IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

CEPHALON, INC., and CIMA LABS, INC.	)	
Plaintiffs,	)	
v.	)	Civ. No. 08-330-SLR
WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC., and WATSON PHARMA, INC.,	)	
Defendants.	)	

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OPINION

Dated: March 11, 2011
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application ("ANDA")[1] by defendants Watson Pharmaceuticals, Inc., Watson Laboratories, Inc., and Watson Pharma, Inc. (collectively, "Watson") in 2008 for a generic version of Fentora® (fentanyl buccal tablets), used to treat breakthrough pain in cancer patients. Plaintiff CIMA Labs, Inc. ("CIMA") is the assignee of U.S. Patent Nos. 6,200,604 ("the '604 patent") and 6,974,590 ("the '590 patent"), directed to a sublingual buccal effervescent pharmaceutical dosage form. Plaintiff Cephalon, Inc. ("Cephalon") is the exclusive licensee of the '604 and '590 patents (hereinafter, collectively the "Khankari patents") and is also the owner of U.S. Patent No. 6,264,981 ("the '981 patent").[2] Cephalon is the holder of an approved New Drug Application ("NDA")[3] for the manufacture and sale of fentanyl buccal tablets for the treatment of breakthrough cancer pain. Cephalon listed with the Food and Drug Administration ("FDA") the '604 and '590 patents in the Orange Book in connection with its NDA. In response to Watson's ANDA filing, which contained a paragraph IV certification as to the '604 and '590 patents,[4] plaintiffs filed a

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[1]No. 79-075.

[2]CIMA is a wholly-owned subsidiary of Cephalon, managing Cephalon's drug delivery technologies. *See gen.* http://http://www.cephalon.com/healthcare-professionals/drug-delivery-technologies.shtml.

[3]No. 21-947.

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

patent infringement suit on June 2, 2008.[5] (Civ. No. 08-330, D.I. 1) The court denied defendants' (renewed) motion to dismiss certain counts of the complaint on April 3, 2009.

On September 25, 2009, plaintiffs filed a second complaint of patent infringement against defendants seeking a declaratory judgment of infringement of U.S. Patent No. 6,264,981 ("the '981 patent"), directed to a method for oral transmucosal drug delivery. (Civ. No. 09-724, D.I. 1) In both cases, defendants asserted defenses and counterclaims of noninfringement and invalidity. The two actions were consolidated for purposes of discovery and tried together in a bench trial held between May 10 and 17, 2010. (Civ. No. 09-724, D.I. 23) The issues of infringement and invalidity have been fully briefed post-trial. Having been advised that the 30-month stay on the FDA's approval of defendants' ANDA (triggered by plaintiffs' first suit) expired,[6] the court recently enjoined defendants' launch of generic fentanyl buccal tablets pending the issuance of its decision. (Civ. No. 08-330, D.I. 157)[7] The court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

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[5]*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[.]").

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

[7]Hereinafter, the court's citation to docket numbers will reference Civ. No. 08-330, unless specifically noted.

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Technology at Issue

1. Drug delivery across the oral mucosa

1. There are several methods by which a drug may be delivered to the human bloodstream. In traditional oral administration, a dosage form is swallowed and drug absorption occurs across the gastrointestinal mucosa (the stomach or intestines). (D.I. 282 at 108:22-109:10) By contrast, when a drug is administered by an oral transmucosal route, the drug is absorbed across the mucous membranes of the mouth and directly into the blood stream. (*Id.* at 116:2-21)

2. The inventions at bar 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 109:17-110:10) 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. (*Id.*)

3. Cells in the intestinal tract, an area naturally designed for absorption, are present in a single layer lining the intestinal wall. (*Id.* at 114:8-115:11) Between these cells are "tight junctions," or certain proteins that act as a gate controlling what substances may pass through the intestine into the body. (*Id.*) Tight junctions are generally not present in the oral mucosa,[8] however, the oral mucosa lining comprises multiple, staggered layers of cells such that a "molecule has to take a tortuous path to get to the other end." (*Id.*) The surface area for absorption of the oral mucosa is also

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[8]They may be present in intermediate layers. (D.I. 282 at 154:3-6)

small. (*Id.*) Despite these disadvantages, drug delivery across the oral mucosa offers the advantage of a faster onset of action. This is because the drug need not travel through the gastrointestinal tract and the liver prior to blood absorption, and the "first-pass effect" – a percentage of drug lost to metabolization in the liver – is avoided. (*Id.* at 115:14-116:21) Consequently, the same therapeutic effect can be achieved with a lower dose of drug administered across the oral mucosa. (*Id.*) Rapid entry of the drug into the bloodstream benefits the treatment of conditions requiring fast relief, such as breakthrough cancer pain.

4. For both the traditional oral and transmucosal routes of administration, the drug traverses the relevant mucosa and can reach the bloodstream primarily by two pathways: paracellular or transcellular. (*Id.* at 110:11-15.) With paracellular absorption, the drug moves between cells to reach the bloodstream. (*Id.* at 110:16-23) With transcellular absorption, the drug moves across the mucosa by passing through cells until reaching the bloodstream. (*Id.* at 110:24-111:8; 112:23-113:7) In doing so, the drug must breach the cell membrane wall. (*Id.* at 113:5-7)

5. Fentanyl is a lipophilic drug, meaning that it dissolves much more readily in lipid (fats and oils) than in water. (*Id.* at 113:13-17) Highly lipophilic compounds like fentanyl are absorbed primarily through the transcellular route. (*Id.* at 120:9-20; 154:10-20) Lipophilicity and, thus, the ability to absorb via the transcellular route, is increased by increasing the pH. At a higher pH, unionized (lipophilic) species of the drug are favored. (*Id.* at 122:2-124:7)

6. A high starting pH level is impracticable, however, because a high pH hinders

the dissolution of the drug. (*Id.* at 124:8-16) Herein lies the formulator's quandary: while a high pH is favored for absorption, a low pH is favored for solubility. Put in terms of ionization, when a weakly acidic or basic drug dissolves, it becomes ionized. The ionized form is hydrophilic while the dissolved, unionized form is favored for transcellular absorption. (*Id.* at 123:9-13; 124:4-7) Therefore, the "holy grail" is to provide a drug designed for oral mucosal delivery having both improved solubility and absorption.

2. The Khankari patents: overview

7. A method for achieving this result is claimed by 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"): using an effervescent agent to enhance the penetration of the medicament across the buccal, sublingual and gingival mucosa. ('590 patent, col. 2:13-15)

8. Dr. Khankari testified that the inventors achieved a dynamic change in pH – a low starting pH, promoting dissolution, followed by an increase in pH, favoring absorption – by incorporating effervescent agents that react to form carbon dioxide (CO_2). (D.I. 282 at 120:9-23) When CO_2 dissolves in saliva, it forms a weak acid (carbonic acid) that reduces the salival pH. (*Id.* at 121:1-11) The carbonic acid thereafter dissociates into CO_2 and water; CO_2 is released as gas, causing the pH to slowly rise. (*Id.* at 121:13-20) In this manner, a balance between dissolution and absorption is achieved. The inventors believed that effervescence increases the rate and extent of absorption of an active drug 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)

9. The Khankari patents characterize the invention as the use of "an effervescent agent effective to aid penetration of the drug across the oral mucosa." (*Id.*, col. 2:32-34) To this end, specific quantities of an effervescent agent (between 5% and 95% by weight and, preferably, 30% to 80% by weight) are provided for formulation purposes. (*Id.*, col. 2:34-38) This quantity, in turn, should be sufficient to provide "about 5 cm^3 to but less than about 30 cm^3 [of evolved gas] upon exposure of the tablet to an aqueous environment." (*Id.*, col. 2:38-41) While most often a soluble acid source and a carbonate source (such as potassium bicarbonate) will be used, which reaction produces CO_2 gas, reactants may also be used which evolve other gases. (*Id.*, col. 2:48-col.3:3)

10. Other pharmaceutical ingredients are preferably incorporated into the dosage form of the invention for a variety of purposes, including aiding disintegration. "Disintegrants may comprise up to about 20 weight percent" of the composition and, preferably, between 2% and 10% of the composition. (*Id.*, col. 4:41-51) "[S]uitable non-effervescent disintegration agents" may be used. (*Id.*) Excipient fillers "desirably will also assist in the rapid dissolution of the dosage form in the mouth." (*Id.*, col. 5:28-32) Mannitol is listed among the (non-limiting) examples of such excipient fillers. (*Id.*)

11. The Khankari patents also disclose the use of suitable pH-adjusting substances that permit a sufficient concentration of the drug to be present in the

unionized (and more absorbable) form. (*Id.*, col. 3:40-46) "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. Suitable pH-adjusting substance[s] for use in the present invention include, but are not limited to, any of the acids or bases previously mentioned as effervescent compounds[.]" (*Id.*, col. 3:47-55) (emphasis added)

12. The '604 patent was filed (as U.S. Patent Application No. 09/327,814, hereinafter, "the '814 application") on June 8, 1999 and issued March 13, 2001. Priority is claimed to a provisional patent application (No. 60/079,652) filed March 27, 1998. The '590 patent was filed on February 20, 2002 (as U.S. Patent Application No. 10/080,616, hereinafter, "the '616 application") and issued on December 13, 2005. It is a grandchild, continuation application claiming priority to the '814 application. As such, the Khankari patents share a common disclosure.

13. Claim 1 of the '604 patent is the sole independent claim of that patent, and reads as follows.

> 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)

14. The '590 patent discloses fentanyl as the pharmaceutical agent, and contains one independent claim, as follows.

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)

B. Claim Construction

1. Standards

15. 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.

16. 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 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

17. While the parties have separately addressed the "effervescent agent" and "amount sufficient to increase absorption" terms of the claims, the court finds it more appropriate to address the "at least one [saliva activated] effervescent agent in an amount sufficient to increase absorption . . . across [the] oral mucosa" term as a whole.[9] The court, however, will briefly frame the parties' arguments on each portion of the term prior to addressing the intrinsic record.

18. There is no dispute among the parties that an "effervescent agent" must generally "evolve gas" "by means of a reaction." (D.I. 187; D.I. 253 at 39) The claim construction issue before the court, therefore, is whether two (or more) compounds are required to do so. Specifically, Cephalon asserts that "at least one effervescent agent"

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[9]Claim 1 of the '604 patent recites "at least one effervescent agent," while claim 1 of the '590 patent provides for "at least one saliva activated effervescent agent." The parties do not frame their arguments in such a manner that the "saliva activated" adjective is relevant to construction of "effervescent agent."

means "at least one compound that evolves gas by means of a reaction," without limitation as to the nature of the reaction. Watson argues that, while "at least one" has its ordinary meaning, "effervescent agent" is "synonymous with effervescent couple, which is a combination of two or more compounds that evolve gas by means of a reaction" upon exposure to saliva. (D.I. 187)

19. With respect to the "in an amount sufficient" portion, the parties agree that the term means, at least, "in an amount sufficient to increase the rate and/or extent of absorption of [an orally administerable medicament/fentanyl or pharmaceutically acceptable salt thereof] across [said/the] oral mucosa." (D.I. 187) Watson proposes the additional limitation that the amount sufficient be "an amount greater than the amount required for tablet disintegration" and "not include any amount of pH-adjusting substance present in the tablet." (*Id.*)

3. Intrinsic evidence

20. The Khankari patents' specification provides that "effervescent agents can be used alone or in combination with other penetration enhancers, which leads to an increase in the rate and extent of absorption of an active drug." ('590 patent, col. 2:21-23)

> The preferred effervescent agents evolve gas by means of a chemical reaction which takes place upon exposure of **the effervescent agent (an effervescent couple)** to water and/or to saliva in the mouth. The reaction is most often the result of a soluble acid source and a source of carbon dioxide such as an alkaline carbonate or bicarbonate. The reaction of these **two general compounds** produces carbon dioxide gas upon contact with water or saliva.

('590 patent, col. 2:44-53) (emphasis added)

21. Further, "[t]he dosage form preferably includes an effervescent couple, in

combination with the other ingredients to enhance the absorption of the pharmaceutical ingredient across the oral mucosa and to improve the disintegration profile and the organoleptic properties of the dosage form." (*Id.*, col. 4:23-27)

a. '604 patent

22. The parties do not dispute that the meaning of the claim term "at least one effervescent agent" was not addressed during prosecution of the '604 patent (from 1999 to 2001).

23. The phrase "and at least one effervescent agent in an amount sufficient to increase absorption of said orally administerable medicament across the oral mucosa" was added to the claims during prosecution of the '604 patent in response to an anticipation and obviousness rejection by U.S. Patent No. 5,178,878 ("Wehling"). (JA-146-47) The applicants provided that:

> Both rejections appear to be based on the fact that the use of effervescents as disintegration agents or taste masking agents in solid oral dosage forms was known in the art. Although the prior art's teachings of the use of effervescents in this manner is acknowledged, the present invention, as recited in claims 9-10, is directed to a new use for effervescent agents. Namely, the present invention is directed to the use of effervescent agents alone or in combination with pH adjusting substances to promote the absorption of medicaments across the oral mucosa. The claimed invention therefore provides improvements in the field of the oral delivery of medicaments, including, for example, by **increasing the onset of action** of some orally administerable drugs, **improving the bioavailability** of some orally administerable drug, and enabling delivery of drugs across the oral mucosa that were previously not suited for this route of administration due to their poor absorption properties.

(JA-147) (emphasis added) These arguments were deemed unpersuasive, and a final rejection issued. (JA-351) In response, the applicants added additional limitations to the independent claim, specifically, the "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" and the requirement that the patient hold the oral dosage form in the mouth as it dissolves and as absorption is improved (issued claim 1, subpart (c)). (JA-393) The claims were thereafter allowed in view of the latter amendment, as the prior art taught swallowing of the dosage form and absorption in the stomach. (JA-404)

b. '590 patent

24. The "effervescent agent" term was addressed while the later-filed '590 patent was pending (as the '016 application). Claim 1 of the '016 application (filed in 2002) was drawn to a pharmaceutical dosage form comprising fentanyl and "**at least one saliva activated effervescent agent**." (JA-2310)[10] (emphasis added) Dependent claims 2 to 4 added the requirements for a pH-adjusting substance, a basic pH-adjusting substance, and more specific bases to be used. (*Id.*) Claims 2 to 4 were provisionally rejected for obviousness-type double patenting over copending U.S. Patent Application No. 09/661,693 ("the '693 application") – the parent to the '016 application, and the child to the '604 patent in the chain of continuation applications.[11] (JA-2508) The examiner identified two sets of overlapping claims in a provisional obviousness-type double patenting rejection: '693 application claim 95 with '016 application claim 2, and '693 application claims 85 and 86 with '016 application claim 4.

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[10]The parties docketed several volumes of joint appendices at D.I. 197. The court will hereinafter refer only to the particular JA- citation in referencing these documents.

[11]The '693 application, therefore, had an identical specification and disclosure to its copending child.

(JA-2508-09)

25. In this same rejection, the examiner also rejected the pending claims as obvious in view of the combination of U.S. Patent No. 6,071,539 to Robinson et al. ("Robinson") and U.S. Patent No. 4,671,953 to Stanley et al. ("Stanley"). (JA-2509) The examiner stated that Robinson taught oral formulations containing effervescent granules containing "an effervescent couple (i.e., an acidic agent such as citric acid, tartaric acid, fumaric acid **and** an alkaline agent such as sodium bicarbonate, sodium dihydrogen phosphate, potassium carbonate) and a binder." (*Id.*) (emphasis added)

26. The applicants traversed the rejection by arguing, *inter alia*, that Robinson discussed an effervescent couple in the context of disintegration and did not disclose adjusting the amount of effervescence to increase absorption across the oral mucosa. (JA-2599-600) Robinson did not disclose or recognize that "adjusting the amount of effervescent couple, or the pH, [would] improve penetration of an [API] across the oral mucosa[.]" (JA-2599, JA-2600)

> In particular, there is nothing in Robinson to suggest that the amount of effervescent couple required for substantially complete disintegration of the tablet and a positive organoleptic sensation to a patient is anything more than that required to just cause the tablet to disintegrate. Clearly, an effervescent couple, when activated in the mouth, will cause "fizzing" and thereby be perceived by the patient.
>
> It is only the present invention that teaches **that the amount of effervescent couple should be greater than that required for disintegration in order to achieve an improvement in transport of the active ingredient across the oral mucosa**. It is only as a consequence of applicants' teaching regarding this effect that the examiner has extrapolated the teachings of Robinson in order to suggest that it is desirable to increase the amount of the effervescent couple and the pH of the composition in order to achieve the effect taught by applicants; Robinson contains no such teaching or suggestion.

(JA-2600-01) (emphasis added) In sum, Robinson did not teach the "critical limitations" of the present invention, that is, improving the transport of an API across the oral mucosa "by appropriate control of the amount of effervescent couple and, additionally, the pH achieved by the composition." (JA-2601)

27. Thereafter, the examiner rejected claims 1-19 of the '016 application over claims 22, 23, 25-28, 83-91 and 93-95 of the '693 application.[12] (JA-2618) While the '016 application contained "effervescent agent" in the claims, claim 22 of the '693 application, the independent claim from which the others in this group depend, included a limitation to "at least one saliva activated effervescent couple."[13] The examiner stated that the conflicting claims were "not identical, [but] not patentably distinct." (*Id.*) Furthermore, the provisional double-patenting rejection was forged on the ground that the claims of the '693 application were "directed to a tablet for oral administration across the oral mucosa comprising a pharmaceutically effective amount of a medicament, at least one pH adjusting substance and at least one saliva activated effervescent couple **present in an amount which is greater than the amount necessary for tablet disintegration and which is sufficient to increase absorption of the medicament across the oral mucosa**," which encompassed the '016 fentanyl dosage form.[14] (JA-2619) (emphasis added)

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[12]A double-patenting rejection was also issued based on claims 1-8 and 10-12 of the '604 patent. (JA-2619)

[13]As of May 29, 2003. The rejection at issue in the '016 application was mailed August 4, 2003.

[14]An obviousness-type double patenting rejection was made vis a vis the '604 patent, which is not relevant to claim construction. (JA-2619-20) A terminal disclaimer

28. The obviousness rejection of Robinson and Stanley was replaced with a rejection of the claims over a combination of Robinson and either U.S. Patent No. 5,958,458 to Norling et al. ("Norling"), teaching the use of analgesics in effervescent tablets, or U.S. Patent No. 5,073,374 to McCarty, teaching non-effervescent but fast dissolving buccal medicaments. (JA-2620-24)

29. In response, the applicants added oral administration limitations and weight percent limitations to the independent claims of the '016 application. Independent claims 1 and 10 of the '016 application were amended to require "wherein said amount of said at least one effervescent couple is between about 5% by weight and about 80% by weight." (JA-2645) At the time the amendment was entered, "effervescent couple" had as its antecedent basis only "at least one saliva activated effervescent agent" as recited previously in the claim. (*Id.*)

30. Following a final rejection, in which the double patenting and obviousness rejections based on Robinson and Norling were maintained, a terminal disclaimer was filed by the applicants. (JA-2671, 2678) The applicants cancelled claims 1 through 9. (JA-2680) Then-pending claim 10 of the '016 application read as follows:

> 10. (previously presented) 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 couple** is between about 5% by weight and about 80% by weight; and bucally, sublingually or gingivally administering fentanyl or a pharmaceutically acceptable salt thereof to said mammal across said oral mucosa.

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was later filed to rectify the issue. (JA-2677)

(JA-2680) (emphasis added) Claim 10 (and dependent claims 11-15 and 17-19) were subsequently allowed by the PTO, however, the applicants filed a request for continued examination ("RCE") in order to make additional art of record in the application. The applicants provided the following remarks in their RCE request transmittal:

> On June 10, 2005 the undersigned received a telephone call from Examiner Lamm during which the Examiner advised that pursuant to a quality review by the Patent Office of the allowed claims following mailing of the above-identified Notice of Allowance, further amendments to the claims were being requested. As stated by the Examiner, the requested amendments were directed to making the claim language in the terminal part of independent claim 10 consistent with that used in the earlier part of the claim and are **considered by the Office to be minor changes not affecting the scope of the claim**. **In particular, it was requested that the word "couple" be changed to "agent"** and that the phrase "fentanyl or a pharmaceutically acceptable salt thereof" be changed to "said solid oral dosage form." These changes are acceptable to Applicants and the amendment submitted herein is consistent with that request. Furthermore, Applicants have also amended the last line of claim 10 to conform the overall claim language to be consistent with the amendments proposed as a consequence of the quality review. **Respectfully, this amendment is not intended to narrow the scope of the claim and no narrowing has occurred, either as a result of this amendment or those proposed by the Office**. Entry of these claim amendments is respectfully requested.

(JA-2911) (emphasis added) A Notice of Allowance followed and the issue fee for the '016 application was paid. A Certificate of Correction was later issued in which the term "agents" was added to the Detailed Description of the Invention, to read: "One aspect of this invention is to use **effervescent agents** as penetration enhancers for influencing oral drug absorption." ('590 patent, col. 2:19-20) (emphasis added) Two Certificates of Correction were filed for the '604 patent; neither contained this addition to the specification.

c. '693 application

31. The '693 application was filed (as a continuation of the '604 patent

application) in September 2000 and was ultimately abandoned in 2009. As a continuation, the '693 application shares the same specification as the Khankari patents.

32. The originally presented claims of the '693 application were drawn to a solid pharmaceutical dosage form comprising "at least one saliva activated agent present in an amount sufficient to increase absorption . . . across the oral mucosa." (JA-450-51) The claims were later amended to require "at least one saliva activated effervescent agent present in an amount 5% by weight and about 80% by weight." (JA-791) The claims were rejected over U.S. Patent No. 6,117,912 ("DiSanto"), teaching an effervescent selegiline tablet for sublingual or buccal administration. (JA-788) Specifically, DiSanto provided that "[t]he amount of sodium bicarbonate (effervescent) present in example 3 is more than 61%[.]" (JA-787-88) In response to the examiner's 102(b) and 103 rejections, the applicants provided:

> Claim 22 referred to an effervescent "agent." As explained at page 5 of the specification, the term "effervescent agent" includes compounds that evolve gas. The preferred effervescent agents evolve gas by means of a chemical reaction, which takes place upon exposure of the effervescent agent (an effervescent couple) to water and/or to saliva in the mouth. Accordingly, it is inconsistent with both applicants' definition and the common definition of effervescence to consider only the weight percentage of the sodium bicarbonate without also consideration of, at the very least, the citric acid recited within example 3. If citric acid is considered, then the amount of effervescent material is well above 80% as claimed. Therefore, the DiSanto reference cannot anticipate the claim.
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> To alleviate any possible ambiguity, applicants have amended claim 22 to delete the term "agent" and to specifically refer to an effervescent "couple." As noted above, these terms are of identical scope and are clearly supported by at least the specification at page 5 quoted above.

(JA-792) The claims were amended to recite "at least one saliva activated effervescent couple present in an amount between about 5% by weight and about 80% by weight."

(JA-791, 796)

33. After receiving a new matter objection to the amendment (JA-885), the inventors reiterated to the PTO (in October 2002) that an effervescent agent is "identical in scope" in this context to an "effervescent couple." (JA-950)

34. The applicants also added a limitation that the "at least one saliva activated effervescent couple" is "present in an amount which is greater than the amount necessary for tablet disintegration and which is sufficient to increase either the rate [or] the extent of absorption of said medicament across the oral mucosa." (JA-948-49) The applicants' comments on this limitation were as follows:

> To further accentuate the differences between the present invention and the prior art, applicants have amended claim 22 to make it clear that in the invention, a saliva activated effervescent couple is present in an amount that is greater than the amount necessary for tablet disintegration. Indeed, the amount of saliva activated effervescent disintegration couple present must be sufficient to increase either the rate or the extent of absorption of the medication across the oral mucosa. Applicants have found that effervescents can be used for far more than merely allowing for disintegration of the tablet. While rapid disintegration exposes the drug such that it may be used by the body, unless an effervescent couple is present in sufficient amounts, amounts greater than that necessary for disintegration, it does not significantly participate in the drug absorption process. By providing effervescents in an amount that is greater than that necessary for achieving disintegration of the dosage form, it is possible to obtain these benefits. Nothing in DiSanto teaches or suggests the need for such additional amounts of effervescent agent.

(JA-951)

35. The examiner responded to the applicants' remarks on DiSanto as follows:

> Applicant asserts that the term "effervescent agent" is synonymous with "effervescent couple" and therefore it is improper to consider only one component (as shown in the prior art) to determine the amount of effervescent in the composition. Whereas "effervescent couple" is referred to in the instant specification, it is not evidence that the "effervescent couple" refers to an agent containing multiple components. The specification does not state the reaction is most often the result of a[n] acid source and carbon source, but it is the

examiner's position that this is a preferred reaction and not a necessary one. Therefore, the effervescent couple can be one agent or multiple agents. As such, the teachings of DiSanto anticipate claim 22, and the rejection is maintained.

(JA-958) The applicants responded:

> The examiner asserts that sodium bicarbonate in the formulation qualifies as the claimed "effervescent couple" **on its own**. **Since sodium bicarbonate cannot be an effervescent couple, i.e., comprising two components**, it appears, without there being an explicit statement in the office action, that **the examiner is suggesting that**, even if citric acid were not present in the formulation, **sodium bicarbonate would produce effervescence by reacting with the hydrochloric acid in the selegiline salt**. . . .
>
> It is respectfully suggested that the examiner misconstrues "effervescent couple." First of all, the instant claims recite a "couple," not just one "agent." Clearly, sodium bicarbonate cannot, by itself, be a "couple." Even if, as the examiner argues, the "effervescent couple" could be produced *in situ* by hydrochloric acid in the drug and sodium bicarbonate, the citric acid, as well as the fumaric acid present in the formulation cannot be ignored and must also be part of such "couple." If anything, since the HCl adds more acid, it accentuates the fact that DiSanto does not teach or suggest the range of claim 22. . . .
>
> [T]he instant claims also require that the amount of the effervescent couple be sufficient for tablet disintegration. If the examiner's view is adopted that, e.g., the citric acid in selegiline is the source of acid for the effervescent couple, the example is inadequate to anticipate the instant claims. . . **Even if the reaction between sodium bicarbonate and the trivial amount of hydrochloric acid in the selegiline salt does take place, the effervescent effect would be minimal. The amount of gas evolved from such a reaction would be very small, and thus insufficient for noticeable effervescence, let alone for tablet disintegration**.
>
> When the claims of the instant application are read on DiSanto's example 3, the combination of citric acid (and, additionally, the fumaric acid also present) and sodium bicarbonate could qualify as an "effervescent couple." Considering the combined weight of citric acid and sodium bicarbonate, or both citric acid and fumaric acid plus sodium bicarbonate, the amount of effervescent couple in the example 3 is substantially greater than 80% and thus outside the range of claim 22.

(JA-975-77) (first emphasis in original) The examiner found the arguments persuasive

36. The prosecution continued for several more years and claim 22 (among others) was ultimately allowed with additional limitations presented in Markush form. That is, claim 22 required "at least one saliva activated effervescent couple" comprising an acid selected from a specified group and a base selected from a specified group, wherein the amount of said at least one effervescent couple is present in an amount greater than necessary for tablet disintegration, and is between 20% and 80% by weight. (JA-2151) As noted previously, the '693 application was abandoned prior to issuance.

4. Discussion

37. For the reasons discussed *infra*, the court construes the disputed claim language consistent with the tenets of claim construction set forth above as follows: "**[A]t least one [saliva activated] effervescent agent in an amount sufficient to increase absorption . . . across [the] oral mucosa**" means that 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.

a. Singularity of "agent"

38. The term "agent" is, on its face, a singular term distinguishable from the plural "couple." "When construing terms in the body of a claim, the general assumption is that different terms have different meanings[.]" *Symantec Corp. v. Computer*

Associates Intern., 522 F.3d 1279, 1289 (Fed. Cir. 2008) (citation omitted). Notwithstanding that the Khankari patents' specification does not disclose a single-compound effervescent "agent" that could produce gas on its own upon exposure to water or saliva,[15] there is no indication that the court should ignore the applicants' choice of language. *See SEB S.A. v. Montgomery Ward & Co., Inc.*, 594 F.3d 1360, 1369 (Fed. Cir. 2010) (stating that the presumption simply "carries less weight" where the specification only describes one embodiment). Put another way, the specification does not contain a "clear and unambiguous" disavowal of a single effervescent compound. *See Microsoft*, 357 F.3d at 1350.

39. The reference to "the effervescent agent (an effervescent couple)" is a general one. That the claims of the '590 patent briefly contained the term "effervescent couple" is also not compelling. The term "effervescent **couple**" was introduced to the claims by the amendment adding the 5-80% limitation to the '590 patent. (JA-2645) As explained *supra*, the claims were internally inconsistent and the PTO recommended changing "couple" to "agent." The inventors characterized the change as minor and non-narrowing (JA-2911), a view consistent with the court's construction insofar as the term "at least one effervescent agent" is broader than "effervescent couple."

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[15]Cephalon does not argue that the Khankari patents disclose the use of a singular-compound effervescent for use in the invention, nor identifies any such compound disclosed in the specification. The effervescent couple is not only the preferred embodiment but it is the only embodiment disclosed. (*See, e.g.*, '590 patent at col. 2:51-53) (the "reaction of these **two** general compounds produces carbon dioxide upon contact with water or saliva")

40. Most notably, during prosecution of the '693 application,[16] the applicants explicitly rejected the examiner's view that the "effervescent couple" of the claims could be "one agent or multiple agents." The applicants emphasized that "couple" is plural while one "agent," such as the sodium bicarbonate in DiSanto example 3, cannot itself be considered an effervescent "couple." (JA-975-77) The examiner withdrew the DiSanto rejections based on this understanding of "couple."

41. In view of the foregoing, the claims are broad enough to encompass at least one compound that evolves gas by means of an effervescent reaction. While the claims do not require that the oral dosage form contain both halves of the effervescent couple, leaving open the possibility that the other reactant be present in the oral cavity,[17] effervescence (as compared to a reaction of a different nature) is required.

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[16]Statements made during the pendency of the prosecution of the '693 application are relevant to the construction of terms in the Khankari patents, which share a common specification. That the '604 patent issued prior to the statements made during prosecution of the '693 application does not affect this relevance. *See Microsoft Corp. v. Multi-Tech Systems, Inc.*. 357 F.3d 1340, 1350 (Fed. Cir. 2004) ("Any statement of the patentee in the prosecution of a related application as to the scope of the invention would be relevant to claim construction, and the relevance of the statement made in this instance is enhanced by the fact that it was made in an official proceeding in which the patentee had every incentive to exercise care in characterizing the scope of its invention.").

The court notes that Cephalon argued that statements made during prosecution of the now-abandoned '693 patent could not form the basis for a disclaimer vis a vis the Khankari patents because the public was not informed of these statements. (D.I. 210 at 6) Cephalon did not (and could not) argue that the '693 application did not publish; its file wrapper is accessible online in public PAIR. Under *Microsoft*, statements made during prosecution of the '693 patent are relevant to the court's construction and, ironically, lend credence to Cephalon's position.

[17]Whether inherent to the saliva or by co-administration. This is consistent with Khankari's testimony that the effervescent agent must be activated by an acid, whether "from other excipients of the formulation or the conditions of the mouth;" the acidic environment "doesn't have to be in the couple." (D.I. 282 at 173:9-16, 174:2-10)

b. The quantity of effervescent agent is distinct

42. The court is next tasked with determining the nature of the "effervescent agent" of the invention. Watson argues all pH-adjusting substances present in the tablet cannot be subsumed by the "effervescent agent" limitation or the related requirement that the effervescent agent be present "in an amount sufficient to increase absorption" across the oral mucosa. (D.I. 187) Cephalon admits that the concepts of effervescence and pH-adjustment are different, but that one component (namely, the potassium bicarbonate present in Watson's tablets) can perform both functions. (D.I. 193 at 20) While both parties agree that the "amount [of effervescent agent] sufficient to increase absorption" requires the "rate and/or extent" of absorption to be increased, Watson argues that the amount of effervescent agent must be greater than that required for tablet disintegration.[18] (D.I. 187)

43. The court agrees with Watson's position. As set out *supra* (¶¶ 9-11), the inventors distinguished the effervescent agent(s) from the other ingredients of the composition. The claims separately require at least one "effervescent agent in an amount sufficient to increase absorption" and "at least one pH-adjusting substance."[19] While one compound may both adjust pH and participate in effervescence, only the quantity of effervescent agent above that needed for effervescence may be considered the "pH adjusting substance." ('590 patent, col. 3:47-55) The inventors noted a

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[18]These claim construction arguments are common to both claim 1 of the '604 and claim 1 of the '590 patents, from which all other asserted claims of the Khankari patents depend.

[19]In the '590 patent, the terms appear separately in claim 1, while in the case of the '604 patent, dependent claim 2 adds the latter limitation.

distinction between the effervescent agent and pH-adjusting substance during the prosecution of the '590 patent in distinguishing Robinson, wherein they stated: "[C]laim 1 of the present application, in addition to an effervescent couple, requires the use of a pH- adjusting substance. . . There is no parallel structure or function in Robinson, nor does Robinson teach or suggest the use of an effervescent couple and, **as a separate agent**, a pH-adjusting substance." (JA-2637-38) (emphasis added)

44. A similar conclusion is warranted with respect to disintegration. The court has previously described the applicants' argument with respect to Robinson made during prosecution of the '590 patent. (*supra*, ¶ 24) The applicants argued, *inter alia*, that "[i]t is only the present invention that teaches that the amount of effervescent couple **should be** greater than that required for disintegration in order to achieve an improvement in transport of the active ingredient across the oral mucosa." (JA-2601) (emphasis added) Although the emphasized language is not unequivocal, the applicants' comments are consistent with the specification's separate treatment of effervescents and disintegrants. While the "effervescent agent" is provided in an amount between 5% and 90% and, preferably, 30% and 80% by weight, "disintegrants" may comprise up to 20% by weight and, preferably, between about 2% and about 10% of the total weight of the composition. ('590 patent, col. 2:34-38; col. 4:49-51) In further acknowledgment of the difference between effervescents and disintegrants, the Khankari patents' specification states that "effervescents have been employed to obtain rapid dissolution and/or dispersion of the medicament in the oral cavity" but, "[d]espite these and other efforts toward increasing the permeation of medicaments across the

oral mucosa, there have been unmet needs for improved methods of administering medicaments across the oral mucosa" until the present invention. (*Id.*, col. 1:42-45, col. 2:5-8) Thus, although the "effervescent couple in combination with the other ingredients" will "improve the disintegration profile" of the dosage form (*id.* at col. 4:22-31), and while a certain (surplus) amount of effervescents will also confer pH-adjusting benefits to the formulation, Watson is correct that these are distinct ingredients.

c. Amount sufficient to increase absorption

45. With the exceptions adopted above, the parties agree that the effervescent agent must be present in "an amount sufficient to increase the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa." Watson does not contend, therefore, that the "amount sufficient" is ambiguous or indefinite or that a person of ordinary skill in the art could not determine the appropriate amount without undue experimentation. (D.I. 59 at 21-22)

C. Infringement

1. Standards

46. 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 v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). 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).

47. "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). "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). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). 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 Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

2. Discussion

48. To prove infringement under the court's construction, Cephalon must

demonstrate that Watson's ANDA product contains at least one compound that evolves gas by means of an effervescent reaction and that is present in an amount sufficient to increase the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa.

49. Watson's ANDA product contains fentanyl citrate, potassium bicarbonate, mannitol, sodium starch glycolate, and magnesium stearate. (D.I. 283 at 280:17-281:1; DTX-1456 at 9992) Potassium bicarbonate is a carbonate (or CO_2) source listed in the Khankari patents as capable of effervescence.[20] ('590 patent, col. 2:62) Cephalon admits that potassium bicarbonate will not react without an acid source. (D.I. 244 at 25 (citing D.I. 282 at 188:21-192:9; PTX-379); *see also id.* at 31 (citing D.I. 283 at 464:22-465:4)) The question at bar, therefore, is whether Cephalon demonstrated at trial that the potassium bicarbonate in Watson's ANDA product reacts with an acid source to evolve CO_2 and, ultimately, increases the absorption of fentanyl across the oral mucosa. ('590 patent, col. 2:33-60)

50. Cephalon devoted all of one sentence to the standard for determining infringement: "'Direct infringement requires a party to perform or use each and every step or element of a claimed method or product,'" citing (as did the court) *BMC Resources, Inc. v. Paymentech, L.P.*, 498 F.3d at 1378, a case in which the Federal Circuit reviewed the proper standard for joint infringement by multiple parties of a single claim. The Federal Circuit in *BMC Resources* went on to state that "[i]ndirect

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[20]The court notes that, in the context of arguing (under Watson's construction) the ANDA product contains the "effervescent couple" of potassium bicarbonate and mannitol, Cephalon identifies the potassium bicarbonate as a pH-adjusting substance. (D.I. 244 at 32)

infringement requires, as a predicate, a finding that some party amongst the accused actors has committed the entire act of direct infringement,'" citing *Dynacore Holdings Corporation v. U.S. Philips Corp.*, 363 F.3d 1263, 1272 (Fed. Cir. 2004). In *Dynacore Holdings*, the Federal Circuit reiterated that, to establish the underlying direct infringement, a plaintiff must show that the accused infringer "meet[s] each limitation of the [asserted] claims, either literally or under the doctrine of equivalents." *Id.*

51. There is no specific discussion by Cephalon of either literal infringement or infringement by equivalents. Indeed, Cephalon's summary of its infringement analysis does not use the word "infringement" at all: "The foregoing evidence - that Watson's tablets evolve CO_2 gas, exhibit a dynamic pH, and are bioequivalent to Fentora® - demonstrates that the amount of effervescent agent in Watson's tablets is an amount sufficient to increase the rate and/or extent of fentanyl absorption across the oral mucosa." (D.I. 244 at 27) Nevertheless, because Cephalon depends at least in part on the bioequivalence of Watson's tablets to Fentora® and uses the word "equivalent" in various of its discussions,[21] the court will proceed on the understanding that Cephalon is asserting infringement by equivalents only.

52. With respect to the disputed limitation, that is, "at least one [saliva activated] effervescent agent in an amount sufficient to increase absorption . . . across [the] oral mucosa," both parties have used the evolution of CO_2 gas as the benchmark for determining whether effervescence occurs. (D.I. 244; D.I. 253 at 40) For instance, video evidence was introduced at trial with respect to the release (or non-release) of

[21]For instance, Cephalon argued that potassasium bicarbonate and mannitol are equivalent to an effervescent couple. (D.I. 244 at 34)

gas bubbles by Watson's ANDA product. (DTX-721) Given the court's claim construction,[22] however, it is not enough to argue (as Cephalon does) that if it looks like effervescence, and produces CO_2 like effervescence, then there must be effervescence.[23]

53. In this regard, Cephalon has not provided any affirmative proof regarding the precise nature of the chemical reaction allegedly occurring. Although the parties agree that the potassium bicarbonate in the ANDA product (the "at least one effervescent agent" according to Cephalon) requires the presence of a soluble acid source in order to evolve CO_2 gas, Cephalon states only that said acid source is "at least" the mannitol contained the ANDA product[24] (D.I. 244 at 31) and does not identify any external acid source.

54. More specifically, Cephalon's analytical chemist expert, Dr. Bernard Olsen ("Olsen"), testified that he conducted pH experiments and found mannitol to be acidic in water; the more concentrated the mannitol, the more acidic the solution. (D.I. 283 at 328:23-330:10; PTX-431) Cephalon presents no evidence regarding the acidity of

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[22]Requiring that the amount of the effervescent compound be greater than that required for disintegration and does not include the pH-adjusting substance separately claimed.

[23]Even if effervescence were the only reaction that could produce CO_2 under the circumstances, and even if an acid must necessarily be present for this result to occur, the court has previously declined to take judicial notice of a "basic principle of science" or "scientific truth" absent specific facts of record. *See Senju Pharma. Co. Ltd. v. Apotex Inc.*, Civ. No. 07-779, 2010 WL 4538265 (D. Del. Nov. 3, 2010).

[24]The court notes that it was not asked to construe "effervescent agent" as excluding "excipient fillers" (as mannitol is characterized in the Khankari patents) as it was so asked with respect to pH-adjusting substances and disintegrants.

mannitol in artificial saliva. Notably, there is no evidence of record regarding the properties of human saliva. As Watson's expert put it, "the important piece of information that is missing [in this case] is what the potential or alleged acidity of mannitol in either artificial saliva or, even more important, in the human mouth . . . and there is no evidence that mannitol would be acidic under those conditions." (D.I. 286 at 1174:11-16) Even were the court to assume that Olsen's data translates to human saliva, Cephalon's infringement expert, Dr. Robert O. Williams III ("Williams"), stated that he did not "do any testing to determine definitively whether it was the mannitol that was reacting with the potassium bicarbonate [in the ANDA product] as opposed to a different excipient." (D.I. 283 at 406:11-15)[25]

55. Had Cephalon demonstrated effervescence in the first instance, nevertheless, the court finds that Cephalon did not meet its burden to demonstrate that the effervescent reaction increases the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa. Cephalon emphasizes Williams' testimony that, like Fentora®, the ANDA products exhibit a dynamic pH profile, or a gradual increase from a more acidic to a more basic pH. (D.I. 244 at 33-34 (citing D.I. 150 at 410:20-411:24; 445:14-17; 455:6-456:22; 459:20-460:2)) Williams based his opinion on both pH data and Olsen's CO_2-emission data. Regardless of **how** the ANDA product may be working, the only proffered evidence that the ANDA product actually

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[25]The only other compound identified by Cephalon in its analysis was citric acid, based on a statement made by Dr. Simon Bates ("Bates"), who was not involved in the Orange Book (Khankari patents) portion of the trial, and who did not opine as to whether Watson's formulation **actually** created citric acid. (D.I. 244 at 34; D.I. 284 at 609:23-610:3)

results in an increase in the rate and/or extent of absorption across the oral mucosa is the fact that the ANDA product is "bioequivalent" to Fentora® (and Fentora® has proven improved bioavailability over Actiq® and non-effervescent fentanyl citrate tablets). (D.I. 244 at 33; *id.* at 35 (citing D.I. 150 at 462:8-13); *see also* D.I. 150 at 410:15-19 (Williams' explaining that the basis of his opinion is bioequivalence))

56. As the Federal Circuit has recently explained,

> [w]hile bioequivalency may be relevant to the function prong of the function-way-result test, bioequivalency and equivalent infringement are different inquiries. Bioequivalency is a regulatory and medical concern aimed at establishing that two compounds are effectively the same for pharmaceutical purposes. In contrast, equivalency for purposes of patent infringement requires an element-by-element comparison of the patent claim and the accused product, requiring not only equivalent function but also equivalent way and result. Different attributes of a given product may thus be relevant to bioequivalency but not equivalent infringement, and vice versa. As the Northern District of Illinois observed in the *Sandoz* case, "[i]f bioequivalency meant per se infringement, no alternative to a patented medicine could ever be offered to the public during the life of a patent." Thus, while potentially relevant, the bioequivalency of an accused product with a product produced from the patent at issue is not sufficient to establish infringement by equivalents.

Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1298 (Fed. Cir. 2009) (internal citations omitted); *compare Johns Hopkins Univ. v. Datascope Corp.*, 543 F.3d 1342, 1349 (Fed. Cir. 2008) ("FDA equivalence is irrelevant to patent law because it involves fundamentally different inquiries."). Bioequivalence, therefore, is insufficient to establish infringement under the doctrine of equivalents. As the foregoing indicates, the inquiry is not identicality to Fentora®, it is whether the ANDA product meets the limitations of the asserted Khankari patent claims.

57. Cephalon did not perform any absorption testing, or experiments comparing the rate and/or extent of absorption of the fentanyl citrate (API) in the ANDA product

across the oral mucosa to the rate and/or extent of absorption of the fentanyl citrate from any non-effervescent delivery system. There were no experiments comparing the rate and/or extent of absorption of the fentanyl citrate in the ANDA product to the rate and/or extent of absorption of the APIs from the Khankari patents' examples. Cephalon cites no testimony regarding rates of absorption at all. There is no comparator that the court can use to determine whether the potassium bicarbonate in the ANDA product is present in "an amount sufficient to **increase** absorption" upon effervescence.[26] In its reply papers, Cephalon argues that it had no "obligation to perform any testing at all, let alone a particular kind of testing" in order to establish infringement. (D.I. 262 at 10) Although Cephalon is correct that a plaintiff may rely upon circumstantial evidence as proof of direct infringement,[27] the record at bar does not contain sufficient (i.e., a preponderance of) circumstantial evidence in this regard.

3. Conclusion on infringement

58. For the foregoing reasons, Cephalon has not demonstrated, by a preponderance of the evidence, that an effervescent agent in the Watson ANDA product (potassium bicarbonate) participates in an effervescent reaction (with mannitol or with citric acid, whether present in the tablet or in the mouth) such as to increase absorption of fentanyl across the oral mucosa. The court does not address the additional contested limitations in view of its holding.

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[26]The court need not speculate as to what the appropriate comparator(s) would be under the circumstances.

[27]*See, e.g., Metabolite Labs., Inc. v. Lab. Corp. of America Holdings*, 370 F.3d 1354, 1364-65 (Fed. Cir. 2004).

D. Validity

The court next determines whether, under the foregoing construction of "effervescent agent," the Khankari patents are invalid.

1. 35 U.S.C. § 112, first paragraph

a. Standards

59. The statutory basis for the written description and enablement requirements is found in 35 U.S.C. § 112, paragraph 1, which provides in relevant part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.

The Federal Circuit has explained that "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. . . . Tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

60. To satisfy the enablement requirement, a specification must teach those skilled in the art how to make and to use the full scope of the claimed invention without undue experimentation. *Genentech*, 108 F.3d at 1365. "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Id.* at 1366. The specification need not teach what is well known in the art. *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

61. Enablement is determined as of the filing date of the patent application. *In re Brana,* 51 F.3d, 1560, 1567 n.19 (Fed. Cir. 1995). The use of prophetic examples does not automatically make a patent non-enabling. The burden is on one challenging validity to show, by clear and convincing evidence, that the prophetic examples together with the other parts of the specification are not enabling. *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

62. Some experimentation may be necessary in order to practice a claimed invention; the amount of experimentation, however, "must not be unduly extensive." *Id.* at 1576.

> The test for whether undue experimentation would have been required is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

PPG Indus. Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting Ex parte Jackson, 217 U.S.P.Q. 804, 807 (1982)).

63. The enablement requirement is a question of law based on underlying factual inquiries. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A court may consider several factors in determining whether undue experimentation is required to practice a claimed invention, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (6) the predictability of the art; and (7) the breadth of the claims. *Wands*, 858 F.2d at 737. These factors are

sometimes referred to as the "Wands factors." A court need not consider every one of the Wands factors in its analysis. Rather, a court is only required to consider those factors relevant to the facts of the case. *See Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

b. Discussion

64. The question at bar is whether the full scope of the Khankari patent claims as the court has construed them – covering a drug form having a single compound effervescent agent – is enabled by the specification. Watson asserts that persons of ordinary skill in the art could not practice the invention of the Khankari patents without undue experimentation. Watson's arguments in this regard are best described against a backdrop of Cephalon's validity position. Cephalon argues that claims to a single-compound effervescent are enabled because a person of ordinary skill in the art could easily "co-administer" a soluble acid source to react with a tablet containing a single compound effervescent agent. According to Cephalon's expert (Williams), a person of skill in the art would know that orange juice contains citric acid and would be able to put citric acid in a "second, fast-dissolve film or quick-dissolve tablet" to accompany the administration of the effervescent agent. (D.I. 287 at 1382:17-1383:22)

65. As Watson points out, inventors Hontz and Pather both testified that only sodium bicarbonate (a base) and citric acid were used to create effervescence in their formulations. Neither could recall any other acid-base formulations they used, or even used in the industry – nor could they name any single-compound effervescent on the stand. (D.I. 282 at 145:19-148:18; D.I. 283 at 340:13-18; 343:9-13) Pather confirmed that, at the time the Khankari patents were filed, he was only in possession of a method

for creating effervescence using a formulation containing both an acid and base.[28] (D.I. 286 at 1154:10-19)

66. Watson presented a prima facie case of nonenablement through its expert, Dr. Russell Mumper ("Mumper"). Mumper testified that a person of ordinary skill in the art would not be able to practice Cephalon's co-administration method without undue experimentation. Specifically, there are questions as to what to drink, how acidic it is, what the volume is, and how to prevent materials in the tablet from being diluted by the acidic drink. (*Id.* at 1186:10-19) "I would think this would be very complicated and would require [ ] the partnering with a clinician to talk about timing effects and volume effects and how this would actually be translated to a patient actually doing this."[29] (*Id.*)

67. In response, Cephalon emphasizes inventor Khankari's testimony that "[t]he patent is not about how to **create** effervescence[, but] how to **use** effervescence to improve absorption." (D.I. 282 at 172:13-14; 175:3-5) (emphasis added) The court agrees with this characterization, insofar as it is consistent with the disclosure (which is unquestionably silent as to drug forms containing only one effervescent agent)[30] and

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[28]Watson does not assert that the Khankari patents are invalid for lack of written description.

[29]Cephalon is correct that Mumper did not specifically analyze many of the *Wands* factors at trial. Although counsel could have better walked Mumper through the factors, there is no genuine question as to the lack of direction or guidance (on co-administeration) in the patent or the absence of working examples (factors 2 and 3). The nature of the invention, state of the art, relative skill in the art and claim scope (factors 4 to 7) were addressed by Watson within the context of its obviousness arguments and Markman briefing. Cephalon has not cited, and the court has not located, any caselaw requiring more specific testimony on each *Wands* factor under such circumstances.

[30]The Khankari patents are presumed valid and enabled.

with Hontz and Pather's testimony that they are unaware of how to create effervescence using a formulation having only half of the acid-base couple. Nevertheless, the patents still must disclose how to **use** a single compound effervescent agent in the manner claimed (i.e., how to provide such a compound "in an amount sufficient to increase the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa" upon reacting with another agent).

68. Cephalon has not cited any such disclosure in the specification. Williams does not assert that the Khankari patents teach co-administration of an acid, in fact, he admits that they do not. (D.I. 287 at 1384:15-17) Cephalon points only to the disclosure of a "soluble acid source" as enabling the claims. (D.I. 251 at 58 (citing '604 patent at col. 2:45-48[31])) According to Cephalon, this is the "guidepost" from which a person of ordinary skill in the art could navigate easily to co-administration. (*Id.;* D.I. 287 at 1384:15-17)

69. Cephalon also cites the testimony of Williams that a person of ordinary skill in the art, "knowing in that example [that] orange juice contains citric acid, would be able to calculate the amount of citric acid and put it in a second, fast-dissolve tablet, or something, to do a concomitant administration of two dosage forms, for example."[32]

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[31]In full: "This [effervescent] reaction is most often the result of the reaction of a soluble acid source and a source of carbon dioxide such as an alkaline carbonate or bicarbonate."

[32]The court notes that, while Williams stated that orange juice would inspire a "tablet or something" that could be co-administered, Mumper's testimony addressed the difficulties in co-administering orange juice itself. (*supra*, ¶ 66) That is, William's theory is even more attenuated than that specifically addressed by Mumper. As the specification discloses neither method, the difference is ultimately irrelevant.

(D.I. 251 at 58 (citing D.I. 287 at 1382:24-1383:22)) Further, Williams "think[s] it would be routine given what's in the patent about how to actually create the effervescence to use in the invention." (*Id.*) Cephalon also cites Khankari's cross-examination testimony, wherein he generally explains that the activator could be "available either from other excipients of the formulation or the conditions of the mouth," but does not provide details of any particular known co-administration methods. (*Id.* (citing D.I. 282 at 173:9-175:7))

70. Finally, Cephalon cites evidence outside of the specification as evidence of enablement. Cephalon argues that one of Watson's asserted prior art references "mentions *in situ* carbonation," or using **stomach** acid (an external acid source) to activate the effervescent agent. (DTX-434 at 4975; D.I. 286 at 1208:17-20) This general reference is not, however, a teaching relating to co-administration in the mouth – the locus of effervescence and absorption claimed by the Khankari patents. Moreover, Cephalon does not suggest that any acid present in human saliva is the activator, rather, that orange juice or another soluble acid in the mouth is co-administered to activate the drug form by external means.

71. Drug delivery is neither a predictable field of art nor a straightforward inquiry. The disclosure of a "soluble acid source" is not equivocal to a disclosure of any method of **co-administration** of such an acid source. There is no evidence of record that co-administration is inherent to solubility (a "soluble acid source") such that the disclosure of one implicates the other. Cephalon appears to recognize as much when it states that this passage is merely a "guidepost" from which a skilled artisan could "navigate to"

co-administration.

72. As the Federal Circuit has repeatedly stated,

> the rule that a specification need not disclose what is well known in the art is merely a rule of supplementation, not a substitute for a basic enabling disclosure. To satisfy the plain language of § 112, ¶ 1, [Cephalon] was required to provide an adequate enabling disclosure in the specification; it cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification.

ALZA Corp. v. Andrx Pharmaceuticals, LLC, 603 F.3d 935, 940-41 (Fed. Cir. 2010) (internal quotations and citations omitted). Thus, evidence regarding such "navigation" that is not in the specification is insufficient.

73. With respect to undue experimentation, the court found Mumper's testimony to be convincing. Despite testifying that co-administration of a soluble acid was routine, Williams also stated that orange juice (or another acid source) would need to remain in the mouth as long as required to activate the carbonate, and testified that he was not sure how long that would be. (D.I. 287 at 1384:23-24) To develop such a method, *in vitro* experiments could be done and then a formulator would have to work with a clinician to test the activation of the tablet by the acidic drink. (*Id.* at 1384:25-1385:7) This testimony lends further credence to Mumper's testimony.

74. Hontz and Pather lent additional credibility to Mumper's testimony. If the inventors did not possess a method for creating the effervescence necessary to their invention using a drug delivery form having only one half of an effervescent couple, surely they could not have described such a method. That the inventors were unable **at trial** to discern such a method is further indicative of the difficulty faced by a person of ordinary skill in the art at the time the patents were filed (and not having the benefit of

additional studies and advances to date).

c. Conclusion on § 112

75. The Khankari patents are presumed valid and enabled, and it is Watson's burden to prove invalidity by clear and convincing evidence. The record at bar, as described above, satisfies Watson's burden. Cephalon has not rebutted Watson's evidence of non-enablement. For the foregoing reasons, the claims are not enabled as construed (to a single compound effervescent agent) and the Khankari patents are invalid as a matter of law.

2. Anticipation

76. Watson argues that claims 1, 2, 8 and 10 of the '604 patent are anticipated by International Publication No. WO 96/29993 ("Hesnard").[33] (DTX-64) Hesnard published internationally on October 3, 1996; it was filed (under the PCT) on March 28, 1996 and claims priority to March 29, 1995. Hesnard is prior art vis a vis the Khankari patents, which claim priority to March 27, 1998. 35 U.S.C. § 102(b).

a. Standards

77. An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. *See Key Phar. 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

[33]Hesnard's international application number is PCT/FR96/00470.

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 Hesnard

78. Hesnard discloses a solid delivery drug form for oral use that, unlike other oral medicaments, is neither in liquid form nor ingested with water. (DTX-64 at 3) Rather, upon introduction into the oral cavity, the delivery form becomes a gelled dispersion that: (1) rapidly reaches its absorption site (the gastrointestinal mucous membrane); (2) provides a lubricating effect along the intestinal walls while lining the mucous membranes; and (3) makes possible the delivery of the drug form to reach its

absorption site in a more continuous manner. (*Id.* at 3-4) Hesnard provides that the drug form obtains a viscosity that "makes it possible to contemplate treatments by perlingual means." (*Id.* at 4) After introduction to the oral cavity, an overpressure is created which generates a minor gas release, allowing the principal drug to rapidly reach its absorption site. (*Id.* at 4, 9) The gas can also be used to deliver drug to the mucous membranes of the upper and lower air passages. (*Id.* at 5)

79. The gas release occurs by the formation of microbubbles during the reaction, causing the drug form to destabilize and solubilize or disperse the active principal in to the gel-like disperson. (*Id.*) "The compound or the mixture of compounds capable of forming microbubbles is present in a given quantity in such a way that it releases, when it is in contact with the oral cavity, a gas volume ranging between 1 and 100 cm^3." (*Id.* at 7) The compound or mixture comprises a "filler" that is inert to the principal drug.[34] (*Id.*) "The compound or mixture of compounds capable of forming microbubbles is chosen from within the group made of the acids, the acid anhydrides and the physiologically acceptable acid salts." (*Id.*) Citric acid is among the preferred acids. (*Id.* at 7, 10) The overpressure "makes possible a nontoxic gas release ('carbon dioxide')" in the provided range. (*Id.* at 10) "The volume of CO_2 released is proportional to the quantities of effervescent agents used." (*Id.* at 17)

80. Hesnard's preferred embodiment consists of a cellulose derivative and the foregoing "effervescent pair." (*Id.* at 12-14) Carboxymethylcellulose ("CMC") is the most preferred cellulose derivative.

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[34]Hesnard lists bicarbonates as an example of such "chemically inert" fillers.

> The effervescent pair which is added thereto makes it possible to offset the pasty feelings of the gel developing in the mouth through the formation of molecules of water intrinsic to the effervescence reaction. In fact, the effervescence reaction, already known for a long time, has the distinctive feature of producing molecules of water which thus mitigate the high water-retention capacity of the CMC. . . .
>
> [T]his effervescence reaction makes it possible to keep the active substances solubilized or dispersed within the gel, by virtue of the formation of microbubbles. The latter also make[s] it possible to increase the exchange surface with the gastrointestinal mucous membranes.

(*Id.* at 13) Examples 3 and 5 of Hesnard disclose formulations containing analgesics as the principal drug, specifically, aspirin and codeine. (*Id.* at 19)

c. Discussion

81. As the foregoing indicates, the focus of Hesnard is improved absorption across the gastrointestinal mucosa. Watson's expert, Mumper, noted Hesnard's disclosure of contemplated "treatments by perlingual means." (DTX-64 at 4; D.I. 286 at 1188:16-21) According to Mumper, Hesnard anticipates because it discloses using a drug delivery system in combination with the formed mircobubbles for the drug to better diffuse and reach the "general circulation." (D.I. 245 at 35 (citing D.I. 286 at 1190:1-16, 1207:3-11)) Mumper did not testify, and the court does not observe any disclosure, that the effervescent pair of Hesnard is present in an amount sufficient to increase absorption across the oral mucosa. More fundamentally, while Hesnard discloses an effervescent pair, it does not disclose a dosage form containing a single effervescent agent. Hesnard does not reach, therefore, the full scope of the claims as construed by the court.

82. Watson's argument appears to be one of inherent anticipation. A prior art reference may anticipate without explicitly disclosing a feature of the claimed invention

if that missing characteristic is inherently present in the single anticipating reference. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit has explained that an inherent limitation is one that is "necessarily present" and not one that may be established by "probabilities or possibilities." *See id.* at 1268-69. That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269 (emphasis in original) (citations omitted).

83. Watson has not pointed to evidence that the effervescence disclosed by Hesnard always and necessarily results in an improved absorption across the oral mucosa. Hesnard briefly mentioned only a "contemplate[d]" perlingual application of that technology. (DTX-64 at 4) In view of the foregoing, Watson has not met its burden to prove anticipation by clear and convincing evidence.

3. Obviousness

84. Watson next argues that the asserted claims of the Khankari patents are obvious in view of U.S. Patent No. 5,288,497 to Stanley et al. ("Stanley") in combination with Hesnard or with the master's thesis by Khankari patent inventor Dr. Eichman, entitled "Increased Drug Absorption Through Carbonation: Assessment of Biological Membranes" (hereinafter, "Eichman").

a. Standards

85. "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) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

86. "[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).

87. "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. Stanley

88. Stanley is entitled "Compositions of Oral Dissolvable Medicaments;" it was filed September 5, 1989 and issued February 22, 1994. Stanley is prior art to the Khankari patents, which claim an earliest priority date of March 27, 1998. 35 U.S.C. § 102(b).

89. Stanley discloses the oral transmucosal delivery of drugs such as, specifically, fentanyl. (DTX-55 at abstract, col. 9:52-53; col. 17:49-52) Stanley states that the administration of certain drugs through the oral mucosal tissues has previously "shown promise" but that acceptable methods have "been elusive." (Stanley, col. 4:38-42) The relationship between pH and absorption versus solubility was discussed as follows:

> It should also be noted that pH conditions within the mouth may tend to adversely affect the administration of certain lipophilic drugs by the mucosal administration route. It has been found in the art that administration of drugs

through the mucosal tissues generally occurs best when the drug is in the unionized form. Variations in pH affect the percentage of the drug which is unionized at a particular point in time. As a result, the pH conditions within the mouth can limit the effectiveness of certain drugs administered buccally or sublingually in that those conditions cause the drug to exist in the ionized form which is largely unavailable for transfer across the mucosal tissues.

Other potent drugs are substantially nonlipophilic and do not naturally permeate mucosal tissues. Hence it would be a significant advancement in the art of administering potent, fast-acting drugs, if suitable methods and compositions permitted both lipophilic and nonlipophilic drugs to be administered transmucosally.

(*Id.*, col. 4:46-64)

90. The invention of Stanley was, most informally, a drug-containing lollipop. Stanley taught that precise control over the dosage and effect of a drug could be obtained by administering the drug transmucosally by sucking a drug-containing dissolvable dosage form having a handle. (*Id.*, col. 5:42-52, col. 21:59-64) The dissolvable matrix on a handle is an effective method for administering potent and fast-acting drugs transmucosally "in a dose-to-effect manner[35] such that sufficient drug is administered to produce precisely the desired effect." (*Id.*, col. 5:19-26) The matrix includes the drug and may include other dissolvable ingredients such as carbohydrates, fats, or waxes, and may also include colors and sweeteners. (*Id.*, col. 5:42-52; col. 10:60-col. 11:51)

Buffering agents and other types of pH control can also be added simultaneously in order to provide for maximum drug efficiency. It will be appreciated that drugs in the unionized form are more readily transported across the mucosal membrane. Therefore, if pH conditions can be adjusted to maximize the

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[35]"According to the present invention, the drug dose is given over a period of time rather than all at once . . . Once a sufficient drug response has been achieved, the patient can simply stop sucking on the dosage form" or it may be removed from the mouth. (Stanley, col. 7:32-34)

percentage of unionized drug available, the effectiveness of the drug is maximized.

(*Id.*, col. 6:36-43) Permeation enhancers are also provided as an important feature of the invention. (*Id.*, col. 6:51-55, col. 10:26-32, col. 12:21-29)

91. Further with respect to the control of pH, Stanley provides as follows:

> It is well known that most drugs are weak acids or weak bases and are present in solution in both the unionized and ionized forms. It has been found that the unionized portion of the drug is usually lipid soluble and can readily diffuse across the cell membrane. The ionized portion, conversely, is often lipid insoluble and in some instances, may not effectively penetrate the lipid membrane of the cell. As a result, drugs in the ionized form are generally inefficient in producing a drug effect on the central nervous, cardiovascular, and renal vascular systems.
>
> Whether a drug exists in the ionized or unionized form is largely dependent upon its pKa, and correspondingly on the pH of the solution. The present invention provides the unique ability to control the pH of the solution and thus the ratio of unionized to ionized form of the drug.

(*Id.*, col. 14:62-col. 15:10) According to Stanley, change in pH can be accomplished by incorporating particular buffer systems within the composition, preferably, "a citric acid/sodium citrate system," or a conventional phosphate buffer. (*Id.*, col. 16:13-21) Use of a buffer dramatically improves results and makes "buccal drug absorption a fully feasable and optimal delivery method." (*Id.*) Stanley also provides that "pH may enhance drug permeability by unknown mechanisms [such as] affect[ing] drug molecular configuration[.]" (*Id.* at col. 16:32-39)

c. Eichman

92. Eichman was a thesis submitted in support for a Master of Science in Pharmaceutics at the University of Wisconsin-Madison in 1995. (DTX-434) The parties dispute whether Eichman has been publicly available in the University of Wisconsin

library since 1996, more than one year prior to the filing date of the application to which the Khankari patents claim priority, and thus constitutes prior art under 35 U.S.C. § 102(b).

93. Cephalon argues that Watson did not establish that Eichman was actually on the library shelves as of January 23, 1996, as alleged. Watson called at trial Mr. Richard Reeb ("Reeb"), Associated Director for Collection Development and Technical Services at the University of Wisconsin-Madison (the "University"), who testified at trial that: (1) since 1991, the policy for cataloguing theses has not changed; (2) according to the catalog record, Eichman was catalogued on January 23, 1996; (4) it was shelved within three to four weeks; and (4) it was electronically catalogued before the end of February 1996. (D.I. 285 at 969:25-970:20; DTX-432C; D.I. 285 at 972:2-6; DTX-423; D.I. 285 at 975:21-25) While Reeb admitted on cross that there is a University policy that an author may request an "intellectual property hold" on publication of his or her thesis to pursue patent protection, he also stated that, in 25 years at the library, he was unaware of anyone initiating such a hold. (D.I. 285 at 978:7-11; 980:16-19) The court finds the foregoing clear and convincing evidence that Eichman was publicly available by March 1996 such that it constitutes prior art against the Khankari patents. Cephalon asks the court to infer that Dr. Robinson, who was at that time Dr. Eichman's professor at the University, asked for a hold so that patent protection could be pursued in view of testimony that Robinson had approached CIMA about the work.[36] (D.I. 282 at 117:5-118:1) The court declines to do so on the record presented.

[36]Dr. Robinson was not deposed and did not testify as he passed away prior to this litigation.

94. Eichman disclosed the results of a study on the effect of effervescence on benzoic acid absorption across rat duodenum – or gastrointestinal tract – tissue. The study's objective was to determine whether membrane alteration was occurring in this tissue which could affect the transcellular and/or paracellular pathways. (DTX-434 at 31) A small amount of membrane disruption was noted but the author could not substantiate any affect on drug movement across the transcellular pathway. (*Id.* at 76) It was theorized, however, that membrane alterations are produced by effervescence "that may aid in combination with other potential mechanisms to increase drug absorption." (*Id.*) Although the reference concerns research on the gastrointestinal tract, Watson relies on Eichman's disclosure in an Appendix of that reference (concerning the anatomy of the gastrointestinal tract) that "[t]he gastrointestinal tract begins at the oral cavity and proceeds sequentially to the . . . large intestine" in support for its arguments here. (*Id.* at 78)

d. Disclosure of the combined references

95. Watson asserts that a person of ordinary skill in the art, looking to improve the permeability or the absorption rate for oral transmucosal drug delivery systems, would have been motivated to combine Hesnard or Eichman's disclosure that effervescence increases drug absorption with Stanley's disclosure that using pH-adjusting substances increases drug absorption across the oral mucosa.[37] (D.I. 245 at 40-41) Cephalon does not specifically argue that these combinations do not result in all

[37]The parties dispute the level of ordinary skill in the art, however, Watson states that the subtle differences between the parties' positions on the relative experience of the person of ordinary skill are immaterial to its obviousness arguments. Thus, the court need not resolve the issue.

of the claimed limitations, rather, that there are teachings that caution the combinations Watson proposes. The court focuses its analysis, therefore, on the motivation to combine.

e. Motivation to combine

96. Watson's argument on the motivation to combine is that a skilled artisan would know that: (1) effervescence could be used in drug delivery systems; (2) effervescence could be used to taste-mask bitter drugs; and (3) permeation enhancers increase the absorption of drugs across the oral mucosa. (D.I. 245 at 42-44)

97. At the time of the inventions, there were several fentanyl drug products on the market, most notably Actiq®, a lollipop-type fentanyl delivery system covered by Stanley. Actiq® was developed by Anesta, which was purchased by Cephalon. Khankari testified that Actiq® was the foundation for the development efforts that led to Fentora®. (D.I. 282 at 169:24-170:2) Khankari was Vice President of Research and Development at CIMA when CIMA was acquired by Cephalon in 2004. (*Id.* at 104:5-105:1) When Khankari started with Cephalon, he was working on the "OraSolv" drug-delivery technology, which is based on effervescence.[38] (*Id.* at 106:5-107:18) Stanley articulated obstacles in the field that Khankari (and others) sought to resolve: achieving a desirable pH; the rapid onset of fentanyl; and the bitterness of fentanyl. (D.I. 286 at 1199:16-23)

98. There is no genuine debate that the use of effervescence in drug delivery systems, generally, was known in the art. (D.I. 245 at 42) Khankari testified that the

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[38]The OraSolv technology is separately patented as U.S. Patent No. 5,178,878. (PTX-640)

OraSolv patent discloses that effervescence can be used as a taste-mask. (D.I. 282 179:23-171:1) Williams agreed that a person of ordinary skill in the art would want to mask the bitterness of fentanyl.[39] (D.I. 283 at 464:7-9) There is also no dispute that permeation enhancers were known. (D.I. 245 at 43) Mumper testified, generally, that a person of ordinary skill in the art would have been motivated to incorporate a permeation enhancer into a buccal drug. (*Id.* at 43 (citing D.I. 286 at 1200:4-9)) Williams, relying on Stanley, testified that a person of ordinary skill in the art would understand from Stanley's disclosure that a permeation enhancer useful for one biological tissue may not be useful in another. (D.I. 287 at 1377:14-1378:8) The court deems Williams' testimony more convincing, considering Stanley's direction that "it is **almost impossible** to predict which enhancer will work best for a given drug."[40]

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[39]Cephalon objected to this line of questioning (on validity) as beyond the scope of Williams's direct examination. In view of the court's holding, the objection is moot.

[40]For context, the full passage of Stanley provides:

> It is almost impossible to predict which enhancer will work best for a given drug. For each individual drug, only experiments can tell which enhancer is the most suitable. However, it is generally believed that bile salts are good enhancers for hydrophilic drugs and long chain fatty acids, their salts, derivatives, and anologs are more suitable for lipophilic drugs. DMSO, SDS, and medium chain fatty acids (C-8 to about C-14) their salts, derivatives, and anologs may work for both hydrophilic and lipophilic drugs.
>
> The effectiveness of some enhancers may vary depending on the chemical compound to be permeated. One particular enhancer may work very well on one drug but may not have any effect on another drug. For example, oleic acid greatly improves the transdermal permeability of estradiol, a very lipophilic drug, but oleic acid does not have any effect on the transmucosal permeability of glucose, a very hydrophilic drug. Although it is possible to speculate whether a given enhancer may or may not enhance a given drug's permeability, the actual effectiveness of an enhancer should be verified experimentally.

(Stanley, col. 16:64-66) (emphasis added) Even if a motivation to combine the asserted references were present, Stanley's teaching cuts against a reasonable expectation of success.[41]

99. Having addressed all of Watson's cited evidence in support of the motivation to combine Stanley with either Hesnard or Eichman,[42] the court concludes that Watson did not meet its burden to prove obviousness by clear and convincing evidence. Because Watson did not establish a prima facie case of obviousness, the court need not address Cephalon's evidence of secondary considerations or Watson's responses thereto.

4. Conclusion on Validity

100. For the aforementioned reasons, the court finds that the Khankari patents are invalid for lack of enablement. Because Watson did not meet its burden to demonstrate invalidity under § 102 or § 103, however, the Khankari patents are not invalid on either of these grounds.

III. CONCLUSION

(Stanley, col. 16:64-col. 17-17)

[41]As does the additional prior art cited by Cephalon – a chapter in the book Oral Mucosal Drug Delivery published in 1996, entitled "Oral Mucosal Permeation Enhancement: Possibilities and Limitations" (hereinafter, "Aungst") – which provides, *inter alia*, that "although many absorption enhancers for nasal, rectal, and intestinal drug delivery have been described, it should not be assumed that they will have similar effects on oral mucosal drug delivery. This would be particularly true if the mechanism involves opening tight junctions," such as disclosed in Eichman. (DTC-298 at 78; DTX-434 at 4970; D.I. 287 at 1289:1-2))

[42]Watson provides additional Mumper citations in its reply papers; they do not buttress its position. (D.I. 261 at 27)

101. For the reasons discussed above, the court concludes that Cephalon has not proven, by a preponderance of the evidence, that Watson's ANDA product infringes either the '604 or '590 patent under the court's construction.

102. Watson has proven, by clear and convincing evidence, that the '604 and '590 patents are invalid for lack of enablement. Watson has not proven that the patents are invalid as anticipated by Hesnard or are obvious in view of Stanley in combination with either Hesnard or Eichman.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

CEPHALON, INC., and CIMA LABS, INC.	)	
Plaintiffs,	)	
v.	)	Civ. No. 08-330-SLR
WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC., and WATSON PHARMA, INC.,	)	
Defendants.	)	

ORDER

At Wilmington this 14th day of March, consistent with the opinion issued this same date;

IT IS ORDERED that the Clerk of Court enter judgment against plaintiffs and in favor of defendants, as plaintiffs have failed to prove, by a preponderance of the evidence, that defendants infringe the asserted claims of U.S. Patent Nos. 6,974,590 and 6,200,604, and defendants have proven, by clear and convincing evidence, that the asserted claims are invalid for lack of enablement.

United States District Judge