IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

OREXO AB and OREXO US, INC.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	Civ. No. 14-829-SLR
	)	
ACTAVIS ELIZABETH LLC,	)	
	)	
Defendant.	)	

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OPINION

Dated: November 15, 2016
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application ("ANDA") by defendant Actavis Elizabeth LLC ("Actavis") seeking to market a generic sublingual tablet containing buprenorphine and naloxone. Plaintiffs Orexo AB and Orexo US. Inc. (collectively "Orexo") brought this action alleging infringement of U.S. Patent Nos. 8,454,996 ("the '996 patent") and 8,940,330 ("the '330 patent"). The court held a *Markman* hearing on August 31, 2015 and issued a claim construction order on October 6, 2015 construing certain disputed limitations. (D.I. 127) The court held a final pretrial conference on May 11, 2016 and a five-day bench trial from June 6-13, 2016 on the issues of infringement and validity, and the parties have since completed post-trial briefing. The 30-month stay of FDA final approval on Actavis's ANDA expires on November 16, 2016. The court has jurisdiction over this matter 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 Federal Rule of Civil Procedure 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. Technology at Issue

1. Buprenorphine

Buprenorphine is an opioid agonist used to treat patients for opioid dependence, such as heroin or other prescription pain medication. Buprenorphine may be solubilized and injected by patients seeking to abuse it. To address the abuse potential, naloxone (an opioid antagonist that reverses the effects of opioid analgesics) may be added to

some buprenorphine formulations. Naloxone has poor transmucosal bioavailability, therefore, if used in a sublingual formulation, the small amount of naloxone absorbed should not interfere with the desired effects of buprenorphine. If the formulation is dissolved and injected by an abuser, the increased availability of naloxone "serve[s] to antagonize the effects of buprenorphine, at the same time as precipitating unpleasant opioid withdrawal symptoms." Naloxone only partially blocks buprenorphine's action for a short time, thus, there is still potential for abuse of a formulation containing both naloxone and buprenorphine. ('330 patent, 1:54-2:36; D.I. 206 at 901:24-902:8)

Suboxone® ("Suboxone") is a sublingual tablet containing buprenorphine and naloxone in a 4/1 ratio, which was on the market in the United States in 2004. ('330 patent, 2:5-8; JTX 69 at 2; D.I. 206 at 901:16-23) The 4/1 ratio is the preferred dose ratio of buprenorphine and naloxone to treat opioid addiction and deter abuse. ('330 patent, 10:27-29; D.I. 202 at 58:18-59:2)

2. Zubsolv®

Orexo developed Zubsolv® ("Zubsolv"), a sublingual tablet formulation containing buprenorphine and naloxone in a 4/1 ratio intended for the treatment of opioid dependence. (D.I. 202 at 53:9-14; D.I. 205 at 770:22-771:3) According to Thomas Lundqvist ("Lundqvist"), co-founder of Orexo, Orexo invested approximately $60 million to research and develop a more abuse-resistant buprenorphine product from 2009-2014. (D.I. 202 at 56:19-22; D.I. 196 at 6) Andreas Fischer ("Fischer"), the inventor of the '330 patent, testified that the "goal was to develop a product with at least 25% higher bioavailability compared to Suboxone." (D.I. 202 at 83:20-84:3; D.I. 196 at 9)

Fischer's first laboratory notebook entry set forth a formulation of an "interactive mixture (tablet)" for "sublingual administration." The ingredients included buprenorphine, naloxone, citric acid, and sodium citrate.[1] (JTX 122 at 148; D.I. 202 at 88:1-6; JTX 123 at 12; D.I. 202 at 85:16-86:3; 124:15-24; 122:10-17) Anders Pettersson ("Pettersson"), first inventor on the '996 patent, testified that he suggested using a mucoadhesive component in order to reduce the risk of the active ingredient being swallowed. (D.I. 203 at 333:4-8) He stated that he knew about such agents from the literature, which described that "they had the ability to adhere to biological mucous surfaces." (D.I. 203 at 334:17-20; D.I. 211 at 48)

Lundqvist testified that the first clinical results showed that Zubsolv had a 66% improvement in bioavailability. (D.I. 202 at 58:9-15; D.I. 211 at 36) According to a bioequivalence study, Zubsolv increases the bioavailability of buprenorphine, such that patients require a 29% lower dose using Zubsolv as compared to Suboxone. (JTX 153; D.I. 202 at 63:11-17; D.I. 205 at 770:22-771:3; D.I. 196 at 12) Orexo's pharmaceutical development report stated that "[d]ue to the anticipated improved dissolution of buprenorphine the selected dose of 6 mg buprenorphine is expected to give approximately the same systemic buprenorphine exposure in humans as a Suboxone® tablet with 8 mg buprenorphine." (JTX 123 at 4; JTX 128 at 32; D.I. 203 at 352:11-22)

2. The '996 patent

The '996 patent, titled "Pharmaceutical Composition for the Treatment of Acute

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[1] The explanation regarding the function and inclusion of citric acid and sodium citrate is redacted.

Disorders," was filed on November 26, 2011 and issued on June 4, 2013, with a priority date of September 24, 1998.[2] It claims a method of sublingually administering a tablet comprising (1) microparticles of buprenorphine, "presented at" (claim 1) or alternatively "adhered to" (claim 2) the surfaces of carrier particles, and (2) a bio/mucoadhesion promoting agent also in a mixture with carrier particles. ('996 patent, 12:18-43) The patent states that using "ordered mixtures for sublingual administration, where the volume of liquid available as a solvent is limited to a few milliliters, has not been considered as a feasible approach. It was therefore unexpected that the present form of a solid dosage form preparation and administration route gives positive and useful results." ('996 patent, 3:56-61) The patent explains that "[a] variety of polymers known in the art can be used as bio/mucoadhesion promoting agents," and provides examples thereof. ('996 patent, 5:8-51) At issue are claims 1 and 2. Claim 1 recites:

> A method comprising sublingual administration to an individual of a pharmaceutical composition in the form of a tablet sized for placement under a tongue, wherein the composition comprises
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> (a) water-soluble carrier particles having exterior surfaces,
>
> (b) microparticles of buprenorphine or a pharmaceutically-acceptable salt thereof, wherein said microparticles are smaller than the carrier particles and are admixed with the carrier particles, and
>
> (c) particles of a bioadhesion and/or mucoadhesion promoting agent consisting essentially of a polymer that swells when brought into contact with saliva, admixed with the carrier particles,
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> wherein the microparticles of buprenorphine or a pharmaceutically-acceptable salt thereof are presented at the exterior surfaces of the carrier particles.

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[2] The inventors are Christer Nyström and Anders Pettersson. The patent is assigned to Orexo AB and is listed in the FDA's Orange Book for Zubsolv.

('996 patent, 12:18-33) Claim 2 adds additional requirements, including that the composition be "essentially water free." ('996 patent, 12:34-43)

Orexo's expert, Dr. Sinko, and Actavis' expert, Dr. Dyar, agreed that the limitation "microparticles . . . presented at the exterior surfaces of the carrier particles" describes an interactive mixture. An interactive mixture is made up particles of active ingredient adhered to the surface of carrier particles by interactive forces. (D.I. 205 at 676:4-18; D.I. 203 at 360:25-361:4, 365:13-366:9, 367:1-16; D.I. 127 at 3) The three "major elements" of the claims are a sublingual tablet; water soluble carrier particles and buprenorphine formulated as an interactive mixture; and a bioadhesive agent. (D.I. 203 at 387:2-14, 388:4-9; D.I. 205 at 734:6-22) Dr. Dyar explained that the "water free" requirement "relates to the bio-mucoadhesive, because if you have moisture in the tablet, then it could activate the mucoadhesive properties of that tablet and result in it sticking potentially to the package prior to being placed in the mouth." (D.I. 204 at 416:1-15)

3. The '330 patent

The '330 patent, titled "Abuse-Resistant Pharmaceutical Composition for the Treatment of Opioid Dependence," was filed on September 18, 2012 and issued on January 27, 2015.[3] Claim 1 of the '330 patent recites:

> A tablet composition suitable for sublingual administration comprising:
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> microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, presented upon the surface of carrier particles, wherein microparticles of buprenorphine or a pharmaceutically acceptable salt thereof are in contact with particles

[3] The listed inventor is Andreas Fischer. The '330 patent is assigned to Orexo AB and is listed in the FDA's Orange Book for Zubsolv.

comprising citric acid, wherein the buprenorphine or pharmaceutically acceptable salt thereof and the citric acid are not in the same particle;

a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof; and

a disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone and mixtures thereof.

('330 patent, 24:17-32) The specification provides a pH timing diagram comparing the in vitro pH for the composition of the invention to that of Suboxone and certain other formulations in a small-volume funnel dissolution test. It also provides a graph of the release of buprenorphine and naloxone, respectively, from such formulations. ('330 patent, figures 5 and 6)

Claim 1 is directed to a sublingual tablet comprising buprenorphine, naloxone, one of three named disintegrants, and citric acid. The parties' experts, Dr. Sinko and Dr. Dyar, explained that the limitation "microparticles . . . presented upon the surface of carrier particles" represents an interactive mixture. (D.I. 205 at 676:4-18; D.I. 203 at 360:25-361:4, 365:13-366:9; 367:1-16; D.I. 127 at 3) Orexo also asserted dependent claims 3-6. ('330 patent, 24:35-44)

B. Obviousness

1. Standard

"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 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. of Kansas City*, 383 U.S. 1, 17-18 (1966)).

"[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).

A combination of prior art elements may have been "obvious to try" where there existed "a design need or market pressure to solve a problem and there [were] a finite number of identified, predictable solutions" to it, and the pursuit of the "known options

within [a person of ordinary skill in the art's] technical grasp" leads to the anticipated success. *Id.* at 421. In this circumstance, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.*

A fact finder is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). "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." *Graham*, 383 U.S. at 17-18.

"Patents are presumed to be valid, and overcoming that presumption requires clear and convincing evidence." 35 U.S.C. § 282; *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1333 (Fed. Cir. 2015) (citing *Microsoft Corp. v. i4i Ltd. P'ship.*, 564 U.S. 91, 95 (2011) (holding that an invalidity defense must be proved by clear and convincing evidence)). 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) (citations omitted).

2. The '996 patent

a. Prior art references

i. Interactive mixtures

European Patent Application No. EP 0324725 ("the '725 application"), titled "A Pharmaceutical Composition," was filed on January 12, 1989.[4] (JTX 54) It teaches "an ordered mixture of particles of a water-soluble, pharmaceutical carrier substance and smaller particles of at least one pharmaceutically active substance which adhere to the carrier particles." ('725 application, abstract, 2:50-53) The '725 application sought to increase the amount of pharmaceutically active substance contained in an ordered mixture without decreasing the dissolution speed. (*Id.* at 1:38-48) It explains that ordered mixtures are advantageous as they enable "the therapeutically active substances to dissolve more quickly . . . when administered and consequently act more quickly." (*Id.* at 1:32-37) It provides that a "suitable carrier particle size is from 50 to 1000 microns, and . . . preferably from 100 to 500 microns." (*Id.* at 2:43-45) "The pharmaceutically active substances present in the preparation will suitably have a maximum particle size of about 24 microns, preferably not greater than about 10 microns." (*Id.* at 4:3-7) It further explains that "the preparation is essentially free from water, since the presence of water would result in premature dissolution of the active substance." (*Id.* at 5:1-4)

> The ordered mixtures prepared in accordance with the invention can be incorporated in various kinds of pharmaceutical preparations. Such preparations are preferably intended for enteral administration, primarily orally. The preparations will then, for instance, be in the form of table[t]s, capsules, powders or granulates, or in the form of suppositories for rectal administration. It is also possible to use the ordered mixtures of the

[4] The parties agree that such reference is prior art to the '996 and '330 patents. (D.I. 164, ex. 1 at 7-8)

present invention in certain preparations . . . intended for external application, such as ointments or creams.

(*Id.* at 4:55-65) The formulation contains a pharmaceutical disintegrant, for example Ac-Di-Sol®, a modified cellulose gum, which is highly swellable in water. (*Id.* at 3:8-22)

The parties dispute whether the '725 application disclosed sublingual administration by discussing "enteral administration." The parties' experts offer a confusing and largely unhelpful explanation of the term "enteral," with Dr. Dyar concluding that sublingual administration would be understood by the disclosure of "oral" and Dr. Sinko reaching the opposite conclusion.[5] (D.I. 203 at 363:12-20, 394:18-395:2; D.I. 204 at 491-494, 608-610; D.I. 205 at 748-759) The '725 application does not use the term "sublingual" and does not describe any such administration. The court determines that the '725 application does not disclose sublingual administration.

The **Westerberg thesis**[6] aims "to evaluate the extent to which ordered mixing can be used to improve the dissolution rate of a sparingly soluble drug." (JTX 58 at 16) It explains that "the rate of dissolution is an important determinant for the evaluation of bioavailability of drugs with a low aqueous solubility."[7] (JTX 58 at 8) It states, by

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[5] Orexo argues that Dr. Dyar's opinion on the meaning of "enteral system" was first presented at trial and moves to strike such testimony. (D.I. 200 at 10-11) The parties each objected to the opposing experts' testimony at trial and each argued that their expert's testimony was supported by their respective reports. (D.I. 203 at 363:22-364:11; D.I. 204 at 487:18-494:19, 609:1-21) At the post-trial stage, the court concludes that both parties' experts were permitted to offer testimony on the meaning of "enteral" as used in the '725 application – the actual issue at bar. The court will not strike such testimony.

[6] Marie Westerberg, *Studies on Ordered Mixtures for Fast Release and Dissolution of Drugs with Low Aqueous Solubility*, Doctoral Thesis at Uppsala University (1992).

[7] The parties agree that such reference is prior art to the '996 and '330 patents. (D.I. 164, ex. 1 at 7-8)

reference to an article from 1976, that "the advantage of an ordered mixture is the ready availability of the drug for dissolution and absorption in the gastrointestinal track." (JTX 58 at 15) The disclosed formulation also uses Ac-Di-Sol®. (JTX 58 at 17)

ii. Buprenorphine

The Rote Liste 1997 publication[8] lists **Temgesic® ("Temgesic")** as an analgesic.[9] Temgesic is a sublingual tablet containing buprenorphine, indicated for the treatment of "[m]oderate to severe pain." The ingredients of the sublingual tablet are buprenorphine and the additional components are lactose, cornstarch, mannitol, polyvidone (also known as povidone), citric acid, sodium citrate, and magnesium stearate. (JTX 66; JTX 67) **U.S. Patent No. 4,935,428 ("the '428 patent")**, titled "Treating Opiate Dependence," was filed on November 25, 1998 and issued on June 19, 1990. (JTX 46) The '428 patent is related to Temgesic and discloses that the sublingual tablet compositions contain "binding agents such as povidone."[10] ('428 patent, 4:15)

iii. Bioadhesives

U.S. Patent No. 4,259,686 ("the '686 patent"), titled "Pharmaceutical Preparation for Oral Cavity Administration," was filed on September 22, 1975 and

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[8] A compendium of commercial pharmaceutical products.

[9] According to Orexo, the Rote Liste 1997 publication's disclosure of Temgesic is cumulative to U.S. Patent No. 4,582,835 ("the '835 patent"), titled "Analgesic Compositions," filed December 5, 1984 and issued April 15, 1986. (JTX 139) The '835 patent discloses a sublingual tablet formulation containing buprenorphine and naloxone.

[10] The parties agree that both the Rote Liste 1997 publication and the '428 patent are prior art to the '996 and '330 patents. (D.I. 164, ex. 1 at 7-8)

issued on November 22, 1977.[11] (JTX 44) The '686 patent describes the use of sodium polyacrylate ("PANA") in making a pharmaceutical preparation for oral cavity administration with superior adhesion to local sites. ('686 patent, 1:4-12) According to the '686 patent, the available sublingual tablets give "patients an impulse to crunch and swallow the tablet" and are hard to hold in the mouth for a long period of time. Incorporating an adequate amount of PANA into a preparation allows it to become "strongly adherent to [the] local site and dissolve[] gradually over a long period of time while releasing appropriate amounts of the active component." ('686 patent, 1:15-43) PANA "first absorbs water and adheres strongly to the local site, then swells and dissolves gradually at the site over a long period of time, while releasing the medicinal agent substantially uniformly." (*Id.* at 2:34-44) More specifically, the '686 patent states that the "buccal tablet and sublingual tablet are pharmaceutical preparations intended for a systemic effect" and are conducive to formulations that are susceptible to decomposition "in the digestive tract and the liver, resulting in decreased drug effect." These tablets allow the drugs to be efficiently "absorbed through the oral mucous membrane . . . directly, through the systemic circulation." (*Id.* at 1:62-2:5)

> An advantage of these tablets is in the efficient absorption of the drug, because the drug is not decomposed by the liver. However, if the disintegration and dissolution of the tablet are too rapid, the object of such a way of administration is not achieved. The tablet should be prepared so that it may gradually disintegrate or dissolve in the mouth over a period of more than one hour, but actually there is not available a satisfactory preparation.

(*Id.* at 2:5-13)

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[11] The parties agree that such reference is prior art to the '996 and '330 patents. (D.I. 164, ex. 1 at 7-8)

U.S. Patent No. 4,755,386 ("the '386 patent"), titled "Buccal Formulation," was filed on January 22, 1986 and issued on July 5, 1988.[12] (JTX 45) The '386 patent describes a "buccal formulation" which includes a soluble, pharmaceutically acceptable adhesive of a pharmaceutically acceptable disintegrant and a soluble, directly compressible tablet excipient. ('386 patent, abstract) The specification explains that the buccal formulation must "remain in contact with the oral mucosa for a time sufficient for absorption of the medicament to be administered. If the formulation falls apart too quickly, the active ingredient is swallowed, and an insufficient amount of medicament is delivered." (*Id.* at 1:34-39) The "adhesive is used to provide tackiness to the buccal formulation so that it will be held in place upon administration." Use of less than 1% adhesive "may result in insufficient adhesive properties or the formulation falling apart too quickly while excessive amounts may result in the formulation lasting for a longer period than is desirable." (*Id.* at 2:3-12) The "adhesive forms a gel-like substance which is gradually broken up by a pharmaceutically acceptable disintegrant which swells upon administration, thus exposing more of the formulation to saliva. This causes the formulation to break up gradually." (*Id.* at 2:45-50)

The **Gandhi reference**[13] states "unlike the buccal region, the sublingual region does not appear promising for attachment of a bioadhesive system, primarily because of the physical structure and mobility of tissue in this area." The "sublingual route has

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[12] The parties agree that such reference is prior art to the '996 and '330 patents. (D.I. 164, ex. 1 at 7-8)

[13] Rajesh B. Gandhi and Joseph R. Robinson, *Oral Cavity as a Site for Bioadhesive Drug Delivery*, 13 Advanced Drug Delivery Reviews 43, 64 (1994). (JTX 63)

been used extensively for delivery of drugs which require a rapid onset of action." (JTX 63 at 67)

b. Motivation to combine

Dr. Dyar identified each of the three major elements of asserted claim 1 in the prior art. He explained that "[i]f you're trying to relieve pain, you want something to work rapidly." Therefore, a person of ordinary skill would select an interactive mixture to do so. (D.I. 203 at 398:8-15) In other words, a person of ordinary skill would have started with Temgesic and understood that the bioavailability of buprenorphine needed to be enhanced. The person of ordinary skill would have tried an interactive mixture based upon the '725 application and added a mucoadhesive based upon the '686 patent to arrive at a product with enhanced bioavailability. Dr. Dyar also opined that a person of ordinary skill would have expected such combination to work based on the fact that Temgesic and interactive mixtures separately worked. (D.I. 203 at 396:10-397:10; 400:25-401:19, 408:10-22) The mucoadhesive element of the '996 patent is known from the '686 and '386 patents, as well as from Temgesic. The '996 patent only requires the presence of the bioadhesive, not any particular amount. (D.I. 203 at 406:18-25) As to claim 2, Dr. Dyar explained that the additional limitation of "being water free" was a well-known requirement of an interactive mixture as disclosed by the '725 application. (D.I. 203 at 387:15-20, 407:16-25)

According to Dr. Sinko, Dr. Dyar improperly combined references from three competing and incompatible groups to arrive at his obviousness conclusion: swallowed formulations using interactive mixtures; sublingual administration of buprenorphine without interactive mixtures; and bioadhesives. (D.I. 204 at 567:21-568:3, 578:11-24,

581:6-13, 583:11-19) There would be no motivation to combine the references as "you would not expect the interactive mixture to work sublingually; . . . would expect that the bioadhesive formulations would not allow rapid dissolution of the drug; and that the bioadhesives . . . would not be promising for sublingual administration . . . ." (D.I. 204 at 583:11-19) The '996 invention combines these three "unexpected" features. (D.I. 204 at 573:4-574:2)

The first question addressed by the experts was whether the application of an interactive mixture to a sublingual formulation would be expected to increase dissolution in the sublingual space (as compared to a sublingual formulation without an interactive mixture). The '725 application generally provides that the use of an ordered mixture increases dissolution rate. Orexo argues that a person of ordinary skill would not have expected interactive mixtures to accelerate dissolution sublingually, because the sublingual volume is much smaller than the stomach volume. Dr. Sinko pointed to the explanation in the '996 patent that the volume of liquid sublingually is not conducive to dissolution. He explained that the small volume of liquid in the sublingual environment would affect both absorption and concentration, as compared to the stomach where the volumes are much larger. The absorption and concentration in the sublingual space would be "much different" than for the stomach. In the small volume of the sublingual space, drug concentration is increased and the elevated concentration can decrease dissolution rate. The decreased dissolution rate from the high concentration "competes" with the improved dissolution rate from the ordered mixture. Saliva flow may reduce the concentration by causing swallowing, but the flow is not fast enough to dilute it out to a low concentration. (D.I. 204 at 592:13-598:14) Dr. Dyar opined that, even though the

sublingual volume is small, it is not a closed system. Instead, "the drug is actually moving in a continuous manner across the mucosal membrane and getting absorbed into the body. So once it's removed, then there's more space for drug to be absorbed." (D.I. 203 at 399:1-400:18) The parties' experts have each offered a plausible explanation for whether or not a person of ordinary skill would have expected interactive mixtures to increase dissolution sublingually.

The experts then addressed whether there would be a motivation to combine the various prior art references described above. "[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR*, 550 U.S. at 416. A reference teaches away from a claimed invention when a person of ordinary skill, "upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The "mere disclosure of alternative designs does not teach away." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). "[C]ourts must take an 'expansive and flexible approach' to the question of obviousness." *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015) (citing *KSR*, 550 U.S. at 415). "The degree of teaching away will of course depend on the particular facts." *In re Gurley*, 27 F.3d at 553. "[O]bviousness must be determined in light of all the facts, and there is no rule that a single reference that teaches away will mandate a finding of nonobviousness." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

Dr. Sinko characterized interactive mixtures (the '725 application) and bioadhesives (the '686 and '386 patents, as well as the Gandhi reference) as "competing technologies" because "bioadhesives were associated with kind of slow release and interactive mixtures with fast release." (D.I. 204 at 603:2-15, 604:1-13, 613:25-614:4) Bioadhesives "would be expected . . . to slow dissolution." They would increase residence time, slow the release, and "hinder rapid dissolution of the active ingredient." (D.I. 204 at 612:15-21) Dr. Sinko explained that fast release to get fast absorption is wanted for sublingual delivery. (D.I. 204 at 606:11-19) Therefore, a person of ordinary skill would not expect slowly dissolving formulations to be good for sublingual administration. (D.I. 204 at 604:14-16) He testified (contrary to Dr. Dyar's opinion) that "the art is suggesting to a person of ordinary skill that if you increase dissolution, you're going to decrease absorption." (D.I. 204 at 577:2-8) Dr. Sinko explained that many factors may affect sublingual absorption, including the permeability of the drug and the environment under the tongue. (D.I. 204 at 600:7-602:13)

Dr. Sinko referenced the '686 patent's statement – a dissolution period of more than one hour is desirable – as "not something" which would be associated with sublingual administration. He concluded that the '686 patent "in some ways . . . expressly teaches away from formulations that dissolve rapidly in the mouth." (D.I. 204 at 604:24-605:5) Dr. Sinko pointed to the '386 patent's explanation – if disintegration occurs too quickly, the active ingredient is swallowed, resulting in less absorption and insufficient amount of medicament delivered to the body – to explain that increasing dissolution rate does not always increase absorption. (D.I. 204 at 574:14-577:1) Dr. Sinko concluded that both the '686 and '386 patents "taught that speeding up

dissolution would decrease bioavailability and absorption." (D.I. 204 at 613:10-15) Dr. Sinko pointed to the Gandhi reference to argue that a person of ordinary skill in the art would understand that bioadhesives would not be promising for a fast releasing formulation. (D.I. 204 at 606:23-607:22)

According to Dr. Dyar, the '686 patent teaches a person of ordinary skill to "keep the tablet in place for the time that you need to keep it in place." (D.I. 203 at 404:22-405:1) The '386 patent teaches a person of ordinary skill that adjusting the amount of adhesive allows for different amounts of adhesion. The formulation includes sufficient adhesive for the formulation to remain in contact with the oral mucosa for a time sufficient for the absorption of the medicament. (D.I. 203 at 402:22-403:19) Dr. Dyar testified that the '725 application explained that when the active ingredient is dissolved more quickly, it can act more quickly. Dr. Dyar also relied on the Westerberg thesis to explain that the rate of dissolution "is very important for determining the evaluation of bioavailability of drugs with a low aqueous solubility." (D.I. 203 at 391:1-392:3)

A motivation to combine can be found implicitly or explicitly in the prior art, or can be demonstrated by proving "by clear and convincing evidence that a person of ordinary skill in the [drug formulation arts] at the time of the invention" would have recognized the problem identified by the inventors and found it obvious to solve such problem in the manner claimed in the invention. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). The court has determined that the '725 application does not disclose sublingual administration. The record also supports Dr. Sinko's observation that interactive mixtures and sublingual tablets were known in the art for over twenty years, but not combined before September 24, 1998, the priority date for the '996 patent. (D.I.

204 at 572:21-24; D.I. 205 at 737:21-740:10) The question is whether Actavis has proven, by clear and convincing evidence, that a person of ordinary skill would be motivated to combine all the prior art references, representing three competing and incompatible groups of formulations, to arrive at the inventive concept of the '996 patent. The court concludes that, although a person of ordinary skill upon reading the prior art[14] would not necessarily be discouraged from trying interactive mixtures in a sublingual formulation, Actavis has not carried its burden to prove that a person of ordinary skill would be motivated to use the competing prior art teachings to arrive at the '996 patent combination.[15]

4. The '330 patent

a. Prior art references[16]

U.S. Patent Application No. 2010/0129443 ("the '443 application"), titled "Non-Abusable Pharmaceutical Composition comprising Opioids," was filed December 3, 2007 and published May 27, 2010. (JTX 50) The '443 application discloses interactive mixture compositions, i.e., "where smaller particles (of, for example, opioid analgesic and/or bioadhesion and/or mucoadhesion promoting agent) are attached to . . . the surfaces of larger opioid antagonist-containing, or opioid antagonist-based, carrier

[14] The '725 application, the Westerberg thesis, Temgesic, and the '386 and '686 patents.

[15] Orexo did not present secondary considerations of nonobviousness separately from its "teaching away" arguments.

[16] In addition to the art disclosed above for the '996 patent, the parties agree that the following references are prior art to the '330 patent, which has a later priority date (September 2012) than does the '996 patent (September 1998). (D.I. 164, ex. 1 at 8)

particles." ('443 application at [20]) It discloses naloxone as an opioid antagonist and describes preparations for sublingual administration. (*Id.* at [23], [73])

The prior art commercial formulations contain citric acid. Citric acid is a common excipient, used as a buffer system. (D.I. 204 at 420:20-421:5) For example, a **Suboxone tablet** contains buprenorphine and naloxone.[17] It uses citric acid and sodium citrate as a buffer system to improve the absorption of buprenorphine. (JTX 69 at 2; D.I. 204 at 420:8-15) Temgesic, Subutex®[18] ("Subutex"), and Suboxone film each use citric acid and sodium citrate. (JTX 66, JTX 69, JTX 49 at 16:1-31)

U.S. Patent No. 8,475,832 ("the '832 patent"), titled "Sublingual and Buccal Film Compositions," was filed on August 7, 2009 and issued on July 2, 2013.[19] (JTX 49) The '832 patent is directed to films containing therapeutic actives, including buprenorphine (a film formulation of Suboxone). ('832 patent, 1:6-15, 5:6-13) The '832 patent provides that the combination of antagonist and agonist (such as Suboxone)

> in tablet form have the potential for abuse. In some instances, the patient who has been provided the drug may store the tablet in his mouth without swallowing the tablet, then later extract the agonist from the tablet and inject the drug into the individual's body. Although certain antagonists (such as highly water-soluble antagonists) may be used to help reduce the ability to separate the agonist, the potential for abuse still exists. It is desired to provide a dosage that cannot be easily removed from the mouth once it has been administered.

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[17] Suboxone is described in the *Physicians' Desk Reference* ("PDR") (58th ed. 2004). The parties agree that such reference is prior art to the '330 patent. (D.I. 164, ex. 1 at 7-8)

[18] Sublingual tablet containing buprenorphine.

[19] The parties agree that such reference is prior art to the '330 patent. (D.I. 164, ex. 1 at 7-8)

(*Id.* at 1:53-64) In describing preferred embodiments, the specification provides that "it has been surprisingly discovered that the absorption of one particular agonist, buprenorphine, can provide an optimum absorption at a pH of about 2-4 as well as about 5.5-6.5. Thus, one may 'optimize' the absorption of buprenorphine by providing a pH of about 2-4 or about 5.5-6.5." (*Id.* at 3:27-32) The buffer used "to control the local pH of the film composition . . . may include sodium citrate, citric acid, and combinations thereof." (*Id.* at 12:62-13:10)

> An important consequence of nonionic diffusion is that a difference in pH between two compartments will have an important influence upon the partitioning of a weakly acidic or basic drug between those compartments. The partition is such that the un-ionized form of the drug has the same concentration in both compartments, since it is the form that is freely diffusible; the ionized form in each compartment will have the concentration that is determined by the pH in that compartment, the pK and the concentration of the un-ionized form. The governing effect of pH and pK on the partition is known as the pH partition principle [or theory].

(JTX 61 at 715-16)

> [T]he local pH of the dosage is preferably controlled to provide the desired release and/or absorption of the agonist and antagonist. Buprenorphine is known to have a pKa of about 8.42, while naloxone has a pKa of about 7.94. According to pH partition theory, one would expect that saliva (which has a pH of about 6.5) would maximize the absorption of both actives. However, it has been surprisingly discovered by the [a]pplicants that by buffering the dosage to a particular pH level, the optimum levels of absorption of the agonist and antagonist may be achieved. Desirably, the local pH of a composition including an agonist and an antagonist is between about 2 to about 4, and most desirably is from 3 to 4. At this local pH level, the optimum absorption of the agonist and the antagonist is achieved.

('832 patent, 11:44-57) "The term 'local pH' refers to the pH of the region of the carrier matrix immediately surrounding the active agent as the matrix hydrates and/or dissolves, for example, in the mouth of the user." (*Id.* at 3:35-38) The buffer is used to

provide a "local pH of the composition within a range that provides the desired level of absorption of the buprenorphine." (*Id.* at 11:65-67) In example 8,

> the in vivo data indicated that the absorption of buprenorphine was substantially bioequivalent to that of the one dose tablet when the film composition local pH was lowered to about 3-3.5. This result was surprising as it did not appear to follow the pH partition theory. Further, at a local pH of about 3-3.5, it was seen that the absorption of naloxone was substantially bioequivalent to that of the one dose tablet.

(*Id.* at 21:35-23:7)

b. Motivation to combine

The court starts with the observation that the scope of the prior art for the '330 patent had expanded greatly from that just discussed for the '996 patent. The most significant change was the introduction in 2004 of a commercial product, Suboxone, which was a tablet administered sublingually containing buprenorphine, naloxone, and citric acid. The art, of course, developed even further after Suboxone tablets came to the market, to include prior art references which disclosed the use of an interactive mixture to improve the absorption of buprenorphine (the '443 application).[20] The ultimate question is whether Actavis has carried its burden to prove, by clear and convincing evidence, a motivation to combine these references. *See, e.g., Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1368 (Fed. Cir. 2016) ("'If all elements of a claim are found in the prior art, as is the case here, the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that

[20] Dr. Sinko conceded that the '443 application showed that "sublingual formulations with interactive mixtures could be used with formulations of buprenorphine and naloxone," and that the prior art taught each element of claim 1 other than the use of citric acid. (D.I. 205 at 674:3-13-675:1 and 677:1-11; *see also* D.I. 204 at 620:10-14)

combination, a person of ordinary skill would have had a reasonable expectation of success.'") (citation omitted).

The court concludes that the expert opinions offered by Dr. Dyar were more credible than those offered by Dr. Sinko in this regard. Dr. Dyar opined that claim 1 was obvious in light of the combination of Suboxone with the interactive mixture disclosures (the '443 application and '725 application). Dr. Dyar testified that a person of ordinary skill would have started with the Suboxone sublingual tablet (which contains buprenorphine, naloxone, and citric acid) and then would have used an interactive mixture in order to enhance bioavailability. The person of ordinary skill would have looked to an interactive mixture to enable the active ingredient to dissolve more rapidly (as disclosed in the '443 and '725 applications) and, consequently, to act more quickly. The use of disintegrants was disclosed in the art, for example, the '725 application discloses disintegrants, including Ac-di-sol, which swells in water. He further explained that citric acid is present in many pharmaceutical products and is used as a pH buffering system. The citric acid also fits the definition of a carrier particle – "a pharmaceutically acceptable substance that is water soluble." As citric acid is of appropriate size, "it would act as a carrier if you made an interactive mixture." According to Dr. Dyar, "mannitol was also in Suboxone and would form a[n] . . . active carrier." The combination would have been expected to work as Suboxone was a commercial product and interactive mixtures had been shown to enhance bioavailability. As to claim 6, Dr. Dyar opined that "citric acid is pharmaceutically acceptable, water soluble, and of the right size, so therefore it would act as a carrier particle, because it is in the Suboxone tablet." (D.I. 204 at 417-427, 433)

Orexo offers several different arguments in opposition, notwithstanding the undisputed fact that, as of 2012, every other sublingual buprenorphine formulation that was sold commercially contained citric acid and Dr. Sinko's admissions that, by the time of the '330 patent, the prior art taught a person of ordinary skill that "sublingual formulations with interactive mixtures could be used with formulations of buprenorphine and naloxone together." (D.I. 205 at 674:3-12) In the first instance, Orexo argues that Suboxone taught away from using an interactive mixture; i.e., it does not teach one of skill in the art how to formulate an interactive mixture. The record demonstrates, however, that the prior art was replete with instructions on how to make interactive mixtures, the appropriate particle sizes to use, and the mixing that is required to achieve adhesion to a variety of carrier particles. (*See, e.g.*, D.I. 203 at 391:4-11; D.I. 204 at 423:20-24, 426:3-11, 433:8-15; D.I. 205 at 674:8-12, 682:5-15; JTX 50 at ¶¶ 1, 20, 22, 23, 31, 33, 51; JTX 54 at 4-5, 56-57) Given the teachings of the '443 application and the fact that Suboxone's description in the PDR "does not criticize, discredit, or otherwise discourage" the use of interactive mixtures, *In re Fulton*, 391 F.3d at 1201, the evidence of record clearly weighs in favor of a finding of obviousness in this regard.

Orexo also argues that a person of ordinary skill would not have been motivated to combine the prior art references at issue because buprenorphine would have been expected to follow the pH partition theory, which stands for the proposition that the lower the pH (an ionized state), the lower the transmucosal absorption of a drug such as buprenorphine. (D.I. 205 at 650-654; JTX 61 at 716) To put the point another way, "[f]aster disintegration/dissolution would be expected to release citric acid faster, lowering the pH and putting buprenorphine in the wrong state for absorption." (D.I. 200

at 29-30) According to Orexo, the '330 patent discloses a new theory of how the transmucosal absorption of buprenorphine occurs:

> The separate particles of buprenorphine and citric acid allow the citric acid to be more freely soluble, providing a more rapid pH decrease (as seen in Fig. 5). . . . The contact between buprenorphine and citric acid creates a localized area of lower pH that shifts buprenorphine into the ionized (more soluble) form, allowing for rapid release of buprenorphine into sublingual solution (as seen in Fig. 6). . . . Then, after the citric acid has dissolved quickly as a result of being in separate particles, the buffering capacity of the saliva brings the pH back to nearly neutral values, which shifts the buprenorphine to the non-ionized (more permeable) form (as seen in Fig. 5) allowing for improved absorption. . . . Prior to the '330 inventor's discovery, nowhere was the pH timing effect disclosed or suggested in the art. . . .

(*Id.* at 33) This argument persuaded the examiner to issue the '330 patent. (JTX 4 at 945)

Orexo presented exhaustive explanations with citations to technical references in connection with its arguments that the unclaimed pH timing effect disclosed in the '330 patent is relevant to a finding that one of skill in the art would not be motivated to combine the prior art references at issue. *See Intelligent Bio-Systems*, 821 F.3d at 1368.[21] As acknowledged by Orexo, Dr. Sinko's opinions are based on "a close reading of the '832 patent disclosures relating to 'local pH' and its effect on drug behavior; an examination of the pH and bioavailability data presented in the '832 patent examples; and '330 patent Fig. 8 that showed that there is a difference between the '832 patent's definition of Suboxone® film's 'local pH' (3-3.5) and an actual sublingual pH of about 6.8, as well as Suboxone® film's relatively static and nearly neutral pH profile compared to the '330 invention's dynamic pH dip and return." (D.I. 200 at 45) In other words, Dr.

[21] According to the Federal Circuit, unclaimed features are irrelevant to the reasonable expectation of success requirement. *Id.* at 1367.

Sinko's opinions are based on a hindsight critique of the prior art references, as opposed to what the prior art references actually taught a person of skill in the art at the time.

Contrary to Orexo's position, the court finds that the '832 patent[22] expressly taught a person of ordinary skill that the addition of citric acid facilitated an increased level of absorption of buprenorphine despite a lower pH.[23] (JTX 49 at 11:50-53; *see also* D.I. 205 at 707-709, 712) The court concludes, therefore, that the credible evidence of record clearly demonstrates that a person of ordinary skill in the art would have been motivated to reformulate Suboxone tablets as an interactive mixture to improve bioavailability (the '443 application), that the use of citric acid with an interactive mixture would also improve bioavailability (the '832 patent), and that a person of skill would have known how to form an interactive mixture using citric acid. (D.I. 205 at 674-676, 682, 733; D.I. 202 at 106-107, 126; JTX 54 at 2:43-45) Other than Dr. Sinko's reliance on unclaimed features and subjective criticisms, there is nothing in the prior art which would have discouraged a person of ordinary skill from following the path set out in the various references.[24] The court concludes that a person of ordinary skill, in light

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[22] Orexo's prior art references to the contrary were published before the '832 patent and only one, J.P. Cassidy, et al., *Controlled buccal delivery of buprenorphine*, 25 Journal of Controlled Release, 21-29 (1993) (JTX62 at 8), addressed buprenorphine, albeit without addressing the pH partition theory.

[23] According to Dr. Sinko, examples 6-8 of the '832 patent show that, as the buprenorphine bioavailability is adjusted through pH variations, the naloxone availablity is compromised - that is, the desired 4/1 ratio is lost. (D.I. 205 at 666-668) Again, the 4:1 ratio is an unclaimed feature of the '330 patent, and any problems with maintaining the ratio forecast by the '832 patent goes to the reasonable expectation of success requirement, not to motivation to combine; i.e., this argument is irrelevant in this context.

[24] Even if (as Orexo contends) "it is not the mere use of interactive mixture principles, but rather the claimed combination of features, including the structural arrangement of citric acid and buprenorphine in the '330 invention that provides the unexpected

of the relevant prior art, would have been motivated to combine the references and formulate the interactive mixture described by claims 1 and 6 of the '330 patent.[25]

As to claims 8-10, Orexo argues that Actavis "fails to refer to citric acid, a required element." Orexo offers the same criticisms of the prior art (addressed above) and concludes that "there is no teaching that particles of buprenorphine and citric acid should be dry mixed together." (D.I. 200 at 51) For the reasons articulated above, a person of ordinary skill in the art would not have excluded citric acid. Interactive mixtures were known in the art and the '725 application described how to make such a mixture using dry mixing.[26] The court concludes that Actavis has demonstrated, by clear and convincing evidence, a motivation to combine as to claims 1, 3-6, and 8-10.

c. Secondary considerations

Orexo argues that the '330 patent is nonobvious in light of unexpectedly increased bioavailability; teaching away arguments;[27] a long-felt need for a therapy less prone to diversion and abuse; additional clinical benefits;[28] and copying.

i. Unexpected results

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increase in bioavailability through the 'pH timing effect'" (D.I. 200 at 32), the prior art references do not teach away from the claimed combination. The resulting "unexpected increase" is a separate argument analyzed below under secondary considerations.

[25] Orexo does not offer separate reasons for the nonobviousness of claims 3-5.

[26] The court precluded reliance on the '443 application for the dependent claims.

[27] Such arguments were addressed and found to be not persuasive above.

[28] Orexo states that "[c]ontrolled clinical trials show that Zubsolv® is superior to Suboxone® in dissolve time, (and taste, mouthfeel, and ease of administration), which improve patient acceptability and tolerability of treatment." (D.I. 200 at 58) Orexo does not tie such arguments to a particular secondary consideration and closes its argument with the fact that Dr. Santoro and Dr. Sumner "agree that the products are equally efficacious." The court does not consider these arguments as pertinent to the issue of secondary considerations.

"To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (citations omitted). A new compound is not necessarily rendered nonobvious by unexpected properties. "While a 'marked superiority' in an expected property may be enough in some circumstances to render a compound patentable, a 'mere difference in degree' is insufficient." *Id.* (citations omitted). "'[D]ifferences in degree' of a known and expected property are not as persuasive in rebutting obviousness as differences in 'kind'—i.e., a new property dissimilar to the known property." *Id.* (citations omitted).

Orexo points to the patent's disclosure of 66% improved bioavailability for the claimed structure compared to Suboxone, and to Zubsolv having 29% less opioid than Suboxone. ('330 patent, 19:47-52; JTX 153; D.I. 202 at 63:11-17; D.I. 205 at 770:22-771:3) The prior art sought to improve the bioavailability of the opioid. Generally, interactive mixtures were known to improve bioavailability. Although the court rejected Orexo's arguments that the use of citric acid was expected to decrease bioavailability,[29] the increase in bioavailability (albeit a "difference in degree," not a difference in "kind") provides some support to Orexo's argument for nonobviousness.

ii. Long-felt need

[29] Each party also points to its interpretation and conclusions regarding the prior art. The court will not address these arguments again.

Orexo identifies a long-felt need for an abuse-resistant formulation of Suboxone, based on diversion[30] and abuse. The parties' experts agree that buprenorphine is subject to diversion. (D.I. 205 771:23-772:6; D.I. 206 at 923-924, 927-928, 944-946; PTX 104, PTX 106) Orexo sought approval for Zubsolv pursuant to § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, relying on the safety and efficacy data for Suboxone tablets. 21 U.S.C. § 355(b)(2). (D.I. 202 at 71:21-73:3) Orexo argued to the FDA that the total buprenorphine dose that could be diverted and misused in Zubsolv was decreased. The FDA disagreed.[31] (DTX 287 at 9; DTX 225 at 15; DTX 204 at 17; D.I. 206 at 903-905) Orexo's vice president of regulatory affairs testified that there were no "claims made in the label that Suboxone and Zubsolv are different from an abuse deterrent perspective." (D.I. 205 at 814:1-4) The label warns that buprenorphine "has the potential for being abused" and "can be abused in a similar manner to other opioids." (DTX 333 at 4, 8; D.I. 206 at 951:1-15)

Orexo's global chief medical officer, Dr. Michael Sumner ("Dr. Sumner"), opined that Zubsolv is less susceptible to diversion based on "Study 006;" a decrease in utilization of buprenorphine when Zubsolv is the preferred product for an insurance plan; and his interactions with healthcare professionals. Study 006 revealed that certain patients with a preference for Zubsolv still selected the Suboxone film when offered a choice of drug. Moreover, certain patients requested higher doses of Suboxone film. (JTX 156; DTX 232; PTX 558) Dr. Sumner testified that, in certain circumstances,

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[30] A drug is diverted when a patient either sells or gives a prescription drug to someone else. (D.I. 205 at 771:23-772:2; D.I. 206 at 892:9-15)

[31] Such material is redacted.

reduced prescriptions were observed. Moreover, Dr. Sumner also testified regarding interactions with physicians.[32] (D.I. 205 at 772:7-780:4) On cross-examination, Dr. Sumner agreed that the primary objective of Study 006 was not to determine the diversion of Zubsolv as compared to Suboxone film. (D.I. 205 at 785:5-14) Moreover, Orexo has not conducted a clinical trial to fulfill FDA regulations with respect to the decreased abuse argument. (D.I. 205 at 801:4-11)

Dr. William Santoro ("Dr. Santoro"), Actavis' expert, testified that he has treated between 4,000 and 5,000 patients for opioid dependence since 1988. He explained that he prescribes Suboxone tablets, Suboxone film, and Zubsolv tablets to his patients. A physician treating opioid dependence is limited to 100 patients (the "patient cap"). Dr. Santoro described an instance of finding out that one of his patients was diverting her medication to her father ("therapy sharing"), who later became a patient. He cited the **Smith article**,[33] which states that the level of abuse of Subutex and Suboxone is low compared to the number of prescriptions dispensed. Dr. Santoro opined that the majority of the products are being diverted due to lack of access to care, because of the patient cap. He testified that Orexo agreed with this opinion and requested his support in sending a form letter addressing this issue to the Department of Health and Human Services to request an increase in the patient cap. (DTX 343-44) Dr. Santoro explained that the abuse profile of Zubsolv is identical to that of Suboxone, and that he has not seen data to support that Zubsolv is abused less frequently than other products or that it reduces the diversion of buprenorphine. He concluded that Zubsolv (or other

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[32] Details are redacted.

[33] Meredith Smith et al., *Abuse of Buprenorphine in the United States*, Journal of Addictive Diseases, 26:3, 107-111 (2007). (DTX 297)

medications) could not solve the issue of therapy sharing, so long as the patient cap remains at 100. (D.I. 206 at 886:1-900:17; 907:1-908:12)

On cross-examination, Dr. Santoro testified that he has treated approximately 40 patients with Zubsolv and only a few patients with both Zubsolv and Suboxone. He has not participated in clinical trials regarding opioid dependence. He spent four to five hours reviewing the documentation provided to him (approximately 5,000 pages). (D.I. 206 at 910:7-913:16) Dr. Santoro stated that the Suboxone film is beneficial in that it cannot be crushed and snorted, as opposed to Suboxone (and Zubsolv) tablets. (D.I. 206 at 923:17-924:12) He agreed that the **Monte article**[34] and the **Cicero article**[35] described the risks of therapy sharing and other abuse, but he maintained that lack of access to care was the most common reason for therapy sharing. (D.I. 206 at 936:25-938:16; 944-946) Dr. Santoro testified that Zubsolv and Suboxone have the identical abuse potential because they have the identical formulations of 4/1 naloxone and buprenorphine. Subutex has more abuse potential due to the lack of naloxone. Dr. Santoro agreed that the warning in the label was the same for all three products. (D.I. 206 at 946-954)

Orexo argues that facts learned after FDA approval show that Zubsolv reduces diversion and abuse. Orexo's "real world evidence" set forth above is not compelling or unrebutted. Dr. Santoro attributed the majority of diversion to the need for more access to care (raising the patient cap). Dr. Sumner's testimony regarding insurance plans is

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[34] Andrew Monte, MD et al., *Diversion of Buprenorphine/Naloxone Coformulated Tablets in a Region with High Prescribing Prevalence*, Journal of Addictive Diseases, 28:226-231 (2009). (JTX 145)

[35] Theodore J. Cicero et al., *Factors contributing to the rise of buprenorphine misuse: 2008-2013*, Drug and Alcohol Dependence (2014). (DTX 324)

speculative, as there was no focused effort to determine why the prescription volume decreased. Dr. Sumner's testimony regarding physician feedback is not an unbiased opinion. Orexo's criticisms of Dr. Santoro do not lead the court to attribute little or no weight to his testimony as requested. The only objective evidence for this factor is that which was presented to, and rejected by, the FDA.

iii. Copying

Orexo's contention that Actavis copied the ratios and proportion of key ingredients[36] from a preferred patent example does not compel a finding of nonobviousness. The Federal Circuit has held that it "do[es] not find compelling ... evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval." *Purdue Pharma Products LP v. Par Pharm., Inc.*, 377 Fed. Appx. 978, 983 (Fed. Cir. 2010); *see also Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) ("[C]opying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval."). Accordingly, the court finds that, even if the process of reverse-engineering Zubsolv amounted to copying of the '330 patent, such conduct is not persuasive evidence of nonobviousness.

iv. Hindsight

Orexo alleges Dr. Dyar used improper hindsight, by mixing and matching between the Suboxone reference, the Suboxone tablet, and the '443 application. Orexo argues that Dr. Dyar saw citric acid and then searched the art for references to citric

[36] The court rejected many of Orexo's interpretations of the prior art, on which it relies for this proposition.

acid included in buprenorphine formulations. (D.I. 204 at 507:4-508:25) In light of the secondary considerations analyzed above, the court concludes that Actavis' obviousness combination should not be discounted because of hindsight.

d. Conclusion

The court determined that Actavis demonstrated, by clear and convincing evidence, a motivation to combine and a reasonable expectation of success. Having reviewed the secondary considerations, the court concludes that the unexpected result of increased bioavailability provides some support for nonobviousness, while Orexo's long-felt need and copying arguments are not persuasive evidence of such. The court finds that Actavis has met its burden to prove, by clear and convincing evidence, that claims 1, 3-6, and 8-10 are obvious.

C. Infringement

1. Standard

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). To prove direct infringement, the patentee must establish that one or more claims of the patent read on the accused device literally or under the doctrine of equivalents. *See Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001). 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), aff'd, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope, a question of law. *See id.* at 976-77; *see also Teva Pharms. USA, Inc. v. Sandoz, Inc.*, _ U.S. _, 135 S. Ct. 831, 837

(2015). 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. *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1337 (Fed. Cir. 2015) (citing *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998)). "Direct infringement requires a party to perform each and every step or element of a claimed method or product." *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1320 (Fed. Cir. 2009) (quoting *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007)). "If any claim limitation is absent . . ., 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. *Ferring B.V. v. Watson Labs., Inc.-Florida*, 764 F.3d 1401, 1411 (Fed. Cir. 2014) (citing *Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F.2d 1546, 1552 (Fed. Cir. 1989) ("One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that claim.")). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). The patent owner has the burden of proving literal infringement by a preponderance of the evidence. *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, _ U.S. _, 134 S. Ct. 1749, 1758 (2014).

2. Analysis

The parties dispute whether Actavis' products are interactive mixtures, i.e., whether the products meet the "presented at,"[37] "adhered to,"[38] and "presented upon"[39] limitations of the asserted claims. To show infringement of these limitations, Orexo provided evidence about the preparation and testing of sample precompression blends, Actavis' documents, and testing of Actavis' tablets.

a. Sample precompression blends

Orexo's expert, Dr. Martyn Davies ("Dr. Davies"), testified that his laboratory scientist, Dr. Shen Luk ("Dr. Luk"), drafted instructions to manufacture the precompression blend pursuant to Dr. Davies' instructions based on Actavis' ANDA. A laboratory technician made the precompression blends ("the 1.4 mg blend" and "the 5.7 mg blend"). (D.I. 202 at 190-196; PTX 316) Dr. Davies was not present for the manufacturing. Actavis criticizes the manufacturing process and the documentation for the blends.[40] Actavis alleges that the mixture for the 5.7 mg blend was mixed for longer than it should have been. (D.I. 202 at 218) Dr. Davies testified that this was a notation error and the technician inadvertently noted the stopwatch number instead of the minutes, as blend time would have been noted as minutes and seconds not as "XX."

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[37] Claim 1 of the '996 patent.

[38] Claim 2 of the '996 patent.

[39] Claim 1 of the '330 patent. Actavis does not separately contend that its products do not meet the "in contact with" limitation.

[40] Orexo points out that of the 166 paragraphs in Dr. Dyar's report, 6 focused on the manufacture. At trial, Dr. Dyar's entire opinion on infringement focused on the manufacture. (D.I. 204 at 452:10-23)

Dr. Davies also spoke with the technician to confirm the blend time used.[41] (PTX 154-56; JTX 31; D.I. 202 at 158-160; D.I. 194-196)

Actavis next argues that it is unclear whether the proper procedure was followed as to "the retains." (D.I. 203 at 370-372) Certain materials are passed through a 40 mesh stainless steel screen and collected in an appropriate vessel ("the screened ingredients"). Dr. Davies testified that screening is a common practice in the pharmaceutical industry and retains are usually added back into the screened ingredients.[42] (D.I. 202 at 161:18-162:11, 212-218) Lastly, Actavis pointed out that the steps in the batch record were misnumbered, resulting in a mismatch of steps requiring the addition of ingredients.[43] (D.I. 202 at 208-214; D.I. 203 at 373-374; PTX 155) Dr. Davies testified that the misnumbering occurred as a result of copying the Actavis form, which had additional steps not applicable to lab-scale processing. (D.I. 202 at 201:2-8; D.I. 203 at 259:23-261:5) Moreover, Dr. Davies testified that he reviewed these errors with the technician and Dr. Luk to verify that the process was done correctly. (D.I. 202 at 212-213)

There can be no real question that the documentation was not up to usual laboratory or commercial standards. Dr. Davies agreed that looking at just the documentation leads to the conclusion that the ANDA procedure was not followed, and

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[41] Dr. Davies also testified that even if it occurred, the increased blend time at this juncture before the mannitol is added is immaterial. (D.I. 202 at 160:21-161:13)

[42] Dr. Dyar testified that operators in the pharmaceutical industry would know from having previously performed a process what to do if retains were or were not present if no instruction was provided. (D.I. 204 at 468-470)

[43] For example, step 2 requires holding the screened ingredients for step 8, but step 8 requires adding different ingredients (not the screened ingredients) to the blend of step 7.

Dr. Dyar testified that if such errors were detected in the manufacturing documentation, the product would need to be remade. Dr. Dyar, however, also testified that if an investigation revealed that the proper process was followed after errors like these were detected, he would accept the manufactured product.[44] (D.I. 202 at 212:7-15; D.I. 203 at 382:12-20; D.I. 204 at 466:14-467:1) At bar, Dr. Davies testified that he conducted an investigation and determined that the correct process was followed. Testing showed that the final product contained all the ingredients. (D.I. 202 at 212-213)

Actavis also criticizes Dr. Davies' use of a lab-scale bin blender as opposed to the commercial scale V-blender used by Actavis, and points out that Dr. Davies did not conduct a validation test of the two blenders to assess any differences. The **Lemieux article**[45] states that "[i]ndustrial experience has shown that changing from a V-blender to a bin-blender cannot generally be done in a straightforward manner since such a change may have a significant impact on the powder blend uniformity. Indeed, the geometrical characteristics of tumbling blenders may lead to different granular mixing behaviors . . . ." (JTX 133 at 1783) The parties' experts interpreted this statement to refer to changing from one blender type at lab-scale to another type at industrial-scale. (D.I. 203 at 242:3-8, 378:9-24) The Lemieux article compared two lab-scale versions of industrial V- and conical bin-blenders, in part by analyzing the relative standard deviation ("RSD"), a well-known mixing criterion in the pharmaceutical industry. RSD curves for a particular sample "can be compared with the so-called RSD for a

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[44] This statement was made in response to questioning regarding multiple errors found in Actavis' manufacturing documentation.

[45] M. Lemieux, et al., *Comparative study of the mixing of free-flowing particles in a V-blender and a bin-blender*, 62 Chemical Engineering Science 1783 (2007).

completely random binary mixture in order to determine mixing time and blend uniformity." (JTX 133 at 1784, 1792-93, fig. 9(e)) The Lemieux article concluded that the mixing properties and performance of the lab-scale V-blender and bin-blender using industrial operating parameters were comparable. (*Id.* at abstract, 1800-01)

The **Malmqvist article**[46] sought to "evaluate the effect of scaling up on the time needed to deagglomerate a fine powder and form ordered mixtures with coarse carrier particles." (JTX 143 at 22) The Malmqvist article used dry mixes of smaller particles of riboflavin with larger sodium chloride and lactose carrier particles. A deagglomeration or sieve classification test was used to determine whether the mixing endpoint (the formation of an interactive mixture) had been reached. After the mixing endpoint was reached, tablets were produced, and a homogeneity test thereon was used to confirm "that the deagglomeration test had detected the endpoint in the mixing operations." The Malmqvist article concluded that the results of the homogeneity test of the tablets "indicate that mechanically stable mixtures have been formed." Moreover, "[t]he time needed to produce ordered mixtures is reduced as the batch size is increased." (JTX 143 at 28-29)

The Lemieux article provides support for Dr. Davies' conclusion that the use of a lab-scale bin-blender instead of a lab-scale V-blender does not render the precompression blend unrepresentative of Actavis' precompression blend. The issue at bar is one of scale, i.e., the substitution of a lab-scale blender for the industrial scale V-blender used by Actavis. Dr. Davies relied on the Malmqvist article to opine that

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[46] K. Malmqvist and C. Nystrom, *Studies on direct compression of tablets*, 21 Acta Pharm. Suec., 21 (1984).

because scaling up increases interactive forces, the lab-scale mixing process would have underestimated the interactive forces. (D.I. 202 at 151-156) Actavis' insistence that Orexo should have performed industrial size testing by either making the precompression blends in an industrial blender or validating the use of the lab-scale blender is unreasonable. Such experiments would entail considerable expense and logistical challenges.

Dr. Davies used scanning electron microscopy ("SEM") to demonstrate that the precompression blends were interactive mixtures.[47] (D.I. 143:8-11, 164-171; JTX 127; PTX 247-261, PTX 265-289, PTX 290-314) Dr. Davies also relied on his testing of the blend uniformity and Raman imaging.[48] (PTX 157-58, PTX 164-67, PTX 169-70, PTX 563, PTX 581) He concluded that the blend uniformity of the 5.7 mg blend is representative of Actavis' blends. The Raman imaging shows that the 1.4 and 5.7 mg blends are the same and that the 5.7 and 1.4 mg tablets are identical to the Actavis' tablets. (D.I. 202 at 160-162) Although the documentation for Dr. Davies' manufacture of the precompression blends contained numerous errors, his explanations were not wholly unreasonable. While not a perfect reproduction of Actavis' product, particularly given the scaling issue, the precompression blends are at least circumstantial evidence of infringement.

b. Actavis' documents

Dr. Sinko analyzed Actavis' documents and concluded that Actavis' blend uniformity tests over time show the existence of interactive forces. He opined that the

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[47] As Actavis does not dispute this conclusion, the court will not elaborate thereon.

[48] Actavis' criticisms of these methods to show the presence of an interactive mixture are addressed below.

different particle sizes and free flowing blend would need interactive forces to remain uniform over time, otherwise segregation of the particles would occur. (D.I. 203 at 287-88; JTX 28, JTX 106; D.I. 212 at 26-28) On cross-examination, Dr. Sinko conceded that mixtures with "large particles like carrier particles and smaller particles" do not "necessarily" exhibit interactive forces. (D.I. 203 at 322:14-17) Dr. Davies explained that mixing particles of very different particle sizes (like those present in Actavis' blend) can cause problems with content uniformity. He concluded that the content uniformity of Actavis' mixtures is due to the presence of an interactive mixture. (D.I. 203 at 258-59) On cross-examination, Dr. Davies maintained his position regarding mixtures with different sized particles, but agreed that "for particles which are . . . the same particle size," it was "possible to have a random mixture, not an interactive mixture, but still have good content uniformity." (D.I. 203 at 246-247) Dr. Davies also maintained that the Malmqvist article used blend uniformity to indicate the presence of ordered mixing. (D.I. 203 at 249:2-251:16) Dr. Dyar opined briefly that blend uniformity "measur[ed] the uniformity of the blend prior to it being compressed" and "tells you if you have a well-mixed material." He stated that "[w]hether it's interactive mixture or a random mixture, you cannot determine from content uniformity or blend uniformity alone." (D.I. 203 at 379:25-380:15)

Actavis argues that the above testimony[49] demonstrates that blend uniformity does not show that Actavis' ANDA products contain an interactive mixture. The court

[49] The court does not find particularly helpful the snippet of testimony from Dr. Bret Berner (and Dr. Sinko's interpretation thereof):

> In order to function as a carrier particle, it has to hang on to the carrier particle. If it's falling apart, it's no longer functioning as a carrier particle. . .

disagrees. In context, the Malmqvist article suggests that blend uniformity may indicate the presence of an interactive mixture. Orexo's experts have adequately supported their opinion that blend uniformity (not in isolation) may provide information as to whether an interactive mixture exists.

c. Testing of Actavis' tablets

Dr. Davies performed Raman imaging on Actavis' tablets and concluded that the consistent special positioning of the particles was due to interactive forces.[50] Dr. Sinko agreed with this opinion. (D.I. 202 at 143-145; 185; D.I. 203 at 285:14-17; PTX 149-150, PTX 564) Actavis avers that such testing is not indicative of the existence of an interactive mixture. Actavis points to Dr. Dyar's testimony that "[t]he blend is the best place to look at. The compressed tablets . . . will have content uniformity if you have a good blend, and it's extremely difficult to be able to tell if you had an interactive mixture just based upon looking at the tablet." Dr. Dyar also stated that "[t]he only real way that you can tell if there's an interactive mixture formed is by looking at the blend itself and seeing if the particles are attached to the carrier particles." (D.I. 203 at 383:8-18; 369:11-16)

Actavis represents that it "argued [during discovery] that the only samples it should have to produce are samples of the final product" because it "did not have any of the precompressed blend to produce." However, Actavis represented to the court that it did not have intermediates to produce and the intermediates (which would include the

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. To make that tablet, the mix has to stay together and remain uniform. And if it falls apart, you get segregation and not uniformity.

(D.I. 203 at 265:21-266:3; D.I. 203 at 287:2-6)

[50] Details are redacted.

precompression blend) were "irrelevant" as "it is Actavis' ANDA product that is accused of infringement in this case, not its 'intermediates.'" (D.I. 119 at 3) The court did not compel the production of the intermediates as they were not available. (D.I. 126; D.I. 148) Such non-production shaped Orexo's case, making it incongruous for Actavis to now argue that analysis of the final tablets cannot provide **any** evidence of the presence of an interactive mixture.

d. Characteristics of ingredients and manufacturing

Dr. Sinko offered a brief opinion that the characteristics of Actavis' manufacturing process would result in an interactive mixture. He compared Actavis' process, key ingredients, particle sizes, and resulting products to the examples of the '330 patent. (D.I. 203 at 292-295) On cross-examination, Dr. Sinko conceded that "large particles like carrier particles and smaller particles" do not "necessarily" exhibit interactive forces. (D.I. 203 at 322:14-17) Dr. Sinko acknowledged that the mixing times in the examples of the '330 patent were much longer (7 hours and 40 hours). (D.I. 203 at 318-319)

Actavis argues that this testimony has no value and points to a statement by Dr. Dyar made while discussing blend uniformity.[51] (D.I. 203 at 380:16-22) Actavis concludes that there "is simply no comparison" and the processes "are different." (D.I. 212 at 31-32) Although Dr. Sinko's testimony is brief, Actavis cannot (other than through attorney argument) refute his opinion, therefore, such opinion should be afforded some weight.

3. Conclusion

[51] Which statement is redacted.

Dr. Davies manufactured a representative precompression blend on a lab-scale following Actavis' ANDA protocol, which was determined to be an interactive mixture. Orexo's experts attributed the blend uniformity of Actavis' precompression blend documented in its records and the consistent special positioning of particles in Actavis' tablets to interactive forces. Dr. Sinko testified that Actavis' manufacturing process would yield an interactive mixture. Despite Actavis' criticisms of such opinions, for the reasons articulated above, the court finds that Orexo has proven, by a preponderance of the evidence, that Actavis' tablets infringe the asserted claims.

III. CONCLUSION

For the foregoing reasons, the court finds that the asserted claims of the '996 patent are not invalid as obvious; the asserted claims of the '330 patent are invalid as obvious; and Actavis infringes the asserted claims of the '996 patent. An appropriate order shall issue.