refers to components [*sic*] that are intimately mixed, such as for example in mixtures, coatings and matrices.” EX1001 (the ’729 patent) at 3:6-10 (“The term “intimately associated”, as used herein to describe the spatial relationship between two or more components of a composition refers to components that are

intimately mixed, such as for example in mixtures, coatings and matrices.”). I have applied this definition.

144. Dohil discloses the claimed adhesive agent because its tablets are beneficially “formulated with at least one excipient to deliver a viscous form of the corticosteroid to the esophagus.” EX1002 (Dohil) at ¶[0013] (“In certain embodiments, these tablets, wafers, and capsules are formulated with at least one excipient to deliver a viscous form of the corticosteroid to the esophagus.”). The excipient promotes adhesion of budesonide to the esophagus for reasons discussed above regarding claims 4-5. Dohil further discloses “combining the corticosteroids with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules... to obtain tablets or dragee cores.” EX1002 (Dohil) at ¶[0037] (“Pharmaceutical preparations for oral use may be obtained by combining the corticosteroids with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.”). The process of grinding corticosteroids with adhesive agent excipients creates an intimate mixture that meets the claimed intimate association.

145. Dohil further discloses that the “[d]rage cores are provided with suitable coatings,” that include adhesive excipients of “polyvinylpyrrolidone.” EX1002 (Dohil) at ¶[0039] (“Dragee cores are provided with suitable coatings. For

this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.”). The dragee core contains the corticosteroid and is surrounded by the coating of adhesive excipient. Dohil therefore renders obvious claims 20-21.

J. Claim 27

146. Dohil in view of the knowledge of a person of ordinary skill in the art renders obvious claim 27 for the same reasons as claims 1 and 15, discussed above. Below is a table with a side-by-side comparison of claim 27 relative to claims 1 and 15:⁶

Claim 27 of the '729 patent	Claims 15 and 1 of the '729 patent
Claim 27. An orally disintegrating tablet comprising	Claim 15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of an orally disintegrating tablet (ODT).
[i] less than or equal to about 20 mg of a corticosteroid selected from the group consisting of fluticasone, budesonide,	Claim 1. An orally disintegrating solid pharmaceutical composition comprising

⁶ Bracketed labels, e.g., “[i]” and “[ii],” have been added for convenient referencing to the claim limitations.

Claim 27 of the '729 patent	Claims 15 and 1 of the '729 patent
mometasone, and salts, solvates and esters thereof, and	[i] less than or equal to about 20 mg of a topically administrable corticosteroid and
[ii] at least one disintegrant,	[ii] at least one disintegrant,
	[iii] wherein the solid pharmaceutical composition has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration,
[iii] wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.	[iv] wherein the solid pharmaceutical composition disintegrates within 60 seconds when tested using the USP <701> Disintegration Test, and
	[v] wherein upon administration the corticosteroid is deposited topically in the upper gastrointestinal tract.

1. Preamble

147. The preamble of claim 27 recites: “An orally disintegrating tablet comprising”.

148. Dohil renders the preamble of claim 27 obvious for reasons discussed above regarding claim 15.

2. Limitation 27[i]

149. Limitation 27[i] recites “[i] less than or equal to about 20 mg of a corticosteroid selected from the group consisting of fluticasone, budesonide, mometasone, and salts, solvates and esters thereof”.

150. Dohil renders obvious limitation 27[i] for reasons discussed above regarding limitation 1[i].

3. Limitation 27[ii]

151. Limitation 27[ii] recites “at least one disintegrant”.

152. Dohil renders obvious limitation 27[ii] for reasons discussed above regarding limitation 1[ii].

4. Limitation 27[iii]

153. Limitation 27[iii] recites “wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.”

154. Dohil renders obvious limitation 27[iii] for reasons discussed above regarding limitation 1[iv].

K. Claims 29-34

155. Claim 29 recites:

Claim 29. A method for treating an inflammatory condition of the gastrointestinal tract comprising administering to an individual in need thereof a pharmaceutical composition according to claim 1.

156. Claim 30 recites:

Claim 30. The method of claim 29, wherein said inflammation of the gastrointestinal tract comprises inflammation of the esophagus.

157. Claim 31 recites:

Claim 31. The method of claim 29, wherein said condition is eosinophilic esophagitis.

158. Claim 32 recites:

Claim 32. The method of claim 29, wherein said inflammation comprises inflammation of the glottis, epiglottis, tonsils, or oropharynx.

159. Claim 33 recites:

Claim 33. The method of claim 29, wherein said condition is viral or bacterial pharyngitis.

160. Claim 34 recites:

Claim 34. The method of claim 29, wherein said condition is gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD) or erosive esophagitis.

161. Dohil discloses using its formulations to treat inflammation, including inflammation of the esophagus, such as eosinophilic esophagitis as follows:

The methods of the present invention are useful, for example, for preventing and *alleviating the symptoms and inflammation of eosinophilic esophagitis*, inflammatory bowel diseases involving the esophagus, Crohn's disease, *esophageal inflammation* secondary to caustic/irritant ingestion, *persistent/recurrent esophageal strictures of*

any cause and including caustic/irritant ingestion, pill-induced esophagitis, systemic diseases, congenital diseases, Epidermolysis bullosa, and post-surgery inflammation. The present methods are also useful for preventing or *alleviating symptoms and inflammation associated with other diseases or conditions of the gastrointestinal tract, for example, the upper gastrointestinal tract*, where it is beneficial to target a particular target site, rather than provide systemic therapy.

EX1002 (Dohil) at ¶[0010]; *id.* at ¶[0011] (“Thus, in one embodiment is provided a method of *preventing or alleviating esophageal inflammation* in an individual comprising orally administering to said individual a corticosteroid in association with at least one excipient to increase the viscosity of the composition.”); ¶[0015] (“The pharmaceutical composition in certain embodiments comprises a therapeutically effective amount of corticosteroid to *prevent or alleviate esophageal inflammation.*”) (emphasis added).

162. It was known that budesonide was beneficial for treating eosinophilic gastroenteritis, which is a disorder that “may involve any area of the gastrointestinal tract.” EX1010 (Tan) at 425 (“Eosinophilic gastroenteritis is an uncommon disorder that may involve any area of the gastrointestinal tract.”); EX1036 (Cherukuri) at 9:6-10 (“Still yet another preferred active material used in the composition of the present inventive matter is a gastrointestinal therapeutic.”). Dohil renders obvious treating the inflammatory conditions recited by claims 29-34.

163. Further, it is basic human anatomy that the upper gastrointestinal tract includes the esophagus, glottis, epiglottis, tonsils, and oropharynx. Solid orally disintegrating compositions were known to promote absorption through the pharynx and oesophagus. EX1019 (Shulka) at 311 (“More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.”); EX1018 (Fu) at 466 (“It has been found that FDTs can promote pregastric absorption of the active ingredients through buccal, sublingual, oropharyngeal, and esophageal membranes.”). Thus, a person of ordinary skill in the art would understand that Dohil’s budesonide formulations that treat inflammation of the upper gastrointestinal tract include treating inflammation of the glottis, epiglottis, tonsils, and oropharynx. Dohil therefore renders obvious claims 29-34.

L. Claims 35-36

164. Claim 35 recites:

Claim 35. The solid composition of claim 1, formulated for topical administration to the upper gastrointestinal tract.

165. Claim 36 recites:

Claim 36. The solid composition of claim 35, wherein the upper gastrointestinal tract is further defined as the esophagus.

166. Dohil renders obvious claim 35 for reasons discussed above regarding Claim 1 limitation 1[v].

167. Dohil discloses that its lozenge or tablet “dissolve[s] rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.” EX1002 (Dohil) at ¶[0032] (“In other illustrative embodiments of the invention, the Budesonide is provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus.”); *id.* at ¶[0013] (“In certain embodiments, these tablets, wafers, and capsules are formulated with at least one excipient to deliver a viscous form of the corticosteroid to the esophagus.”), *id.* at ¶[0010] (“The methods of the present invention are useful, for example, for preventing and alleviating the symptoms and inflammation of eosinophilic esophagitis, inflammatory bowel diseases involving the esophagus, Crohn’s disease, esophageal inflammation secondary to caustic/irritant ingestion, persistent/recurrent esophageal strictures of any cause and including caustic/irritant ingestion, pill-induced esophagitis, systemic diseases, congenital diseases, Epidermolysis bullosa, and post-surgery inflammation.”). Dohil therefore renders obvious the topical administration of the corticosteroid to the esophagus in the upper gastrointestinal tract recited by claim 35 and 36.

X. GROUND 2: GROTHER IN VIEW OF THE FDA GUIDANCE

168. Grother discloses an orally disintegrating solid composition having the same ingredients claimed by the ’729 patent. A person of ordinary skill in the art would have been motivated to follow the FDA Guidance in formulating Grother’s

orally disintegrating solid composition to disintegrate within 60 seconds using the USP <701> Disintegration Test with a reasonable expectation of success. This section introduces Grother, and then explains how Grother in view of the FDA Guidance renders obvious claims 1-7, 9-15, 20, 27-28, 35-36, and 38-40 of the '729 patent.

A. Introduction to Grother

169. Grother discloses “fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.” EX1008 (Grother) at Abstract (“The present invention relates to fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.”). Grother’s fast dispersing dosage form comprises an active ingredient, a modified starch, and a matrix forming agent as follows:

There is disclosed a fast dispersing solid dosage form designed to release an active ingredient rapidly in the oral cavity characterized in that said dosage form is essentially free of mammalian gelatin and comprises:

- at least one active ingredient;
- at least one modified starch at a concentration of from 20 to 90% by weight of said solid dosage form; and
- at least one matrix forming agent;

wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.

EX1008 (Grother) at 12:10-19. Grother discloses that “[a]ny drug may be used as the active ingredient in the composition of the present invention,” EX1008 (Grother) at 15:19-20, including budesonide, *id.* at 18:15-18 (“**Corticosteroids:** beclomethasone, betamethasone, ***budesonide***, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.”) (emphasis added).

B. Claim 1

170. Grother in view of the FDA Guidance discloses orally disintegrating solid compositions that render obvious all limitations of claim 1.

1. Claim 1 Preamble

171. The preamble of claim 1 recites: “[a]n orally disintegrating solid pharmaceutical composition.”

172. Grother discloses the recited orally disintegrating solid pharmaceutical composition. For example, Grother discloses “a fast dispersing solid dosage form designed to release an active ingredient rapidly in the oral cavity.” EX1008 (Grother) at 12:10-19 (“There is disclosed a ***fast dispersing solid dosage form designed to release an active ingredient rapidly in the oral cavity*** characterized in

that said dosage form is essentially free of mammalian gelatin and comprises: at least one active ingredient; at least one modified starch at a concentration of from 20 to 90% by weight of said solid dosage form; and at least one matrix forming agent; wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.”); *id.* at 1:10-11 (“This invention relates to a ***pharmaceutical composition for oral administration in the form of a fast dispersing dosage form.***”) (emphasis added), 3:18-20 (“It has now been found that modified starches may be used instead of mammalian-derived gelatin to prepare ***fast dispersing dosage forms.***”) (emphasis added), 32:10 (“This invention relates to ***fast dissolving dosage forms for oral administration.***”) (emphasis added). Grother discloses “fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.” EX1008 (Grother) at Abstract (“The present invention relates to fast dispersing ***solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30),*** most preferably within ten (10) seconds.”) (emphasis added); *id.* 13:19-22 (“As used herein and in the claims, the term ‘fast dispersing dosage form (FDDF)’ refers to ***compositions which disintegrate/disperse within 1 to 60 seconds, preferably 1 to 30 seconds,*** more preferably 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity.”) (emphasis added).

2. Limitation 1[i]

173. Limitation 1[i] recites “less than or equal to about 20 mg of a topically administrable corticosteroid.”

174. Grother discloses that “the active ingredient is generally present in an amount from 0.2 to 95%, normally 1 to 20%, by weight of the composition of the dried dosage form.” EX1008 (Grother) 21:16-18 (“The precise quantity of active ingredient will depend on the drug selected. However, *the active ingredient is generally present in an amount from 0.2 to 95%, normally 1 to 20%, by weight of the composition* of the dried dosage form.”) (emphasis added). Grother discloses that 60 mg is generally the “upper value” per dosage form. *Id.* 26:22-27:1 (“Seagers et al. recognize that the dose of water soluble drugs is generally limited to *an upper value of about 60 mg per dosage form.*”) (emphasis added). Grother discloses specific examples of 10 mg and 12.5 mg of active ingredient per dosage form. *Id.* at 29, Table I.

175. Grother discloses that “[a]ny drug may be used as the active ingredient in the composition of the present invention,” EX1008 (Grother) at 15:19-20, including budesonide, *id.* at 18:15-18 (“**Corticosteroids:** beclomethasone, betamethasone, *budesonide*, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.”)

(emphasis added). A person of ordinary skill in the art would have been motivated to select budesonide as an active ingredient in Grother's fast dispersing solid dosage form based on Grother's express disclosure to do so. In addition, as discussed above, budesonide was a well-known corticosteroid with desirable anti-inflammatory activity. The '729 patent states that budesonide is a topically administrable corticosteroid. EX1001 (the '729 patent) at 3:11-28 ("Exemplary corticosteroids suitable for use in the compositions of the present invention include, but are not limited to budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone and tixocortol.").

176. It was generally known in the art that dosages of budesonide in solid oral tablets often ranged from 3-9 mg. For example, Budenofalk[®] contained 3 mg of budesonide in each dosage unit. EX1026 (Budenofalk[®] Brochure) at 8 ("Budenofalk[®] 3 mg capsules and Budenofalk[®] Rectal Foam contained budesonide as active ingredient, a glucocorticoid with high topical activity and low systemic effects leading to substantially reduced side effects."). Entocort EC tablets contained 3 mg of budesonide. EX1009 (Svoboda) at 859 ("Entocort EC is composed of 3 mg of budesonide in tablet form."). Other tablets contained 4.5 mg, 6 mg, 9 mg of budesonide. *Id.* ("Tremaine et al. compared budesonide 9 mg given once daily or divided into twice-daily dosing to placebo with a dose reduction during weeks 9 and 10 to 6 mg daily in the budesonide group."). Dohil discloses budesonide

formations containing, e.g., 1-2 mg and 5-6 mg per dosage unit. EX1002 (Dohil) at ¶¶[0058] (“In some embodiments of the invention, 0-1 mg/day, 1-2 mg/day, 2-3 mg/day, [3-4] mg/day, 4-5 mg/day, or 5-6 mg/day of corticosteroid, for example topical corticosteroid, for example, Budesonide, are administered to a patient.”), [0015] (“In certain embodiments, 1-2 mg or 2-3 mg or corticosteroid per day is administered to said individual.”), Table 1. Based on Grother’s instruction that its compositions should normally have 1-20% by weight active ingredient and the general knowledge in the art that formulations of budesonide typically contain, e.g., 3 mg of budesonide, a person of ordinary skill in the art would have been motivated to formulate budesonide in Grother’s compositions at, e.g., 3 mg, with a reasonable expectation of success. Grother therefore renders obvious a pharmaceutical composition that comprises less than or equal to about 20 mg of a topically administrable corticosteroid.

3. Limitation 1[ii]

177. Limitation 1[ii] recites “at least one disintegrant.”

178. The ’729 patent states that disintegrants include “starch” and modified starches such as “pregelatinized starch” and “carboxymethyl starch.” EX1001 (the ’729 patent) at 9:26-31 (“Examples of suitable disintegrants include e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium

starch glycolate, *starch*, *pregelatinized starch*, and *carboxymethyl starch* (e.g. Primogel® and Explotab®).”) (emphasis added).

179. Grother’s fast dispersing dosage form comprises “at least one modified starch at a concentration of from 20 to 90% by weight of said solid dosage form.” EX1008 (Grother) at 12:10-19. Grother discloses that modified starches, including pregelatinized starches and oxidized starches having carboxyl groups, “may be used as the primary structure forming agent in FDDF's [fast dispersing dosage forms] to form physically robust products while maintaining the desired rapid dispersion characteristics of the products.” EX1008 (Grother) at 4:2-4 (“Modified starches may be used as the primary structure forming agent in FDDF's to form physically robust products while maintaining the desired rapid dispersion characteristics of the products.”). Grother teaches that useful modified starches are generally readily dispersible in water. EX1008 (Grother) at 13:5-8 (“While many specific examples are provided on the useful modified starches, a general characteristic of the useful modified starches in the fast dispersing solid dosage form according to the invention is that they are readily soluble or dispersible in water at ambient temperature.”). Grother further discloses that a range of commercially available modified starches, including *pregelatinized starches*, are suitable for use in their orally dispersing tablets. EX1008 (Grother) at 5:10-6:5 (“A range of modified starches are commercially available and useful in the present invention and include:

Pregelatinized starches, produced by drum drying or extrusion; Low-viscosity starches, produced by controlled hydrolysis of glycosidic bonds; Dextrins, produced by roasting dry starch in the presence of a small amount of acid; Acid modified starches, produced by suspension in dilute acid until the required viscosity is reached; *Oxidized starches, oxidizing agents cause the introduction of carbonyl or carboxyl groups, wherein depolymerization occurs, leading to decreased retrogradation and gelling capacities*; Enzymatically modified starch, produced by controlled enzyme degradation to attain required physicochemical properties; Crosslinked starches, bi- or polyfunctional reagents react with hydroxyl groups to form crosslinks, examples of specific reagents include phosphorus oxychloride, sodium trimetaphosphate and epichlorohydrin; and Stabilized starches, starches are reacted with etherifying or esterifying reagents in the presence of an alkaline catalyst to give a wide range of products.”) (emphasis added). The at least one modified starch in Grother’s formulation meets the “at least one disintegrant” required by limitation 1[ii]. Grother therefore discloses at least one disintegrant.

4. Limitation 1[iii]

180. Limitation 1[iii] recites “wherein the solid pharmaceutical composition has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration.”

181. **Claim construction:** The '729 patent defines “having no significant systemic glucocorticoid or mineralocorticoid activity” to refer “to corticosteroid compositions which do not provide a generalized effect in the body through absorption into the circulation, but do provide local effects through topical contact with a diseased tissue.” EX1001 (the '729 patent) at 3:11-16 (“The term ‘having no significant systemic glucocorticoid or mineralocorticoid activity’, as used herein refers to corticosteroid compositions which do not provide a generalized effect in the body through absorption into the circulation, but do provide local effects through topical contact with a diseased tissue.”). I have applied this definition.

182. The '729 patent states that budesonide has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration. EX1001 (the '729 patent) at 3:11-28 (“Exemplary corticosteroids suitable for use in the compositions of the present invention include, but are not limited to budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone and tixocortol.”). I understand that budesonide must have no significant systemic glucocorticoid or mineralocorticoid activity for dependent claim 3 (which recites “budesonide”) to properly depend from claim 1.

183. Grother discloses the use of budesonide as the active ingredient in its composition. EX1008 (Grother) at 15:19-20, 18:15-18. Grother therefore discloses a solid pharmaceutical composition having no significant systemic glucocorticoid or

mineralocorticoid activity after oral administration. As a result, Grother discloses limitation 1[iii].

5. Limitation 1[iv]

184. Limitation 1[iv] recites “wherein the solid pharmaceutical composition disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.”

185. Grother discloses “fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.” EX1008 (Grother) at Abstract (“The present invention relates to fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.”); *id.* at 13:19-22 (“As used herein and in the claims, the term ‘fast dispersing dosage form (FDDF)’ refers to compositions which disintegrate/disperse within 1 to 60 seconds, preferably 1 to 30 seconds, more preferably 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity.”).

186. It would have been obvious to formulate budesonide in Grother’s fast dispersing solid dosage form to disintegrate within 60 seconds when tested using the USP <701> Disintegration Test in view of the FDA Guidance for Industry on orally disintegrating tablets. The FDA Guidance recommended that orally disintegrating

should have “an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative (see Section IV).” EX1005 (FDA Guidance) at 2. The FDA Guidance “recommend[s] that applicants use the USP method for disintegration testing,” *id.* at 3 (“[t]o provide both a standard for and consistency in disintegration testing, we recommend that applicants use the USP method for disintegration testing.”), specifically “USP 29, <701> Disintegration,” *id.* at 3 n.3 (“USP 29, <701> Disintegration, at 2670-2672.”).⁷

187. A person of ordinary skill in the art would have been motivated to follow the FDA Guidance in formulating Grother’s fast dispersing solid dosage form containing budesonide. The FDA Guidance provides the agency’s recommendations on the topic of orally disintegrating pharmaceutical compositions. *Id.* at 1 (“This guidance provides pharmaceutical manufacturers of new and generic drug products with an Agency perspective on the definition of an orally disintegrating tablet (ODT)—which is a different dosage form than, for example, a chewable tablet or a tablet that should be swallowed whole with liquid—and also provides

⁷ Also, the FDA published draft guidance on April 8, 2007 that include the same key technical content as the final 2008 Guidance. *See* FDA DRAFT Guidance at page 1, 2 and 3.

recommendations to applicants who would like to designate proposed products as ODTs.”). The FDA regulates the use of pharmaceutical compositions in the United States. Grother’s formulations were intended to “enhance patient compliance.” EX1008 (Grother) 32:5-7 (“This unexpected result is advantageous in that the smaller dosage forms utilizing the modified starch will enhance patient compliance and reduce the cost of manufacture.”). A person of ordinary skill in the art seeking to formulate budesonide into an orally disintegrating pharmaceutical composition would be highly motivated to follow the FDA Guidance that such a composition should disintegrate within 30 seconds or less when tested using the USP <701> Disintegration Test.

188. A person of ordinary skill in the art would have had a reasonable expectation of success in doing so based Grother’s description of how to formulate active ingredients into a fast dispersing solid dosage form. See, e.g., EX1008 (Grother) 13:18-15:20. In addition, formulating orally disintegrating pharmaceutical compositions that dissolve within several seconds to about a minute would have been a routine exercise for the person of ordinary skill in the art by 2009. For example, the Fu review article is representative of the person of ordinary skill in the art’s understanding and Fu explains that “[t]he disintegration time for good FDTs [fast disintegrating tablets] varies from several seconds to about a minute.” EX1018 (Fu) at 434. The FDA Guidance is similarly representative of the person of ordinary

skill in the art's understanding and it explains that orally disintegrating tablets were “solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative (see Section IV).” EX1005 (FDA Guidance) at 2. Based on the numerous commercially available orally disintegrating systems and products available by 2009, the person of ordinary skill in the art would have had a high expectation of success. For example, the Danckwerts and Fu review articles are representative of the knowledge of the person of ordinary skill in the art. These references disclose several commercially available orally disintegrating systems and products. *See* EX1017 (Danckwerts) at 179-181; EX1018 (Fu) at 436-439. Thus, the development of an orally disintegrating dosage form would be readily achievable by 2009.

189. Grother in view of the FDA Guidance therefore renders obvious a solid pharmaceutical composition that disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.

1. Limitation 1[v]

190. Limitation 1[v] recites “wherein upon administration the corticosteroid is deposited topically in the upper gastrointestinal tract.”

191. Grother discloses “a pharmaceutical composition for oral administration in the form of a fast dispersing dosage form designed to release an

active ingredient rapidly in the oral cavity.” EX1008 (Grother) at 3:18-20 (“According to the present invention there is therefore provided a pharmaceutical composition for oral administration in the form of a fast dispersing dosage form designed to release an active ingredient rapidly in the oral cavity characterized in that the essentially gelatin free composition comprises a modified starch and at least one matrix forming agent.”); *id.* at 1:10-11 (“This invention relates to a pharmaceutical composition for oral administration in the form of a fast dispersing dosage form.”); *id.* at 13:19-22 (“As used herein and in the claims, the term ‘fast dispersing dosage form (FDDF)’ refers to compositions which disintegrate/disperse within 1 to 60 seconds, preferably 1 to 30 seconds, more preferably 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity.”); *id.* at 32:10 (“This invention relates to fast dissolving dosage forms for oral administration.”). A person of ordinary skill in the art would understand that oral administration of budesonide in the form of a fast dispersing dosage form would release budesonide rapidly in the oral cavity, which would topically deposit budesonide in the oral cavity of the upper gastrointestinal tract. Grother therefore discloses topical deposition of a corticosteroid in the upper gastrointestinal tract.

192. Claim 1 is therefore obvious over the prior art.

C. Claim 2

193. Claim 2 recites:

Claim 2. The solid pharmaceutical composition of claim 1, wherein said solid pharmaceutical composition disintegrates within 30 seconds.

194. Grother discloses “fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.” EX1008 (Grother) at Abstract (“The present invention relates to fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.”); *id.* at 13:19-22 (“As used herein and in the claims, the term ‘fast dispersing dosage form (FDDF)’ refers to compositions which disintegrate/disperse within 1 to 60 seconds, preferably 1 to 30 seconds, more preferably 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity.”).

195. As discussed above regarding limitation 1[iv], a person of ordinary skill in the art would have been motivated to formulate Grother’s fast dispersing dosage form to disintegrate within 30 seconds with a reasonable expectation of success. The FDA recommended that such compositions have “an in-vitro disintegration time of approximately 30 seconds or less,” EX1005 (FDA Guidance) at 2 (“Based on the original product rationale and Agency experience, we recommend that, in addition to the original definition, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of

approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative.”), using the “USP 29, <701> Disintegration” test. *Id.* at 3 n.3 (“USP 29, <701> Disintegration, pp. 2670-2672.”). Claim 2 is therefore obvious over the prior art.

D. Claim 3

196. Claim 3 recites:

Claim 3. The solid pharmaceutical composition of claim 1, wherein said corticosteroid is selected from the group consisting of budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, and salts, solvates and esters thereof.

197. Grother discloses the use of budesonide as the active ingredient in its composition. EX1008 (Grother) at 15:19-20 (“Any drug may be used as the active ingredient in the composition of the present invention.”); *id.* at 18:15-18 (“**Corticosteroids:** beclomethasone, betamethasone, **budesonide**, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.”) (emphasis added). As discussed above regarding limitation 1[i], Claim 3 is obvious over the prior art.

E. Claims 4 and 5

198. Claim 4 recites:

Claim 4. The solid pharmaceutical composition of claim 1, further comprising an adhesive agent.

199. Claim 5 recites:

Claim 5. The solid pharmaceutical composition of claim 4, wherein the adhesive agent is selected from the group consisting of sucrose aluminum sulfate complex, chitosan and derivatives thereof, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, cross-linked or uncross-linked polyacrylates, cross-linked polyacrylates, acidic cross-linked or uncross-linked polyacrylates, polyacrylic acid homopolymers or copolymers, aminoalkyl methacrylate copolymers, methacrylic acid/methylmethacrylate copolymer, alkylacrylate/alkylmethacrylate copolymers, ammoniomethacrylate copolymers, carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof.

200. **Claim construction:** The '729 patent defines “adhesive agent” to refer “to agents which promote adhesion of the corticosteroid to biological surfaces, and includes, but is not limited to bio-adhesive agents.” EX1001 (the '729 patent) at 2:66-3:2 (“The term ‘adhesive agent’, as used herein refers to agents which promote adhesion of the corticosteroid to biological surfaces, and includes, but is not limited to bio-adhesive agents.”). I have applied this definition. The '729 patent states that suitable adhesive agents include polyvinylpyrrolidone, sodium

carboxymethylcellulose, and hydroxypropyl cellulose. *Id.* at 10:23-39 (“Suitable adhesive agents include sucrose aluminum sulfate complex, chitosan and derivatives thereof (e.g., trimethylchitosan, chitosan salts), *polyvinylpyrrolidone*, methylcellulose, *sodium carboxymethylcellulose*, *hydroxypropyl cellulose*, cross-linked or uncross-linked polyacrylates, cross-linked polyacrylates, acidic cross-linked or uncross-linked polyacrylates, polyacrylic acid homopolymers or copolymers, aminoalkyl methacrylate copolymers, methacrylic acid/methylmethacrylate copolymer, alkylacrylate/alkylmethacrylate copolymers, ammoniomethacrylate copolymers, Eudragit® polymers (E, L, S, NE, RL, and RS grades), carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof[.]”) (emphasis added). I have adopted this definition.

201. Grother discloses that “[t]he fast dispersing dosage form according to the invention may also contain, in addition to the active ingredient and modified starch, other matrix forming agents and secondary components.” EX1008 (Grother) at 14:7-9.

202. “Matrix forming agents suitable for use in the present invention include... carboxymethylcelluloses... polyvinylpyrrolidone” *Id.* at 14:9-15 (“Matrix forming agents suitable for use in the present invention include materials

derived from animal or vegetable proteins, such as non- mammalian gelatins, dextrans and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; *carboxymethylcelluloses*; carrageenans; dextrans; pectins; synthetic polymers such as *polyvinylpyrrolidone*; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.”) (emphasis added). Grother discloses that “[o]ne or more matrix forming agents may be incorporated into the solution or suspension prior to solidification.” *Id.* at 14:22-23. Thus, Grother discloses a solid pharmaceutical composition comprising polyvinylpyrrolidone or carboxymethylcelluloses, which a person of ordinary skill in the art would understand can function as an adhesive agent. Claims 4-5 are therefore obvious over the prior art.

F. Claim 6

203. Claim 6 recites:

Claim 6. The solid pharmaceutical composition of claim 1, wherein the at least one disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, low-substituted hydroxylpropylcellulose, mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

204. As discussed above regarding limitation 1[ii], the '729 patent states that disintegrants include starches such as carboxymethyl starch, for example sodium starch glycolate, i.e., Primogel® and Explotab®. EX1001 (the '729 patent) at 9:26-

31 (“Examples of suitable disintegrants include e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, *sodium starch glycolate*, starch, pregelatinized starch, and *carboxymethyl starch (e.g. Primogel® and Explotab®)*.”) (emphasis added). A person of ordinary skill in the art would understand that sodium starch glycolate is a disintegrant made from starch by carboxymethylation and crosslinking and is found in both Primogel® and Explotab®.

205. Grother discloses that modified starches “may be used as the primary structure forming agent in FDDF's [fast dispersing dosage forms] to form physically robust products while maintaining the desired rapid dispersion characteristics of the products.” EX1008 (Grother) at 4:2-4 (“Modified starches may be used as the primary structure forming agent in FDDF's to form physically robust products while maintaining the desired rapid dispersion characteristics of the products.”). Grother teaches that useful modified starches are generally readily dispersible in water. EX1008 (Grother) at 13:5-8 (“While many specific examples are provided on the useful modified starches, a general characteristic of the useful modified starches in the fast dispersing solid dosage form according to the invention is that they are readily soluble or dispersible in water at ambient temperature.”). Grother further discloses that a range of commercially available modified starches, including pregelatinized starches, oxidized starches, and crosslinked starches, are suitable for

use in their orally dispersing tablets. EX1008 (Grother) at 5:10-6:5 (“A range of modified starches are commercially available and useful in the present invention and include: Pregelatinized starches, produced by drum drying or extrusion; Low-viscosity starches, produced by controlled hydrolysis of glycosidic bonds; Dextrins, produced by roasting dry starch in the presence of a small amount of acid; Acid modified starches, produced by suspension in dilute acid until the required viscosity is reached; *Oxidized starches, oxidizing agents cause the introduction of carbonyl or carboxyl groups*, wherein depolymerization occurs, leading to decreased retrogradation and gelling capacities; Enzymatically modified starch, produced by controlled enzyme degradation to attain required physicochemical properties; *Crosslinked starches*, bi- or polyfunctional reagents react with hydroxyl groups to form crosslinks, examples of specific reagents include phosphorus oxychloride, sodium trimetaphosphate and epichlorohydrin; and Stabilized starches, starches are reacted with etherifying or esterifying reagents in the presence of an alkaline catalyst to give a wide range of products.”) (emphasis added). Sodium starch glycolate is a commercially available disintegrant made from potato starch by carboxymethylation and crosslinking and is found in both Primogel® and Explotab®. A person of ordinary skill in the art would understand that the term ‘modified starch’ would include sodium starch glycolate which is commercially available as Primogel® and Explotab®. Grother therefore discloses at least one disintegrant selected from the list

comprising sodium starch glycolate. Claim 6 is therefore obvious over the prior art.

G. Claim 7

206. Claim 7 recites:

Claim 7. The solid pharmaceutical composition of claim 1, further comprising an excipient selected from the group consisting of mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, cyclodextrin, and combinations thereof.

207. Grother also discloses that “[m]atrix forming agents suitable for use in the present invention include sugars such as *mannitol, dextrose, lactose....*” EX1008 (Grother) at 14:16-21 (“Matrix forming agents suitable for use in the present invention include sugars such as *mannitol, dextrose, lactose*, galactose and trehalose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicates; and amino acids having from 2 to 12 carbon atoms such as a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.”) (emphasis added). “One or more matrix forming agents may be incorporated into the solution or suspensions prior to solidification.” *Id.* at 14:22-23. Claim 7 is therefore obvious over the prior art.

H. Claims 9-11

208. Claim 9 recites:

Claim 9. The solid pharmaceutical composition of claim 1, further comprising at least one antifungal agent.

209. Claim 10 recites:

Claim 10. The solid pharmaceutical composition of claim 9, wherein the antifungal agent is selected from the group consisting of mitotic inhibitor antifungals, pyrimidine analog antifungals, polyene antifungals, benzimidazole antifungals, imidazole antifungals, polyene antifungals, triazole antifungals, thiazole antifungals, allylamine antifungals, echinocandin antifungals, and uncategorized antifungals.

210. Claim 11 recites:

Claim 11. The solid pharmaceutical composition of claim 10, wherein the antifungal agent is selected from the group consisting of anidulafungin, caspofungin, clotrimazole, fluconazole, itraconazole, micafungin, nystatin, posaconazole, and voriconazole.

211. Grother discloses that the fast dispersing solid dosage form comprises “at least one active ingredient.” EX1008 (Grother) at 12:10-19 (“There is disclosed a fast dispersing solid dosage form designed to release *an active ingredient* rapidly in the oral cavity characterized in that said dosage form is essentially free of mammalian gelatin and comprises: at least one active ingredient; at least one modified starch at a concentration of from 20 to 90% by weight of said solid dosage form; and at least one matrix forming agent; wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.”) (emphasis added), *id.* at 34

(“1. A fast dispersing solid dosage form designed to release *an active ingredient* rapidly in the oral cavity characterized in that said dosage form is essentially free of mammalian gelatin and comprises: a) at least one active ingredient; b) at least one modified starch at a concentration of from 20 to 90% by weight; and c) at least one matrix forming agent; wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.”) (emphasis added).

212. The “at least one active ingredient” informs the person of ordinary skill in the art that Grother’s fast dispersing solid dosage form would include two active ingredients. Grother discloses that “[a]ny drug may be used as the active ingredient in the composition of the present invention,” EX1008 (Grother) at 15:19-20, including “**Anti-fungal agents:** amphotericin, butoconazole nitrate, *clotrimazole*, econazole nitrate, *fluconazole*, flucytosine, griseofulvin, *itraconazole*, ketoconazole, miconazole, natamycin, *nystatin*, sulconazole nitrate, terbinafine HCl, terconazole, tioconazole, undecenoic acid,” *id.* at 17:1-5 (emphasis added). Claims 9-11 are therefore obvious over the prior art.

I. Claims 12-14

213. Claim 12 recites:

Claim 12. The solid pharmaceutical composition of claim 1, further comprising at least one antiviral agent.

214. Claim 13 recites:

Claim 13. The solid pharmaceutical composition of claim 12, wherein the antiviral agent is selected from the group consisting of *interferons*, nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, fusion inhibitors, maturation inhibitors, purine analogs, pyrimidine analogs, and uncategorized antiviral drugs. (emphasis added).

215. Claim 14 recites:

Claim 14. The solid pharmaceutical composition of claim 12, wherein the antiviral agent selected from the group consisting of aciclovir, brivudine, docosanol, famciclovir, ganciclovir, idoxuridine, penciclovir, trifluridine, tromantadine, valaciclovir, and valganciclovir.

216. Grother discloses that the fast dispersing solid dosage form comprises “at least one active ingredient.” EX1008 (Grother) at 12:10-19 (“There is disclosed a fast dispersing solid dosage form designed to release *an active ingredient* rapidly in the oral cavity characterized in that said dosage form is essentially free of mammalian gelatin and comprises: at least one active ingredient; at least one modified starch at a concentration of from 20 to 90% by weight of said solid dosage form; and at least one matrix forming agent; wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.”) (emphasis added), *id.* at 34 (“1. A fast dispersing solid dosage form designed to release *an active ingredient* rapidly in the oral cavity characterized in that said dosage form is essentially free of

mammalian gelatin and comprises: a) at least one active ingredient; b) at least one modified starch at a concentration of from 20 to 90% by weight; and c) at least one matrix forming agent; wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.”) (emphasis added).

217. The “at least one active ingredient” informs the person of ordinary skill in the art that Grother’s fast dispersing solid dosage form would include two active ingredients. Grother discloses that “[a]ny drug may be used as the active ingredient in the composition of the present invention,” EX1008 (Grother) at 15:19-20, including “Proteins, peptides and recombinant drugs: insulin... *interferons* (especially Alpha-2 interferon for treatment of common colds)...” *Id.* at 20:22-21:8 (“Proteins, peptides and recombinant drugs: insulin (hexameric/dimeric/monomeric forms), glucagon, growth hormone (somatotropin), polypeptides or their derivatives, (preferably with a molecular weight from 1000 to 300,000), calcitonins and synthetic modifications thereof, enkephalins, *interferons* (especially Alpha-2 interferon for treatment of common colds), LHRH and analogues (nafarelin, buserelin, zolidex), GHRH (growth hormone releasing hormone), secretin, bradykin antagonists, GRF (growth releasing factor), THF, TRH (thyrotropin releasing hormone), ACTH analogues, IGF (insulin like growth factors), CGRP (calcitonin gene related peptide), atrial natriuretic peptide, vasopressin and analogues (DDAVP, lypressin),

factor VIII, G-CSF (granulocyte-colony stimulating factor), EPO (erythropoitin).”) (emphasis added). Grother in view of the FDA Guidance therefore renders obvious the “interferons” recited by claim 13. Grother in view of the FDA Guidance therefore renders obvious claims 12-13.

218. Grother discloses that “[a]ny drug may be used as the active ingredient in the composition of the present invention,” EX1008 (Grother) at 15:19-20, including “herpes” and “herpes simplex.” *Id.* at 19:18-20:21 (“Oral vaccines: Vaccines designed to prevent or reduce the symptoms of diseases of which the following is a representative but not exclusive list: Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, **Herpes**, Typhoid, HIV, AIDS, Measles, Lyme disease, Travellers’ Diarrhea, Hepatitis A, B and C, Otitis Media, Dengue Fever, Rabies, Parainfluenza, Rubella, Yellow Fever, Dysentery, Legionnaires Disease, Toxoplasmosis, Q-Fever, Haemorrhagic Fever, Argentina Haemorrhagic Fever, Caries, Chagas Disease, Urinary Tract Infection caused by E.coli, Pneumococcal Disease, Mumps, and Chikungunya. Vaccines to prevent or reduce the symptoms of other disease syndromes of which the following is a representative but not exclusive list of causative organisms: Vibrio species, Salmonella species, Bordetella species, Haemophilus species, Toxoplasmosis gondii, Cytomegalovirus, Chlamydia species, Streptococcal species, Norwalk Virus, Escherischia coli, Helicobacter pylori,

Rotavirus, Neisseria gonorrhoeae, Neisseria meningitidis, Adenovirus, Epstein Barr Virus, Japanese Encephalitis Virus, Pneumocystis carinii, *Herpes simplex*, Clostridia species, Respiratory Syncytial Virus, Klebsiella species, Shigella species, Pseudomonas aeruginosa, Parvovirus, Campylobacter species, Rickettsia species, Varicella zoster, Yersinia species, Ross River Virus, J.C. Virus, Rhodococcus equi, Moraxella catarrhalis, Borrelia burgdorferi and Pasteurella haemolytica.”) (emphasis added).

219. Drugs that were known by the person of ordinary skill in the art to prevent or reduce symptoms of herpes were known to include acyclovir, idoxuridine, trifluridine, valacyclovir, and famciclovir. For example, Goodman & Gillman’s teaches that these drugs were known to prevent or reduce symptoms of herpes. EX1025 (Goodman & Gillman’s) at 1246-1256. In addition, the use these drugs to prevent or reduce symptoms of herpes in solid orally disintegrating pharmaceutical compositions was described in the patent literature beyond that of Grother. For example, Singh discloses such compositions containing acyclovir, idoxuridine, and trifluridine. EX1035 (Singh) at 14:25-37 (“Antiviral Purines/Pyrimidines such as 2-Acetyl-pyridine 5-((2-pyridylamino) thiocarbonyl), Thiocarbonohydrazone, *Acyclovir*, Dideoxyadenosine, Dideoxycytidine, Dideoxyinosine, Edoxudine, Floxuridine, Ganciclovir, *Idoxuridine*, MADU, Pyridinon, *Trifluridine*, Vidarabine, Zidovudine. Others such as Acetyl-leucine, Monoethanolamine, Acridi

anamine, Alkylisoxazoles, Amantadine, Amidinomyacin, Cuminaldehyde, Thiosemicarbazone, Foscarnet Sodium, Kethoxal, Lysozyme, Methisazone, Moroxydine, Podophyllotoxin, Ribavirin, Rimantadine, stallimycin, statolon, Thymosins, Tromantadine, Xenazoic Acid.”) (emphasis added). As another example, Cherukuri discloses such compositions containing acyclovir, valacyclovir, and famciclovir. EX1036 (Cherukuri) at 10:55-61 (“Another preferred active material used in the composition of the present invention is an anti-herpetic. Anti-herpetics are used to treat infections from the varicella-zoster virus. Classes of drugs useful for treating herpes include synthetic purine nucleoside analogs, nucleoside analogs, and antiviral agents. Specific examples include *acyclovir, Valacyclovir HCL and famciclovir.*”) (emphasis added). A person of ordinary skill in the art would have been motivated to include acyclovir, idoxuridine, trifluridine, valacyclovir, and famciclovir in Grother’s solid orally disintegrating pharmaceutical composition based on Grother’s instruction to include anti-herpetic drugs in its compositions and because those drugs were known to be anti-herpetic as well as known to be used in other solid orally disintegrating pharmaceutical compositions (such as the compositions of Singh and Cherukuri). Claim 14 is therefore obvious over the prior art.

J. Claim 15

220. Claim 15 recites:

Claim 15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of an orally disintegrating tablet (ODT).

221. **Claim construction:** The '729 patent defines “orally disintegrating tablet”, “orally dispersing tablet”, or “ODT” to refer “to a solid dosage form of the present invention, which disintegrates rapidly in the oral cavity of a patient after administration, without chewing.” EX1001 (the '729 patent) at 2:41-44 (“The terms “orally disintegrating tablet”, “orally dispersing tablet”, or “ODT” refer to a solid dosage form of the present invention, which disintegrates rapidly in the oral cavity of a patient after administration, without chewing.”). I have applied this definition. This definition is substantively the same as the definition of an orally disintegrating tablet adopted by the FDA. EX1005 (FDA Guidance) at 2 (“A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”). I have applied this definition.

222. Grother discloses “fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most preferably within ten (10) seconds.” EX1008 (Grother) at Abstract; *id.* at 13:19-22. A person of ordinary skill in the art would understand that Grother’s fast dispersing solid dosage forms dissolve rapidly within the oral cavity without chewing. Claim 15 is therefore obvious over the prior art.

K. Claim 20

223. Claim 20 recites:

Claim 20. The pharmaceutical composition of claim 4, wherein the adhesive agent and the corticosteroid are intimately associated.

224. **Claim construction:** The '729 patent defines “intimately associated” to “to describe the spatial relationship between two or more components of a composition refers to components [sic.] that are intimately mixed, such as for example in mixtures, coatings and matrices.” EX1001 (the '729 patent) at 3:6-10 (“The term ‘intimately associated’, as used herein to describe the spatial relationship between two or more components of a composition refers to components that are intimately mixed, such as for example in mixtures, coatings and matrices.”). I have applied this definition.

225. Grother discloses that “wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.” EX1008 (Grother) at 12:10-19 (“There is disclosed a fast dispersing solid dosage form designed to release an active ingredient rapidly in the oral cavity characterized in that said dosage form is essentially free of mammalian gelatin and comprises: at least one active ingredient; at least one modified starch at a concentration of from 20 to 90% by weight of said solid dosage form; and at least one matrix forming agent; wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient,

said modified starch and said matrix forming agent.”); *id.* at Abstract (“Further, the solid dosage forms according to the invention are obtainable by removing a solvent, such as water, from a mixture comprising an active ingredient, a modified starch and a matrix forming agent via freeze drying.”), 13:15-16 (“In one preferred embodiment according to the invention, the removal of the solvent from the mixture is preferably carried out by freeze drying.”). Grother’s matrix forming agent includes *carboxymethylcelluloses*, *id.* at 14:9-15 (“Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as non-mammalian gelatins, dextrans and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; *carboxymethylcelluloses*; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.”) (emphasis added).

226. The ’729 patent states that sodium carboxymethylcellulose is an adhesive agent. EX1001 (the ’729 patent) at 10:23-39 (“Suitable adhesive agents include sucrose aluminum sulfate complex, chitosan and derivatives thereof (e.g., trimethylchitosan, chitosan salts), polyvinylpyrrolidone, methylcellulose, *sodium carboxymethylcellulose*, hydroxypropyl cellulose, cross-linked or uncross-linked polyacrylates, cross-linked polyacrylates, acidic cross-linked or uncross-linked polyacrylates, polyacrylic acid homopolymers or copolymers, aminoalkyl

methacrylate copolymers, methacrylic acid/methylmethacrylate copolymer, alkylacrylate/alkylmethacrylate copolymers, ammoniomethacrylate copolymers, Eudragit® polymers (E, L, S, NE, RL, and RS grades), carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof[.]” (emphasis added).

227. The process of mixing Grother’s active ingredient with the matrix forming agent and modified starch creates an intimate mixture that meets the claimed intimate association. Claim 20 is therefore obvious over the prior art.

L. Claim 27

228. Grother in view of the FDA Guidance renders obvious claim 27 for the same reasons as claims 1 and 15, discussed above. Below is a table with a side-by-side comparison of claim 27 relative to claims 1 and 15:⁸

Claim 27 of the ’729 patent	Claims 15 and 1 of the ’729 patent
Claim 27. An orally disintegrating tablet comprising	Claim 15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of an orally disintegrating tablet (ODT).

⁸ Bracketed labels, e.g., “[i]” and “[ii],” have been added for convenient referencing to the claim limitations.

Claim 27 of the '729 patent	Claims 15 and 1 of the '729 patent
[i] less than or equal to about 20 mg of a corticosteroid selected from the group consisting of fluticasone, budesonide, mometasone, and salts, solvates and esters thereof, and	Claim 1. An orally disintegrating solid pharmaceutical composition comprising [i] less than or equal to about 20 mg of a topically administrable corticosteroid and
[ii] at least one disintegrant,	[ii] at least one disintegrant,
	[iii] wherein the solid pharmaceutical composition has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration,
[iii] wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.	[iv] wherein the solid pharmaceutical composition disintegrates within 60 seconds when tested using the USP <701> Disintegration Test, and
	[v] wherein upon administration the corticosteroid is deposited topically in the upper gastrointestinal tract.

1. Preamble

229. The preamble of claim 27 recites: “An orally disintegrating tablet comprising”.

230. Grother renders the preamble obvious for reasons discussed above regarding the claim 1 preamble and claim 15.

2. Limitation 27[i]

231. Limitation 27[i] recites “[i] less than or equal to about 20 mg of a corticosteroid selected from the group consisting of fluticasone, budesonide, mometasone, and salts, solvates and esters thereof”.

232. Grother renders obvious limitation 27[i] for reasons discussed above regarding limitation 1[i].

3. Limitation 27[ii]

233. Limitation 27[ii] recites “at least one disintegrant”.

234. Grother renders obvious limitation 27[ii] for reasons discussed above regarding limitation 1[ii].

4. Limitation 27[iii]

235. Limitation 27[iii] recites “wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.”

236. Grother in view of the FDA Guidance renders obvious limitation 27[iii] for reasons discussed above regarding limitation 1[iv].

M. Claims 35-36

237. Claim 35 recites:

Claim 35. The solid composition of claim 1, formulated for topical administration to the upper gastrointestinal tract.

238. Claim 36 recites:

Claim 36. The solid composition of claim 35, wherein the upper gastrointestinal tract is further defined as the esophagus.

239. Grother in view of the FDA Guidance renders obvious claim 35 for reasons discussed above regarding limitation 1[v].

240. Grother discloses “a pharmaceutical composition for oral administration in the form of a fast dispersing dosage form designed to release an active ingredient rapidly in the oral cavity.” EX1008 (Grother) at 3:18-22 (“According to the present invention there is therefore provided a pharmaceutical composition for oral administration in the form of a fast dispersing dosage form designed to release an active ingredient rapidly in the oral cavity characterized in that the essentially gelatin free composition comprises a modified starch and at least one matrix forming agent.”); *id.* at 1:10-11 (“This invention relates to a pharmaceutical composition for oral administration in the form of a fast dispersing dosage form.”), 13:19-22 (“As used herein and in the claims, the term ‘fast dispersing dosage form (FDDF)’ refers to compositions which disintegrate/disperse within 1 to 60 seconds, preferably 1 to 30 seconds, more preferably 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity.”), 32:10 (“This invention relates to fast dissolving dosage forms for oral administration.”).

241. It was known to the person of ordinary skill in the art that releasing an active ingredient in the oral cavity promotes absorption of the active ingredient in the esophagus. For example, the Shukla and Fu review articles are representative of

the person of ordinary skill in the art's understanding. The Shukla review article teaches that an advantage of MDDDS (mouth dissolving drug delivery systems) is that they provide "[m]ore rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action." EX1019 (Shukla) at 311. The Fu review article teaches that "[i]t has been found that FDTs can promote pregastric absorption of the active ingredients through buccal, sublingual, oropharyngeal, and esophageal membranes." EX1018 (Fu) at 466.

242. Grother in view of the FDA Guidance therefore renders obvious the topical administration of budesonide to the esophagus in the upper gastrointestinal tract recited by claim 36. Claim 36 is therefore obvious over the prior art.

N. Claims 28 and 38-40

243. Claim 28 recites:

Claim 28. The orally disintegrating tablet of claim 27, that comprises from about 2 to about 10 mg fluticasone.

244. Claim 38 recites:

Claim 38. The orally disintegrating tablet of claim 27, that comprises from about 0.01 mg and about 20 mg fluticasone.

245. Claim 39 recites:

Claim 39. The solid pharmaceutical composition of claim 1, that comprises from about 0.01 mg and about 20 mg fluticasone.

246. Claim 40 recites:

Claim 40. The solid pharmaceutical composition of claim 1, that comprises from about 2 to about 10 mg fluticasone.

247. As discussed above regarding limitation 1[i], Grother discloses that “[t]he precise quantity of active ingredient will depend on the drug selected. However, the active ingredient is generally present in an amount from 0.2 to 95%, normally 1 to 20%, by weight of the composition of the dried dosage form.” EX1008 (Grother) at 21:16-18.

248. Grother discloses that “[a]ny drug may be used as the active ingredient in the composition of the present invention,” EX1008 (Grother) at 15:19-20, including fluticasone, *id.* at 18:15-18 (“**Corticosteroids:** beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, *fluticasone propionate*, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.”) (bold/italic emphasis added and bold emphasis in original).

249. Beyond the teachings of Grother, it was generally known to the person of ordinary skill in the art that topical corticosteroids, including budesonide and fluticasone, were a suitable treatment for eosinophilic esophagitis. For example, practical applications of the use of budesonide and fluticasone for this treatment were disclosed by Aceves 2007. *See* EX1015 (Aceves 2007) at 1 (“Systemic corticosteroids and swallowed topical steroids, such as fluticasone propionate (Flovent™) administered through metered-dose inhaler (MDI), have been shown to

induce and maintain low esophageal eosinophil levels (25–30).”) (emphasis added).

Another practical application includes Teitlebaum, which discloses treatment of eosinophilic esophagitis in children with between 44µg and 440µg (between 0.044-0.44mg) of swallowed fluticasone delivered twice daily via a metered dose inhaler. *See* EX1033 at 1217 (Teitelbaum) (“If they had persistence of symptoms despite strict adherence to the diet, they were placed on FP (2–4 years old, 44 µg/puff; 5–10 years old, 110 µg/puff; 11 years and older, 220 µg/puff) 2 puffs by mouth twice daily swallowed without inhaling and without use of a spacing device.”), *id.* at 1216 (“In 1998, Faubion et al. reported the successful use of a novel treatment method in which patients swallowed metered doses of a trifluorinated steroid preparation, fluticasone propionate (FP).”).

250. Yet another practical application for this treatment is Noel, which discloses treatment of eosinophilic esophagitis with between 440 µg and 1320 µg (between 0.44-1.32mg) of swallowed fluticasone. EX1034 (Noel) at 573 (“First, we report that FP treatment is associated with an efficacious response in the majority of patients with EE.”); *id.* at Table 1. Moreover, Noel discloses that fluticasone is likely to mediate its therapeutic effects by acting topically, as studies have indicated that systemic effects such as decreased serum cortisol levels are not seen in patients ingesting 18 mg of fluticasone. *Id.* at 574 (“Swallowed FP is likely to mediate therapy by topical absorption in the esophagus. Pharmacokinetic studies have shown

that approximately 1% of the drug is absorbed systemically and then metabolized efficiently in the liver at a rate approaching that of portal-hepatic circulation. No alteration of morning serum cortisol level has been seen in volunteers after ingesting as much as 18 mg of FP.”).

251. The patients treated with fluticasone in Teitelbaum and Noel were each administered fluticasone by metered dose inhaler, without a spacer. *See* EX1033 (Teitelbaum) at 1217 (“In addition, we performed an open-label, prospective trial to determine whether the use of diet restriction (DR) or swallowed FP metered-dose units would diminish symptoms and induce a histologic remission.”); *see also* EX1034 (Noel) at 569 (“Patients were prescribed metered-dose inhalers of FP. They were instructed not to use a spacer.”). Moreover, the patients were instructed not to eat or drink for 30 minutes following administration of the fluticasone. *See* EX1033 (Teitelbaum) at 1217 (“Patients were instructed not to eat or drink for 30 minutes after taking the medication.”); *see also* EX1034 (Noel) at 569 (“Additionally, they were instructed to spray the medication into the pharynx, and not to rinse, eat, or drink for 30 minutes after administration.”). A person of skill in the art would understand that this mode of administration would result in topical deposition of the fluticasone on the patient’s esophagus.

252. Based on Grother’s instruction that its compositions should normally have 1-20% by weight active ingredient and the general knowledge in the art that

topical corticosteroid formulations that are effective at treating eosinophilic esophagitis, for example formulations of fluticasone, containing, e.g., between 0.04 mg and 1.32 mg of fluticasone and formulations of budesonide containing, e.g., 0.5 mg, 1 mg, and 2 mg of budesonide, a person of ordinary skill in the art would have been motivated to formulate fluticasone in Grother's compositions at, e.g., 0.044-0.44 mg and 0.44-1.32mg, with a reasonable expectation of success. These ranges overlap with the claimed range of between about 2-10 mg and 0.01-20 mg of fluticasone. Grother in view of the general knowledge of a person of ordinary skill in the art regarding topical dosage formulations of fluticasone and budesonide therefore renders obvious a pharmaceutical composition that comprises between about 2-10 mg and 0.01-20 mg of fluticasone.

XI. GROUND 3: DOHIL AND VENKATESH IN VIEW OF THE KNOWLEDGE OF THE PERSON OF ORDINARY SKILL IN THE ART

253. This section introduces Venkatesh, and then explains how Dohil and Venkatesh in view of the knowledge of a person of ordinary skill in the art renders obvious dependent claims 8 and 16-18 of the '729 patent.

A. Introduction to Venkatesh

254. Venkatesh discloses “orally disintegrating tablets and a method for their manufacture.” EX1020 (US2005/0232988, “Venkatesh”) at ¶[0001]. Venkatesh discloses that “[m]ore particularly [the invention] relates to an orally

disintegrating tablet made up of rapidly dispersing microgranules and taste-masked microcapsules.” *Id.*

255. Venkatesh discloses manufacturing its orally disintegrating tablets using an external lubrication system to pre-lubricate the dies and punches so that the tablet is otherwise free of lubricant as follows:

It is yet another embodiment of the invention to provide a method to manufacture rapidly disintegrating tablets, which are characterized by the property that it is formed by compressing in a tablet press equipped with an externally lubricating system to pre-lubricate dies and punches and the tablet formulation otherwise being free of lubricant.

EX1020 (Venkatesh) at ¶[0017] (emphasis added); *see also id.* at ¶[0018] (“The invention also provides a method of manufacturing pharmaceutical tablets, produced by mixing microgranules of a sugar alcohol such as D-mannitol or a saccharide such as lactose, each having an average particle diameter of not more than 301 µm, preferably not more than 20 µm and a disintegrant with one or more taste-masked microcapsules and other excipients (for example: flavor, color, sweetener etc.) and compressing the blend into rapidly disintegrating tablets, ***the tablet thus produced having the property that it is formed by compressing in a tablet press equipped with an externally lubricating system to pre-lubricate dies and punches and the tablet formulation otherwise being free of lubricant.***”) (emphasis added).

256. Venkatesh states that the orally disintegrating tablet preferably dissolves in less than 60 seconds in the buccal cavity as follows:

It is still another embodiment of the invention to provide a method of blending taste-masked microcapsules with rapidly dispersing microgranules produced by granulating, without a conventional binder, a sugar alcohol or a saccharide or a mixture thereof, with an average particle size of not more than 30 μm and a disintegrant, and other pharmaceutically acceptable excipients and compressing the blend into tablets which rapidly disintegrate (e.g., less than 120 seconds, preferably less than 60 seconds) in the buccal cavity.

EX1020 (Venkatesh) at ¶[0016].

257. Venkatesh discloses that its orally disintegrating tablets can be formulated using any therapeutic active agent indicated for oral administration as follows:

The term ‘drug’, ‘active’ or ‘active pharmaceutical ingredient’ as used herein is meant to include any therapeutic active agent indicated for oral administration such as macrolide antibiotic agents, analgesics, antidepressants, antihistamines, antihypertensives, antimigrane agents, proton pump inhibitors, antipsychotic agents, antiemetic agents, antiparkinson agents, and H2 antagonists.

EX1020 (Venkatesh) at ¶[0025].

B. Claim 8

258. Claim 8 recites:

Claim 8. The solid pharmaceutical composition of claim 1, which is substantially free of lubricant.

259. A person of ordinary skill in the art would have been motivated to formulate Dohil’s rapidly dissolving lozenge or tablet with budesonide as an anti-inflammatory active ingredient to be substantially free of lubricant based on Venkatesh.

260. As discussed above, Venkatesh is directed to “orally disintegrating tablets.” EX1020 (Venkatesh) at ¶[0001]. Venkatesh’s orally disintegrating tablet formulations are compatible with “any therapeutic active agent indicated for oral administration.” EX1020 (Venkatesh) at ¶[0025]. Budesonide is a therapeutic active agent indicated for oral administration for reasons discussed above.

261. Venkatesh discloses manufacturing its orally disintegrating tablets using an external lubrication system to pre-lubricate the dies and punches so that the tablet is otherwise free of lubricant as follows:

It is yet another embodiment of the invention to provide a method to manufacture rapidly disintegrating tablets, which are characterized by the property that it is formed by compressing in a tablet press equipped with an externally lubricating system to pre-lubricate dies and punches *and the tablet formulation otherwise being free of lubricant.*

EX1020 (Venkatesh) at ¶[0017] (emphasis added); *see also id.* at ¶[0018] (“The invention also provides a method of manufacturing pharmaceutical tablets, produced by mixing microgranules of a sugar alcohol such as D-mannitol or a saccharide such

as lactose, each having an average particle diameter of not more than 301 μm , preferably not more than 20 μm and a disintegrant with one or more taste-masked microcapsules and other excipients (for example: flavor, color, sweetener etc.) and compressing the blend into rapidly disintegrating tablets, *the tablet thus produced having the property that it is formed by compressing in a tablet press equipped with an externally lubricating system to pre-lubricate dies and punches and the tablet formulation otherwise being free of lubricant.*”) (emphasis added).

262. The formation of Venkatesh’s tablets via compression uses “a conventional rotary tablet press equipped with an external lubrication system to pre-lubricate the dies and punches.” EX1020 (Venkatesh) ¶[0024]; *id.* ¶[0008] (disclosing “conventional granulating, drying and tableting equipment”). The ’729 patent uses the same language as Venkatesh in stating that a “rotary tablet press equipped with an external lubrication system to pre-lubricate the dies and punches” was “conventional” in the prior art. EX1001 (the ’729 patent) at 16:41-43, 17:7-9. The ’729 patent states that using such “an externally lubricating system to pre-lubricate dies and punches, thereby provid[es] a tablet formulation otherwise free of lubricant.” *Id.* at 16:11-13, 17:34-36.

263. A person of ordinary skill in the art would have been motivated to manufacture Dohil’s rapidly dissolving lozenge or tablet using conventional punch and die surfaces with an external lubricating system to provide lozenges and tablets

that are substantially free of lubricant. Such conventional manufacturing was desirable to mass produce such lozenges and tablets with a reasonable expectation of success, as evidenced Venkatesh. Claim 8 is therefore obvious over the prior art.

C. Claim 16

264. Claim 16 depends from claim 15 and recites:

Claim 16. The pharmaceutical composition of claim 15, wherein the ODT comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid, and the rapidly dispersing granules comprise the disintegrant and a sugar alcohol and/or saccharide.

260. **Claim construction:** The '729 patent defines “sugar alcohols” as “hydrogenated forms of carbohydrates in which the carbonyl group (i.e., aldehyde or ketone) has been reduced to a primary or secondary hydroxyl group.” EX1001 (the '729 patent) at 13:10-12. I have applied this definition. The '729 patent states that “[n]on-limiting examples of suitable sugar alcohols for the rapidly dispersing granules of the pharmaceutical compositions of the present invention include e.g. arabitol, isomalt, erythritol, glycerol, lactitol, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.” *Id.* at 13:12-17.

261. **Claim construction:** The '729 patent states that “[t]he term ‘saccharide’ is synonymous with the term ‘sugars’ includes monosaccharides such as glucose, fructose, the lactose, and ribose; and disaccharides such as sucrose,

lactose, maltose, trehalose, and cellobiose.” EX1001 (the ‘729 patent) at 13:17-20.

I have applied this definition.

262. As discussed above for claim 15, Dohil discloses that budesonide is formulated as a lozenge or tablet that “dissolve[s] rapidly in the mouth or esophagus,” EX1002 (Dohil) at ¶[0032], which renders obvious the claimed orally disintegrating tablet recited by claim 15.

263. Venkatesh discloses “an orally disintegrating tablet made up of rapidly dispersing microgranules and taste-masked microcapsules.” EX1020 (Venkatesh) at ¶[0001]. Venkatesh discloses that “this invention relates to pharmaceutical compositions comprising *rapidly dispersing microgranules of a disintegrant and sugar alcohol or a saccharide whose average particle size is not more than 30 µm, resilient (hard, flexible, less-friable) microgranules of bitter active pharmaceutical ingredients effectively taste-masked by coacervation*, and other pharmaceutically acceptable excipients in the form of tablets which rapidly disintegrate in the buccal cavity.” *Id.* at ¶[0014] (emphasis added); *see also id.* at ¶[0018] (“The invention also provides a method of manufacturing pharmaceutical tablets, *produced by mixing microgranules of a sugar alcohol such as D-mannitol or a saccharide such as lactose*, each having an average particle diameter of not more than 301 µm, preferably not more than 20 µm *and a disintegrant with one or more taste-masked microcapsules* and other excipients (for example: flavor, color, sweetener etc.) and

compressing the blend into rapidly disintegrating tablets, the tablet thus produced having the property that it is formed by compressing in a tablet press equipped with an externally lubricating system to pre-lubricate dies and punches and the tablet formulation otherwise being free of lubricant.”) (emphasis added). Venkatesh therefore discloses orally disintegrating tablets comprising drug particles and rapidly dispersing microgranules comprising a disintegrant, a sugar alcohol and/or saccharide.

264. Venkatesh discloses that “[t]he sugar alcohol may be selected from the group consisting of mannitol, sorbitol, xylitol, maltitol and the like while the saccharide may be selected from the group consisting of lactose, sucrose, maltose or as a mixture of two or more, each of which is characterized by an average particle size of not more than about 30 μm .” EX1020 (Venkatesh) at ¶[0028]. Venkatesh therefore discloses the “sugar alcohol” and “saccharide” recited by claim 16.

265. A person of ordinary skill in the art would have been motivated to formulate budesonide in an orally disintegrating tablet based on Dohil for reasons discussed above regarding claim 15. The person of ordinary skill in the art would have further been motivated for the budesonide to comprise drug particles and the disintegrant to be rapidly dispersing granules that include a sugar alcohol and/or saccharide based on Venkatesh. Venkatesh teaches that formulating orally disintegrating tablets to have drug particles and rapidly-dispersing microgranules

comprising sugar alcohol and/or saccharide in combination with the disintegrant beneficially “avoid[ed] gritty mouthfeel,” EX1020 (Venkatesh) at ¶[0012], to assist with providing a “smooth creamy mouthfeel (no grittiness).” *Id.* at ¶[0002].

266. The person of ordinary skill would have reasonably expected success in doing so based on the detailed disclosures within Venkatesh regarding the manufacture of such formulations. Venkatesh teaches that its formulations “don't require a special pharmaceutical production technique and can be simply and easily produced by a normal equipment.” EX1020 (Venkatesh) at ¶[0018]. Claim 16 is therefore obvious over the prior art.

D. Claim 17

267. Claim 17 depends from claim 16 and recites:

Claim 17. The pharmaceutical composition of claim 16, wherein the drug particles have an average particle size of less than about 400 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm , and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 μm .

268. Venkatesh discloses that the drug particles have an average particle size of less than 400 μm as follows:

In accordance with the one embodiment of the invention, milled/micronized drug particles (e.g., *average particle diameter less than about 50 μm , preferably less than about 25 μm*) are blended with a water soluble ductile polymeric binder such as modified starch and

hydroxypropyl methylcellulose with a viscosity of 100 cps or higher, alone or in combination with a widely used binder such as PVP (polyvinylpyrrolidone), hydroxypropylcellulose and hydroxypropyl methylcellulose with a viscosity of 15 cps or less.

EX1020 (Venkatesh) at ¶[0015] (emphasis added); *id.* ¶[0015] (“These granules can be obtained with an average particle size of 200 μm and can be effectively taste masked by coacervation by phase separation to produce taste-masked particles with optimum size distribution (e.g., mean particle size of not more than 400 μm) for incorporation into tablets, which rapidly disintegrate in the buccal cavity with a smooth creamy mouthfeel.”); *id.* ¶[0022], ¶[0025].

269. Venkatesh discloses that the rapidly dispersing granules have an average particle size of less than 300 μm as follows:

(a) granulating a sugar alcohol or a saccharide, or a combination thereof, each of which has an average particle diameter of not more than 30 μm with a disintegrant such as Crospovidone using water or an alcohol-water mixture at a ratio of 1:3 to 3:1, without the addition of a binder, in a typical high shear granulator, wet milling to produce a desired particle size distribution, and drying in a fluid bed equipment to produce dispersible microgranules with an average particle size of not more than 400 μm (*typically the average particle size of not more than 300 μm*);

EX1020 (Venkatesh) at ¶[0020] (emphasis added); *see also id.* EX1020 (Venkatesh) at ¶[0009] (“Another requirement for being incorporated into rapidly disintegrating

tablets is that the taste-masked microcapsules/granules should be smaller than 500 μm in diameter, preferably be smaller than 400 μm in diameter to avoid gritty mouthfeel.”).

270. Venkatesh discloses that the average particle size of the disintegrant, sugar alcohol or saccharide should be less than 30 μm as follows:

One embodiment of this invention relates to pharmaceutical compositions comprising *rapidly dispersing microgranules of a disintegrant and sugar alcohol or a saccharide whose average particle size is not more than 30 μm* , resilient (hard, flexible, less-friable) microgranules of bitter active pharmaceutical ingredients effectively taste-masked by coacervation, and other pharmaceutically acceptable excipients in the form of tablets which rapidly disintegrate in the buccal cavity.

EX1020 (Venkatesh) at ¶[0014] (emphasis added); *see also id.* ¶[0018] (“preferably not more than 20 μm ”); ¶[0028].

271. A person of ordinary skill in the art would have been motivated to formulate budesonide in an orally disintegrating tablet based on Dohil, and also having drug particles with an average particle size of less than about 400 μm , rapidly dispersing granules with an average particle size of less than about 300 μm , and a disintegrant and sugar alcohol and/or saccharide with an average particle size of less than about 30 μm based on Venkatesh to avoid a gritty texture and improve

mouthfeel with a reasonable expectation of success. Claim 17 is therefore obvious over the prior art.

E. Claim 18

272. Claim 18 depends from claim 16 and recites:

Claim 18. The pharmaceutical composition of claim 16, wherein the drug particles have an average particle size of less than about 4 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm .

273. Venkatesh discloses that the drug particles have an average particle size of less than 400 μm as follows:

In accordance with the one embodiment of the invention, milled/micronized drug particles (e.g., *average particle diameter less than about 50 μm , preferably less than about 25 μm*) are blended with a water soluble ductile polymeric binder such as modified starch and hydroxypropyl methylcellulose with a viscosity of 100 cps or higher, alone or in combination with a widely used binder such as PVP (polyvinylpyrrolidone), hydroxypropylcellulose and hydroxypropyl methylcellulose with a viscosity of 15 cps or less.

EX1020 (Venkatesh) at ¶[0015] (emphasis added). Venkatesh's ranges of less than less than 50 μm , and less than 25 μm each overlap with the range of "less than about 4 μm " recited by claim 18.

274. Venkatesh discloses rapidly dispersing granules having an average particle size of less than about 300 μm for reasons discussed above with respect to claim 17.

275. A person of ordinary skill in the art would have been motivated to formulate budesonide in an orally disintegrating tablet based on Dohil, and also having drug particles with an average particle size of less than about 4 μm and rapidly dispersing granules with an average particle size of less than about 300 μm , based on Venkatesh to avoid a gritty texture and improve mouthfeel with a reasonable expectation of success. Claim 18 is therefore obvious over the prior art.

XII. GROUND 4: GROTHER, FDA GUIDANCE, AND VENKATESH

276. This section explains how Grother, the FDA Guidance, and Venkatesh in view of the knowledge of a person of ordinary skill in the art renders obvious dependent claims 8, 16-26, and 37 of the '729 patent.

A. Claim 8

277. Claim 8 recites:

Claim 8. The solid pharmaceutical composition of claim 1, which is substantially free of lubricant.

278. A person of ordinary skill in the art would have been motivated to formulate Grother's fast dispersing dosage form with budesonide, and further for the dosage form to be substantially free of lubricant based on Venkatesh.

279. As discussed above, Venkatesh is directed to “orally disintegrating tablets.” EX1020 (Venkatesh) at ¶[0001]. Venkatesh’s orally disintegrating tablet formulations are compatible with “any therapeutic active agent indicated for oral administration.” EX1020 (Venkatesh) at ¶[0025]. Budesonide is a therapeutic active agent indicated for oral administration for reasons discussed above.

280. Venkatesh discloses manufacturing its orally disintegrating tablets using an external lubrication system to pre-lubricate the dies and punches so that the tablet is otherwise free of lubricant as follows:

It is yet another embodiment of the invention to provide a method to manufacture rapidly disintegrating tablets, which are characterized by the property that it is formed by compressing in a tablet press equipped with an externally lubricating system to pre-lubricate dies and punches ***and the tablet formulation otherwise being free of lubricant.***

EX1020 (Venkatesh) at ¶[0017] (emphasis added); *see also id.* at ¶[0018] (“The invention also provides a method of manufacturing pharmaceutical tablets, produced by mixing microgranules of a sugar alcohol such as D-mannitol or a saccharide such as lactose, each having an average particle diameter of not more than 301 μm , preferably not more than 20 μm and a disintegrant with one or more taste-masked microcapsules and other excipients (for example: flavor, color, sweetener etc.) and compressing the blend into rapidly disintegrating tablets, ***the tablet thus produced having the property that it is formed by compressing in a tablet press equipped***

with an externally lubricating system to pre-lubricate dies and punches and the tablet formulation otherwise being free of lubricant.”) (emphasis added).

281. Venkatesh teaches manufacturing tablets via compression uses “a conventional rotary tablet press equipped with an external lubrication system to pre-lubricate the dies and punches.” EX1020 (Venkatesh) ¶[0024]; *id.* ¶[0008] (disclosing “conventional granulating, drying and tableting equipment”). The ’729 patent uses the same language as Venkatesh in stating that a “rotary tablet press equipped with an external lubrication system to pre-lubricate the dies and punches” was “conventional” in the prior art. EX1001 (the ’729 patent) at 16:41-43, 17:7-9. The ’729 patent states that using such “an externally lubricating system to pre-lubricate dies and punches, thereby provid[es] a tablet formulation otherwise free of lubricant.” *Id.* at 16:11-13, 17:34-36.

282. A person of ordinary skill in the art would have been motivated to manufacture Grother’s fast dispersing dosage form using conventional punch and die surfaces with an external lubricating system to provide tablets that are substantially free of lubricant. Such conventional manufacturing was desirable to mass produce such dosage forms with a reasonable expectation of success, as evidenced Venkatesh. Claim 8 is therefore obvious over the prior art.

B. Claim 16

283. Claim 16 depends from claim 15 and recites:

Claim 16. The pharmaceutical composition of claim 15, wherein the ODT comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid, and the rapidly dispersing granules comprise the disintegrant and a sugar alcohol and/or saccharide.

284. As discussed in Ground 2 for claim 15, Grother's fast dispersing solid dosage forms render obvious the claimed orally disintegrating tablet recited by claim 15 in view of the FDA Guidance.

285. Venkatesh discloses "an orally disintegrating tablet made up of rapidly dispersing microgranules and taste-masked microcapsules." EX1020 (Venkatesh) at ¶[0001]. Venkatesh discloses that "this invention relates to pharmaceutical compositions comprising *rapidly dispersing microgranules of a disintegrant and sugar alcohol or a saccharide whose average particle size is not more than 30 µm, resilient (hard, flexible, less-friable) microgranules of bitter active pharmaceutical ingredients effectively taste-masked by coacervation*, and other pharmaceutically acceptable excipients in the form of tablets which rapidly disintegrate in the buccal cavity." *Id.* at ¶[0014] (emphasis added); *see also id.* at ¶[0018] ("The invention also provides a method of manufacturing pharmaceutical tablets, *produced by mixing microgranules of a sugar alcohol such as D-mannitol or a saccharide such as lactose*, each having an average particle diameter of not more than 301 µm, preferably not more than 20 µm *and a disintegrant with one or more taste-masked*

microcapsules and other excipients (for example: flavor, color, sweetener etc.) and compressing the blend into rapidly disintegrating tablets, the tablet thus produced having the property that it is formed by compressing in a tablet press equipped with an externally lubricating system to pre-lubricate dies and punches and the tablet formulation otherwise being free of lubricant.”) (emphasis added). Venkatesh therefore discloses orally disintegrating tablets comprising drug particles and rapidly dispersing microgranules comprising a disintegrant, a sugar alcohol and/or saccharide.

286. Venkatesh discloses that “[t]he sugar alcohol may be selected from the group consisting of mannitol, sorbitol, xylitol, maltitol and the like while the saccharide may be selected from the group consisting of lactose, sucrose, maltose or as a mixture of two or more, each of which is characterized by an average particle size of not more than about 30 μm .” EX1020 (Venkatesh) at ¶[0028]. Venkatesh therefore discloses the “sugar alcohol” and “saccharide” recited by claim 16.

287. A person of ordinary skill in the art would have been motivated to formulate budesonide in an orally disintegrating tablet based on Grother for reasons discussed above regarding claim 15. The person of ordinary skill in the art would have further been motivated for the budesonide to comprise drug particles and the disintegrant to be rapidly dispersing granules that include a sugar alcohol and/or saccharide based on Venkatesh. Venkatesh teaches that formulating orally

disintegrating tablets to have drug particles and rapidly-dispersing microgranules comprising sugar alcohol and/or saccharide in combination with the disintegrant beneficially allowed “avoid[ed] gritty mouthfeel,” EX1020 (Venkatesh) at ¶[0012], to assist with providing a “smooth creamy mouthfeel (no grittiness).” *Id.* at ¶[0002].

288. The person of ordinary skill would have reasonably expected success in doing so based on the detailed disclosures within Venkatesh regarding the preparation of such formulations. Venkatesh teaches that its formulations “don't require a special pharmaceutical production technique and can be simply and easily produced by a normal equipment.” EX1020 (Venkatesh) at ¶[0018]. Claim 16 is therefore obvious over the prior art.

C. **Claim 17**

289. Claim 17 depends from claim 16 and recites:

Claim 17. The pharmaceutical composition of claim 16, wherein the drug particles have an average particle size of less than about 400 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm , and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 μm .

290. Venkatesh discloses that the drug particles have an average particle size of less than 400 μm as follows:

In accordance with the one embodiment of the invention, milled/micronized drug particles (e.g., *average particle diameter less than about 50 μm , preferably less than about 25 μm*) are blended with

a water soluble ductile polymeric binder such as modified starch and hydroxypropyl methylcellulose with a viscosity of 100 cps or higher, alone or in combination with a widely used binder such as PVP (polyvinylpyrrolidone), hydroxypropylcellulose and hydroxypropyl methylcellulose with a viscosity of 15 cps or less.

EX1020 (Venkatesh) at ¶[0015] (emphasis added); *id.* ¶[0015] (“These granules can be obtained with an average particle size of 200 μm and can be effectively taste masked by coacervation by phase separation to produce taste-masked particles with optimum size distribution (e.g., mean particle size of not more than 400 μm) for incorporation into tablets, which rapidly disintegrate in the buccal cavity with a smooth creamy mouthfeel.”); *id.* ¶[0022], ¶[0025].

291. Venkatesh discloses that the rapidly dispersing granules have an average particle size of less than 300 μm as follows:

(a) granulating a sugar alcohol or a saccharide, or a combination thereof, each of which has an average particle diameter of not more than 30 μm with a disintegrant such as Crospovidone using water or an alcohol-water mixture at a ratio of 1:3 to 3:1, without the addition of a binder, in a typical high shear granulator, wet milling to produce a desired particle size distribution, and drying in a fluid bed equipment to produce dispersible microgranules with an average particle size of not more than 400 μm (*typically the average particle size of not more than 300 μm*);

EX1020 (Venkatesh) at ¶[0020] (emphasis added); *see also id.* EX1020 (Venkatesh) at ¶[0009] (“Another requirement for being incorporated into rapidly disintegrating tablets is that the taste-masked microcapsules/granules should be smaller than 500 µm in diameter, preferably be smaller than 400 µm in diameter to avoid gritty mouthfeel.”).

292. Venkatesh discloses that the average particle size of the disintegrant, sugar alcohol or saccharide should be less than 30 µm as follows:

One embodiment of this invention relates to pharmaceutical compositions comprising *rapidly dispersing microgranules of a disintegrant and sugar alcohol or a saccharide whose average particle size is not more than 30 µm*, resilient (hard, flexible, less-friable) microgranules of bitter active pharmaceutical ingredients effectively taste-masked by coacervation, and other pharmaceutically acceptable excipients in the form of tablets which rapidly disintegrate in the buccal cavity.

EX1020 (Venkatesh) at ¶[0014] (emphasis added); *see also id.* ¶[0018] (“preferably not more than 20 µm”); ¶[0028].

293. A person of ordinary skill in the art would have been motivated to formulate budesonide in an orally disintegrating tablet based on Grother, and also having drug particles with an average particle size of less than about 400 µm, rapidly dispersing granules with an average particle size of less than about 300 µm, and a disintegrant and sugar alcohol and/or saccharide with an average particle size of less

than about 30 μm based on Venkatesh to avoid a gritty texture and improve mouthfeel with a reasonable expectation of success. Claim 17 is therefore obvious over the prior art.

D. Claim 18

294. Claim 18 depends from claim 16 and recites:

Claim 18. The pharmaceutical composition of claim 16, wherein the drug particles have an average particle size of less than about 4 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm .

295. Venkatesh discloses that the drug particles have an average particle size of less than 400 μm as follows:

In accordance with the one embodiment of the invention, milled/micronized drug particles (e.g., *average particle diameter less than about 50 μm , preferably less than about 25 μm*) are blended with a water soluble ductile polymeric binder such as modified starch and hydroxypropyl methylcellulose with a viscosity of 100 cps or higher, alone or in combination with a widely used binder such as PVP (polyvinylpyrrolidone), hydroxypropylcellulose and hydroxypropyl methylcellulose with a viscosity of 15 cps or less.

EX1020 (Venkatesh) at ¶[0015] (emphasis added). Venkatesh's ranges of less than less than 50 μm , and less than 25 μm each overlap with the range of "less than about 4 μm " recited by claim 18.

296. Venkatesh discloses rapidly dispersing granules having an average particle size of less than about 300 μm for reasons discussed above with respect to claim 17.

297. A person of ordinary skill in the art would have been motivated to formulate budesonide in an orally disintegrating tablet based on Grother, and also having drug particles with an average particle size of less than about 4 μm and rapidly dispersing granules with an average particle size of less than about 300 μm , based on Venkatesh to avoid a gritty texture and improve mouthfeel with a reasonable expectation of success. Claim 18 is therefor obvious over the prior art.

E. Claim 19

298. Claim 19 depends from claim 16 and recites:

Claim 19. The pharmaceutical composition of claim 16, wherein the corticosteroid is disposed over the surface of an excipient, the rapidly dispersing granules have an average particle size of less than about 300 μm .

299. Grother discloses that “[a] further technique is to dose a non-aqueous solution of the active ingredient onto preformed placebo FDDF [fast dispersing dosage form] units.” EX1008 (Grother) at 27:11-14. This technique advantageously strengthens the structure of the fast dispersing dosage form. *Id.* at 27:7-14. Grother therefore discloses a formulation of budesonide where the budesonide is disposed

over the surface of an excipient, in this case a preformed placebo fast dispersing dosage form. Claim 19 is therefore obvious over the prior art.

F. Claim 20

300. Claim 20 depends from claim 16 and recites:

Claim 20. The pharmaceutical composition of claim 4, wherein the adhesive agent and the corticosteroid are intimately associated.

301. **Claim construction:** The '729 patent defines “adhesive agent” to refer “to agents which promote adhesion of the corticosteroid to biological surfaces, and includes, but is not limited to bio-adhesive agents.” EX1001 (the '729 patent) at 2:66-3:2 (“The term ‘adhesive agent’, as used herein refers to agents which promote adhesion of the corticosteroid to biological surfaces, and includes, but is not limited to bio-adhesive agents.”). I have applied this definition. The '729 patent states that suitable adhesive agents include polyvinylpyrrolidone. *Id.* at 10:23-39 (“Suitable adhesive agents include sucrose aluminum sulfate complex, chitosan and derivatives thereof (e.g., trimethylchitosan, chitosan salts), polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, cross-linked or uncross-linked polyacrylates, cross-linked polyacrylates, acidic cross-linked or uncross-linked polyacrylates, polyacrylic acid homopolymers or copolymers, aminoalkyl methacrylate copolymers, methacrylic acid/methylmethacrylate copolymer, alkylacrylate/alkylmethacrylate copolymers, ammoniomethacrylate copolymers, Eudragit® polymers (E, L, S, NE, RL, and RS

grades), carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof[.]”). I have applied this definition.

302. Grother discloses the claimed “adhesive agent” for reasons discussed above regarding claims 4-5. For example, Grother discloses that “[t]he fast dispersing dosage form according to the invention may also contain, in addition to the active ingredient and modified starch, other matrix forming agents and secondary components.” EX1008 (Grother) at 14:7-9. “Matrix forming agents suitable for use in the present invention include... carboxymethylcelluloses... polyvinylpyrrolidone” *Id.* at 14:9-15 (“Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as non-mammalian gelatins, dextrans and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; *carboxymethylcelluloses*; carrageenans; dextrans; pectins; synthetic polymers such as *polyvinylpyrrolidone*; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.”) (emphasis added). Grother discloses that “[o]ne or more matrix forming agents may be incorporated into the solution or suspensions prior to solidification.” *Id.* at 14:22-23. Thus, Grother discloses a solid pharmaceutical composition comprising polyvinylpyrrolidone or

carboxymethylcelluloses, which a person of ordinary skill in the art would understand function as an adhesive agent.

303. As discussed above for Ground 2, Grother discloses that “wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.” EX1008 (Grother) at 12:10-19. The process of mixing Grother’s active ingredient with the matrix forming agent and modified starch creates an intimate mixture that meets the claimed intimate association.

304. Venkatesh discloses an intimate association between the active ingredient and adhesive agent as follows:

In accordance with the one embodiment of the invention, *milled/micronized drug particles* (e.g., average particle diameter less than about 50 μm , preferably less than about 25 μm) *are blended with* a water soluble ductile polymeric binder such as modified starch and hydroxypropyl methylcellulose with a viscosity of 100 cps or higher, alone or in combination with a widely used binder such as *PVP (polyvinylpyrrolidone)*, hydroxypropylcellulose and hydroxypropyl methylcellulose with a viscosity of 15 cps or less.

EX1020 (Venkatesh) at ¶[0015] (emphasis added). The process of blending the milled/micronized drug particles with polyvinylpyrrolidone creates an intimate mixture that meets the claimed intimate association.

305. Claim 20 is therefore obvious over the prior art.

G. Claim 21

306. Claim 21 depends from claim 20 and recites:

Claim 21. The pharmaceutical composition of claim 20, wherein said corticosteroid is surrounded or encapsulated by the adhesive agent.

307. Venkatesh discloses that the orally disintegrating tablet is manufactured by “(c) microencapsulating these resilient granules (mean size: 200 μm or less) by coacervation in cyclohexane containing ethylcellulose to produce effectively taste-masked microcapsules with a desired particle size distribution (average particle size of not more than 400 μm , typically not more than 300 μm) wherein the average membrane thickness is in the range of 30% to 50% by weight of the coated granules.”

EX1020 (Venkatesh) ¶[0022]; *see also id.* ¶[0013].

308. Venkatesh further discloses that “[p]olymers suitable for microencapsulation of bitter drugs include *ethylcellulose, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate* depending on solubility in water or cyclohexane.” EX1020 (Venkatesh) ¶[0027]. Ethylcellulose, cellulose acetate phthalate, and hydroxypropyl methylcellulose phthalate are cellulose derivatives.

309. The ’729 patent states that “cellulose derivatives” are suitable “bio-gelling polymers.” EX1001 at 6:39-51 (“*Other bio-gelling polymers which may be included within the liquid pharmaceutical compositions of the present invention include cellulose derivatives (e.g., esters and/or ethers, crosslinked cellulose esters*

and/or ethers) cellulose esters, methacrylic acid and methacrylate polymers, polylactides, polyglycolides, polycaprolactones, polydioxanones, polycarbonates, polyhydroxybutyrates, polyalkylene oxalates, polyanhydrides, polyamides, polyesteramides, polyurethanes, polyacetals, polyketals, polyorthocarbonates, polyphosphazenes, polyhydroxyvalerates, polyalkylene succinates, poly(malic acid), poly(amino acids), chitin, chitosan, polyorthoesters, and copolymers, terpolymers and mixtures thereof.”) (emphasis added). The ’729 patent further states that “[b]io-gelling polymers swell, and/or form hydrogels upon contact with moisture in the gastrointestinal tract, *thereby adhering or increasing the viscosity of the compositions of the present invention on the mucosa of the gastrointestinal tract*. Consequently, the contact of the corticosteroid with the gastrointestinal mucosa is enhanced and/or prolonged.” EX1001 (the ’729 patent) at 6:51-57 (emphasis added); *see also id.* at 2:66-3:2 (defining “adhesive agent” as an agent which promotes “adhesion of the corticosteroid to biological surfaces, and includes, but is not limited to bio-adhesive agents.”).

310. A person of ordinary skill in the art would understand that the cellulose derivatives disclosed by Venkatesh are a type of bio-gelling polymer that meet the “adhesive agent” recited by claim 21. Claim 21 is therefore obvious over the prior art.

H. Claim 22

311. Claim 22 depends from claim 20 and recites:

Claim 22. The pharmaceutical composition of claim 20, wherein the corticosteroid is disposed on the surface of said adhesive agent.

312. Grother discloses that “[t]he fast dispersing dosage form according to the invention may also contain, in addition to the active ingredient and modified starch, other matrix forming agents and secondary components.” EX1008 (Grother) at 14:7-9.

313. “Matrix forming agents suitable for use in the present invention include... polyvinylpyrrolidone” *Id.* at 14:9-15 (“Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as non- mammalian gelatins, dextrans and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as *polyvinylpyrrolidone*; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.”) (emphasis added). Grother discloses that “[o]ne or more matrix forming agents may be incorporated into the solution or suspensions prior to solidification.” *Id.* at 14:22-23. Thus, Grother discloses a solid pharmaceutical composition comprising polyvinylpyrrolidone, which a person of ordinary skill in the art would understand functions as an adhesive agent.

314. As discussed above for claim 20, Grother discloses that “wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.” EX1008 (Grother) at 12:10-19. A person of ordinary skill in the art would understand that the process of mixing Grother’s active ingredient with a matrix forming agent such as polyvinylpyrrolidone would, result in deposition of the corticosteroid on the surface of the polyvinylpyrrolidone.

315. Likewise, Venkatesh discloses deposition of the active ingredient on the surface of the adhesive agent as follows:

In accordance with the one embodiment of the invention, *milled/micronized drug particles* (e.g., average particle diameter less than about 50 μm , preferably less than about 25 μm) *are blended with* a water soluble ductile polymeric binder such as modified starch and hydroxypropyl methylcellulose with a viscosity of 100 cps or higher, alone or in combination with a widely used binder such as **PVP (polyvinylpyrrolidone)**, hydroxypropylcellulose and hydroxypropyl methylcellulose with a viscosity of 15 cps or less.

EX1020 (Venkatesh) at ¶[0015] (emphasis added). A person of ordinary skill in the art would understand that the process of blending the milled/micronized drug particles with polyvinylpyrrolidone creates an intimate mixture with the drug particle deposited on the surface of the polyvinylpyrrolidone.

316. Claim 22 is therefore obvious over the prior art.

I. Claim 23

317. Claim 23 depends from claim 16 and recites:

Claim 23. The pharmaceutical composition of claim 16, wherein the ODT comprises a lyophilized matrix, wherein the lyophilized matrix comprises the corticosteroid in combination with at least one excipient.

318. Grother discloses that “the solid dosage forms according to the invention are obtainable by removing a solvent, such as water, from a mixture comprising an active ingredient, a modified starch and a matrix forming agent via freeze drying.” EX1008 (Grother) at Abstract; *id.* at 13:15-16, 32:14-15. “The resulting tablet has an open porous matrix that dissolves rapidly on contact with saliva.” *Id.* at 32:15-17. A person of ordinary skill in the art understood that freeze drying Grother’s mixture containing a modified starch and a matrix forming agent is a lyophilization process forms a lyophilized matrix with at least one excipient. Claim 23 is therefore obvious over the prior art.

J. Claim 24

319. Claim 24 depends from claim 23 and recites:

Claim 24. The pharmaceutical composition of claim 23, wherein the excipient is selected from the group consisting of mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

320. Grother discloses that “[t]he preferred matrix forming agent is mannitol.” EX1008 (Grother) at 13:12; *see also id.* at 14:16-21. Claim 24 is therefore obvious over the prior art.

K. Claims 25-26

321. Claim 25 depends from claim 23 and recites:

Claim 25. The pharmaceutical composition of claim 23, wherein the ODT is in the form of a wafer or film.

322. Claim 26 depends from claim 16 and recites:

Claim 26. The pharmaceutical composition of claim 16, wherein the ODT is in the form of a wafer or film.

323. It was well known to a person of ordinary skill in the art that orally disintegrating tablets were beneficially provided in the form of a film. For example, the Zydis[®] fast-dissolving wafer was developed in the late 1970s. *See* EX1017 (Danckwerts) at 178 (“Zydis[®] was the first quick-disintegrating intraoral drug delivery system to be commercialized on a large scale.”). Dohil discloses budesonide in the form of “a dissolving wafer.” EX1002 (Dohil) ¶[0013]. A wafer has a relatively large surface area compared to a tablet of the same weight, and the large surface area increases the amount of surface that comes into contact with saliva in a patient’s mouth thereby providing beneficial dissolution. Claims 25 and 26 are therefore obvious over the prior art.

L. Claim 37

324. Claim 37 depends from claim 16 and recites:

Claim 37. The pharmaceutical composition of claim 16, wherein the ODT further comprises a sugar alcohol, a disintegrant, and microcrystalline cellulose, wherein the drug particles comprise fluticasone, and rapidly dispersing granules comprise a disintegrant and a sugar alcohol or saccharide or a mixture thereof.

325. As discussed above for claim 16, Venkatesh discloses “an orally disintegrating tablet made up of rapidly dispersing microgranules and taste-masked microcapsules.” EX1020 (Venkatesh) at ¶[0001]. Venkatesh discloses that “this invention relates to pharmaceutical compositions comprising *rapidly dispersing microgranules of a disintegrant and sugar alcohol or a saccharide whose average particle size is not more than 30 µm, resilient (hard, flexible, less-friable) microgranules of bitter active pharmaceutical ingredients effectively taste-masked by coacervation*, and other pharmaceutically acceptable excipients in the form of tablets which rapidly disintegrate in the buccal cavity.” *Id.* at ¶[0014]; *see also id.* at ¶[0018] (“The invention also provides a method of manufacturing pharmaceutical tablets, *produced by mixing microgranules of a sugar alcohol such as D-mannitol or a saccharide such as lactose*, each having an average particle diameter of not more than 301 µm, preferably not more than 20 µm *and a disintegrant with one or more taste-masked microcapsules* and other excipients (for example: flavor, color,

sweetener etc.) and compressing the blend into rapidly disintegrating tablets, the tablet thus produced having the property that it is formed by compressing in a tablet press equipped with an externally lubricating system to pre-lubricate dies and punches and the tablet formulation otherwise being free of lubricant.”) (emphasis added). Venkatesh therefore discloses orally disintegrating tablets comprising drug particles and rapidly dispersing microgranules comprising a disintegrant, a sugar alcohol and/or saccharide.

326. Venkatesh discloses that “[t]he sugar alcohol may be selected from the group consisting of mannitol, sorbitol, xylitol, maltitol and the like while the saccharide may be selected from the group consisting of lactose, sucrose, maltose or as a mixture of two or more, each of which is characterized by an average particle size of not more than about 30 μm .” EX1020 (Venkatesh) at ¶[0028]. Venkatesh therefore discloses the “sugar alcohol” and “saccharide” recited by claims 16 and 37.

327. A person of ordinary skill in the art would have been motivated to formulate an orally disintegrating tablet based on Grother for reasons discussed in Ground 2 regarding claim 15. The person of ordinary skill in the art would have further been motivated for the orally disintegrating tablet to comprise drug particles and the disintegrant to be rapidly dispersing granules that include a sugar alcohol and/or saccharide based on Venkatesh. Venkatesh teaches that formulating orally

disintegrating tablets to have drug particles and rapidly-dispersing microgranules comprising sugar alcohol and/or saccharide in combination with the disintegrant beneficially allowed “avoid[ed] gritty mouthfeel,” EX1020 (Venkatesh) at ¶[0012], to assist with providing a “smooth creamy mouthfeel (no grittiness).” *Id.* at ¶[0002].

328. The person of ordinary skill would have reasonably expected success in doing so based on the detailed disclosures within Venkatesh regarding the preparation of such formulations. Venkatesh teaches that its formulations “don’t require a special pharmaceutical production technique and can be simply and easily produced by a normal equipment.” EX1020 (Venkatesh) at ¶[0018].

329. Venkatesh teaches that microcrystalline cellulose beneficially imparts resilient characteristics to orally disintegrating tablets. See EX1020 (Venkatesh) at ¶[0021] (“(b) granulating a bitter active pharmaceutical ingredient and optionally one or more pharmaceutically acceptable diluents such as mannitol, lactose and microcrystalline cellulose with at least one polymeric binder such as modified starch and hydroxypropylmethylcellulose with a viscosity of 100 cps or higher, which imparts resilient, characteristics to the dried granules and wet milling using a size reduction mill such as Comil™ equipped with an appropriate sieve size to produce granules with a desired particle size distribution in order to avoid excessive dry milling which typically results in fines undesirable from the taste-masking point of view.”). Grother discloses that excipients for orally disintegrating tablets were

known to “include microcrystalline cellulose, corn starch and lactose.” EX1008
(Grother) at 10:9-10.

330. As discussed above for claims 28 and 38-40 in Ground 2, Grother renders obvious using fluticasone as the active ingredient in its fast dispersing dosage form. Claim 37 is therefore obvious over the prior art.

XIII. CONCLUSION

331. For the reasons described above, a person of ordinary skill in the art would have found Claims 1-40 of the '729 patent obvious in view of the prior art.

332. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 17Apr2024 By: Alan Frank PARR

Alan F. Parr, Pharm.D., Ph.D.