

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. IPR2025-00056

U.S. Patent No. 11,260,061

**DECLARATION OF ALAN F. PARR, PHARM.D, PH.D.,
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 11,260,061**

Dr. Falk Pharma Ex. 1070 IPR Petition - USP 11,260,061
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LIST OF MATERIALS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 11,260,061 to Gosselin et al.
1002	U.S. Publication No. 20070111978 to Dohil et al. (“Dohil”)
1005	“Guidance for Industry: Orally Disintegrating Tablets,” U.S. Food & Drug Administration, Center for Drug Evaluation and Research (CDER), 2008.
1006	Notice of Publication of FDA Guidance for Industry on Orally Disintegrating Tablets, Federal Register, Vol. 73, No. 242 at 76366, December 16, 2008.
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).
1014	Aceves et al., “Topical viscous budesonide suspension for treatment of eosinophilic esophagitis,” <i>Journal of Allergy and Clinical Immunology</i> 116:705-706 (2005)
1015	Aceves et al., “Oral Viscous Budesonide: A potential new therapy for eosinophilic esophagitis in children,” <i>American Journal of Gastroenterology</i> , 102:1-9 (2007)

Exhibit No.	Description
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)
1029	<i>Curriculum Vitae</i> of Alan F. Parr, Pharm.D., Ph.D.
1041	Conway, “Solid dosage forms,” Chapter 4.1 in Pharmaceutical Manufacturing Handbook: Production and Processes, ed. Gad, pages 235-265 (2008)
1054	Wen, “Adsorption at solid surfaces: pharmaceutical applications,” in Encyclopedia of Pharmaceutical Technology, Third Edition, ed. Swarbrick, pages 34-45 (2007)
1055	Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences, Fourth Edition, eds. Martin et al. (1993)
1057	U.S. Publication No. 2011/0081411 to Perrett et al.

Exhibit No.	Description
1058	U.S. Publication No. 2009/0191275 to Dohil et al. (“Dohil2009”)
1059	Redline comparison of Dohil and Dohil2009
1060	McGraw-Hill Dictionary of Scientific and Technical Terms, Sixth Edition (2003), “Adsorption”
1062	The Opposition Division of the European Patent Office decision regarding EP3041476
1063	International Publication No. WO2011041509
1064	Roeder et al., “Safety and efficacy of fluticasone propionate in the topical treatment of skin diseases,” Skin Pharmacology Physiology, 18:3-11 (2004)
1065	Remedios et al., “Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate,” Gastrointestinal Endoscopy, 63:3-12 (2006)
1066	Konikoff et al., “A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis,” Gastroenterology, 131:1381-1391 (2006)
1067	Khan et al., “An approach for rapid disintegrating tablet: a review,” Int’l J. Pharm. Research and Development, 21:170-183 (2011)
1069	“Cellulose, Silicified Microcrystalline,” Handbook of Pharmaceutical Excipients, 5th edition, eds. Rowe et al., pages 139-141 (2006)

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. 11,260,061 (“the ’061 patent,” EX1001) and requests that the United States Patent and Trademark Office cancel all claims of the ’061 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 September of 2013.¹

**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

¹ I understand that September 2013 is the relevant time frame for analyzing the obviousness of the ’061 patent. In contrast, I understand that October 2009 is the relevant time frame for analyzing the obviousness of the four other Ellodi patents that I have analyzed, which are U.S. Patent Nos. 9,486,407; 10,632,069; 11,246,828; and 10,471,071.

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 dispersing tablet (ODT) dosage formulations. My experience in developing ODTs includes reviewing and giving guidance on the formulation development plan of the ODT formulation, reviewing details from executed experiments and data

generated on ODT formulations, and making recommendations to improve the ODT 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].

D. Current Related Testimony

17. I am currently serving as an expert witness in the following related matter:

- *Dr. Falk Pharma GmbH v. Ellodi Pharmaceuticals LP*, IPR2024-01197, regarding U.S. Patent No. 8,771,729.

II. MATERIALS CONSIDERED

18. 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

19. 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.

20. 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

21. 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.

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

23. 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.

24. 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

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

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.²

26. 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

² I understand that 35 U.S.C. § 103 was amended by the America Invents Act of 2011, and that the amendment applies to U.S. patents having an effective filing date of March 16, 2013 or later.

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.

27. 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.

28. 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

29. 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.

30. I understand that September 2013 is the relevant time frame for analyzing the obviousness of the '061 patent. A person of ordinary skill in the art related to the '061 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.

31. My opinions concerning the obviousness of the '061 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

32. 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 today 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.”).

33. 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.”).

34. 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 this 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 this field.”).

35. 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.

36. 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).

37. 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 '061 PATENT

38. The '061 patent (EX1001) is directed to “Corticosteroid containing orally disintegrating tablet compositions for eosinophilic esophagitis.” EX1001 (“the '061 patent”) at Title.

39. The '061 patent has 30 claims, with claims 1 and 19 being independent claims. *See* EX1001 (“the '061 patent”) at Claims.

A. Independent claim 1 and its dependent claims

40. Independent claim 1 of the '061 patent recites:

Claim 1. An orally disintegrating tablet comprising:

a. a topically acting corticosteroid or pharmaceutically acceptable salt or ester thereof, adsorbed onto a pharmaceutically acceptable carrier; and

b. at least one disintegrant;

[c.i] wherein the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is present in an amount ranging from about 0.5 mg to about 10 mg, and

[c.ii] the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, has a mean particle size of ranging from about 100 nm to about 100 μ m; and

[d] wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701>method for disintegration time.³

EX1001 (“the '061 patent”) at Claim 1.

41. Claims 2-18, and 29-30 depend, either directly or indirectly through another claim, from independent claim 1. These claims are reproduced below.

³ Bracketed labels, e.g., “[c.i]” and “[c.ii],” have been added for convenient referencing to the claim limitations.

Claim 2. The orally disintegrating tablet of claim 1, wherein the pharmaceutically acceptable carrier is selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, and amorphous magnesium aluminum silicate.

Claim 3. The orally disintegrating tablet of claim 2, wherein the pharmaceutically acceptable carrier is silicified microcrystalline cellulose.

Claim 4. The orally disintegrating tablet of claim 2, wherein said topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, or a pharmaceutically salt or ester thereof.

Claim 5. The orally disintegrating tablet of claim 4, wherein the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is present in an amount ranging from about 0.5 mg to about 3 mg.

Claim 6. The orally disintegrating tablet of claim 4, wherein said topically acting corticosteroid is fluticasone or an ester thereof.

Claim 7. The orally disintegrating tablet of claim 4, wherein said topically acting corticosteroid is fluticasone propionate.

Claim 8. The orally disintegrating tablet of claim 1, wherein fluticasone propionate is present in an amount of about 3 mg in the orally disintegrating tablet.

Claim 9. The orally disintegrating tablet of claim 1, wherein fluticasone propionate is present in an amount of about 1.5 mg in the orally disintegrating tablet.

Claim 10. The orally disintegrating tablet of claim 1, wherein the corticosteroid has a mean particle size of ranging from about 100 nm to about 10 μ m.

Claim 11. The orally disintegrating tablet of claim 1, wherein the corticosteroid has a mean particle size ranging from about 100 nm to about 4 μ m.

Claim 12. The orally disintegrating tablet of claim 1, wherein the at least one disintegrant is present in a rapidly dispersing microgranule, which comprises a sugar alcohol, or a saccharide, or a mixture thereof in addition to the at least one disintegrant.

Claim 13. The orally disintegrating tablet of claim 12, wherein the sugar alcohol or saccharide and the disintegrant are present in a ratio of sugar alcohol or saccharide to disintegrant of from 90:10 to 99:1.

Claim 14. The orally disintegrating tablet of claim 12, wherein the disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, and low-substituted hydroxylpropylcellulose.

Claim 15. The orally disintegrating tablet of claim 12, wherein the sugar alcohol or saccharide is selected from the group consisting of sucralose, lactose, sucrose, maltose, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.

Claim 16. The orally disintegrating tablet of claim 12, wherein the rapidly dispersing microgranule has a mean particle size of less than about 300 μm , and the sugar alcohol and/or saccharide has an average particle size of less than about 30 μm .

Claim 17. The orally disintegrating tablet of claim 1, wherein the pharmaceutically acceptable carrier is present at an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

Claim 18. The orally disintegrating tablet of claim 1, wherein the total weight of the tablet is in the range of from about 300 to about 900 mg.

Claim 29. A method for treating eosinophilic esophagitis in an individual in need thereof, comprising administering to the individual the orally disintegrating tablet of claim 1.

Claim 30. A method of preparing the orally disintegrating tablet of claim 1, comprising the steps of:

(a) micronizing the corticosteroid;

(b) preparing preblend 1 by blending (i) a pharmaceutically acceptable carrier, (ii) corticosteroid or pharmaceutically ester thereof, and (iii) glidant, under conditions suitable for the corticosteroid to be adsorbed onto the pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier is microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, and amorphous magnesium aluminum silicate;

(c) preparing preblend 2 by blending filler, preblend 1 of step (b), disintegrant, and sweetener;

(d) preparing a final compressible blend, by blending a disintegrant, lubricant, filler, and preblend 2 of step (c);

(e) compressing the blend of step (d) to form a tablet.

EX1001 (“the ’061 patent”) at Claims 2-18 and 29-30.

B. Independent claim 19 and its dependent claims

42. Independent claim 19 of the ’061 patent recites:

Claim 19. An orally disintegrating tablet comprising:

a. fluticasone propionate adsorbed onto microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, amorphous magnesium aluminum silicate, or combinations thereof; and

b. at least one disintegrant, wherein:

[c.i] the fluticasone propionate is present in an amount ranging from about 0.5 mg to about 6 mg, and

[c.ii] the fluticasone propionate has a mean particle size ranging from about 100 nm to about 10 µm; and

[d] wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701>Disintegration test.⁴

EX1001 (“the ’061 patent”) at Claim 19.

43. Claims 20-28 depend, either directly or indirectly through another claim, from independent claim 19. These claims are reproduced below.

⁴ Bracketed labels have been added for convenient referencing to the claim limitations.

Claim 20. The orally disintegrating tablet of claim 19, wherein the microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, or amorphous magnesium aluminum silicate, or a combination thereof, is present in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

Claim 21. The orally disintegrating tablet of claim 19, comprising silicified microcrystalline cellulose in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

Claim 22. The orally disintegrating tablet of claim 19, wherein fluticasone propionate has a mean particle size of about 4 μm or less.

Claim 23. The orally disintegrating tablet of claim 21, wherein the disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, and low-substituted hydroxylpropylcellulose.

Claim 24. The orally disintegrating tablet of claim 20, wherein the at least one disintegrant is present in a rapidly dispersing microgranule, which comprises a sugar alcohol, or a saccharide, or a mixture thereof in addition to the at least one disintegrant.

Claim 25. The orally disintegrating tablet of claim 24, wherein the sugar alcohol or saccharide and the disintegrant are present in a ratio of sugar alcohol or saccharide to disintegrant of from 90:10 to 99:1.

Claim 26. The orally disintegrating tablet of claim 24, wherein the sugar alcohol or saccharide is selected from the group consisting of

sucralose, lactose, sucrose, maltose, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.

Claim 27. The orally disintegrating tablet of claim 24, wherein the rapidly dispersing microgranule has a mean particle size of less than about 300 μm , and the sugar alcohol and/or saccharide has an average particle size of less than about 30 μm .

Claim 28. The orally disintegrating tablet of claim 19, wherein the silicified microcrystalline cellulose is present in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet, fluticasone propionate is present in an amount ranging from about 1 mg to about 3 mg, and fluticasone propionate has a mean particle size ranging from about 100 nm to about 4 μm .

EX1001 (“the ’061 patent”) at Claims 20-28.

VII. SCOPE AND CONTENT OF THE PRIOR ART

44. 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 and content of the prior art as of September 2013. I begin with a discussion of budesonide and fluticasone, followed by a discussion of orally dispersing tablets (ODTs), FDA Guidance regarding in vitro testing of such tablets, as well as particle sizes used for preparing ODTs and adsorption of drug particles onto pharmaceutical carriers for preparing ODTs.

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

45. Glucocorticoids were known to be an important class of drugs that were used by clinicians due to their anti-inflammatory and immunosuppressive effects by September of 2013. *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 September of 2013. 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 that of 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.

46. 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.”).⁵ Tan teaches that eosinophilic gastroenteritis is a disorder “that may 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.

47. Before September of 2013, 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

⁵ All emphases supplied unless otherwise noted.

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

48. 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.”).

49. 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.”).

50. 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.”).

51. 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 a 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.”).

52. 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.”).

53. 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):

(19) **United States**

(12) **Patent Application Publication**
Dohil et al.

(10) **Pub. No.: US 2007/0111978 A1**
(43) **Pub. Date: May 17, 2007**

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

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(21) Appl. No.: **11/595,513**

(22) Filed: **Nov. 9, 2006**

Related U.S. Application Data

(60) Provisional application No. 60/735,340, filed on Nov.
12, 2005.

Publication Classification

(51) **Int. Cl.**
A61K 31/573 (2006.01)
(52) **U.S. Cl.** **514/179**

(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.

54. The Aceves team of clinicians filed a “continuation-in-part” application
on November 12, 2008. *See* US2009/0191275 (EX1058, hereinafter “Dohil2009”)
at title page items (22) and (63):

(19) **United States**

(12) **Patent Application Publication**
Dohil et al.

(10) **Pub. No.: US 2009/0191275 A1**
(43) **Pub. Date: Jul. 30, 2009**

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

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(22) Filed: **Nov. 12, 2008**

Related U.S. Application Data

(63) Continuation-in-part of application No. 11/595,513,
filed on Nov. 9, 2006.

(60) Provisional application No. 60/735,340, filed on Nov.
12, 2005, provisional application No. 61/090,575,
filed on Aug. 20, 2008.

Publication Classification

I understand that a “continuation-in-part” application includes additional disclosure
that was not included in the earlier application. I understand that Exhibit 1059

contains a redline comparison of Dohil and Dohil2009, which shows the differences in the disclosures of the two patent application publications.

55. Dohil2009 summarizes the data from Aceves 2005 in Examples 1 and 2. *See* EX1058 (Dohil2009) at ¶¶[0103]-[0104]. Dohil2009 also summarizes the data from Aceves 2007 in Example 3. *See id.* at ¶¶[0105]-[0125]. Dohil2009’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.

EX1058 (Dohil2009) at Abstract; *see also id.* at ¶[0003] (“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.”).

56. Dohil2009 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.”

EX1058 (Dohil2009) at ¶[0007]. Dohil2009 emphasizes that topical steroid formulations are advantageous for treating the upper gastrointestinal tract. *Id.* at ¶[0009] (“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.”).

57. Dohil2009 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 (26). Improvised puff and swallow techniques may be difficult for patients, especially smaller children, and especially children with developmental delays, to perform efficiently. This may result in a less than effective dose of a topical steroid being delivered to the esophagus.

EX1058 (Dohil2009) at ¶[0008].

58. Dohil2009 teaches that the budesonide is the preferred topically administered corticosteroid for its compositions as indicated by the following five quotations from Dohil2009:

- “In certain aspects, the corticosteroid is a topical corticosteroid, such as, for example, Budesonide.” EX1058 (Dohil2009) at ¶[0010];
- “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.” EX1058 (Dohil2009) at ¶[0012];
- “In certain embodiments, the corticosteroids used in the present invention include topical steroids including, for example, budesonide.” EX1058 (Dohil2009) at ¶[0049];
- “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.” EX1058 (Dohil2009) at ¶[0062];
- “10. The method of claim 1, wherein said corticosteroid is Budesonide.” EX1058 (Dohil2009) at 21, claim 10; and
- “23. The oral pharmaceutical composition of claim 22, wherein the topical corticosteroid is budesonide.” EX1058 (Dohil2009) at 22, claim 23.

59. Dohil2009 discloses at least two types of formulations of budesonide:

- (1) a viscous oral suspension of budesonide (*see, e.g.*, Dohil2009 at ¶¶[0034], [0053], [0103]-[0125]); and
- (2) a solid oral lozenge formulation that dissolves rapidly in the mouth or esophagus (*see, e.g.*, Dohil2009 at ¶¶[0062], [0012], [0070], claim 6).

60. With respect to the solid oral lozenge formulation, Dohil2009 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, would dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.” EX1058 (Dohil2009) at ¶[0062] (“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.”). Dohil2009 discloses budesonide in the form of a dissolving tablet and a dissolving wafer. *See id.* at ¶[0012] (“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.”). Dohil2009 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 ¶[0070] (“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.”). Dohil2009’s claim 6 recites dissolving tablets and wafers. EX1058 (Dohil2009) at 21 (“6. The method of claim 2, wherein the pharmaceutical composition is in the form of a dissolvable tablet, a dissolvable wafer, or a dissolvable capsule.”).

61. 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 an ODT containing budesonide based on at least, for example, Dohil2009 and additional references discussed herein. By 2013, methods for formulating ODTs containing pharmaceutically active ingredients were well known in the prior art for reasons discussed below.

B. Fluticasone Was A Known Corticosteroid With Desirable Anti-Inflammatory Activity

62. Fluticasone propionate was known to be a desirable anti-inflammatory corticosteroid before September of 2013. For example, Roeder discloses that “[t]he synthetic carbothioate corticosteroid fluticasone propionate (FP, Flutivate) combines excellent clinical efficacy with minimal risk for local or systemic adverse events.” Roeder et al., “Safety and efficacy of fluticasone propionate in the topical treatment of skin diseases,” *Skin Pharmacology Physiology*, 18:3-11 (2004)

(“Roeder,” EX1064) at page 3. Roeder explains that “[c]omparative trials indicate that this unique carbothioate combines potent anti-inflammatory effects and a low potential for unwanted systemic and local side effects: topical activity of FP [fluticasone propionate] judging from vasoconstriction provided to be high, while skin thinning, allergenic potential and hypothalamic-pituitary-adrenal inhibitory potency are exceptionally weak.” *Id.* at page 10.

63. Fluticasone was known to treat eosinophilic esophagitis. For example, Remedios disclosed that “FP [fluticasone propionate] is an appealing treatment for EE [eosinophilic esophagitis].” Remedios et al., “Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate,” *Gastrointestinal Endoscopy*, 63:3-12 (2006) (“Remedios,” EX1065) at page 10. Remedios explains “[s]imple administration [of fluticasone propionate] allows maximal topical effect and minimal side effects, thus enhancing compliance.” *Id.* Remedios states “[o]ur prospective study confirms the utility of FP in adults. FP previously has been used successfully in pediatric patients and recently in adults.” *Id.* Remedios concluded “[s]wallowed fluticasone propionate is an effective treatment” for eosinophilic esophagitis. *Id.* at page 3.

64. As another example, Konikoff reports that “[s]wallowed FP [fluticasone propionate] is effective in inducing histologic remission in eosinophilic esophagitis, with a more pronounced effect in nonallergic and younger individuals,

especially in the proximal esophagus.” Konikoff et al., “A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis,” *Gastroenterology*, 131:1381-1391 (2006) (“Konikoff,” EX1066) at page 1381. Konikoff explains that “[b]ecause of its low oral bioavailability and rapid first-pass metabolism in the liver, FP has a favorable side effect profile relative to systemic glucocorticoids.” *Id.* at 1382.

65. Based on at least the foregoing, the desirability of using fluticasone to treat inflammation of the upper gastrointestinal tract was known in the prior art. A person of ordinary skill in the art would have been motivated to use fluticasone based on at least, for example, Konikoff and additional references discussed herein.

C. Orally dispersing tablets (ODTs)

66. ODTs were well-known in the prior art by September of 2013. ODTs dissolve or disintegrate in a patient’s mouth in the absence of additional water. The patient’s saliva causes the ODT 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.

67. Several review articles describing ODTs were available by 2013. 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).

68. In the following paragraphs, I discuss (1) synonyms used to refer to ODTs in the prior art literature, (2) the desirability of ODTs to dissolve rapidly in saliva for the improvement of patient compliance with taking medication, (3) the desirability of ODTs for oral administration and delivery of active ingredients, and (4) commercially available ODTs that existed by the year 2013.

1. Synonyms for orally dispersing tablets (ODTs)

69. The prior art uses several terms to refer to ODTs. For example, Fu refers to these compositions as “fast disintegrating tablets (FDTs).” *See* 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. 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.”).

70. A person of ordinary skill would have recognized that such terms were used relatively interchangeably in the literature to refer to ODTs. 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’.”).

71. Fu explains that “[a]ll FDTs [fast disintegrating tablets] approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets.” EX1018 (Fu) at 434. In particular, the FDA defines “orally disintegrating tablets (ODTs)”⁶ 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

72. A desirable feature of ODTs 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

⁶ The ’061 patent equates “orally dispersing tablets,” “orally disintegrating tablets,” and “ODTs.” EX1001 (the ’061 patent) at 5:12-15.

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 ODTs 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 medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”).

73. ODTs 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 in 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.”).

74. 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 ODT. 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.

75. As discussed above, it was desirable for ODTs 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.

76. The patient’s saliva provides an important role in dissolving and dispersing the active ingredient from an ODT. 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, such as ODTs, for oral administration and delivery

77. Solid orally dispersing 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.

78. Another advantage of solid orally dispersing 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 the 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 the nasal mucosa. Another major advantage of the oral mucosa as a site for drug delivery is that it facilitates removal in cases of emergency.

EX1017 (Danckwerts) at 172.

79. Another advantage of solid orally dispersing 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 an ODT. *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.”).

80. Danckwerts contrasts ODTs 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”). ODTs were often more desirable than intraoral mucoadhesive formulations for at least these reasons.

4. Commercially available ODTs

81. By 2013, there were several commercially available ODT formulations. 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.

82. 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.”).

83. 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.”).

84. “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’.”).

85. 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.*

86. Fu compiled several of the commercially available ODT 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).

87. 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:

Dr. Falk Pharma GMBH v. Ellodi Pharmaceuticals LP
IPR Petition – U.S. Patent No. 11,260,061

Brand name	Active ingredient	Application	Company	Technology
Claritin® RediTabs®	Loratadine	Antihistamine	Schering Corporation	Zydis®
Feldene Melt®	Piroxicam	NSAID	Pfizer	
Maxalt®-MLT®	Rizatriptan benzoate	Migraine	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).”).

88. Ideally, an ODT 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.”).

89. In sum, the prior art teaches that ODTs were desirable to assist with patient compliance in taking medications and that many classes of drugs would benefit from being formulated into an ODT. For example, Danckwerts concludes that “[t]here is no doubt that the need for these systems is real, and many classes of drugs could benefit from this noninvasive type of drug delivery.” EX1017 (Danckwerts) at 171. 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.

D. FDA Guidance regarding in vitro testing of ODTs.

90. In December of 2008, the FDA published its guidance for the pharmaceutical industry regarding ODTs. *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>.

91. The FDA Guidance explains that ODTs 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.

92. The FDA Guidance defines ODTs 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 ODTs 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.

93. 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 2013.

E. Reduced Particle Size Improves Performance Of And Patient Compliance With ODTs

94. The particle size of the active ingredient in an ODT often impacts the composition's dissolution performance. For example, Fu teaches that "the solubility, crystal morphology, *particle size*, hygroscopicity, compressibility, and bulk density *of a drug can significantly affect the final tablet's characteristics, such as tablet strength and disintegration.*" EX1018 (Fu) at 435. A smaller particle size generated through micronization or other methods tends to improve disintegration and dissolution of an ODT. For example, Khan discloses that "[t]he rate of dissolution [in a rapidly disintegrating tablet] can be increased by increasing the surface area of available drug by various methods (*micronization*, complexation and solid dispersion)." Khan et al., "An approach for rapid disintegrating tablet: a review," Int'l J. Pharm. Research and Development, 21:170-183 (2011) ("Khan," EX1067) at page 172. Khan further discloses that "[r]apider disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and rapider dissolution." *Id.* at 172.

95. The particle size of the active ingredient in an ODT often impacts patient compliance. For example, a smaller particle size tends to improve mouthfeel by reducing the risk of the tablet disintegrating into fragments that a patient might

feel. EX1020 (Venkatesh) ¶[0012] (“For use in an orally disintegrating tablet, the particle size of most of the taste-masked microcapsules should be less than 400 μm or less to avoid gritty mouthfeel.”); *id.* ¶[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.”); *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.”).

F. Adsorption Of Drug Particles Onto The Solid Surface Of A Carrier And Other Excipients Through Mixing Was Routine

96. By 2013, the adsorption of drug particles onto the solid surface of a carrier and other excipients was routine and common. For example, it was well known that “achieving content uniformity, especially for low-dose drugs” can be achieved “by adsorbing small drug particles onto the surface of large excipients.” Wen, “Adsorption at solid surfaces: pharmaceutical applications,” in Encyclopedia of Pharmaceutical Technology, Third Edition, ed. Swarbrick, pages 34-45 (2007) (“Wen,” EX1054) at page 34 (“Achieving content uniformity, especially for low-dose drugs, exhibits a challenge faced in the manufacturing of solid dosage

formulations. One of the solutions is by adsorbing small drug particles onto the surface of large excipients.”). Adsorption of drug particles onto the solid surface of larger carrier particles is depicted below:

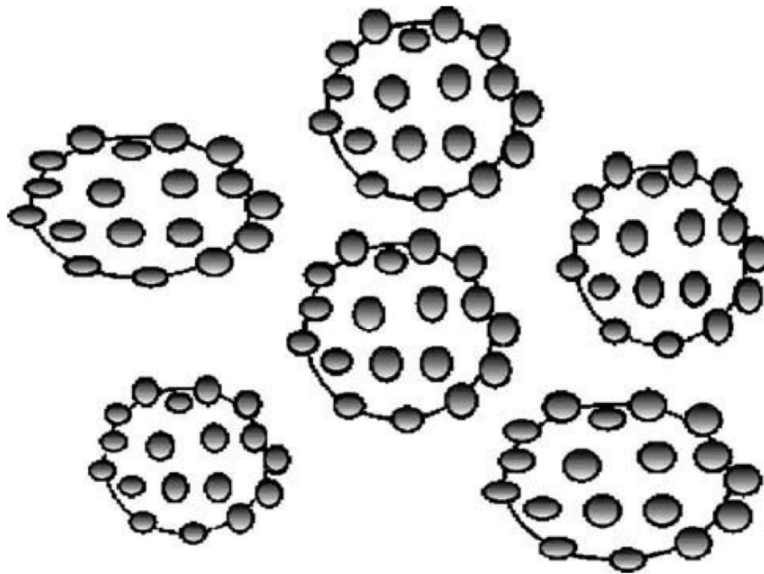


Fig. 1 Adsorption of small particles onto the surfaces of larger carrier particles.

EX1054 (Wen) at page 35 (Figure 1).

97. Adsorption of small drug particles onto the surface of carrier excipients is generally accomplished via mixing or blending. EX1054 (Wen) at 35 (“During mixing, there are many factors that can affect the content uniformity of mixtures, and adsorption generally plays a role when the average particle size is $\leq 400 \mu\text{m}$.”). Martin explains that, “[d]uring blending, a fine powder of an antibiotic is adsorbed onto the surface of coarse particles of sorbitol.” *See Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*, Fourth Edition, eds. Martin et

al. (1993) (“Martin,” EX1055) at page 383. This process involves “the solid-solid adsorption of a fine cohesive powder onto the surface of coarse free-flowing particles.” *Id.* at 382.

98. The inventors of the ’061 patent explain that the process for adsorbing drug particles onto a carrier includes repeatedly mixing the drug with the carrier. *See* EX1001 (the ’061 patent) at 10:5-8 (“The corticosteroid particles are typically adsorbed onto the carrier. The process for the preparation includes repeatedly mixing corticosteroid and carrier so that the blend is adsorbed onto the carrier.”).

99. By 2013, a person of ordinary skill in the art would have known that adsorbing drug particles onto the surface of a pharmaceutically acceptable carrier can be beneficial in formulating ODTs. For example, Wen teaches that “[a]dsorbing drugs onto carrier particles (Fig. 1) by ordered mixing can be very beneficial in several ways, such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage.” EX1054 (Wen) at 35; *id.* at 43 (“In pharmaceutical processing, adsorbing drugs onto the solid surface of other excipients can help to achieve content uniformity, especially for low-dose drugs, during the mixing process.”). Shukla teaches that adsorption of drug particles on pharmaceutical carriers for use in ODTs beneficially provides “fast disintegration/dissolution,” as well as “increased absorption and hence higher

bioavailability and reduction in dose, cost effective manufacturing process, [and] conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).” EX1019 (Shukla) at 320 (describing “nanonization” and “nanomelt” technology where “nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs [mouth dissolving tablets].”).

G. ODTs Containing Micronized Budesonide And Fluticasone Propionate To Treat Eosinophilic Esophagitis Were Disclosed In The Prior Art

100. ODTs containing micronized budesonide and fluticasone propionate for treating eosinophilic esophagitis were disclosed in the prior art. For example, Perrett discloses orally disintegrating tablets of budesonide and fluticasone propionate particles with an average particular size of less than about 4 μm , that disintegrate on the order of about 60 seconds or less” as follows:

- Perrett discloses ODTs. *See* EX1057 (Perrett) ¶[0015] (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.”).
- Perrett discloses using budesonide and fluticasone in its ODTs. *See* EX1057 (Perrett) ¶[0039] (“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*. In a particular embodiment, the compositions of the present invention comprise *fluticasone*. In other embodiments, the compositions of the present invention comprise *budesonide*.”).

- Perrett discloses drug microparticles. See EX1057 (Perrett) ¶[0045] (“In most embodiments in which the pharmaceutical compositions of the present invention is provided as an ODT dosage form, the average particle size of the taste-masked non-opioid analgesic/opioid analgesic drug-containing microparticles is not more than about 400 μm , or in some embodiments not more than about 300 μm .”); *id.* ¶[0085] (mean particle size of about 100-400 μm); *id.* ¶[0086] (mean particle size of about 100-400 μm); *id.* ¶[0089] (average particle size of 5-50 μm); *id.* at page 10 (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 , and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 μm .”).

- Perrett discloses disintegration rates of 60 seconds or less. *See* EX1057 (Perrett) ¶[0060] (“The rate of disintegration of the solid pharmaceutical compositions of the present invention can be measured using various in vitro test methods, for example the USP <701> Disintegration Test. When using the USP <701> Disintegration Test, the rate of disintegration of the compositions of the present invention typically is about 60 seconds or less, about 45 seconds or less, about 30 seconds or less, about 20 seconds or less, or about 10 seconds or less.”).

101. Perrett teaches that using corticosteroid particles on the micron scale provides “a smooth, easy-to-swallow suspension” formulation as follows:

- EX1057 (Perrett) ¶[0045] (“The corticosteroid containing particles of the ODT dosage form should also have a small enough particle size such that after disintegration of the ODT in the oral cavity of the patient, *a smooth, easy-to-swallow suspension results*. In most embodiments in which the pharmaceutical compositions of the present invention is provided as an ODT dosage form, the average particle size of the taste-masked non-opioid analgesic/opioid analgesic drug-containing microparticles is not more than about 400 μm , or in some embodiments not more than about 300 μm .”),

- EX1057 (Perrett) ¶[0085] (disclosing corticosteroid microparticles with a mean particle size of about 100-400 µm and explaining “[t]hese ODT tablets rapidly disintegrate upon exposure to the saliva in the mouth into *a smooth, easy-to-swallow suspension with no gritty aftertaste.*”).

102. Perrett discloses and claims ODTs where “the corticosteroid is disposed over the surface of an excipient.” EX1057 (Perrett) at page 10 (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, and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 µm.”); *id.* (Claim 22 “The pharmaceutical composition of claim 20, *wherein the corticosteroid is disposed on the surface of said adhesive agent.*”); *id.* ¶[0063] (“In another such embodiment the solid pharmaceutical composition comprises *corticosteroid disposed on the surface of the adhesive agent.*”).

103. Perrett directs the person of ordinary skill in the art to consider Venkatesh’s method for preparing microgranules. EX1057 (Perrett) ¶[0042] (“Rapidly dispersing microgranules can be prepared as described in *US 2005/0232988* [Venkatesh] or US 20010014340 by granulating a disintegrant having an average particle size of not more than about 30 µm with a sugar alcohol and/or

saccharide having an average particle size of not more than about 30 μm .”); *id.* ¶[0089] (describing the production of “rapidly-dispersing microgranules with an average particle size of not more than about 400 μm , as described in *U.S. Patent Publication No. US 20050232988* [Venkatesh]”).

104. Venkatesh teaches that micronized drug particles provide good mouthfeel with no grittiness. EX1020 (Venkatesh) ¶[0012] (“For use in an orally disintegrating tablet, the particle size of most of the taste-masked microcapsules should be less than 400 μm or less to avoid gritty mouthfeel.”); *id.* ¶[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.”).

VIII. INTRODUCTION TO OBVIOUSNESS GROUNDS

105. This section provides a summary of the obviousness grounds for claims 1-30 that are addressed in this declaration.

Ground	Reference(s)	Challenged Claims
1	Perrett	1-30
2	Dohil2009 in view of the knowledge of a person of ordinary skill in the art	1-2, 4-11, 17-20, 22, 29-30
3	Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art	1-30

IX. CLAIM CONSTRUCTION

106. All claim terms not specifically addressed in this section have been accorded their plain and ordinary meaning.

A. Terms Expressly Defined In The '061 Patent Specification

107. The '061 patent defines “orally disintegrating tablet”, “orally dispersing tablet”, or “ODT” as “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 '061 patent) at 5:12-15 (“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.”). 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.”).

108. The '061 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 '061 patent) at 9:29-31. The '061 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.* 9:32-36.

109. The ’061 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 ’061 patent) at 9:36-40.

110. The ’061 patent states that “[t]he term ‘about’, as used herein to refer to a numerical quantity, includes ‘exactly.’ For example, ‘about 30 seconds’ includes 30 seconds, exactly, as well as values close to 30 seconds (e.g., 25 seconds, 29 seconds, 31 seconds, 35 seconds, etc.). When the term ‘about’ is used in reference to a range of values, the term ‘about’ refers to both the minimum and maximum value of the range (e.g., ‘about 1-50 μm ’ means ‘about 1 μm to about 50 μm ’).” EX1001 (the ’061 patent) at 5:21-27.

111. I have applied each of these definitions.

B. “Rapidly Dispersing Microgranule”

112. Claims 12, 16, 24, and 27 recite a “rapidly dispersing microgranule.”

113. The specification of the ’061 patent does not define this term. I understand that this term should therefore be accorded its plain and ordinary meaning.

114. I note that Perrett and Venkatesh use the term “rapidly dispersing microgranule” and disclose ODTs comprising “rapidly dispersing microgranules.” *See, e.g.*, EX1057 (Perrett) ¶[0042] (“In one embodiment, the composition of the present invention is in the form of an ODT. An ODT comprises drug containing particles (e.g., a corticosteroid as described herein optionally coated or combined with an adhesive agent as described herein), combined with ***rapidly dispersing microgranules***. ***Rapidly dispersing microgranules*** can be prepared as described in US 2005/0232988 [Venkatesh, EX1020] or US 20010014340 by granulating a disintegrant having an average particle size of not more than about 30 µm with a sugar alcohol and/or saccharide having an average particle size of not more than about 30 µm.”); *see also, e.g.*, EX1020 (Venkatesh) ¶[0028] (“One or more sugar alcohols and/or saccharides with an average particle size of not more than 30 µm and a disintegrant are granulated with approximately 20-25% water in a high shear granulator, wet milled, dried in a fluid bed equipment to produce ***rapidly dispersible microgranules*** of desired particle size (average particle size of not more than about 300 µm in accordance with methods disclosed in USP Application No. 200100114340 published on Aug. 16, 2001).”).

115. I understand Perrett and Venkatesh’s disclosures of “rapidly dispersing microgranule” refer to the same type of “rapidly dispersing microgranule” recited by claims 12, 16, 24, and 27 of the ’061 patent. It would be reasonable for a person

of ordinary skill in the art to interpret this term to refer to the same type of rapidly dispersing microgranule in each of Perrett, Venkatesh, and the '061 patent given that all three patent documents share a common inventor (Gopi Venkatesh) and disclose overlapping ODT subject matter.

116. I reserve the right to provide further commentary on the meaning of “rapidly dispersing microgranule” if Ellodi provides a construction of this term during the trial phase of this proceeding.

C. “Adsorbed Onto A Pharmaceutically Acceptable Carrier”

117. Claims 1 and 30 recite a corticosteroid “adsorbed onto a pharmaceutically acceptable carrier.” Claim 19 recites fluticasone propionate “adsorbed” onto a list of specific carriers.

118. The specification of the '061 patent does not define these limitations. I understand that this term should therefore be accorded its plain and ordinary meaning.

119. Adsorption is a broad term that refers to “[t]he surface retention of solid, liquid, or gas molecules, atoms, or ions by a solid or liquid.” EX1060 (“McGraw-Hill Dictionary”) at 41 (distinguishing “adsorption” from “absorption, the penetration of substances into the bulk of the solid or liquid”). Adsorption typically involves an “adsorbent” (the material upon which adsorption occurs) and an “adsorbate” (the substance being adsorbed). EX1060 (McGraw-Hill Dictionary) at

41 (“adsorbent” is “[a] solid or liquid that adsorbs other substances” and “adsorbate” is “[a] solid, liquid, or gas which is adsorbed”).

120. Physical adsorption is associated with van der Waals’ forces and is reversible. EX1055 (Martin) at 380 (“Physical adsorption, associated with van der Waals’ forces, is reversible, the removal of the adsorbate from the adsorbent being known as desorption.”). In contrast, chemical adsorption, also called “chemisorption,” occurs when an adsorbate is attached to the adsorbent by a covalent bond. *Id.* at 380 (“Chemisorption, in which the adsorbate is attached to the adsorbent by primary chemical bonds, is irreversible.”).

121. An exemplary depiction of small drug particles adsorbed onto the surface of larger carrier particles is depicted below:

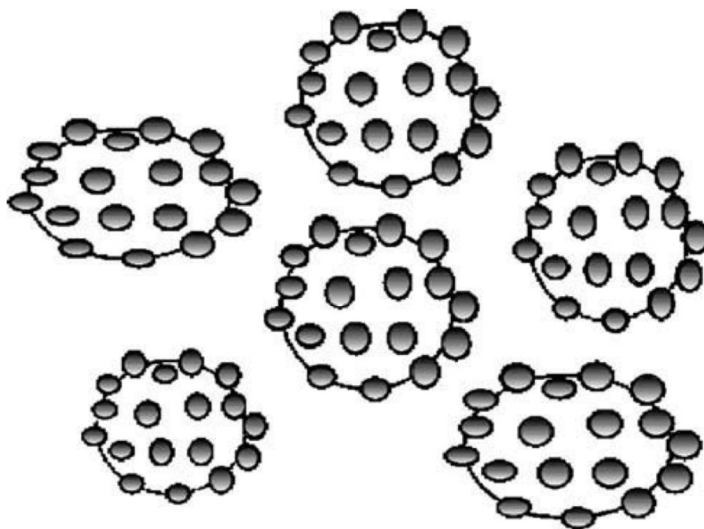


Fig. 1 Adsorption of small particles onto the surfaces of larger carrier particles.

EX1054 (Wen) at 35 (Fig. 1).

122. Based on the foregoing, the plain and ordinary meaning of a corticosteroid “adsorbed onto a pharmaceutically acceptable carrier” includes at least “the reversible disposition of a corticosteroid particle on the surface of a pharmaceutically acceptable carrier.”

123. I understand that the European Patent Office (EPO) considered the meaning and patentability of similar claims in EP3041476. EX1062 (EPO Decision) at pages 15-18. I understand that the EPO considered the meaning of adsorption with respect to, for example, claim 1 of Ellodi’s Auxiliary Request 1. *Id.* A side-by-side comparison of claim 1 of the ‘061 patent and Ellodi’s Auxiliary Request 1 from the EPO proceeding is reproduced below to help identify similarities between the claims:

Claim 1 of U.S. 11,260,061	Claim 1 of EP3041476 Auxiliary Request 1
1. An orally disintegrating tablet comprising:	1. A pharmaceutical composition in the form of an orally disintegrating tablet comprising
a. a topically acting corticosteroid or pharmaceutically acceptable salt or ester thereof, adsorbed onto a	a. particles of a topically acting corticosteroid or pharmaceutically acceptable salt, ester, or polymorph in

Claim 1 of U.S. 11,260,061	Claim 1 of EP3041476 Auxiliary Request 1
<p>pharmaceutically acceptable carrier; and b. at least one disintegrant, wherein the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is present in an amount ranging from about 0.5 mg to about 10 mg, and the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, has a mean particle size of ranging from about 100 nm to about 100 μm; and</p>	<p>an amount of about 5% or less by weight in the composition; b. a pharmaceutically acceptable carrier; and c. rapidly dispersing microgranules; wherein the corticosteroid or pharmaceutically acceptable salt, ester, or polymorph particles are adsorbed onto the pharmaceutically acceptable carrier, and</p>
	<p>wherein the pharmaceutically acceptable carrier is selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn</p>

Claim 1 of U.S. 11,260,061	Claim 1 of EP3041476 Auxiliary Request 1
	starch, colloidal silica, and amorphous magnesium aluminum silicate.
wherein the orally disintegrating table disintegrates within 60 seconds when tested using the USP <701> method for disintegration time.	

EX1001 (the '061 patent) at claim 1; EX1062 (EPO Decision) at page 5.

124. The EPO interpreted adsorption as follows:

For the interpretation of the term “is adsorbed”, the OD [Opposition Division] considers that this term is rather broad and covers different degrees and mechanisms of adsorption. If drug particles and a carrier are blended, leading to contact between the carrier particles and the drug, and the mixture is granulated and compressed, leading to even more intense contact between the carrier powder and the drug, then for the OD this implies at least some adsorption of the drug on the carrier. The proprietor [Ellodi] considered that the feature “is adsorbed” could only be obtained with the treatment as in the opposed patent [EP3041476], i.e. repeated mixing and milling with a carrier from the claimed list, otherwise there was no adsorption. For the OD this is a more restricted definition of adsorption, which is not reflected in claim 1 of auxiliary request 1.

EX1062 (EPO Decision) at 15-16. I agree with the EPO's interpretation of adsorption.

125. The EPO determined that reference "D3" discloses adsorption of a corticosteroid onto a pharmaceutical carrier as follows:⁷

In example 1 of D3, an ODT was prepared by blending 4 wt% fluticasone propionate (topically active glucocorticoid), 91.2 wt% mannitol 25 (carrier, filler), and 4.8 wt% crospovidone (carrier, disintegrant) for 3-5 minutes. This provides contact between the drug and carrier, leading implicitly to at least some adsorption. The adsorption is fixed on the carrier by a subsequent granulation step by spraying with water. This leads to some sinter bridges between the drug particles and their carrier, which is not excluded by claim 1. In addition agglomeration of the particles to microgranules takes place, but this is also not excluded by the wording of present claim 1. The microgranules were then lubricated with magnesium stearate and compressed to tablets. The wording of claim 1 does not exclude that the drug and carrier are inside the microgranules. The powder blending in D3 implicitly leads to at least some adsorption of the drug on the carrier.

⁷ Reference D3 in the EPO opposition proceeding was WO2011/041509 (EX1063).
See EX1062 (EPO Decision) at page 3. I understand that WO2011/041509 (EX1063) contains the same disclosures as Perrett (EX1057).

EX1062 (EPO Decision) at 17-18. The EPO further explained that D3 discloses granulating a corticosteroid with a carrier that results in drug particles being adsorbed onto the carrier as follows:

D3 also discloses (page 24, line 25 – page 26, line 15) in other embodiments methods of making ODTs comprising the step of preparing a drug-containing core particle by either (i) granulating the drug and optionally one or more diluents/fillers (=carrier) such as lactose, mannitol, microcrystalline cellulose with a polymeric binder, or alternatively by (ii) drug-layering on an inert particle (sugar sphere or cellulosesphere, e.g., Celphere® CP-203 = microcrystalline cellulose) from a suspension comprising a polymeric binder. In both options MCC [microcrystalline cellulose] can be selected from a list, and in both options drug particles are adsorbed onto carrier.

Id. at 23. I agree with the EPO’s determination and explanation.

X. GROUND 1: PERRETT IN VIEW OF THE KNOWLEDGE OF A PERSON OF ORDINARY SKILL IN THE ART

126. This section introduces Perrett, and then explains how Perrett renders obvious claims 1-30 of the ’061 patent.

A. Perrett

127. Perrett is directed to ODTs comprising corticosteroids such as budesonide and fluticasone, which is the same subject matter claimed by the ’061 patent. *See* EX1057 (Perrett) ¶[0007] (“In one embodiment, the present invention is directed to a solid pharmaceutical composition comprising less than or equal to 20

mg of a corticosteroid, wherein the composition has no significant systemic glucocorticoid or mineralcorticoid activity after oral administration, wherein the solid pharmaceutical composition disintegrates within 60 seconds in simulated saliva when tested using the USP <701> Disintegration Test, and/or which disintegrates within 60 seconds when placed in the oral cavity of a human.”), ¶[0019] (“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.”), ¶[0047] (“Tablet dosage forms, including ODT dosage forms, comprising the pharmaceutical composition of the present invention have a low friability...”), ¶[0082] (“In one embodiment, the solid pharmaceutical composition of the present invention is in the form of an orally disintegrating tablet (ODT).”). Perrett shares a common inventor with the ’061 patent (Gopi Venkatesh). *See* EX1057 (Perrett) at Title Page, item 76 (listing Stephen Perrett, Fredric Jay Cohen, and Gopi Venkatesh as inventors). Perrett discloses and renders obvious all claims of the ’061 patent.

B. Claim 1

1. Preamble

128. The preamble of claim 1 recites “[a]n orally disintegrating tablet.”

129. Perrett discloses orally disintegrating tablets (ODTs). EX1057 (Perrett) ¶[0015] (“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.”), ¶[0042] (“In one embodiment, the composition of the present invention is in the form of an ODT.”), ¶[0082] (“In one embodiment, the solid pharmaceutical composition of the present invention is in the form of an orally disintegrating tablet (ODT).”).

2. Limitation 1.a

130. Limitation 1.a recites “a topically acting corticosteroid or pharmaceutically acceptable salt or ester thereof, adsorbed onto a pharmaceutically acceptable carrier.”

131. Perrett discloses ODTs comprising a topically acting corticosteroid, such as budesonide and fluticasone propionate. EX1057 (Perrett) ¶[0019] (“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.”), ¶[0024] (“*Topical administration of a corticosteroid* for conditions associated with inflammation of the gastrointestinal tract is desirable because it results in fewer side-effects than systemic corticosteroid administration.”), ¶[0039] (“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*. In a particular embodiment, the

compositions of the present invention comprise *fluticasone*. In other embodiments, the compositions of the present invention comprise *budesonide*.”).

132. Perrett discloses preparing ODTs and provides exemplary four step processes. EX1057 (Perrett) ¶¶[0089]-[0090] (*see* steps (a)-(d)). Step (a) involves “preparing corticosteroid-containing microgranules by granulating crystalline corticosteroid material having an average particle size of about 5-50 μ m and one or more diluents/fillers such as lactose, mannitol, microcrystalline cellulose and mixtures thereof, with a polymeric binder in a high-shear granulator or fluid-bed coater.” *Id.* ¶[0089]. Perrett step (a) is a wet granulation step, which involves mixing corticosteroid microgranules with one or more diluents/fillers. The mixing of the corticosteroid microgranules with one or more diluents/fillers during the wet granulation process leads to at least some adsorption, as explained in more detail below. I note that limitation 1.a. does not require adsorption to be achieved by any particular type of process (for example, limitation 1.a does not require direct compression in order to achieve adsorption of the corticosteroid onto the carrier).

133. Perrett teaches that exemplary fillers/diluents/binders include microcrystalline cellulose, and starches or modified starches, such as pregelatinized starch and maize starch (i.e., corn starch). EX1057 (Perrett) ¶[0051] (“*Examples of suitable fillers, diluents and/or binders include* lactose (e.g. spray-dried lactose, α -lactose, β -lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-

Flo®), *microcrystalline cellulose* (various grades of Avicel®, Ceolus®, Eclema®, Vivacel®, Ming Tai® or Solka-Floc), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), low molecular weight hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K from Dow Chemical, Metolose SH from Shin-Etsu, Ltd), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrans, maltodextrins, *starches or modified starches* (including potato starch, *maize starch* and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate and collagen.”); ¶[0052] (“*Examples of suitable diluents include* e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, *microcrystalline cellulose*, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, *starch, pregelatinized starch*, sucrose and sugar.”).

134. Fillers/diluents/binders disclosed by Perrett constitute pharmaceutically acceptable carriers as described by the '061 patent. EX1001 (the '061 patent) at 7:28-38 (“The pharmaceutically acceptable carrier used in the mixture of the present invention is suitable for adsorption of the drug, it should have the properties of an excellent carrier for dry blends providing blend flowability and workability and preventing the segregation. It may concur in providing

corticosteroid content uniformity. *It is selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, or amorphous magnesium aluminum silicate (commercially available as VEEGUM™ or NEUSILIN™).*”).

135. Perrett’s Example 1 discloses an ODT prepared by blending fluticasone drug particles, mannitol, and crospovidone for 3-5 minutes, and then granulating using a fluid-bed apparatus. EX1057 (Perrett) ¶[0091] (“Fluticasone Propionate Microgranules A: Mannitol 25 (91.2% w/w) and Crospovidone XL-10 (4.8% w/w) at a ratio of 95/5 are co-milled individually by passing the mixture through a Comil® milling apparatus, equipped with 0.225” spacers, at a speed of about 1400-1500 rpm. The mannitol, crospovidone, and fluticasone propionate (4% w/w) crystalline material are blended for about 3-5 minutes to mix the ingredients. A Glatt GPCG-3 fluid-bed apparatus equipped with a top spray granulation chamber and a granulation bowl is charged with the pre-blend of mannitol, crospovidone, and fluticasone propionate (batch size: 1500 g) and granulated by spraying purified water (nozzle: 1.2 mm tip) at an atomization pressure of about 1.25 bar and at a spray rate of 30-50 mL/min and an outlet temperature of >70° C. and at a product temperature of >33° C.”).

136. I note that the EPO determined that this example from reference D3 results in at least some adsorption as follows:⁸

In example 1 of D3, an ODT was prepared by blending 4 wt% fluticasone propionate (topically active glucocorticoid), 91.2 wt% mannitol 25 (carrier, filler), and 4.8 wt% crospovidone (carrier, disintegrant) for 3-5 minutes. This provides contact between the drug and carrier, leading implicitly to at least some adsorption. The adsorption is fixed on the carrier by a subsequent granulation step by spraying with water. This leads to some sinter bridges between the drug particles and their carrier, which is not excluded by claim 1. In addition agglomeration of the particles to microgranules takes place, but this is also not excluded by the wording of present claim 1. The microgranules were then lubricated with magnesium stearate and compressed to tablets. The wording of claim 1 does not exclude that the drug and carrier are inside the microgranules. The powder blending in D3 implicitly leads to at least some adsorption of the drug on the carrier.

⁸ Reference D3 in the EPO opposition proceeding was WO2011/041509 (EX1063). See EX1062 (EPO Decision) at page 3. I understand that WO2011/041509 (EX1063) contains the same disclosures as Perrett (EX1057), including the same Example 1.

EX1062 (EPO Decision) at 17-18. The EPO further explained that D3 discloses granulating a corticosteroid with a carrier that results in drug particles being adsorbed onto the carrier as follows:

D3 also discloses (page 24, line 25 – page 26, line 15) in other embodiments methods of making ODTs comprising the step of preparing a drug-containing core particle by either (i) granulating the drug and optionally one or more diluents/fillers (=carrier) such as lactose, mannitol, microcrystalline cellulose with a polymeric binder, or alternatively by (ii) drug-layering on an inert particle (sugar sphere or cellulosesphere, e.g., Celphere® CP-203 = microcrystalline cellulose) from a suspension comprising a polymeric binder. In both options MCC [microcrystalline cellulose] can be selected from a list, and in both options drug particles are adsorbed onto carrier.

Id. at 23. I agree with the EPO’s determination and explanation.

137. It was known that adsorption generally plays a role when mixing occurs with a mixture of particle sizes at or below approximately 400 μm . EX1054 (Wen) at 35 (“During mixing, there are many factors that can affect the content uniformity of mixtures, and adsorption generally plays a role when the average particle size is $\leq 400 \mu\text{m}$.”); EX1055 (Martin) at 383 (“During blending, a fine powder of an antibiotic is adsorbed onto the surface of coarse particles of sorbitol.”).

138. Perrett’s corticosteroids “have an average particle size of about 5-50 μm .” EX1057 (Perrett) ¶[0089]; *id.* ¶[0045] (disclosing drug microparticles of not more than about 300 or 400 μm), ¶[0066] (“The corticosteroid crystals can have an

average particle size ranging from about 1-300 μm , for example about 1-50 μm , about 1-100 μm , about 1-150 μm , about 1-200 μm , about 1-250 μm , about 50-100 μm , about 50-150 μm , about 50-200 μm , about 50-250 μm , about 50-300 μm , about 100-150 μm , about 100-200 μm , about 150-200 μm , about 150-250 μm , about 150-300 μm , about 200-250 μm , about 200-300 μm , or about 250-300 μm .”), ¶[0067] (“In another embodiment, the corticosteroid may be in the form of crystals. Such crystals may have an average size in the sub-micron range (e.g., average particle size of about $<1\ \mu\text{m}$), or may be nanoparticles (e.g., average particle size in the range of about 1-100 nm).”).

139. A person of ordinary skill in the art would understand that Perrett’s granulating and blending processes in which microparticles of corticosteroid are mixed with fillers/diluents/binder carriers results in at least some of the corticosteroid being adsorbed onto a filler/diluent/binder carrier.

140. The ’061 patent appears to agree that mixing corticosteroid particles and a carrier results in adsorption onto the carrier as follows:

The corticosteroid particles are typically adsorbed onto the carrier. The process for the preparation includes repeatedly mixing corticosteroid and carrier so that the blend is adsorbed onto the carrier.

EX1001 (the ’061 patent) at 10:5-8.

141. In addition, Perrett discloses ODTs comprising the “rapidly dispersing microgranules” described in Venkatesh. EX1057 (Perrett) ¶[0042] (“In one

embodiment, the composition of the present invention is in the form of an ODT.”), ¶[0089] (describing the production of “rapidly-dispersing microgranules with an average particle size of not more than about 400 μm , as described in *U.S. Patent Publication No. US 20050232988* [Venkatesh]”).

142. Venkatesh discloses formulating ODTs wherein “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,” and that the resulting mixture can be “milled using a size reduction mill.” EX1020 (Venkatesh) ¶[0015].

143. Venkatesh also discloses granulating an active pharmaceutical ingredient with one or more pharmaceutically acceptable diluents. EX1020 (Venkatesh) ¶[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 ComilTM 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;”).

144. The granulating, blending, and milling disclosed by Perrett and Venkatesh involve repeatedly mixing the corticosteroid and carrier. For example, granulation involves mixing smaller particles such that the smaller particles agglomerate into larger granules. Blending involves mixing. Milling is a process that involves, for example, grinding, cutting, or crushing a material having relatively large particles sizes into smaller particle sizes. Milling processes typically involve mixing. Ingredients are often preblended before a granulation or milling step.

145. The granulating, blending, and milling disclosed by Perrett and Venkatesh involve repeatedly mixing the corticosteroid and carrier, which results in at least some adsorption of the corticosteroid on the surface of the carrier. In fact, Perrett expressly discloses and claims ODTs where “the corticosteroid is disposed over the surface of an excipient,” which confirms that the corticosteroid is adsorbed on the surface of the excipient carrier. EX1057 (Perrett) at page 10 (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 , and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 μm .”); *id.* (Claim 22 (“The pharmaceutical composition of claim 20, *wherein the corticosteroid is disposed on the surface of said adhesive agent*.”); *id.* ¶[0063] (“In another such

embodiment the solid pharmaceutical composition comprises *corticosteroid disposed on the surface of the adhesive agent.*”).

146. A person of ordinary skill in the art would have been motivated to adsorb Perrett’s corticosteroid onto a carrier. It was known that such adsorption “can be very beneficial in several ways, such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage.” EX1054 (Wen) at 35; *id.* at 43 (“In pharmaceutical processing, adsorbing drugs onto the solid surface of other excipients can help to achieve content uniformity, especially for low-dose drugs, during the mixing process.”).

147. Surface adsorption of drugs on pharmaceutical carriers is advantageous for ODTs because it provides “fast disintegration/dissolution,” as well as “increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, [and] conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).” EX1019 (Shukla) at 320. A person of ordinary skill in the art would have had a reasonable expectation of success in achieving adsorption because it was known that adsorption “generally plays a role when the average particle size is $\leq 400\text{ }\mu\text{m}$,” EX1054 (Wen) at 35, and Perrett’s disclosure that the corticosteroid particles should have a diameter “of about 5-50 μm .” EX1057 (Perrett) ¶[0089]; *id.* ¶¶[0045], [0066]-[0067].

3. Limitation 1.b

148. Limitation 1.b recites “at least one disintegrant.”

149. Perrett discloses ODTs comprising a disintegrant. EX1057 (Perrett) ¶[0048] (“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.”), ¶[0089] (“(b) granulating one or more sugar alcohols and/or saccharides, each having an average particle diameter of not more than about 30 μm , *with a disintegrant such as crospovidone*, using water or an alcohol-water mixture in a conventional granulator, and drying the granulate in fluid-bed equipment or a conventional oven to produce rapidly-dispersing microgranules with an average particle size of not more than about 400 μm ”), ¶[0090] (“(c) granulating one or more sugar alcohols and/or saccharides, each of which has an average particle diameter of not more than about 30 μm , *with a disintegrant such as crospovidone*, as disclosed herein;”).

4. Limitation 1[c.i]

150. Limitation 1[c.i] recites “wherein the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is present in an amount ranging from about 0.5 mg to about 10 mg.”

151. Perrett discloses that its ODTs contain corticosteroid amounts ranging between 0.01 mg and 20 mg, including from about 0.5 mg to about 10 mg. EX1057 (Perrett) ¶[0040] (“In the case of solid pharmaceutical compositions of the present invention, *the amount of corticosteroid in the composition typically is less than or equal to 20 mg*. In one embodiment the amount of corticosteroid in the pharmaceutical composition is *between about 0.01 mg and about 20 mg*. In another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 1 mg and about 15 mg. In still another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 2 mg and about 10 mg. In yet another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 2 mg and about 5 mg. In still other embodiments, the amount of corticosteroid is about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, *about 0.5 mg*, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, *about 10 mg*, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 90 mg, or about 20 mg, *inclusive of all ranges and subranges therebetween.*”), ¶[0041] (“Typical amounts of corticosteroid in the solid pharmaceutical compositions of the present invention include about 0.25 mg, about 0.5 mg, about 1

mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg and about 5 mg.”).

5. Limitation 1[c.ii]

152. Limitation 1[c.ii] recites “the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, has a mean particle size of ranging from about 100 nm to about 100 μm .”

153. Perrett discloses that its ODTs include corticosteroid particles having a particle size ranging from about 1 nm to about 300 μm . EX1057 (Perrett) ¶[0066] (“The corticosteroid crystals can have an average particle size ranging from about 1-**300 μm** , for example about 1-50 μm , about 1-100 μm , about 1-150 μm , about 1-200 μm , about 1-250 μm , about 50-100 μm , about 50-150 μm , about 50-200 μm , about 50-250 μm , about 50-300 μm , about 100-150 μm , about 100-200 μm , about 150-200 μm , about 150-250 μm , about 150-300 μm , about 200-250 μm , about 200-300 μm , or about 250-300 μm .”); ¶[0067] (“Such crystals may have an average size in the sub-micron range (e.g., average particle size of about <1 μm), *or may be nanoparticles (e.g., average particle size in the range of about 1-100 nm)*.”); *id.* ¶[0089] (“(a) preparing corticosteroid-containing microgranules by granulating **crystalline corticosteroid material having an average particle size of about 5-50 μm** and one or more diluents/fillers such as lactose, mannitol, microcrystalline

cellulose and mixtures thereof, with a polymeric binder in a high-shear granulator or a fluid-bed coater;”).

6. Limitation 1[d]

154. Limitation 1[d] recites “wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> method for disintegration time.”

155. Perrett discloses that its orally disintegrating corticosteroid tablets are formulated to disintegrate within 60 seconds when tested using the USP <701> Disintegration Test. EX1057 (Perrett) ¶[0007] (“In one embodiment, the present invention is directed to a solid pharmaceutical composition comprising less than or equal to 20 mg of a corticosteroid, wherein the composition has no significant systemic glucocorticoid or mineralcorticoid activity after oral administration, *wherein the solid pharmaceutical composition disintegrates within 60 seconds in simulated saliva when tested using the USP <701> Disintegration Test*, and/or which disintegrates within 60 seconds when placed in the oral cavity of a human.”), ¶[0030] (“In one embodiment, the present invention provides a solid pharmaceutical composition which comprises less than or equal to 20 mg of a corticosteroid, wherein the composition has no significant systemic glucocorticoid or mineralocorticoid activity, *and wherein the solid pharmaceutical composition disintegrates within 60 seconds in simulated saliva when tested using the USP <701> Disintegration*

Test.”), ¶[0060] (“When using the USP <701> Disintegration Test, the rate of disintegration of the compositions of the present invention typically is about 60 seconds or less, about 45 seconds or less, about 30 seconds or less, about 20 seconds or less, or about 10 seconds or less.”).

156. In conclusion, Perrett discloses all limitations of claim 1. A person of ordinary skill in the art would have been motivated to arrive at an ODT that contains all limitations of claim 1 based on Perrett because Perrett’s ODT disclosures are interrelated to each other and are contained within a single prior art reference.

C. Claim 2

157. Claim 2 recites:

Claim 2. The orally disintegrating tablet of claim 1, wherein the pharmaceutically acceptable carrier is selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, and amorphous magnesium aluminum silicate.

158. Perrett discloses formulating its ODTs with microcrystalline cellulose, pregelatinized starch, and maize starch (i.e., corn starch) as fillers/diluents/binders. EX1057 (Perrett) ¶[0052] (“***Examples of suitable fillers, diluents and/or binders include*** lactose (e.g. spray-dried lactose, α -lactose, β -lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Flo®), ***microcrystalline cellulose*** (various grades of Avicel®, Ceolus®, Eclema®, Vivacel®, Ming Tai® or Solka-

Floc), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), low molecular weight hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K from Dow Chemical, Metolose SH from Shin-Etsu, Ltd), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrans, maltodextrins, **starches or modified starches** (including potato starch, **maize starch** and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate and collagen.”), ¶[0052] (“**Examples of suitable diluents include** e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, **microcrystalline cellulose**, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, **starch, pregelatinized starch**, sucrose and sugar.”), ¶[0070] (“**Non-limiting examples of other pharmaceutically acceptable ingredients** for the corticosteroid-containing granules include, for example, mannitol, lactose, **microcrystalline cellulose**, potassium sulfate, calcium phosphate, modified starch, and mixtures thereof.”), ¶[0072] (“For example, the corticosteroid-containing granules can be prepared by granulation of corticosteroid crystals, one or more disintegrants, **and one or more fillers** (e.g., sugar alcohol, saccharide and/or **microcrystalline cellulose**) in a high shear granulator or a fluid-bed granulator using a solution of one or more polymeric binders, and dried in fluid

bed equipment or on trays in a conventional oven to produce the corticosteroid-containing granules.”), ¶[0089] (“(a) preparing corticosteroid-containing microgranules by granulating crystalline corticosteroid material having an average particle size of about 5-50 μm *and one or more diluents/fillers such as* lactose, mannitol, *microcrystalline cellulose* and mixtures thereof, with a polymeric binder in a high-shear granulator or a fluid-bed coater;”).

159. These fillers/diluents/binders disclosed by Perrett constitute pharmaceutically acceptable carriers as described by the '061 patent. EX1001 (the '061 patent) at 7:28-38 (“The pharmaceutically acceptable carrier used in the mixture of the present invention is suitable for adsorption of the drug, it should have the properties of an excellent carrier for dry blends providing blend flowability and workability and preventing the segregation. It may concur in providing corticosteroid content uniformity. *It is selected from the group consisting of microcrystalline cellulose*, silicified microcrystalline cellulose, *pregelatinized starch, corn starch*, colloidal silica, or amorphous magnesium aluminum silicate (commercially available as VEEGUM™ or NEUSILIN™).”).

160. A person of ordinary skill in the art would recognize Perrett's fillers/diluents/binders are carriers. For example, the Perrett's granulating and blending processes in which microparticles of corticosteroid are mixed with fillers/diluents/binder results in at least some of the corticosteroid being adsorbed

onto a filler/diluent/binder. In at least this sense, Perrett's fillers/diluents/binders function as carriers.

D. Claim 3

161. Claim 3 recites:

Claim 3. The orally disintegrating tablet of claim 2, wherein the pharmaceutically acceptable carrier is silicified microcrystalline cellulose.

162. As discussed above for claim 2, Perrett discloses ODTs formulated with microcrystalline cellulose. EX1057 (Perrett) ¶¶[0051]-[0053], [0070], [0072], [0089]-[0090].

163. A person of ordinary skill in the art would have been motivated to use silicified microcrystalline cellulose in Perrett's granulation and/or blending processes with an expectation of success based on the general knowledge in the field regarding silicified microcrystalline cellulose as represented by, for example, the Handbook of Pharmaceutical Excipients. That handbook explains that silicified microcrystalline cellulose "has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose." EX1069 ("Cellulose, Silicified Microcrystalline," in Handbook Pharma. Excipients) at page 139. The Handbook further explains that "[s]ilicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation," *id.*,

and it “has greater tensile strength and requires lower compression pressures than regular grades of microcrystalline cellulose.” *Id.* at 140. In view of these known advantages of silicified microcrystalline cellulose, a person of ordinary skill in the art would have been motivated to use silicified microcrystalline cellulose in Perrett’s granulation and/or blending processes.

E. Claim 4

164. Claim 4 recites:

Claim 4. The orally disintegrating tablet of claim 2, wherein said topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, or a pharmaceutically salt or ester thereof.

165. Perrett discloses ODTs comprising each of the corticosteroids recited in claim 4. EX1057 (Perrett) ¶[0019] (“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.”), ¶[0039] (“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.”), ¶[0041] (“In a particular embodiment, the

compositions of the present invention comprise about 0.25 mg of fluticasone.”), ¶[0091] (Example 1 using fluticasone propionate).

F. Claim 5

166. Claim 5 recites:

Claim 5. The orally disintegrating tablet of claim 4, wherein the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is present in an amount ranging from about 0.5 mg to about 3 mg.

167. Perrett discloses that the amount of corticosteroid in its ODTs ranges from about 0.01 mg to about 20 mg, including between 0.5 mg and about 3 mg. EX1057 (Perrett) ¶[0040] (“In the case of solid pharmaceutical compositions of the present invention, the amount of corticosteroid in the composition typically is less than or equal to 20 mg. In one embodiment the amount of corticosteroid in the pharmaceutical composition is between about 0.01 mg and about 20 mg. In another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 1 mg and about 15 mg. In still another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 2 mg and about 10 mg. In yet another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 2 mg and about 5 mg. In still other embodiments, the amount of corticosteroid is about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08

mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, ***about 0.5 mg***, about 1 mg, about 2 mg, ***about 3 mg***, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 90 mg, or about 20 mg, ***inclusive of all ranges and subranges therebetween.***”), ¶[0041] (“Typical amounts of corticosteroid in the solid pharmaceutical compositions of the present invention include about 0.25 mg, ***about 0.5 mg***, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, ***about 3 mg***, about 3.5 mg, about 4 mg, about 4.5 mg and about 5 mg.”).

G. Claims 6 and 7

168. Claim 6 recites:

Claim 6. The orally disintegrating tablet of claim 4, wherein said topically acting corticosteroid is fluticasone or an ester thereof.

169. Claim 7 recites:

Claim 7. The orally disintegrating tablet of claim 4, wherein said topically acting corticosteroid is fluticasone propionate.

170. As discussed above for claim 1, Perrett discloses ODTs comprising fluticasone and fluticasone propionate. EX1057 (Perrett) ¶¶[0019], [0039], [0091]-[0092].

H. Claims 8 and 9

171. Claim 8 recites:

Claim 8. The orally disintegrating tablet of claim 1, wherein fluticasone propionate is present in an amount of about 3 mg in the orally disintegrating tablet.

172. Claim 9 recites:

Claim 9. The orally disintegrating tablet of claim 1, wherein fluticasone propionate is present in an amount of about 1.5 mg in the orally disintegrating tablet.

173. As discussed above for claim 5, Perrett discloses ODTs containing fluticasone propionate in amounts ranging between 0.01 mg and 20 mg, including about 1.5 mg and about 3 mg. EX1057 (Perrett) ¶[0040] (“In the case of solid pharmaceutical compositions of the present invention, the amount of corticosteroid in the composition typically is less than or equal to 20 mg. In one embodiment the amount of corticosteroid in the pharmaceutical composition is between about 0.01 mg and about 20 mg. In another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 1 mg and about 15 mg. In still another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 2 mg and about 10 mg. In yet another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 2 mg and about 5 mg. In still other embodiments, the amount of corticosteroid is about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg,

about 0.4 mg, about 0.5 mg, about 1 mg, about 2 mg, ***about 3 mg***, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 90 mg, or about 20 mg, ***inclusive of all ranges and subranges therebetween.***”), ¶[0041] (“Typical amounts of corticosteroid in the solid pharmaceutical compositions of the present invention include about 0.25 mg, about 0.5 mg, about 1 mg, ***about 1.5 mg***, about 2 mg, about 2.5 mg, ***about 3 mg***, about 3.5 mg, about 4 mg, about 4.5 mg and about 5 mg.”).

I. Claims 10 and 11

174. Claim 10 recites:

Claim 10. The orally disintegrating tablet of claim 1, wherein the corticosteroid has a mean particle size of ranging from about 100 nm to about 10 µm.

175. Claim 11 recites:

Claim 11. The orally disintegrating tablet of claim 1, wherein the corticosteroid has a mean particle size ranging from about 100 nm to about 4 µm.

176. Perrett discloses that its ODTs include corticosteroid particles having a particle size ranging from about 1 nm to about 300 µm, including about 100 nm, and between about 1-50 µm. EX1057 (Perrett) ¶[0066] (“The corticosteroid crystals can have an average particle size ranging from about 1-300 µm, for example ***about 1-50***

μm, about 1-100 *μm*, about 1-150 *μm*, about 1-200 *μm*, about 1-250 *μm*, about 50-100 *μm*, about 50-150 *μm*, about 50-200 *μm*, about 50-250 *μm*, about 50-300 *μm*, about 100-150 *μm*, about 100-200 *μm*, about 150-200 *μm*, about 150-250 *μm*, about 150-300 *μm*, about 200-250 *μm*, about 200-300 *μm*, or about 250-300 *μm*.”), ¶[0067] (“In another embodiment, the corticosteroid may be in the form of crystals. *Such crystals may have an average size in the sub-micron range (e.g., average particle size of about <1 μm), or may be nanoparticles (e.g., average particle size in the range of about 1-100 nm).*”). The particle size ranges disclosed by Perrett overlap with the claimed range of about 100 nm to about 4 *μm*.

J. Claim 12

177. Claim 12 recites:

Claim 12. The orally disintegrating tablet of claim 1, wherein the at least one disintegrant is present in a rapidly dispersing microgranule, which comprises a sugar alcohol, or a saccharide, or a mixture thereof in addition to the at least one disintegrant.

178. As discussed above for claim 1, Perrett discloses that its ODTs comprise rapidly dispersing microgranules as described in Venkatesh. EX1057 (Perrett) ¶¶[0042], [0089].

179. Venkatesh discloses orally disintegrating tablets that comprise rapidly dispersing microgranules prepared by granulating a sugar alcohol or a saccharide or a mixture thereof and a disintegrant. EX1020 (Venkatesh) at Abstract (“A tablet that

rapidly disintegrates in the oral cavity comprising a compressed blend of *rapidly dispersing microgranules prepared by granulating a sugar alcohol or a saccharide or a mixture thereof having an average particle size less than about 30 microns and a disintegrant*, and a taste-masked microcapsule containing at least one drug, the microcapsule being prepared by granulating a pharmaceutically acceptable formulation comprising at least one drug in a therapeutically effective amount and at least one polymeric binder that improves resilience of the microgranules, wet milling the granulated mass, and microencapsulating the milled granules to provide microcapsules.”), ¶[0014] (“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.”), ¶[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.”).

180. A person of ordinary skill in the art would have been motivated to formulate Perrett’s ODTs with rapidly dispersing microgranules according to Venkatesh’s disclosure with an expectation of success based on Perrett’s affirmative discussion of Venkatesh.

K. Claim 13

181. Claim 13 recites:

Claim 13. The orally disintegrating tablet of claim 12, wherein the sugar alcohol or saccharide and the disintegrant are present in a ratio of sugar alcohol or saccharide to disintegrant of from 90:10 to 99:1.

182. Example 1 of Perret states that “Mannitol 25 (91.2% w/w) and Crospovidone XL-10 (4.8% w/w) at a ratio of 95/5 are co-milled individually by passing the mixture through a Comil® milling apparatus, equipped with 0.225” spacers, at a speed of about 1400-1500 rpm.” EX1057 (Perrett) ¶[0091]. Mannitol is a sugar alcohol. Crospovidone is a disintegrant. The ratio of 95/5 disclosed by Perrett falls within the claimed ratio ranging from 90:10 to 99:1. Perrett therefore renders obvious claim 13.

183. The specification of the '061 patent discloses the opposite ratio of *disintegrant to sugar alcohol or saccharide* than the claimed range. EX1001 (the '061 patent) at 9:65-10:4 (“***The ratio of the disintegrant to the sugar alcohol, saccharide, or mixture thereof in the rapidly dispersing microgranules ranges from about 90/10 to about 99/01***, for example about 90/10, about 91/9, about 92/8, about 93/7, about 94/6, about 95/5, about 96/4, about 97/3, about 98/2, about 99/1, inclusive of all values, ranges, and sub-ranges there between.”). There seems to be an inconsistency between the specification and the claims in that they have the opposite ratios. Perrett discloses the same ratio of disintegrant to sugar alcohol or saccharide that is disclosed in the specification of the '061 patent. EX1057 (Perrett) ¶[0043] (“The ratio of the disintegrant to the sugar alcohol, saccharide, or mixture thereof in the rapidly dispersing microgranules ranges from about 90/10 to about 99/01, for example about 90/10, about 91/9, about 92/8, about 93/7, about 94/6, about 95/5, about 96/4, about 97/3, about 98/2, about 99/1, inclusive of all values, ranges, and subranges therebetween.”).

L. Claim 14

184. Claim 14 recites:

Claim 14. The orally disintegrating tablet of claim 12, wherein the disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, and low-substituted hydroxylpropylcellulose.

185. Perrett discloses each of the claimed disintegrants in Perrett’s rapidly dispersing microgranules. EX1057 (Perrett) ¶[0048] (“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.”).

M. Claim 15

186. Claim 15 recites:

Claim 15. The orally disintegrating tablet of claim 12, wherein the sugar alcohol or saccharide is selected from the group consisting of sucralose, lactose, sucrose, maltose, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.

187. Perrett discloses that the sugar alcohol or saccharide for its rapidly dispersing microgranules comprises mannitol, sorbitol, xylitol, maltitol, lactose, sucrose, maltose, and sucralose. EX1057 (Perrett) ¶[0049] (“A non-limiting list of suitable sugar alcohols includes *mannitol, sorbitol, xylitol, maltitol*, arabitol, ribitol, dulcitol, iditol, isomalt, lactitol, erythritol and combinations thereof. A non-limiting list of suitable saccharides includes *lactose, sucrose, maltose*, and combinations thereof.”); ¶[0077] (“In one embodiment, the solid pharmaceutical compositions of the present invention comprise about 25-35% of corticosteroid crystals, microencapsulated with a taste-masking layer comprising a water-insoluble polymer (e.g., ethylcellulose); about 60-70% of rapidly-dispersing granules (e.g., comprising

crospovidone and mannitol); about 5% of additional disintegrant (e.g., crospovidone); about 1% of one or more flavors, ***and about 0.5%-1% of a sweetener (e.g., sucralose).***”).

N. **Claim 16**

188. Claim 16 recites:

Claim 16. The orally disintegrating tablet of claim 12, wherein the rapidly dispersing microgranule has a mean particle size of less than about 300 μm , and the sugar alcohol and/or saccharide has an average particle size of less than about 30 μm .

189. Perrett discloses that its rapidly dispersing microgranules comprise an average particle size of less than about 300 μm and the sugar alcohol or saccharide has an average particle size of less than about 30 μm . EX1057 (Perrett) ¶[0042] (“Rapidly dispersing microgranules can be prepared as described in US 2005/0232988 or US 20010014340 by granulating a disintegrant having an average particle size of not more than about 30 μm with ***a sugar alcohol and/or saccharide having an average particle size of not more than about 30 μm*** . The granulation can be carried out, for example, in a high shear granulator with approximately 20-25% water as the granulating fluid, and if needed wet milled and dried ***to produce rapidly dispersing microgranules having an average particle size of not more than about 300 μm*** (e.g., about 175-300 μm).”).

O. Claim 17

190. Claim 17 recites:

Claim 17. The orally disintegrating tablet of claim 1, wherein the pharmaceutically acceptable carrier is present at an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

191. Perrett further discloses that the granules comprise excipients, such as fillers and diluents, in amounts ranging from about 5% to about 80%. EX1057 (Perrett) ¶[0070] (“The amount of other pharmaceutically acceptable ingredients (e.g. fillers or diluents) in the corticosteroid-containing granules can range from about 5%-80%, including about 5%-70%, about 5%-60%, about 5%-50%, about 5%-40%, about 5%-30%, about 5%-20%, about 5%-15%, about 5%-10%, about 10%-70%, about 10%-60%, about 10%-50%, about 10%-40%, about 10%-30%, about 10%-20%, about 10%-15%, about 20%-70%, about 20%-60%, about 20%-50%, about 20%-40%, about 20%-30%, about 20%-25%, about 30%-70%, about 30%-60%, about 30%-50%, about 30%-40%, about 30%-35%, about 40%-70%, about 40%-60%, about 40%-50%, about 40%-45%, about 50%-70%, about 50%-60%, about 50%-55%, about 60%-70%, or about 60%-65%.”). As discussed above for claim 1, Perrett’s fillers/diluents constitute carriers.

192. Perrett discloses that its ODTs comprise corticosteroid granules in amounts ranging from about 5% to about 50% by weight of the tablet. EX1057 (Perrett) ¶[0084] (“The amount of corticosteroid-containing granules in the solid

compositions of the present invention can range from about 5% to about 50%, including about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, and about 50%, inclusive of all values, ranges, and sub-ranges therebetween.”).

193. Perrett’s ranges of fillers/diluents and granules in the ODTs include tablets with carrier present at an amount of about 10% by weight of the finished tablet. For example, when Perrett’s fillers/diluents are present at 80% by weight of the granules, and the granules are present at 13% by weight of the tablet, the fillers/diluents are present at 10% by weight of the tablet. As another example, when Perrett’s fillers/diluents are present at 70% by weight of the granules, and the granules are present at 14% by weight of the tablet, the fillers/diluents are present at 10% by weight of the tablet. Another example is when Perrett’s fillers/diluents are present at 20% by weight of the granules and the granules are present at 50% by weight of the tablet, then the fillers/diluents are present at 10% by weight of the tablet.

P. Claim 18

194. Claim 18 recites:

Claim 18. The orally disintegrating tablet of claim 1, wherein the total weight of the tablet is in the range of from about 300 to about 900 mg.

195. A POSA would have been motivated to formulate Perrett's ODTs to have a total weight falling between about 300-900mg in view of the general knowledge of the person of ordinary skill in the art as reflected in the FDA Guidance on ODTs. The FDA Guidance teaches that ODTs should have a weight of less than 500 mg. EX1005 (FDA Guidance) at 3 ("We generally recommend that the weight of the tablet not exceed 500 mg; however, if a tablet intended for use as an ODT weighs more than 500 mg, its ability to perform effectively as an ODT should be justified based on product performance.").

Q. Claim 19

1. Preamble

196. The preamble recites "[a]n orally disintegrating tablet."

197. Perrett discloses the preamble of claim 19 for the reasons outlined, *supra*, in Section X.B.1, regarding the preamble of claim 1.

2. Limitation 19.a

198. Limitation 19.a recites "fluticasone propionate adsorbed onto microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, amorphous magnesium aluminum silicate, or combinations thereof."

199. Perrett renders obvious Limitation 19.a for the reasons outlined, *supra*, at Sections X.B.2 and X.G, regarding Limitation 1.a and claims 6 and 7.

3. Limitation 19.b

200. Limitation 19.b recites “at least one disintegrant.”

201. Perrett renders obvious Limitation 19.b for the reasons outlined, *supra*, at Section X.B.3, regarding Limitation 1.b.

4. Limitation 19[c.i]

202. Limitation 19[c.i] recites “the fluticasone propionate is present in an amount ranging from about 0.5 mg to about 6 mg.”

203. Perrett renders obvious Limitation 19[c.i] for the reasons outlined, *supra*, at Sections X.B.4 and X.H, regarding Limitation 1[c.i] and claims 8 and 9.

5. Limitation 19[c.ii]

204. Limitation 19[c.ii] recites that “the fluticasone propionate has a mean particle size ranging from about 100 nm to about 10 μ m.”

205. Perrett renders obvious Limitation 19[c.ii] for the reasons outlined, *supra*, at Sections X.B.5 and X.I, regarding Limitation 1[c.ii] and claim 10.

6. Limitation 19[d]

206. Limitation 19[d] recites “wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration test.”

207. Perrett renders obvious Limitation 19[d] for the reasons outlined, *supra*, at Section X.B.6, regarding Limitation 1[d]. *See also* EX1057 (Perrett) ¶[0030] (“In still other embodiments, the solid pharmaceutical compositions of the

present invention disintegrate within 30 seconds in simulated saliva (using the USP <701> Disintegration Test), or in the oral cavity of a patient.”).

R. Claim 20

208. Claim 20 recites:

Claim 20. The orally disintegrating tablet of claim 19, wherein the microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, or amorphous magnesium aluminum silicate, or a combination thereof, is present in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

209. Perrett renders obvious claim 20 for the reasons outlined, *supra*, at Section X.O, regarding claim 17.

S. Claim 21

210. Claim 21 recites:

Claim 21. The orally disintegrating tablet of claim 19, comprising silicified microcrystalline cellulose in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

211. Perrett renders obvious claim 21 for the reasons outline, *supra*, at Sections X.D and X.O, regarding claims 3 and 17.

T. Claim 22

212. Claim 22 recites:

Claim 22. The orally disintegrating tablet of claim 19, wherein fluticasone propionate has a mean particle size of about 4 μm or less.

213. Perrett renders obvious claim 22 for the reasons outlined, *supra*, at Section X.I, regarding claims 10 and 11.

U. Claim 23

214. Claim 23 recites:

Claim 23. The orally disintegrating tablet of claim 21, wherein the disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, and low-substituted hydroxypropylcellulose.

215. Perrett discloses that its orally disintegrating corticosteroid tablets are formulated with a disintegrant including crospovidone (crosslinked PVP), sodium starch glycolate, crosslinked sodium carboxymethyl cellulose, and low-substituted hydroxypropyl cellulose. EX1057 (Perrett) ¶[0048] (“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.”).

V. Claim 24

216. Claim 24 recites:

Claim 24. The orally disintegrating tablet of claim 20, wherein the at least one disintegrant is present in a rapidly dispersing microgranule, which comprises a sugar alcohol, or a saccharide, or a mixture thereof in addition to the at least one disintegrant.

217. Perrett renders obvious Claim 24 for the reasons outlined, *supra*, at Section X.J, regarding claim 12.

W. Claim 25

218. Claim 25 recites:

Claim 25. The orally disintegrating tablet of claim 24, wherein the sugar alcohol or saccharide and the disintegrant are present in a ratio of sugar alcohol or saccharide to disintegrant of from 90:10 to 99:1.

219. Perrett renders obvious Claim 25 for the reasons outlined, *supra*, at Section X.K, regarding claim 13.

X. Claim 26

220. Claim 26 recites:

Claim 26. The orally disintegrating tablet of claim 24, wherein the sugar alcohol or saccharide is selected from the group consisting of sucralose, lactose, sucrose, maltose, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.

221. Perrett renders obvious Claim 26 for the reasons outlined, *supra*, at Section X.M, regarding claim 15.

Y. Claim 27

222. Claim 27 recites:

Claim 27. The orally disintegrating tablet of claim 24, wherein the rapidly dispersing microgranule has a mean particle size of less than about 300 μm , and the sugar alcohol and/or saccharide has an average particle size of less than about 30 μm .

223. Perrett renders obvious Claim 27 for the reasons outlined, *supra*, at Section X.N, regarding claim 16.

Z. Claim 28

224. Claim 28 recites:

Claim 28. The orally disintegrating tablet of claim 19, wherein the silicified microcrystalline cellulose is present in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet, fluticasone propionate is present in an amount ranging from about 1 mg to about 3 mg, and fluticasone propionate has a mean particle size ranging from about 100 nm to about 4 μ m.

225. Perrett renders obvious Claim 28 for the reasons outlined, *supra*, at Sections X.D, X.H-I, X.O, and X.S-T, regarding claims 3, 8-11, 17, and 21-22.

AA. Claim 29

226. Claim 29 recites:

Claim 29. A method for treating eosinophilic esophagitis in an individual in need thereof, comprising administering to the individual the orally disintegrating tablet of claim 1.

227. Perrett discloses that its ODTs are administered to treat eosinophilic esophagitis. EX1057 (Perrett) ¶[0025] (“Inflammatory conditions of the gastrointestinal tract which may be treated according to the present invention include inflammation of the esophagus, inflammation of the glottis, inflammation of the epiglottis, inflammation of the tonsils, inflammation of the oropharynx, *eosinophilic*

esophagitis, gastroesophageal reflux disease (GERD), non-erosive reflux disease (NERD), erosive esophagitis, Barrett's esophagus, eosinophilic gastroenteritis, hypereosinophilic syndrome, corrosive (caustic) chemical esophagitis, radiation-induced esophagitis, chemotherapy-induced esophagitis, transient drug-induced esophagitis (also known as medication esophagitis), persistent drug-induced esophagitis, Crohn's disease of the esophagus, scleroderma, and scleroderma sine scleroderma, systemic lupus erythematosus, systemic vasculitides, leukocytoclastic vasculitis, polyarteritis nodosa, Churg-Strauss syndrome, rheumatoid vasculitis, and pseudomembranous esophagitis.”), ¶[0027] (“In one such embodiment, the present invention includes *a method for treating eosinophilic esophagitis* comprising administering to a patient in need thereof a pharmaceutical composition of the present invention.”).

BB. Claim 30

228. Claim 30 depends from claim 1. The preamble recites a “method of preparing the orally disintegrating tablet of claim 1.”

229. Perrett renders obvious the ODTs of claim 1 for the reasons outlined, *supra*, in Section X.B, regarding claim 1. Perrett renders obvious the method recited by claim 30 for reasons discussed below.

1. Limitation 30(a)

230. Limitation 30(a) recites “micronizing the corticosteroid.”

231. As discussed above for limitation 1[c.ii], Perrett discloses formulating its ODTs using corticosteroid in the micron scale. EX1057 (Perrett) ¶¶[0066]-[0067], [0089].

2. Limitation 30[b.i]

232. Limitation 30[b.i] recites “preparing preblend 1 by blending (i) a pharmaceutically acceptable carrier, (ii) corticosteroid or pharmaceutically ester thereof, and (iii) glidant, under conditions suitable for the corticosteroid to be adsorbed onto the pharmaceutically acceptable carrier.”

233. Perrett discloses preparing a preblend for formulating an ODT by blending a pharmaceutically acceptable carrier and corticosteroid under conditions suitable for the corticosteroid to be adsorbed onto the pharmaceutically acceptable carrier for the reasons outlined discussed above for Limitation 1.a. *Supra* Section X.B.2; *see also* EX1057 (Perrett) ¶[0089] (“(a) preparing corticosteroid-containing microgranules by granulating crystalline corticosteroid material having an average particle size of about 5-50 μm and one or more diluents/fillers such as lactose, mannitol, microcrystalline cellulose and mixtures thereof, with a polymeric binder in a high-shear granulator or a fluid-bed coater;”), ¶[0090] (“(a) preparing a drug-containing core particle (e.g., corticosteroid crystals, drug-layered beads, or corticosteroid-containing microgranules) by granulating the drug and optionally one or more diluents/fillers such as lactose, mannitol, microcrystalline cellulose and

mixtures thereof with a polymeric binder in a high-shear granulator or a fluid-bed coater, or drug-layering on an inert particle (60-100 mesh sugar sphere or cellulose sphere, e.g., Celphere® CP-203) from a solution/suspension comprising a polymeric binder and the drug in a fluid-bed coater and optionally applying a seal-coat (e.g., Opadry® Clear);”), ¶[0091] (“Mannitol 25 (91.2% w/w) and Crospovidone XL-10 (4.8% w/w) at a ratio of 95/5 are co-milled individually by passing the mixture through a Comil® milling apparatus, equipped with 0.225” spacers, at a speed of about 1400-1500 rpm. The mannitol, crospovidone, and fluticasone propionate (4% w/w) crystalline material are blended for about 3-5 minutes to mix the ingredients.”).

234. It was common to prepare a preblend to assist with achieving homogeneity of drug dispersal throughout the tablet manufacturing process. For example, Wen teaches that “[a]dsorbing drugs onto carrier particles (Fig. 1) by ordered mixing can be very beneficial in several ways, such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage.” EX1054 (Wen) at 35.

235. Perrett discloses the use of glidants in its formulations. EX1057 (Perrett) ¶[0050] (“Pharmaceutically acceptable excipients include fillers, diluents, *glidants*, disintegrants, binders and lubricants.”), ¶[0054] (“*Specific examples of glidants* and lubricants include stearic acid, magnesium stearate, calcium stearate or

other metallic stearates, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate and sodium acetate.”).

236. A POSA would have understood that glidants are fine powders that improve the flow properties of the blended ingredients. EX1041 (Conway) at 241 (“Like lubricants, glidants are fine powders and may be required for tablet compression at high production speeds to improve the flow properties of the material into the die or during initial compression stages.”). A person of ordinary skill in the art therefore would have been motivated to use a glidant in Perrett’s preblend to improve the flow properties of the granulated material.

3. Limitation 30[b.ii]

237. Limitation 30[b.ii] recites “wherein the pharmaceutically acceptable carrier is microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, and amorphous magnesium aluminum silicate.”

238. Perrett discloses this limitation for the reasons outline, *supra*, in Section X.C, regarding claim 2.

4. Limitation 30(c)

239. Limitation 30(c) recites “preparing preblend 2 by blending filler, preblend 1 of step (b), disintegrant, and sweetener.”

240. Perrett discloses formulating its ODTs by combining preblended corticosteroid granules with filler, disintegrants and sweetener. EX1057 (Perrett) ¶¶[0042]-[0055] (disclosing the addition of fillers, disintegrant, and sweetener), [0079]-[0092] (disclosing processes for preparing ODTs). For example, Perrett discloses blending the preblend of corticosteroid and carrier from step (a) of ¶[0089] with “sugar alcohols and/or saccharides” fillers and a disintegrant in step (b) and a sweetener in step (c) to prepare a second preblend. *Id.* ¶[0089].

241. Venkatesh similarly discloses preparing blends by adding fillers, disintegrants, and sweeteners. EX1020 (Venkatesh) ¶¶[0018], [0023], [0030]. Adding filler, disintegrants, and sweetener to a preblend was a common technique to gradually increase the bulk of the blended materials during tablet manufacturing processes. The ordered mixing of ingredients assists with achieving a homogenous dispersal of the ingredients throughout the preblend. For example, Wen teaches that “ordered mixing can be very beneficial in several ways, such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage.” EX1054 (Wen) at 35.

5. Limitation 30(d)

242. Limitation 30(d) recites “preparing a final compressible blend, by blending a disintegrant, lubricant, filler, and preblend 2 of step (c).”

243. Perrett discloses formulating its orally disintegrating tablets by combining preblended corticosteroid granules with disintegrant, lubricant, and filler. EX1057 (Perrett) ¶¶[0042]-[0055] (disclosing the addition of disintegrant, lubricant, and filler), [0079]-[0092] (disclosing processes for preparing ODTs). For example, Perrett discloses adding to the second preblend from step (c) of ¶[0089] an “additional disintegrant” and “microcrystalline cellulose” filler. A person of ordinary skill in the art would have been motivated to include a lubricant based on Perrett’s teachings to use a lubricant. EX1057 (Perrett) ¶¶[0046], [0050], [0054].

244. Venkatesh similarly discloses preparing blends by adding disintegrants, lubricant, and filler. EX1020 (Venkatesh) ¶¶[0002], [0018]-[0023], [0030]. Adding a disintegrant, lubricant, and filler to a preblend was a common technique to gradually increase the bulk of the blended materials for tablet manufacturing processes. The ordered mixing of ingredients assists with achieving a homogenous dispersal of the ingredients throughout the blend. For example, Wen teaches that “ordered mixing can be very beneficial in several ways, such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting

excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage.” EX1054 (Wen) at 35.

6. Limitation 30(e)

245. Limitation 30(e) recites “compressing the blend of step (d) to form a tablet.”

246. Perrett discloses compressing blends to form a tablet. EX1057 (Perrett) ¶¶[0085]-[0087], [0089]-[0090]. Venkatesh similarly discloses compressing blends to form a tablet. EX1020 at Abstract, ¶¶[0002], [0024].

XI. GROUND 2: DOHIL2009 IN VIEW OF THE KNOWLEDGE OF A PERSON OF ORDINARY SKILL IN THE ART

247. Dohil2009 discloses orally disintegrating tablets having the same ingredients claimed by the '061 patent. This section introduces Dohil2009, and then explains how Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious claims 1-2, 4-11, 17-20, 22, and 29-30 of the '061 patent.

A. Dohil2009

248. Dohil2009 discloses budesonide formulations in the form of lozenges or tablets that will “dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.” EX1058 (Dohil2009) ¶[0062]. Dohil2009 teaches that other topically acting corticosteroids can be used in the formulations, including fluticasone propionate. *Id.* ¶[0049]. Dohil2009 also teaches “grinding” the topically acting corticosteroid particles and formulating tablets with

“corticosteroid microparticles hav[ing] a diameter less than 10 microns.” *Id.* ¶¶[0019], [0070]. Dohil2009 also teaches that exemplary dosage amounts of corticosteroid in its formulations range from less than 1 mg to less than 10 mg. *Id.* ¶¶[0042]-[0043].

B. Claim 1

1. Preamble

249. The preamble of claim 1 recites “[a]n orally disintegrating tablet.”

250. Dohil2009 discloses the recited orally disintegrating tablets. For example, Dohil2009 discloses budesonide formulations in the form of tablets that “*dissolve rapidly in the mouth* or esophagus to produce a solution that can then coat the esophagus.” EX1058 (Dohil2009) ¶[0062] (“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.”). Dohil2009 further discloses “[b]udesonide, in the form of *a dissolving tablet*.” *Id.* ¶[0012] (“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.* ¶[0070] (disclosing “dissolving tablets”).

251. The “rapid” dissolution of Dohil2009’s lozenges and tablets in the patient’s mouth indicates to the person of ordinary skill in the art that the lozenges and tablets dissolve in the mouth without chewing. *See, e.g.* EX1005 (FDA Guidance) at 2 (“As briefly discussed in section II, an ODT has previously been distinguished as a separate dosage form because of the specific, intended performance characteristics of such a product, which are *rapid oral disintegration in saliva with no need for chewing* or drinking liquids to ingest these products.”). Thus, a person of ordinary skill in the art would understand that Dohil2009’s lozenges and tablets that dissolve rapidly in the oral cavity do so without chewing.

2. Limitation 1.a

252. Limitation 1.a recites “a topically acting corticosteroid or pharmaceutically acceptable salt or ester thereof, adsorbed onto a pharmaceutically acceptable carrier.”

253. Dohil2009 discloses that the oral formulations, including tablets, comprise topically acting corticosteroids, such as budesonide and fluticasone propionate. EX1058 (Dohil2009) ¶[0012] (“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.”), ¶[0049] (“In some embodiments, corticosteroids are selected from, by way of non-limiting example, aclometasone, amcinomide,

beclometasone, betamethasone, **budesonide**, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, cortivazol, deflazacort, deoxycorticosterone, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, fluclorolone, fludrocortisone, fludroxycortide, flumetasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin, fluocortolone, fluorometholone, fluperolone, **fluticasone**, **fluticasone propionate**, fuprednidene, formocortal, halcinonide, halometasone, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone butyrate, loteprednol, medrysone, meprednisone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, paramethasone, prednicarbate, prednisone, prednisolone, prednylidene, remexolone, tixocortol, triamcinolone and ulobetasol, and combinations, pharmaceutically acceptable salts and esters thereof.”), ¶[0062] (“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.”), ¶[0070] (“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.”).

254. Dohil2009 further teaches formulating the tablets by “combining the corticosteroids with solid excipients,” “optionally grinding the resulting mixture,”

and then “processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets.” EX1058 (Dohil2009) ¶[0070] (“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”).

255. Dohil2009 teaches that exemplary solid excipients include cellulose preparations, such as maize starch (i.e., corn starch), gelatin, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose and sugars. EX1058 (Dohil2009) ¶[0070] (“Suitable excipients are, in particular, fillers such as *sugars*, including lactose, sucrose, sucralose (Splenda®, Distributed By: McNeil Nutritionals, LLC, Fort Washington, Pa. 19034-2299), 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).”).

256. Such excipients disclosed by Dohil2009 constitute pharmaceutically acceptable carriers as described by the '061 patent. EX1001 (the '061 patent) at 7:28-38 (“*The pharmaceutically acceptable carrier used in the mixture of the present invention is suitable for adsorption of the drug, it should have the*

properties of an excellent carrier for dry blends providing blend flowability and workability and preventing the segregation. It may concur in providing corticosteroid content uniformity. *It is selected from the group consisting of microcrystalline cellulose*, silicified microcrystalline cellulose, pregelatinized starch, *corn starch*, colloidal silica, or amorphous magnesium aluminum silicate (commercially available as VEEGUM™ or NEUSILIN™).”).

257. It was known that adsorption generally plays a role when mixing occurs with a mixture of particle sizes at or below approximately 400 µm. EX1054 (Wen) at 35 (“During mixing, there are many factors that can affect the content uniformity of mixtures, and adsorption generally plays a role when the average particle size is ≤400 µm.”); EX1055 (Martin) at 383 (“During blending, a fine powder of an antibiotic is adsorbed onto the surface of coarse particles of sorbitol.”).

258. Dohil2009 discloses corticosteroid particles having a diameter of less than 10 microns. EX1058 (Dohil2009) ¶[0022] (“In certain embodiments, provided herein are pharmaceutical compositions comprising corticosteroid microparticles, wherein at least 95% of the corticosteroid microparticles have a diameter of less than 10 microns.”), ¶[0019] (“In certain embodiments, the pharmaceutical composition comprises corticosteroid microparticles, wherein at least 95% of the corticosteroid microparticles have a diameter of less than 10 microns.”), ¶[0050] (“In some embodiments, the microparticles have a mean diameter of about 0.1 microns to about

50 microns. In specific embodiments, the microparticles have a mean diameter of about 1 micron to about 20 microns. In certain embodiments, at least 95%, at least 98%, or at least 99% of the microparticles have a diameter of less than 10 microns.”). As discussed above, it was known that a small particle size tends to improve disintegration, dissolution, and patient compliance. *Supra* Section VII.E.

259. A person of ordinary skill in the art would understand that Dohil2009’s combining, grinding, and processing steps result in at least some of the micronized corticosteroid being adsorbed onto the excipient carrier.

260. The ’061 patent appears to agree that mixing corticosteroid particles and a carrier results in adsorption onto the carrier as follows:

The corticosteroid particles are typically adsorbed onto the carrier. The process for the preparation includes repeatedly mixing corticosteroid and carrier so that the blend is adsorbed onto the carrier.

EX1001 (the ’061 patent) at 10:5-8.

261. A person of ordinary skill in the art would have been motivated to adsorb Dohil2009’s corticosteroid onto a carrier. It was known that such adsorption “can be very beneficial in several ways, such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage.” EX1054 (Wen) at 35; *id.* at 43 (“In pharmaceutical processing, adsorbing drugs onto

the solid surface of other excipients can help to achieve content uniformity, especially for low-dose drugs, during the mixing process.”).

262. Surface adsorption of drugs on pharmaceutical carriers is advantageous for ODTs because it provides “fast disintegration/dissolution,” as well as “increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, [and] conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).” EX1019 (Shukla) at 320. A person of ordinary skill in the art would have had a reasonable expectation of success in achieving adsorption because it was known that adsorption “generally plays a role when the average particle size is $\leq 400\text{ }\mu\text{m}$,” EX1054 (Wen) at 35, and Dohil2009’s disclosure that the corticosteroid particles have a diameter of less than 10 microns. EX1058 (Dohil2009) ¶¶[0022], [0019], [0050].

3. Limitation 1.b

263. Limitation 1.b recites “at least one disintegrant.”

264. Dohil2009 discloses “[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.” EX1058 (Dohil2009) ¶[0070]. 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. EX1018 (Fu) at 446-47 (heading “Disintegrants Used in FDTs”).

4. Limitation 1[c.i]

265. Limitation 1[c.1] recites “wherein the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is present in an amount ranging from about 0.5 mg to about 10 mg.”

266. As discussed above for limitation 1.a, Dohil2009 discloses that its ODTs comprise topically acting corticosteroids, such as budesonide and fluticasone propionate. EX1058 (Dohil2009) ¶¶[0012], [0049], [0062], [0070].

267. Dohil2009 further discloses that “a dissolving tablet” will contain amounts of corticosteroid ranging between, e.g., “0.1-10 mg.” EX1058 (Dohil2009) ¶[0042] (“In some embodiments, a composition or unit dose described herein is administered as a nebulized composition, an aerosolized composition, an emulsion, a solution, a suspension, a syrup, a slurry, a dispersion, a colloid, a dissolving tablet, a dissolving wafer, a capsule, a gel capsule, a semi-solid, a solid form a gel, a gel matrix, a cream, a paste, or the like. In certain aspects, about 0.01 mg to about 20 mg, about 0.01 mg to about 15 mg, or about 0.01 mg to about 10 mg (e.g., about 0.1-10 mg, about 0.25-5 mg, about 0.25-2.5 mg, about 1-2 mg or about 2-3 mg, about 0.25 mg to about 6 mg corticosteroid, about 0.5 mg to about 6 mg corticosteroid, about 0.5 mg to about 2 mg of corticosteroid, about 1 mg to about 2 mg of

corticosteroid, about 2 mg to about 3 mg of corticosteroid, about 3 mg to about 4 mg of corticosteroid, about 4 mg to about 5 mg of corticosteroid, or about 5 mg to about 6 mg of corticosteroid per day or per dose is administered to an individual. In some embodiments, the corticosteroid is present in a composition or a unit dose of a composition described herein in an amount of from about 0.01 mg to about 10 mg (e.g., about 0.1-10 mg, about 0.25-5 mg, about 0.25-2.5 mg, about 1-2 mg or about 2-3 mg, about 0.5 mg to about 2 mg, about 1 to about 2 mg, about 1 mg, or about 2 mg). In some embodiments, the amount of corticosteroid administered daily or in a unit dose is between about 0.5 mg and about 3 mg. In other embodiments, the amount of corticosteroid present in a unit dose or administered daily is between about 1 and about 3 mg, or between about 1 and about 2 mg, or between about 2 and about 3 mg.”), ¶[0043] (disclosing amounts of corticosteroid administered per day), ¶[0014] (“In certain embodiments, 1-2 mg or 2-3 mg or corticosteroid per day is administered to said individual.”).

268. Dohil2009’s patients were actually dosed with budesonide at 0.5, 1, and 2 mg/day. EX1058 (Dohil2009) ¶[0115] (“Fifteen patients received OVB 1 mg/day, four received 2 mg/day and one unintentionally received 0.5 mg/day [Table 1].”); *see also id.* at Table 1.

5. Limitation 1[c.ii]

269. Limitation 1[c.ii] recites “[wherein] the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, has a mean particle size of ranging from about 100 nm to about 100 μm.”

270. Dohil2009 discloses that its ODTs comprise topically acting corticosteroid particles with a mean diameter ranging from about 0.1-50 microns (i.e., 100 nm to 50 μm). EX1058 (Dohil2009) ¶[0050] (“In some embodiments, *the microparticles have a mean diameter of about 0.1 microns to about 50 microns*. In specific embodiments, the microparticles have a mean diameter of about 1 micron to about 20 microns. In certain embodiments, at least 95%, at least 98%, or at least 99% of the microparticles have a diameter of less than 10 microns.”), ¶[0019] (“In certain embodiments, the pharmaceutical composition comprises corticosteroid microparticles, wherein at least 95% of *the corticosteroid microparticles have a diameter of less than 10 microns*.”), ¶[0092] (“In certain embodiments, a composition provided herein comprises (1) *commercially available micronized corticosteroid particles (e.g., micronized budesonide)*, or other commercially available corticosteroid particles;”), ¶[0093] (disclosing “micronized budesonide”). A person of ordinary skill in the art would readily understand that “mean particle size” and “mean diameter” are interchangeable terms.

6. Limitation 1[d]

271. Limitation 1[d] recites “wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> method for disintegration time.”

272. Dohil2009 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.” EX1058 (Dohil2009) ¶[0062]. A person of ordinary skill in the art would have understood that it was desirable for the disintegration time of Dohil2009’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.”).

273. It would have been obvious to formulate Dohil2009’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.”).

274. A person of ordinary skill in the art would have been motivated to follow the FDA Guidance in formulating Dohil2009’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.

275. Dohil2009’s formulations were intended to “be used in therapy for human patients,” EX1058 (Dohil2009) at ¶[0051] (“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 of its formulations was conducted within the United States, *id.* at ¶[0106] (“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.

276. 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 Dohil2009's description of how to formulate such rapidly disintegrating lozenges or tablets. See, e.g., EX1058 (Dohil2009) ¶¶[0051]-[0094] (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 2013, 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 designating 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 2013. Dohil in view of the knowledge of the person of ordinary skill in the art therefore renders obvious limitation 1[d].

277. Dohil2009 in view of the knowledge of a person of ordinary skill in the art therefore renders obvious claim 1.

C. **Claim 2**

278. Claim 2 recites:

Claim 2. The orally disintegrating tablet of claim 1, wherein the pharmaceutically acceptable carrier is selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, and amorphous magnesium aluminum silicate.

279. Dohil2009 teaches that exemplary solid excipients include cellulose preparations, such as maize starch (i.e., corn starch). EX1058 (Dohil2009) ¶[0070] (“Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, sucralose (Splenda®, Distributed By: McNeil Nutritionals, LLC, Fort Washington, Pa. 19034-2299), 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).”).

280. At least the maize starch disclosed by Dohil2009 constitutes a pharmaceutically acceptable carrier as described by the '061 patent. EX1001 (the '061 patent) at 7:28-38 (“The pharmaceutically acceptable carrier used in the mixture of the present invention is suitable for adsorption of the drug, it should have the properties of an excellent carrier for dry blends providing blend flowability and workability and preventing the segregation. It may concur in providing corticosteroid content uniformity. *It is selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, **corn starch**, colloidal silica, or amorphous magnesium aluminum silicate (commercially available as VEEGUM™ or NEUSILIN™).*”).

281. A person of ordinary skill in the art would recognize Dohil2009's excipients are carriers. For example, Dohil2009's combining, grinding, and processing steps result in at least some of the micronized corticosteroid being adsorbed onto the excipient carrier. In at least this sense, Dohil2009's excipients function as carriers.

D. Claim 4

282. Claim 4 recites:

Claim 4. The orally disintegrating tablet of claim 2, wherein said topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is budesonide, fluticasone, flunisolide, ciclesonide,

mometasone, beclomethasone, or a pharmaceutically salt or ester thereof.

283. Dohil2009 discloses ODTs comprising the corticosteroids recited in claim 4. EX1058 (Dohil2009) ¶[0049] (“In some embodiments, corticosteroids are selected from, by way of non-limiting example, aclometasone, amcinomide, *beclometasone*, betamethasone, *budesonide*, *ciclesonide*, clobetasol, clobetasone, clocortolone, cloprednol, cortivazol, deflazacort, deoxycorticosterone, desonide desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, flucolorolone, fludrocortisone, fludroxycortide, flumetasone, *flunisolide*, fluocinolone acetonide, fluocinonide, fluocortin, fluocortolone, fluorometholone, fluperolone, *fluticasone*, *fluticasone propionate*, fuprednidene, formocortal, halcinonide, halometasone, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone butyrate, loteprednol, medrysone, meprednisone, methylprednisolone, methylprednisolone aceponate, *mometasone furoate*, paramethasone, prednicarbate, prednisone, prednisolone, prednylidene, remexolone, tixocortol, triamcinolone and ulobetasol, and combinations, *pharmaceutically acceptable salts and esters thereof*.”), ¶[0012] (“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.”), ¶[0062] (“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.”).

E. Claim 5

284. Claim 5 recites:

Claim 5. The orally disintegrating tablet of claim 4, wherein the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is present in an amount ranging from about 0.5 mg to about 3 mg.

285. Dohil2009 discloses ODTs containing corticosteroid amounts ranging between 0.01 mg and 20 mg, including between “about 0.5 mg to about 2 mg.” EX1058 (Dohil2009) ¶[0042] (“In some embodiments, a composition or unit dose described herein is administered as a nebulized composition, an aerosolized composition, an emulsion, a solution, a suspension, a syrup, a slurry, a dispersion, a colloid, a dissolving tablet, a dissolving wafer, a capsule, a gel capsule, a semi-solid, a solid form a gel, a gel matrix, a cream, a paste, or the like. In certain aspects, *about 0.01 mg to about 20 mg*, about 0.01 mg to about 15 mg, or about 0.01 mg to about 10 mg (e.g., about 0.1-10 mg, about 0.25-5 mg, about 0.25-2.5 mg, about 1-2 mg or about 2-3 mg, about 0.25 mg to about 6 mg corticosteroid, about 0.5 mg to about 6 mg corticosteroid, *about 0.5 mg to about 2 mg of corticosteroid*, about 1 mg to about 2 mg of corticosteroid, about 2 mg to about 3 mg of corticosteroid, about 3 mg to about 4 mg of corticosteroid, about 4 mg to about 5 mg of corticosteroid, or about 5

mg to about 6 mg of corticosteroid per day or per dose is administered to an individual. In some embodiments, the corticosteroid is present in a composition or a unit dose of a composition described herein in an amount of from about 0.01 mg to about 10 mg (e.g., about 0.1-10 mg, about 0.25-5 mg, about 0.25-2.5 mg, about 1-2 mg or about 2-3 mg, about 0.5 mg to about 2 mg, about 1 to about 2 mg, about 1 mg, or about 2 mg). In some embodiments, the amount of corticosteroid administered daily or in a unit dose is between *about 0.5 mg and about 3 mg*. In other embodiments, the amount of corticosteroid present in a unit dose or administered daily is between about 1 and about 3 mg, or between about 1 and about 2 mg, or between about 2 and about 3 mg.”), ¶[0043] (disclosing amounts of corticosteroid administered per day), ¶[0014] (“In certain embodiments, 1-2 mg or 2-3 mg or corticosteroid per day is administered to said individual.”).

F. Claims 6-9

286. Claim 6 recites:

Claim 6. The orally disintegrating tablet of claim 4, wherein said topically acting corticosteroid is fluticasone or an ester thereof.

287. Claim 7 recites:

Claim 7. The orally disintegrating tablet of claim 4, wherein said topically acting corticosteroid is fluticasone propionate.

288. Claim 8 recites:

Claim 8. The orally disintegrating tablet of claim 1, wherein fluticasone propionate is present in an amount of about 3 mg in the orally disintegrating tablet.

289. Claim 9 recites:

Claim 9. The orally disintegrating tablet of claim 1, wherein fluticasone propionate is present in an amount of about 1.5 mg in the orally disintegrating tablet.

290. As discussed above for claim 1, Dohil2009 discloses ODTs comprising fluticasone and fluticasone propionate. EX1058 (Dohil2009) ¶[0049]. As discussed above for claim 5, Dohil2009 discloses ODTs containing corticosteroid amounts of about 1.5 mg and about 3mg. EX1058 (Dohil2009) ¶[0042] (“In some embodiments, the amount of corticosteroid administered daily or in a unit dose is between about 0.5 mg and **about 3 mg.**”), ¶[0043] (“In certain aspects, about 0.25 mg to about 20 mg, about 0.25 mg to about 15 mg, about 0.25 mg to about 10 mg, or about 0.25 mg to about 5 mg (e.g., about 0.1 to about 5 mg, about 0.25 to about 2.5 mg, about 0.3 mg to about 2 mg, about 0.5 mg to about 1 mg, about 0.7 mg to about 1.5 mg, about 0.375 mg, about 0.75 mg, about 1 mg, about 1.25 mg, **about 1.5 mg** or about 2 mg) corticosteroid per day is administered to a patient or individual.”), ¶[0014] (“In certain embodiments, 1-2 mg or 2-3 mg or corticosteroid per day is administered to said individual.”).

G. Claims 10 and 11

291. Claim 10 recites:

Claim 10. The orally disintegrating tablet of claim 1, wherein the corticosteroid has a mean particle size of ranging from about 100 nm to about 10 μ m.

292. Claim 11 recites:

Claim 11. The orally disintegrating tablet of claim 1, wherein the corticosteroid has a mean particle size ranging from about 100 nm to about 4 μ m.

293. Dohil2009 discloses ODTs comprising topically acting corticosteroid particles with a mean diameter ranging from about 0.1-50 microns (i.e., 100 nm to 50 μ m), including diameters less than 10 μ m. EX1058 (Dohil2009) ¶[0050] (“In some embodiments, *the microparticles have a mean diameter of about 0.1 microns to about 50 microns*. In specific embodiments, the microparticles have a mean diameter of about 1 micron to about 20 microns. In certain embodiments, at least 95%, at least 98%, or at least 99% of the microparticles have a diameter of less than 10 microns.”), ¶[0019] (“In certain embodiments, the pharmaceutical composition comprises corticosteroid microparticles, wherein at least 95% of *the corticosteroid microparticles have a diameter of less than 10 microns*.”), ¶[0092] (“In certain embodiments, a composition provided herein comprises (1) *commercially available micronized corticosteroid particles (e.g., micronized budesonide)*, or other

commercially available corticosteroid particles;”), ¶[0093] (disclosing “micronized budesonide”). The particle size ranges disclosed by Dohil2009 overlap with the claimed range of about 100 nm to about 4 µm.

H. Claims 17 and 18

294. Claim 17 recites:

Claim 17. The orally disintegrating tablet of claim 1, wherein the pharmaceutically acceptable carrier is present at an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

295. Claim 18 recites:

Claim 18. The orally disintegrating tablet of claim 1, wherein the total weight of the tablet is in the range of from about 300 to about 900 mg.

296. Dohil2009 discloses that its tablets comprise various amounts of the topically acting corticosteroid, and that the amount of excipients used can affect the quantity of corticosteroid required. EX1058 (Dohil2009) ¶[0033] (“In one aspect of the invention, the use of the excipients may act to decrease the quantity of active agents needed to elicit a response in the absence of the excipients. In some embodiments, the excipients may decrease the amount of corticosteroid used, for example, from about 1 to about 3 mg of budesonide in the absence of an excipient to about 250 µg to about 2 mg of budesonide in the presence thereof.”), ¶[0055] (“In an illustrative embodiment, the dosage is provided in a sufficient volume that the

composition reaches the esophagus in an effective amount.”). Modifying Dohil2009’s formulations to result in ODTs with a carrier present at an amount of about 10% w/w based on the total weight of the tablet, would have been a matter of routine experimentation and optimization.

297. A POSA would have been motivated to formulate Dohil2009’s ODTs to have a total weight falling between about 300-900mg in view of the general knowledge of the person of ordinary skill in the art as reflected in the FDA Guidance on ODTs. The FDA Guidance teaches that ODTs should have a weight of less than 500 mg. EX1005 (FDA Guidance) at 3 (“We generally recommend that the weight of the tablet not exceed 500 mg; however, if a tablet intended for use as an ODT weighs more than 500 mg, its ability to perform effectively as an ODT should be justified based on product performance.”).

I. Claim 19

1. Preamble

298. The preamble recites “[a]n orally disintegrating tablet.”

299. Dohil2009 renders the preamble obvious for the reasons outlined, *supra*, in Section XI.B.1, regarding the preamble of claim 1.

2. Limitation 19.a

300. Limitation 19.a recites “fluticasone propionate adsorbed onto microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized

starch, corn starch, colloidal silica, amorphous magnesium aluminum silicate, or combinations thereof.”

301. Dohil2009 renders obvious Limitation 19.a for the reasons outlined, *supra*, at Sections XI.B.2 and XI.F, regarding Limitations 1.a and claims 6 and 7.

3. Limitation 19.b

302. Limitation 19.b recites “at least one disintegrant.”

303. Dohil2009 renders obvious Limitation 19.b for the reasons outlined, *supra*, at Section XI.B.3, regarding Limitation 1.b.

4. Limitation 19[c.i]

304. Limitation 19[c.i] recites “the fluticasone propionate is present in an amount ranging from about 0.5 mg to about 6 mg.”

305. Dohil2009 renders obvious Limitation 19[c.i] for the reasons outlined, *supra*, at Sections XI.B.4 and XI.E-F, regarding Limitation 1[c.i] and claims 5 and 6-9.

5. Limitation 19[c.ii]

306. Limitation 19[c.ii] recites that “the fluticasone propionate has a mean particle size ranging from about 100 nm to about 10 µm.”

307. Dohil2009 renders obvious Limitation 19[c.ii] for the reasons outlined, *supra*, at Section XI.B.5, regarding Limitation 1[c.ii].

6. Limitation 19[d]

308. Limitation 19[d] recites “wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.”

309. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious Limitation 19[d] for the reasons outlined, *supra*, at Section XI.B.6, regarding Limitation 1[d].

J. Claim 20

310. Claim 20 recites:

Claim 20. The orally disintegrating tablet of claim 19, wherein the microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, or amorphous magnesium aluminum silicate, or a combination thereof, is present in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

311. Claim 20 would have been obvious over Dohil2009 in view of the knowledge of a person of ordinary skill in the art for the reasons outlined, *supra*, at Section XI.H, regarding claim 17.

K. Claim 22

312. Claim 22 recites:

Claim 22. The orally disintegrating tablet of claim 19, wherein fluticasone propionate has a mean particle size of about 4 μm or less.

313. Claim 22 would have been obvious over Dohil2009 in view of the knowledge of a person of ordinary skill in the art for the reasons outlined, *supra*, at Section XI.G, regarding claims 10-11.

L. Claim 29

314. Claim 29 recites:

Claim 29. A method for treating eosinophilic esophagitis in an individual in need thereof, comprising administering to the individual the orally disintegrating tablet of claim 1.

315. Dohil2009 discloses that its ODTs should be administered to treat eosinophilic esophagitis. EX1058 (Dohil2009) ¶[0009] (“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.”), ¶[0019] (“In certain embodiments, the esophageal inflammation is eosinophilic esophagitis.”), ¶[0037] (“The methods of the present invention are useful, for example, for preventing and alleviating the symptoms of *eosinophilic esophagitis*, inflammatory bowel diseases involving the esophagus, Crohn's disease, acute esophageal inflammation secondary to caustic/irritant ingestion,

persistent/recurrent esophageal strictures secondary to caustic/irritant, conditions due to ingestion, systemic diseases, congenital diseases, and post-surgery inflammation.”).

M. Claim 30

316. Claim 30 depends from claim 1. The preamble recites a “method of preparing the orally disintegrating tablet of claim 1.”

317. Dohil2009 renders obvious the ODTs of claim 1 for the reasons outlined, *supra*, in Sections XI.B, regarding claim 1. Dohil2009 renders obvious the recited method for reasons discussed below.

1. Limitation 30(a)

318. Limitation 30(a) recites “micronizing the corticosteroid.”

319. As discussed above for limitation 1[c.ii], Dohil2009 discloses formulating ODTs with “corticosteroid microparticles hav[ing] a diameter less than 10 microns.” EX1058 (Dohil2009) ¶¶[0019], [0022], [0050].

2. Limitation 30[b.i]

320. Limitation 30[b.i] recites “preparing preblend 1 by blending (i) a pharmaceutically acceptable carrier, (ii) corticosteroid or pharmaceutically ester thereof, and (iii) glidant, under conditions suitable for the corticosteroid to be adsorbed onto the pharmaceutically acceptable carrier.”

321. Dohil2009 discloses preparing a preblend for formulating an ODT by blending a corticosteroid with solid excipients to produce granules under conditions where the corticosteroid is adsorbed onto the pharmaceutically acceptable carrier for the reasons outlined, *supra*, in Section XI.B.2, regarding Limitation 1.a. It was common to prepare a preblend to assist with achieving homogeneity of drug dispersal throughout the tablet manufacturing process. For example, Wen teaches that “[a]dsorbing drugs onto carrier particles (Fig. 1) by ordered mixing can be very beneficial in several ways, such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage.” EX1054 (Wen) at 35.

322. A POSA would have understood that glidants are fine powders that improve the flow properties of blended ingredients. EX1041 (Conway) at 241 (“Like lubricants, glidants are fine powders and may be required for tablet compression at high production speeds to improve the flow properties of the material into the die or during initial compression stages.”). Starches and talc are popular glidants. *Id.* at 241 (“Colloidal silica is popular, as are starches and talc.”). Magnesium stearate is an example glidant. *Id.* at 240 (Table 3, stating “Glidants” include “Fine silica, talc, magnesium stearate”). Dohil2009 discloses using starches, talc, and magnesium stearate in its formulations. EX1058 (Dohil2009) ¶¶[0013],

[0071]-[0072] (disclosing starches); ¶[0091] (disclosing starches, talc, and magnesium stearate). A person of ordinary skill in the art would have been motivated to use a glidant in Dohil2009’s preblend to improve the flow properties of the granules.

3. Limitation 30[b.ii]

323. Limitation 30[b.ii] recites “wherein the pharmaceutically acceptable carrier is microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, and amorphous magnesium aluminum silicate.”

324. Dohil2009 discloses this Limitation for the reasons outline, *supra*, in Section XI.C, regarding claim 2.

4. Limitation 30(c)

325. Limitation 30(c) recites “preparing preblend 2 by blending filler, preblend 1 of step (b), disintegrant, and sweetener.”

326. Dohil2009 discloses “adding suitable auxiliaries” to the preblended granules. EX1058 (Dohil2009) ¶[0070] (“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.”).

327. Dohil2009 discloses that suitable auxiliaries include “fillers such as sugars [and] cellulose preparations,” “disintegrating agents,” and “sweeteners.” EX1058 (Dohil2009) ¶[0070] (“Suitable excipients are, in particular, ***fillers such as sugars***, including lactose, sucrose, sucralose (Splenda®, Distributed By: McNeil Nutritionals, LLC, Fort Washington, Pa. 19034-2299), 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). 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. ... Appropriate excipients may also, for example, include those that render the dissolving tablet palatable, ***such as sweeteners.***”), ¶[0075] (“Excipients useful herein include, by way of non-limiting example, mucoadhesive agents, viscosity enhancing agents, binders, ***fillers***, lubricants, solvents, flavoring agents, ***sweeteners***, antioxidants, buffering agents, surfactants, and the like.”), ¶[0080] (“Any of the compositions or formulations described herein optionally comprise one or more agent for increasing the mucoadhesive character of a composition, optionally comprise one or more binder, ***one or more filler***, optionally comprise one or more lubricant, optionally comprise one or more solvent, ***optionally comprise one or more sweetener***, optionally comprise one or more antioxidant, optionally comprise one or

more buffering agent, optionally comprise one or more surfactant, or combinations thereof.”).

328. Dohil2009’s instruction to add such auxiliaries to the preblended granules renders obvious the “preblend 2” recited by Limitation 30(c). Adding filler, disintegrants, and sweetener to a preblend was a common technique to gradually increase the bulk of the blended materials during tablet manufacturing processes. The ordered mixing of ingredients assists with achieving a homogenous dispersal of the ingredients throughout the preblend. For example, Wen teaches that “ordered mixing can be very beneficial in several ways, such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage.” EX1054 (Wen) at 35.

5. Limitation 30(d)

329. Limitation 30(d) recites “preparing a final compressible blend, by blending a disintegrant, lubricant, filler, and preblend 2 of step (c).”

330. As discussed for Limitation 30(c), Dohil2009 discloses “adding suitable auxiliaries” that include a disintegrant, lubricant, and filler before processing the resulting blend into a tablet. EX1058 (Dohil2009) ¶¶[0070], [0075], [0080]. It would have been a matter of routine experimentation and optimization to a person of ordinary skill in the art to follow Dohil2009’s instruction to add suitable

auxiliaries to its mixture of granules to arrive at a blend that renders obvious Limitation 30(d). Adding a disintegrant, lubricant, and filler to a preblend was a common technique to gradually increase the bulk of the blended materials for tablet manufacturing processes. The ordered mixing of ingredients assists with achieving a homogenous dispersal of the ingredients throughout the blend. For example, Wen teaches that “ordered mixing can be very beneficial in several ways, such as facilitating the preparation of master batches, avoiding segregation in stable systems, promoting excellent homogeneity in mixtures, and improving content uniformity of tablets especially at low dosage.” EX1054 (Wen) at 35.

6. Limitation 30(e)

331. Limitation 30(e) recites “compressing the blend of step (d) to form a tablet.”

332. Dohil2009 discloses “processing” a mixture or blend “to obtain tablets.” EX1058 (Dohil2009) ¶[0070] (“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.”). A person of ordinary skill in the art would readily recognize that tablets are advantageously and routinely formed by compressing a blend. EX1041 (Conway) at 238 (“The simplest tablet formulations are uncoated products that are made by direct compression or

compression following wet or dry granulation.”), *id.* at 261 (“Direct compression is, as for normal tablets, the most straightforward process for manufacturing ODTs. Conventional equipment can be used and high doses can be incorporated.”). Dohil2009’s disclosure of “processing” a mixture or blend “to obtain tablets” comprises compressing the blend to form a tablet.

XII. GROUND 3: DOHIL2009 AND VENKATESH IN VIEW OF THE KNOWLEDGE OF THE PERSON OF ORDINARY SKILL IN THE ART

333. This section describes Venkatesh, and then explains how Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art renders obvious claims 1-30 of the ’061 patent.

A. Venkatesh

334. Gopi Venkatesh is listed as a co-inventor on the ’061 patent and on Venkatesh (EX1020).

335. Venkatesh discloses “orally disintegrating tablets made up of rapidly dispersing microgranules.” EX1020 (Venkatesh) ¶[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.*

336. 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].

337. 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, antimigraine agents, proton pump inhibitors, antipsychotic agents, antiemetic agents, antiparkinson agents, and H2 antagonists.

EX1020 (Venkatesh) at ¶[0025].

B. Claim 1

338. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious claim 1. Venkatesh reinforces that a person of ordinary skill in the art would have been motivated to arrive at an ODT encompassed by claim 1 with a reasonable expectation of success for reasons discussed below.

1. Preamble

339. The preamble of claim 1 recites “[a]n orally disintegrating tablet.”

340. Dohil2009 renders the preamble of claim 1 obvious for the reasons outlined, *supra*, at Section XI.B.1 regarding claim 1. Moreover, Venkatesh discloses “a tablet that rapidly disintegrates in the oral cavity.” EX1020 (Venkatesh) at Abstract, ¶[0001].

2. Limitation 1.a

341. Limitation 1.a recites “a topically acting corticosteroid or pharmaceutically acceptable salt or ester thereof, adsorbed onto a pharmaceutically acceptable carrier.”

342. Dohil2009 renders Limitation 1.a obvious for the reasons outlined, *supra*, at Section XI.B.2 regarding Limitation 1.a.

343. Moreover, Venkatesh discloses formulating ODTs where “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,” and that the resulting mixture can be “milled using a size reduction mill.” EX1020 (Venkatesh) ¶[0015].

344. Venkatesh also discloses granulating an active pharmaceutical ingredient with one or more pharmaceutically acceptable diluents. EX1020

(Venkatesh) ¶[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;”).

345. The blending/grinding/milling disclosed by Dohil2009 and Venkatesh renders obvious adsorbing corticosteroid drug particles on the surface of a carrier in an ODT. *Supra* Section XI.B.2.

3. Limitation 1.b

346. Limitation 1.b recites “at least one disintegrant.”

347. Dohil2009 renders Limitation 1.b obvious for the reasons outlined, *supra*, at Section XI.B.3 regarding Limitation 1.b.

348. Venkatesh discloses ODTs comprising a “disintegrant.” EX1020 (Venkatesh) at Abstract (“A tablet that rapidly disintegrates in the oral cavity comprising a compressed blend of rapidly dispersing microgranules prepared by granulating a sugar alcohol or a saccharide or a mixture thereof having an average

particle size less than about 30 microns *and a disintegrant*, and a taste-masked microcapsule containing at least one drug, the microcapsule being prepared by granulating a pharmaceutically acceptable formulation comprising at least one drug in a therapeutically effective amount and at least one polymeric binder that improves resilience of the microgranules, wet milling the granulated mass, and microencapsulating the milled granules to provide microcapsules.”), ¶[0014] (“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.”).

4. Limitation 1[c.i]

349. Limitation 1[c.1] recites “wherein the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is present in an amount ranging from about 0.5 mg to about 10 mg.”

350. Dohil2009 renders Limitation 1[c.i] obvious for the reasons outlined, *supra*, at Section XI.B.4 regarding Limitation 1[c.i].

351. Venkatesh discloses ODTs that weigh 1 gram. EX1020 (Venkatesh) ¶[0037] (“Unit dose was measured on an analytical balance and compressed into

tablet (*weighing approximately one gram* with a disintegration time of 45-60 seconds) at an optimized compression force on a carver press.”), ¶[0045] (“*Unit dose weighing approximately one gram* was measured on an analytical balance and compressed into tablet at an optimized compression force on a carver press.”).

352. Venkatesh discloses ODTs that comprise an active ingredient in “an amount of about 0.01 to 30% by weight.” EX1020 (Venkatesh) ¶[0025] (“The active, in one embodiment has a particle size less than about 50 microns and is present in the tablet in an amount of about 0.01 to 30% by weight.”). Venkatesh’s 1 gram ODT that contains 0.01 to 30% active ingredient by weight discloses between about 0.1 mg and 300 mg of the active ingredient per tablet.

5. Limitation 1[c.ii]

353. Limitation 1[c.ii] recites “[wherein] the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, has a mean particle size of ranging from about 100 nm to about 100 µm.”

354. Dohil2009 renders Limitation 1[c.ii] obvious for the reasons outlined, *supra*, at Section XI.B.5 regarding Limitation 1[c.ii].

355. Venkatesh discloses ODTs comprising an active ingredient with a “particle size of less than about 50 microns.” EX1020 (Venkatesh) ¶[0025] (“The active, in one embodiment has a particle size less than about 50 microns and is present in the tablet in an amount of about 0.01 to 30% by weight.”). This particle

size provides a smooth creamy mouthfeel without grittiness. *Id.* ¶[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.”).

6. Limitation 1[d]

356. Limitation 1[d] recites “wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> method for disintegration time.”

357. Dohil2009 renders Limitation 1[d] obvious for the reasons outlined, *supra*, at Section XI.B.6 regarding Limitation 1[d].

358. Venkatesh discloses ODTs that “rapidly disintegrate (e.g., less than 120 seconds, preferably less than 60 seconds) in the buccal cavity.” EX1020 (Venkatesh) ¶[0016] (“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.*”).

7. Combining Dohil2009 And Venkatesh

359. Dohil2009 and Venkatesh disclose ODTs and methods of making such tablets. As discussed above, they both disclose the same or similar formulation ingredients to arrive at ODTs. A person of ordinary skill in the art would have been motivated to modify Dohil2009’s ODTs in view of Venkatesh’s disclosures because such modifications would have been expected to lead to an ODT with improved “smooth creamy mouthfeel” having “no grittiness.” EX1020 (Venkatesh) ¶¶[0002], [0012] [0018]. The person of ordinary skill in the art had a reasonable expectation of success based on the disclosures within Venkatesh and its teaching that such ODT formulations “don’t require a special pharmaceutical production technique and can be simply and easily produced by a normal equipment.” EX1020 (Venkatesh) ¶[0018].

C. Claim 2

360. Claim 2 recites:

Claim 2. The orally disintegrating tablet of claim 1, wherein the pharmaceutically acceptable carrier is selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, and amorphous magnesium aluminum silicate.

361. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders claim 2 obvious for the reasons outlined, *supra*, at Section XI.C regarding claim 2.

362. Venkatesh discloses that formulating ODTs with microcrystalline cellulose beneficially imparts resilient characteristics to the tablet. EX1020 (Venkatesh) ¶[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;”).

D. Claim 3

363. Claim 3 recites:

Claim 3. The orally disintegrating tablet of claim 2, wherein the pharmaceutically acceptable carrier is silicified microcrystalline cellulose.

364. As discussed for claim 2, a person of ordinary skill in the art would have been motivated to use microcrystalline cellulose in Dohil2009’s ODTs based

on Venkatesh’s disclosure that microcrystalline cellulose imparts resilient characteristics to the resulting tablet. EX1020 (Venkatesh) ¶[0021].

365. A person of ordinary skill in the art would have been motivated to further improve the tablet by modifying the microcrystalline cellulose to be silicified microcrystalline cellulose with an expectation of success based on the general knowledge in the field regarding silicified microcrystalline cellulose as represented by, for example, the Handbook of Pharmaceutical Excipients. That handbook explains that silicified microcrystalline cellulose “has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose.” EX1069 (“Cellulose, Silicified Microcrystalline,” in Handbook Pharma. Excipients) at page 139. The Handbook further explains that “[s]ilicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation,” *id.*, and it “has greater tensile strength and requires lower compression pressures than regular grades of microcrystalline cellulose.” *Id.* at 140. In view of these known advantages of silicified microcrystalline cellulose, a person of ordinary skill in the art would have been motivated to use silicified microcrystalline cellulose in an ODT based on Dohil2009 and Venkatesh.

E. Claim 4

366. Claim 4 recites:

Claim 4. The orally disintegrating tablet of claim 2, wherein said topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, or a pharmaceutically salt or ester thereof.

367. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders claim 4 obvious for the reasons outlined, *supra*, at Section XI.D regarding claim 4.

368. Venkatesh reinforces that the inclusion of any particular corticosteroid in an ODT was obvious because such tablets can be formulated with “any therapeutic active agent indicated for oral administration.” EX1020 (Venkatesh) ¶[0025] (“The term ‘drug’, ‘active’ or ‘active pharmaceutical ingredient’ as used herein is meant to include any therapeutic active agent indicated for oral administration.”).

F. Claim 5

369. Claim 5 recites:

Claim 5. The orally disintegrating tablet of claim 4, wherein the topically acting corticosteroid, or pharmaceutically acceptable salt or ester thereof, is present in an amount ranging from about 0.5 mg to about 3 mg.

370. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders claim 5 obvious for the reasons outlined, *supra*, at Section XI.E regarding claim 5.

371. Venkatesh discloses ODTs that weigh 1 gram and comprise an active ingredient in “an amount of about 0.01 to 30% by weight,” which is between about 0.1 mg and 300 mg. EX1020 (Venkatesh) ¶¶[0025], [0037].

G. Claims 6-9

372. Claim 6 recites:

Claim 6. The orally disintegrating tablet of claim 4, wherein said topically acting corticosteroid is fluticasone or an ester thereof.

373. Claim 7 recites:

Claim 7. The orally disintegrating tablet of claim 4, wherein said topically acting corticosteroid is fluticasone propionate.

374. Claim 8 recites:

Claim 8. The orally disintegrating tablet of claim 1, wherein fluticasone propionate is present in an amount of about 3 mg in the orally disintegrating tablet.

375. Claim 9 recites:

Claim 9. The orally disintegrating tablet of claim 1, wherein fluticasone propionate is present in an amount of about 1.5 mg in the orally disintegrating tablet.

376. Dohil2009 and Venkatesh render claims 6-9 obvious for the reasons outlined, *supra*, at Section XI.F regarding claims 6-9.

377. Venkatesh reinforces that the inclusion of any particular corticosteroid in an ODT was obvious because such tablets can be formulated with “any therapeutic

active agent indicated for oral administration.” EX1020 (Venkatesh) ¶[0025].

Venkatesh further reinforces the obviousness of the amounts recited by claims 8-9 by disclosing ODTs that weigh 1 gram and comprise an active ingredient in “an amount of about 0.01 to 30% by weight,” which is between about 0.1 mg and 300 mg. EX1020 (Venkatesh) ¶¶[0025], [0037].

H. Claims 10 and 11

378. Claim 10 recites:

Claim 10. The orally disintegrating tablet of claim 1, wherein the corticosteroid has a mean particle size of ranging from about 100 nm to about 10 μ m.

379. Claim 11 recites:

Claim 11. The orally disintegrating tablet of claim 1, wherein the corticosteroid has a mean particle size ranging from about 100 nm to about 4 μ m.

380. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders claims 10-11 obvious for the reasons outlined, *supra*, at Section XI.G regarding claims 10-11.

381. Venkatesh reinforces the obviousness of claims 10-11 by disclosing ODTs comprising an active ingredient with a “particle size of less than about 50 microns.” EX1020 (Venkatesh) ¶[0025] (“The active, in one embodiment has a

particle size less than about 50 microns and is present in the tablet in an amount of about 0.01 to 30% by weight.”).

I. Claim 12

382. Claim 12 recites:

Claim 12. The orally disintegrating tablet of claim 1, wherein the at least one disintegrant is present in a rapidly dispersing microgranule, which comprises a sugar alcohol, or a saccharide, or a mixture thereof in addition to the at least one disintegrant.

383. Venkatesh discloses ODTs comprising rapidly dispersing microgranules prepared by granulating a sugar alcohol or a saccharide or a mixture thereof and a disintegrant. EX1020 (Venkatesh) at Abstract (“A tablet that rapidly disintegrates in the oral cavity comprising a compressed blend of *rapidly dispersing microgranules prepared by granulating a sugar alcohol or a saccharide or a mixture thereof having an average particle size less than about 30 microns and a disintegrant*, and a taste-masked microcapsule containing at least one drug, the microcapsule being prepared by granulating a pharmaceutically acceptable formulation comprising at least one drug in a therapeutically effective amount and at least one polymeric binder that improves resilience of the microgranules, wet milling the granulated mass, and microencapsulating the milled granules to provide microcapsules.”), ¶[0014] (“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.”), ¶[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.”).

384. A person of ordinary skill in the art would have been motivated to formulate Dohil2009’s ODTs with the rapidly dispersing microgranules disclosed in Venkatesh because the rapidly dispersing microgranules (1) facilitate rapid disintegration of the tablet, (2) facilitate formulating active ingredients into taste-masked formulations, and (3) facilitate good mouthfeel. See EX1020 (Venkatesh) ¶¶[0002], [0009], [0015], [0018]. A person of ordinary skill in the art would

reasonably expect to successfully make this combination because Venkatesh provides detailed disclosures regarding the manufacture of its formulations. Indeed, 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) ¶[0018].

J. Claim 13

385. Claim 13 recites:

Claim 13. The orally disintegrating tablet of claim 12, wherein the sugar alcohol or saccharide and the disintegrant are present in a ratio of sugar alcohol or saccharide to disintegrant of from 90:10 to 99:1.

386. As discussed above for claim 12, Venkatesh discloses rapidly dispersing microgranules prepared by granulating a sugar alcohol or a saccharide or a mixture thereof and a disintegrant. EX1020 (Venkatesh) at Abstract, ¶¶[0014], [0018].

387. Example 1 of Venkatesh states that “The dispersible microgranules comprise a sugar alcohol such as mannitol and a disintegrant. 6.65 kg of mannitol with an average particle size of approximately 10 µm (Pearlitol 25 from Roquette, France) was blended with 350 g of crosslinked povidone (Crospovidone XL 10 from ISP) in a high shear granulator (GMX 25 from Vector) and granulated with sufficient amount of purified water (approximately 1.6 kg) and wet milled using Comil (from Quadro) and dried in a fluid bed drier, Glatt GPCG 5.” EX1020 (Venkatesh)

¶[0032]. Crospovidone is a disintegrant. The ratio of 6.65 kg (i.e., 6650 grams) mannitol to 350 grams of crospovidone is a ratio of 95:5. The 95:5 ratio disclosed by Venkatesh falls within the claimed ratio ranging from 90:10 to 99:1.

K. Claim 14

388. Claim 14 recites:

Claim 14. The orally disintegrating tablet of claim 12, wherein the disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, and low-substituted hydroxypropylcellulose.

389. The '061 patent states that crospovidone is “cross-linked PVP [polyvinylpyrrolidone].” EX1001 (the '061 patent) at 9:22-24, 11:22-23.

390. Dohil2009 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.” EX1058 (Dohil2009) ¶[0070].

391. Venkatesh discloses “[a] disintegrant is selected from the group consisting of crospovidone (crosslinked PVP), sodium starch glycolate, crosslinked sodium carboxymethyl cellulose, calcium silicate and low substituted hydroxypropyl cellulose.” EX1020 (Venkatesh) ¶[0029].

L. Claim 15

392. Claim 15 recites:

Claim 15. The orally disintegrating tablet of claim 12, wherein the sugar alcohol or saccharide is selected from the group consisting of sucralose, lactose, sucrose, maltose, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.

393. Dohil discloses budesonide orally disintegrating tablets formulated with mannitol and sorbitol as sugar alcohol excipients. EX1002 (Dohil) ¶[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).”); ¶[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).”). Mannitol was the bulk excipient of choice for ODTs. EX1041 (Conway) at 261 (“*Most commercial ODTs have been developed using mannitol as the bulk excipient of choice* because of its extremely low hygroscopicity, excellent compatibility, good compressibility, better sweetness, and relatively slower dissolution kinetics.”).

394. Venkatesh also discloses that “the 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.” EX1020 (Venkatesh) ¶[0028].

M. Claim 16

395. Claim 16 recites:

Claim 16. The orally disintegrating tablet of claim 12, wherein the rapidly dispersing microgranule has a mean particle size of less than about 300 μm , and the sugar alcohol and/or saccharide has an average particle size of less than about 30 μm .

396. Venkatesh discloses that the rapidly dispersing granules “typically” have an “average particle size of not more than 300 μm .” EX1020 (Venkatesh) ¶[0020]. A small particle size assists with mouthfeel. *Id.* ¶¶[0019], [0009], [0025].

397. Venkatesh discloses “rapidly dispersing microgranules of a disintegrant and sugar alcohol or a saccharide whose average particle size is not more than 30 μm ,” which is advantageous in “effectively taste-mask[ing] by coacervation.” EX1020 (Venkatesh) ¶[0014]; *id.* ¶[0018] (“preferably not more than 20 μm ”), ¶[0028] (“average particle size of not more than about 300 μm ”).

N. Claims 17 and 18

398. Claim 17 recites:

Claim 17. The orally disintegrating tablet of claim 1, wherein the pharmaceutically acceptable carrier is present at an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

399. Claim 18 recites:

Claim 18. The orally disintegrating tablet of claim 1, wherein the total weight of the tablet is in the range of from about 300 to about 900 mg.

400. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders claims 17 and 18 obvious for the reasons outlined, *supra*, at Section XI.H regarding claims 17 and 18.

401. In addition, Venkatesh discloses finished tablets that weigh 1 gram. EX1020 (Venkatesh) ¶¶[0037], [0045]. A POSA would have been motivated to formulate Dohil2009's ODTs to have a total weight falling between about 300-900mg in view of the general knowledge of the person of ordinary skill in the art as reflected in the FDA Guidance on ODTs. The FDA Guidance teaches that ODTs should have a weight of less than 500 mg. EX1005 (FDA Guidance) at 3 ("We generally recommend that the weight of the tablet not exceed 500 mg; however, if a tablet intended for use as an ODT weighs more than 500 mg, its ability to perform effectively as an ODT should be justified based on product performance.").

O. Claim 19

1. Preamble

402. The preamble recites "[a]n orally disintegrating tablet."

403. Dohil2009 and Venkatesh render the preamble of claim 19 obvious for the reasons outlined, *supra*, at Sections XI.B.1 and XII.B.1, regarding the preamble of claim 1.

2. Limitation 19.a

404. Limitation 19.a recites “fluticasone propionate adsorbed onto microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, amorphous magnesium aluminum silicate, or combinations thereof”

405. Dohil2009 and Venkatesh render obvious Limitation 19.a for the reasons outlined, *supra*, at Sections XI.B.2, XI.F, XII.B.2 and XII.G, regarding Limitations 1.a and claims 6 and 7.

3. Limitation 19.b

406. Limitation 19.b recites “at least one disintegrant.”

407. Dohil2009 and Venkatesh render obvious Limitation 19.b for the reasons outlined, *supra*, at Sections XI.B.3 and XII.B.3, regarding Limitation 1.b.

4. Limitation 19[c.i]

408. Limitation 19[c.i] recites “the fluticasone propionate is present in an amount ranging from about 0.5 mg to about 6 mg.”

409. Dohil2009 and Venkatesh render obvious Limitation 19[c.i] for the reasons outlined, *supra*, at Sections XI.B.4 and XII.B.4, regarding Limitation 1[c.i].

5. Limitation 19[c.ii]

410. Limitation 19[c.ii] recites that “the fluticasone propionate has a mean particle size ranging from about 100 nm to about 10 μ m.”

411. Dohil2009 and Venkatesh render obvious Limitation 19[c.ii] for the reasons outlined, *supra*, at Sections XI.B.5 and XII.B.5, regarding Limitation 1[c.ii].

6. Limitation 19[d]

412. Limitation 19[d] recites “wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.”

413. Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art renders obvious Limitation 19[d] for the reasons outlined, *supra*, at Sections XI.B.6 and XII.B.6, regarding Limitation 1[d].

P. Claim 20

414. Claim 20 recites:

Claim 20. The orally disintegrating tablet of claim 19, wherein the microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, or amorphous magnesium aluminum silicate, or a combination thereof, is present in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

415. Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art render obvious Claim 20 for the reasons outlined, *supra*, at Sections XI.H and XII.N, regarding claim 17.

Q. Claim 21

416. Claim 21 recites:

Claim 21. The orally disintegrating tablet of claim 19, comprising silicified microcrystalline cellulose in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.

417. Claim 21 depends from claim 19 and further requires “silicified microcrystalline cellulose in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet.”

418. Dohil2009 in view of Venkatesh renders obvious claim 21 for the same reasons outlined, *supra*, at Sections XI.H, XII.D, and XII.N, regarding claims 3 and 17.

R. Claim 22

419. Claim 22 recites:

Claim 22. The orally disintegrating tablet of claim 19, wherein fluticasone propionate has a mean particle size of about 4 μm or less.

420. Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art render obvious Claim 22 for the reasons outlined, *supra*, at Sections XI.G and XII.H, regarding claims 10-11.

S. Claim 23

421. Claim 23 recites:

Claim 23. The orally disintegrating tablet of claim 21, wherein the disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, and low-substituted hydroxypropylcellulose.

422. The '061 patent states that crospovidone is “cross-linked PVP [polyvinylpyrrolidone].” EX1001 (the '061 patent) at 9:22-24, 11:22-23.

423. Dohil2009 discloses “[i]f desired, *disintegrating agents* may be added, such as the cross-linked polyvinylpyrrolidone.” EX1058 (Dohil2009) ¶[0070].

T. Claim 24

424. Claim 24 recites:

Claim 24. The orally disintegrating tablet of claim 20, wherein the at least one disintegrant is present in a rapidly dispersing microgranule, which comprises a sugar alcohol, or a saccharide, or a mixture thereof in addition to the at least one disintegrant.

425. Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art render obvious Claim 24 for the reasons outlined, *supra*, at Section XII.I, regarding claim 12.

U. Claim 25

426. Claim 25 recites:

Claim 25. The orally disintegrating tablet of claim 24, wherein the sugar alcohol or saccharide and the disintegrant are present in a ratio of sugar alcohol or saccharide to disintegrant of from 90:10 to 99:1.

427. Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art render obvious Claim 25 for the reasons outlined, *supra*, at Section XII.J, regarding claim 13.

V. Claim 26

428. Claim 26 recites:

Claim 26. The orally disintegrating tablet of claim 24, wherein the sugar alcohol or saccharide is selected from the group consisting of sucralose, lactose, sucrose, maltose, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.

429. Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art render obvious Claim 26 for the reasons outlined, *supra*, at Section XII.L, regarding claim 15.

W. Claim 27

430. Claim 27 recites:

Claim 27. The orally disintegrating tablet of claim 24, wherein the rapidly dispersing microgranule has a mean particle size of less than about 300 μm , and the sugar alcohol and/or saccharide has an average particle size of less than about 30 μm .

431. Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art render obvious Claim 27 for the reasons outlined, *supra*, at Section XII.M, regarding claim 16.

X. Claim 28

432. Claim 28 recites:

Claim 28. The orally disintegrating tablet of claim 19, wherein the silicified microcrystalline cellulose is present in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet, fluticasone propionate is present in an amount ranging from about 1 mg to about 3 mg, and fluticasone propionate has a mean particle size ranging from about 100 nm to about 4 μ m.

433. Claim 28 depends from claim 19 and further requires that “the silicified microcrystalline cellulose is present in an amount of about 10% w/w based on the total weight of the orally disintegrating tablet, fluticasone propionate is present in an amount ranging from about 1 mg to about 3 mg, and fluticasone propionate has a mean particle size ranging from about 100 nm to about 4 μ m.”

434. Dohil2009 in view of Venkatesh renders obvious claim 28 for reasons outlined, *supra*, at Sections XI.F-H, XII.D, XII.G-H, XII.N, and XII.Q-R, regarding claims 3, 8-11, 17, and 21-22.

Y. Claim 29

435. Claim 29 recites:

Claim 29. A method for treating eosinophilic esophagitis in an individual in need thereof, comprising administering to the individual the orally disintegrating tablet of claim 1.

436. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious claim 29 for the reasons outlined, *supra*, at Section XI.L regarding claim 29. Venkatesh is consistent with Dohil2009's disclosures by teaching that ODTs comprise "any therapeutic active agent." EX1020 (Venkatesh) ¶[0025].

Z. Claim 30

437. Claim 30 depends from claim 1. The preamble recites a "method of preparing the orally disintegrating tablet of claim 1."

438. Dohil2009 and Venkatesh in view of the knowledge of a person of ordinary skill in the art renders obvious the ODTs of claim 1 for the reasons outlined, *supra*, in Sections XI.B and XII.B, regarding claim 1. Dohil2009 and Venkatesh render obvious the method recited by claim 30 for reasons discussed below.

1. Limitation 30(a)

439. Limitation 30(a) recites "micronizing the corticosteroid."

440. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious Limitation 30(a) for the reasons outlined, *supra*, in Section XI.M.1, regarding Limitation 30(a).

441. Venkatesh discloses formulating orally disintegrating tablets by micronizing or milling the active ingredient particles to reduce particle size to the micron scale. EX1020 (Venkatesh) ¶¶[0015], [0021].

2. Limitation 30[b.i]

442. Limitation 30[b.i] recites “preparing preblend 1 by blending (i) a pharmaceutically acceptable carrier, (ii) corticosteroid or pharmaceutically ester thereof, and (iii) glidant, under conditions suitable for the corticosteroid to be adsorbed onto the pharmaceutically acceptable carrier.”

443. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious Limitation 30[b.i] for the reasons outlined, *supra*, in Section XI.M.2, regarding Limitation 30[b.i].

444. Venkatesh discloses preparing a preblend for formulating an ODT by blending an active ingredient under conditions suitable for the active ingredient to be adsorbed onto the pharmaceutically acceptable carrier for the reasons outlined, *supra*, in Section XII.B.2, regarding Limitation 1.a.

445. A POSA would have understood that glidants are fine powders that improve the flow properties of the blended ingredients. EX1041 (Conway) at 241 (“Like lubricants, glidants are fine powders and may be required for tablet compression at high production speeds to improve the flow properties of the material into the die or during initial compression stages.”). Starches and talc are popular

glidants. *Id.* at 241 (“Colloidal silica is popular, as are starches and talc.”). Magnesium stearate is an example glidant. *Id.* at 240 (Table 3, stating “Glidants” include “Fine silica, talc, magnesium stearate”). Dohil2009 discloses using starches, talc, and magnesium stearate in its formulations. EX1058 (Dohil2009) ¶¶[0013], [0071]-[0072] (disclosing starches); ¶[0091] (disclosing starches, talc, and magnesium stearate). A person of ordinary skill in the art would have been motivated to use a glidant in Dohil2009’s preblend to improve the flow properties of the granules.

3. Limitation 30[b.ii]

446. Limitation 30[b.ii] recites “wherein the pharmaceutically acceptable carrier is microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, and amorphous magnesium aluminum silicate”

447. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious Limitation 30[b.ii] for the reasons outlined, *supra*, in Section XI.M.3, regarding Limitation 30[b.ii].

448. Venkatesh discloses this limitation for the reasons outline, *supra*, in Section XII.C, regarding claim 2.

4. Limitation 30(c)

449. Limitation 30(c) recites “preparing preblend 2 by blending filler, preblend 1 of step (b), disintegrant, and sweetener.”

450. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious Limitation 30(c) for the reasons outlined, *supra*, in Section XI.M.4, regarding Limitation 30(c).

451. Venkatesh discloses mixing and granulating the active ingredient with fillers, disintegrants, and sweeteners to prepare blends. EX1020 (Venkatesh) ¶¶[0018], [0023], [0030].

5. Limitation 30(d)

452. Limitation 30(d) recites “preparing a final compressible blend, by blending a disintegrant, lubricant, filler, and preblend 2 of step (c).”

453. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious Limitation 30(d) for the reasons outlined, *supra*, in Section XI.M.5, regarding Limitation 30(d).

454. Venkatesh discloses mixing and granulating the active ingredient with fillers, disintegrants, and lubricants to prepare blends for tableting. EX1020 (Venkatesh) ¶¶[0002], [0018], [0023], [0030].

6. Limitation 30(e)

455. Limitation 30(e) recites “compressing the blend of step (d) to form a tablet.”

456. Dohil2009 in view of the knowledge of a person of ordinary skill in the art renders obvious Limitation 30(e) for the reasons outlined, *supra*, in Section XI.M.6, regarding Limitation 30(e).

457. Venkatesh discloses compressing blends to form a tablet. EX1020 (Venkatesh) at Abstract, ¶[0002].

XIII. CONCLUSION

458. For the reasons described above, a person of ordinary skill in the art would have found Claims 1-30 of the '061 patent obvious in view of the prior art.

459. 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: 21Oct2024 By: Alan Frank PARR

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