IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

CEPHALON INC. and CIMA LABS, INC.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 11-164-SLR
MYLAN PHARMACEUTICALS INC., and MYLAN INC.,	)	
Defendants.	)	

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OPINION

Dated: July 22, 2013
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This Hatch-Waxman action arises out of the filing of an Abbreviated New Drug Application ("ANDA") by defendants Mylan Pharmaceuticals Inc. and Mylan Inc. (collectively, "Mylan") seeking to market generic fentanyl buccal tablets. Plaintiff Cephalon Inc. is the holder of approved New Drug Application ("NDA") No. 21-947 for Fentora® brand fentanyl buccal tablets, used to treat breakthrough pain in cancer patients. (D.I. 138, ex. 1 at ¶ 35) It is also the assignee of U.S. Patent Nos. 6,200,604 ("the '604 patent"), 6,974,590 ("the '590 patent"), 8,092,832 ("the '92,832 patent"),and 8,119,158 ("the '158 patent") (collectively, "the patents-in-suit"), which are directed to oral effervescent pharmaceutical dosage forms. (*Id.*, ex. 1 at ¶¶ 12, 17, 30, 34) The patents-in-suit are among six patents listed in the Food and Drug Administration's ("FDA's") publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (known as the "Orange Book") for Fentora®.[1] (*Id.*, ex. 1 at ¶ 36) Plaintiff CIMA Labs, Inc. ("Cima") is a wholly owned subsidiary of Cephalon Inc. (*Id.*, ex. 1 at ¶ 3) It was previously the assignee of the '604 and '590 patent. (*Id.*, ex. 1 at ¶¶ 13, 18)

In January 2011, pursuant to 21 U.S.C. § 355(j)(2)(B), Mylan notified Cephalon Inc. and Cima (hereinafter, collectively "Cephalon") that it had submitted ANDA No. 202577 for a 300 mcg generic version of fentanyl citrate buccal tablets with a paragraph IV certification stating that the '604 and '590 patents are not infringed and are invalid.[2]

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[1]The Orange Book must list "each drug which has been approved for safety and effectiveness through an NDA." *See* 21 U.S.C. § 355(j)(A)(ii).

[2]*See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

(*Id.*, ex. 1 at ¶ 38) Cephalon responded by filing this suit for infringement of the '604 and '590 patents.[3] (D.I. 1)

On September 29, 2011, Cephalon received a second paragraph IV letter from Mylan regarding an amendment to Mylan's ANDA, which sought FDA approval for additional dosages of Mylan's generic version of fentanyl citrate buccal tablets. (D.I. 138, ex. 1 at ¶ 41) This notice again alleged that the '604 and '590 patents are not infringed and are invalid; it further alleged that U.S. Patent Nos. 7,862,832 ("the 62,832 patent") and 7,862,833 ("the '833 patent") are not infringed and are invalid.[4] (*Id.*) On November 9, 2011, Cephalon filed a second suit (Civ. No. 11-1111) alleging infringement of those four patents. (*Id.*, ex. 1 at ¶ 42)

Thereafter, on January 10, 2012 and February 21, 2012, Cephalon Inc. obtained issuance of the '92,832 and '158 patents, respectively. Cephalon filed suits (Civ. Nos. 12-73 and 12-247) alleging infringement of the '92,832 and '158 patents. (*Id.*, ex. 1 at ¶¶ 43, 45) On October 4, 2012, Cephalon received a third paragraph IV letter from Mylan, which alleged that the '92,832 and '158 patents are not infringed and are invalid. (*Id.*, ex. 1 at ¶¶ 44, 46) The parties subsequently agreed to consolidate the four actions into the instant action.

The court held a *Markman* hearing on February 8, 2013. Prior to trial, the parties informed the court that Cephalon would not assert infringement of the '62,832 and '833

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[3]*See* 35 U.S.C. § 271(e)(2)(A) ("(2) It shall be an act of infringement to submit - (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent . . . .").

[4]The '62,832 and '833 patents are also listed in the Orange Book for Fentora®.

patents and that Mylan would not challenge the validity of those two patents. (D.I. 144) In addition, Mylan dropped its invalidity counterclaims for the '604 and '590 patents and did not contest infringement of the '92,832 patent. (*Id.*; D.I. 154 at 1 n.1) Therefore, the issues presented at trial were as follows: infringement of claims 1-3, 11, and 12 of the '604 patent; infringement of claims 1, 2, and 7 of the '590 patent; validity of claims 1 and 3-5 of the '92,832 patent; and infringement and validity of claims 1, 15, 17, 19, and 21 of the '158 patent. (*See* D.I. 154 at 1 n.1) The court held a bench trial on these issues between March 11 and 15, 2013, and the parties have since completed post-trial briefing. The 30-month stay of FDA final approval on Mylan's ANDA having expired on July 13, 2013,[5] the court entered an order enjoining Mylan from launching its generic product until July 22, 2013 or the issuance of the court's decision, whichever was earlier. (D.I. 164) The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202. Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Technology at Issue

1. Drug delivery across the oral mucosa

1. There are several different ways to deliver drugs to the human bloodstream. In traditional oral administration, the dosage form is swallowed and the drug is absorbed across the gastrointestinal mucosa of the stomach or intestines. (D.I. 147 at 150:17-25,

[5]*See* 21 U.S.C. § 355(j)(5)(B)(iii).

153:11-14, 158:1-4) By contrast, in oral transmucosal administration, the drug is absorbed across the mucosa of the mouth and directly into the blood stream. (*Id.* at 79:6-11, 154:9-19)

2. The inventions of the patents-in-suit relate to oral transmucosal drug delivery. The oral mucosa are the mucous membranes lining the mouth, and include the buccal, sublingual, and gingival mucosa. (*Id.* at 77:14-21, 154:4-8; D.I. 149 at 724:2-16) The buccal mucosa is along the inside of the cheek; the sublingual mucosa is under the tongue; and the gingival mucosa is between the upper lip and gum. (D.I. 147 at 77:14-21, 154:4-8; D.I. 149 at 724:2-16)

3. Oral transmucosal drug delivery results in faster onset of action than traditional oral drug delivery and avoids the "first pass effect," or degradation of the drug by the liver. (D.I. 147 at 79:6-12, 157:8-158:24; D.I. 149 at 723:10-22; D.I. 150 at 915:23-916:15) As a result, the same therapeutic effect can be achieved with a lower dose of drug administered by oral transmucosal delivery than by traditional oral delivery. Rapid absorption of the drug into the bloodstream is also advantageous to the treatment of conditions requiring fast relief, such as breakthrough cancer pain – occasional flares of severe and intense pain that cancer patients experience. (D.I. 147 at 69:2-7, 71:25-72:1) Such pain is termed breakthrough pain because it "breaks through" the around-the-clock medication used to treat persistent, or background, pain caused by cancerous tumors or side effects of cancer therapy. (*Id.* at 68:12-70:12, 71:8-72:1) Breakthrough pain is debilitating and lasts for about one hour, but can last anywhere from a half-hour to two or more hours. (*Id.* at 69:5-21, 76:3-11; D.I. 151 at 1141:13-1143:9)

4. Drugs may be absorbed across the oral mucosa through two pathways: paracellular or transcellular absorption. (D.I. 147 at 154:9-155:20) In paracellular absorption, the drug travels in between cells, through gateways called tight junctions, to reach the bloodstream. (*Id.* at 154:12-14, 155:1-20, 157:1-7, 161:24-162:2; D.I. 149 at 725:14-20) In transcellular absorption, the drug travels from cell to cell, through cell membranes, until reaching the bloodstream. (D.I. 147 at 154:14-15, 155:14-20; D.I. 149 at 725:21-24)

5. Fentanyl, a potent narcotic analgesic,[6] is a lipophilic drug, meaning that it is soluble in lipids (e.g., fats and oils). (D.I. 147 at 155:25-156:3) Lipophilic drugs like fentanyl reach the bloodstream primarily by the transcellular pathway. (*Id.* at 155:21-24, 156:4-10) In order for a drug to be absorbed, it must dissolve into solution first. (*Id.* at 162:14-21) Acidic (low) pH levels favor dissolution of weakly basic drugs, including fentanyl. (*Id.* at 162:18-21, 164:21-165:1; DTX411 at 150-51) When dissolved, fentanyl becomes ionized. (D.I. 147 at 164:23-165:1; DTX411 at 150-51)

6. For transcellular absorption, however, fentanyl needs to be in its unionized form. (D.I. 147 at 162:22-24, 165:2-5) The unionized form of fentanyl is favored at a more basic (higher) pH. (*Id.* at 162:23-24, 165:6-8) Herein lies the drug formulator's quandary; while low pH conditions promote dissolution of fentanyl, the opposite (high) pH conditions promote absorption. (*Id.* at 162:3-163:6, 164:16-165:6) Therefore, the

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[6]Fentanyl is many times more potent than morphine. (*See* PTX361.3) (stating that fentanyl is 100 to 300 times more potent than morphine) (*see* D.I. 147 at 74:1-6) ("[Fentanyl is] about fifty to a hundred times as potent as morphine, and that's why it's – it's delivered in micrograms, not milligrams, as all the other opioids are.")

"holy grial" for formulators is to provide a drug for oral mucosal delivery that has both improved solubility and absorption. (*Id.* at 162:2-3)

2. The Khankari patents

7. The '604 and '590 patents (hereinafter, collectively the "Khankari patents") claim inventions that achieve this result by using an effervescent agent to enhance absorption of a medicament across oral mucosa. The Khankari patents list the same five inventors: Drs. Sathasivan Indiran Pather ("Dr. Pather"), Rajentra K. Khankari ("Dr. Khankari"), Jonathan D. Eichman ("Dr. Eichman"), Joseph R. Robinson ("Dr. Robinson"), and John Hontz ("Dr. Hontz"). The '604 patent was filed on June 8, 1999 and issued on March 13, 2001. The '590 patent was filed on February 20, 2002 as a progeny of the '604 patent and issued on December 13, 2005. Both patents claim priority, at the earliest, to a provisional application filed March 27, 1998 and share a common disclosure.

8. Dr. Khankari testified that the inventions achieve enhanced absorption of the medicament by a "dynamic change" in pH. (*Id.* at 163:7-164:10, 191:18-192:8) The dynamic change in pH occurs due to the incorporation of effervescent agents that react to form carbon dioxide (CO_2) in the oral cavity. (*Id.* at 163:7-13, 164:8-10) First, the effervescent reaction forms a weak acid (carbonic acid) in saliva, which depresses the pH of the saliva. (*Id.* at 163:12-19, 164:11-17, 194:3-6) The carbonic acid then dissociates into water and CO_2, which leaves the solution as a gas, causing the pH to slowly rise. (*Id.* at 163:20-164:1, 164:18-20, 166:22-167:2) This dynamic change in pH achieves a balance between dissolution and absorption. The inventors believed that effervescence increases the rate and extent of absorption of a medicament by "one or

all of the following mechanisms: (1) reducing the mucosal layer thickness and/or viscosity; (2) tight junction alteration; (3) inducing a change in the cell membrane structure; and (4) increasing the hydrophobic environment within the cellular membrane." ('590 patent, col. 2:23-31)[7]

9. The Khankari patents teach that the inventions "should include an amount of an effervescent agent effective to aid in penetration of the drug across the oral mucosa." (*Id.*, col. 2:32-34) The detailed description teaches that the preferred amount of effervescent agent is between 5% and 95% and, more preferably, between 30% and 95%.[8] (*Id.*, col. 2:34-38) While most often a soluble acid source (including food acids) and a carbonate source will be used, which reaction produces CO_2 gas, reactants which evolve other gases and are safe for human consumption may also be used. (*Id.*, col. 2:48-3:3)

10. The Khankari patents also disclose the use of suitable pH-adjusting substances (or "pH adjustors"), which permit a sufficient concentration of the drug that is known or suspected to be absorbed via the transcellular pathway to be present in the unionized (and more absorbable) form. (*Id.*, col. 3:18-20, 3:31-37) "Suitable pH-adjusting substance[s] for use in the present invention include any weak acid or weak base in amounts additional to that required for the effervescence or, preferably, any buffer system that is not harmful to the oral mucosa." (*Id.*, col. 3:47-51) Suitable disintegrants include, but are not limited to, "any of the acids or bases

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[7]Because the Khankari patents share a common specification, the court will cite to the '590 patent for convenience when referring to both the '604 and '590 patents.

[8]Throughout the opinion, the court refers to percentage composition by weight when discussing percentage compositions.

previously mentioned as effervescent compounds, disodium hydrogen phosphate, sodium dihydrogen phosphate and the equivalent potassium salt." (*Id.*, col. 3:51-55)

11. Other ingredients, including non-effervescent disintegration agents ("disintegrants") and excipient fillers ("fillers"), may also be incorporated into the dosage form of the invention for a variety of purposes. "Disintegrants may comprise up to about 20[%]" of the composition and, preferably, between 2% and 10% of the composition. (*Id.*, col. 4:41-51) The specification lists non-limiting examples of disintegrants, including "microcrystalline, cellulose, croscarmelose sodium, crospovidone, starches, corn starch, potato starch and modified starches thereof, sweeteners, clays, such as bentonite, alginates, gums such as agar, guar, locust bean, karaya, pecitin and tragacanth." (*Id.*, col. 4:44-49) Fillers may be used "to facilitate tableting" of a solid, oral tablet dosage form and "desirably will also assist in the rapid dissolution of the dosage form in the mouth." (*Id.*, col. 5:28-32) "Non-limiting examples of suitable fillers include: mannitol, dextrose, lactose, sucrose, and calcium carbonate." (*Id.*, col. 5:30-32)

12. The '604 patent has one independent claim, which reads:

> 1. A method of administering at least one systemically distributable pharmaceutical agent across the oral mucosa comprising:
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> a) providing a solid oral dosage form including a pharmaceutically effective amount of an orally administerable medicament; and **at least one effervescent agent in an amount sufficient to increase absorption** of said orally administerable medicament across the oral mucosa; wherein said orally administerable medicament is not substantially encompassed by or dispersed in a material that prevents absorption of said medicament across the oral mucosa;
>
> b) placing said solid oral dosage form in the mouth of a patient so that saliva in said patient's mouth activates said at least one effervescent agent in said tablet; and

c) holding said solid oral dosage form and the dissolving contents of said solid oral dosage form in the mouth of a patient whereby said at least one effervescent agent promotes absorption of said orally administerable medicament across the oral mucosa.

(Emphasis added)

13. The '590 patent discloses fentanyl as the pharmaceutical agent. Its only independent claims reads:

1. A method of administration of fentanyl to a mammal across the oral mucosa thereof, said method comprising:

providing a solid oral dosage form comprising fentanyl or a pharmaceutically acceptable salt thereof and **at least one saliva activated effervescent agent in an amount sufficient to increase absorption** of said fentanyl or pharmaceutically acceptable salt thereof across said oral mucosa, at least one pH adjusting substance, and wherein said amount of said at least one effervescent agent is between about 5% by weight and about 80% by weight; and buccally, sublingually or gingivally administrating said solid oral dosage form to said mammal.

(Emphasis added)

3. The Moe patents

14. The '92,832 and '158 patents (hereinafter, collectively the "Moe patents") are directed to orally disintegrable dosage forms of fentanyl, as well as methods and uses thereof, which reduce the dose of fentanyl compared to prior art doses of fentanyl. Both of the Moe patents were filed on November 29, 2010 and claim priority, at the earliest, to a provisional application filed on December 31, 2003. They share a common disclosure and list the same three inventors: Drs. Derek Moe ("Dr. Moe"), Vikas Agarwal ("Dr. Agarwal"), and Walib Habib ("Dr. Habib"). The '92,832 patent issued on January 10, 2012, and the '158 patent issued on February 21, 2012.

15. According to the specification of the Moe patents, reducing the dose of fentanyl "while still achieving beneficial management of breakthrough pain in cancer patients" is desirable for several reasons. ('158 patent, col. 1:61-2:24, 2:41-45)[9] In particular, using less of the potent opiate may reduce the cost of patient care and reduce the risk of side effects, such as drug dependence or serious or fatal respiratory depression. (*Id.*, col. 2:61-3:24)

16. The orally disintegrable dosage forms taught by the Moe patents contain "at least about 45% less fentanyl" compared to prior art fentanyl dosage forms, such as "noneffervescent lollipop formulations." (*Id.*, col. 2:56-58) Those "lollipop" fentanyl formulations are available in the form of an oral lozenge or compressed tablet on a stick and are sold under the trade name Actiq®. (*Id.*, col. 1:24-47; *see also* DTX586; D.I. 147 at 73:4-10) The Moe patents incorporate the Actiq® label by reference.[10] ('158 patent, col. 1:46-47)

17. Despite the lower dose of fentanyl, the oral dosage forms taught by the Moe patents have a C_{max}, or "the highest observed concentration in the blood of a patient after administration," that is "comparable to other dosage forms containing much more, e.g., about twice as much drug." (*Id.*, col. 2:58-61, 3:63-64) "'Comparable' in this context means that the C_{max} of a dosage form of the . . . invention is at least about 75%

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[9]Because the Moe patents share a common specification, the court will cite to the '158 patent for convenience when referring to both the '158 and '92,382 patents.

[10]The FDA approved Actiq® in 1998 as the first oral transmucosal therapy specifically indicated for the treatment of breakthrough pain in opioid-tolerant cancer patients. (D.I. 147 at 73:4-10; DTX586) Actiq® was developed by Anesta Corp. ("Anesta"). (D.I. 149 at 708:8-10)

to about 125% of that of A[ctiq®] having about twice as much fentanyl." (*Id.*, col. 2:63-64)

18. The oral dosage form of the Moe patents excludes lollipop formulations like Actiq® and are preferably effervescent tablets. (*Id.*, col. 3:18-22) The dosage form may be delivered through the oral transmucosa (like the inventions of the Khankari patents). (*Id.*, col. 3:3:30-41) The Moe patents disclose that "the use of effervescence and/or a pH adjusting substance, and most preferably both, can provide significant advantages particularly in terms of the amount of fentanyl that is required for dosing." (*Id.*, col. 8:65-9:1; *see also id.*, col. 4:29-32)

19. The dosage form may also include a disintegrant and filler. (*Id.*, col. 3:23-27) The specification teaches that "[i]t has . . . been found that certain disintegrants and fillers in combination with at least one effervescent couple and at least one pH adjusting substance can provide even better, and very unexpected, results." (*Id.*, col. 9:1-5) The preferred disintegrant is SSG, and the preferred filler is mannitol. (*Id.*, col. 4:43-50)

20. Claim 1 is the only independent claim among the asserted claims of the '158 patent:

> 1. A dosage form comprising: from about 200 micrograms to about 800 micrograms of fentanyl, a salt form of fentanyl, or combinations thereof, calculated as fentanyl free base;
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> an effervescent material in an amount of about 15% to no more than about 60% by weight of the dosage form;
>
> a pH adjusting substance in an amount of about 0.5 to about 25% by weight of the dosage form, wherein said pH adjusting substance is not a component of said effervescent material;
>
> mannitol in an amount of between about 10 and about 80% by weight of the dosage form;

a starch glycolate in an amount of about 0.25 to about 20% by weight of the dosage form;

wherein said dosage form is suitable for delivery of said fentanyl across the oral mucosa of a patient by buccal, gingival or sublingual administration.

21. The '92,832 patent claims a tablet as the dosage form and particular dosages of about 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg of fentanyl free base. Furthermore, it includes a limitation of "a dwell time that is less than about 30 minutes." Claim 1 of the '92,832 patent reads:

1. A tablet comprising:

an amount of fentanyl free base or an equivalent amount of salt thereof selected from the group consisting of about 100 micrograms, about 200 micrograms, about 300 micrograms, about 400 micrograms, about 600 micrograms, and about 800 micrograms, calculated as fentanyl free base,

an effervescent agent comprising a food acid and a bicarbonate in an amount of about 15 to about 60% by weight of said tablet;

a pH adjusting substance comprising a carbonate in an amount of about 0.5 to about 25% by weight of said tablet, wherein said pH adjusting substance is different from the food acid and the bicarbonate in the effervescent agent;

a starch glycolate in an amount of about 0.25 to about 20% by weight of said tablet;

mannitol in an amount of about 10 to about 80% by weight of said tablet;

said tablet being suitable for delivery of said fentanyl across the oral mucosa of a patient by buccal administration and having a dwell time that is less than about 30 minutes.

4. Mylan's ANDA products

22. Mylan's proposed generic fentanyl citrate buccal tablets (hereinafter, the "ANDA products") contain dosage strengths of 100 mcg, 200, mcg, 300 mcg, 400 mcg,

600 mcg, and 800 mcg of fentanyl free base.[11] (PTX188.1) There is no dispute that Mylan's ANDA products contain the same ingredients as Fentora®, namely mannitol (between 46-47%); sodium bicarbonate (21.0%); citric acid (anhydrous) (15.0%), sodium carbonate (10.0%), sodium starch glycolate ("SSG") (4.0%), magnesium stearate (1.0%), and fentanyl citrate. (*Id.;* PTX264.18) The amount of fentanyl citrate, the active ingredient, varies between 0.16% and 0.63% depending on the dosage strength of the tablet. (PTX188.1) The ANDA products also contain silicon dioxide (2.0%), which is not found in Fentora®. (*Id.* at .1, .3; PTX264.18)

B. Claim Construction

1. Standard

23. Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence – the claims, specification, and prosecution history – because intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips*, 415 F.3d at 1313.

24. Claim construction starts with the claims, *id.* at 1312, and remains centered on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to

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[11]These dosage strengths correspond to 157 mcg, 314 mcg, 471 mcg, 628 mcg, 942 mcg, and 1,256 mcg of fentanyl citrate, respectively. (PTX188.1)

impart different meaning to claim terms, the terms are presumed to have their ordinary meaning. *Id.* Claims, however, must be read in view of the specification and prosecution history. Indeed, the specification is often "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

2. Issues at bar

25. The parties agree that the court should apply at bar the same claim construction for the Khankari patents as found in *Cephalon, Inc. v. Watson Pharm., Inc.*, 769 F. Supp. 2d 729 (D. Del. 2011), *rev'd on other grounds*, 707 F.3d 1330 (Fed. Cir. 2013), except for two disputed claim terms: "providing a solid oral dosage form" from the '604 patent and "pH adjusting substance is not a component of said effervescent material" from the '158 patent. The constructions of the other disputed terms have either been mooted because the '62,832 and '833 patents are no longer at issue or, in the case of the "dwell time" limitation, are no longer being disputed. (*See* D.I. 122 at 8 n.4; D.I. 126)

3. "Providing a solid oral dosage form"

26. The "providing a solid oral dosage form" limitation appears in claim 1 of the '604 patent.[12] Cephalon avers that no construction is necessary because the plain and ordinary meaning is apparent. (D.I. 117) Mylan proposes the construction "supplying a solid oral dosage form to a patient," which would exclude a patient supplying the dosage form to herself. (*Id.*)

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[12]In the joint claim construction statement, the parties did not identify the same limitation that appears in the '590 patent as one needing construction. (D.I. 117) Mylan's answering claim construction brief, however, asserts that Mylan is seeking the same construction of "providing a solid oral dosage form" for the '590 patent. (D.I. 126 at 6 n.3; *see also* D.I. 132 at 3 n.2) The court agrees that this is appropriate.

27. Both parties purport to adhere to the ordinary meaning of "providing." (D.I. 122 at 9; D.I. 126 at 7) Cephalon asserts that "providing" means "supplying" or "making available" and that "a patient can provide a dosage form for herself just like she can provide food or shelter for herself." (D.I. 122 at 9; D.I. 132 at 3) Mylan asserts that "[i]n ordinary English usage, one does not 'provide' things to oneself" but that "one party (the supplier) suppl[ies] the needs of another." (D.I. 126 at 7)

28. The dictionary definition of "providing" is "[t]o furnish; supply" or "[t]o make available, afford." *Am. Heritage Dictionary* (4th ed. 2009). Nothing in the claims, specification, or prosecution history narrows the meaning of "providing" to specify who must do the providing. A medical doctor or nurse may "furnish" or "supply" a dosage form by administering it to a patient, but the patient may also provide a dosage form to herself. For instance, a patient may make the drug available for use by removing it from a package. *See Meyers Intellectual Props. Ltd. v. Bodum*, 690 F.3d 1354, 1369 (Fed. Cir. 2012) (construing a "providing" step broadly such that any single party could perform it because "nothing in the claim language or the patent specification limit[ed] the 'providing' step to a specific party").

29. Mylan argues that if "providing" were construed to include a patient supplying the drug to herself, the limitation would be superfluous for covering all the necessary steps within the "providing" step. (D.I. 126 at 6) The court disagrees. "Providing" a specified dosage form is not the same as "placing" or "holding" said dosage form in the mouth so as to activate and promote absorption of the medicament, respectively. The "providing" step, even given its broad ordinary meaning, does not supplant the other claimed steps.

30. Mylan also contends that requiring a non-patient party to perform the "providing" step is consistent with how a person of ordinary skill in the art would understand the limitation, given that the medicament is fentanyl, a narcotic subject to strict regulatory oversight, and that healthcare providers and patients of fentanyl products must enroll in a Risk Evaluation Mitigation Strategy Access program. (*Id.* at 7) (citing D.I. 128, ex. 3 at ¶ 39, ex. 4 at ¶ 21) There are two problems with Mylan's reliance on this extrinsic evidence. First, the '604 patent claims are not limited to fentanyl or any specific drug.[13] Second, the routes or requirements for a patient to obtain fentanyl are of no moment. Even if a patient must obtain a prescription, enroll in a risk mitigation program, or take a medication under close supervision, neither the intrinsic nor the extrinsic evidence indicates that a patient, or any single party, cannot still perform the claimed "providing" step.

31. Therefore, the court agrees with Cephalon that the "providing a solid oral dosage form" step is not limited to any particular party. As the ordinary meaning suffices, construction of the limitation is not necessary.

4. "pH adjusting substance is not a component of said effervescent material"

32. The parties also dispute the limitation "pH adjusting substance is not a component of said effervescent material." This term appears in independent claims 1 and 5 of the '158 patent. Cephalon proposes that no construction is necessary or, to the extent the court finds that the term requires construction, "pH adjusting substance is in addition to the components of said effervescent agent." (D.I. 117) Mylan's proposed

[13]Only the claims of the '590 patent provide that the medicament must be "fentanyl or a pharmaceutically acceptable salt thereof."

construction – "the pH adjusting substance is not one of the components used to generate effervescence" – adds the limitation that the pH-adjusting substance cannot participate at all in any effervescent reaction. (*Id.*; D.I. 126 at 12)

33. The specification of the '158 patent teaches that the use of an effervescent substance with a pH-adjusting substance can offer advantages: "[E]ffervescence and/or a pH adjusting substance, and most preferably both, can provide significant advantages particularly in terms of the amount of fentanyl that is required for dosing." ('158 patent, col. 8:65-9:1; *see also id.*, col. 4:29-32) The specification further provides that, if a pH-adjusting substance is used, "[m]ost preferably, the pH adjusting substance is something other than one of the components, compounds or molecules used to generate effervescence" (*id.*, col. 4:32-35); and "[t]he selection of another pH adjusting substance such as, for example, anhydrous sodium carbonate which operates separate and apart from the effervescent agents would be preferred." (*Id.*, 26:64-67) Even if it is highly preferred that the pH-adjusting substance does not also generate effervescence, such a preference is an embodiment that is not properly read into the limitation. *See Phillips*, 415 F.3d at 1323 ("[A]lthough the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments."). The specification does not require that the pH-adjusting substance be entirely noneffervescent, i.e., that it not participate at all in any effervescent reaction.

34. In fact, the specification of the '158 patent identifies sodium carbonate, potassium carbonate, magnesium carbonate "and the like" as possible effervescent agents, while also noting that each may be "more preferably used as a pH adjusting

substance." ('158 patent, col. 26:26-29) In other words, an agent which generates effervescence may also be suitable – perhaps even more preferable – as a pH-adjusting substance. Mylan's proposed construction would read out this embodiment by requiring that the pH-adjusting substance not generate effervescence. The specification clearly does not contemplate such a narrowing limitation.

35. Therefore, while the effervescent agent and pH-adjusting substance must be separate and distinct, there is no further requirement that the pH-adjusting substance cannot be used to generate effervescence. The court adopts Cephalon's proposed construction: "pH adjusting substance is not a component of said effervescent material" means "pH adjusting substance is in addition to the components of said effervescent agent."

C. Infringement

1. Standard

36. A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman*, 52 F.3d at 976. First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* Construction of the claims is a question of law subject to de novo review. *See Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

37. "Direct infringement requires a party to perform each and every step or element of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007), *overruled on other grounds by* 692 F.3d 1301 (Fed. Cir. 2012). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

38. To establish indirect infringement, a patent owner has available two theories: active inducement of infringement and contributory infringement. *See* 35 U.S.C. § 271(b) & (c). To establish active inducement of infringement, a patent owner must show that an accused infringer "knew or should have known [its] actions would induce actual infringements." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). To establish contributory infringement, a patent owner must show that an accused infringer sells "a component of a patented [invention] . . . knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing

use." *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1061 (Fed. Cir. 2004) (quoting 35 U.S.C. § 271(c)). Liability under either theory, however, depends on the patent owner having first shown direct infringement. *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 774 (Fed. Cir. 1993).

2. The Khankari patents

39. Cephalon asserts indirect infringement of the Khankari patents; it does not assert direct infringement. Also, Cephalon only asserts literal infringement of the Khankari patents; it does not assert any arguments under the doctrine of equivalents. (*See* D.I. 153 at 30) The only limitation of the asserted claims of the Khankari patents that Mylan argues is not met by the ANDA products is "at least one [salival activated] effervescent agent in an amount sufficient to increase absorption." As such, the court will only address this limitation for infringement of the Khankari patents.

40. The parties agree that the court's construction from *Watson*, 769 F. Supp. 2d at 743,[14] applies to this limitation:

> At least one compound that evolves gas by means of an effervescent reaction is present in an amount sufficient to increase the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa. This amount is greater than that required for disintegration and does not include the pH-adjusting substance separately claimed.

(*See* D.I. 117) Cephalon argues that the citric acid and sodium bicarbonate components of Mylan's ANDA products satisfy the court's construction. Namely, these components allegedly: (1) are effervescent agents; (2) do not include the pH-adjusting substance in Mylan's ANDA products; (3) are present in an amount sufficient to enhance the rate and/or extent of absorption of fentanyl across the

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[14]The parties to *Watson* did not appeal the court's construction of this limitation.

oral mucosa; and (4) are present in an amount greater than required for tablet disintegration. (D.I. 153 at 4-5)

a. At least one effervescent agent

41. Cephalon avers that the sodium bicarbonate and citric acid in Mylan's ANDA products are effervescent agents under the agreed-upon construction because they evolve carbon dioxide gas by means of an effervescent reaction. (*Id.* at 34) Cephalon's expert, Dr. Bernard Olsen ("Dr. Olsen"), offered mass loss testing to demonstrate the volume of CO_2 that evolves when the ANDA products are exposed to water or saliva and visual observation testing, including videos, to show that the ANDA products evolve CO_2 gas when exposed to water and artificial saliva. (D.I. 148 at 359:5-360:15, 361:4-12, 362:3-365:8, 366:5-371:19, 372:18-376:19; PTX371; PTX373; PTX375; PTX376; PTX377; PTX378; PTX379; PTX380) Another Cephalon expert, Dr. Elizabeth Illum ("Dr. Illum"), agreed with Dr. Olsen's testing methods and also opined that citric acid and sodium bicarbonate in the ANDA products evolve CO_2 gas by means of an effervescent reaction. (D.I. 149 at 552:20-553:11, 687:13-15)

42. Mylan does not dispute that the sodium bicarbonate and citric acid in its ANDA products evolve gas by means of an effervescent reaction. (D.I. 154 at 23-57; *see also* D.I. 150 at 908:4-14) Therefore, the ANDA products meet this requirement of the agreed-upon construction.

b. Amount of effervescent agent that does not include the pH-adjusting substance separately claimed

43. Cephalon also submits that the ANDA products meet the agreed-upon construction's requirement that the amount of effervescent agent that is present to enhance absorption "does not include the pH-adjusting substance separately claimed." (D.I. 153 at 47) Cephalon avers that the effervescent agents are citric acid and sodium bicarbonate and that the pH-adjusting substance separately claimed is sodium carbonate. (*Id.*) Cephalon's expert, Dr. Illum, opined that sodium carbonate is a well-known basic pH-adjusting substance and is included in Mylan's ANDA products for that function. (D.I. 149 at 578:6-579:13, 608:11-609:9) He also opined that the ANDA tablets contain sodium bicarbonate and citric acid in amounts that will cause the sodium bicarbonate to fully react to produce effervescence. (*Id.* at 609:19-23)

44. The only factual issue that Mylan disputes is whether some portion of the sodium carbonate will also effervesce; it does not otherwise contest this requirement. (*See* D.I. 154 at 23-57) Whether some sodium carbonate will effervesce, however, is not relevant to the Khankari patents. It is not a requirement of the agreed-upon construction that the pH-adjusting substance cannot effervesce. The sodium bicarbonate and citric acid in the ANDA products are the effervescent agents and meet the requirement that the amount of effervescent agent that is present to enhance absorption does "not include the pH-adjusting substance separately claimed."

c. Effervescent agent sufficient to increase the rate and/or extent of absorption

45. Mylan focuses its non-infringement position for the Khankari patents on the remaining two requirements of the agreed-upon construction. It argues that the effervescent agents in the ANDA products do nothing more than their prior art function of disintegration and that the pH-adjusting substance, not effervescence, is responsible for any enhanced absorption. In essence, Mylan asserts that the Khankari patents do not teach anything new about effervescence because the only beneficial effect of effervescence is its prior art use to speed up tablet disintegration. (*Id.* at 23-39)

46. The agreed-upon construction requires that the amount of effervescent agent be sufficient to increase the rate and/or extent of absorption. As a threshold matter, the parties disagree on what Cephalon must show regarding the relationship between effervescence and absorption in the ANDA products. Cephalon contends that the agreed-upon construction only requires the effervescent formulation to increase absorption compared to a non-effervescent formulation (D.I. 153 at 32), whereas Mylan asserts that any increase in absorption attributable to effervescence must be separate and distinct from any absorption attributable to the pH adjustor. (D.I. 154 at 3, 8) Put another way, Cephalon avers that the effervescence must enhance absorption, whether by itself or synergistically with another component, while Mylan avers that the effervescence, alone, must enhance absorption.

47. Contrary to Mylan's assertion, the agreed-upon construction does not require effervescence to improve absorption independently from pH adjustors. Rather, it only requires that the effervescent agent be present in "an amount

sufficient to increase the rate and/or extent of absorption" and that said amount "not include the pH-adjusting substance separately claimed." The agreed-upon construction does require that the effervescent agent function to enhance absorption separately and independently from the pH-adjusting substance. It does not preclude the pH-adjusting substance and the effervescent agent from acting synergistically to increase absorption.

48. Mylan also attempts to discredit the various theories, including the dynamic pH effect, that would explain why effervescence would increase absorption. However, the agreed-upon construction does not require proof of the mechanism or mechanisms by which effervescence increases absorption. It is irrelevant, for purposes of infringement, **why** effervescence increases absorption.

49. To prove that the citric acid and sodium bicarbonate in the ANDA products enhance the rate or extent of fentanyl absorption across the oral mucosa, Cephalon's expert, Dr. Illum, relied primarily on data and results from the following: (1) an *in vivo* study in dogs conducted by Anesta at Cima's direction ("the dog study"); (2) a clinical study in Ireland conducted by Cima ("the Ireland study"); (3) an *in vitro* human study conducted by Absorption Systems at Cima's direction ("the Absorption Systems study"); and (4) development efforts by Mylan.

50. During the development of Fentora®, Cima enlisted Anesta to conduct the dog study on prototype fentanyl formulations named the OraVescent® technology. (PTX320.6) OraVescent® technology incorporated components for both effervescence and pH adjustment. (D.I. 147 at 179:23-

180:8) The dog study tested four different tablets: short disintegrating and long disintegrating tablets with effervescence and pH adjustment ("the OraVescent® tablets"), and short disintegrating and long disintegrating tablets lacking both effervescence and pH adjustment ("the nonenhanced tablets").[15] (D.I. 149 at 587:24-588:12; D.I. 150 at 879:15-880:25, 950:14-23; PTX320.6, .9) Two fentanyl solutions were also tested, one with a pH of 7, and one with a target pH of 8.5 but that reached a pH of 8.05. (D.I. 149 at 588:13-589:4; D.I. 150 at 950:14-951:2; PTX320.11; DTX397 at CEP-FEN00395029; DTX204; DDX215) "The objective of [the dog] study was to evaluate the hypothesis that effervescence, independent of pH, enhances the permeability of fentanyl through the buccal mucosa." (PTX320.6; D.I. 149 at 587:8-10)

51. The results showed that the OraVescent® tablets had significantly higher C_{max} values and shorter T_{max} values than the nonenhanced tablets and fentanyl solutions. (D.I. 149 at 587:5-591:6, 591:19-593:10, 705:4-22; D.I. 150 at 956:1-958:8; PTX320.20) The parties' experts agreed that the C_{max} value reflects the rate and extent of absorption and that the T_{max} value is related to the rate of absorption. (D.I. 149 at 593:3-5, 705:10-12; D.I. 150 at 954:14-955:7)

52. Anesta's scientists concluded that the dog study's design and results "d[id] not support the hypothesis that effervescence enhances fentanyl absorption, as pH was not constant during the administration of the fentanyl tablets." (D.I. 153 at 11; PTX320.2, .20) This conclusion is consistent with

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[15]The short disintegrating tablets contained 5% of the superdisintegrant crospovidone, and the long disintegrating tablet contained 2% crospovidone. (DDX215)

Mylan's contention that the dog study does not show that effervescence alone, isolated from pH adjustment, increases absorption. Cima, however, concluded from the dog study that pH was not constant during the experiment because of effervescence, that is, "effervescence is the mechanism whereby pH is continually changing." (D.I. 149 at 707:16-708:7; DTX320.32-.34) As Mylan's expert, Dr. Norman Weiner ("Dr. Weiner"), testified, Anesta and Cima's different conclusions were akin to "two ships passing in the night." (D.I. 150 at 962:10-14) They did not necessarily conflict but, rather, focused on answering different hypotheses. While Anesta was focused on isolating the effect of effervescence, which it could not do from the results, Cima concluded from the enhanced absorption data that effervescence, through pH adjustment, at least partially contributed to absorption. (DTX320.32-.34) Because the agreed-upon construction at issue does not require a showing that effervescence, alone, increases absorption, the results of the dog study support Cima's argument that citric acid and sodium bicarbonate, as effervescent agents, at least contribute to an enhancement in absorption.

53. Thereafter, Cima conducted the Ireland study to evaluate the OraVescent® tablets in humans. (D.I. 147 at 180:11-18) The Ireland study compared the OraVescent® tablets with Actiq® (the commercially available lollipop formulation) and a "nonenhanced" buccal tablet, both of which lacked effervescence and pH-adjusting components. (D.I. 147 at 181:13-25; PTX266A.3-.4; DTX541 at CEP-FEN00150997-98) All three formulations contained the same amount of fentanyl. (D.I. 149 at 554:15-20) It was reported

that the OraVescent® tablets had better pharmacokinetic ("pK")[16] parameters than both Actiq® and the nonenhanced buccal tablet formulations. (PTX266A.4-6) Specifically, fentanyl absorption was faster and more complete with the OraVescent® tablets and also reached a higher peak level in the blood. (D.I. 147 at 182:1-183:21; D.I. 149 at 554:1-555:24, 616:17-25, 688:18-689:11; PTX266A.5-6) Mylan's expert, Dr. Weiner, did not dispute these findings. (D.I. 150 at 940:7-941:3)

54. Mylan concedes that the Ireland study compared formulations that had effervescent agents **and** pH-adjusting substances to formulations that had neither effervescent agents **nor** pH-adjusting substances. Like the dog study, the Ireland study showed that formulations containing both effervescent agents and pH-adjusting substances enhanced absorption compared to formulations without any effervescence or pH-altering mechanisms. Because the formulations tested in the Ireland study contained the same effervescent agents (citric acid and sodium bicarbonate) and pH-adjusting substance (sodium carbonate) as the ANDA products, the Ireland study is additional evidence that the ANDA products contain effervescent agents in an amount sufficient to increase the rate and/or extent of absorption.

55. Furthermore, Cephalon points to the Absorption Systems study, an *in vitro* study on human buccal cells that allegedly confirms that effervescence improves absorption as compared to pH modification alone. (D.I. 153 at 42) The

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[16]As stated by Dr. Markus Jerling ("Dr. Jerling") at trial, pK parameters summarize "the time course of drug concentrations associated with a certain drug input." (D.I. 151 at 1126:25-1127:13)

Absorption Systems study is the only study cited by Cephalon that attempted to isolate the effect of effervescence, alone, on absorption. As discussed *supra*, however, the court need not determine whether Cephalon has shown that effervescence enhances absorption separate and distinct from pH adjustors.

56. In the Absorption Systems study, the rate of fentanyl permeating across a cultured buccal cell membrane (from a donor chamber to a receiver chamber) was measured for six different fentanyl tablets: an "effervescent" tablet; a "half effervescent" tablet; a "no sodium carbonate" tablet; a "citric acid only" tablet; a "sodium carbonate only" tablet; and a "noneffervescent" tablet. (D.I. 149 at 666:23-667:11, 709:24-710:6; DTX56 at CEP-FEN00471812-13, CEP-FEN00471819) The "effervescent" tablet contained effervescent agents (citric acid and sodium bicarbonate) and a pH-adjusting substance (sodium carbonate), and the "half effervescent" tablet contained those same ingredients in half the concentrations. (D.I. 149 at 667:7-19) The "no sodium carbonate" formulation contained effervescent agents (citric acid and sodium bicarbonate) but not the pH-adjusting substance sodium carbonate, whereas the "citric acid only" and "sodium carbonate only" tablets each contained an effervescent agent with no pH adjustor. (*Id.* at 667:20-667:23, 668:14-668:24, 669:6-11) Finally, the "noneffervescent" tablet did not contain any citric acid, sodium bicarbonate, or sodium carbonate; it had no components for generating effervescence or controlling pH. (*Id.* at 668:25-669:5)

57. The "effervescent" and "half effervescent" tablets both had significantly greater permeability values than the "no sodium carbonate" (pH-

adjusting substance only) tablet and the "noneffervescent" tablet (no effervescent agents or pH-adjusting substances). (*Id.* at 713:18-714:21; D.I. 150 at 964:13-966:16; DTX56 at CEP-FEN00471819; DTX57 at CEP-FEN01146467) Cephalon's expert, Dr. Illum, opined that the Absorption Systems study thus demonstrated that the synergy of using both effervescence and a separate pH adjustor enhances absorption. (D.I. 149 at 713:18-714:21)

58. The tablets in the Absorption Systems study were allowed to dissolve for four minutes, followed by application of a donor solution for approximately one minute "to provide appropriate dispersion of the dissolved content." (DTX56 at CEP-FEN00471813) As a result,"time [zero]," when the first measurements were taken, actually corresponded to approximately five minutes after the tablets were exposed to the mucosa. (*Id.*; D.I. 149 at 710:9-711:3; D.I. 150 at 970:3-11) The parties' experts disagree as to whether the Absorption Systems study accounted for the amount of drug that passed through the membrane during the first five minutes of the experiment, an important omission because the dynamic pH effect of the effervescence would allegedly occur within those first few minutes. (*Compare* D.I. 148 at 374:5-375:19; D.I. 149 at 690:15-24, 709:24-710:18, 711:1-713:17; DTX57 at CEP-FEN01146466 (fig. 6) *with* D.I. 150 at 965:4-11, 966:11-23, 967:5-20) Regardless of whether the Absorption Systems study accounted for absorption during the first five minutes, the parties' experts agreed that the average apparent permeability ("P_{app}") of the "effervescent" and "half effervescent" tablets was greater than the average P_{app} of the "no sodium carbonate" tablet. (D.I. 149 at 713:18-714:21; D.I. 150 at 964:13-966:16) The

only two tablets that showed absorption greater than zero at the time zero measurement (five minutes after exposure to the buccal tissue) were the "effervescent" and the "no sodium carbonate" tablets – the tablets that contained the full concentration of effervescent agents and provided rapid disintegration. (DTX56 at CEP-FEN00471826-29; D.I. 150 at 972:13-973:2) These results support the notion that a combination of effervescence and a pH-adjusting substance, identical to that of the ANDA products, improves absorption compared to tablets lacking effervescence and a pH-adjusting substance.

59. Finally, Cephalon points to Mylan's development path to argue that the amount of effervescence in the ANDA products increases the rate and extent of fentanyl absorption. (D.I. 153 at 37-39) Mylan initially tried three different noneffervescent formulations – the 1000306, 1000367, and 1000368 tablets (collectively, "Mylan's noneffervescent tablets") – all of which were "unsuccessful." (PTX75.4; PTX188.3; D.I. 149 at 561:4-565:17) The noneffervescent formulations all had pH-adjusting mechanisms but lacked effervescence. (PTX115.3; D.I. 149 at 562:18-563:8) In a presentation reviewing fentanyl tablet development, Mylan noted that the pH profiles of these formulations did not directly correlate to observed pK and that the "pH modifier effect [was] unclear." (DTX680 at MYLAN518098) After finding that the noneffervescent formulations were not bioequivalent to Fentora®, Mylan proceeded to test three formulations that were effervescent – the 1000489, 1000490, and 1000544 tablets (collectively, "Mylan's effervescent tablets"). (PTX75.3-4; D.I. 148 at 423:16-424:3; D.I. 149 at 565:18-23) These formulations

contained sodium bicarbonate, citric acid, and sodium carbonate.[17] (PTX75.3-4; D.I. 148 at 423:16-424:3) Dr. Illum opined that, when Mylan turned to the effervescent formulations, there was "an enormous change" in the pK profiles of the effervescent formulations compared to the noneffervescent formulations. (D.I. 149 at 567:10-568:3; PTX75.4) The effervescent formulations showed higher pK profiles and absorption than the noneffervescent formulations. (D.I. 149 at 580:20-582:1, 583:11-584:3; PTX75.4)

60. Cephalon asserts that Mylan itself concluded during the formulation process that "effervescence has [a] larger effect on PK than other pH modifiers; pH modification alone and effervescence are not equivalent." (PTX75.4; D.I. 149 at 569:24-570:12) Another Mylan presentation states both "Fentora[®] and [Mylan's] [b]uccal formulation use effervescent couple [sic] to take advantage of" the dynamic pH effect. (PTX115.8; D.I. 149 at 558:1-559:22) Mylan avers that Ms. Tammy Bartley ("Ms. Bartley"), a senior principal scientist at Mylan, and Dr. David Wargo ("Dr. Wargo"), Mylan's Vice President of Product Development, testified at trial that these statements were mere quotations or regurgitations of principles that Mylan did not independently evaluate or test. (D.I. 154 at 15-16) (citing D.I. 148 at 389:16-390:18, 457:2-7, 507:12-24) Even if Mylan did not explicitly test the dynamic pH theory, it did test and conclude, at a minimum, that the combination of effervescent agents and a pH-adjusting substance improved absorption (regardless of why such improvement came about).

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[17]The 1000544 tablet was the formulation that became the basis for Mylan's ANDA. (D.I. 149 at 572:14-18)

61. Cephalon has presented substantial evidence that effervescence, at least in combination with a pH-adjusting substance, increases the rate and/or extent of absorption. Mylan's argument that Cephalon has failed to demonstrate that the ANDA products' effervescence, acting alone, would increase absorption is of no avail under the agreed-upon construction. Cephalon did not need to demonstrate how much of the improved absorption in the ANDA products is due to the effervescent agents as compared to the pH-adjusting substance. Accordingly, the court finds that Cephalon has carried its burden of proving, by a preponderance of the evidence, that the amount of effervescent agent in the ANDA products is sufficient to increase the rate and/or extent of absorption.

d. Amount of effervescent agent that is greater than that required for disintegration

62. With respect to the remaining requirement of the agreed-upon construction, Cephalon asserts that the effervescent agents are also present in an amount greater than that required to disintegrate Mylan's ANDA products. Specifically, Cephalon claims that **no** amount of effervescent agent is required for disintegration because a separate component, the superdisintegrant SSG, is sufficient for tablet disintegration. (D.I. 153 at 39-41, 44-47)

63. There is no dispute that the ANDA products contain 4% SSG as a separate ingredient. There is also no dispute that SSG is a known superdisintegrant. According to the Handbook of Pharmaceutical Excipients ("the Handbook"), "[t]he usual concentration [of SSG] employed in a formulation is between 2-8%, with the optimum concentration about 4% although in many

cases 2% is sufficient." (DTX723 at 501) The fact that SSG is a superdisintegrant is consistent with Mylan's ANDA, which identified SSG as the only component that functions as a "disintegrant" in its ANDA products. (PTX188.1, .3)

64. Cephalon argues that the ANDA products use even more SSG (4%) than Fentora® (3%) and that the Ireland study showed that 3% crospovidone, which is also a superdisintegrant, was sufficient to disintegrate tablets without effervescent assistance. (D.I. 153 at 45) (citing PTX264.18; D.I. 149 at 577:13-25; PTX226A.3; D.I. 150 at 940:17-941:3) The Ireland study reported that 3% crospovidone tablets with effervescence and a pH adjustor and 3% crospovidone tablets with neither effervescence nor a pH adjustor "had similar disintegration times (10 minutes) as tested by a specially developed method for buccal tablets." (PTX266A.3; D.I. 150 at 940:17-941:3) Although the ANDA products contain SSG (not crospovidone) as the superdisintegrant, the conclusion of the Ireland study is circumstantial evidence from which one can reasonably conclude that the ANDA products contain an amount of effervescent agent greater than that required for disintegration.

65. At trial, Cephalon's expert, Dr. Illum, opined that the amount of SSG in the ANDA products is more than sufficient to disintegrate the ANDA products without the aid of any effervescent agent. (PTX264.18; D.I. 149 at 571:9-572:13, 577:13-25, 578:1-5) Dr. Illum relied, in part, on Mylan's *in vivo* testing ("the *in vivo* testing") that compared the disintegration of Fentora® to that of Mylan's noneffervescent formulations, which contained 5% SSG but did not have

absorption that was bioequivalent to Fentora®. She opined that "the reason for not having [] significant absorption from these [noneffervescent] formulations was not due to the tablets not disintegrating," i.e., the 5% SSG did not cause any disintegration issues. (D.I. 149 at 572:22-573:2)

66. The results of the *in vivo* testing showed that the 1000306 tablet had a mean disintegration time of 27.5 minutes, compared to 24.2 minutes for Fentora®. (DTX27 at MYLAN487574; DTX680 at MYLAN518160; PTX102.14; PTX115.74) Mylan concluded from the *in vivo* testing that the disintegration of the 1000306 tablet and Fentora® was "similar when administered to the buccal membrane," even though "[l]ittle or no buccal absorption [was] observed." (PTX102.15, .18) The 1000367 and 1000368 tablets had mean disintegration times of 30.1 and 30.2 minutes, respectively, after which the subject was instructed to swallow the tablet, compared to a mean disintegration time of 25.5 minutes for Fentora®. (D.I. 150 at 849:16-850:8; PTX115.74; DTX680 at MYLAN518160) None of the 1000367 and 1000368 tablets disintegrated completely within the 30-minute administration time. (D.I. 150 at 851:8-9) Because the testing stopped at 30 minutes, it was not possible to determine how long it would take for tablets that had remnants left at 30 minutes to disintegrate completely. (*Id.* at 850:9-12) Dr. Illum testified that the mean disintegration time disguised the fact that five out of seven Fentora® tablets also failed to disintegrate completely within 30 minutes. (D.I. 149 at 576:12-20) She concludes from this observation that there was "hardly any difference" in

disintegration among the 1000367 tablets, the 1000368 tablets, and Fentora®. (*Id.* at 576:12-20)

67. Mylan, on the other hand, argues that the 1000367 and 1000368 tablets "failed to achieve adequate disintegration within the requisite administration time." (D.I. 154 at 39) Its expert, Dr. Weiner, emphasized that two of the Fentora® tablets in the *in vivo* testing were able to disintegrate completely within 30 minutes and that the mean disintegration time for Fentora® was shorter, from which he concluded that Fentora® had a higher disintegration rate. (D.I. 150 at 849:4-15, 850:17-851:12, 855:1-9; *see also* D.I. 148 at 481:7-12)

68. Mylan further submits evidence from an *in vitro* "screen test" ("the screen test") that also studied disintegration of Mylan's noneffervescent tablets compared to Fentora®. (D.I. 154 at 39) Unlike traditional oral drugs for delivery through the gastrointestinal mucosa, there is no standardized disintegration test for tablets directed at delivering drugs through the oral mucosa. (D.I. 150 at 852:5-853:4) Dr. Wargo devised and conducted the screen test, in which he partially exposed tablets to water (up to about 20% of the tablets' height) in a petri dish and observed disintegration over time. (D.I. 148 at 479:15-481:6, 496:15-18; DTX32 at MYLAN026040) At trial, he pointed to time-lapse pictures to show that, while Fentora® started disintegrating immediately and had completely disintegrated within about 1 minute, the cores of the 1000367 and 1000368 tablets remained after 20 minutes. (*Id.* at 479:15-480:20; DTX32 at MYLAN026040) He testified that he attributed the faster disintegration of Fentora® to its effervescent characteristics. (*Id.* at 481:21-482:1)

69. As a threshold matter, the parties' experts disagreed on whether the screen test was an appropriate method to demonstrate disintegration. While Mylan's expert, Dr. Weiner, opined that the screen test was appropriate and reliable (D.I. 150 at 854:7-11), Cephalon's expert, Dr. Illum, opined that the screen test did not have very much relation to what would actually happen in a patient's mouth. (D.I. 149 at 576:21-577:12) The court agrees with Dr. Illum that the screen test does not reliably mimic *in vivo* disintegration. In a patient's mouth, a tablet would be moist on all surfaces, rather than just on one side and up to 20% of its height. (D.I. 148 at 497:11-14) As such, the court gives the screen test little weight.

70. Even were the court to assume that the screen test appropriately modeled tablet disintegration, it only documented disintegration for 20 minutes. (*Id.* at 497:16-23) Similarly, the *in vivo* testing only documented disintegration for 30 minutes. The agreed-upon construction does not require disintegration within a prescribed amount of time or at a certain rate. Therefore, the court does not find testing that placed an artificial temporal limitation on disintegration to be particularly helpful.[18] To the extent the *in vivo* testing did document the complete disintegration of the 1000306 tablets, however, that data is probative of disintegration of a tablet containing 5% SSG.

71. Cephalon has submitted circumstantial evidence that 4% SSG is sufficient for tablet disintegration by pointing to its identification as a disintegrant

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[18]The labels for the ANDA products and Fentora® all instruct that, after 30 minutes, if remnants from the tablet remain, they may be swallowed with a glass of water. (PTX202.44; PTX237.16; D.I. 147 at 112:14-24; D.I. 148 at 495:9-23)

in FDA materials; the teaching in the literature; the Ireland study; and the fact that the 1000306 tablets disintegrated completely and comparably to Fentora® (which contains less SSG) during the *in vivo* testing. Mylan's evidence, at most, suggests that effervescence helps to speed up disintegration. As noted before, this is permissible under the agreed-upon construction. Weighing the totality of the evidence, it would be reasonable to infer that, more likely than not, the 4% SSG in the ANDA products is sufficient for tablet disintegration under the agreed-upon construction. Accordingly, Cephalon has carried its burden of showing that the amount of effervescent agent in the ANDA products is greater than required for disintegration.

e. Conclusion regarding infringement of the Khankari patents

72. Mylan does not dispute that its ANDA products meet the additional limitations recited in asserted dependent claims 2 and 7 of the '590 patent and claims 2, 3, 11, and 12 of the '604 patent.[19] (*See* D.I. 153 at 51-56)

73. Regarding indirect infringement, there is no genuine dispute of material fact that Mylan will encourage use through its product labeling and sale of its generic tablets and is aware that the label presents infringement problems.

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[19]Claim 2 of the '590 patent is dependent from claim 1 and includes the additional limitation that "said fentanyl or pharmaceutically acceptable salt thereof is administered via a buccal route." Claim 7 of the '590 patent, also dependent from claim 1, requires the pH-adjusting substance to be a base. With respect to the '604 patent, claims 2, 3, 11, and 12 are dependent from claim 1. Claim 2 of the '604 patent recites the further limitation of at least one pH-adjusting substance, and claim 3 recites a narrower "holding" step for buccal administration. Claim 11 requires the effervescent agent to be present in an amount between about 30% and about 80%, and claim 12 adds the limitation that "said at least one effervescent agent is present in an amount sufficient to evolve a gas in an amount between about 5 $cm^{[3]}$ to about 30 $cm^{[3]}$."

Therefore, it will induce infringement of the Khankari patents.[20] *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056-60 (Fed. Cir. 2010). The only authorized use for the ANDA products would infringe the Khankari patents. As there is no substantial noninfringing use of Mylan's tablets, Mylan will also contribute to infringement. *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926-27 (Fed. Cir. 2011).

74. Because Cephalon has demonstrated that Mylan's ANDA products practice each and every requirement of the disputed limitations, Mylan infringes all asserted claims of the Khankari patents.

3. The '158 patent

75. The court next turns to infringement of the '158 patent. Cephalon asserts both direct and indirect infringement of this patent. It does not assert the doctrine of equivalents. (*See* D.I. 153 at 30) Asserted claims 1, 15, 17, 19, and 21 of the '158 patent recite fentanyl dosage forms that contain, in part, an effervescent material and a pH-adjusting substance. The only dispute for infringement is whether the ANDA products meet the limitation "wherein said pH adjusting substance is not a component of said effervescent material."

76. There is no dispute that Mylan's ANDA products contain sodium carbonate as the pH-adjusting substance and that sodium carbonate is an effervescent material.

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[20]To the extent Mylan argues that no single person will practice the "providing" step in the asserted claims of the Khankari patents, that argument was made only under Mylan's proposed construction that a patient cannot "provide" the ANDA products to herself. (*See* D.I. 153 at 51-52) Under the court's construction, the "providing" step is not limited to any particular individual. Therefore, any argument by Mylan that no single person will practice all the steps of the Khankari patents is moot.

(*See* D.I. 154 at 58) (citing D.I. 149 at 603:3-9, 609:24-611:23) Mylan's noninfringement defense hinges on its proposed claim construction of the limitation "wherein said pH adjusting substance is not a component of said effervescent material," which would require the pH-adjusting substance to not be an effervescent material.[21]

77. The court has construed said limitation to mean "pH adjusting substance is in addition to the components of said effervescent agent." This construction allows the pH-adjusting substance to participate in an effervescent reaction. Mylan does not offer any noninfringement defense under the court's construction. In addition, Mylan does not dispute that the ANDA products satisfy the limitations of the dependent claims.[22] (*See* D.I. 153 at 59)

78. As with the Khankari patents, Mylan will encourage use through its product labeling and sale of its generic tablets and is aware that the label presents infringement problems. Therefore, it will induce infringement of all asserted claims of the '158 patent. *AstraZeneca*, 633 F.3d at 1056-60. The only authorized use for the ANDA products would infringe the '158 patent. As there is no substantial noninfringing use of Mylan's tablets, Mylan will also contribute to infringement of all asserted claims of the '158 patent. *Eli Lilly*, 435 F. App'x at 926-27.

4. Conclusions on infringement

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[21]Mylan concedes infringement of the '92,832 patent, which requires the pH-adjusting substance to be a carbonate, wherein the carbonate may participate in an effervescent reaction. (D.I. 154 at 58-59 & n.64)

[22]Claims 15, 17, 19, and 21 of the '158 patent are dependent from claim 1 and recite specific amounts of fentanyl free base (200, 400, 600, and 800 mcg) within the range of about 200 to about 800 mcg recited in claim 1.

79. For the foregoing reasons, the court finds that Mylan indirectly infringes the Khankari patents and directly and indirectly infringes the '158 patent.

D. Validity of the Moe patents

1. Anticipation

80. Mylan argues that claims 1, 3, 4, and 5 of the '92,832 patent and claims 1, 15, 17, 19, and 21 of the '158 patent are anticipated by the '604 patent. The '604 patent issued on March 13, 2001 from an application filed June 8, 1999. The parties do not dispute that the '604 patent is prior art vis a vis the Moe patents, which claim priority to, at the earliest, a provisional application filed on December 31, 2003. 35 U.S.C. § 102(b).

a. Standard

81. An anticipation inquiry involves two steps. First, the court must construe the claims of the patents in suit as a matter of law. *See Key Pharm. v. Hercon Labs. Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998). Second, the finder of fact must compare the construed claims against the prior art. *See id.* Proving a patent invalid by anticipation "requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys. Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (citations omitted). The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). The elements of the prior art must be arranged or

combined in the same manner as in the claim at issue, but the reference need not satisfy an *ipsissimis verbis* test. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (citations omitted). "In determining whether a patented invention is [explicitly] anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prosecution history and the prior art may be consulted "[i]f needed to impart clarity or avoid ambiguity" in ascertaining whether the invention is novel or was previously known in the art. *Id.* (internal citations omitted).

b. Disclosure by the '604 patent

82. The specification of the '604 patent discloses using an effervescent agent comprising a food acid and a bicarbonate, such as citric acid and sodium bicarbonate.[23] ('604 patent, col. 2:41-61, 6:14-15) In example 1 of the '604 patent, the citric acid and sodium bicarbonate make up 36% of the tablet. (*Id.*, col. 6:1-2) Example 1 further discloses the use of 8-9% sodium carbonate, which is a carbonate pH-adjusting substance different from the food acid (citric acid) and bicarbonate (sodium bicarbonate) in the formulation. (*Id.*, col. 6:11-12) The '604 patent also teaches a tablet for delivering fentanyl across the oral mucosa by buccal administration. (*Id.*, col. 5:34-54, 5:61)

83. Independent claim 1 of the '604 patent, which is not limited to any specific medicament, teaches the use of "a pharmaceutically effective amount" of an orally

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[23]Citric acid is a food acid, and sodium bicarbonate is a bicarbonate. (D.I. 150 at 1007:8-9)

administerable medicament. Example 1 of the '604 patent, the only example in which the medicament is fentanyl, describes a 1000 mcg dose of fentanyl free base.[24] (*Id.*, col. 6:9, 6:21)

84. The written description of the '604 patent identifies mannitol in a list of five suitable fillers. (*Id.*, col. 5:30-32) It also uses mannitol as a component of the formulation in example 2. (*Id.*, col. 6:58, 7:6)

85. The '604 patent further discloses the use of non-effervescent disintegrants, including crospovidone and "potato starch and modified starches thereof." (*Id.*, col. 4:40-47) Cephalon's expert, Dr. Illum, drew attention to the fact that SSG is not mentioned by name in the '604 patent. (D.I. 151 at 1215:5-7) There is no dispute, however, that SSG is a modified potato starch. (*See id.* at 1196:18-22, 1214:22-24) Mylan's expert, Dr. Arthur Kibbe ("Dr. Kibbe"), opined that the '604 patent's disclosure of "potato starches and modified starches thereof" is synonymous with SSG. (*Id.* at 1079:8-9) Dr. Illum's testimony that at least four other modified starches may also be suitable as disintegrants (*id.* at 1196:23-1197:7) does not conflict with Dr. Kibbe's testimony that a person of ordinary skill in the art at the time of the invention would have known that SSG was the only modified potato starch available for use as a disintegrant in pharmaceutical formulations.[25] (*Id.* at 1077:21-25; D.I. 150 at 1013:5-7, 1013:13-25)

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[24]Example 1 of the '604 patent discloses a dosage form with 1.57 mg (1570 mcg) of fentanyl citrate, which the parties agree contains 1000 mcg of fentanyl free base. (*See* D.I. 152 at 36; *see also* D.I. 150 at 1004:16-21; D.I. 151 at 1192:15-21)

[25]Similarly, Dr. Illum's testimony that "at least 50 different disintegrants could be contrived" from the list of disintegrants disclosed by the '604 patent does not change the court's conclusion. (*See* D.I. 151 at 1197:9-15) It is undisputed that the '604 patent explicitly named modified potato starch in a shorter list of disintegrants, and Dr. Kibbe's uncontroverted testimony establishes that the only modified potato starch disintegrant

c. Discussion

86. Cephalon avers that the following limitations found in the asserted claims of the Moe patents are not disclosed by the '604 patent: (1) the amounts of fentanyl; and (2) the combination of the filler mannitol and the disintegrant SSG. (D.I. 155 at 4-11) In its post-trial briefing, Cephalon also asserts that the '604 patent does not disclose a dwell time less than 30 minutes, which is only a limitation of the asserted claims of the '92,832 patent. (*Id.* at 11-13) Cephalon does not dispute that the '604 patent discloses the other limitations recited in the asserted claims of the Moe patents. (*See* D.I. 152 at 33-35, 43-45) Because the court finds that the '604 patent does not disclose the claimed amounts of fentanyl, the Moe patents are not invalid for anticipation.

87. Claim 1 of the '92,832 patent requires that the claimed tablet contain specific dosages between about 100 and about 800 mcg of fentanyl free base, and claim 1 of the '158 patent requires that the claimed dosage form contain about 200 to about 800 mcg of fentanyl free base. Mylan's expert, Dr. Kibbe, contends that a person of ordinary skill in the art would understand that the "pharmaceutically effective amount" taught by the '604 patent includes fentanyl free base in the range of 100 to 800 mcg. (D.I. 150 at 1005:15-24) However, Dr. Kibbe did not provide any support for his conclusive statement. The court finds as more credible and consistent with the 604 patent's disclosure the testimony from Cephalon's expert, Dr. Illum, that the '604 patent only discloses fentanyl in doses greater than 800 mcg to a person of ordinary skill in the art. (D.I. 151 at 1186:25-1187:7)

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available at the relevant time was SSG. (*Id.* at 1077:19-25; D.I. 150 at 1013:5-7, 1013:13-25)

88. Mylan points to Dr. Kibbe's testimony that a person of ordinary skill would have looked to Actiq®, an FDA-approved product, and recognized that its range of fentanyl, 200-1600 mcg, was pharmaceutically effective. (D.I. 150 at 1022:21-1023:4) Extrinsic evidence of anticipation "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference." *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991); *see, e.g.*, *Advanced Display Sys.*, 212 F.3d at 1282 ("Material not explicitly contained in the single, prior art document may still be considered for purposes of anticipation if that material is incorporated by reference into the document."). Actiq® is not mentioned in the '604 patent or incorporated therein. Mylan points to *Key Pharmaceuticals*, which noted that "it is quite sensible to look to the FDA to determine what amounts are considered pharmaceutically effective." *Key Pharm.*, 161 F.33d at 717. However, *Key Pharmaceuticals* is inapplicable in the anticipation context. In *Key Pharmaceuticals*, the Federal Circuit averred that, in the context of **claim construction**, it would be sensible for the court to look to the FDA for extrinsic evidence of what "pharmaceutically effective" means. *Id.* The '604 patent itself only discloses a 1000 mcg dosage of fentanyl, and Mylan has not offered evidence sufficient to show that a "pharmaceutically effective amount" necessarily discloses a dosage between 100 and 800 mcg of fentanyl.[26]

89. As the claimed fentanyl ranges are not found in the four corners of the '604 patent, the Moe patents are not anticipated. *See Advanced Display Sys.*, 212 F.3d at 1282 (holding that a patent claim is anticipated only if every element of a claimed invention can be found in "the four corners of a single, prior art document"). To the

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[26]Mylan does not assert any argument of inherent anticipation. (D.I. 156 at 6)

extent Mylan relies on the Actiq® brochure for the disclosure of the fentanyl ranges, its argument relates to obviousness, not anticipation, because the Actiq® brochure is a separate reference.

2. Obviousness

90. Mylan next argues that the asserted claims of the Moe patents are obvious in view of the '604 patent in combination with the Actiq® brochure and the Handbook. Cephalon contends that "[c]ombining certain ranges of fentanyl with effervescence, mannitol, and SSG are the novel aspects of the Moe patent inventions" and does not dispute the other limitations of the Moe patents for purposes of obviousness. (D.I. 155 at 32)

a. Standard

91. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on several underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (internal quotation marks omitted) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

92. "[A] patent composed of several elements is not proved obvious merely by

demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id.* at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007). "Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

b. Actiq® brochure

93. As discussed *supra*, Actiq® is a commercial fentanyl product, available in dosages between 200 and 1600 mcg. (PTX472 at 7-8; DTX586 at 1; D.I. 147 at 100:22-101:9) The parties do not dispute that the Actiq® package insert ("the Actiq® brochure") disclosing these dosages is a prior art reference. Mylan's expert, Dr. Kibbe, avers that a person of ordinary skill in the art would have been motivated to look at the Actiq® brochure and combine it with the teachings of the '604 patent. (D.I. 150 at 1023:21-1024:4)

c. The Handbook

94. The Handbook – which describes the physical and chemical characteristics, uses, and methods of manufacture for individual compounds – bears a copyright date of 2000 for the third edition and is a prior art reference. (*Id.* at 997:7-17; DTX722; DTX723; DTX737) It disclosed mannitol and its characteristics, as well as the disintegrants approved for use in pharmaceutical products at the time. (DTX722 at 327; DTX737 at 651; D.I. 150 at 997:7-17) Of the disintegrants, Mylan's expert, Dr. Kibbe, asserted that the Handbook only disclosed three different superdisintegrants that were known in the art at the time of the alleged invention: sodium croscarmelose, crospovidone, and SSG. (D.I. 150 at 1015:6-11, 1024:10-1026:3) Cephalon's expert, Dr. Illum, agreed that the Handbook identified only those superdisintegrants, and

possibly a fourth – tragacanth.[27] (D.I. 151 at 1215:13-22) The Handbook further disclosed that SSG is a modified potato starch. (DTX723 at 503)

d. Disclosure of the combined references

95. Mylan's expert, Dr. Kibbe, testified that a person of ordinary skill in the art would have been motivated by the '604 patent's disclosure of pharmaceutically effective amounts of fentanyl to look to known, FDA-approved amounts of fentanyl.[28] (D.I. 150 at 1023:21-1024:4; D.I. 151 at 1101:6-14) Cephalon's expert, Dr. Illum, recognized that, at the time of the claimed inventions of the Moe patents, a person of ordinary skill would have been familiar with Actiq®. Except to argue that Mylan's position regarding the disclosure of the fentanyl dosage range is an obviousness argument, not an anticipation argument, Cephalon offers no evidence to rebut Mylan's evidence that the fentanyl range claimed in the Moe patents is disclosed by the '604 patent in combination with the Actiq® brochure.[29] (*See* D.I. 155 at 4, 13-37)

96. As noted *supra*, the '604 patent explicitly discloses mannitol as a filler and, although the '604 patent does not disclose SSG by name, there is no dispute that its

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[27]SSG was commercially available as a superdisintegrant at the time of the inventions. (D.I. 148 at 325:19-326:14)

[28]The parties offer slightly different definitions for a person of ordinary skill in the art. (*See* D.I. 148 at 543:3-19; D.I. 150 at 998:17-999:7; D.I. 151 at 1186:8-15; *see also* D.I. 155 at 13 n.4) To the extent there is any dispute, the court finds that a person of ordinary skill in the art would have a Masters or Ph.D. degree in pharmaceutics, chemistry, or a related field (substitutable by practical experience in industry of academia), with a few years of experience in developing oral solid dosage forms.

[29]The only dosage not explicitly covered by Actiq® was the 100 mcg dosage, which Dr. Kibbe opined a person of ordinary skill in the art would understand "might be useful to have a lower claim for a smaller patient," for instance for individuals who have lost a significant amount of body weight due to cancer. (D.I. 150 at 1023:5-16) Cephalon does not rebut Dr. Kibbe's testimony in this regard.

disclosure of "potato starches and modified starches thereof" as a disintegrant includes the superdisintegrant SSG.[30] (*See* D.I. 151 at 1196:18-22, 1214:22-24) The Handbook also discloses the mannitol and SSG components. (*See* DTX722 at 327; DTX723 at 503; DTX737 at 651)

97. Cephalon does not specifically argue that the combination of the disclosures of the '604 patent with the dosage range from the Actiq® brochure and the use of SSG from the Handbook does not result in all of the claimed limitations.[31] Rather, it argues that Mylan has not borne its burden of showing that persons of ordinary skill in the art would have been motivated to abandon the use of lactose and crospovidone for mannitol and SSG in oral transmucosal fentanyl tablets. (D.I. 155 at 13-23) Cephalon also points to various secondary considerations as objective evidence of nonobviousness. (D.I. 155 at 24-37) Therefore, the court focuses its analysis on the motivation to combine and the secondary considerations. *See Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1375 (Fed. Cir. 2013) ("With every

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[30]To the extent Cephalon argues that the '604 does not identify the claimed ranges for mannitol and SSG (*see* D.I. 155 at 7), Dr. Kibbe opined that the '604 patent recommends using mannitol and SSG in the range of amounts claimed by the Moe patents. (D.I. 150 at 1013:5-12, 1015:18-1017:8)

[31]Cephalon does not seem to argue, for purposes of obviousness, that the combined references do not disclose the '92,832 patent's limitation of a "dwell time of less than about 30 minutes." (D.I. 155 at 2, 11-13; *see also* D.I. 151 at 1188:1-1189:6) In any event, Mylan offered expert testimony and other evidence that the dwell time of every formulation made in accordance with example 1 of the '604 patent exhibited a dwell time under 30 minutes (D.I. 150 at 1021:7-24; *see also* PTX317.7; PTX456A.6), and Cephalon has not offered any evidence to rebut that evidence. (*See* D.I. 155 at 11-13) Moreover, Cephalon did not dispute this limitation in the joint pretrial order or during trial. (*See* D.I. 142 at ex. 7.1; D.I. 151 at 1186:25-1187:13, 1188:1-1189:6) As a result, Mylan has established by clear and convincing evidence that the '604 patent discloses a dwell time of less than about 30 minutes.

limitation of the asserted claims thus disclosed in the cited references, the question . . . becomes whether a person of ordinary skill in the art would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success.").

e. Motivation to combine

98. Mylan's expert, Dr. Kibbe, cited stability problems with formulations containing lactose and crospovidone as a motivation to substitute those components with mannitol and SSG, respectively. For support, he averred that it was known at the time of the claimed invention that crospovidone contains "contaminant peroxides," whereas SSG does not. (D.I. 150 at 1027:10-12) He then referred to the stability issues that Cima encountered when trying to develop a commercial version of Fentora®, which led to the inventions claimed in the Moe patents. (*See id.* at 1028:21-1029:20) He relied on a Cima memorandum and the data contained therein to opine that "[c]rospovidone appears to play a role in the oxidative degradation pathway of fentanyl. This has been shown with stability and forced degradation data." (*Id.* at 1027:25-1029:20) Accordingly, Dr. Kibbe opined that, "**if** a person of ordinary skill in the art encountered oxidation issues, he would have substituted crospovidone with SSG." (*Id.* at 1027:9-19, 1028:2-5; D.I. 151 at 1099:8-21) (emphasis added) Cephalon contends that this is an inappropriate reliance on hindsight. (D.I. 155 at 17-18)

99. "The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) (citing 35 U.S.C. § 103(a)). Dr.

Kibbe never testified that a person of ordinary skill in the art, **based on the prior art**, would have realized that there were stability issues in tablets containing lactose and crospovidone. He only opined that **once** a stability issue was identified, a person of ordinary skill in the art would have found it obvious to substitute SSG for crospovidone. In short, Dr. Kibbe does not offer an opinion that one of ordinary skill in the art, absent the benefit of Cima's internal observations and documents, would have had any reason to suspect stability issues and, therefore, be motivated to solve such issues. He cannot rely on the problems that the inventors "unexpected[ly]" ran into in order to support a person of ordinary skill's motivation to combine. (*See* D.I. 147 at 246:9-18, 247:7-251:25, 252:8-262:11)

100. As long as the person of ordinary skill in the art would have been motivated to combine references by the prior art taken as a whole, however, it is not necessary that the references be combined for the same reasons contemplated by the inventor or to address the specific problem solved by the invention. *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (citing *In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992)); *see also KSR*, 550 U.S. at 420 ("[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed."). In this regard, Dr. Kibbe opined that mannitol has been "commonly used in every single chewable tablet that has been on the market for the last 50 to 60 years" and was known to provide a sweet, cooling, and comfortable feeling in the mouth, or a "good mouth feel." (D.I. 150 at 1016:12-22, 1031:8-11) Dr. Moe agreed, testifying that, at the time he was formulating the Fentora® formulation, mannitol was known to have a cooling effect. (D.I. 148 at 321:9-18) In addition,

lactose, though inexpensive, is incompatible with several compounds because it participates in the Maillard reaction, which causes mottling, or browning, of tablets. (D.I. 150 at 1031:24-1032:18) Mannitol, on the other hand, does not participate in the Maillard reaction. (DTX722 at 327; D.I. 148 at 320:7-15; D.I. 150 at 1032:10-18) In light of these advantages, Mylan's expert, Dr. Kibbe, averred that a person of ordinary skill in the art would have found the use of mannitol to be "dead obvious" because it was "the best" and "the most efficient" choice for a stable and effective orally disintegrating buccal delivery system. (D.I. 150 at 1032:24-1033:13)

101. Even if a person of ordinary skill would have been motivated to substitute lactose with mannitol, however, the court does not find that Mylan has submitted sufficient evidence of motivation to use SSG, alone or in combination, with mannitol. "To render a claim obvious, prior art cannot be 'vague' and must collectively, although not explicitly, guide an artisan of ordinary skill **towards a particular solution**" to a particular problem. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011) (emphasis added) (quoting *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009)). Indeed, Dr. Kibbe opined that the use of mannitol and SSG instead of lactose and crospovidone would not have been expected to benefit the pK characteristics of a formulation. (D.I. 151 at 1082:9-17) The only motivation that he provided for using SSG was that "the '604 patent gives you license . . . to select a – a noneffervescent disintegrating agent to use in your tablet. And I think [SSG] is a very popular one." (D.I. 150 at 1027:1-8) The mere identification of SSG as a component known in the art at the time of the invention, however, is not a motivation to move away from using crospovidone in favor of using another superdisintegrant, SSG. *See KSR*,

550 U.S. at 418 ("[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.").

102. Because Mylan has not provided sufficient evidence of motivation to use SSG, alone or in combination with mannitol, Mylan has not met its burden of showing obviousness.

f. Secondary considerations

103. Cephalon points to unexpected results, commercial success, praise, failure of others, copying, and long-felt need as objective evidence of nonobviousness. (D.I. 155 at 24-37)

(1) Unexpected results

104. With respect to objective indicia of nonobviousness based on unexpected results, the Moe patents teach that the claimed invention surprisingly permitted the use of a lower dosage of fentanyl while maintaining pK characteristics comparable with prior art fentanyl dosage forms. ('158 patent, abstract, col. 2:41-61, 4:43-50) The specification teaches that "certain disintegrants and fillers in combination with at least one effervescent couple and at least one pH adjusting substance can provide even better, and very unexpected, results." (*Id.*, col. 9:1-5) It then names mannitol and SSG as the preferred filler and disintegrant, respectively. (*Id.*, col. 4:43-50) The broadest asserted claims of the Moe patents recite mannitol in "an amount between about 10% and about 80%" and SSG in "an amount of about 0.25% to 20%."

105. The Moe patents reported the unexpected benefits of higher maximum plasma concentration (C_{max}) and higher area under the curve (AUC) – a value related to

the extent of absorption – for the first hour after administration compared to the same dosage with lactose and crospovidone. (D.I. 151 at 1126:9-17) Mylan argues that Cephalon's assertion of unexpected benefits is drawn from cherry-picking and inappropriately comparing data and that the evidence of unexpected benefits is not commensurate with the scope of the claims. (D.I. 152 at 24-29)

106. The court finds that the unexpected results are sufficiently supported by Cephalon's testing. Dr. Jerling analyzed two studies on formulations based on the Khankari patents ("the Khankari formulations") (the 099-09 and 099-10 studies) and two studies on formulations based on the Moe patents ("the Moe formulations") (the 099-11 and 099-18 studies). (D.I. 151 at 1133:23-1134:17; PTX546A; PTX317; PTX261; PTX367A) The four studies collected the same bioavailability data, and the 99-10 and 99-11 studies tested the Khankari and Moe formulations, respectively, against 1600 mcg Actiq® as a control. (PTX317; PTX261; D.I. 151 at 1132:22-1133:13, 1134:20-1135:2, 1136:15-1140:10) Dr. Jerling opined that, because the 1600 mcg Actiq® data in the 99-10 and 99-11 studies were similar, the 1600 mcg Actiq® served as an "active control" that allowed him to compare pK data from those two studies. (D.I. 151 at 1139:15-1140:10, 1146:15-23, 1148:8-22; PTX357.4) He concluded, from comparing the 99-10 and 99-11 studies, that the Moe formulations resulted in significantly higher C_{max} and *AUC* values than the Khankari formulations. (D.I. 151 at 1140:22-1145:3, 1146:24-1149:20, 1150:18-1153:8; PTX357; PTX361; PTX362) Specifically, the Moe formulations had C_{max} and *AUC* values that were about 30% higher than that of the Khankari formulations, and these results were statistically significant at the 5% significance level. (D.I. 151 at 1147:17-1148:22, 1152:18-1153:8; PTX357.5, .6, .7)

107. Mylan's expert, Dr. Kibbe, took issue with Dr. Jerlin's analysis because the Moe and Khankari formulations were not compared in a "head-to-head" study. (D.I. 151 at 1225:20-1227:7, 1239:12-24) Even if a "head-to-head" study would have been more robust (*see* D.I. 151 at 1159:10-16), the court is satisfied with the reliability of Dr. Jerling's analysis because the similarity of the 1600 Actiq® control data across the 99-10 and 99-11 studies served as a common baseline for comparison. The court also finds that it was valid for Dr. Jerling to focus on comparing the data from the 99-10 and 99-11 studies, rather than all four studies, because the 99-09 and 99-18 studies did not share the same active control. (*See* PTX456A; D.I. 151 at 1138:14-1140:21, 1183:22-1184:5) The court is also persuaded by Dr. Jerling's testimony that the 5% significance level[32] he used was typical in the field and permitted extrapolation of the findings to the general population. (D.I. 151 at 1152:18-1153:8; PTX357.7) Therefore, the evidence demonstrates that the Moe formulations had pK results that were unexpectedly better than the Khankari formulations.

108. In addition to challenging the robustness of the evidence, Mylan asserts that the scope of the unexpected results is disproportionate to the Moe patents' claims. (D.I. 152 at 54-56) For unexpected results to support nonobviousness, the unexpected results must be reasonably commensurate with the scope of the claims. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308-09 (Fed. Cir. 2011). "[A]bsolute identity of scope" is not required; rather, unexpected results are rejected "where the evidence [i]s plainly disproportionate to the scope of the claim." *Id.*

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[32]A 5% significance level indicates that the risk of a difference being falsely identified is 5% or less. (D.I. 151 at 1154:13-16, 1155:21-1156:18)

Cephalon does not dispute that the unexpected benefits of using mannitol and SSG were based on only one study which tested a formulation containing 3% SSG and 47-49% mannitol. (*See* D.I. 155 at 30) Cephalon avers that the unexpected results that were observed support the conclusion that unexpected results occur over the claimed ranges of SSG and mannitol because those ranges cover typical and reasonable amounts of mannitol and SSG for use in tablet formulations. (D.I. 148 at 343:21-2, 344:6-11; D.I. 151 at 1209:20-1210:13)

109. There is no evidence of record to the contrary. Mylan's argument that the unexpected results may not occur for higher or lower amounts of mannitol and SSG is based solely on attorney argument. (*See* D.I. 152 at 25-26) The court finds that the unexpected results at bar are not so disproportionate to the scope of the claim as to reject unexpected results. *See, e.g.*, *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003) (finding a few data points did not evidence unexpected results for the entire claimed range of about 1-3% rhenium, where evidence suggested that 3% rhenium possessed inferior properties); *In re Greenfield*, 571 F.2d 1185, 1189 (C.C.P.A. 1978) (affirming the obviousness of a genus containing "several hundred compounds," where unexpected results were demonstrated for only one compound); *cf. In re Glatt Air Techniques, Inc.*, 630 F.3d 1026, 1030 (Fed. Cir. 2011) (stating that objective evidence of commercial success relating "only to a single embodiment" should be considered even if claim covers "multiple embodiments"). On the facts of record, the court finds that unexpected results weigh in favor of nonobviousness.

(2) Commercial success

110. Cephalon also claims that the success of Fentora® supports a finding of nonobviousness. (D.I. 155 at 33-36) For evidence of commercial success, Mr. Jeffrey G. Snell ("Mr. Snell"), an economic evaluation consultant for Cephalon, cited Cephalon's sales and profits, as well as the fact that three other transmucosal immediate-release fentanyl products that entered the market between January 2011 and January 2012 have each failed to gain more than 6% market share. (D.I. 151 at 1107:4-9, 1109:14-16, 1113:18-22; *see also id.* at 1270:7-10)

111. "When a patentee offers objective evidence of nonobviousness, there must be a sufficient relationship between that evidence and the patented invention." *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994). "A prima facie case of nexus is made when the patentee shows both that there is commercial success, and that the product that is commercially successful is the invention disclosed and claimed in the patent." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010);. Commercial success must be "due to the merits of the claimed invention beyond what was readily available in the prior art." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *see also Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1345 (Fed. Cir. 2007). There is no relevant commercial success when market entry of others is precluded due to the patentee's ownership of earlier patents covering the product. *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

112. Mylan asserts that the Khankari patents, not the Moe patents, are responsible for any of Fentora®'s commercial success because the listing of the Khankari patents in the Orange Book blocked market entry even before the Moe patents issued. (D.I. 152 at 60) On his cross-examination, Mr. Snell testified that he did not

distinguish commercial success attributable to the Moe patents and that the Khankari patents allowed Fentora® to enter the market. (D.I. 147 at 113:5-16; D.I. 151 at 1117:9-20) There is no dispute that the Orange Book listed the Khankari patents for Fentora® before the Moe patents were issued. Therefore, Fentora®'s success is at least partially attributable to the monopoly that Cephalon had on the market before the issuance of the Moe patents. Given Cephalon's failure to show sufficient nexus to the Moe patents, commercial success is not a persuasive secondary consideration in this case.

(3) Praise

113. Cephalon avers that nonobviousness is further supported by praise in the field for Fentora®. (D.I. 155 at 35-36) Mylan's expert, Dr. Johnston Loeser ("Dr. Loeser"), co-authored a book in 2010 entitled "Cancer Pain: Assessment, Diagnosis and Management." (D.I. 151 at 1289:23-1290:7, 1292:4-5) Chapter 19 of the book, entitled "Opioid Analgesics," describes Fentora® as a drug that employs a "novel" drug delivery platform using effervescence to enhance fentanyl absorption through the buccal mucosa and notes that a single dose of Fentora® provides "clinically significant improvement to pain intensity." (*Id.* at 1298:7-1300:13; DTX502 at 205) For the same reasons that Cephalon has not established a sufficient nexus for commercial success, the court finds that the purported praise in Dr. Loeser's book is not sufficiently related to the novel aspects of the Moe patents. *See Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA*, 699 F.3d 1340, 1351 (Fed. Cir. 2012) (considering whether industry praise was sufficiently related to features made possible by the patented technology). Praise in the field also does not weigh toward a finding of nonobviousness.

(4) Failure of others

114. Cephalon argues that Mylan's failure to develop a noneffervescent formulation that was bioequivalent to Fentora® is an indication of nonobviousness. (D.I. 155 at 32) (citing *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 759 (N.D. W. Va. 2004). Cephalon's argument, however, is misplaced. "The purpose of evidence of failure of others is to show 'indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan.'" *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1082 (Fed. Cir. 2012). Here, Mylan's experimentation with noneffervescent formulations does not show that it struggled to solve a prior art defect that was addressed by the Moe patents. Rather, it struggled to make a formulation that was bioequivalent to Fentora®. Mylan's testing, which was geared at avoiding a patent, is distinguishable from evidence that others had attempted and failed to develop a solution to the drawback identified by the Moe patents (the use of high amounts of fentanyl). As a result, there is no evidence of the failure of others relevant to obviousness.

(5) Copying

115. Cephalon also contends that Mylan's copying of Fentora® should be considered an objective indicia of nonobviousness. "[J]ust as with the commercial success analysis, a nexus between the copying and the novel aspects of the claimed invention must exist for evidence of copying to be given significant weight in an obviousness analysis." *Wm. Wrigley Jr. Co.*, 683 F.3d at 1364. The Federal Circuit, however, has held that it "do[es] not find compelling . . . evidence of copying in the

ANDA context where a showing of bioequivalency is required for FDA approval." *Purdue Pharma Products LP v. Par Pharm., Inc.*, 377 F. App'x 978, 983 (Fed. Cir. 2010); *see also Bayer*, 713 F.3d at 1377 ("[C]opying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval."). Given the FDA's stringent requirement for showing bioequivalence, it is not surprising that such a showing would require copying of the brand name drug.

(6) Long-felt need

116. Finally, Cephalon points to the long-felt need in the area of breakthrough pain management for opioid-tolerant patients. (D.I. 155 at 36-37) (citing D.I. 147 at 68:3-10) Specifically, it avers that treatment options for breakthrough pain were not absorbed fast enough by the body. (*Id.* at 36) (citing D.I. 147 at 76:12-77:4) Actiq® allegedly had clinical limitations due to its lozenge-on-a-stick dosage form, requirement for active manipulation by the patient (which many ill patients have trouble doing), social stigma from use, attractiveness to children, risk of diversion, and dental caries or teeth decay. (D.I. 147 at 78:20-79:2, 81:3-8, 82:14-86:1) Cephalon asserts that Fentora® provides a more rapid onset of delivery, eliminates the lozenge-on-a-stick dosage form, and produces greater fentanyl bioavailability. (D.I. 155 at 37) (citing D.I. 147 at 87:19-88:7, 92:8-25; PTX247.8-0.9)

117. Cephalon's argument fails to take into account the prior art '604 patent. As Cephalon's expert, Dr. Craig Blinderman ("Dr. Blinderman"), admitted, the long-felt needs that Cephalon points to – rapid onset of delivery, elimination of the lozenge-on-a-stick dosage form, and enhanced fentanyl absorption – were satisfied by the invention of the '604 patent. (D.I. 147 at 113:5-114:24) Cephalon presented no evidence that the

Moe patents' differences over the '604 patent – the lower amount of fentanyl (which still provided comparable pK characteristics) and the use of mannitol and SSG (as the filler and disintegrant) – solved the alleged long-felt needs.[33] *See Geo M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304-05 (Fed. Cir. 2010) ("Where the differences between the prior art and the claimed invention are as minimal as they are here, . . . it cannot be said that any long-felt need was unsolved."). As a result, the consideration of long-felt need does not weigh in favor of finding nonobviousness.

g. Conclusion on obviousness

118. Mylan has not provided sufficient evidence that a person of ordinary skill in the art, at the time of invention, would have been motivated to use the disintegrant SSG, alone or in combination with mannitol. The unexpected pK results from combining SSG and mannitol also support this finding of nonobviousness. Therefore, Mylan has not met its burden of proof that the Moe patents are invalid for being obvious.

3. Conclusion on validity of the Moe patents

119. The court concludes that Mylan has not shown, by clear and convincing evidence, that the Moe patents are either anticipated or obvious in light of the prior art references. Accordingly, the court finds that the Moe patents are valid.

III. CONCLUSION

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[33]To the extent Cephalon asserts that there was also a long-felt need for dosage forms with lower amounts of fentanyl that could achieve comparable bioavailability, the court finds that such a need would have been much weaker than the other long-felt needs identified by Cephalon. (*See* D.I. 147 at 92:8-25) In any case, Cephalon has not provided sufficient evidence that such a long-felt need existed.

120. For the foregoing reasons, the court finds that Mylan infringes the asserted claims of the '604, '590, and '158 patents and that the '92,832 and '158 patents are valid. An appropriate order shall issue.