

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. PGR2025-00086

U.S. Patent No. 12,290,598

**DECLARATION OF ALAN F. PARR, PHARM.D, PH.D.,
IN SUPPORT OF PETITION FOR POST GRANT REVIEW OF
U.S. PATENT NO. 12,290,598**

TABLE OF CONTENTS

Page No.

I. BACKGROUND AND QUALIFICATIONS, AND PREVIOUS TESTIMONY	1
A. Background and Qualifications.....	1
B. Compensation.....	5
C. Previous Testimony.....	5
D. Current Testimony.....	6
II. MATERIALS CONSIDERED.....	7
III. LEGAL STANDARDS	7
A. Claim Construction.....	7
B. Written Description.....	8
C. Enablement.....	9
D. Indefiniteness.....	10
E. Anticipation.....	10
F. Obviousness.....	10
IV. THE PERSON OF ORDINARY SKILL IN THE ART	12
V. BACKGROUND REGARDING DR. FALK PHARMA	13
VI. THE '598 PATENT	18
VII. SCOPE AND CONTENT OF THE PRIOR ART	23
A. Orally disintegrating tablets (ODTs).....	23
1. Synonyms for orally disintegrating tablets (ODTs).....	24

TABLE OF CONTENTS
(cont'd)

	Page No.
2. FDA Guidance regarding <i>in vitro</i> testing of ODTs.	26
3. Rapid disintegration/dissolving in saliva can improve patient compliance.....	29
4. Desirability of solid formulations, such as ODTs, for oral administration and delivery.....	32
5. Commercially available ODTs	36
B. Hardness	40
C. Friability	43
D. Budesonide Was A Known Corticosteroid With Desirable Anti-Inflammatory Activity.....	44
E. Fluticasone Was A Known Corticosteroid With Desirable Anti-Inflammatory Activity	56
F. The Prior Art Discloses Budesonide And Fluticasone ODTs	57
1. Grother	58
2. Singh	60
3. Cherukuri	64
VIII. INTRODUCTION TO GROUNDS OF UNPATENTABILITY	65
IX. GROUND 1: LACK OF WRITTEN DESCRIPTION.....	66
X. INTRODUCTION TO GROUNDS 2-3: LACK OF ENABLEMENT	72
XI. GROUND 2: LACK OF ENABLEMENT FOR HARDNESS OF 4-7 N	73

TABLE OF CONTENTS
(cont'd)

	Page No.
A. Quantity of experimentation necessary, and Amount of guidance presented	74
B. Working examples.....	75
C. Nature of the invention.....	75
D. State of the prior art, Relative skill in the art, Predictability of the art	75
E. Breadth of the claims.....	76
F. Conclusion.....	76
XII. GROUND 3: LACK OF ENABLEMENT FOR HARDNESS OF 4-48 N	77
A. State of the prior art.....	78
B. Quantity of experimentation necessary, and Amount of guidance presented	80
C. Working examples.....	80
D. Nature of the invention.....	81
E. The relative skill in the art, and Predictability of the art.....	81
F. Breadth of the claims.....	82
G. Conclusion.....	82
XIII. GROUND 4: INDEFINITENESS	83
XIV. GROUND 5: ANTICIPATION BY PERRETT	84
A. Perrett qualifies prior art	84

TABLE OF CONTENTS
(cont'd)

	Page No.
B. Claim 1	84
1. Preamble.....	85
2. Limitation 1(i).....	86
3. Limitation 1(ii).....	87
4. Limitation 1[iii].....	89
5. Limitation 1[iv].....	89
6. Limitation 1[v].....	90
C. Claims 2 and 3	91
D. Claim 4	92
E. Claims 5-8	93
F. Claim 9	96
G. Claims 10-12	96
H. Claims 13-14	98
I. Claims 15-16	99
J. Claim 17	100
K. Claims 18-19 and 31-32	100
L. Claim 20	102
M. Claims 21, 29-30, and 33	103
N. Claims 22 and 34.....	105
O. Claims 23-27	105

TABLE OF CONTENTS
(cont'd)

	Page No.
P. Claim 28	106
XV. GROUND 6: OBVIOUSNESS OVER PERRETT.....	106
XVI. GROUND 7: DOHIL IN VIEW OF KARARLI, THE FDA GUIDANCE, AND THE USP.....	107
A. Dohil.....	107
B. Kararli.....	108
C. Claim 1	109
1. Preamble.....	109
2. Limitation 1(i).....	111
3. Limitation 1(ii).....	114
4. Limitation 1[iii].....	115
5. Limitation 1[iv].....	117
6. Limitation 1[v].....	121
D. Claims 2-3	126
E. Claim 4	126
F. Claim 9	127
G. Claims 13-14	127
H. Claims 18-19	128
I. Claim 20	130
J. Claim 22	131

TABLE OF CONTENTS
(cont'd)

	Page No.
K. Claims 23-25	131
L. Claims 31-32	131
XVII. GROUND 8: DOHIL IN VIEW OF KARARLI, THE FDA GUIDANCE, THE USP, AND VENKATESH988	132
A. Introduction to Venkatesh988	132
B. Claim 5	132
C. Claims 6-8	135
D. Claims 15-16	136
XVIII. GROUND 9: DOHIL IN VIEW OF KARARLI, THE FDA GUIDANCE, THE USP, AND VENKATESH516	137
A. Venkatesh516	137
B. Claims 26-27	138
C. Claim 28	139
D. Claim 34	140
XIX. GROUND 10: GROTHOR IN VIEW OF KARARLI, THE FDA GUIDANCE, AND THE USP	141
A. Introduction to Grother	141
B. Claim 1	142
1. Preamble	142
2. Limitation 1(i)	145
3. Limitation 1(ii)	150

TABLE OF CONTENTS

(cont'd)

	Page No.
4. Limitation 1[iii].....	152
5. Limitation 1[iv].....	154
6. Limitation 1[v].....	157
C. Claims 2-3	162
D. Claim 4	162
E. Claim 9	162
F. Claim 11	163
G. Claims 13-14	163
H. Claims 18-19	166
I. Claim 20	168
J. Claims 21 and 29.....	169
K. Claim 22	170
L. Claims 23-25	170
M. Claims 31-32	171
XX. GROUND 11: GROTHOR IN VIEW OF KARARLI, THE FDA GUIDANCE, THE USP, AND VENKATESH988	171
A. Claim 5	171
B. Claims 6-8	173
C. Claims 10, 12, and 30.....	174
D. Claims 15-16	175

TABLE OF CONTENTS
(cont'd)

	Page No.
E. Claim 17	176
XXI. GROUND 12: GROTHER IN VIEW OF KARARLI, THE FDA GUIDANCE, THE USP, AND VENKATESH516	177
A. Claims 26-27	177
B. Claim 28	178
C. Claim 33	179
D. Claim 34	179
XXII. CONCLUSION	180

TABLE OF CONTENTS
(cont'd)

Page No.

LIST OF MATERIALS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 12,290,598 to Perrett et al.
1002	U.S. Publication No. 20070111978 to Dohil et al.
1003-1004	RESERVED
1005	“Guidance for Industry: Orally Disintegrating Tablets,” U.S. Food & Drug Administration, Center for Drug Evaluation and Research (CDER), 2008.
1006	RESERVED
1007	“DRAFT Guidance for Industry: Orally Disintegrating Tablets,” U.S. Food & Drug Administration, Center for Drug Evaluation and Research (CDER), 2007.
1008	International Publication No. WO2000044351 to Grother et al.
1009	Svoboda et al., “Oral formulations of budesonide: a novel treatment for inflammatory bowel disease,” <i>Drugs of Today</i> , 44:857-863 (2008) at 857.
1010	Tan et al., “Eosinophilic gastroenteritis treated with non-enteric-coated budesonide tablets,” <i>European Journal of Gastroenterology & Hepatology</i> , 13:425-427 (2001)
1011	Kolkman et al., “Evaluation of oral budesonide in the treatment of active distal ulcerative colitis,” <i>Drugs of Today</i> , 40:589-601 (2004)
1012	Siewert et al., “Eosinophilic gastroenteritis with severe protein-losing enteropathy: Successful treatment with budesonide,” <i>Digestive and Liver Disease</i> , 38:55-59 (2006)

TABLE OF CONTENTS
(*cont'd*)

Page No.

Exhibit No.	Description
1013	Elsing et al., “Budesonide for the treatment of obstructive eosinophilic jejunitis,” Z. Gastroenterology, 45:187-189 (2007).
1014	Aceves et al., “Topical viscous budesonide suspension for treatment of eosinophilic esophagitis,” Journal of Allergy and Clinical Immunology 116:705-706 (2005)
1015	Aceves et al., “Oral Viscous Budesonide: A potential new therapy for eosinophilic esophagitis in children,” American Journal of Gastroenterology, 102:1-9 (2007)
1016	RESERVED
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. (“Venkatesh988”)
1021-1024	RESERVED
1025	Goodman & Gilman’s: The Pharmacological Basis of Therapeutics, 11th edition, eds. Brunton, Lazo, Parker, 2005
1026	Budenofalk® Brochure (2005)
1027	Budenofalk® Advertisement (2007)

TABLE OF CONTENTS
(*cont'd*)

Page No.

Exhibit No.	Description
1028	Dr. Falk Pharma Brochure (2008)
1029	<i>Curriculum Vitae</i> of Alan F. Parr, Pharm.D., Ph.D.
1030-1032	RESERVED
1033	Teitelbaum et al., Eosinophilic esophagitis in children: Immunopathological analysis and response to fluticasone propionate,” <i>Gastroenterology</i> 122:1216-1225 (2002)
1034	Noel et al., “Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis,” <i>Clinical Gastroenterology and Hepatology</i> 2:568-575 (2004)
1035	U.S. Patent No. 7,122,198 to Singh et al.
1036	U.S. Patent No. 7,229,641 Cherukuri et al.
1037-1039	RESERVED
1040	USP Convention 701 Disintegration, Revision Bulletin August 1, 2008
1041	Conway, “Solid dosage forms,” Chapter 4.1 in <i>Pharmaceutical Manufacturing Handbook: Production and Processes</i> , ed. Gad, pages 235-265 (2008)
1042-1046	RESERVED
1047	El-Arini et al., “Evaluation of disintegration testing of different fast dissolving tablets using the texture analyzer,” <i>Pharmaceutical Development & Technology</i> , 7:361-371 (2002)
1048-1063	RESERVED

TABLE OF CONTENTS
(*cont'd*)

Page No.

Exhibit No.	Description
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)
1067-1095	RESERVED
1096	Prosecution history excerpts from U.S. Application No. 17/569,047, which issued as U.S. 12,290,598
1097	U.S. Application No. 17/569,047 as filed on January 5, 2022 (“the ’047 Application”)
1098	U.S. Application No. 16/821,464 as filed on March 17, 2020 (“the ’464 Application”)
1099	U.S. Application No. 15/816,154 as filed on November 17, 2017 (“the ’154 Application”)
1100	U.S. Application No. 15/205,390 as filed on July 8, 2016 (“the ’390 Application”)
1101	U.S. Application No. 14/311,732 as filed on June 23, 2014 (“the ’732 Application”)
1102	U.S. Application No. 12/896,005 as filed on October 1, 2010 (“the ’005 Application”)

TABLE OF CONTENTS
(cont'd)

Page No.

Exhibit No.	Description
1103	U.S. Provisional Application No. 61/247,642 as filed on October 1, 2009 (“the ’642 Application”)
1104	The United States Pharmacopeia, USP 31, 2008 (“USP”)
1105	The European Pharmacopeia, 6.0, 2008
1106	Remington: The science and practice of pharmacy, 20th edition, pages 882-884 (2000).
1107	Lee, “Pharmaceutical Preformulation,” in Pharmaceutical Manufacturing Handbook: Production and Processes, pages 881-931 (2008).
1108	Seitz et al., “Evaluation of the physical properties of compressed tablets I,” Journal of Pharmaceutical Sciences, 54:1353-1357 (1965)
1109	U.S. Patent No. 8,771,729 to Perrett et al.
1110	International Publication No. WO2002015884 to Kararli et al. (“Kararli”)
1111	International Publication No. WO2009006516 to Venkatesh et al. (“Venkatesh516”)
1112	International Publication No. WO2010127345 to Venkatesh et al. (“Venkatesh345”)
1113	International Publication No. WO2010127346 to Venkatesh et al. (“Venkatesh346”)

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 post grant review of U.S. Patent No. 12,290,598 (“the ’598 patent,” EX1001) and requests that the United States Patent and Trademark Office cancel all claims of the ’598 patent as unpatentable. The following discussion and analysis provide my opinions in support of Dr. Falk Pharma’s petition for post grant review.

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

A. Background and Qualifications

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

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

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

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

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

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

7. During my career, I worked on a variety of drug products, including orally disintegrating tablet (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 Testimony

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

- *Dr. Falk Pharma GmbH v. Ellodi Pharmaceuticals LP*, IPR2024-01197, regarding U.S. Patent No. 8,771,729;
- *Dr. Falk Pharma GmbH v. Ellodi Pharmaceuticals LP*, IPR2025-00052, regarding U.S. Patent No. 10,632,069;
- *Dr. Falk Pharma GmbH v. Ellodi Pharmaceuticals LP*, IPR2025-00054, regarding U.S. Patent No. 11,246,828;
- *Dr. Falk Pharma GmbH v. Ellodi Pharmaceuticals LP*, IPR2025-00055, regarding U.S. Patent No. 9,486,407; and
- *Dr. Falk Pharma GmbH v. Ellodi Pharmaceuticals LP*, IPR2025-00056, regarding U.S. Patent No. 11,260,061.

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. Written Description

25. I am informed that under 35 U.S.C. § 112, a patent must, as of its priority date, provide an adequate written description of the invention. I understand that the basic inquiry for written description is whether the specification provides sufficient information for the person of ordinary skill in the art to recognize that the named inventors possessed the full scope of the claimed invention as of the filing date of the patent application. I have been informed that original claims that were filed with a patent application are part of the specification.

26. I understand that in order to satisfy the written description requirement, the patent specification must describe each and every limitation of a patent claim, although the exact words found in the claim need not be used. I understand that a description which merely renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention. For example, I understand this means that Ellodi is not permitted to assert that the lack of written description in the '047 Application regarding a hardness of 4-7 N can be cured by such a hardness being obvious to the person of ordinary skill in the art.

C. Enablement

27. I understand that under 35 U.S.C. § 112, a patent must, as of its priority date, enable a person of ordinary skill in the art to make and use the full scope of the claimed invention without undue experimentation. I understand that the following factors should be considered when determining whether the amount of experimentation required to make and use the full scope of an invention would be undue:

- the breadth of the claims;
- the nature of the invention;
- the state of the prior art;
- the level of one of ordinary skill in the art;
- the level of predictability in the art;

- the amount of direction provided by the inventor;
- the existence of working examples; and
- the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

D. Indefiniteness

28. I understand that a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the claimed invention.

E. Anticipation

29. I understand that a claim would have been “anticipated,” and therefore unpatentable, if each and every limitation of the claim is found either expressly or inherently in a single prior art reference arranged in the same manner as claimed. I further understand that if the prior art discloses a single species falling within a claimed genus, the claim is anticipated.

F. Obviousness

30. 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 and the

prior art are such that 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.

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

32. 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 is 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.

33. 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

34. I understand that unpatentability 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.

35. I understand that January 5, 2022 is the relevant time frame for analyzing the unpatentability of the '598 patent.¹ A person of ordinary skill in the

¹ January 5, 2022 is the filing date of U.S. Application No. 17/569,047, which eventually issued as the '598 patent. *See* EX1001 (the '598 patent) at title page, item

art related to the '598 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.

36. My opinions concerning the unpatentability of the '598 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

37. 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

(22). My opinion on the qualifications of the person of ordinary skill in the art would be the same if the Board were to determine that October 2009 is the relevant time frame for analyzing unpatentability of the '598 patent.

outset, Herbert Falk specialized in research and development in the fields of gastroenterology and hepatology. Guided by the conviction that a specialist working in his or her chosen area will deliver better results, the company went on to develop innovative drugs for the treatment of chronic diseases.”); *id.* at 7 (“1960 Founding of Dr. Falk Pharma in the family pharmacy in Freiburg, Germany.”). Also in 1960, he developed the company’s first hepatological formulation, Hepatofalk®. *Id.* at 7 (“1960 Development of the first hepatological preparation, Hepatofalk®”). In 1974, Dr. Falk Pharma launched the world’s first bile acid preparation for the dissolution of gallstones, Chenofalk®. *Id.* (“1974. . . Chenofalk® is launched as the world’s first ever bile acid preparation for the dissolution of gallstones.”). In 1979, Dr. Falk Pharma released Ursofalk® for the treatment of cholestatic liver disease. *Id.* (“1979 Launch of Ursofalk®, which is still the leading medication for the treatment of cholestatic liver diseases.”). In 1984, Dr. Falk Pharma released Salofalk® for treating inflammatory bowel diseases. *Id.* (“1984 Salofalk® becomes the world’s first mesalazine preparation for treating inflammatory bowel diseases; it still leads the market in many countries.”). In 1998, Dr. Falk Pharma released Budenofalk®, which contains budesonide as a topical corticosteroid for the treatment of inflammatory bowel diseases.” *Id.* (“1998 Launch of Budenofalk®, a topical corticosteroid for the treatment of inflammatory bowel diseases.”).

38. 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.”).

39. 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.”).

40. 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.

41. 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).

42. 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 '598 PATENT

43. The '598 patent (EX1001) is directed to “Orally administered corticosteroid compositions.” EX1001 (“the '598 patent”) at Title.

44. The '598 patent has 34 claims, with claim 1 being the sole independent claim. *See* EX1001 (“the '598 patent”) at Claims.

45. Independent claim 1 of the '598 patent recites:

Claim 1. An orally disintegrating tablet comprising:

(i) about 0.5 mg to about 6 mg of a corticosteroid selected from fluticasone propionate or budesonide; and

(ii) at least one disintegrant;

[iii] wherein upon administration a therapeutically effective amount of the corticosteroid is deposited topically in the esophagus,

[iv] wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test, and

[v] wherein the orally disintegrating tablet has a hardness of 4-48 N or a friability of not more than 1%.²

EX1001 (“the '598 patent”) at Claim 1.

46. Claims 2-34 depend, either directly or indirectly through another claim, from independent claim 1. These claims are reproduced below.

² Bracketed labels “[iii]”, “[iv]” and “[v]” have been added for convenient referencing to the claim limitations.

Claim 2. The orally disintegrating tablet of claim 1, comprising about 0.5 mg to about 2 mg of the corticosteroid.

Claim 3. The orally disintegrating tablet of claim 1, comprising about 3 mg of the corticosteroid.

Claim 4. The orally disintegrating tablet of claim 1, comprising a sugar alcohol and/or saccharide.

Claim 5. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid and at least one excipient, and the rapidly dispersing granules comprise the disintegrant and a sugar alcohol and/or saccharide.

Claim 6. The orally disintegrating tablet of claim 5, wherein the rapidly dispersing granules have an average particle size of less than about 300 μm , and each of the disintegrant and sugar alcohol and/or saccharide have an average particle size of about 1-30 μm .

Claim 7. The orally disintegrating tablet of claim 5, wherein the drug particles have an average particle size of about 100-400 μm .

Claim 8. The orally disintegrating tablet of claim 5, wherein the drug particles have an average particle size of about 100-400 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm , and each of the disintegrant and sugar alcohol and/or saccharide have an average particle size of about 1-30 μm .

Claim 9. The orally disintegrating tablet of claim 2, wherein the corticosteroid is budesonide.

Claim 10. The orally disintegrating tablet of claim 5, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 11. The orally disintegrating tablet of claim 3, wherein the corticosteroid is fluticasone propionate.

Claim 12. The orally disintegrating tablet of claim 8, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 13. The orally disintegrating tablet of claim 1, wherein the disintegrant is crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, low-substituted hydroxylpropylcellulose, mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, or combinations thereof.

Claim 14. The orally disintegrating tablet of claim 13, wherein the disintegrant is crospovidone.

Claim 15. The orally disintegrating tablet of claim 5, wherein the sugar alcohol and/or saccharide is mannitol, sorbitol, xylitol, maltitol, arabitol, ribitol, dulcitol, iditol, isomalt, lactitol, erythritol, lactose, sucrose, maltose, or combinations thereof.

Claim 16. The orally disintegrating tablet of claim 15, wherein the sugar alcohol is mannitol.

Claim 17. The orally disintegrating tablet of claim 5, wherein the ratio of disintegrant to sugar alcohol, saccharide or mixture thereof in the rapidly dispersing microgranules ranges from about 90/10 to about 99/01.

Claim 18. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet disintegrates within 60 seconds when tested in simulated saliva fluid using the USP <701> Disintegration Test.

Claim 19. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.

Claim 20. A method for treating eosinophilic esophagitis comprising administering to a patient in need thereof the orally disintegrating tablet according to claim 1.

Claim 21. The method of claim 20, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 22. The method of claim 20, wherein the orally disintegrating tablet comprises about 0.5 mg to about 2 mg of budesonide.

Claim 23. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a hardness of 4-48 N.

Claim 24. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a friability of not more than 1%.

Claim 25. The orally disintegrating tablet of claim 1, wherein the orally disintegrating has a hardness of 4-48 N and a friability of not more than 1%.

Claim 26. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a friability of not more than 0.6%.

Claim 27. The orally disintegrating tablet of claim 25, wherein the orally disintegrating tablet has a friability of not more than 0.6%.

Claim 28. The orally disintegrating tablet of claim 27, wherein the orally disintegrating tablet has a thickness of 2-2.8 mm.

Claim 29. The orally disintegrating tablet of claim 14, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 30. The orally disintegrating tablet of claim 16, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 31. The method of claim 20, wherein the orally disintegrating tablet disintegrates within 60 seconds when tested in simulated saliva fluid using the USP <701> Disintegration Test.

Claim 32. The method of claim 20, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.

Claim 33. The orally disintegrating tablet of claim 28, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 34. The orally disintegrating tablet of claim 28, wherein the orally disintegrating tablet comprises about 0.5 mg to about 2 mg of budesonide.

VII. SCOPE AND CONTENT OF THE PRIOR ART

47. 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. I begin with a discussion of orally disintegrating tablets (ODTs), followed by tablet hardness and friability, and the use of budesonide and fluticasone in tablets (including ODTs).

A. Orally disintegrating tablets (ODTs)

48. ODTs were well-known in the prior art by October of 2009. 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.

49. Several review articles describing ODTs were available by 2009. These reviews included:

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

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

50. In the following paragraphs, I discuss (1) synonyms used to refer to ODTs in the prior art literature, (2) the FDA Guidance regarding ODTs, (3) the desirability of ODTs to dissolve rapidly in saliva for the improvement of patient compliance with taking medication, (4) the desirability of ODTs for oral administration and delivery of active ingredients, and (5) commercially available ODTs that existed by the year 2009.

1. Synonyms for orally disintegrating tablets (ODTs)

51. 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 (MDDDS).” *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.”).

52. 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 system, 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’.”).

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

2. FDA Guidance regarding *in vitro* testing of ODTs.

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

55. 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.

56. 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.

57. 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 31, NF 26, Volume 1 (2008) (EX1104, hereinafter “USP”) at 266-67. The USP <701> Disintegration Test involves immersing a tablet into an immersion fluid at $37\pm 2^{\circ}\text{C}$ for a specified amount of time to observe if the tablet disintegrates. *Id.* at 266-267. “For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent.” *Id.* at 266. “Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core.” *Id.* A person of ordinary skill in the art would have been familiar with the USP <701> Disintegration Test in 2009.

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

58. 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 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 2 (“A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”).

59. 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 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.”).

60. 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.

61. 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.

62. 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.

4. Desirability of solid formulations, such as ODTs, for oral administration and delivery

63. Solid orally disintegrating pharmaceutical compositions were known to have several desirable properties as compared with liquid compositions. For example, Shulka teaches that a solid mouth-dissolving tablet formulation can provide "[c]onvenience of administration and accurate dosing as compared to liquid formulations." EX1019 (Shulka) at 311. Dosing accuracy can be improved when a solid pharmaceutical composition is formulated for a single-unit dose as compared with a liquid formulation that is not premeasured (for example, inaccurate measuring during dosing or reconstitution of liquid formulations can lead to under- or over-dosing). Also, solid pharmaceutical compositions can provide greater pharmaceutical stability, improved transportability, be easier to manufacture, be easier to store, lower the risk of contamination, and be lower in cost than a liquid

formulation. For example, Fu teaches that “FDTs [fast disintegrating tablets] have all the advantages of solid dosage forms, such as good stability, accurate dosing, easy manufacturing, small packaging size, and easy handling by patients.” EX1018 (Fu) at 434. As another example, some liquid formulations require refrigeration during storage, which is less commonly required for solid formulations.

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

The oral cavity, however, does not have the same problems as 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 nasal mucosa. Another major advantage of oral mucosa as a site for drug delivery is that it facilitates removal in cases of emergency.

EX1017 (Danckwerts) at 172.

65. Another advantage of solid orally disintegrating pharmaceutical compositions is that they can promote absorption of active ingredients through the oral mucosa, pharynx, and esophagus. For example, Shulka teaches that a solid mouth-dissolving tablet formulation can provide “[m]ore rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid

onset of action.” EX1019 (Shukla) at 311. Danckwerts teaches that transmucosal delivery through oral or esophageal mucosa can beneficially “avoid long-term parenteral therapy.” EX1017 (Danckwerts) at 172 (“To avoid long-term parenteral therapy, current research is focused mainly on the transmucosal and transdermal routes of drug delivery. Transmucosal routes available include the nasal passage, oral mucosa, vaginal passage or rectal mucosa as sites for possible drug application.”). Fu similarly discloses that bioavailability can be increased with 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.”).

66. 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.

5. Commercially available ODTs

67. By 2009, 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.

68. 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.”).

69. 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.”).

70. “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’.”).

71. 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.*

72. 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).

73. 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).” EX1018 (Fu) at 469. Table 2 from Fu is reproduced below:

Dr. Falk Pharma GMBH v. Ellodi Pharmaceuticals LP
PGR Petition – U.S. Patent No. 12,290,598

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	Quicksolv®
Propulsid® Quicksolv®	Cisapride monohydrate	Gastrointestinal prokinetic agent	Janssen	
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).”).

74. 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.”).

75. 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 such compositions. For example, Danckwerts concludes that “[t]here is no doubt that the need for these systems is real, and many classes of drugs could benefit from this noninvasive type of delivery.” EX1017 (Danckwerts) at 183. Fu similarly explains that “[t]he popularity and usefulness of the formulation resulted in development of several FDT [fast disintegrating tablet] technologies” and they have “received ever-increasing demand” and “the field has become a rapidly growing area in the pharmaceutical industry.” EX1018 (Fu) at Abstract (“Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry.”). Fu concludes by stating that, “[c]onsidering the many benefits of FDTs [fast disintegrating tablets], it is only a matter of time until a majority of oral formulations are prepared in FDT forms.” EX1018 (Fu) at 469.

B. Hardness

76. One test of the mechanical integrity of a tablet evaluates the force required to cause it to break in a specific plane. This breaking force is commonly

called “hardness.” EX1104 (USP <1217>) at 676 (“Another measure of the mechanical integrity of tablets is their *breaking force*, which is the force required to cause them to fail (i.e., break) in a specific plane.”); *id.* at 676 (“The breaking force of tablets is commonly called *hardness* in the pharmaceutical literature; however, the use of this term is misleading. In material science, the term *hardness* refers to the resistance of a surface to penetration or indentation by a small probe. The term *crushing strength* is also frequently used to describe the resistance of tablets to the application of a compressive load. Although this term describes the true nature of the test more accurately than does *hardness*, it implies that tablets are physically crushed during the test, which often is not the case. Moreover, the term *strength* in this application can be questioned, because in the physical sciences that term is often used to describe a stress (e.g., tensile strength). Thus, the term *breaking force* is preferred and will be used in the present discussion.”).

77. There are several methods to quantitate tablet hardness. For example, the “Monsanto” hardness tester “measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet.” EX1106 (Remingtons) at 883. This tester was later distributed by Stokes Div, and is therefore also known as the “Stokes” tester. *Id.* The “Strong-Cobb” hardness tester uses a manually operated air pump to increase the pressure at which a plunger is forced against a tablet placed on an anvil. *Id.* Another instrument is the “Pfizer” hardness

tester, which operates on the mechanistic principles of pliers. *Id.* The most common instrument used today is the “Schleuniger” apparatus, which is electrically operated. *Id.* However, there are other hardness testers manufactured by Key, Van Kel, Erweka, and others. *Id.*; *see also* EX1107 (Lee) at 928 (“Devices to test tablet hardness include the Monsanto tester, the Strong-Cobb tester, the Pfizer tester, the Erweka tester, and the Schleuniger tester.”); EX1104 (USP <1217>) at 676-678 (describing hardness testing according to the U.S. Pharmacopeia); EX1105 (European Pharmacopeia) at 2.9.8 (describing hardness testing according to the European Pharmacopeia).

78. The hardness values measured by different testers often differ significantly from each other. *See, e.g.,* EX1106 (Remingtons) at 883 (“The hardness values of the Stokes and Strong-Cobb instruments are not equivalent. Values obtained with the Strong-Cobb tester have been found to be 1.6 times those of the Stokes tester.”). “The rate at which the compressive load is applied can significantly affect results, because time-dependent processes may be involved in tablet failure.” EX1104 (USP <2017>) at 677. “The different methods may lead to numerically different results for a particular tablet sample, requiring that the rate of load application or displacement must be specified along with the determined breaking force.” *Id.* Even automated testers “do not produce uniform results for the same tablet due to operator variation, lack of calibration, spring fatigue, and

manufacturer variation.” EX1107 (Lee) at 928. The literature warns that tablet hardness values that are reported without describing the method used to measure the hardness should be seriously questioned. *See* EX1108 (Seitz) at 1357 (“Because the physical properties of compressed tablets are dependent on so many factors, it is apparent that reporting tablet hardness values without citing the compressing conditions, moisture content, granule distribution, etc., should be seriously questioned. In describing the physical properties of compressed tablets, the test results should be stated in terms of what they specifically measure.”).

C. Friability

79. Another test of the mechanical integrity of tablets requires tumbling the tablets in a rotating cylinder to determine their ability to resist chipping and surface abrasion. EX1104 (USP <1217>) at 676 (“One commonly employed test of the ability of tablets to withstand mechanical stresses determines their resistance to chipping and surface abrasion by tumbling them in a rotating cylinder. The percentage weight loss after tumbling is referred to as the *friability* of the tablets. Standardized methods and equipment for testing friability have been provided in general chapter *Tablet Friability* <1216>.”).

80. The percentage weight loss after tumbling is referred to as the “friability” of the tablets. EX1104 (USP <1217>) at 676 (“The percentage weight loss after tumbling is referred to as the *friability* of the tablets.”).

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

81. Glucocorticoids were known to be an important class of drugs that were used by clinicians due to their anti-inflammatory and immunosuppressive effects by October of 2009. *See* EX1025 (Goodman & Gillman’s) at 1014-1015 (“The effects of glucocorticoids on the inflammatory response are numerous and well documented.”). Budesonide was known to be a potent anti-inflammatory glucocorticoid before October of 2009. For example, Goodman & Gillman’s explains that budesonide “is proposed to deliver adequate steroid therapy to a specific portion of inflamed gut while minimizing systemic side effects owing to extensive first pass hepatic metabolism to inactive derivatives. Topical therapy (e.g., enemas and suppositories) also is effective in treating colitis limited to the left side of the colon. While the topical potency of budesonide is 200 times higher than 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.

82. 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.”).³ Tan teaches that eosinophilic gastroenteritis is a disorder “that can involve any area of the gastrointestinal tract.” *Id.* at page 425 (“Eosinophilic gastroenteritis is an uncommon disorder that may involve any area of the gastrointestinal tract. Treatment consists of corticosteroids, which induce a quick response.”). A person of ordinary skill in the art would have considered budesonide to be a desirable drug for treating inflammation of the gastrointestinal tract.

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

³ All emphasis supplied unless otherwise noted.

diseases.”). Budenofalk[®] was also used for treatment of patients suffering from Crohn’s Disease. *Id.* at 9.

84. 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.”).

85. 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.”).

86. 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.”).

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

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

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

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

88. 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.”).

89. 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**

Related U.S. Application Data

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

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Publication Classification

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

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(57) **ABSTRACT**

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.

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

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

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

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

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

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

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

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

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

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

EX1002 (Dohil) at ¶[0006].

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

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

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

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

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

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

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

96. 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 orally disintegrating tablet (ODT) containing budesonide based on at least, for example, Dohil and additional references discussed herein.

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

97. Fluticasone propionate was known to be a desirable anti-inflammatory corticosteroid in the prior art. 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.

98. 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.

99. 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.

100. 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.

F. The Prior Art Discloses Budesonide And Fluticasone ODTs

101. The formulation of budesonide and/or fluticasone as an ODT was disclosed in at least the following four references by October of 2009:

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

Dohil's disclosure of ODTs containing budesonide has been discussed above. Each of Grother, Singh, and Cherukuri are discussed below.

1. Grother

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

cavity.”). Grother catalogues over 15 different fast dispersing dosage forms described in the prior art. *See id.* at 6:7-12:6, 13:22-14:6.

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

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

at least one active ingredient;

at least one modified starch at a concentration of from 20 to 90% by weight of said solid dosage form; and

at least one matrix forming agent;

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

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

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

a) at least one active ingredient;

b) at least one modified starch at a concentration of from 20 to 90% by weight; and

c) at least one matrix forming agent;

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

EX1008 (Grother) at page 34, claim 1.

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

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

EX1008 (Grother) at 18:15-18.

2. Singh

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

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

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

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

EX1035 (Singh) at 1:18-38.

106. Singh discloses that “fast dissolving tablets disperse readily to form a suspension or solution of the drug after mixing with the saliva, which is easily swallowed by the patients.” EX1035 (Singh) at 1:20-23. The fast dissolving tablet preferably “dissolves or disperses in the mouth within one minute.” *Id.* at 2:29-36 (“It is the object of the present invention to provide a pharmaceutical preparation in

solid dosage form, preferably in the form of a compressed tablet which when orally administered dissolves or disperses in the mouth within one minute requiring very little amount of body fluids like saliva to produce a smooth solution or suspension of the drug with a prolonged sweet taste.”). Singh discloses a fast dissolving pharmaceutical composition in solid dosage form with a prolonged sweet taste comprising a pharmaceutically active reagent, a water soluble sugar, a non-sugar sweetener in a fast release form, and a non-sugar sweetener in a mucoadhesive slow release form as follows:

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

- a) at least one pharmaceutically active agent in an amount of from 0.1 to 99 weight % of the total dosage form;
- b) at least one water soluble sugar in an amount of from 5 to 95 weight % of the total dosage form;
- c) at least one non-sugar sweetener in a fast release form in an amount of from 0 to 10 weight % of the total dosage form; and
- d) at least one non-sugar sweetener in a mucoadhesive slow release form in an amount of from 0.5 to 20 weight % of the total dosage form.

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

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

GLUCOCORTICOID such as 21-Acetoxyprogesterone, Alclometasone, Algestone, Amcinonide, Beclomethasone, Betamethasone, Betamethasone dipropionate, **Budesonide**, Chloroprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Corticosterone, Cortisone, Cortivazol, Deflazacort, Desonide, Desoximetasone, Dexamethasone, Diflorasone, Diflucortolone, Difluprednate[,] Enoxolone, Fluazacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone acetonide, Fluocinonide, Fluocortin butyl, Fluocortolone, Fluorometholone, Fluperolone acetate, Fluprednidene acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halometasone, Halopredone Acetate, Hydrocotramate, Hydrocortisone, Hydrocortisone Acetate, Hydrocortisone phosphate, Hydrocortisone 21-Sodium Succinate, Hydrocortisone Tebutate, Mazipredone, Medrysone, Meprednisone, Methylprednisolone, Mometasone furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 21-Diethylaminoacetate, Prednisolone Sodium Succinate, Prednisolone Sodium Phosphate, Prednisolone Sodium 21-mSulfobenzoate, Prednisolone 21-Stearoylglycolate, Prednisolone Tebutate[,] Prednisolone 21-Trimethylacetate, Prednisone, Prednival,

Prednylidene, Prednylidene 21-Diethylaminoacetate, Tixocortal,
Triamcinolone, Triamcinolone acetonide, Triamcinolone benetonide,
Triamcinolone hexacetonide,

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

3. Cherukuri

108. Cherukuri discloses “a rapid-melt composition for delivery of prophylactic and therapeutic active materials,” that preferably is “a gastrointestinal therapeutic.” EX1036 (Cherukuri) at 1:15-20 (“The present invention relates to a rapid-melt composition for delivery of prophylactic and therapeutic active materials to a mammal, methods of making the same, and methods of using the same.”); *id.* 9:6-10 (“Still yet another preferred active material used in the composition of the present inventive matter is a gastrointestinal therapeutic. Gastrointestinal therapeutics are used to treat gastritis, nausea and vomiting, gastroesophageal reflux disease, colitis, Crohn's disease and diarrhea.”). Cherukuri discloses that “it is an important aspect of the present inventive subject matter that the compressed rapid-melt product disintegrates quickly in the mouth of the mammal,” preferably “in less than 20 seconds of being placed in the mammal’s mouth.” *Id.* at 14:50-56 (“As stated previously, it is an important aspect of the present inventive subject matter that the compressed rapid-melt product disintegrates quickly in the mouth of the mammal. Preferably, the compressed rapid-melt product disintegrates in less than 20 seconds of being placed in the mammal's mouth, preferably within 10 seconds,

and more preferably within 7 seconds.”). Cherukuri discloses that several classes of active ingredients can be formulated in the rapid-melt composition. *See id.* at 7:51-11:52. Cherukuri discloses the use of budesonide and fluticasone in the rapid-melt composition. *Id.* at 9:64-67 (“Other drugs which can also be used are fluticasone propionate, mometasone furoate, epinastine, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and azelastine.”).

109. Based on the foregoing, each of Dohil, Grother, Singh, and Cherukuri, disclose the formulation of budesonide and/or fluticasone in an ODT.

VIII. INTRODUCTION TO GROUNDS OF UNPATENTABILITY

110. This section provides a summary of the unpatentability grounds for claims 1-34 that are addressed in this declaration.

Ground	Reference(s)	Challenged Claims
1	Lack of Written Description	1-34
2	Lack of Enablement for hardness of 4-7 N	1-34
3	Lack of Enablement for hardness of 4-48 N	1-34
4	Indefiniteness	1-34
5	Anticipation by Perrett	1-34
6	Obviousness over Perrett	1-34
7	Obviousness over Dohil in view of Kararli, the FDA Guidance, and the USP	1-4, 9, 13-14, 18-20, 22-25, 31-32

Ground	Reference(s)	Challenged Claims
8	Obviousness over Dohil in view of Kararli, the FDA Guidance, and the USP, and Venkatesh988	5-8, 15-16
9	Obviousness over Dohil in view of Kararli, the FDA Guidance, the USP, and Venkatesh516	26-28, 34
10	Obviousness over Grother in view of Kararli, the FDA Guidance, and the USP	1-4, 9, 11, 13-14, 18-25, 29, 31- 32
11	Obviousness over Grother, Kararli, the FDA Guidance, the USP, and Venkatesh988	5-8, 10, 12, 15-17, 30
12	Obviousness over Grother, Kararli, the FDA Guidance, the USP, and Venkatesh516	26-28, 33-34

IX. GROUND 1: LACK OF WRITTEN DESCRIPTION

111. This section explains why claims 1-34 do not have written description support in U.S. Application No. 17,569,047 (“the ’047 application, EX1097), which is the application that eventually issued as the ’598 patent.

112. The ’047 application does not describe the invention with all its claimed limitations because claim limitation 1[v], which recites a “hardness of 4-48 N,” is not disclosed in the ’047 application. I understand that the Patent Owner first introduced this hardness limitation during examination via an Amendment on July 23, 2024, as follows:

Dr. Falk Pharma GMBH v. Ellodi Pharmaceuticals LP
PGR Petition – U.S. Patent No. 12,290,598

1. (Currently Amended) An orally disintegrating tablet comprising:
 - (i) about ~~[[1]]~~0.5 mg to about 6 mg of ~~fluticasone propionate~~ a corticosteroid selected from fluticasone propionate or budesonide; and
 - (ii) at least one disintegrant;wherein upon administration a therapeutically effective amount of ~~fluticasone propionate~~ the corticosteroid is deposited topically in the ~~upper gastrointestinal tract~~ esophagus, and wherein the orally ~~dispersing~~ disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test, and
wherein the orally disintegrating tablet has a hardness of 4-48 N or a friability of not more than 1%.

EX1096 (Prosecution History of '598 Patent) at 151 (yellow highlighting added).

113. I understand that the Patent Owner asserted that support for this limitation is found in the '047 application as it was originally filed with the USPTO, including Example 1, and further asserted that no new matter was added by the amendment as follows:

Dr. Falk Pharma GMBH v. Ellodi Pharmaceuticals LP
PGR Petition – U.S. Patent No. 12,290,598

In this response, claims 1-3, 5, 8-12, 18, 19, and 28 have been amended. Claim 1 has been amended to recite “about 0.5 mg to about 6 mg of a corticosteroid selected from fluticasone propionate or budesonide”, to further specify that a therapeutically effective amount of the corticosteroid is deposited topically in the “esophagus”, and to state that the “orally disintegrating tablet has a hardness of 4-48 N or a friability of not more than 1%.” Conforming amendments were made the dependent claims. Support for the claim amendments can be found throughout the application as originally filed, for example in Example 1.

Claim 8 has been amended to correct a clerical error.

Claims 1, 18, 19, and 28 have been amended to refer to an “orally disintegrating tablet.”

Claim 28 has been further amended to refer to “a patient.”

Claims 31-44 are newly added and recite additional properties of the orally disintegrating tablet.

No new matter is added. Entry of the present amendments is therefore respectfully requested.

The above-noted amendments are supported by the application as originally filed and do not introduce any new matter. The amendments are made without prejudice to the prosecution of any canceled or amended subject matter in one or more continuing application(s).

EX1096 (Prosecution History of '598 Patent) at 156 (yellow highlighting added). I disagree with the Patent Owner's assertions for reasons discussed below.

114. First, I note that Example 1 from the '047 application does not disclose a hardness range between 4-48 N. The '047 application only describes a hardness range from 8-48 N:

TABLE:

Tablet Parameters		
Parameter	Target	Range
Weight (mg)	100	95-105
Thickness (mm)	2.4	2.0-2.8
Hardness (N)	28	8-48
Friability	NMT 0.6%	1.0%
Weight 10 tablets (g)	1.0g	0.96-1.04

EX1097 (the '047 application) ¶[0092] (annotated). There is no description of an ODT having a hardness other than 8-48 N in the '047 application (EX1097). There is no description of an ODT having a hardness of less than 8 N anywhere in the '047 application (EX1097). For example, there is no description of an ODT having a hardness of 7 N, 6 N, 5 N, or 4 N.

115. The '047 application (EX1097) also does not provide any guidance to the skilled person as to how to make ODTs having a hardness of less than 8 N. The lack of any disclosure of the lower end of the claimed hardness range and lack of information to guide a person of ordinary skill in the art to arrive at the low end of the claimed range does not allow a person of ordinary skill in the art to recognize that the named inventors invented an ODT having the claimed range of hardness.

116. The '598 patent claims priority to six patent applications as follows:

Related U.S. Application Data

- (60) Continuation of application No. 16/821,464, filed on Mar. 17, 2020, now Pat. No. 11,246,828, which is a continuation of application No. 15/816,154, filed on Nov. 17, 2017, now Pat. No. 10,632,069, which is a continuation of application No. 15/205,390, filed on Jul. 8, 2016, now Pat. No. 9,849,084, which is a continuation of application No. 14/311,732, filed on Jun. 23, 2014, now Pat. No. 9,387,167, which is a division of application No. 12/896,005, filed on Oct. 1, 2010, now Pat. No. 8,771,729.
- (60) Provisional application No. 61/247,642, filed on Oct. 1, 2009.

EX1001 (the '598 patent) at cover page (yellow highlighting added). I have reviewed each of the six priority applications: (1) 16/821,464 (EX1098), (2) 15/816,154 (EX1099), (3) 15/205,390 (EX1100), (4) 14/311,732 (EX1101), (5) 12/896,005 (EX1102), and (6) 61/247,642 (EX1103). The contents of '047 application (EX1097) is not materially different from the six priority applications with respect to hardness. None of the six priority applications provide any additional details regarding hardness than is provided by the '047 application (EX1097). In particular, none of the six priority applications disclose an ODT having a hardness of less than 8 N or provide any guidance to the skilled person to consider manufacturing an ODT having a hardness of less than 8 N.

117. I understand that claim 1 of the '598 patent is not entitled to claim priority to any of the six earlier filed applications because none of the six earlier filed

applications disclose a hardness of less than 8 N. I have been informed that the earliest effective filing date for the challenged claims is therefore January 5, 2022 (which is the filing date of the application that issued as the '598 patent):

(12) United States Patent Perrett et al.	(10) Patent No.: US 12,290,598 B2 (45) Date of Patent: *May 6, 2025
(54) ORALLY ADMINISTERED CORTICOSTEROID COMPOSITIONS	(56) References Cited
(71) Applicant: Ellodi Pharmaceuticals, L.P. , Lawrenceville, NJ (US) (72) Inventors: Stephen Perrett , Princeton, NJ (US); Fredric Jay Cohen , Washington Crossing, PA (US); Gopi M. Venkatesh , Vandalia, OH (US) (73) Assignee: Ellodi Pharmaceuticals, L.P. , Lawrenceville, NJ (US) (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 205 days. This patent is subject to a terminal dis- claimer.	U.S. PATENT DOCUMENTS 3,705,172 A 12/1972 Buchel et al. 3,929,768 A 12/1975 Brattsand et al. 4,080,448 A 3/1978 Mirsky 4,335,121 A 6/1982 Philipps et al. 4,363,806 A 12/1982 Bergstrom et al. 4,472,393 A 9/1984 Shapiro 4,985,418 A 1/1991 Richards 5,135,740 A 8/1992 Katz et al. 5,252,337 A 10/1993 Powell 5,278,175 A 1/1994 Ray et al. 5,403,893 A 4/1995 Tanaka et al. 5,446,070 A 8/1995 Mantelle 5,482,934 A 1/1996 Calatayud et al. 5,639,475 A 6/1997 Bettman et al. 5,776,433 A 7/1998 Tzou et al. 5,863,910 A 1/1999 Bolonick et al. 6,139,865 A 10/2000 Friend et al. 6,171,617 B1 1/2001 Gruber 6,316,027 B1 11/2001 Johnson et al. 6,495,160 B2 12/2002 Esposito et al. 6,534,549 B1 3/2003 Newton et al. 6,596,298 B2 7/2003 Leung et al. 6,596,311 B1 7/2003 Dobetti 6,740,332 B2 5/2004 Zyck et al. 7,033,606 B1 4/2006 Besse et al. 7,122,198 B1 10/2006 Singh et al.
(21) Appl. No.: 17/569,047	
(22) Filed: Jan. 5, 2022	
(65) Prior Publication Data US 2022/0339098 A1 Oct. 27, 2022	

EX1001 (the '598 patent) at cover page (yellow highlighting added).

118. In sum, the '047 application (which issued as the '598 patent) does not demonstrate that the named inventors had possession of ODTs having a hardness below 8 N. A person of ordinary skill in the art would not have comprehended ODTs having such a hardness based on the lack of written description provided in the '047 application regarding hardness. As a result, the '047 application does not provide

written description support for an ODT having a hardness within the range of 4-7 N, which is covered by the “hardness of 4-48 N” recited by claim limitation 1[v]. I understand that the lack of written description support for limitation 1[v] renders the entirety of claim 1 unpatentable for lack of written description support.

119. I understand that each of claims 2-34 depends directly or indirectly from claim 1. None of the dependent claims further limit the claimed hardness range of 4-48 N. I understand that claims 2-34 therefore lack written description support for the same reasons that claim 1 lacks written description support.

X. INTRODUCTION TO GROUNDS 2-3: LACK OF ENABLEMENT

120. Claims 1-34 are not enabled for at least two reasons, which are discussed in Grounds 2 and 3. Ground 2 explains that the specification of the '047 application fails to enable the lower end of the claimed hardness range of 4-7 N.⁴ Ground 3 demonstrates that the specification of the '047 application fails to enable the full scope of the entirety of the claimed hardness range of 4-48 N.

⁴ I understand that the specification of the '047 application is the same as the specification of the '598 patent. *See* EX1097 (the '047 application) ¶¶[0001]-[0098]; EX1001 (the '598 patent) at 1:7-18:47. I refer to the specification of the '047 application for the convenience of continuity in citing to EX1097 in this declaration.

XI. GROUND 2: LACK OF ENABLEMENT FOR HARDNESS OF 4-7 N

121. Claim limitation 1[v] recites an ODT having “a hardness of 4-48 N.” However, as discussed above for Ground 1, the ’047 application does not provide any written description support for an ODT having a hardness at the lower end of the claimed range of 4-7 N. The ’047 application also does not provide any guidance that would enable a person of ordinary skill in the art to arrive at an ODT having a hardness of 4-7 N.

122. In view of ’047 application’s lack of disclosure for the lower end of the claimed hardness range, a person of ordinary skill in the art would not have been able to practice the lower end of the claimed hardness range without undue experimentation. I understand that the Patent Owner cannot rely on general knowledge in the art to fill in the missing disclosure from its application. Without the ’047 application providing guidance that would have led the person of ordinary skill in the art to envision an ODT having the lower end of the claimed hardness range of 4-7 N, the person of ordinary skill in the art is likewise without the information needed to make an ODT having a hardness of 4-7 N.

123. I understand that lack of enablement is demonstrated by analyzing the following factors:

- the quantity of experimentation needed to make or use the invention based on the content of the disclosure;

- the amount of guidance presented by the inventor;
- the existence of working examples;
- the nature of the invention;
- the state of the prior art;
- the level of one of ordinary skill in the art;
- the level of predictability in the art; and
- the breadth of the claims.

I analyze these factors below.

A. Quantity of experimentation necessary, and Amount of guidance presented

124. As discussed above for Ground 1, the specification of the '047 application lacks any disclosure of an ODT having a hardness of 4-7 N. The specification of the '047 application lacks any description of an ODT having a hardness value other than 8-48 N. Thus, a person of ordinary skill in the art would have to make and test numerous ODT formulations to empirically determine the design parameters that would lead to the claimed ODTs having a hardness of 4-7 N without any guidance to do so from the '047 application. In view of a person of ordinary skill in the art having to experiment empirically to determine how to arrive at the claimed ODT having a hardness of 4-7 N and the lack of any discussion or guidance in the '047 Application regarding how to arrive at an ODT having a

hardness of 4-7 N, the amount of experimentation would be undue. These factors favor non-enablement.

B. Working examples

125. The specification of the '047 application does not provide a working example of an ODT having a hardness of 4-7 N. This factor favors non-enablement.

C. Nature of the invention

126. Claim 1 recites an ODT having a hardness between 4-48 N. As discussed above under the heading “Quantity of experimentation necessary, and Amount of guidance presented,” a person of ordinary skill in the art would have to determine empirically how to arrive at the claimed ODT having a hardness of 4-7 N due to the lack of guidance in the specification of the '047 application. This factor favors non-enablement.

D. State of the prior art, Relative skill in the art, Predictability of the art

127. As discussed above in the section entitled “The Person of Ordinary Skill in the Art,” the person of ordinary skill in the art would have a Ph.D., another advanced degree, or its equivalent and 2-3 years of experience in formulation development; or a lesser degree, with at least five or more years of experience in formulation development. This is a relatively high degree of skill as compared to a layperson. However, the lack of guidance in the specification of the '047 application regarding an ODT having a hardness of 4-7 N would not allow the person of ordinary

skill in the art to practice the full scope of the claimed ODTs. As discussed above under the heading “Quantity of experimentation necessary, and Amount of guidance presented,” a person of ordinary skill in the art would have to experiment to empirically determine how to arrive at the claimed ODT having a hardness of 4-7 N because the specification of the ’047 application does not provide any guidance for arriving at the claimed ODT. This empirical process introduces unpredictability for the person of ordinary skill in the art in arriving at an ODT having a hardness of 4-7 N. Taken together, these factors favor non-enablement.

E. Breadth of the claims

128. Claim 1 cover a hardness with a breadth ranging from 4-48 N. The specification of the ’047 application, however, lacks any disclosure of an ODT having a hardness of 4-7 N. This factor favors non-enablement.

F. Conclusion

129. I understand that determining whether the amount of experimentation required to practice the claimed invention is “undue” is reached by weighing all the above noted factors. Based on the foregoing analyses of the above factors, and my opinion that each factor favors non-enablement, a person of ordinary skill in the art would require undue experimentation to make the claimed ODT having a hardness of 4-7 N. I understand that claim 1 is therefore unpatentable for lack of enablement.

130. I understand that each of claims 2-34 depends directly or indirectly from claim 1. None of the dependent claims further limit the claimed hardness range of 4-48 N. I understand that claims 2-34 therefore are also not enabled.

**XII. GROUND 3: LACK OF ENABLEMENT FOR
HARDNESS OF 4-48 N**

131. Claim limitation 1[v] recites an ODT having “a hardness of 4-48 N.” Ground 3 demonstrates that the specification of the ’047 application fails to enable the full scope of the claimed hardness range of 4-48 N.

132. As mentioned above for Ground 2, I understand that lack of enablement is demonstrated by analyzing the following factors:

- the quantity of experimentation needed to make or use the invention based on the content of the disclosure;
- the amount of guidance presented by the inventor;
- the existence of working examples;
- the nature of the invention;
- the state of the prior art;
- the level of one of ordinary skill in the art;
- the level of predictability in the art; and
- the breadth of the claims.

I understand that the factors can be analyzed in any order. I analyze each of these factors below.

A. State of the prior art

133. The prior art shows that there were numerous ways to quantify hardness, and that the different quantification methods provide significantly different hardness values. Prior art hardness testers were manufactured by Monsanto/Stokes, Strong-Cobb, Pfizer, Schleuniger, Key, Van Kel, Erweka, and others. EX1106 (Remingtons) at 883 (describing Monsanto/Stokes, Strong-Cobb, and Schleuniger testers and stating “[m]anufacturers, such as Key, Van Kel, Erweka, and others, make similar hardness testers”).

134. The different hardness testers used different methods to apply compressive forces to tablets. For example, the Monsanto/Stokes hardness tester “measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet.” EX1106 (Remingtons) at 883. The “Strong-Cobb” hardness tester uses a manually operated air pump to increase the pressure at which a plunger is forced against a tablet placed on an anvil. *Id.* The “Pfizer” hardness tester operates on mechanistic principles of pliers. *Id.* The Schleuniger apparatus is electrically operated. *Id.*

135. Hardness values measured by different methods often differed significantly from each other. *See, e.g.,* EX1106 (Remingtons) at 883 (“The hardness values of the Stokes and Strong-Cobb instruments are not equivalent. Values obtained with the Strong-Cobb tester have been found to be 1.6 times those

of the Stokes tester.”). “The rate at which the compressive load is applied can significantly affect results, because time-dependent processes may be involved in tablet failure.” EX1104 (USP <2017>) at 677. Even automated testers “do not produce uniform results for the same tablet due to operator variation, lack of calibration, spring fatigue, and manufacturer variation.” EX1107 (Lee) at 928. The literature warns that tablet hardness values reported without describing the method used to measure hardness should be seriously questioned. *See* EX1108 (Seitz) at 1357 (“Because the physical properties of compressed tablets are dependent on so many factors, it is apparent that reporting tablet hardness values without citing the compressing conditions, moisture content, granule distribution, etc., should be seriously questioned. In describing the physical properties of compressed tablets, the test results should be stated in terms of what they specifically measure.”).

136. Here, the specification of the '047 application does not inform the person of ordinary skill in the art how hardness should be measured. This is a significant issue in view of the numerous different methods for quantifying hardness that were known in the prior art to provide significantly different hardness values. The specification of the '047 application does not provide any guidance to the person of ordinary skill in the art as to how hardness should be determined in making ODTs having the full scope of the claimed hardness of 4-48 N. This factor favors non-enablement.

B. Quantity of experimentation necessary, and Amount of guidance presented

137. The specification of the '047 application provides one example that resulted in tablets having a hardness of 8-48 N. *See* EX1097 ('047 application) at ¶¶[0091]-[0094] (Example 1); *see also* EX1001 (the '598 patent) at 17:40-18:23 (Example 1). The specification of the '047 application lacks any description of an ODT having a hardness value other than 8-48 N.

138. The specification of the '047 application, however, does not specify how the hardness values were measured for the tablets in Example 1. The specification does not provide any guidance how hardness values should be determined. This is a significant omission in view of the numerous hardness testing methods in the prior art that were known to significantly impact the quantification of hardness for the reasons discussed in the above section of Ground 3 entitled “State of the prior art.” A person of ordinary skill in the art would have to experiment with numerous formulations and testing parameters to empirically arrive at ODTs having the full scope of the claimed range of hardness across 4-48 N. This amount of experimentation would be undue in view of the lack of guidance in the specification as to how hardness should be determined. These factors favor non-enablement.

C. Working examples

139. The specification of the '047 application provides one example that resulted in tablets having a hardness of 8-48 N. *See* EX1097 ('047 application) at

¶¶[0091]-[0094] (Example 1); *see also* EX1001 (the '598 patent) at 17:40-18:23 (Example 1). There is no explanation or guidance how the hardness values in the example were measured. Having a single example that lacks explanation or guidance as to how hardness should be measured favors non-enablement.

D. Nature of the invention

140. Claim 1 recites an ODT having a hardness between 4-48 N. As discussed above in the section of Ground 3 entitled “Quantity of experimentation necessary, and Amount of guidance presented,” a person of ordinary skill in the art would have to determine empirically how to arrive at an ODT having the full scope of the claimed hardness range. This factor favors non-enablement.

E. The relative skill in the art, and Predictability of the art

141. As discussed above in the section entitled “The Person of Ordinary Skill in the Art,” the person of ordinary skill in the art would have a Ph.D., another advanced degree, or its equivalent and 2-3 years of experience in formulation development; or a lesser degree, with at least five or more years of experience in formulation development. This is a relatively high degree of skill as compared to a layperson. However, the lack of guidance in the specification of the '047 application regarding how to measure the claimed hardness would not allow the person of ordinary skill in the art to practice the full scope of the claimed invention. As discussed above in the Ground 3 section entitled “Quantity of experimentation

necessary, and Amount of guidance presented,” a person of ordinary skill in the art would have to experiment to empirically determine how to arrive at the full scope of the claimed ODT due to the lack of guidance in the specification on how hardness should be measured. This empirical process introduces unpredictability for the person of ordinary skill in the art in arriving at an ODT having the full scope of the claimed hardness of 4-48 N. Taken together, these factors favor non-enablement.

F. Breadth of the claims

142. Claim 1 broadly covers an ODT having a hardness ranging from 4-48 N. The specification of the '047 application, however, provides no guidance how to measure the claimed hardness. As discussed above in the Ground 3 section entitled “State of the prior art,” different methods of measuring hardness lead to significantly different results. The specification does not allow the person of ordinary skill in the art to practice the full scope of the claimed ODT for at least this reason.

G. Conclusion

143. Based on the foregoing analysis, a person of ordinary skill in the art would require undue experimentation to make an ODT having a hardness across the full scope of the claimed range of 4-48 N. I understand that claim 1 is therefore unpatentable for lack of enablement.

144. I understand that each of claims 2-34 depends directly or indirectly from claim 1. None of the dependent claims further limit the claimed hardness range of 4-48 N. I understand that claims 2-34 therefore are also not enabled.

XIII. GROUND 4: INDEFINITENESS

145. Claim limitation 1[v] recites an ODT having “a hardness of 4-48 N.” Ground 4 demonstrates that the person of ordinary skill in the art cannot be reasonably certain of the scope of the claimed ODT because there are multiple different ways to measure hardnesses. I understand that this means that claim 1 is unpatentable for being indefinite.

146. As discussed above in the Ground 3 section entitled “State of the prior art,” there were numerous ways to quantify hardness in the prior art, and the different quantification methods provide significantly different hardness values. For example, prior art hardness testers were manufactured by Monsanto/Stokes, Strong-Cobb, Pfizer, Schleuniger, Key, Van Kel, Erweka, and others. EX1106 (Remingtons) at 883. These testers use several different methods to apply compressive forces to tablets. *Id.* Hardness values measured by different methods often differ significantly from each other. *Id.*

147. The '598 patent does not discuss any of the different methods for measuring hardness. The '598 patent does not provide any guidance as to how hardness should be ascertained. Thus, the person of ordinary skill in the art would

not be reasonably certain of the scope of the claimed ODT because there are multiple different ways to measure hardnesses that yield significantly different results, and it is unclear which method of measurement is required by the claims.

148. Based on the foregoing, a person of ordinary skill in the art is not reasonably able to discern the scope of the ODT recited by claim 1 because there were multiple ways to measure ODT hardness, which produce significantly different hardness values. I understand that claim 1 is therefore unpatentable for being indefinite.

149. I understand that each of claims 2-34 depends directly or indirectly from claim 1. None of the dependent claims clarify how hardness is measured. I understand that claims 2-34 therefore are also unpatentable for being indefinite.

XIV. GROUND 5: ANTICIPATION BY PERRETT

A. Perrett qualifies prior art

150. I understand that Perrett (EX1109) qualifies as prior art to the '598 patent because the '598 patent is not entitled to claim priority to any of the applications filed before its effective filing date of January 5, 2022.

151. Below, I provide an analysis as to why Perrett anticipates claims 1-34 of the '598 patent.

B. Claim 1

152. Claim 1 recites:

Claim 1. An orally disintegrating tablet comprising:

- (i) about 0.5 mg to about 6 mg of a corticosteroid selected from fluticasone propionate or budesonide; and
- (ii) at least one disintegrant;
- [iii] wherein upon administration a therapeutically effective amount of the corticosteroid is deposited topically in the esophagus,
- [iv] wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test, and
- [v] wherein the orally disintegrating tablet has a hardness of 4-48 N or a friability of not more than 1%.

EX1001 (“the ’598 patent”) at Claim 1.

153. I explain how Perrett discloses each limitation of claim 1 below.

1. Preamble

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

155. Perrett discloses an ODT. For example, Example 1 of Perrett discloses a tablet that is “tested in the USP <701> Disintegration test and disintegrates in about 60 seconds of less.” EX1109 (Perrett) at 17:61-62; *see also id.* at 15:1-3 (“In one embodiment, the solid pharmaceutical composition of the present invention is in the form of ***an orally disintegrating tablet (ODT)***.”); *id.* at 5:16-20 (“Solid pharmaceutical compositions of the present invention can include, for example, ***an ODT (as described herein)***, a wafer, a film, or other solid dosage form which disintegrates or dissolves rapidly in the mouth to form a solution or dispersion of a corticosteroid, which can readily be swallowed.”); *id.* at 19:31-33 (“The

pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of an *orally disintegrating tablet (ODT)*.”).

2. Limitation 1(i)

156. Limitation 1(i) recites “about 0.5 mg to 6 mg of a corticosteroid selected from fluticasone propionate or budesonide.”

157. Perrett Example 1 discloses an ODT having 4 mg of fluticasone propionate. *See* EX1109 (Perrett) at 17:18-19 (Example 1 disclosing a tablet with a target weight of 100 mg (*see* Table) and containing “fluticasone propionate (4% w/w).”). The Table from Perrett’s Example 1 is reproduced below with yellow highlighting added to show the target weight of 100 mg:

TABLE		
Tablet Parameters		
Parameter	Target	Range
Weight (mg)	100	95-105
Thickness (mm)	2.4	2.0-2.8
Hardness (N)	28	8-48
Friability	NMT 0.6%	1.0%
Weight 10 tablets (g)	1.0 g	0.96-1.04

A 100 mg tablet that is 4% by weight fluticasone propionate contains 4 mg of fluticasone propionate.

158. Perrett elsewhere discloses fluticasone and budesonide for use in its ODT. *See, e.g.,* EX1109 (Perrett) at 7:6-10 (“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.”).

159. Perrett discloses dosages of fluticasone and budesonide between 0.5-6 mg. *See, e.g.*, EX1109 (Perrett) at 7:25-49 (“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***. ... 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***.”); *id.* at 20:16-22 (““An orally disintegrating tablet ***comprising less than or equal to about 20 mg of a corticosteroid selected from the group consisting of fluticasone, budesonide***, mometasone, and salts, solvates and esters thereof, and at least one disintegrant, wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.”).

3. Limitation 1(ii)

160. Limitation 1(ii) recites “at least one disintegrant.”

161. Perrett Example 1 discloses a tablet containing “Crospovidone XL-10 (4.8% w/w).” EX1109 (Perrett) at 17:14-15. Perrett discloses that crospovidone is

a disintegrant. *See, e.g., id.* at 8:49-55 (“A non-limiting list of *suitable disintegrants for the rapidly dispersing micro granules includes crospovidone* (crosslinked PVP), sodium starch glycolate, cross-linked sodium carboxymethylcellulose, calcium silicate, and low substituted hydroxypropyl cellulose. The amount of disintegrant in the ODT is typically in the range of about 1 % to about 10% by weight.”).

162. Perrett elsewhere discloses an ODT comprising a disintegrant. *See, e.g.,* EX1109 (Perrett) at 12:66-13:1 (“The solid pharmaceutical compositions of the present invention may include rapidly dispersing granules *comprising a disintegrant* and a sugar alcohol and/or a saccharide.”); *id.* at 15:3-7 (“In one such embodiment the ODT comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid, and *the rapidly dispersing granules comprise a disintegrant* and a sugar alcohol and/or saccharide.”); *id.* at 18:58-63 (“The solid pharmaceutical composition of claim 1, *wherein the at least one disintegrant is selected from the group consisting of crospovidone*, sodium starch glycolate, crosslinked carboxymethyl cellulose, low-substituted hydroxylpropylcellulose, mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.”).

4. Limitation 1[iii]

163. Limitation 1[iii] recites “wherein upon administration a therapeutically effective amount of the corticosteroid is deposited topically in the esophagus.”

164. Perrett discloses topical administration to the esophagus. *See, e.g.*, EX1109 (Perrett) at 3:59-62 (“The solid and liquid pharmaceutical compositions of the present invention are suitable for topical administration of a corticosteroid to the gastrointestinal tract, for example the upper gastrointestinal tract *such as the esophagus.*”); *id.* at 4:3-6 (“The pharmaceutical compositions of the present invention are suitable for treating inflammatory conditions of the gastrointestinal tract, for example inflammatory conditions of the upper gastrointestinal tract *such as the esophagus.*”); *id.* at 5:11-15 (“In still other embodiments, the solid or liquid pharmaceutical compositions of the present invention topically provide a therapeutically effective amount of a corticosteroid to inflamed tissues of the gastrointestinal tract, after oral administration to a patient in need thereof”); *id.* at 20:42-45 (“The solid composition of claim 35, wherein the upper gastrointestinal tract is further *defined as the esophagus.*”).

5. Limitation 1[iv]

165. Limitation 1[iv] recites “wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.”

166. Perrett Example 1 discloses an ODT that is “tested in the USP <701> Disintegration test and disintegrate in about 60 seconds or less.” EX1109 (Perrett) at 17:61-62.

167. Elsewhere it discloses an ODT that meets limitation 1[iv]. *See, e.g. id.* at 4:66-5:5 (“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 when tested using the USP <701> Disintegration Test.***”); *id.* at 10:4-11 (“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.***”).

6. Limitation 1[v]

168. Limitation 1[v] recites “wherein the orally disintegrating tablet has a hardness of 4-48 N or a friability of not more than 1%.”

169. Perrett Example 1 discloses an ODT having a hardness of 8-48 N and friability of 1% in the Table, which is reproduced below with yellow highlighting added:

TABLE		
Tablet Parameters		
Parameter	Target	Range
Weight (mg)	100	95-105
Thickness (mm)	2.4	2.0-2.8
Hardness (N)	28	8-48
Friability	NMT 0.6%	1.0%
Weight 10 tablets (g)	1.0 g	0.96-1.04

EX1109 (Perrett) at 17:46-55.

170. I have been informed that Perrett's disclosure of an ODT having a hardness of 8-48 N is sufficient for anticipation because it falls within the claimed hardness range of 4-48 N. In contrast, Perrett's disclosure of an ODT having hardness of between 8-48 N is insufficient to enable a person of ordinary skill in the art to make and use the full scope of the claimed range for the reasons discussed above in Grounds 2 and 3 of my declaration. I understand that the test for anticipation and enablement are different.

C. Claims 2 and 3

171. Claims 2-3 recite:

Claim 2. The orally disintegrating tablet of claim 1, comprising about 0.5 mg to about 2 mg of the corticosteroid.

172. Claim 3 recites:

Claim 3. The orally disintegrating tablet of claim 1, comprising about 3 mg of the corticosteroid.

173. Perrett discloses an ODT having the claimed amounts of corticosteroid for reasons discussed above regarding limitation 1(i). *See also* EX1109 (Perrett) at 7:25-49, 10:16-21 (disclosing the claimed amounts of corticosteroid).

D. Claim 4

174. Claim 4 recites:

Claim 4. The orally disintegrating tablet of claim 1, comprising a sugar alcohol and/or saccharide.

175. Perrett discloses ODTs comprising a sugar alcohol and/or saccharide. EX1109 (Perrett) at 2:49-56 (“ODT compositions of the present invention can contain pharmaceutically acceptable ingredients which swell, dissolve or otherwise facilitating the disintegration or dissolution of the ODT composition. Such ingredients can include pharmaceutical a disintegrant, ***a sugar alcohol, a saccharide, or a mixture thereof***, a water-soluble binder, a meltable solid (e.g., a wax), which can release the corticosteroid upon entering the stomach, etc.”); *id.* at 8:56-62 (“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. The amount of sugar alcohol and/or saccharide in the ODT ranges from about 30% to about 70% by weight.”).

E. Claims 5-8

176. Claims 5-8 recite:

Claim 5. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid and at least one excipient, and the rapidly dispersing granules comprise the disintegrant and a sugar alcohol and/or saccharide.

Claim 6. The orally disintegrating tablet of claim 5, wherein the rapidly dispersing granules have an average particle size of less than about 300 μm , and each of the disintegrant and sugar alcohol and/or saccharide have an average particle size of about 1-30 μm .

Claim 7. The orally disintegrating tablet of claim 5, wherein the drug particles have an average particle size of about 100-400 μm .

Claim 8. The orally disintegrating tablet of claim 5, wherein the drug particles have an average particle size of about 100-400 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm , and each of the disintegrant and sugar alcohol and/or saccharide have an average particle size of about 1-30 μm .

177. Perrett discloses an ODT that anticipates claims 5-8. Perrett Example 1 discloses an ODT with rapidly dispersing granules. *See* EX1109 (Perrett) at 17:21-27 (“a granulation bowl...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.”).

178. With respect to claim 5, Perrett discloses the claimed drug particles and rapidly dispersing granules. *See* EX1109 (Perrett) at 15:3-7 (“In one such embodiment *the ODT comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid, and the rapidly dispersing granules comprise a disintegrant and a sugar alcohol and/or saccharide.*”); *see also id.* at 15:14-16, 20:4-7.

179. With respect to claims 6-8, Perrett discloses an ODT having the claimed particle sizes. *See* EX1109 (Perrett) at 16:44-17:2 (“In another embodiment, a method of manufacturing orally disintegrating tablets of the present invention comprises the following steps:...b) taste-masking core particles by microencapsulation, e.g. by solvent coacervation or fluid-bed coating with a water-insoluble polymer such as ethylcellulose, or with a mixture of a water-insoluble functional polymer and a water-soluble/gastrosoluble pore-former (e.g., ethylcellulose and sodium chloride or calcium carbonate at a ratio ranging from about 50/50 to 95/5) to produce pleasant-tasting microparticles with a desired particle size distribution (e.g., an average particle size of *not more than about 400*

μm, or an average particle size of not more than about 300 μm); 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..."); *id.* at 8:1-11 ("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 micro granules having an average particle size of not more than about 300 μm (e.g., about 175-300 μm)*"); *id.* at 19:39-44 ("The pharmaceutical composition of claim 16, wherein the drug particles have an average particle size of less than about 400 μm, the rapidly dispersing granules have an average particle size of less than about 300 μm, and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 μm."); *id.* at 15:28-31 ("One embodiment of a method for producing pleasant tasting corticosteroid ODT formulations of the present invention, comprising corticosteroid microparticles with a mean particle size of about 100-400 μm, comprises."); *id.* at 15:47-54 ("In another embodiment, the method for preparing ODT formulations of the present invention comprising corticosteroid microparticles

with a mean particle size of about 100-400 μm can also include a unit process for taste-masking the corticosteroid-containing particles (e.g., corticosteroid crystals, corticosteroid-containing granules or drug-layered beads) by coacervation or fluid bed coating prior to blending and compression into ODT tablets.”); *id.* at 8:22-31, 11:40-52.

F. Claim 9

180. Claim 9 recites:

Claim 9. The orally disintegrating tablet of claim 2, wherein the corticosteroid is budesonide.

181. Perrett discloses an ODT containing budesonide. *See* EX1109 (Perrett) at 7:6-13 (“Suitable corticosteroids which may be included in the pharmaceutical compositions of the present invention include **budesonide**, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, tixocortol and salts, solvates, and esters thereof...In other embodiments, the compositions of the present invention comprise budesonide.”); *id.* at 18:35-39 (“The solid pharmaceutical composition of claim 1, wherein said corticosteroid is selected from the group consisting of **budesonide**, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, and salts, solvates and esters thereof.”).

G. Claims 10-12

182. Claims 10-12 recite:

Claim 10. The orally disintegrating tablet of claim 5, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 11. The orally disintegrating tablet of claim 3, wherein the corticosteroid is fluticasone propionate.

Claim 12. The orally disintegrating tablet of claim 8, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

183. Perrett discloses an ODT having fluticasone. *See* EX1109 (Perrett) at 7:6-11 (“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.***”);

184. Perrett discloses an ODT having the claimed amounts of fluticasone. *See* EX1109 (Perrett) at 7:25-49 (“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 0.5mg, 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 there between.”); *id.* at 10:16-21; *id.* at 20:23-24 (“The orally disintegrating tablet of claim 27, that comprises from ***about 2 to about 10 mg fluticasone***.”).

H. Claims 13-14

185. Claims 13-14 recite:

Claim 13. The orally disintegrating tablet of claim 1, wherein the disintegrant is crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, low-substituted hydroxylpropylcellulose, mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, or combinations thereof.

Claim 14. The orally disintegrating tablet of claim 13, wherein the disintegrant is crospovidone.

186. Example 1 of Perrett discloses an ODT containing crospovidone. *See* EX1109 (Perrett) at 17:14-15 (disclosing an ODT containing “***Crospovidone XL-10*** (4.8% w/w).”); *see also id.* at 8:49-55 (“A non-limiting list of suitable disintegrants for the rapidly dispersing micro granules includes ***crospovidone*** (crosslinked PVP), sodium starch glycolate, cross-linked sodium carboxymethylcellulose, calcium

silicate, and low substituted hydroxypropyl cellulose. The amount of disintegrant in the ODT is typically in the range of about 1 % to about 10% by weight.”); *id.* at 13:59-66 (“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).”).

I. Claims 15-16

187. Claims 15-16 recite:

Claim 15. The orally disintegrating tablet of claim 5, wherein the sugar alcohol and/or saccharide is mannitol, sorbitol, xylitol, maltitol, arabitol, ribitol, dulcitol, iditol, isomalt, lactitol, erythritol, lactose, sucrose, maltose, or combinations thereof.

Claim 16. The orally disintegrating tablet of claim 15, wherein the sugar alcohol is mannitol.

188. Example 1 of Perrett discloses an ODT containing mannitol, which is a sugar alcohol. *See* EX1109 (Perrett) at 17:14-15 (disclosing an ODT containing “***Mannitol*** 25 (91.2% w/w)”); *id.* at 8:56-60 (“A non-limiting list of suitable ***sugar alcohols*** includes ***mannitol***, sorbitol, xylitol, maltitol, arabitol, ribitol, dulcitol, iditol, isomalt, lactitol, erythritol and combinations thereof.”); *id.* at 13:59-66 (“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).”).

J. Claim 17

189. Claim 17 recites:

Claim 17. The orally disintegrating tablet of claim 5, wherein the ratio of disintegrant to sugar alcohol, saccharide or mixture thereof in the rapidly dispersing microgranules ranges from about 90/10 to about 99/01.

190. Perrett discloses the claimed ratio. *See* EX1109 (Perrett) at 8:12-17 (“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 15 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.”).

K. Claims 18-19 and 31-32

191. Claims 18-19 and 31-32 recite:

Claim 18. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet disintegrates within 60 seconds when tested in simulated saliva fluid using the USP <701> Disintegration Test.

Claim 19. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.

Claim 31. The method of claim 20, wherein the orally disintegrating tablet disintegrates within 60 seconds when tested in simulated saliva fluid using the USP <701> Disintegration Test.

Claim 32. The method of claim 20, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.

192. Example 1 of Perrett discloses ODTs that are “tested in the USP <701> Disintegration test and disintegrate in about 60 seconds or less.” EX1109 (Perrett) at 17:61-62

193. Perrett discloses an ODT that disintegrates within 30 or 60 seconds via USP <701>. *See* EX1109 (Perrett) at 4:66-5:11 (“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 solid pharmaceutical composition disintegrates ***within 60 seconds when tested using the USP <701> Disintegration Test.*** In still other embodiments, the solid pharmaceutical compositions of the present invention disintegrate ***within 30 seconds (using the USP <701>***

Disintegration Test), or in the oral cavity of a patient.”); *id.* at 10:4-11 (“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.*”).

L. Claim 20

194. Claim 20 recites:

Claim 20. A method for treating eosinophilic esophagitis comprising administering to a patient in need thereof the orally disintegrating tablet according to claim 1.

195. Perrett discloses the claimed method of treating eosinophilic esophagitis. *See* EX1109 (Perrett) at 4:3-26 (“The pharmaceutical compositions of the present invention are suitable for treating inflammatory conditions of the gastrointestinal tract, for example inflammatory conditions of the upper gastrointestinal tract such as the esophagus. Thus, the present invention includes treating inflammatory conditions of the gastrointestinal tract by administering to a patient in need thereof a solid or liquid pharmaceutical composition of the present invention. Inflammatory conditions of the gastrointestinal tract which may be treated according to the present invention include inflammation of the esophagus...

eosinophilic esophagitis....”); *id.* at 4:50-57 (“In one embodiment, the present invention includes a method for treating inflammation of the esophagus comprising administering to a patient in need thereof a pharmaceutical composition of the present invention. 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.”); *id.* at 20:25-33 (“31. The method of claim 29, wherein said condition is *eosinophilic esophagitis*.”).

M. Claims 21, 29-30, and 33

196. Claim 21, 29-30, and 33 recite:

Claim 21. The method of claim 20, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 29. The orally disintegrating tablet of claim 14, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 30. The orally disintegrating tablet of claim 16, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 33. The orally disintegrating tablet of claim 28, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

197. Perrett discloses an ODT having fluticasone. *See* EX1109 (Perrett) at 7:6-11 (“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*.”);

198. Perrett discloses an ODT having the claimed amounts of fluticasone. See EX1109 (Perrett) at 7:25-49 (“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 0.5mg, 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 there between.”); *id.* at 10:16-21; *id.* at 20:23-24 (“The orally disintegrating tablet of claim 27, that comprises from *about 2 to about 10 mg fluticasone*.”).

N. Claims 22 and 34

199. Claims 22 and 34 recite:

Claim 22. The method of claim 20, wherein the orally disintegrating tablet comprises about 0.5 mg to about 2 mg of budesonide.

Claim 34. The orally disintegrating tablet of claim 28, wherein the orally disintegrating tablet comprises about 0.5 mg to about 2 mg of budesonide.

200. Perrett discloses an ODT having the claimed amounts of corticosteroid for reasons discussed above regarding limitation 1(i) and claim 2. *See also* EX1109 (Perrett) at 7:25-49, 10:16-21 (disclosing the claimed amounts of corticosteroid).

O. Claims 23-27

201. Claims 23-27 recite:

Claim 23. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a hardness of 4-48 N.

Claim 24. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a friability of not more than 1%.

Claim 25. The orally disintegrating tablet of claim 1, wherein the orally disintegrating has a hardness of 4-48 N and a friability of not more than 1%.

Claim 26. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a friability of not more than 0.6%.

Claim 27. The orally disintegrating tablet of claim 25, wherein the orally disintegrating tablet has a friability of not more than 0.6%.

202. Perrett anticipates claims 23-27 for the same reason it anticipates claim 1, limitation 1[v].

P. Claim 28

203. Claim 28 recites:

Claim 28. The orally disintegrating tablet of claim 27, wherein the orally disintegrating tablet has a thickness of 2-2.8 mm.

204. Perrett discloses an ODT having the claimed thickness. *See* EX1109 (Perrett) at 17:46-55 (Table in Example 1), which is reproduced below with yellow highlighting added:

TABLE		
Tablet Parameters		
Parameter	Target	Range
Weight (mg)	100	95-105
Thickness (mm)	2.4	2.0-2.8
Hardness (N)	28	8-48
Friability	NMT 0.6%	1.0%
Weight 10 tablets (g)	1.0 g	0.96-1.04

XV. GROUND 6: OBVIOUSNESS OVER PERRETT

205. The discussion of Perrett from Ground 5 is incorporated by reference here. Should the Board find that Perrett does not anticipate claims 1-34, these claims would have been obvious based on Perrett's disclosures.

206. Perrett’s disclosure is directed to ODTs and various embodiments of ODTs. Perrett instructs the person of ordinary skill in the art that “although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention” and that the “invention is not limited” by the specifically disclosed embodiments. *See* EX1109 (Perrett) at 18:14-19. To the extent that any of the referenced disclosures in Ground 5 of this declaration are considered separate embodiments, a person of ordinary skill in the art would have been motivated with a reasonable expectation of success to prepare an ODT having the claimed properties based on Perrett’s disclosures of ODTs having the ingredients and properties falling within the claimed ranges, as well as Perrett’s express instruction to make modifications to the specific embodiments. Claims 1-34 are therefore obvious over Perrett.

XVI. GROUND 7: DOHIL IN VIEW OF KARARLI, THE FDA GUIDANCE, AND THE USP

207. This section introduces Dohil and Kararli, and then explains how Dohil in view of Kararli, the FDA Guidance, and the USP render obvious claims 1-4, 9, 13-14, 18-20, 22-25 and 31-32 of the ’598 patent.

A. Dohil

208. Dohil discloses a budesonide formulation “provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the

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

B. Kararli

209. Kararli discloses rapidly disintegrating tablets for treating the upper gastrointestinal tract. *See* EX1110 (Kararli) at Title (“Rapidly disintegrating oral formulation of a cyclooxygenase-2 inhibitor”); *id.* at Abstract, 9:19-25, 15:3-15, 25:15-26:13.

210. Kararli discloses that its tablets “disintegrate within about 30 to about 300 seconds” when tested using the USP <701> Disintegration Test. *Id.* at 25:15-22 (“Preferred tablets of the invention disintegrate within about 30 to about 300 seconds, more preferably within about 30 to about 200 seconds, and still more preferably within about 30 to about 150 seconds, in a standard in vitro disintegration

assay (e.g., conducted according to U.S. Pharmacopeia 24 (2000), Test No. 701).

Alternatively or additionally, preferred tablets of the invention disintegrate within about 5 to about 60 seconds, more preferably within about 5 to about 40 seconds, and still more preferably within about 5 to about 30 seconds, for example within about 25 seconds, after placement in the oral cavity of a subject.”).

211. Kararli’s tablets preferably have a hardness of about 9.8 to about 49.1 N. *Id.* at 25:23-27 (“Preferably, compositions of the invention have a hardness of about 1 to about 10 kp, *and more preferably of about 1 to about 5 kp.*”). Kararli’s more preferred hardness of “about 1 to about 5 kp” is equivalent to a hardness of about 9.8 to about 49.1 N.⁵

C. Claim 1

1. Preamble

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

213. **Claim construction:** The ’598 patent defines “orally disintegrating tablet”, “orally dispersing tablet”, or “ODT” to refer “to a solid dosage form of the present invention, which disintegrates rapidly in the oral cavity of a patient after

⁵ A hardness of 1 to 5 kp is equivalent to a hardness of 9.8 to 49.1 N. *See* EX1104 (USP <1217>) at 677 (“The relationship between these units of force is 1 kilopond (kp) = 1 kilogram-force (kgf) = 9.8 N.”).

administration, without chewing.” EX1001 (the ‘598 patent) at 2:54-57 (“The terms “orally disintegrating tablet”, “orally dispersing tablet”, or “ODT” refer to a solid dosage form of the present invention, which disintegrates rapidly in the oral cavity of a patient after administration, without chewing.”). I have applied this definition. This definition is substantively the same as the definition of an orally disintegrating tablet adopted by the FDA. EX1005 (FDA Guidance) at 2 (“A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”).

214. Dohil discloses the recited orally disintegrating tablet. For example, Dohil discloses that “[b]udesonide is provided in the form of a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus. The lozenge or other similar tablet, capsule, or other solid, would dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.” EX1002 (Dohil) at ¶[0032]. Dohil discloses “[b]udesonide, in the form of a dissolving tablet.” *Id.* at ¶[0013] (“Also provided are pharmaceutical compositions comprising a corticosteroid, for example a topical corticosteroid, such as, for example, Budesonide, in the form of a dissolving tablet, a dissolving wafer, a capsule, or a gel capsule.”); *id.* at ¶[0037] (“For dissolving tablets, appropriate excipients include those that increase the resulting liquid viscosity of the dissolved tablet, enabling it to reach the esophagus, for example, to coat the esophagus.”).

215. The “rapid” dissolution of Dohil’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 Dohil’s lozenges and tablets that dissolve rapidly in the oral cavity do so without chewing. Accordingly, Dohil’s lozenges and tablets are orally disintegrating tablets that dissolve rapidly in the mouth and meet the preamble.

2. Limitation 1(i)

216. Limitation 1(i) recites “about 0.5 mg to 6 mg of a corticosteroid selected from fluticasone propionate or budesonide.”

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

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

219. Dohil’s patients were dosed with budesonide at 0.5, 1, and 2 mg/day. *Id.* ¶[0058] (“Treatment. Patients received OVB for a mean of 3.6 months before repeat endoscopy. Fifteen patients received OVB 1 mg/day, four received 2 mg/day and one unintentionally received 0.5 mg/day [Table 1].”), ¶[0053] (“Treatment. Patients received OVB 0.5 to 2 mg daily and were instructed not to ingest any solids

Dr. Falk Pharma GMBH v. Ellodi Pharmaceuticals LP
PGR Petition – U.S. Patent No. 12,290,598

or liquids for 30 minutes afterwards.”). Dohil’s Table 1 discloses these dosages in the “Budes Dose” column:

TABLE 1

Patient characteristics pre- and post-viscous Budesonide (Budes.) therapy. Patient response was determined by counting the highest eosinophil count/hpf after viscous budesonide and categorized into responders (0–7 eos/hpf), partial-responders (8–23 eos/hpf) and non-responders (≥ 24 eos/hpf).																	
Age		Res***	Sex	ΔWt^{****}	IgE*	Prior**	PPI before	Budes Dose	Highest Eos. count/ hpf			Basal Zone Hyperplasia (site*)		Endoscopy Score		Symptom Score	
Pt.	mths					Budes.	mths	Pre/Post	Budesonide	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	42	R	M	−0.1	F, A	ELIM (4)	No	1 mg (4)	M	70	1	Yes (P, M, D)	Yes (P, M)	6	1	3	2
2	33	R	M	0.15	X		No	1 mg (3)	D	30	7	Yes (D)	Yes (D)	1	0	7	3
3	71	R	M	0.73	F, A		Yes	1 mg (3)	D	74	0	Yes (P, D)	No	2	0	5	0
4	109	R	M	0.85	X	FLU (3)	Yes	1 mg (4)	M	100	2	Yes (M, D)	No	4	2	4	0
5	41	R	M	−0.07	F, A	ELIM (2)	Yes	1 mg (3)	D	50	0	Yes (M, D)	No	2	1	8	3
6	66		M		F, A	FLU (3)		1 mg (3)	P	60	50			6	1	4	3
		R	M	0.5	F, A		Yes	2 mg (3)	P	50	0	Yes (M)	No	1	0	3	2
7	88		M		F, A	FLU (12)	Yes	1 mg (3)	D	50	80			4	4	0	0
		R		0.375			Yes	2 mg (3)	D	80	1	Yes (P, M, D)	No	4	0	0	0
8	90	R	F	0.65	X		No	1 mg (4)	P	170	0	Yes (P, D)	No	6	1	9	0
9	41	R	M	0.18	A		Yes	1 mg (4)	P, D	70	0, 0	Yes (P, M, D)	No	2	0	3	0
10	20	R	M	0.03	F		Yes	1 mg (4)	D	80	0	Yes (P, M, D)	No	4	0	3	0
11	201	R	F	0.1	A		No	2 mg (4)	D	130	0	Yes (P, M, D)	No	6	0	5	1
12	34	R	M	−0.15	X		No	1 mg (3)	D	100	0	Yes (P, M, D)	No	5	0	3	0
13	51	R	F	0.08	F	ELIM (5)	No	1 mg (6)	D	120	0	Yes (D)	No	2	0	0	0
14	48	R	M	1.5	F	ELIM (5)	No	1 mg (3)	D, M, P	30	0	Yes (P, M, D)	No	4	0	3	0
15	31	R	M	0.2	F	ELIM (3)	Yes	1 mg (4)	D	100	5	Yes (P, D)	No	2	0	7	0
16	121	R	M	0.13	F, A		Yes	2 mg (3)	M	90	3	Yes (P, M, D)	Yes (P, M, D)	4	2	4	1

TABLE 1-continued

Patient characteristics pre- and post-viscous Budesonide (Budes.) therapy. Patient response was determined by counting the highest eosinophil count/hpf after viscous budesonide and categorized into responders (0–7 eos/hpf), partial-responders (8–23 eos/hpf) and non-responders (≥ 24 eos/hpf).																	
Age		Res***	Sex	Δ Wt****	IgE*	Prior**		Budes. mths	Highest Eos. count/ hpf			Basal Zone Hyperplasia (site*)		Endoscopy Score		Symptom Score	
Pt.	mths					mths	Budes.		Pre/Post	Budesonide	Site*	Pre	Post	Pre	Post	Pre	Post
17	36	P	M	0.46	F, A	FLU (12)	No	0.5 mg (3)	D	100	16	Yes (M, D)	No	6	1	6	2
18	32	N	M	0.83	F		No	1 mg (3)	D	100	50	Yes (M, D)	Yes (P, D)	2	3	3	1
19	68	N	F	0.15	F	ELIM (2)	Yes	1 mg (4)	D	100	28	Yes (P, M, D)	Yes (P, M, D)	4	0	2	0
20	93	N	M	0.15	F, A	FLU	No	1 mg (4)	D	100	25	Yes (P, M, D)	Yes (P, M, D)	5	2	8	0

Patient 6 and 7 failed treatment with 1 mg viscous budesonide, but responded to an increased dose. Patient 11 was started on 2 mg viscous budesonide because of her age and size. Patient 16 had dose increased from 1 mg to 2 mg viscous budesonide after one month because symptoms persisted on lower dose.

*Specific IgE. Sensitization to food (F) or aeroallergens (A) as determined by RAST or skin-prick testing. X = none.

**Prior therapy was with elimination diet (ELIM), topical fluticasone propionate and/or proton pump inhibitors (PPI).

*Site of esophageal involvement is divided into distal (D), mid (M), and proximal (P).

***Response Category R = Responder, N = Non-Responder, P = Partial Responder.

****Weight change per month. mths = months.

The highest eosinophil count/hpf, presence of basal zone hyperplasia, endoscopy and symptom scores are given pre- and post-viscous budesonide therapy.

Maximum Endoscopy Score is 8 and maximum Symptom Score is 14.

EX1002 (Dohil) at Table 1.

220. Dohil discloses a lozenge or tablet containing a daily dose of budesonide. *Id.* ¶[0031] (“In one illustrative example, the dose is provided once a day.”). Dohil thus discloses a lozenge or tablet containing a daily dose of budesonide containing, e.g., 0.5, 1, 2, and/or 3 mg. Dohil therefore discloses limitation 1(i).

3. Limitation 1(ii)

221. Limitation 1(ii) recites “at least one disintegrant.”

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

a lozenge which may be dissolved in the mouth, thus reaching and coating the esophagus.”). It was known to the person of ordinary skill in the art that the rapid dissolution of the lozenge is desirably aided by at least one disintegrating agent. For example, the Fu review article is representative of the person of ordinary skill in the art’s understanding and Fu describes several disintegrating agents used in orally disintegrating pharmaceutical compositions. *See* EX1018 (Fu) at 446-47 (heading “Disintegrants Used in FDTs”). Dohil teaches “[i]f desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate.” EX1002 (Dohil) at ¶[0037].

223. Dohil therefore discloses limitation 1(ii).

4. Limitation 1[iii]

224. Limitation 1[iii] recites “wherein upon administration a therapeutically effective amount of the corticosteroid is deposited topically in the esophagus.”

225. Dohil discloses a lozenge or tablet that “comprises a therapeutically effective amount of corticosteroid to prevent or alleviate esophageal inflammation. In certain embodiments, 1-2 mg or 2-3 mg of corticosteroid per day is administered to said individual.” EX1002 ¶[0015]. Dohil discloses a lozenge or tablet containing a daily dose of budesonide containing, e.g., 0.5 mg, 1 mg, 2 mg, and/or 3 mg. *Supra* Section discussing limitation 1(i). Thus, a person of ordinary skill in the art would understand that a dose of, e.g., 0.5 mg to 3 mg of budesonide per day is a

therapeutically effective amount of the corticosteroid. Therefore, Dohil's lozenge or tablet comprises a therapeutically effective amount of corticosteroid.

226. Upon administration of Dohil's lozenge or tablet, it "dissolve[s] rapidly in the mouth or esophagus to produce a solution" of budesonide that is deposited topically in the upper gastrointestinal tract by "*coat[ing] the esophagus.*" EX1002 (Dohil) at ¶[0032] ("The lozenge or other similar tablet, capsule, or other solid, [would] dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus."). Dohil repeatedly discloses that its formulations are designed to topically deposit a therapeutically effective amount of budesonide in the "upper gastrointestinal tract," *id.* at ¶[0010] ("The present methods are also useful for preventing or alleviating symptoms and inflammation associated with other diseases or conditions of the gastrointestinal tract, for example, the upper gastrointestinal tract, where it is beneficial to target a particular target site, rather than provide systemic therapy."), *such as "to the esophagus,"* *id.* at ¶¶[0013] ("In certain embodiments, these tablets, wafers, and capsules are formulated with at least one excipient to deliver a viscous form of the corticosteroid to the esophagus."), [0037] ("For dissolving tablets, appropriate excipients include those that increase the resulting liquid viscosity of the dissolved tablet, enabling it to reach the esophagus, for example, to coat the esophagus."), [0041] ("In one illustrative

embodiment, the corticosteroid of the composition has a low bioavailability, so that much of it will remain in the gastrointestinal tract, for example, in the esophagus”).

227. Dohil therefore discloses limitation 1[iii].

5. Limitation 1[iv]

228. Limitation 1[iv] recites “wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.”

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

230. It would have been obvious to formulate Dohil’s rapidly dissolving lozenge or tablet to disintegrate within 60 seconds when tested using the USP <701> Disintegration Test in view of the knowledge of the person of ordinary skill in the

art. The knowledge of the person of ordinary skill in the art is represented by, for example, the FDA’s Guidance for Industry on ODTs. The FDA Guidance explains that ODTs “disintegrate rapidly, usually within a matter of seconds.” EX1005 (FDA Guidance) at 2 (“ODTs are “[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.”).⁶

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

⁶ Also, the FDA published draft guidance on April 8, 2007 that included the same key technical content as the final 2008 Guidance. *See* FDA DRAFT Guidance at page 1, 2, and 3.

the United States, *id.* at ¶[0049] (“This retrospective review was approved by Children’s Hospital, San Diego (CHSD) and University of California at San Diego (UCSD), Human Research Protection Program. Patients were referred from CHSD subspecialty clinics and other institutions to the EE clinic.”). A person of ordinary skill in the art seeking to formulate budesonide into an ODT 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.

232. A person of ordinary skill in the art would have had a reasonable expectation of success in formulating budesonide into a rapidly disintegrating lozenge or tablet that dissolved within 60 seconds using the USP <701> Disintegration Test based on Dohil’s description of how to formulate such rapidly disintegrating lozenges or tablets. *See, e.g.,* ¶¶[0027]-[0041] (section entitled “Formulation”). Formulating ODTs 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.”); EX1020

(Venkatesh) ¶[0001] (“The present invention relates to orally disintegrating tablets and a method for their manufacture.”), ¶[0016] (“compressing the blend into tablets which rapidly disintegrate (e.g., less than 120 seconds, preferably less than 60 seconds) in the buccal cavity”), ¶[0018] (explaining the disclosed rapidly disintegrating tablets “don’t require a special pharmaceutical production technique and can be simply and easily produced by a normal equipment”). Based on the numerous commercially available orally disintegrating systems and products available by 2009, the person of ordinary skill in the art’s expectation of success would have been high. For example, the Danckwerts and Fu review articles are representative of the knowledge of the person of ordinary skill in the art. These references disclose several commercially available orally designating systems and products. *See* EX1017 (Danckwerts) at 179-181; EX1018 (Fu) at 436-439. Thus, the development of an ODT would be readily achievable by 2009.

233. Dohil in view of the FDA Guidance therefore renders obvious limitation 1[iv].

6. Limitation 1[v]

234. Limitation 1[v] recites “wherein the orally disintegrating tablet has a hardness of 4-48 N or a friability of not more than 1%.”

235. A person of ordinary skill in the art would have been motivated to formulate Dohil’s rapidly dissolving lozenge or tablet to have a hardness of between

4-48 N or a friability of not more than 1% with a reasonable expectation of success in view of Kararli and the USP.

236. Kararli is directed to ODTs. *See* EX1110 (Kararli) at Title (“Rapidly disintegrating oral formulation of a cyclooxygenase-2 inhibitor”); *id.* at 3:14-4:18 (discussing drawbacks of traditional tablets).

237. Kararli teaches ODTs have a hardness “more preferably of about 1 to about 5 kp.” *Id.* at 25:23-27. A hardness of 1-5 kp is equivalent to a hardness of 9.8-49.1 N.⁷ Kararli teaches that this hardness is important for an ODT to “have sufficient hardness for handling,” and to “withstand removal from at least a standard type of blister packaging,” and “withstand other handling such as packaging, delivery, carrying and the like.” *Id.* at 25:28-26:13; *id.* at 9:19-26 (“Preferably, such tablets have a hardness of about 1 kp to about 10 kp.”).

238. Kararli’s teaching is reinforced by the knowledge of the person of ordinary skill in the art, which is represented by, for example, the United States Pharmacopeia (“USP”). USP standards have been recognized as an authority in the pharmaceutical field for over 200 years “because they are authoritative and science-

⁷ 1 kilopond (kp) is equivalent to 9.8N. *See* EX1104 (USP <1217>) at 677 (“The relationship between these units of force is 1 kilopond (kp) = 1 kilogram-force (kgf) = 9.8 N.”).

based and are established by a transparent and credible process.” EX1104 (USP) at viii. USP is “recognized by law and custom in many countries throughout the world,” including the U.S. *Id.* USP teaches that hardness is an important indicator of mechanical strength for tablets to “be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users (patients/consumers).” *Id.* at 676. USP also teaches that friability is another important indicator of mechanical strength for tablets and recommends a friability “of not more than 1.0% is considered acceptable for most products.” *Id.*

239. A person of ordinary skill in the art would have been motivated to follow Kararli and USP’s recommendations in formulating Dohil’s rapidly dissolving lozenge/tablet to have a hardness of 9.8-49.1 N and a friability of not more than 1% to provide a lozenge/tablet of sufficient mechanical strength to handle packaging, transportation, and handling. A person of ordinary skill in the art had a reasonable expectation of success in formulating Dohil’s rapidly dissolving lozenge/tablet to have a hardness falling within the range of 4-48 N or a friability falling within the range of not more than 1% given the disclosures of Kararli, and the USP.

240. The reasonable expectation of success is supported by several of Patent Owner’s prior art publications by Venkatesh that disclose ODTs having hardness

and friability within the claimed ranges. Example 1 of Venkatesh516 discloses ODTs with a hardness of “8-48 N” and friability of “NMT [not more than] 1.0%”:

Tablet Parameters	Target	Range
Weight per tablet (mg)	100	95-105 (± 5%)
Thickness (mm)	2.40	2.00-2.80
Hardness (N)	28	8 - 48
Friability (%)	NMT 0.6	NMT 1.0
Weight/10 tablets (g)	1.00	0.96 – 1.04 (± 4%)

EX1111 (Venkatesh516) at 22:7-26. Tables 3 and 12 of Venkatesh345 disclose ODTs with hardness of 6.80 and 6.92-6.95 N and friability of 0.24-0.31% (Table 3), or hardnesses between 41.3-67 N and friability between 0.05-0.51% (Table 12):

Table 3: Tableting Parameters for Hydrocodone Bitartrate/Acetaminophen ODTs:

Parameter	5 mg/500 mg ODT	10 mg/300 mg ODT
Tooling - round, flat face, radius edge	17 mm	15 mm
Target tablet weight (mg)	1600	1250
Lower target tablet weight × 0.985 (mg)	1576	1231
Target tablet weight × 1.015 (mg)	1624	1269
Turn table speed with range (rpm)	15 (10 - 20)	15 (10 - 20)
Fill depth (mm)	10.94-10.98	5.11
Main position (mm)	10.6-11.1	4.44
Pre. Position (mm)	6.2-6.4	4.61
Scale on the feed shoe	2 (0 – 4)	2 (0 – 4)
Tablet Weight (mg)	1597	1248.6
Hardness with range (n)	6.80	6.92-6.95
Thickness with range (mm)	47-49	40-42
Friability with range (%)	0.25-0.31	0.24-0.31

EX1112 (Venkatesh345) at 38 (Table 3).

Table 12: Tableting Properties of Hydrocodone Bitartrate / Acetaminophen ODTs

Lot#	Compression Force	Weight	Thickness	Hardness	Friability
<u>ODTs 10-mg/300-mg</u>					
1334-142	13 kN	1102 mg	6.12 mm	41.3 N	0.51%
	14 kN	1101 mg	6.03 mm	46.4 N	0.37%
1198-062	12.5 kN	1099 mg	6.09mm	46.0 N	0.20%
<u>ODTs 5-mg/500-mg</u>					
1198-046	18 kN	1402 mg	6.11 mm	53 N	0.18%
	20 kN	1394 mg	6.03 mm	61 N	0.05%
	22 kN	1390 mg	5.97 mm	67 N	0.17%

EX1112 (Venkatesh345) at 48 (Table 12). Table 12 of Venkatesh346 also discloses ODTs with hardness and friability within the claimed ranges:

Table 12: Tableting Properties of Hydrocodone Bitartrate / Acetaminophen ODTs

Lot#	Compression Force	Weight	Thickness	Hardness	Friability
<u>ODTs 10-mg/300-mg</u>					
1334-142	13 kN	1102 mg	6.12 mm	41.3 N	0.51%
	14 kN	1101 mg	6.03 mm	46.4 N	0.37%
1198-062	12.5 kN	1099 mg	6.09mm	46.0 N	0.20%
<u>ODTs 5-mg/500-mg</u>					
1198-046	18 kN	1402 mg	6.11 mm	53 N	0.18%
	20 kN	1394 mg	6.03 mm	61 N	0.05%
	22 kN	1390 mg	5.97 mm	67 N	0.17%

EX1113 (Venkatesh346) at 48 (Table 12).

241. Dohil in view of Kararli, the FDA Guidance, and the USP therefore render obvious claim 1.

D. Claims 2-3

242. Claims 2-3 recite:

Claim 2. The orally disintegrating tablet of claim 1, comprising about 0.5 mg to about 2 mg of the corticosteroid.

243. Claim 3 recites:

Claim 3. The orally disintegrating tablet of claim 1, comprising about 3 mg of the corticosteroid.

244. Claims 2 and 3 are obvious for the same reasons discussed above for limitation 1(i).

E. Claim 4

245. Claim 4 recites:

Claim 4. The orally disintegrating tablet of claim 1, comprising a sugar alcohol and/or saccharide.

246. Dohil discloses the use of mannitol in its ODT formulations. *See* EX1002 (Dohil) ¶¶[0014], [0037]. Mannitol was the bulk excipient of choice for ODTs. *See* 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.”).

247. The '598 patent states that mannitol is a sugar alcohol that was “typically used in disintegrating tablet formulations.” EX1001 (the '598 patent) at 8:52-60, 9:10-11.

248. Claim 4 is therefore obvious.

F. Claim 9

249. Claim 9 recites:

Claim 9. The orally disintegrating tablet of claim 2, wherein the corticosteroid is budesonide.

250. Claim 9 is obvious for the same reasons discussed above for Claim 1.

G. Claims 13-14

251. Claims 13-14 recite:

Claim 13. The orally disintegrating tablet of claim 1, wherein the disintegrant is crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, low-substituted hydroxylpropylcellulose, mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, or combinations thereof.

Claim 14. The orally disintegrating tablet of claim 13, wherein the disintegrant is crospovidone.

252. The '598 patent states that crospovidone is “cross-linked PVP [polyvinylpyrrolidone].” EX1001 (the '598 patent) at 9:3-7, 13:8; *id.* at 12:13 (“polyvinylpyrrolidone (PVP)”), 12:31-32.

253. Dohil teaches that, “[i]f desired, disintegrating agents may be added, such as the *cross-linked polyvinylpyrrolidone*, agar, or alginic acid or a salt thereof such as sodium alginate.” EX1002 (Dohil) at ¶[0037]. Claims 13-14 are therefore obvious.

H. Claims 18-19

254. Claims 18-19 recite:

Claim 18. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet disintegrates within 60 seconds when tested in simulated saliva fluid using the USP <701> Disintegration Test.

Claim 19. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.

255. Dohil discloses a budesonide lozenge or tablet that “dissolve[s] rapidly in the mouth.” EX1002 (Dohil) at ¶[0032] (“The lozenge or other similar tablet, capsule, or other solid, [would] dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus.”). A person of ordinary skill in the art would have been motivated to formulate Dohil’s rapidly dissolving lozenge or tablet to disintegrate within 30 seconds with a reasonable expectation of success, as discussed above regarding limitation 1[iv]. Indeed, the FDA recommended that such compositions have “an in-vitro disintegration time of approximately 30 seconds or less,” EX1005 (FDA Guidance) at 2 (“Based on the original product rationale and

Agency experience, we recommend that, in addition to the original definition, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative.”), using the “USP 29, <701> Disintegration” test. *Id.* 3 n.3 (“USP 29, <701> Disintegration, pp. 2670-2672.”).

256. The FDA Guidelines explain that ODTs dissolve in the patient’s saliva. EX1005 (FDA Guidance) at 3 (“We recommend that as a primary consideration when developing this type of product, you use the defining characteristics for this dosage form designation (rapid disintegration in saliva without the need for chewing or liquids).”). The USP <701> Disintegration Test called for by the FDA Guidelines “use[s] water or the specified medium as the immersion fluid.” EX1040 (Disintegration 2008) at 2 (“Place 1 dosage unit in each of the six tubes of the basket and, if prescribed, add a disk. Operate the apparatus using water or the specified medium as the immersion fluid, maintained at $37 \pm 2^\circ$.”). A person of ordinary skill in the art would have been motivated to perform the USP <701> Disintegration Test using simulated saliva as the immersion fluid to provide testing conditions that were as close as possible to the *in vivo* conditions in a patient’s mouth and more accurately represent disintegration within the oral cavity. For example, the prior art taught that simulated saliva was a desirable medium for disintegration testing because it

produced conditions that are “as close as possible to the in vivo conditions” within a patient’s mouth. EX1047 (El Arini) at 367 (“In order to select the volume parameter as close as possible to the in vivo conditions, the studies were conducted in 2 mL of artificial saliva.”).

257. Claims 18-19 are therefore obvious.

I. Claim 20

258. Claim 20 recites:

Claim 20. A method for treating eosinophilic esophagitis comprising administering to a patient in need thereof the orally disintegrating tablet according to claim 1.

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

The methods of the present invention are useful, for example, for preventing and *alleviating the symptoms and inflammation of eosinophilic esophagitis*, inflammatory bowel diseases involving the esophagus, Crohn’s disease, esophageal inflammation secondary to caustic/irritant ingestion, persistent/recurrent esophageal strictures of any cause and including caustic/irritant ingestion, pill-induced esophagitis, systemic diseases, congenital diseases, Epidermolysis bullosa, and post-surgery inflammation. The present methods are also useful for preventing or alleviating symptoms and inflammation associated with other diseases or conditions of the gastrointestinal tract, for example, the upper gastrointestinal tract, where it is beneficial to target a particular target site, rather than provide systemic therapy.

EX1002 (Dohil) at ¶[0010]; *id.* ¶¶[0011], [0023]. Claim 20 is therefore obvious.

J. Claim 22

260. Claim 22 recites:

Claim 22. The method of claim 20, wherein the orally disintegrating tablet comprises about 0.5 mg to about 2 mg of budesonide.

261. Claim 22 is obvious for the same reasons discussed above for Claims 1 and 20.

K. Claims 23-25

262. Claims 23-25 recite:

Claim 23. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a hardness of 4-48 N.

Claim 24. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a friability of not more than 1%.

Claim 25. The orally disintegrating tablet of claim 1, wherein the orally disintegrating has a hardness of 4-48 N and a friability of not more than 1%.

263. Claims 23-25 are obvious for the same reasons discussed above for claim limitation 1[v].

L. Claims 31-32

264. Claims 31-32 recite:

Claim 31. The method of claim 20, wherein the orally disintegrating tablet disintegrates within 60 seconds when tested in simulated saliva fluid using the USP <701> Disintegration Test.

Claim 32. The method of claim 20, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.

265. Claims 31-32 are obvious for the same reasons discussed above for Claims 1 and 18-20.

XVII. GROUND 8: DOHIL IN VIEW OF KARARLI, THE FDA GUIDANCE, THE USP, AND VENKATESH988

266. This section introduces Venkatesh988, and then explains how Dohil in view of Kararli, the FDA Guidance, the USP, and Venkatesh988 render obvious dependent claims 5-8 and 15-16 of the '598 patent.

A. Introduction to Venkatesh988

267. Dr. Gopi Venkatesh is listed as a co-inventor on the '598 patent and US2005/0232988 (EX1020, "Venkatesh988").

268. Venkatesh988 discloses "orally disintegrating tablets and a method for their manufacture." EX1020 (Venkatesh988) ¶[0001]. Venkatesh's ODTs can be formulated using "any therapeutic active agent indicated for oral administration." *Id.* ¶[0025].

B. Claim 5

269. Claim 5 recites:

Claim 5. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid and at least one excipient, and the rapidly dispersing granules comprise the disintegrant and a sugar alcohol and/or saccharide.

270. **Claim construction:** The '598 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 '598 patent) at 13:36-38. I have applied this definition. The '598 patent states that “[n]on-limiting examples of suitable sugar alcohols for the rapidly dispersing granules of the pharmaceutical compositions of the present invention include e.g. arabitol, isomalt, erythritol, glycerol, lactitol, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.” *Id.* at 13:39-43.

271. **Claim construction:** The '598 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 '598 patent) at 13:43-57. I have applied this definition.

272. Venkatesh988 discloses “an orally disintegrating tablet made up of rapidly dispersing microgranules and taste-masked microcapsules” of drug particles. EX1020 (Venkatesh988) ¶[0001]; *id.* ¶¶[0018], [0025] (microcapsule drug

particles). The drug particles are granulated with diluent excipients. *Id.* ¶[0021]. Venkatesh988 discloses that “this invention relates to pharmaceutical compositions comprising rapidly dispersing microgranules of a disintegrant and sugar alcohol or a saccharide.” *Id.* ¶[0014]; *id.* ¶[0018], ¶[0028] (“sugar alcohol” and “saccharide”). Venkatesh988 therefore discloses ODTs comprising drug particles comprising excipients and rapidly dispersing microgranules comprising a disintegrant, a sugar alcohol and/or saccharide.

273. The person of ordinary skill in the art would have been motivated for the budesonide in Dohil’s tablet to comprise drug particles with an excipient and the disintegrant to be rapidly dispersing granules that include a sugar alcohol and/or saccharide based on Venkatesh988. Venkatesh988 teaches that formulating ODTs to have drug particles and rapidly-dispersing microgranules comprising sugar alcohol and/or saccharide in combination with the disintegrant beneficially “avoid[ed] gritty mouthfeel,” EX1020 (Venkatesh988) ¶[0012], to assist with providing a “smooth creamy mouthfeel (no grittiness),” *id.* ¶[0002].

274. The person of ordinary skill in the art had a reasonable expectation of success based on Venkatesh988. Venkatesh988 teaches that its formulations “don’t require a special pharmaceutical production technique and can be simply and easily produced by a normal equipment.” EX1020(Venkatesh988) ¶[0018].

275. Dohil in view of Kararli, the FDA Guidance, the USP, and Venkatesh988 therefore render obvious claim 5.

C. Claims 6-8

276. Claims 6-8 recite:

Claim 6. The orally disintegrating tablet of claim 5, wherein the rapidly dispersing granules have an average particle size of less than about 300 μm , and each of the disintegrant and sugar alcohol and/or saccharide have an average particle size of about 1-30 μm .

Claim 7. The orally disintegrating tablet of claim 5, wherein the drug particles have an average particle size of about 100-400 μm .

Claim 8. The orally disintegrating tablet of claim 5, wherein the drug particles have an average particle size of about 100-400 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm , and each of the disintegrant and sugar alcohol and/or saccharide have an average particle size of about 1-30 μm .

277. Venkatesh988 discloses drug particles that advantageously have “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” and provide “a smooth creamy mouthfeel.” EX1020 (Venkatesh988) ¶[0015].

278. Venkatesh988 discloses that the rapidly dispersing granules “typically” have an “average particle size of not more than 300 μm .” EX1020 (Venkatesh988) ¶[0020]. A small particle size assists with mouthfeel. *Id.* ¶¶[0019], [0009], [0025].

279. Venkatesh988 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 (Venkatesh988) ¶[0014]; *id.* ¶[0018] (“preferably not more than 20 μm ”), ¶[0028].

280. A person of ordinary skill in the art would have been motivated to formulate budesonide in an ODT based on Dohil, and also having drug particles with a particle size less than 400 μm , rapidly dispersing granules with a particle size less than 300 μm , and a disintegrant and sugar alcohol and/or saccharide with a particle size less than 30 μm based on Venkatesh988 to avoid a gritty texture and improve mouthfeel with an expectation of success.

281. Claims 6-8 are therefore obvious.

D. Claims 15-16

282. Claims 15-16 recite:

Claim 15. The orally disintegrating tablet of claim 5, wherein the sugar alcohol and/or saccharide is mannitol, sorbitol, xylitol, maltitol, arabitol, ribitol, dulcitol, iditol, isomalt, lactitol, erythritol, lactose, sucrose, maltose, or combinations thereof.

Claim 16. The orally disintegrating tablet of claim 15, wherein the sugar alcohol is mannitol.

283. Dohil discloses budesonide ODTs formulated with mannitol and sorbitol as sugar alcohol excipients. EX1002 (Dohil) ¶¶[0014], [0037]. Mannitol was the bulk excipient of choice for ODTs. EX1041 (Conway) at 261.

284. Venkatesh988 discloses that “[t]he dispersible microgranules comprise a sugar alcohol such as mannitol.” EX1020 (Venkatesh988) ¶¶[0032], [0047]. Venkatesh988 further discloses that “[t]he sugar alcohol may be selected from the group consisting of mannitol, sorbitol, xylitol, maltitol and the like....” *Id.* ¶[0028].

285. Claims 15-16 are therefore obvious.

XVIII. GROUND 9: DOHIL IN VIEW OF KARARLI, THE FDA GUIDANCE, THE USP, AND VENKATESH516

286. This section introduces Venkatesh516, and then explains how Dohil in view of Kararli, the FDA Guidance, the USP, and Venkatesh516 render obvious dependent claims 26-28 and 34 of the ’598 patent.

A. Venkatesh516

287. Venkatesh516 discloses “pleasant tasting, orally dissolving or disintegrating tablet (ODT) compositions comprising lamotrigine.” EX1111 (Venkatesh516) at 1:8-10. Venkatesh516’s ODTs have a friability target of “NMT [not more than] 0.6%” as shown below:

Tablet Parameters	Target	Range
Weight per tablet (mg)	100	95-105 ($\pm 5\%$)
Thickness (mm)	2.40	2.00-2.80
Hardness (N)	28	8 - 48
Friability (%)	NMT 0.6	NMT 1.0
Weight/10 tablets (g)	1.00	0.96 – 1.04 ($\pm 4\%$)

Id. at 22:21; *see also id.* at 22:1 (“friability (target: $<0.6\%$)”); *id.* 23:27 (same).

B. Claims 26-27

288. Claims 26-27 recite:

Claim 26. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a friability of not more than 0.6%.

Claim 27. The orally disintegrating tablet of claim 25, wherein the orally disintegrating tablet has a friability of not more than 0.6%.

289. It was obvious to formulate Dohil’s rapidly dissolving lozenge/tablet to have a friability of less than 1% for reasons discussed above for limitation 1[v]. A person of ordinary skill in the art would have been motivated to formulate Dohil’s lozenge/tablet to have a friability of not more than 0.6% with a reasonable expectation of success in view of Venkatesh516.

290. Venkatesh516’s ODTs have a friability target of “NMT [not more than] 0.6%” as shown below:

Tablet Parameters	Target	Range
Weight per tablet (mg)	100	95-105 ($\pm 5\%$)
Thickness (mm)	2.40	2.00-2.80
Hardness (N)	28	8 - 48
Friability (%)	NMT 0.6	NMT 1.0
Weight/10 tablets (g)	1.00	0.96 – 1.04 ($\pm 4\%$)

EX1111 (Venkatesh516) at 22:21; *see also id.* at 22:1 (“friability (target: <0.6%)”); *id.* 23:27 (same).

291. Venkatesh516 further discloses that such a friability is sufficiently low for the ODT “to be suitable for packaging in HDPE bottles and push-through film backed or peel-off paper backed blister packs using conventional equipment for storage, transportation and commercial distribution.” EX1111 (Venkatesh516) at 16:23-27; *id.* at 19:10-11, 19:25-26.

292. Claims 26-27 are therefore obvious.

C. Claim 28

293. Claim 28 recites:

Claim 28. The orally disintegrating tablet of claim 27, wherein the orally disintegrating tablet has a thickness of 2-2.8 mm.

294. Venkatesh516 discloses ODTs having a “target” thickness of 2.40 mm as follows:

<i>Tablet Parameters</i>	<i>Target</i>	<i>Range</i>
Weight per tablet (mg)	100	95-105 ($\pm 5\%$)
Thickness (mm)	2.40	2.00-2.80
Hardness (N)	28	8 - 48
Friability (%)	NMT 0.6	NMT 1.0
Weight/10 tablets (g)	1.00	0.96 – 1.04 ($\pm 4\%$)

EX1111 (Venkatesh516) at 22:19. A person of ordinary skill in the art would have been motivated to follow Venkatesh516's instruction with a reasonable expectation of success to target a thickness of 2.40 mm when formulating Dohil's rapidly dissolving lozenge/tablet to provide an appropriately thick tablet to impart sufficient mechanical strength while also providing appropriate mouthfeel to the patient.

295. Claim 28 is therefore obvious.

D. Claim 34

296. Claim 34 recites:

Claim 34. The orally disintegrating tablet of claim 28, wherein the orally disintegrating tablet comprises about 0.5 mg to about 2 mg of budesonide.

297. Claim 34 is obvious for the same reasons discussed above for claims 1, 25, and 27-28.

**XIX. GROUND 10: GROTHER IN VIEW OF KARARLI, THE FDA
GUIDANCE, AND THE USP**

298. This section introduces Grother and explains how Grother in view of Kararli, the FDA Guidance, and the USP render obvious claims 1-4, 9, 11, 13-14, 18-25, 29 and 31-32.

A. Introduction to Grother

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

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

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

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

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

B. Claim 1

300. Grother in view of Kararli, the FDA Guidance, and the USP disclose ODTs that render obvious all limitations of claim 1.

1. Preamble

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

302. Grother discloses the recited orally disintegrating tablet. For example, Grother discloses “a fast dispersing solid dosage form designed to release an active ingredient rapidly in the oral cavity.” EX1008 (Grother) at 12:10-19 (“There is disclosed a ***fast dispersing solid dosage form designed to release an active ingredient rapidly in the oral cavity*** characterized in that said dosage form is essentially free of mammalian gelatin and comprises: at least one active ingredient;

at least one modified starch at a concentration of from 20 to 90% by weight of said solid dosage form; and at least one matrix forming agent; wherein said solid dosage form is obtainable by removing a solvent from a mixture comprising said active ingredient, said modified starch and said matrix forming agent.”); *id.* at 1:10-11 (“This invention relates to a ***pharmaceutical composition for oral administration in the form of a fast dispersing dosage form.***”), 3:15-17 (“It has now been found that modified starches may be used instead of mammalian-derived gelatin to prepare ***fast dispersing dosage forms.***”), 32:10 (“This invention relates to ***fast dissolving dosage forms for oral administration.***”).

303. Grother’s process for making the fast dispersing solid dosage forms results in a tablet. *Id.* at 32:10-17 (“This invention relates to fast dissolving dosage forms for oral administration. The advantages of fast dispersing dosage forms include the lingual, sublingual or buccal delivery of drugs. The current, most commercially popular form is a rapidly soluble solid dosage form that is made by aliquoting a slurry of therapeutic agent, solvent, gelatin and other excipients into preformed depressions. The liquid is then frozen and the solvent is then removed by sublimation, typically, freeze drying. ***The resulting tablet*** has an open porous matrix the dissolves rapidly on contact with saliva.”).

304. Grother discloses “fast dispersing solid dosage forms that preferably dissolve in the oral cavity within sixty (60), more preferably within thirty (30), most

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

305. The fast dissolution of Grother’s solid dosage formulations in the patient’s mouth within seconds of being placed in the oral cavity indicates to the person of ordinary skill in the art that the formulations 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 Grother’s fast dispersing solid dosage forms include orally dispersing tablets that dissolve rapidly in the mouth without chewing, which meets the preamble.

2. Limitation 1(i)

306. Limitation 1(i) recites “about 0.5 mg to 6 mg of a corticosteroid selected from fluticasone propionate or budesonide.”

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

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

select budesonide or fluticasone as an active ingredient in Grother's fast dispersing solid dosage form based on Grother's express disclosure to do so. In addition, as discussed above, budesonide and fluticasone were well-known corticosteroids with desirable anti-inflammatory activity.

309. It was generally known in the art that a therapeutically effective dosage of budesonide ranged from, e.g., 0.5-3 mg. For example, Aceves 2005 treated two patients suffering from eosinophilic esophagitis with 0.5 mg dosages of budesonide. EX1014 (Aceves 2005) at 705 ("He was placed on a regimen of twice-daily oral budesonide suspension (Pulmicort, AstraZeneca) 500 µg [which is 0.5 mg] mixed with sucralose (Splenda, McNeils Nutritionals, Washington, PA), a nonabsorbed sugar, to increase fluid viscosity, to be swallowed twice daily."); *id.* at 706 ("As an alternative, she received oral budesonide 500 µg (Pulmicort) mixed with sucralose (Splenda) twice daily as topical esophageal therapy."). Aceves 2007 dosed seventeen patients with 1 mg of daily budesonide. EX1015 (Aceves 2007) at 5 ("Initially seventeen patients received OVB 1 mg/day, 2 patients received 2 mg/day, and 1 patient unintentionally received 0.5 mg/day. Two patients failed treatment with OVB 1 mg daily and their dose was increased to 2 mg/day (Table 1)."; *see id.* at 4 (Table 1). Aceves 2007 reported that "[m]ost of our patients responded to 1 mg daily" of budesonide. *Id.* at 7 ("Most of our patients responded to 1 mg daily, but 2 patients needed 2 mg/day before a response was seen.").

310. Dohil discloses that “[i]n some embodiments of the invention, 0-1 mg/day, 1-2 mg/day, 2-3 mg/day [of]... for example, Budesonide, are administered to a patient.” EX1002 (Dohil) ¶[0058] (“In some embodiments of the invention, 0-1 mg/day, 1-2 mg/day, 2-3 mg/day, 3-4 mg/day, 4-5 mg/day, or 5-6 mg/day of corticosteroid, for example topical corticosteroid, for example, Budesonide, are administered to a patient.”). Dohil’s patients were dosed with topically administered budesonide at 0.5, 1, and 2 mg/day. *Id.* ¶¶[0058] (“Treatment. Patients received OVB for a mean of 3.6 months before repeat endoscopy. Fifteen patients received OVB 1 mg/day, four received 2 mg/day and one unintentionally received 0.5 mg/day [Table 1]. In some embodiments of the invention, 0-1 mg/day, 1-2 mg/day, 2-3 mg/day, 3-4 mg/day, 4-5 mg/day, or 5-6 mg/day of corticosteroid, for example topical corticosteroid, for example, Budesonide, are administered to a patient.”); [0053] (“Treatment. Patients received OVB 0.5 to 2 mg daily and were instructed not to ingest any solids or liquids for 30 minutes afterwards.”); Table 1. “In one illustrative example, the dose is provided once a day.” *Id.* ¶[0031].

311. Based on Grother’s instruction that its compositions should normally have 1-20% by weight active ingredient and the general knowledge in the art that formulations of budesonide contain, e.g., 0.5, 1, or 3 mg of budesonide, a person of ordinary skill in the art would have been motivated to formulate budesonide in Grother’s compositions at, e.g., 0.5, 1, and 3 mg, with a reasonable expectation of

success. Grother therefore renders obvious an orally dispersing tablet that comprises 0.5 mg to 5 mg of budesonide.

312. Beyond the teachings of Grother, it was generally known to the person of ordinary skill in the art that topical corticosteroids, including budesonide and fluticasone, were a suitable treatment for eosinophilic esophagitis. For example, practical applications of the use of budesonide and fluticasone for this treatment were disclosed by Aceves 2007. *See* EX1015 (Aceves 2007) at 1 (“Systemic corticosteroids and swallowed topical steroids, such as fluticasone propionate (Flovent™) administered through metered-dose inhaler (MDI), have been shown to induce and maintain low esophageal eosinophil levels (25–30).”) (emphasis added). Another practical application includes Teitelbaum, which discloses treatment of eosinophilic esophagitis in children with between 44µg and 440µg (between 0.044-0.44mg) of swallowed fluticasone delivered twice daily via a metered dose inhaler. *See* EX1033 at 1217 (Teitelbaum) (“If they had persistence of symptoms despite strict adherence to the diet, they were placed on FP (2–4 years old, 44 µg/puff; 5–10 years old, 110 µg/puff; 11 years and older, 220 µg/puff) 2 puffs by mouth twice daily swallowed without inhaling and without use of a spacing device.”), *id.* at 1216 (“In 1998, Faubion et al. reported the successful use of a novel treatment method in which patients swallowed metered doses of a trifluorinated steroid preparation, fluticasone propionate (FP).”).

313. Yet another practical application for this treatment is Noel, which discloses treatment of eosinophilic esophagitis with between 440 µg and 1320 µg (between 0.44-1.32mg) of swallowed fluticasone. EX1034 (Noel) at 573 (“First, we report that FP treatment is associated with an efficacious response in the majority of patients with EE.”); *id.* at Table 1. Moreover, Noel discloses that fluticasone is likely to mediate its therapeutic effects by acting topically, as studies have indicated that systemic effects such as decreased serum cortisol levels are not seen in patients ingesting 18 mg of fluticasone. *Id.* at 574 (“Swallowed FP is likely to mediate therapy by topical absorption in the esophagus. Pharmacokinetic studies have shown that approximately 1% of the drug is absorbed systemically and then metabolized efficiently in the liver at a rate approaching that of portal-hepatic circulation. No alteration of morning serum cortisol level has been seen in volunteers after ingesting as much as 18 mg of FP.”).

314. The patients treated with fluticasone in Teitelbaum and Noel were each administered fluticasone by metered dose inhaler, without a spacer. *See* EX1033 (Teitelbaum) at 1217 (“In addition, we performed an open-label, prospective trial to determine whether the use of diet restriction (DR) or swallowed FP metered-dose units would diminish symptoms and induce a histologic remission.”); *see also* EX1034 (Noel) at 569 (“Patients were prescribed metered-dose inhalers of FP. They were instructed not to use a spacer.”). Moreover, the patients were instructed not to

eat or drink for 30 minutes following administration of the fluticasone. *See* EX1033 (Teitelbaum) at 1217 (“Patients were instructed not to eat or drink for 30 minutes after taking the medication.”); *see also* EX1034 (Noel) at 569 (“Additionally, they were instructed to spray the medication into the pharynx, and not to rinse, eat, or drink for 30 minutes after administration.”). A person of skill in the art would understand that this mode of administration would result in topical deposition of the fluticasone on the patient’s esophagus.

315. Based on Grother’s instruction that its compositions should normally have 1-20% by weight active ingredient a person of ordinary skill in the art would have been motivated to formulate fluticasone in Grother’s compositions at, e.g., 1.32 mg, with a reasonable expectation of success.

316. Grother therefore renders obvious an ODT that comprises 0.5 mg to 6 mg of budesonide or fluticasone.

3. Limitation 1(ii)

317. Limitation 1(ii) recites “at least one disintegrant.”

318. The ’598 patent states that disintegrants include “starch” and modified starches such as “pregelatinized starch” and “carboxymethyl starch.” EX1001 (the ’598 patent) at 9:49-54 (“Examples of suitable disintegrants include e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium

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

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

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

4. Limitation 1[iii]

320. Limitation 1[iii] recites “wherein upon administration a therapeutically effective amount of the corticosteroid is deposited topically in the esophagus.”

321. As discussed above, a person of ordinary skill in the art would have been motivated to formulate budesonide or fluticasone in Grother’s compositions at

dosage amounts that constitute a therapeutically effective amount of budesonide or fluticasone.

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

5. Limitation 1[iv]

323. Limitation 1[iv] recites “wherein the orally disintegrating tablet disintegrates within 60 seconds when tested using the USP <701> Disintegration Test.”

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

325. It would have been obvious to formulate budesonide in Grother’s fast dispersing solid dosage form to disintegrate within 60 seconds when tested using the USP <701> Disintegration Test in view of the FDA Guidance for Industry on orally disintegrating tablets. The FDA Guidance recommended that orally disintegrating should have “an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or

alternative (*see* Section IV).” EX1005 (FDA Guidance) at 2. The FDA Guidance “recommend[s] that applicants use the USP method for disintegration testing,” *id.* at 3 (“[t]o provide both a standard for and consistency in disintegration testing, we recommend that applicants use the USP method for disintegration testing.”), specifically “USP 29, <701> Disintegration,” *id.* at 3 n.3 (“USP 29, <701> Disintegration, at 2670-2672.”).⁸

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

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

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

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

disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative (*see* Section IV).” EX1005 (FDA Guidance) at 2. Based on the numerous commercially available orally disintegrating systems and products available by 2009, the person of ordinary skill in the art would have had a high expectation of success. For example, the Danckwerts and Fu review articles are representative of the knowledge of the person of ordinary skill in the art. These references disclose several commercially available orally 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 2009.

328. Grother in view of the FDA Guidance therefore renders obvious a solid pharmaceutical composition that disintegrates within 60 seconds when tested using the USP <701> Disintegration Test. Grother in view of the FDA Guidance therefore renders obvious limitation 1[iv].

6. Limitation 1[v]

329. Limitation 1[v] recites “wherein the orally disintegrating tablet has a hardness of 4-48 N or a friability of not more than 1%.”

330. A person of ordinary skill in the art would have been motivated to formulate Grother’s fast dispersing solid dosage form containing budesonide or

fluticasone to have a hardness of between 4-48 N or a friability of not more than 1% with a reasonable expectation of success in view of Kararli and the USP.

331. Kararli is directed to ODTs. *See* EX1110 (Kararli) at Title (“Rapidly disintegrating oral formulation of a cyclooxygenase-2 inhibitor”); *id.* at 3:14-4:18 (discussing drawbacks of traditional tablets).

332. Kararli teaches ODTs have a hardness “more preferably of about 1 to about 5 kp.” *Id.* at 25:23-27. A hardness of 1-5 kp is equivalent to a hardness of 9.8-49.1 N.⁹ Kararli teaches that this hardness is important for an ODT to “have sufficient hardness for handling,” and to “withstand removal from at least a standard type of blister packaging,” and “withstand other handling such as packaging, delivery, carrying and the like.” *Id.* at 25:28-26:13; *id.* at 9:19-26 (“Preferably, such tablets have a hardness of about 1 kp to about 10 kp.”).

333. Kararli’s teaching is reinforced by the knowledge of the person of ordinary skill in the art, which is represented by, for example, the United States Pharmacopeia (“USP”). USP standards have been recognized as an authority in the pharmaceutical field for over 200 years “because they are authoritative and science-

⁹ 1 kilopond (kp) is equivalent to 9.8N. *See* EX1104 (USP <1217>) at 677 (“The relationship between these units of force is 1 kilopond (kp) = 1 kilogram-force (kgf) = 9.8 N.”).

based and are established by a transparent and credible process.” EX1104 (USP) at viii. USP is “recognized by law and custom in many countries throughout the world,” including the U.S. *Id.* USP teaches that hardness is an important indicator of mechanical strength for tablets to “be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users (patients/consumers).” *Id.* at 676. USP also teaches that friability is another important indicator of mechanical strength for tablets and recommends that a friability “of not more than 1.0% is considered acceptable for most products.” *Id.*

334. A person of ordinary skill in the art would have been motivated to follow Kararli and USP’s recommendations in formulating Grother’s fast dispersing solid dosage form to have a hardness of 9.8-49.1 N and a friability of not more than 1% to provide a solid dosage form of sufficient mechanical strength to handle packaging, transportation, and handling. A person of ordinary skill in the art had a reasonable expectation of success in formulating Grother’s fast dispersing solid dosage form to have a hardness falling within the range of 4-48 N or a friability falling within the range of not more than 1% given the disclosures of Kararli, and the USP.

335. The reasonable expectation of success is supported by several of Patent Owner’s prior art publications by Venkatesh that disclose ODTs having hardness

and friability within the claimed ranges. Example 1 of Venkatesh516 discloses ODTs with a hardness of “8-48 N” and friability of “NMT [not more than] 1.0%”:

<i>Tablet Parameters</i>	<i>Target</i>	<i>Range</i>
Weight per tablet (mg)	100	95-105 (± 5%)
Thickness (mm)	2.40	2.00-2.80
Hardness (N)	28	8 - 48
Friability (%)	NMT 0.6	NMT 1.0
Weight/10 tablets (g)	1.00	0.96 – 1.04 (± 4%)

EX1111 (Venkatesh516) at 22:7-26. Tables 3 and 12 of Venkatesh345 disclose ODTs with hardness of 6.80 and 6.92-6.95 N and friability of 0.24-0.31% (Table 3), or hardnesses between 41.3-67 N and friability between 0.05-0.51% (Table 12):

Table 3: Tableting Parameters for Hydrocodone Bitartrate/Acetaminophen ODTs:

Parameter	5 mg/500 mg ODT	10 mg/300 mg ODT
Tooling - round, flat face, radius edge	17 mm	15 mm
Target tablet weight (mg)	1600	1250
Lower target tablet weight × 0.985 (mg)	1576	1231
Target tablet weight × 1.015 (mg)	1624	1269
Turn table speed with range (rpm)	15 (10 - 20)	15 (10 - 20)
Fill depth (mm)	10.94-10.98	5.11
Main position (mm)	10.6-11.1	4.44
Pre. Position (mm)	6.2-6.4	4.61
Scale on the feed shoe	2 (0 – 4)	2 (0 – 4)
Tablet Weight (mg)	1597	1248.6
Hardness with range (n)	6.80	6.92-6.95
Thickness with range (mm)	47-49	40-42
Friability with range (%)	0.25-0.31	0.24-0.31

EX1112 (Venkatesh345) at 38 (Table 3).

Table 12: Tableting Properties of Hydrocodone Bitartrate / Acetaminophen ODTs

Lot#	Compression Force	Weight	Thickness	Hardness	Friability
<u>ODTs 10-mg/300-mg</u>					
1334-142	13 kN	1102 mg	6.12 mm	41.3 N	0.51%
	14 kN	1101 mg	6.03 mm	46.4 N	0.37%
1198-062	12.5 kN	1099 mg	6.09mm	46.0 N	0.20%
<u>ODTs 5-mg/500-mg</u>					
1198-046	18 kN	1402 mg	6.11 mm	53 N	0.18%
	20 kN	1394 mg	6.03 mm	61 N	0.05%
	22 kN	1390 mg	5.97 mm	67 N	0.17%

EX1112 (Venkatesh345) at 48 (Table 12). Table 12 of Venkatesh346 also discloses ODTs with hardness and friability within the claimed ranges:

Table 12: Tableting Properties of Hydrocodone Bitartrate / Acetaminophen ODTs

Lot#	Compression Force	Weight	Thickness	Hardness	Friability
<u>ODTs 10-mg/300-mg</u>					
1334-142	13 kN	1102 mg	6.12 mm	41.3 N	0.51%
	14 kN	1101 mg	6.03 mm	46.4 N	0.37%
1198-062	12.5 kN	1099 mg	6.09mm	46.0 N	0.20%
<u>ODTs 5-mg/500-mg</u>					
1198-046	18 kN	1402 mg	6.11 mm	53 N	0.18%
	20 kN	1394 mg	6.03 mm	61 N	0.05%
	22 kN	1390 mg	5.97 mm	67 N	0.17%

EX1113 (Venkatesh346) at 48 (Table 12).

336. Grother in view of Kararli, the FDA Guidance, and the USP therefore render obvious claim 1.

C. Claims 2-3

337. Claims 2-3 recite:

Claim 2. The orally disintegrating tablet of claim 1, comprising about 0.5 mg to about 2 mg of the corticosteroid.

Claim 3. The orally disintegrating tablet of claim 1, comprising about 3 mg of the corticosteroid.

338. Claims 2 and 3 are obvious for the same reasons discussed above for limitation 1(i).

D. Claim 4

339. Claim 4 recites:

Claim 4. The orally disintegrating tablet of claim 1, comprising a sugar alcohol and/or saccharide.

340. Grother discloses mannitol as its preferred matrix forming excipient. EX1008 (Grother) at 13:12. Mannitol was the bulk excipient of choice for ODTs. EX1041 (Conway) at 261. The '598 patent states that mannitol is a sugar alcohol that was “typically used in disintegrating tablet formulations.” EX1001 (the '598 patent) at 8:52-60, 9:10-11. Claim 4 is therefore obvious.

E. Claim 9

341. Claim 9 recites:

Claim 9. The orally disintegrating tablet of claim 2, wherein the corticosteroid is budesonide.

342. Claim 9 is obvious for the same reasons discussed above for Claim 1.

F. Claim 11

343. Claim 11 recites:

Claim 11. The orally disintegrating tablet of claim 3, wherein the corticosteroid is fluticasone propionate.

344. Claim 11 is obvious for the same reasons discussed above for Claim 1.

G. Claims 13-14

345. Claims 13-14 recite:

Claim 13. The orally disintegrating tablet of claim 1, wherein the disintegrant is crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, low-substituted hydroxypropylcellulose, mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, or combinations thereof.

Claim 14. The orally disintegrating tablet of claim 13, wherein the disintegrant is crospovidone.

346. As discussed above for limitation (ii), the '598 patent states that disintegrants include starches such as carboxymethyl starch, for example sodium starch glycolate, i.e., Primogel® and Explotab®. EX1001 (the '598 patent) at 9:49-54 (“Examples of suitable disintegrants include e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, *sodium starch glycolate*, starch, pregelatinized starch, and *carboxymethyl starch (e.g. Primogel® and Explotab®)*.”) (emphasis added). A person of ordinary skill in the art would

understand that sodium starch glycolate is a disintegrant made from starch by carboxymethylation and crosslinking and is found in both Primogel[®] and Explotab[®].

347. Grother discloses that modified starches “may be used as the primary structure forming agent in FDDF's [fast dispersing dosage forms] to form physically robust products while maintaining the desired rapid dispersion characteristics of the products.” EX1008 (Grother) at 4:2-4 (“Modified starches may be used as the primary structure forming agent in FDDF's to form physically robust products while maintaining the desired rapid dispersion characteristics of the products.”). Grother teaches that useful modified starches are generally readily dispersible in water. EX1008 (Grother) at 13:5-8 (“While many specific examples are provided on the useful modified starches, a general characteristic of the useful modified starches in the fast dispersing solid dosage form according to the invention is that they are readily soluble or dispersible in water at ambient temperature.”). Grother further discloses that a range of commercially available modified starches, including pregelatinized starches, oxidized starches, and crosslinked starches, are suitable for use in their orally dispersing tablets. EX1008 (Grother) at 5:10-6:5 (“A range of modified starches are commercially available and useful in the present invention and include: Pregelatinized starches, produced by drum drying or extrusion; Low-viscosity starches, produced by controlled hydrolysis of glycosidic bonds; Dextrins, produced by roasting dry starch in the presence of a small amount of acid; Acid

modified starches, produced by suspension in dilute acid until the required viscosity is reached; *Oxidized starches, oxidizing agents cause the introduction of carbonyl or carboxyl groups*, wherein depolymerization occurs, leading to decreased retrogradation and gelling capacities; Enzymatically modified starch, produced by controlled enzyme degradation to attain required physicochemical properties; *Crosslinked starches*, bi- or polyfunctional reagents react with hydroxyl groups to form crosslinks, examples of specific reagents include phosphorus oxychloride, sodium trimetaphosphate and epichlorohydrin; and Stabilized starches, starches are reacted with etherifying or esterifying reagents in the presence of an alkaline catalyst to give a wide range of products.”) (emphasis added). Sodium starch glycolate is a commercially available disintegrant made from potato starch by carboxymethylation and crosslinking and is found in both Primogel[®] and Explotab[®]. A person of ordinary skill in the art would understand that the term ‘modified starch’ would include sodium starch glycolate which is commercially available as Primogel[®] and Explotab[®]. Grother therefore discloses at least one disintegrant selected from the list comprising sodium starch glycolate.

348. Kararli discloses that its ODTs may contain one or more additional pharmaceutically acceptable excipients including disintegrants. EX1110 (Kararli) at 22:5-9 (“Optionally, a molded article of the invention can contain *one or more additional pharmaceutically acceptable excipients including, but not limited to,*

binders, wetting agents, water-soluble lubricants, water-insoluble lubricants, *disintegrants*, glidants, sweeteners, flavoring agents, effervescent agents, colorants, etc.”). Kararli discloses that the disintegrant may be sodium starch glycolate or crospovidone. EX1110 (Kararli) at 24:11-17 (“Pharmaceutically acceptable disintegrants that can optionally be present... include starches, sodium starch glycolate,... celluloses, e.g., purified cellulose, methylcellulose, sodium carboxymethylcellulose, carboxymethylcellulose,... *crospovidone*... and mixtures thereof.”).

349. Claims 13-14 are therefore obvious.

H. Claims 18-19

350. Claims 18-19 recite:

Claim 18. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet disintegrates within 60 seconds when tested in simulated saliva fluid using the USP <701> Disintegration Test.

Claim 19. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.

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

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

352. As discussed above regarding limitation 1[iv], a person of ordinary skill in the art would have been motivated to formulate Grother’s fast dispersing dosage form to disintegrate within 30 seconds with a reasonable expectation of success. The FDA recommended that such compositions have “an in-vitro disintegration time of approximately 30 seconds or less,” EX1005 (FDA Guidance) at 2 (“Based on the original product rationale and Agency experience, we recommend that, in addition to the original definition, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative.”), using the “USP 29, <701> Disintegration” test. *Id.* at 3 n.3 (“USP 29, <701> Disintegration, pp. 2670-2672.”).

353. The FDA Guidelines explain that ODTs dissolve in the patient’s saliva. EX1005 (FDA Guidance) at 3 (“We recommend that as a primary consideration when developing this type of product, you use the defining characteristics for this

dosage form designation (rapid disintegration in saliva without the need for chewing or liquids).”). The USP <701> Disintegration Test called for by the FDA Guidelines “use[s] water or the specified medium as the immersion fluid.” EX1040 (Disintegration 2008) at 2 (“Place 1 dosage unit in each of the six tubes of the basket and, if prescribed, add a disk. Operate the apparatus using water or the specified medium as the immersion fluid, maintained at $37 \pm 2^\circ$.”). A person of ordinary skill in the art would have been motivated to perform the USP <701> Disintegration Test using simulated saliva as the immersion fluid to provide testing conditions that were as close as possible to the in vivo conditions in a patient’s mouth and more accurately represent disintegration within the oral cavity. For example, the prior art taught that simulated saliva was a desirable medium for disintegration testing because it produced conditions that are “as close as possible to the in vivo conditions” within a patient’s mouth. EX1047 (El Arini) at 367 (“In order to select the volume parameter as close as possible to the in vivo conditions, the studies were conducted in 2 mL of artificial saliva.”). Grother in view of the FDA Guidance therefore renders obvious an orally dispersing tablet that disintegrates within 60 seconds in simulated saliva when tested using the USP <701> Disintegration Test.

354. Claims 18-19 are therefore obvious.

I. Claim 20

355. Claim 20 recites:

Claim 20. A method for treating eosinophilic esophagitis comprising administering to a patient in need thereof the orally disintegrating tablet according to claim 1.

356. Grother teaches formulating its fast dispersing solid dosage form with budesonide or fluticasone, which were known corticosteroids. EX1008 (Grother) at 18:15. Budesonide and fluticasone were known to be potent, locally acting anti-inflammatory glucocorticoids that were desirable for treating inflammation of the gastrointestinal tract. In particular, budesonide and fluticasone were known to successfully treat several inflammatory conditions of the gastrointestinal tract, including eosinophilic esophagitis. EX1014 (Aceves 2005) at 706 (treating eosinophilic esophagitis); EX1015 (Aceves 2007) at 1, 6, 8 (treating eosinophilic esophagitis); EX1002 (Dohil) ¶¶[0010], [0011], [0015] (treating inflammation of the esophagus, including eosinophilic esophagitis). A person of ordinary skill in the art would have been motivated to formulate Grother's fast dispersing solid oral dosage form with budesonide or fluticasone to treat eosinophilic esophagitis with a reasonable expectation of success.

Claim 20 is therefore obvious.

J. Claims 21 and 29

357. Claims 21 and 29 recite:

Claim 21. The method of claim 20, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 29. The orally disintegrating tablet of claim 14, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

358. Claims 21 and 29 are obvious for the same reasons discussed above for Claims 1, 13-14 and 20.

K. Claim 22

359. Claim 22 recites:

Claim 22. The method of claim 20, wherein the orally disintegrating tablet comprises about 0.5 mg to about 2 mg of budesonide.

360. Claim 22 is obvious for the same reasons discussed above for Claims 1 and 20.

L. Claims 23-25

361. Claims 23-25 recite:

Claim 23. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a hardness of 4-48 N.

Claim 24. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a friability of not more than 1%.

Claim 25. The orally disintegrating tablet of claim 1, wherein the orally disintegrating has a hardness of 4-48 N and a friability of not more than 1%.

362. Claims 23-25 are obvious for the same reasons discussed above for claim limitation 1[v].

M. Claims 31-32

363. Claims 31-32 recite:

Claim 31. The method of claim 20, wherein the orally disintegrating tablet disintegrates within 60 seconds when tested in simulated saliva fluid using the USP <701> Disintegration Test.

Claim 32. The method of claim 20, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> Disintegration Test.

364. Claims 31-32 are obvious for the same reasons discussed above for Claims 1 and 18-20.

XX. GROUND 11: GROTHER IN VIEW OF KARARLI, THE FDA GUIDANCE, THE USP, AND VENKATESH988

365. This section explains how Grother in view of Kararli, the FDA guidance, the USP, and Venkatesh988 render obvious dependent claims 5-8, 10, 12, 15-16 and 30 of the '598 patent.

A. Claim 5

366. Claim 5 recites:

Claim 5. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid and at least one excipient, and the rapidly dispersing granules comprise the disintegrant and a sugar alcohol and/or saccharide.

367. Venkatesh988 discloses “an orally disintegrating tablet made up of rapidly dispersing microgranules and taste-masked microcapsules” of drug particles. EX1020 (Venkatesh988) ¶[0001]; *id.* ¶¶[0018], [0025] (microcapsule drug particles). The drug particles are granulated with diluent excipients. *Id.* ¶[0021]. Venkatesh988 discloses that “this invention relates to pharmaceutical compositions comprising rapidly dispersing microgranules of a disintegrant and sugar alcohol or a saccharide.” *Id.* ¶[0014]; *id.* ¶[0018], ¶[0028] (“sugar alcohol” and “saccharide”). Venkatesh988 therefore discloses ODTs comprising drug particles comprising excipients and rapidly dispersing microgranules comprising a disintegrant, a sugar alcohol and/or saccharide.

368. The person of ordinary skill in the art would have been motivated for the budesonide or fluticasone in Grother’s fast dispersing solid dosage form to comprise drug particles with an excipient and the disintegrant to be rapidly dispersing granules that include a sugar alcohol and/or saccharide based on Venkatesh988. Venkatesh988 teaches that formulating ODTs to have drug particles and rapidly-dispersing microgranules comprising sugar alcohol and/or saccharide in combination with the disintegrant beneficially “avoid[ed] gritty mouthfeel,” EX1020 (Venkatesh988) ¶[0012], to assist with providing a “smooth creamy mouthfeel (no grittiness),” *id.* ¶[0002].

369. The person of ordinary skill in the art had a reasonable expectation of success based on Venkatesh988. Venkatesh988 teaches that its formulations “don’t require a special pharmaceutical production technique and can be simply and easily produced by a normal equipment.” EX1020 (Venkatesh988) ¶[0018].

370. Grother in view of Kararli, the FDA guidance, the USP, and Venkatesh988 render obvious claim 5.

B. Claims 6-8

371. Claims 6-8 recite:

Claim 6. The orally disintegrating tablet of claim 5, wherein the rapidly dispersing granules have an average particle size of less than about 300 μm , and each of the disintegrant and sugar alcohol and/or saccharide have an average particle size of about 1-30 μm .

Claim 7. The orally disintegrating tablet of claim 5, wherein the drug particles have an average particle size of about 100-400 μm .

Claim 8. The orally disintegrating tablet of claim 5, wherein the drug particles have an average particle size of about 100-400 μm , the rapidly dispersing granules have an average particle size of less than about 300 μm , and each of the disintegrant and sugar alcohol and/or saccharide have an average particle size of about 1-30 μm .

372. Venkatesh988 discloses drug particles that advantageously have “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” and provide “a smooth creamy mouthfeel.” EX1020 (Venkatesh988) ¶[0015].

373. Venkatesh988 discloses that the rapidly dispersing granules “typically” have an “average particle size of not more than 300 μm .” EX1020 (Venkatesh988) ¶[0020]. A small particle size assists with mouthfeel. *Id.* ¶¶[0019], [0009], [0025].

374. Venkatesh988 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 (Venkatesh988) ¶[0014]; *id.* ¶[0018] (“preferably not more than 20 μm ”), ¶[0028].

375. A person of ordinary skill in the art would have been motivated to formulate budesonide or fluticasone in an ODT based on Grother, and also having drug particles with a particle size less than 400 μm , rapidly dispersing granules with a particle size less than 300 μm , and a disintegrant and sugar alcohol and/or saccharide with a particle size less than 30 μm based on Venkatesh988 to avoid a gritty texture and improve mouthfeel with an expectation of success.

376. Claims 6-8 are therefore obvious.

C. Claims 10, 12, and 30

377. Claims 10, 12, and 30 recite:

Claim 10. The orally disintegrating tablet of claim 5, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 12. The orally disintegrating tablet of claim 8, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

Claim 30. The orally disintegrating tablet of claim 16, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

378. Claims 10, 12, and 30 are obvious over Grother in view of Kararli, the FDA Guidance, the USP, and Venkatesh988 for the same reasons discussed herein for Claims 1, 5, 8, and 15-16.

D. Claims 15-16

379. Claims 15-16 recite:

Claim 15. The orally disintegrating tablet of claim 5, wherein the sugar alcohol and/or saccharide is mannitol, sorbitol, xylitol, maltitol, arabitol, ribitol, dulcitol, iditol, isomalt, lactitol, erythritol, lactose, sucrose, maltose, or combinations thereof.

Claim 16. The orally disintegrating tablet of claim 15, wherein the sugar alcohol is mannitol.

380. Grother discloses mannitol as its preferred matrix forming excipient. EX1008 (Grother) at 13:12. Mannitol was the bulk excipient of choice for ODTs. EX1041 (Conway) at 261.

381. Venkatesh988 discloses that “[t]he dispersible microgranules comprise a sugar alcohol such as mannitol.” EX1020 (Venkatesh988) ¶¶[0032], [0047]. Venkatesh988 further discloses that “[t]he sugar alcohol may be selected from the group consisting of mannitol, sorbitol, xylitol, maltitol and the like....” *Id.* ¶[0028].

382. Claims 15-16 are therefore obvious.

E. Claim 17

383. Claim 17 recites:

Claim 17. The orally disintegrating tablet of claim 5, wherein the ratio of disintegrant to sugar alcohol, saccharide or mixture thereof in the rapidly dispersing microgranules ranges from about 90/10 to about 99/01.

384. Grother discloses that its fast dispersing solid dosage form comprises at least one modified starch at a concentration of from 20 to 90% by weight, and preferably 50 to 90% by weight. EX1008 (Grother) at 12:14-15, 13:3-4. Grother’s modified starch is a disintegrant.

385. Grother discloses mannitol as its preferred matrix forming excipient. EX1008 (Grother) at 13:12. Mannitol was the bulk excipient of choice for ODTs. EX1041 (Conway) at 261. The ’598 states admits that mannitol is a sugar alcohol. EX1001 (the ’598 patent) at 8:52-60, 9:10-11.

386. In the embodiment where Grother’s fast dispersing solid dosage form has a modified starch at a concentration of 90% by weight, the matrix forming agent

is necessarily present in an amount less than 10% by weight. When this embodiment has mannitol selected as the preferred matrix forming agent, it has a ratio of modified starch (a disintegrant) to mannitol (a sugar alcohol) falling within the claimed range of from about 90/10 to about 99/01.

387. Claim 17 is therefore obvious.

XXI. GROUND 12: GROTHER IN VIEW OF KARARLI, THE FDA GUIDANCE, THE USP, AND VENKATESH516

388. This section explains how Grother in view of Kararli, the FDA Guidance, the USP, and Venkatesh516 render obvious dependent claims 26- 28 and 33-34 of the '598 patent.

A. Claims 26-27

389. Claims 26-27 recite:

Claim 26. The orally disintegrating tablet of claim 1, wherein the orally disintegrating tablet has a friability of not more than 0.6%.

Claim 27. The orally disintegrating tablet of claim 25, wherein the orally disintegrating tablet has a friability of not more than 0.6%.

390. It was obvious to formulate Grother's fast dispersing solid dosage form to have a friability of less than 1% for reasons discussed above regarding limitation 1[v]. A person of ordinary skill in the art would have been motivated to formulate Grother's fast dispersing solid dosage form to have a friability of not more than 0.6% with a reasonable expectation of success in view of Venkatesh516.

391. Venkatesh516's ODTs have a friability target of "NMT [not more than] 0.6%" as shown below:

<i>Tablet Parameters</i>	<i>Target</i>	<i>Range</i>
Weight per tablet (mg)	100	95-105 ($\pm 5\%$)
Thickness (mm)	2.40	2.00-2.80
Hardness (N)	28	8 - 48
Friability (%)	NMT 0.6	NMT 1.0
Weight/10 tablets (g)	1.00	0.96 – 1.04 ($\pm 4\%$)

EX1111 (Venkatesh516) at 22:21; *see also id.* at 22:1 ("friability (target: <0.6%)"); *id.* 23:27 (same).

392. Venkatesh516 further discloses that such a friability is sufficiently low for the ODT "to be suitable for packaging in HDPE bottles and push-through film backed or peel-off paper backed blister packs using conventional equipment for storage, transportation and commercial distribution." EX1111 (Venkatesh516) at 16:23-27; *id.* at 19:10-11, 19:25-26.

393. Claims 26-27 are therefore obvious.

B. Claim 28

394. Claim 28 recite:

Claim 28. The orally disintegrating tablet of claim 27, wherein the orally disintegrating tablet has a thickness of 2-2.8 mm.

395. Venkatesh516 discloses ODTs having a "target" thickness of 2.40 mm as follows:

<i>Tablet Parameters</i>	<i>Target</i>	<i>Range</i>
Weight per tablet (mg)	100	95-105 ($\pm 5\%$)
Thickness (mm)	2.40	2.00-2.80
Hardness (N)	28	8 - 48
Friability (%)	NMT 0.6	NMT 1.0
Weight/10 tablets (g)	1.00	0.96 – 1.04 ($\pm 4\%$)

EX1111 (Venkatesh516) at 22:19. A person of ordinary skill in the art would have been motivated to follow Venkatesh516's instruction with a reasonable expectation of success to target a thickness of 2.40 mm when formulating Grother's fast dispersing solid dosage form to provide an appropriately thick tablet to impart sufficient mechanical strength while also providing appropriate mouthfeel to the patient.

396. Claim 28 is therefore obvious.

C. Claim 33

397. Claim 33 recites:

Claim 33. The orally disintegrating tablet of claim 28, wherein the orally disintegrating tablet comprises about 3 mg of fluticasone propionate.

398. Claim 33 is obvious for the same reasons discussed above for Claims 1, 25, and 27-28.

D. Claim 34

399. Claim 34 recites:

Claim 34. The orally disintegrating tablet of claim 28, wherein the orally disintegrating tablet comprises about 0.5 mg to about 2 mg of budesonide.

400. Claim 34 is obvious for the same reasons discussed above for claims 1, 25, and 27-28.

XXII. CONCLUSION

401. For the reasons described above, a person of ordinary skill in the art would have found Claims 1-34 of the '598 patent to be unpatentable.

402. 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: 19Sep2025 By: Alan Frank PARR

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