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. IPR2024-01197
U.S. Patent No. 8,771,729

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

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LIST OF MATERIALS CONSIDERED

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1003	EP2482822B1 that was revoked by the European Patent Office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1007	"DRAFT Guidance for Industry: Orally Disintegrating Tablets," U.S. Food & Drug Administration, Center for Drug Evaluation and Research (CDER), 2007.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

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

Exhibit No.	Description
1034	Noel et al., "Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis," Clinical Gastroenterology and Hepatology 2:568-575 (2004)
1035	U.S. Patent No. 7,122,198 to Singh et al.
1036	U.S. Patent No. 7,229,641 Cherukuri et al.
1073	Schoepfer et al., "Variation in Endoscopic Activity Assessment and Endoscopy Score Validation in Adults With Eosinophilic Esophagitis," Clinical Gastroenterology and Hepatology, 17:1477-1488 (2019).
1074	2021-04-19 Assignment of U.S. Patent No. 8,771,729 from Adare Pharmaceuticals US, L.P. to Ellodi Pharmaceuticals, L.P. recorded at Reel 055966, Frame 0658.
1075	International Publication No. WO2003074029 to McEntee et al.
1076	International Publication No. WO2009078872 to Martin et al.
1077	U.S. Patent Publication No. 20030124184 to Mezaache et al.
1078	U.S. Patent Publication No. 20050019393 to Augsburger et al.
1079	U.S. Patent No. 7,384,921 to Tang et al.
1080	U.S. Patent Publication No. 20080132535 to Singh et al.
1081	U.S. Patent Publication No. 20090022799 to Barman
1082	Than, "Individualized Drugs for Individual Needs," Review of Optometry, 146:38-43 (2009)
1083	Iorgulescu, "Saliva between normal and pathological. Important factors in determining systemic and oral health," Journal of Medicine and Life 2:3003-307 (2009)
1085	U.S. Patent No. 6,139,865 to Friend et al.

Exhibit No.	Description
1086	2015-09-18 Assignment of U.S. Patent No. 6,139,865 to Adare Pharmaceuticals, Inc. recorded at Reel 036640, Frame 0591
1087	Narmada et al., "Formulation, evaluation and optimization of fast dissolving tablets containing amlodipine besylate by sublimation method," ARS Pharmaceutica, 50:129-144 (2009)
1088	Khan et al., "Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapid-disintegrating tablets," AAPS PharmSciTech 8:E1-E7 (2007)
1089	CLARITIN® (loratidine) FDA-approved package insert
1090	ZOFRAN® (ondansetron) FDA-approved package insert
1091	CLARINEX® (desloratadine) FDA-approved package insert
1092	PEPCID® (famotidine) FDA-approved package insert
2007	Declaration of Dr. Martyn Christopher Davies (and exhibits cited therein)
Paper 10	Decision Granting Institution of IPR2024-01197 (Jan. 27, 2025)

1. I, Alan F. Parr, Pharm.D., Ph.D., submit this reply declaration in response to issues and arguments raised by Patent Owner Ellodi Pharmaceuticals in this proceeding relating to the inter partes review (IPR) of U.S. Patent No. 8,771,729 ("the '729 patent," EX1001). In particular, I submit this declaration to respond to certain factual issues and arguments raised in the declaration of Ellodi's expert, Dr. Martyn Christopher Davies (EX2007).

2. I previously submitted a declaration in support of Dr. Falk Pharma's IPR petition in this proceeding (hereafter "My First Declaration," EX1030).

3. In forming the responses in this declaration, I have considered the materials referenced in this declaration, the materials referenced in My First Declaration (EX1030), the declaration of Dr. Davies (EX2007), and the exhibits cited in Dr. Davies' declaration.

A. THE SCOPE AND CONTENT OF THE PRIOR ART IS RELEVANT

4. My First Declaration provided a summary of the scope and content of the prior art. *See* EX1030 (My First Declaration) ¶¶43-95 (section entitled "Scope and Content of the Prior Art"). I understand that obviousness is based on underlying factual determinations regarding the scope and content of the prior art, as well as the level of ordinary skill in the art. *See id.* ¶25 ("***I further understand that the four factors to be considered in an obviousness inquiry are: (1) the scope and content of the prior art;*** (2) the differences between the prior art and the claims; ***(3) the level***

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of ordinary skill in the pertinent art; and (4) secondary considerations including long-felt need, commercial success, and unexpected results.”).[1]

5. The Davies Declaration does not disagree that obviousness is based on underlying factual determinations regarding the scope and content of the prior art, as well as the level of ordinary skill in the art. *See* EX2007 (Davies Declaration) ¶33 (stating that Dr. Davies understands that the factual determinations underlying obviousness “include (1) the scope and content of the prior art; [and] (2) the level of ordinary skill in the art at the time the claimed invention was made….”).

6. It is therefore surprising that the Davies Declaration asserts that “[o]ver 30 pages of [my] analysis on the scope of the prior art is irrelevant.” EX2007 (Davies Declaration) ¶64; *see generally id.* ¶¶64-90. I disagree with that assertion. The references discussed in the “Scope and Content of the Prior Art” section of my declaration are relevant to establishing the scope and content of the prior art, and also the level of ordinary skill in the art.

7. The Davies Declaration asserts that none of the references cited in My First Declaration “disclose an orally disintegrating solid composition containing budesonide, or topical deposition of budesonide on the upper gastrointestinal tract.” EX2007 (Davies Declaration) ¶66. I disagree. My First Declaration cites to Dohil

[1] All emphases supplied unless otherwise noted.

(EX1002), Grother (EX1008), Singh (EX1035), and Cherukuri (EX1036). *See, e.g.,* EX1030 (My First Declaration) ¶¶56-59, 84-91. Each of these references disclose an orally disintegrating solid composition containing budesonide, and a person of ordinary skill in the art was aware that such orally disintegrating solid compositions would deposit budesonide in the upper gastrointestinal tract. *Id.*; *see also id.* ¶¶122-124, 190-192. For example, My First Declaration explained that budesonide was known to be topically active. *See e.g., id.* ¶¶44-59. It also explained that ODTs rapidly dissolve in the mouth (which is part of the upper gastrointestinal tract), thereby depositing the drug in the upper gastrointestinal tract. *See id.* ¶¶60-65.

8. My First Declaration additionally provided a review article that teaches ODTs were designed to "release the drug to the oral mucosa," EX1017 (Danckwerts) at 178, and that many prior art studies had shown topical therapy with corticosteroids to treat inflammatory mucosal diseases, *id.* at 176. Other prior art teaches that ODTs are beneficial "when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething." EX1087 (Narmada) at 129; EX1088 (Kahn) at E1 (same).

B. MY FIRST DECLARATION IS NOT BASED ON HINDSIGHT

9. The Davies Declaration accuses me of using "impermissible hindsight" and "begin[ing] with the language of the claims and work[ing] backwards to make the prior art fit into" my obviousness analysis. EX2007 (Davies Declaration) ¶77. I

disagree with this accusation. My First Declaration appropriately analyzes obviousness regarding:

(1) the scope and content of the prior art (*see, e.g.,* EX1030 ¶¶43-95 (section entitled "Scope and Content of the Prior Art"));

(2) the similarities and differences between the prior art and the claims (*see, e.g.,* EX1030 ¶¶97-330 (sections analyzing obviousness for Grounds 1-4)); and

(3) the level of ordinary skill in the art (*see* EX1030 ¶¶28-30 (section entitled "The Person of Ordinary Skill in the Art")).

10. The Davies Declaration does not disagree that obviousness is based on underlying factual determinations regarding the scope and content of the prior art, as well as the level of ordinary skill in the art. *See* EX2007 (Davies Declaration) ¶33 (agreeing that the factual determinations underlying obviousness "include (1) the scope and content of the prior art; (2) the level of ordinary skill in the art at the time the claimed invention was made; [and] (3) the differences between the claimed invention and the prior art."). Again, it is surprising that the Davies Declaration asserts that My First Declaration is based on impermissible hindsight when My First Declaration appropriately analyzes the agreed-upon factual determinations underlying the obviousness analysis.

C. MY FIRST DECLARATION PROVIDES SUPPORT FOR MY OPINIONS

11. The Davies Declaration asserts that "[c]onsistent throughout [my First Declaration] is a lack of support for his conclusions" and that My First Declaration contains "conclusory opinions." EX2007 (Davies Declaration) ¶91. I disagree with these assertions. Nearly every paragraph in My First Declaration provides a supporting citation or quote to an exhibit. In addition, My First Declaration provides 164 pages of detailed analyses to support my opinions.

1. Dohil Renders Obvious Claims 1-7, 15, 20-21, 27, And 29-36 Of The '729 Patent (Ground 1)

12. My First Declaration provided a thorough obviousness analysis for claims 1-7, 15, 20-21, 27, and 29-36 of the '729 patent based on Dohil in view of the knowledge of a person of ordinary skill in the art (Ground 1 in My First Declaration). *See* EX1030 (My First Declaration) ¶¶97-167.

13. As discussed in My First Declaration, Dohil discloses solid budesonide compositions in the form of a lozenge or similar tablet that "dissolve[s] rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus." EX1002 (Dohil) ¶[0032]; *see, e.g.,* EX1030 (My First Declaration) ¶¶117-121. It was desirable for the disintegration time of rapidly dissolving tablets to vary "from several seconds to about a minute." EX1018 (Fu) at 434 ("The disintegration time for good FDTs [fast disintegrating tablets] varies from several seconds to about a minute."). The FDA

Guidance recommends that orally dissolving tablets (ODTs) should "disintegrate[] rapidly, usually within a matter of seconds." EX1005 (FDA Guidance) at 2 ("A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."). For at least these reasons, and as further discussed in My First Declaration, Dohil teaches, suggests, and motivates formulating rapidly dissolving solid compositions, including ODTs containing budesonide. *See* EX1030 (My First Declaration) ¶¶117-121.

14. The Davies Declaration disputes Dohil's teaching, suggestion, and motivation by: (i) focusing on Dohil's teachings of ***liquid*** corticosteroid formulations of budesonide and dismissing Dohil's teachings of ***solid*** corticosteroid formulations, (ii) asserting that all lozenges must dissolve slowly, (iii) asserting that there is only 1-2 mL of saliva available in a patient's mouth to dissolve an ODT, and (iv) mischaracterizing Dohil's other embodiments. *See, e.g.,* EX2007 (Davies Declaration) ¶¶92-108. I respond to these issues in the following paragraphs.

a. <u>Dohil Teaches, Suggests, And Motivates Solid ODT Formulations</u>

15. The Davies Declaration asserts that a person of ordinary skill in the art would focus on Dohil's teachings of ***liquid*** corticosteroid formulations of budesonide rather than consider Dohil's teachings of ***solid*** corticosteroid formulations in the form of rapidly dissolving lozenges and tablets. *See, e.g.,* EX2007 (Davies Declaration) ¶¶94-96. However, I understand that a person of ordinary skill in the art would consider Dohil

for everything that it teaches, which includes Dohil's teachings of solid corticosteroid formulations.

16. Dohil instructs the person of ordinary skill in the art to formulate budesonide as a rapidly dissolving lozenge or tablet to treat inflammation of 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. 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.").

17. Dohil's instruction to formulate budesonide as a rapidly dissolving lozenge or tablet would have been intuitive and compelling to a person of ordinary skill in the art in view of Dohil's express desire to treat eosinophilic esophagitis (EOE). *See* EX1002 (Dohil) ¶[0010] ("The methods of the present invention are useful, for example, for preventing and alleviating the symptoms and inflammation of ***eosinophilic esophagitis***, inflammatory bowel diseases involving the esophagus, Crohn's disease, esophageal inflammation secondary to caustic/irritant ingestion, persistent/recurrent esophageal strictures of any cause and including caustic/irritant ingestion, pill-induced esophagitis, systemic diseases, congenital diseases, Epidermolysis bullosa, and post-surgery inflammation."), ¶[0011] ("The individual may, for example, have been diagnosed with a disease or condition selected from the group consisting 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, and post-surgery inflammation.").

18. A primary symptom of EOE is difficulty swallowing. *See* EX1033 (Teitelbaum) at 1218 (Table 1 reporting "Dysphagia" was presented in 11% of patients with EOE, which is the symptom having the largest percentage reported by patients); *see also* EX1073 (Schoepfer) at 1478 ("dysphagia is the most frequent complaint of adult EOE patients").[2] Rapidly dissolving tablets were known to be useful for treating patients that have difficulty swallowing. *See* EX1005 (FDA Guidance) at 1 (explaining that ODTs were "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)."); EX1018 (Fu) at

[2] Schoepfer was co-authored and funded by Adare Pharmaceuticals. *See* EX1073 (Schoepfer) at 1477 (listing co-author Brian A. Meltzer as affiliated with Adare Pharmaceuticals, Inc.); *id.* at 1488 (under the "Funding" heading it states "The data for score responsiveness were generated by Aptalis Pharma, Inc (currently owned by Adare Pharmaceuticals, Inc."). I understand that Adare Pharmaceuticals changed its name to Ellodi Pharmaceuticals in 2020.

434-434 ("Dysphagia, or difficulty in swallowing is common among all age groups. … Solid 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."); EX1030 (My First Declaration) ¶¶66-83. Because EOE tends to be associated with difficulty swallowing, an ODT would be a natural fit for treating EOE in view of ODTs being desirable for patients who have difficulty swallowing.

19. The Davies Declaration asserts there was no motivation to follow Dohl's instruction to prepare a solid rapidly dissolving lozenge/tablet because Dohil did not recognize any problems with the liquid formulations set forth in Dohil's working examples. EX2007 (Davies Declaration) ¶¶104-105. However, as discussed in My First Declaration, rapidly dissolving solid formulations were known to have several benefits as compared with liquid formulations. *See* EX1030 (My First Declaration) ¶71. For example, rapidly dissolving tablets provide "[c]onvenience of administration and accurate dosing as compared to liquid formulations." EX1019 (Shukla) at 311. Rapidly dissolving tablets were known to have the same advantages as other solid dosage forms including their stability, ease of accurate dosing, proven manufacturing methods, and small packaging size and ease of handling. *See, e.g.,* EX1018 (Fu) at 434 ("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.”).

20. Dohil’s liquid formulation was a rudimentary formulation that allowed an initial proof-of-concept study to show that oral formulations of budesonide successfully treat EOE. *See* EX1002 (Dohil) ¶¶[0046]-[0070] (Examples 1-3). Dohil calls for “larger placebo-controlled clinical trials [to] provide more information about dosing, efficacy and long-term safety of this treatment.” EX1002 (Dohil) ¶[0067]. Once the effectiveness of budesonide to treat EOE was proven it would have been a natural next step for the person of ordinary skill in the art to follow Dohil’s instruction to formulate budesonide as a solid rapidly dissolving lozenge or tablet because the known benefits of solid compositions would facilitate Dohil’s larger clinical trial. For example, a solid rapidly dissolving lozenge or tablet would have been expected by the person of ordinary skill in the art to be more convenient to administer to patients, provide more accurate dosing, and be more stable as compared to Dohil’s viscous liquid formulation.

b. <u>Rapidly disintegrating lozenges</u>

21. The Davies Declaration asserts that Dohil ¶[0032] does not teach or suggest a rapidly dissolving solid formulation because it uses the word “lozenge,” which the Davies Declaration interprets as requiring a slowly dissolving formulation. EX2007 (Davies Declaration) ¶¶97-99. I disagree. Dohil ¶[0032] discloses a “rapidly” dissolving lozenge or similar tablet as follows:

> 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, wo[u]ld dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus***. Or, for children or other patients that may have difficulty with a dissolving lozenge, the lozenge may be ground or otherwise dissolved in a small volume of water or other pharmaceutically suitable liquid, for example, reaching a total volume presented in embodiments herein. In other illustrative embodiments of the invention, the Budesonide is provided in the form of a tablet, a capsule, or, for example a gel capsule, designed for slow release and delivery to the esophagus.

EX1002 (Dohil) ¶[0032]. As an initial matter, the plain reading of paragraph [0032] is that at least Dohil's ***tablet*** rapidly dissolves in the mouth, which fairly teaches and suggests an ODT (orally dissolving tablet), especially in view of the industry accepted ODT definition 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.

22. Turning to Dohil's "lozenge or other similar tablet" in paragraph [0032], the Davies Declaration interprets this phrase as describing a solid formulation having an initial rapid "release of budesonide from the lozenge or similar tablet, which would then slowly [*sic*, dissolve] to continuously release the drug." EX2007 (Davies Declaration) ¶97. I disagree with this interpretation. The plain reading of Dohil ¶[0032] is that "[t]he

lozenge or similar tablet" (i.e., the entire lozenge or tablet) would dissolve rapidly in the mouth. Dohil ¶[0032] contrasts its "rapidly" dissolving lozenge/tablet with other formulations "designed for slow release." EX1002 (Dohil) ¶[0032] ("***In <u>other</u> illustrative embodiments of the invention***, the Budesonide is provided in the form of a tablet, a capsule, or, for example a gel capsule, ***designed for slow release*** and delivery to the esophagus."). Dr. Davies' interpretation requires combining the rapidly dissolving lozenge/tablet with the "other" slow-release embodiment. This interpretation does not align with the plain reading of paragraph [0032], which is that Dohil's rapidly dissolving lozenge/tablet is a different embodiment than the "other" slow release embodiment.

23. The Davies Declaration implies that I was unable to identify fast dissolving lozenges in the prior art by citing my deposition transcript (EX2011) at 63:6-21. *See* EX2007 (Davies Declaration) ¶83 (citing EX2011 at 63:6-21). I testified that "I haven't done a literature search on [fast dissolving lozenges]," so I wasn't aware if there were any fast-dissolving lozenges in the prior art. EX2011 (My Deposition Transcript) at 63:6-21. I am now aware of several examples of fast dissolving lozenges that were in the prior art, which include the following references:

24. International Publication No. WO2003074029 to McEntee et al., which teaches:

> ***Fast melt formulations are typically in the form of tablets or lozenges that dissolve or disperse in a patient's mouth within a minute without the need of water or chewing***. Drug delivery formulations which exhibit fast melt properties can improve patient compliance due to the ease of swallowing as well as the absence of a need for the co-administration of water or another fluid.

EX1075 (McEntee) at 3:20-28.

25. International Publication No. WO2009078872 to Martin et al., which teaches:

> Generally, a sublingual tablet, wafer, pellet, ***or lozenge should dissolve or disintegrate quickly, allowing the analgesic to be rapidly absorbed***.

EX1076 (Martin) ¶[0060].

> In certain embodiments, ***the orally disintegrating tablets, wafers, pellets, or lozenges of the present invention release their analgesic content over a period of*** about 5 seconds to about 120 seconds, about 5 seconds to about 90 seconds, ***about 5 seconds to about 60 seconds, about 5 seconds to about 30 seconds, or about 10 seconds to about 60 seconds***, when placed under the tongue of a human. ***In certain embodiments, the orally disintegrating tablets, wafers, pellets, or lozenges of the present invention dissolve completely over a period of about*** 10 seconds to about 120 seconds, about 10 seconds to about 90 seconds, ***about 10 seconds to about 60 seconds, about 10 seconds to about 30 seconds, or about 20 seconds***

> ***to about 60 seconds***, when placed into human saliva or a solution that mimics human saliva.

EX1076 (Martin) ¶[0067].

26. This Martin reference also discloses that its quickly disintegrating formulations include a disintegrant as follows:

> Methods known in the art for producing fast disintegrating tablets, wafers, pellets, ***or lozenges*** may also be used to produce the orally disintegrating tablets, wafers, pellets, ***or lozenges*** of the present invention. For example, U.S. Patent No. 6,596,311 describes a method of producing a fast disintegrating tablet comprising a drug in multiparticulate form, e.g., granular or microencapsulated, by formulating the drug with one or more water insoluble inorganic excipients, ***one or more disintegrants***, and optionally, one or more substantially water soluble excipients, the amounts of said ingredients being such as to provide a disintegration time in the mouth in the order of 75 seconds or less, e.g., 40 seconds or less, preferably less than 30 seconds, most preferably less than 20 seconds.

EX1076 (Martin) ¶[0064].

27. <u>U.S. Patent Publication No. 20030124184 to Mezaache et al., which teaches:</u>

> "Quick dissolve compositions and tablets based thereon."

EX1077 (Mezaache) at Title.

> The invention relates to compressible compositions and dosage forms based thereon, such as tablets and ***lozenges, which, when ingested, quickly***

> ***dissolve in the mouth***, but which effectively mask the taste of unpleasant active agent(s) therein.

EX1077 (Mezaache) ¶[0002].

> One aspect associated with ameliorating the effects of ingesting molecules that are generally unpalatable is to provide the drug in dosage forms, such as tablets and ***lozenges, which, when ingested, quickly dissolve in the mouth***.

EX1077 (Mezaache) ¶[0003].

> Tablets and other dosage forms, e.g., ***lozenges, made therefrom rapidly dissolve when placed in the mouth, generally in less than 30 seconds***.

EX1077 (Mezaache) ¶[0040].

28. Mezaache also discloses that its quick dissolving formulations often include a disintegrant. *See* EX1077 (Mezaache) ¶[0010] ("Disintegrants are often included to ensure that the tablet has an acceptable rate of disintegration. Typical disintegrants include starch derivatives and salts of carboxymethylcellulose.").

29. <u>U.S. Patent Publication No. 20050019393 to Augsburger et al., which teaches:</u>

> The invention still further relates to methods for preparing rapidly-disintegrating dosage forms comprising active cushioning components of the invention. In alternate embodiments, the dosage forms comprise placebo cushioning components and active components which are milled to a very small size, capable of being compressed into tablets or ***lozenges which have rapid disintegration rates***.

EX1078 (Augsburger) ¶[0043].

> In another embodiment, the present invention relates to ***a rapidly disintegrating lozenge***.

EX1078 (Augsburger) ¶[0143].

30. Augsburger also discloses that its quick dissolving lozenges include a disintegrant. *See* EX1078 (Augsburger) ¶¶[0083]-[0084] ("The disintegrant may be the same or different from the highly water-absorbing material. Non-limiting examples of useful disintegrants include croscarmellose sodium, sodium starch glycolate, crospovidone, starch, and pregelatinized starch. In one embodiment, the disintegrant is croscarmellose sodium."); *id.* ¶¶[0079], [0085].

31. U.S. Patent No. 7,384,921 to Tang et al., which teaches:

> In another embodiment, the invention provides a "fast melt" formulation. Such fast melt formulations are typically in the form of a tablet or ***lozenge that dissolve or disperse in a patient's mouth within a minute without the need of water or chewing***.

EX1079 (Tang) at 14:9-13.

32. U.S. Patent Publication No. 20080132535 to Singh et al., which teaches:

> The compositions of the present invention may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets (e.g., chewable, slow-dissolving, quick-dissolving, etc.), pills, capsules, lozenges, gums, powders, solutions, suspensions,

> emulsions, aerosols, foams, creams, gels, lotions, or the like. Preferably, the compositions of the present invention are formulated as a tablet or a lozenge, ***in particular quick-dissolving tablets or lozenges***, such as those described in U.S. Patent Publication No. 20050226925.

EX1080 (Nikhilesh Singh) ¶[0057].

> Claim 11. The pharmaceutical composition of claim 1, ***wherein the composition is a quick-dissolving lozenge*** or tablet.

EX1080 (Nikhilesh Singh) at Claim 11.

33. This Singh reference also discloses that its quick-dissolving lozenges include "***disintegrating agents*** such as crospovidone as well as croscarmellose sodium and other cross-linked cellulose polymers." EX1080 (Nikhilesh Singh) ¶[0061]; *id.* ¶[0083] ("***The lozenge or candy composition may further comprise*** protecting agents, lubricating agents, wetting agents, emulsifying agents, solubilizing agents; suspending agents, preserving agents, sweetening agents, flavoring agents, coloring agents, and ***disintegrating agents***.").

34. <u>U.S. Patent Publication No. 20090022799 to Barman, which teaches:</u>

> ***A fast dissolving dosage form such as a tablet, troche, or lozenge***, or a dry film is preferable for delivery of the β-Glucan containing prophylactic or therapeutic in the oral space.

EX1081 (Barman) ¶[0044].

> Claim 31. A method for preventing oral mucositis comprising the administration of the composition of claim 1 as ***a fast dissolving lozenge*** or troche dissolved in the mouth.
>
> Claim 33. A method for treating oral mucositis comprising the administration of the composition of claim 32 as ***a fast dissolving lozenge*** or troche dissolved in the mouth.

EX1081 (Barman) at Claims 31 and 33.

35. Than, "Individualized Drugs for Individual Needs," Review of Optometry, 146:38-43 (2009), which teaches:

> Compounding pharmacies can also:
>
> Prepare medications that are not commercially available, are not economically feasible to manufacture, or are not stable.
>
> Prepare formulas for individual needs with a special strength.
>
> Add flavor to make an oral medication more palatable.
>
> Prepare unique routes of administration, ***such as a quick-dissolving lozenge***, a lollipop or a transdermal patch.

EX1082 (Than) at 2.

36. Dohil's use of the word "lozenge" to describe a rapidly dissolving solid composition of budesonide is appropriate because lozenges are typically used to formulate topical drugs that "have very few systemic adverse effects" and "treat[] local mouth diseases and sore throats." EX1017 (Danckwerts) at 181. As mentioned above, a primary symptom of EOE is difficulty swallowing due to inflammation of the throat/esophagus. *See* EX1033 (Teitelbaum) at 1218; EX1073 (Schoepfer) at 1478.

As discussed in My First Declaration, budesonide was known to topically treat inflammation of the esophagus. EX1030 (My First Declaration) ¶¶44-59. Dohil's description of a rapidly dissolving "lozenge" in paragraph [0032] signals to the person of ordinary skill in the art that the formulation will rapidly dissolve to release budesonide to topically treat a patient's inflamed throat/esophagus.

37. The Davies Declaration asserts that Dohil's rapidly dissolving lozenge/tablet cannot include a disintegrant based on Danckwerts teaching that lozenges are typically manufactured without disintegrants. *See* EX2007 (Davies Declaration) ¶100 (citing EX1017 (Danckwerts) at 181). However, Dohil expressly discloses using disintegrants in its formulations. *See* EX1002 (Dohil) ¶[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."). As explained in My First Declaration, it was known that the rapid disintegration of a lozenge or tablet is desirably aided by at least one disintegrating agent. *See* EX1030 (My First Declaration) ¶¶109-111; EX1018 (Fu) at 446-47 (heading "Disintegrants Used in FDTs"). Also, several of the fast dissolving lozenges discussed above disclose using disintegrants in such formulations. *See* EX1076 (Martin) ¶[0064]; EX1077 (Mezaache) ¶[0010]; EX1078 (Augsburger) ¶¶[0083]-[0084], [0079], [0085]; EX1080 (Nikhilesh Singh) ¶¶[0061], [0083].

c. **Patients produce sufficient saliva to coat the esophagus**

38. The Davies Declaration asserts that Dohil requires a large volume (8-12 mL) of a viscous liquid to coat the esophagus, and that a patient's alleged saliva production of only 1-2 mL would provide an insufficient volume and viscosity to coat the esophagus with a rapidly dissolving lozenge or tablet. *See* EX2007 (Davies Declaration) ¶¶106, 108. I disagree for several reasons.

39. First, Dr. Davies' position is inconsistent with Dohil's express disclosure. Dohil expressly teaches that its rapidly dissolving lozenge or tablet does "dissolve rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus." EX1002 (Dohil) ¶[0032]. Dohil explains that its tablets "are formulated with at least one excipient to deliver a viscous form of the corticosteroid to the esophagus." *Id.* ¶[0013]. Such an excipient "increase[s] the resulting liquid viscosity of the dissolved tablet, enabling it to reach the esophagus, for example, to coat the esophagus." *Id.* ¶[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."); *id.* ¶[0043] ("Excipients, such as, for example, those listed herein, may be included in the composition to increase the viscosity of the delivered composition. The liquid viscosity may be increased in the oral form, or the excipient may increase the viscosity of the dissolved form of a tablet.").

40. Based on Dohil's express teachings, a person of ordinary skill in the art would have reasonably expected that the patient's saliva would successfully mix with the rapidly dissolving lozenge or tablet to produce a solution of sufficient volume and viscosity to coat the esophagus.

41. Second, the Davies Declaration mischaracterizes my deposition testimony as supposedly admitting that dissolving an "orally disintegrating composition [that] disintegrates in 60 seconds…. would only produce 1-2 mL [of] liquid." EX2007 (Davies Declaration) ¶106 (citing EX2011 at 50:17-24). I actually testified that a patient tends to ***swallow*** 1-2 mL of liquid at a time in response to a question asked by Ellodi's counsel containing two "ands" (thereby making it a three-part question):

> Q. A POSA would also know that this rapidly disintegrating or dissolving tablet would disintegrate quickly in the mouth ***and*** be swallowed ***and*** go straight to the stomach, correct?
>
> A. It would. It has to go through the esophagus. And it's a small volume of liquid, 1 to 2 mils. So it doesn't go down as a bolus. It goes down as a very slow amount.

EX2011 (My Deposition Transcript) at 50:17-24. The "1 to 2 mils" in my answer referred to the amount of saliva that is typically swallowed by a person. It was known that 1-2 mL of saliva triggers a swallowing reflex. *See* EX1083 (Iorgulescu) at 304 ("When the volume of saliva [in the oral cavity] is approximately 1.1 ml, a swallowing reflex is triggered.").

42. Counsel for Ellodi did not ask me how much saliva a patient produces ***when a lozenge or tablet is placed in the mouth***. It was known that placing a substance in the oral cavity (such as a lozenge or tablet) causes a patient's saliva production to increase to about 4-5 mL/min. *See* EX1083 (Iorgulescu) at 303 ("The whole unstimulated saliva flow rate is approximately 0.3-0.4 ml / min. This rate decreases to 0.1 ml / min during sleep ***and increases to about 4,0-5,0 ml / min during eating, chewing and other stimulating activities***."); *id.* at 304 ("***When a substance is placed in the oral cavity, the flow of saliva will increase*** depending on its taste, consistency and concentration. When the volume of saliva is approximately 1.1 ml, a swallowing reflex is triggered. ***Salivary stimulation, dilution of tasting and swallowing will continue until the concentration of the tastings reaches a point where it ceases to stimulate salivary flow***.").

43. This 4-5 mL/min volume of saliva produced by placing a lozenge/tablet in a patient's mouth trickles slowly down the esophagus as it is swallowed approximately 1-2 mL at a time. *See* EX1083 (Iorgulescu) at 304 ("***When a substance is placed in the oral cavity, the flow of saliva will increase*** depending on its taste, consistency and concentration. ***When the volume of saliva is approximately 1.1 ml, a swallowing reflex is triggered***. Salivary stimulation, dilution of tasting and swallowing will continue until the concentration of the tastings reaches a point where it ceases to stimulate salivary flow."). A person of

ordinary skill in the art would have recognized this volume of saliva to be sufficient to dissolve Dohil's lozenge or tablet and produce the viscous solution disclosed by Dohil that coats the esophagus. *See* EX1002 (Dohil) ¶¶[0032], [0013], [0037], [0043] (quoted above).

44. The Davies Declaration asserts that a person of ordinary skill in the art would not have followed Dohil's instruction to prepare a solid rapidly dissolving lozenge or tablet because such a lozenge/tablet would constitute a "fundamentally different formulation" with "dramatic mechanistic" differences than Dohil's liquid formulation. EX2007 (Davies Declaration) ¶¶74-75. I disagree. Dohil explains that its rapidly dissolving lozenge or tablet operates by dissolving "rapidly in the mouth or esophagus to produce a solution that can then coat the esophagus." EX1002 (Dohil) ¶[0032]; *see also id.* ¶¶[0013], [0037], [0043]. Dohil's rapidly dissolving lozenge/tablet and liquid formulations are both orally administered and they both share a mechanistic principle of operation, which is to provide a solution of budesonide that coats the esophagus.

45. Dohil's solid formulation was expected to dissolve rapidly in the mouth to produce a solution that coats the esophagus. Dohil repeatedly explains that the excipients in its rapidly dissolving lozenge or tablet mix with the patient's saliva to produce a viscous solution containing budesonide that coats the esophagus. *See* EX1002 (Dohil) ¶[0032] ("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***."), ¶[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***."), ¶[0043] ("***Excipients, such as, for example, those listed herein, may be included in the composition to increase the viscosity of the delivered composition***."). Dohil's rapidly dissolving lozenges and tablets therefore provide an indirect way of forming a budesonide-containing liquid in the mouth, and that liquid is able to coat the esophagus.

d. <u>The Davies Declaration misinterprets Dohil's alternative embodiments</u>

46. Dohil discloses a rapidly dissolving lozenge/tablet that is dissolved ***in a patient's mouth***, and it also discloses an alternative embodiment where the lozenge is "ground or otherwise dissolved" ***in a liquid prior to administration*** for the minority of patients that "may have difficulty with a dissolving lozenge" as follows:

> 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. ***<u>Or</u>***, for children or other patients that may have difficulty with a dissolving lozenge, the lozenge may be ground or otherwise dissolved in a small volume of water or other

> pharmaceutically suitable liquid, for example, reaching a total volume presented in embodiments herein.

EX1002 (Dohil) ¶[0032]. A person of ordinary skill in the art would understand that Dohil's rapidly dissolving lozenge/tablet that is dissolved ***in a patient's mouth*** is an alternative embodiment from grinding/dissolving a lozenge ***in a liquid prior to administration*** because these two embodiments are separated by the word "***Or***."

47. A person of ordinary skill in the art would recognize that Dohil's description of "children or other patients that may have difficulty with a dissolving lozenge" refers to a subpopulation of children/patients that may suffer dexterity, reflex, or other symptomatic issues leading to them having difficulty with a dissolving lozenge. EX1002 (Dohil) ¶[0032]. For this subpopulation of patients, Dohil provides the alternative embodiment where the lozenge is "ground or otherwise dissolved in a small volume of water or other pharmaceutically suitable liquid" before administration. *Id.* Based on this alternative embodiment, the Davies Declaration argues that Dohil's rapidly dissolving lozenge or tablet cannot suggest an ODT because an ODT must not be ground or dissolved in liquid before administration. EX2007 (Davies Declaration) ¶99. I disagree with the Davies Declaration for reasons discussed in the following paragraph.

48. It is unsurprising that Dohil recognizes that ***not all patients*** will benefit from Dohil's ODT formulation. A person of ordinary skill in the art would understand, however, that ***many patients would*** be expected to benefit from Dohil's

rapidly dissolving lozenge/tablet. As explained in My First Declaration, it was recognized that ODTs desirably provide convenience and improved compliance for many patients. *See* EX1030 (My First Declaration) ¶¶66-83. The expectation that many patients would benefit from Dohil's rapidly dissolving lozenge/tablet is more than sufficient to motivate the person of ordinary skill in the art to follow Dohil's instruction to prepare a rapidly dissolving lozenge/tablet for treating EOE.

e. Dohil Teaches And Suggests The Dosages Recited In Claims 1[i] And 27[i] With An Expectation Of Success

49. The Davies Declaration asserts that a person of ordinary skill in the art cannot extrapolate dosage amounts from Dohil's successful treatment of EOE using the ***liquid*** formulations from Examples 1-3 because there are supposedly "different considerations" in formulating ***solid*** compositions. EX2007 (Davies Declaration) ¶109. I disagree for several reasons.

50. First, the Davies Declaration does not articulate how any supposedly "different considerations" for a solid versus liquid formulation would be material to Dohil's budesonide dosages.

51. Second, as explained in My First Declaration, Dohil teaches appropriate dosages for budesonide that apply to its solid formulations, which provides a reasonable expectation of success. *See* EX1030 (My First Declaration) ¶¶106-107; *see also* EX1002 (Dohil) ¶[0015] ("The pharmaceutical composition in certain embodiments comprises a therapeutically effective amount of corticosteroid

to prevent or alleviate esophageal inflammation. ***In certain embodiments, 1-2 mg or 2-3 mg or corticosteroid per day is administered to said individual***."); *id.* ¶[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 35to 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.").

52. Third, the person of ordinary skill in the art's expectation of success is supported by several FDA-approved prior art examples of solid ODT formulations that have the same drug dosage amount as the corresponding liquid formulation. For example:

- CLARITIN® (loratidine) ODT and liquid syrup are dosed at 10 mg. *See* EX1089 (Claritin Package Insert) at 2.
- ZOFRAN® (ondansetron) ODT and oral solution are both dosed at either 4 or 8 mg and are bioequivalent. *See* EX1090 (Zofran Package Insert) at 5:125-128.
- CLARINEX® (desloratadine) ODT and liquid syrup are dosed at 5 mg. *See* EX1091 (Clarinex Package Insert) at 19.

- PEPCID® (famotidine) ODT and oral suspension are dosed at 40 mg and are bioequivalent. *See* EX1092 (Pepcid Package Insert) at 1-2.

f. Dohil Teaches And Suggests The Claimed Methods Of Treatment (Claims 29-34)

53. For claims 29-34, the Davies Declaration repeats its previous assertion that Dohil does not teach or suggest the claimed orally disintegrating composition. *See* EX2007 (Davies Declaration) ¶111. I disagree for at least the reasons discussed above.

54. The Davies Declaration also repeats its previous assertion that Dohil does not provide an expectation of success in achieving the volume or viscosity required to cover the esophagus. *See* EX2007 (Davies Declaration) ¶112. I disagree for at least the reasons discussed above.

2. Grother In View Of The FDA Guidance Renders Obvious Claims 1-7, 9-15, 20, 27-28, 35-36, And 38-40 Of The '729 Patent (Ground 2)

55. My First Declaration provided a thorough obviousness analysis for claims 1-7, 9-15, 20, 27-28, 35-36, and 38-40 of the '729 patent based on Grother in view of the FDA Guidance (Ground 2 in My First Declaration). *See* EX1030 (My First Declaration) ¶¶168-252. I provide the following response to the Davies Declaration regarding Grother and the FDA Guidance for Ground 2 in the following paragraphs.

a. Grother And The FDA Guidance Teach, Suggest, And Motivate Formulating Orally Disintegrating Compositions/Tablets

56. As discussed in My First Declaration, Grother teaches an ODT formulation, EX1008 (Grother) at 12:10-19, and further teaches that any drug can be used in the formulation, including "budesonide" and "fluticasone." *Id.* at 15:19-20, 18:15-18; EX1030 (My First Declaration) ¶¶171-176. Grother's express instruction to use budesonide and fluticasone in its ODT formulation teaches, suggests, and motivates their use in Grother's ODT.

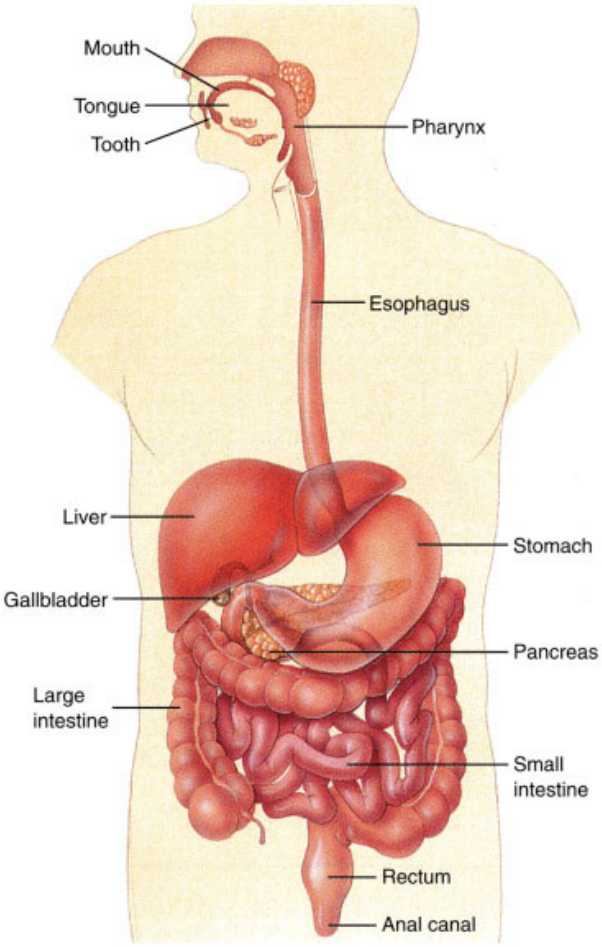
57. The Davies Declaration accuses me of "arbitrarily selecting budesonide from the hundreds of disclosed drugs" within Grother. EX2007 (Davies Declaration) ¶119. But I did not arbitrarily select budesonide to include in Grother's ODT formulation. Rather, Grother itself instructs that budesonide should be used in its ODT formulation. *See* EX1008 (Grother) at 15:19-20, 18:15-18.

58. The Davies Declaration seeks to diminish Grother's instruction to use budesonide because it is included amongst "hundreds of drugs listed in Grother," EX2007 ¶119, and because Grother "does not highlight or point out any particular class of drugs for its ODT formulation," *id.* ¶118. I understand that Grother is relevant for all it discloses and that Grother must be considered for its ability to suggest formulations to the person of ordinary skill in the art. Grother's express instruction to use budesonide in its ODT formulation is more than sufficient to

motivate the person of ordinary skill in the art to use budesonide in Grother's ODT formulation. In addition, Grother's instruction to use budesonide in its ODT formulation is reinforced by at least three other prior art references that also teach the use of budesonide and/or fluticasone in ODTs: (1) Dohil (EX1002), (2) Cherukuri (EX1036), and (3) Singh (EX1035). *See* EX1030 (My First Declaration) ¶¶53-59, 84-91 (discussing EX1002, EX1035, EX1036).

59. The Davies Declaration asserts that a person of ordinary skill in the art would not have been motivated to select budesonide because Grother does not "distinguish between systemic and topical drugs or acknowledge any difference between systemic and topical corticosteroids." EX2007 (Davies Declaration) ¶118. As discussed above, Grother expressly instructs the person of ordinary skill in the art to use budesonide in its ODT formulation. As explained in My First Declaration, the background knowledge of the person of ordinary skill in the art included knowledge that budesonide was a potent topically acting drug that successfully treats inflammation of the gastrointestinal tract, including EOE. EX1030 (My First Declaration) ¶¶44-59. If Grother had to explain all of the background knowledge held by the person of ordinary skill in the art, then the reference would need to be written as a comprehensive tutorial/treatise for a layperson (and likely be hundreds of pages long), instead of being a concise document directed to a person of ordinary skill in the art.

60. The Davies Declaration asserts non-obviousness because Grother doesn't state that its ODT is capable of topically depositing a drug in the upper gastrointestinal tract. EX2007 (Davies Declaration) ¶115. The person of ordinary skill in the art would not require such an express statement to understand that Grother's ODT formulation is capable of topically depositing budesonide in the upper gastrointestinal tract because Grother teaches that its ODT formulation rapidly releases the drug in a patient's oral cavity, which was known to deposit the drug in the upper gastrointestinal tract. *See* EX1030 (My First Declaration) ¶¶190-192; EX1008 (Grother) at 3:18-22, 1:10-11, 32:10. When Grother's ODT releases a drug in the patient's oral cavity, it deposits the drug in the upper gastrointestinal tract because the oral cavity (mouth) is part of the upper gastrointestinal tract. The following figure illustrates components of the upper gastrointestinal tract, including the mouth, esophagus and stomach:



61. In addition, the person of ordinary skill in the art reviewing the FDA Guidance would appreciate that ODTs are designed and expected to deposit drugs in the upper gastrointestinal tract. The FDA Guidance explains that ODTs are "ingested simply by placing them on the tongue" and "disintegrate or dissolve rapidly on contact with saliva." *See* EX1005 (FDA Guidance) at 1 ("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.”). Placement of an ODT on a patient’s tongue takes place in the patient’s mouth, which is part of the upper gastrointestinal tract. A person of ordinary skill in the art would understand that the ODT contacts saliva in the patient’s mouth, which causes the ODT to disintegrate/dissolve and deposit the drug in the mouth. ODTs were therefore expected to deposit a drug in the mouth (which is part of the upper gastrointestinal tract).

b. <u>There was a reasonable expectation of success based on Grother in view of the FDA Guidance.</u>

62. The Davies Declaration asserts that a person of ordinary skill in the art would not have reasonably expected to formulate an orally disintegrating pharmaceutical composition containing budesonide or fluticasone that would topically deposit these drugs in the upper gastrointestinal tract because there are supposedly different considerations in formulating systemic drugs in ODTs than topical drugs. EX2007 (Davies Declaration) ¶121. I disagree for several reasons.

63. First, a POSA would understand that whether a drug acts topically or systemically often depends on the properties of the specific drug rather than the formulation of the drug.

64. Second, the Davies Declaration does not articulate how any supposedly different consideration is material to (or would override) Grother’s express

instruction that "[a]ny drug may be used" in its ODT, including "budesonide" and "fluticasone." EX1008 (Grother) at 15:19-20, 18:15-18; EX1030 (My First Declaration) ¶¶169-176.

65. Third, the expectation of successfully formulating an orally disintegrating pharmaceutical composition containing budesonide or fluticasone that would topically deposit these drugs in the upper gastrointestinal tract based on Grother is reinforced by other prior art references that likewise provide an express instruction to use budesonide and/or fluticasone in ODTs, including Dohil (EX1002), Cherukuri (EX1036), and Singh (EX1035). *See* EX1030 (My First Declaration) ¶¶53-59, 84-91 (discussing EX1002, EX1035, EX1036).

66. Fourth, the '729 specification admits that orally disintegrating compositions are prepared via a "conventional granulator," a "conventional oven," and a "conventional rotary tablet press." EX1001 (the '729 patent) at 16:31-43. A person of ordinary skill in the art would understand that the same conventional equipment may be used to formulate both topically and systemically acting dosage forms. The specification does not provide any special guidance or contribution to the field required to formulate the claimed orally disintegrating compositions, which indicates that the person of ordinary skill in the art would have reasonably expected to be able to formulate the claimed invention based on the knowledge held by the person of ordinary skill in the art.

c. Grother And The FDA Guidance Render Obvious The Dosages Recited In Claims 1[i], 27[i], 28, And 38-40

67. The Davies Declaration asserts that a person of ordinary skill in the art would not have been motivated to arrive at the claimed dosage amounts with a reasonable expectation of success because there are supposedly different considerations in formulating solid ODTs with topical drugs than liquid formulations, enterically coated tablets, and rectal foam. *See* EX2007 (Davies Declaration) ¶122. I disagree for several reasons.

68. First, the Davies Declaration agrees that "there is no dispute that budesonide, fluticasone, or other topical corticosteroids could be used to treat inflammation of the upper gastrointestinal tract." EX2007 (Davies Declaration) ¶65; *id.* ¶76 ("there is no dispute that budesonide was known for treating conditions of the gastrointestinal tract, including the upper gastrointestinal tract"). In order for budesonide, fluticasone, and other topical corticosteroids to be known to treat conditions of the upper gastrointestinal tract, the dosage amount of those corticosteroids would also be known. In view of there being no dispute that budesonide, fluticasone, and other topical corticosteroids were known for treating inflammation of the upper gastrointestinal tract, then the person of ordinary skill in the art would have reasonably expected that budesonide could be dosed at appropriate amounts to treat inflammation of the upper gastrointestinal tract.

69. Second, the Davies Declaration does not articulate how any supposedly "different considerations" for a solid ODT versus liquid formulation, enterically coated tablets, or rectal foam would be material to the dosage amount of corticosteroid used in Grother's ODT formulation.

70. Third (and contrary to Dr. Davies' assertions otherwise at EX2007 ¶123), My First Declaration provided an explanation why a person of ordinary skill in the art would have been motivated to formulate Grother's ODTs with budesonide at, e.g., 3 mg, with a reasonable expectation of success 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 topically administrable formulations of budesonide typically contain, e.g., 3 mg of budesonide. *See, e.g.,* EX1030 (My First Declaration) ¶¶173-176.

71. Fourth, the person of ordinary skill in the art's expectation of success is supported by numerous prior art FDA-approved examples of solid ODT formulations having the same drug dosage as the corresponding liquid formulation. *See, supra* Section C.1.e.

72. Fifth, the '729 patent fails to distinguish between different dosage amounts across different formulations. *See, e.g.,* EX1001 (the '729 patent) at 7:18-60. The '729 specification admits that orally disintegrating compositions are prepared via a "conventional granulator," a "conventional oven," and a

"conventional rotary tablet press." EX1001 (the '729 patent) at 16:31-43. The specification does not provide any special guidance or contribution to the field required to formulate the claimed dosage amounts for orally disintegrating compositions, which indicates that the person of ordinary skill in the art would have reasonably expected to be able to formulate the claimed invention based on the knowledge held by the person of ordinary skill in the art.

3. Dohil In Combination With Venkatesh Renders Obvious Claims 8 And 16-18 Of The '729 Patent (Ground 3)

73. The Venkatesh reference (EX1020) and the '729 patent share co-inventor Dr. Gopi M. Venkatesh. I understand that the Venkatesh reference (EX1020) was assigned to Adare Pharmaceuticals, which changed its name to Ellodi Pharmaceuticals in 2020. As discussed in My First Declaration, Venkatesh (EX1020) previously disclosed the same limitations that Ellodi later claimed in claims 8 and 16-18 of the '729 patent. *See* EX1030 (My First Declaration) ¶¶254-257.

74. The Davies Declaration asserts that Venkatesh requires taste-masking by coating microparticles with a water-insoluble polymer, and it argues this coating prevents Dohil's corticosteroid from being topically deposited in the upper GI tract. *See* EX2007 (Davies Declaration) ¶¶129-130, 136-137. I disagree for reasons discussed below.

75. First, the '729 patent and Venkatesh incorporate-by-reference another of Adare/Ellodi's patents, U.S. 6,139,865 ("the '865 patent," EX1085).[3] *See* EX1001 (the '729 patent) at 2:32-34 ("All documents (e.g., patents, patent publication, journal articles, etc.) cited in the present application are incorporated by reference in their entirety for all purposes."), *id.* at 14:44-46 ("Examples of such a coacervation process are disclosed in U.S. Pat. Nos. 5,252,337, 5,639,475, ***6,139,865*** and 6,495,160."); EX1020 (Venkatesh) ¶[0012] (U.S. 6,139,865 "is incorporated in its entirety by reference"), ¶[0027] ("Examples of such a coacervation process are disclosed in U.S. Pat. No. 6,139,865, which is incorporated in its entirety by reference.").

76. In the '865 patent, Adare/Ellodi explained that taste-masking with a water-insoluble polymer does ***not*** prevent topical disposition of drug in the upper gastrointestinal tract. Rather, the taste-masking allows the drug to be released "virtually immediate[ly]" and "shortly" after passage through the mouth such that the drug is deposited in the upper gastrointestinal tract:

- "Although the use of polymeric materials, particularly cellulosic polymers, to taste mask bittertasting drugs is known, as noted

[3] The '865 patent was assigned Adare Pharmaceuticals, EX1086 (Assignment for '865 patent), which changed its name to Ellodi Pharmaceuticals in 2020, EX1074 (Assignment for '729 patent).

above, the present invention provides for far more effective taste masking than previously possible, using high coating levels ***while nevertheless achieving virtually immediate release of drug***." EX1085 (the '865 patent) at 2:65-3:3.

- "The composition comprises microcapsules of drug ***and a substantially water-insoluble polymeric material, typically a cellulosic polymer***. The microcapsule composition may be incorporated into any number of pharmaceutical formulations, including chewable tablets, effervescent tablets, powders, liquid dispersions, and the like. A method for masking the taste of drugs is also provided, involving a phase separation coacervation technique in which drug is coated with relatively high levels of a polymeric material. These high coating levels give rise to effective taste masking while nevertheless allowing targeted release of drug, ***so that the drug is released shortly after passage through the mouth***." *Id.* at Abstract.
- "In this way, the invention provides for extremely effective taste masking ***while also providing for release of drug shortly after the drug passes through the mouth***." *Id.* at 1:67-2:2.

77. The Adare/Ellodi '865 patent explains that the water-insoluble coating has a porous structure that facilitates the rapid release of the drug from the microparticles:

> Although the present invention is not limited by any theory of operation, it is believed that the polymeric walls of the microcapsules, particularly those formed by coacervation, ***typically have pores***. It is

> further believed that drug dissolution from the microcapsules occurs through these pores. ***Thus, it is believed that water enters the pores and forms a highly concentrated solution of drug and water inside the microcapsule, and that the resulting concentration gradient from the highly concentrated solution to the surrounding aqueous fluid drives diffusion of the drug out through the pores to the surrounding aqueous fluid***. Another mechanism of release which is believed to occur is breakage of the coating on the microcapsule, possibly caused or promoted by swelling of the core material due absorption of water.

Id. at 9:31-45; *see also id.* at 7:52-56 ("As further discussed below, ***it is believed that release of the drug from the microcapsules principally involves pores in the coating*** rather than diffusion of the drug through the first polymeric material itself."); *id.* at 15:60-63 (Claim 6. "The taste-masked microcapsule composition of claim 5 ***wherein said coacervated polymeric material has pores therein and said microcapsules are adapted to release the drug by diffusion through said pores***.").

78. The Adare/Ellodi '865 patent further teaches that the release rate for a particular drug can be adjusted. *Id.* at 9:54-55 ("Regardless of the reasons for these effects, these effects can be used to adjust the release rate for a particular drug.").

79. The '729 patent repeatedly teaches that taste-masking via coating with water-insoluble polymers is compatible with rapidly dissolving tablets of corticosteroids to treat inflammation of the esophagus. *See* EX1001 (the '729 patent) at 13:59-67, 14:19-67, 16:44-17:9 (all discussing taste-masking via coating).

As mentioned above, the ’729 patent incorporates-by-reference Venkatesh. The assertion in the Davies Declaration that taste-masking prevents a drug from contacting the esophagus is not supported by the ’729 specification, Venkatesh, or ’865 patent. Instead, a person of ordinary skill in the art would have expected Venkatesh’s taste-mask coating to beneficially prevent the drug from contacting the tastebuds within the patient’s mouth and then release the drug “virtually immediate[ly]” after it passes through the mouth thereby allowing the drug to contact the esophagus. *See* EX1085 (the ’865 patent) at Abstract, 1:67-2:2, 2:65-3:3 (quoted above).

80. As discussed in My First Declaration, a person of ordinary skill in the art would have been motivated to turn to Venkatesh in formulating Dohil’s rapidly dissolving lozenge or tablet with a reasonable expectation of success based on the detailed disclosures within Venkatesh regarding the manufacture of such rapidly dissolving formulations, as well as the disclosures within Venkatesh detailing how to prepare such formulations with a pleasant taste and smooth creamy mouthfeel to provide better compliance with dosing regimens and, as a consequence, enhanced therapy. *See* EX1030 (My First Declaration) ¶¶259-275.

a. <u>Dohil And Venkatesh Render Obvious Claims 16-18</u>

81. For claims 16-18, the Davies Declaration repeats its argument that Venkatesh’s taste-masking would prevent the drug from being deposited in the upper

gastrointestinal tract. *See* EX2007 (Davies Declaration) ¶138. I disagree for reasons discussed above.

4. Grother, FDA Guidance, and Venkatesh Render Obvious Claims 8, 16-26, And 37 Of The '729 Patent (Ground 4)

82. The Davies Declaration repeats its argument that Venkatesh's taste-masking would prevent the drug from being deposited in the upper gastrointestinal tract. *See* EX2007 (Davies Declaration) ¶¶142, 147-148. I disagree for reasons discussed above.

83. The Davies Declaration asserts there is no motivation for a person of ordinary skill in the art to look to Venkatesh. *See* EX2007 (Davies Declaration) ¶144. As discussed in My First Declaration, a person of ordinary skill in the art would have been motivated to turn to Venkatesh in formulating Grother's ODT's with a reasonable expectation of success based on the detailed disclosures within Venkatesh regarding the manufacture of such rapidly dissolving formulations and how to formulate ODTs having a pleasant taste and smooth creamy mouthfeel that leads to better compliance with dosing regimen and as a consequence, to enhanced therapy. *See* EX1030 (My First Declaration) ¶¶278-330.

a. Grother, the FDA Guidance, and Venkatesh render obvious claims 16-19

84. For claims 16-19, the Davies Declaration repeats its argument that Venkatesh's taste-masking would prevent the drug from being deposited in the upper

gastrointestinal tract. *See* EX2007 (Davies Declaration) ¶149. I disagree for reasons discussed above.

D. CONCLUSION

85. 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: 10Jul2025 By: Alan Frank PARR

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