IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIODELIVERY SCIENCES INTERNATIONAL, INC. and ARIUS TWO, INC., Plaintiffs, v. ALVOGEN PB RESEARCH & DEVELOPMENT LLC, ALVOGEN MALTA OPERATIONS LTD., ALVOGEN PINE BROOK LLC, ALVOGEN, INC., and ALVOGEN GROUP, INC., Defendants.	Civil Action No. 18-1395-CFC

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OPINION

December 20, 2021
Wilmington, Delaware

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COLM F. CONNOLLY
CHIEF JUDGE

Plaintiffs BioDelivery Sciences International, Inc and Arius Two, Inc. (collectively BDSI) have sued Defendants Alvogen PB Research & Development LLC, Alvogen Malta Operations Ltd., Alvogen Pine Brook LLC, Alvogen, Inc., and Alvogen Group, Inc. (collectively Alvogen) under the Drug Price Competition and Patent Term Restoration Act—commonly called the Hatch-Waxman Act. BDSI alleges that Alvogen's submission to the Food and Drug Administration (FDA) of an Abbreviated New Drug Application (ANDA) for approval to market a generic version of BDSI's Belbuca® drug product constitutes infringement of U.S. Patents Nos. 8,147,866 (the #866 patent, JTX-001), 9,655,843 (#843 patent, JTX-002), and 9,901,539 (the #539 patent, JTX-003) pursuant to 35 U.S.C. § 271(e)(2)(A).

BDSI assert claims 3, 4, 5, and 10 of the #866 patent; claims 8, 9, and 20 of the #843 patent; and claims 9 and 20 of the #539 patent. Alvogen stipulated to infringement of the asserted claims but argues that all asserted claims are invalid. Alvogen contends (1) that all of the asserted claims are invalid for obviousness under 35 U.S.C. § 103 and (2) that claims 3, 4, 5, and 10 of the #866 patent and claims 8 and 20 of the #843 patent are invalid for anticipation under § 102.

I held a three-day bench trial, and, as required by Federal Rule of Civil Procedure 52(a)(1), I have set forth separately below my findings of fact and conclusions of law.

I. THE STATUTORY AND REGULATORY FRAMEWORK

The ANDA procedures out of which this case arise were established by FDA regulations promulgated pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 et seq., and specifically by the so-called Hatch-Waxman Amendments to the FDCA. Justice Kagan provided in *Caraco Pharmaceutical Laboratories, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399 (2012), this helpful summary of the provisions of the Amendments and the FDA regulations that bear on this case:

> The FDA regulates the manufacture, sale, and labeling of prescription drugs under a complex statutory scheme. To begin at the beginning: When a brand manufacturer wishes to market a novel drug, it must submit a new drug application (NDA) to the FDA for approval. The NDA must include, among other things, a statement of the drug's components, scientific data showing that the drug is safe and effective, and proposed labeling describing the uses for which the drug may be marketed. The FDA may approve a brand-name drug for multiple methods of use—either to treat different conditions or to treat the same condition in different ways.
>
> Once the FDA has approved a brand manufacturer's drug, another company may seek permission to market a generic version pursuant to legislation known as the Hatch–Waxman Amendments. Those amendments allow a generic competitor to file an abbreviated new drug

application (ANDA) piggy-backing on the brand's NDA. Rather than providing independent evidence of safety and efficacy, the typical ANDA shows that the generic drug has the same active ingredients as, and is biologically equivalent to, the brand-name drug. As we have previously recognized, this process is designed to speed the introduction of low-cost generic drugs to market.

Because the FDA cannot authorize a generic drug that would infringe a patent, the timing of an ANDA's approval depends on the scope and duration of the patents covering the brand-name drug. Those patents come in different varieties. One type protects the drug compound itself. Another kind . . . gives the brand manufacturer exclusive rights over a particular method of using the drug. In some circumstances, a brand manufacturer may hold such a method-of-use patent even after its patent on the drug compound has expired.

To facilitate the approval of generic drugs as soon as patents allow, the Hatch–Waxman Amendments and FDA regulations direct brand manufacturers to file information about their patents. The statute mandates that a brand submit in its NDA the patent number and the expiration date of any patent which claims the drug for which the brand submitted the NDA or which claims a method of using such drug. And the regulations issued under that statute require that, once an NDA is approved, the brand provide a description of any method-of-use patent it holds. That description is known as a use code, and the brand submits it on FDA Form 3542. . . . [T]he FDA does not attempt to verify the accuracy of the use codes that brand manufacturers supply. It simply publishes the codes, along with the corresponding patent numbers and expiration dates, in a fat, brightly hued volume called the Orange Book (less colorfully but more officially denominated Approved Drug Products With Therapeutic Equivalence Evaluations).

After consulting the Orange Book, a company filing an ANDA must assure the FDA that its proposed generic drug will not infringe the brand's patents. When no patents are listed in the Orange Book or all listed patents have expired (or will expire prior to the ANDA's approval), the generic manufacturer simply certifies to that effect. Otherwise, the applicant has two possible ways to obtain approval.

One option is to submit a so-called section viii statement, which asserts that the generic manufacturer will market the drug for one or more methods of use not covered by the brand's patents. A section viii statement is typically used when the brand's patent on the drug compound has expired and the brand holds patents on only some approved methods of using the drug. If the ANDA applicant follows this route, it will propose labeling for the generic drug that "carves out" from the brand's approved label the still-patented methods of use. The FDA may approve such a modified label as an exception to the usual rule that a generic drug must bear the same label as the brand-name product. FDA acceptance of the carve-out label allows the generic company to place its drug on the market (assuming the ANDA meets other requirements), but only for a subset of approved uses—*i.e.*, those not covered by the brand's patents.

* * * *

The generic manufacturer's second option is to file a so-called paragraph IV certification, which states that a listed patent "is invalid or will not be infringed by the manufacture, use, or sale of the generic drug." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). A generic manufacturer will typically take this path in either of two situations: if it wants to market the drug for all uses, rather than carving out those still allegedly under patent; or if it discovers, as described above, that any carve-out label it is willing to adopt cannot avoid the brand's use code. Filing a paragraph IV certification means provoking litigation. The patent statute treats such a filing as itself an act of

> infringement, which gives the brand an immediate right to sue [under] 35 U.S.C. § 271(e)(2)(A). Assuming the brand does so, the FDA generally may not approve the ANDA until 30 months pass or the court finds the patent invalid or not infringed. Accordingly, the paragraph IV process is likely to keep the generic drug off the market for a lengthy period, but may eventually enable the generic company to market its drug for all approved uses.

566 U.S. at 404–08 (irrelevant citations and internal quotation marks omitted).

II. BACKGROUND

Belbuca® is a bioerodable mucoadhesive (BEMA) film for transmucosal delivery of the opioid buprenorphine and is indicated for the treatment of pain. Tr. 91:13; JTX-233 at 23. Belbuca® is a dissolvable film placed on the inside of the patient's check. As the film dissolves, buprenorphine flows into the mucosa, where the drug enters the bloodstream and spreads throughout the body. Belbuca® is applied to the patient's buccal surface, i.e., the inside of the cheek. The film has two layers: (1) a mucoadhesive layer that contains the drug and that adheres to the user's buccal surface and (2) a backing layer that prevents the drug from dissolving into the oral cavity and, thus, from being swallowed. Tr. 593:16–25; JTX-233 at 23. The backing layer creates a unidirectional gradient so that buprenorphine moves from the mucoadhesive layer into the mucosa, the soft tissue that lines the inside of the mouth, where the drug is further absorbed into the bloodstream. Tr. 139:11–14, 586:24–587:19.

BDSI is the assignee of the asserted patents and lists them in connection with Belbuca® in the Orange Book. BDSI also lists U.S. Patent No. 7,579,019 (the #019 patent) in the Orange Book. The #019 patent expired on January 22, 2020. Alvogen filed an ANDA seeking FDA approval for a generic version of Belbuca® after expiration of the #019 patent but before expiration of the asserted patents. Alvogen's ANDA contains a paragraph IV certification alleging that the asserted patents are invalid. *See* 21 U.S.C. § 355 (j)(2)(A)(vii)(IV). In response to that certification, BDSI brought this litigation.

The #866 and #843 patents, both of which are titled "Transmucosal Delivery Devices with Enhanced Uptake," were issued on April 3, 2012 and May 23, 2017 respectively. The #843 is a continuation of the #866 patent and claims the same priority date. The parties dispute what priority date the patents are eligible to claim, but the earliest possible priority date is July 21, 2006. D.I. 229, Ex. 1 ¶¶ 21, 28. The patents teach two-layer bioerodable mucoadhesive buprenorphine delivery devices and methods for administering buprenorphine with those same devices.

The #539 patent, titled "Transmucosal Drug Delivery Devices for Use in Chronic Pain Relief," was issued on February 27, 2018 and claims a priority data of December 21, 2011. JTX-003. The #539 patent discloses the results of a Belbuca® clinical trial and teaches the treatment of chronic pain using a BEMA

device where the backing layer is buffered to a pH of between about 4.0 and about 4.8.

III. LEGAL STANDARDS

A. Obviousness

Under § 103 of the Patent Act,[1] 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 to which said subject matter pertains." 35 U.S.C. § 103 (2006). As the Supreme Court explained in the seminal case *Graham v. John Deere Co.*, 383 U.S. 1 (1966), under § 103, "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." *Id.* at 14. Section 103 ensures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). "Were it otherwise

[1] Congress amended the Patent Act in 2011 when it enacted the Leahy-Smith America Invents Act (AIA). *See* Pub. L. No. 112-29, 125 Stat. 284, 296 (2011). Pre-AIA versions of § 102 and § 103 apply to all patents with an effective filing date before March 16, 2013. *See* § 3(n) 125 Stat. at 293. All three of the patents at issue have effective filing dates earlier than 2013. I will, therefore, cite only to the pre-AIA Act.

patents might stifle, rather than promote, the progress of useful arts." *Id.* (citing U.S. Const. art. I, § 8, cl. 8).

The Court reaffirmed in *KSR* that the "framework" set out in the following paragraph from *Graham* governs the application of § 103, *id.* at 406:

> While the ultimate question of patent validity is one of law, the [§] 103 condition [of patentability] . . . lends itself to several basic 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. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham, 383 U.S. at 14–15 (citations omitted).

It is clear that under this framework, a district court must consider in an obviousness inquiry the three primary factors identified by the Court in *Graham*: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the pertinent art. Less clear is the role, if any, secondary considerations should play in the analysis.

The logical—some would say necessary—implication of the Court's use of the word "secondary" in *Graham* and its holding that the secondary considerations "might be utilized" and "may have relevancy" is that a district court is permitted—

but not required in all cases—to examine such considerations in evaluating an obviousness-based invalidity challenge. The Court seemed to confirm as much in *KSR*, when it noted that "*Graham* set forth a broad inquiry and *invited* courts, where appropriate, to look at any secondary considerations that would prove instructive." *KSR*, 550 U.S. at 415 (emphasis added).

But a district court ignores *Graham*'s "invitation" to examine secondary considerations at its peril. One legal scholar, Harmon, has observed that under Federal Circuit law "[w]e are able now safely to strike the 'may' in the . . . sentence" in *Graham* in which the Court stated that secondary "indicia of obviousness and nonobviousness . . . may have relevancy." Robert Harmon, Cynthia Homan, & Laura Lydigsen, *Patents and the Federal Circuit* 245 (13th ed. 2017). Harmon correctly notes that "[t]he Federal Circuit has emphatically and repeatedly held that objective evidence of non-obviousness must be taken into account always and not just when the decisionmaker is in doubt." *Id.* In *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983), for example, the Federal Circuit held that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Id.* at 1538. And in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), the Federal Circuit reaffirmed that holding, *id.* at 1079, and went on to

say that the Supreme Court in *Graham* "did not relegate . . . to 'secondary status'" the "objective factors" the Supreme Court had explicitly identified in *Graham* as "secondary considerations," *id.* at 1078.

It is true that less than a month after *In re Cyclobenzaprine*, a different Federal Circuit panel held in *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012), that because it found that the defendants had "failed to prove that [the challenged patent claim] would have been *prima facie* obvious over the asserted prior art," it "need not address" the "objective evidence" of commercial success, long-felt need, and the failure of others. *Id.* at 1296. But the safer course for a district court faced with an obviousness challenge is to treat *Graham*'s invitation to look at secondary considerations like a subpoena.

Obviousness is assessed based on the perspective of an artisan of ordinary skill at the time of the invention. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). The court therefore needs to guard against "hindsight bias" that infers from the inventor's success in making the patented invention that the invention was obvious. *In re Cyclobenzaprine*, 676 F.3d at 1079. The ultimate question in the obviousness analysis is "whether there was an apparent reason [for an artisan of ordinary skill] to combine [at the time of the invention] the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. "The analysis is objective." *Id.* at 406. Thus, a court must determine whether an

artisan of ordinary skill "would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success [in] doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069.

The party challenging the patent's validity bears the burden of proving obviousness by clear and convincing evidence. *Id.* at 1068–69. In weighing the *Graham* factors to decide whether the party has met that burden, the district court must be guided by common sense. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010). Indeed, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." *Id.* at 1239. In *KSR*, the Supreme Court warned lower courts to avoid "[r]igid preventative rules that deny factfinders recourse to common sense" and to employ instead "an expansive and flexible approach" under the *Graham* framework. *KSR*, 550 U.S. at 415, 421. Thus, the district court may "reorder[ ] in any particular case" the "sequence" in which it considers the *Graham* factors. *Id.* at 407. And although a court should consider carefully the published prior art, "[t]he obviousness analysis cannot be confined by . . . overemphasis on the importance of published articles and the explicit content of issued patents." *Id.* at 419.

"[A]ny need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. And "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[T]he fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* at 421. But a combination is obvious to try only "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" in the prior art at the time of the invention. *Id.* And the court must also be mindful that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 416.

B. Anticipation

An asserted patent claim is invalid under § 102 of the Patent Act as anticipated if the accused infringer presents clear and convincing evidence that a single prior art reference disclosed, either expressly or inherently, each limitation of the claim. *Brassica Protection Prods. LLC v. Sunrise Farms (In re Cruciferous Sprout Litig.)*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). .

IV. ANALYSIS

Alvogen contends that all the asserted claims are invalid as obvious and that some of the asserted claims of the #866 and #843 patents are anticipated.

A. Obviousness

Alvogen advances distinct theories for the obviousness of the #866 and #843 patents and for the obviousness of the #539 patent. Alvogen argues that claims 3 and 10 of the #866 patent and claims 8, 9, and 20 of the #843 patent are invalid because it would have been obvious to utilize buprenorphine in a two-layer mucoadhesive device for transmucosal delivery of drugs and because it would have been obvious to buffer the mucoadhesive layer to the claimed pH range since that range is optimal for delivering buprenorphine. D.I. 258 at 28. Alvogen additionally argues that claims 4 and 5 of the #866 patent are invalid because, except for obvious pharmacokinetic properties, they are broader than asserted claim 3. D.I. 248 at 38–40.

For the #539 patent, Alvogen argues that claim 9 is invalid for obviousness because the claimed pH range for the backing layer is inherently disclosed in the prior art. D.I. 258 at 43–45. Alvogen argues that claim 20 is obvious because, in addition to buffering the backing layer, the only other previously undisclosed limitations are obvious pharmacological properties. D.I. 258 at 46–50.

1. Definition of the Artisan of Ordinary Skill in the Art

The parties offer different definitions of an artisan of ordinary skill in the art), but BDSI agrees that my choice of definition does not make a difference in this case. Tr. 722:1–4; D.I. 260 ¶ DFF 5. Therefore, I adopt Alvogen's proposed definition, and find that an artisan of ordinary skill would have a bachelor's degree in pharmaceutical sciences, chemistry or related field, plus three to five years of relevant experience in developing transmucosal dosage forms. Alternatively, an artisan of ordinary skill would have a Ph.D. in pharmaceutical sciences, chemistry, or a related field and slightly less practical experience. Tr. 87:5–21.

2. Obviousness of the #866 and #843 Patents

a. Findings of Fact

1) Relevant Chemical and Pharmacological Concepts

When formulating a drug, relevant properties of the active ingredient include solubility (the ability of the molecule to dissolve) and absorption (the tendency of the drug to be absorbed into the body). Uptake is another term for the absorption of a drug from a device into the body. Tr. 175:1–2. Buprenorphine has low solubility and high uptake. Tr. 700:22–25.

The chemical properties of some compounds, including Buprenorphine, are sensitive to pH. pH is a measure of acidity and basicity: the lower the pH of a

solution the more acidic the solution is and the higher the pH of a solution the more basic it is. The pH of pure water is 7, and thus that pH is deemed neutral. Lemon juice is acidic with a pH around 2, and bleach is basic with a pH around 13. Tr. 146:18–147:6. Buffers are solutions that resist pH change upon the addition of acids and bases. Buffers are created with buffering agents, which are pairs of a weak acid or base and its corresponding conjugate base or acid, for example citric acid and sodium citrate. Tr. 153:5-8l; Tr. 694:18–20.

The pH of the surrounding environment influences the electrical charge of buprenorphine. At acidic pHs, below roughly 6.5, nearly 100% of buprenorphine is positively charged. Tr. 12:12–14. An artisan of ordinary skill can easily calculate the portion of a compound that is in a particular ionization state at a given pH using a formula called the Henderson-Hasselbach equation. Tr. 163:18–164:4, 795:22–796:12.

The electrical charge of a drug impacts the solubility of the active ingredient. Molecules generally dissolve more easily in either aqueous solutions or solutions of oils and fats, which chemical artisans call lipids. Molecules that are soluble in lipids are deemed lipophilic, whereas molecules that dissolve in aqueous solutions are hydrophilic. Lipophilicity can be characterized by measuring a compound's partition coefficient; a higher partition coefficient indicates greater lipophilicity. Tr. 791:2–7, 792:13–18, 793:16–794:25. Neutrally charged molecules are

typically lipophilic. Tr. 731:1–7. However, these trends are not universal; the chemical properties of a molecule are determined by the totality of its structure. Crucially, buprenorphine is lipophilic even when ionized. Tr. 98:8–10; DTX-165 at 5.

Whether an active ingredient is ionized also effects how well the drug is absorbed into the body. The body's cells are surrounded by a membrane consisting of a phospholipid bilayer. Lipophilic molecules pass through this bilayer more easily than hydrophilic molecules, and thus lipophilicity is associated with higher absorption. As a result, the neutrally charged form of a compound is usually more readily absorbed into the body than a charged form of the compound. Tr. 782:12–784:4. This trend is called the pH partition theory or pH partition hypothesis. Tr. 795:1–9.

When a drug is absorbed, not all of the drug actually reaches the target tissue. The fraction of the active ingredient that reaches the target tissue intact is the bioavailability of the drug formulation. For buprenorphine, bioavailability is measured based on the portion of the opioid that reaches the blood plasma. When a drug is delivered orally, such as with a pill or a tablet, it goes through first-pass metabolism before reaching the bloodstream. In first-pass metabolism, drugs are processed by the liver where they are broken down into non-therapeutically active

metabolites. Tr. 93:21–94:9. First-pass metabolism and low absorption can both lead to a low bioavailability.

Several of the asserted claims include pharmacokinetic properties. Pharmacokinetics is, roughly speaking, the study of how drugs are absorbed and processed by the body. Tr. 322:5–10. Pharmacokinetic properties depend on the drug, device, and dose of the drug. Tr. 325:17–19. The properties at issue in this case are the time it takes from administration for the drug to have a measurable concentration in the blood (T_{first}), Tr. 327:13–19, the length of time a clinically effective plasma concentration is maintained, and the maximum blood plasma concentration of a drug following administration (C_{max}), Tr. 325:9–15. The steady state C_{max} is the C_{max} that is consistently obtained after multiple administrations of a drug. Tr. 327:4–7.

2) Content of the Asserted Claims

The asserted claims of the #866 and #843 patents are directed to devices for administering buprenorphine and methods using those same devices. Claim 10 (which depends from claim 8) of the #866 patent claims a "mucoadhesive bioerodable drug delivery device suitable for direct transmucosal administration of buprenorphine to a subject" comprising four elements: (1) "a bioerodable mucoadhesive layer comprising an effective amount of buprenorphine disposed in a polymeric diffusion environment," (2) "wherein the polymeric diffusion

environment is a buffered environment," (3) in which "the pH of the polymeric diffusion environment is between about 4.5 and about 5," and (4) "a barrier layer comprising a polymeric barrier environment disposed adjacent to the mucoadhesive layer to provide a unidirectional gradient upon application to a mucosal surface for the rapid and efficient delivery of buprenorphine." Claim 3 (which depends from claim 1) covers a "method for providing enhanced uptake of buprenorphine to a subject by direct transmucosal delivery of buprenorphine" where buprenorphine is administered to a subject by applying the device claimed in claim 10 "to an oral mucosal surface of the subject" where "the unidirectional gradient delivers buprenorphine across the buffered polymeric diffusion environment upon application to the mucosal surface." Claims 4 and 5 (which also depend from claim 1) cover the same method as claim 3 except that they add certain pharmacokinetic properties as limitations and they allow the polymeric diffusion environment to be buffered to a pH between about 4 and about 6. Specifically, claim 4 requires "a first quantifiable plasma concentration of buprenorphine is observed at about 45 minutes" and claim 5 requires "an effective plasma concentration of buprenorphine is maintained for at least 4 hours."

The asserted claims of the #843 patent cover methods and devices "for delivering buprenorphine to humans." #843 patent claims 1 (27:9), 13 (27:54). Claim 20 (which depends from claim 13) covers a device that comprises (1) "a

bioerodible mucoadhesive layer comprising buprenorphine disposed in a polymeric diffusion environment" (2) "wherein the polymeric diffusion environment has a pH buffered to between about 4 to about 6" and (3) "a polymeric barrier environment disposed adjacent to the mucoadhesive layer, and wherein a unidirectional diffusion gradient of buprenorphine is provided upon application to a buccal surface of a human." Claims 8 and 9 (which depend ultimately from claim 1) cover administering the device claimed in claim 20 with some variations in the claimed pH range and additional limitations. Claim 8 requires that the polymeric diffusion environment is buffered to a pH between about 4 and about 6. Claim 9 requires that the polymeric diffusion environment is buffered to a pH between about 4 and about 7.5 and further requires that the polymeric diffusion environment comprises at least one film-forming water-erodible adhesive polymer and at least one bioadhesive polymer.

3) Content of the Prior Art

Alvogen identified in their briefing nine prior art references relevant to the obviousness of the #866 and #843 patents.

a) Tapolsky (DTX-173)

Tapolsky is the application that became the #019 patent. DTX-173. It teaches a two-layer device for delivering a pharmaceutical to the mucosal surface. DTX-173 at abstract. The two layers are an adhesive layer that attaches to the

mucosal surface and a backing layer. Tr. 106:20–107:3; DTX-173 ¶ 30. Tapolsky also suggests using a third layer to create a unidirectional gradient to force the drug towards the mucosa. Tr. 109:15–21; DTX-173 ¶ 60.

Tapolsky does not use the term BEMA, but Dr. Michniak-Kohn, Alvogen's expert on transmucosal drug delivery, explained at trial that Belbuca® is built on the platform technology disclosed in Tapolsky. Tr. 117:6–20. Tapolsky teaches making an adhesive layer with a water erodible polymer, such as hydroxyethyl cellulose or hydroxypropyl cellulose, and a bioadhesive polymer, such as sodium carboxymethyl cellulose. Tr. 107:22–108:18; DTX-173 ¶¶ 31–32. The backing layer is made with a water erodible, film-forming polymer such as hydroxyethyl cellulose or hydroxypropyl cellulose. Tr. 109:7–11; DTX-173 ¶ 35.

Tapolsky teaches that butorphanol, an opioid, may be used with the disclosed device. Tr. 684:12–18; DTX-173 ¶ 53. Tapolsky does not use the words "polymeric diffusion environment" or teach buffering the layers of the device to a particular pH. Tr. 262:3–6.

Tapolsky disclosed experimental pharmacokinetic results for experiments in dogs using testosterone and albuterol sulfate as the chemicals of interest. Tr. 346:4–14; DTX-173 ¶ 128. Tapolsky reported measurable albuterol sulfate levels for over four hours. Tr. 346:4–14; DTX-173 ¶ 139, Table 5. Tapolsky does not

provide any human pharmacokinetic data or any pharmacokinetic data for buprenorphine. Tr. 262:15–18.

b) Moro (DTX-178)

Moro is a patent application titled "Mucoadhesive Erodable Drug Delivery Device for Controlled Administration of Pharmaceuticals and Other Active Compounds." DTX-178. It was published in March 2003. DTX-178 at 1. Moro discloses a multilayer, bioerodable mucosal drug-delivery device with a water-soluble adhesive layer and a non-adhesive bioerodaible backing layer. Tr. 118:14–119:17; DTX-178 at abstract, ¶ 35. Moro explains that a pharmaceutical can be placed in either or both layers. Tr. 118:18–19; DTX-178 at abstract. Moro suggests hydroxyethyl cellulose and hydroxypropyl cellulose as water soluble polymers and sodium carboxymethyl cellulose as a bioadhesive polymer. Tr. 119:2–17; DTX-178 ¶¶ 41, 43. Thus, Moro discloses a bioerdable drug delivery device that is very similar to the Tapolsky device and to the device claimed in the asserted patents. Tr. 118:16–22. Moro lists numerous active ingredients that could be used with this device, including buprenorphine. Tr. 118:8–11; DTX-178 ¶¶ 48, 64.

c) Johnson (DTX-165)

Johnson is a 2005 review article by Rolley E. Johnson, Paul J. Fudala, and Richard Payne titled "Buprenorphine: Considerations for Pain Management."

DTX-165. Johnson reviews what artisans of ordinary skill knew about buprenorphine at the time of publication. Tr. 96:13–98:1; DTX-165 at 1. Buprenorphine was recognized as an extremely lipophilic compound. Tr. 98:8–12; DTX-165 at 5. Johnson also explains that sublingual delivery avoids first-pass metabolism. DTX-165 at 2.

d) Cassidy (JTX-248)

Cassidy is a 1993 article by J.P. Cassidy, N.M. Landzert and E. Quandros, titled "Controlled Buccal Delivery of Buprenorphine." JTX-248. Cassidy teaches that buccal drug delivery devices avoid first-pass metabolism. Tr 95:10–13; JTX-248 at 1. Cassidy further teaches that the solubility of buprenorphine varies with pH. Tr. 147:17–23. Figure 1 of Cassidy shows that the solubility of buprenorphine hydrochloride increases as pH decreases, with the maximum reported solubility between a pH of about 4 and 5. Tr. 150:12–18; JTX-248 at 4, Fig. 1. The solubility of buprenorphine in all measurements at a pH lower than five was considerably greater than the solubility of buprenorphine in all measurements at a pH greater than five. JTX-248 at Fig. 1. Cassidy reports a slightly reduced solubility in the physiological TPS buffer at a pH of 4.2 relative to a phosphate buffer at the same pH. JTX-248 at 4. The measured solubility of buprenorphine in the TPS buffer at a pH of 4.2 was similar to the measured solubility in the TPS buffer solutions at other pH values less than five. JTX-248 at Fig. 1. To the extent

this data point is an outlier it may be explained because the TPS buffer has a lower buffering capacity at this pH. Tr. 149:24–150:9.

e) Bullingham I (DTX-077)

Bullingham I is the 1981 academic publication "Sublingual Buprenorphine Used Postoperatively: Clinical Observations and Preliminary Pharmacokinetic Analysis" by R.E.S. Bullingham et al. DTX-077. Bullingham I investigated the pharmacokinetics of buprenorphine administered via sublingual tablets. Tr. 91:5–19; DTX-077 at 2. Subjects received buprenorphine sublingually only after receiving buprenorphine intravenously earlier in the day. Tr. 404:23–404:22; DTX-077 at 2. Bullingham attempted to account for the intravenous buprenorphine by reducing the measured buprenorphine amounts based on prior research about the pharmacokinetics of buprenorphine when delivered intravenously. Tr. 812:14–814:4; DTX-077 at 3. Bullingham I states that "the suitability of [buprenorphine] for [sublingual administration] is suggested by its high lipophilicity, high first pass effect, long duration of action and low addition potential." DTX-077 at 1; *see also* Tr. 91:16–19.

f) Suboxone® Tablets

The FDA approved Suboxone® sublingual tablets with buprenorphine as the active ingredient in 2002. Tr. 480:12–17; JTX-471 at 3, Fig. 1. Suboxone® is indicated for the treatment of opioid dependence. DTX-172 at 7.

The parties debate the pH of Suboxone®. Among its inactive ingredients, Suboxone® includes citric acid and sodium citrate. Tr. 694:12–23; DTX-172 at 2. Citric acid and sodium citrate can be used to buffer a solution to a pH between four and six. Tr. 174:19–11, 671:16–23, 733:20–23, 804:23–805:2. In 2011, Dr. Finn, an inventor of the asserted patents, told the Patent Office that the pH of Suboxone was "N/A." Tr. 697:24–5; JTX-365 at 4. Later in 2014, Dr. Reitman, a pharmaceutical formulations expert, reported to the Patent Trial and Appeal Board on behalf of BDSI, which was the petitioner an inter partes review proceeding involving Suboxone®, that when a Suboxone® tablet was dissolved in either 1.5 or 3.0 mL of deionized water the resulting pH was 3.5. Tr. 163:20–162:3; DTX-365 ¶ 5. Dr. Michniak Kohn testified that the only source for a pH of Suboxone® was the Reitman declaration. Tr. 154:11–155:3.

g) Weinberg (JTX-249)

Weinberg, an article published in 1988 with the title "Sublingual Absorption of Selected Opioid Analgesics" teaches that buprenorphine has a higher partition coefficient than other common opioids. Tr. 137:20–138:13; JTX-249 at 2, Table 1. Weinberg also teaches that buprenorphine is well-absorbed even when ionized and that its lipophilicity at more basic pHs could not be measured because of poor solubility at those pHs. Tr. 170:14–171:2; JTX-249 at 6.

h) Birch (DTX-203)

Birch is a patent application published in 2005 that teaches aqueous buprenorphine solutions buffered to a pH between 3 and 4.8. Tr. 171:24–172:5; DTX-203 ¶ 71. These solutions were designed for intranasal delivery. Tr. 171:17-21; DTX-203 at abstract.

i) Todd (DTX-174)

Todd is a European patent application published in 1983. It teaches an aqueous buprenorphine solution for sublingual administration. Tr. 173:20–23; DTX-174 at abstract. Todd discloses a pharmaceutical solution with buprenorphine dissolved in 20 to 30 percent ethanol and buffered to a pH between 4.5 and 5.5. Tr. 173:20–23; DTX-174 at 3. This formulation was designed to overcome buprenorphine's inadequate solubility in higher pH solutions. Tr. 653:4–16; DTX-174 at 3. Todd also disclosed that uptake was higher when the buprenorphine solution was buffered to a pH of 5 or 6 compared to 4. DTX-174 at 3. Todd reported that preparing a stable solution with an adequate buprenorphine concentration was "very difficult." Tr. 653:1–9; DTX-174 at 3.

4) Mechanism of Action for the Tapolsky Device

Delivery of buprenorphine using the Tapolsky device requires both the dissolution of buprenorphine and the penetration of the drug into the mucosa. When the claimed drug delivery device is placed into the mouth it is a solid. Tr.

701:11–12. The mucoadhesive layer absorbs moisture from the mucosa, allowing the device to adhere to the mucosal surface. Tr. 132:3–13. To be absorbed into the mucosa, the buprenorphine must dissolve so it is no longer trapped in the mucoadhesive layer's initially solid polymeric environment and is able to pass through cellular membranes into the body. Tr. 132:3–13. Dr. Williams, BDSI's expert on pharmaceutical formulations, agreed that when the claimed invention is placed against the cheek saliva penetrates the mucoadhesive layer, creating a microenvironment in which the molecules of buprenorphine gradually dissolve. Tr. 701:13–702:5.

Because of the backing layer, once the buprenorphine dissolves it largely flows into the cheek's mucosal tissue. Tr. 587:12–18. Dr. Williams testified that an artisan of ordinary skill would have understood that the barrier layer in the asserted patents "stops or slows the diffusion of the drug out into the oral cavity," thereby creating a "unidirectional gradient so that the drug moves from the polymeric diffusion environment directly into the mucosa of the subject." Tr. 587:12–18. While Tapolsky describes using a third layer to achieve unidirectional release, an artisan of ordinary skill would have understood based on Tapolsky that a single backing layer could provide a unidirectional gradient. Tr. 586:21–587:19; DTX-173 ¶ 58. Moro also teaches the use of a backing layer to improve bioavailability and create unidirectional delivery. Tr. 120:1–7; DTX-178 ¶ 46.

5) Use of Buprenorphine in the Tapolsky Device

An artisan of ordinary skill would have been motivated to use buprenorphine in the drug-delivery platform disclosed by Tapolsky (or the similar platform disclosed by Moro). Tapolsky teaches a method for buccal delivery of pharmaceuticals that produces excellent bioavailability, fast onset, and sustained delivery. DTX-173 ¶¶ 13, 131. Tapolsky explains that the disclosed delivery device was appropriate for use with numerous pharmaceuticals. DTX-173 ¶¶ 46–53.

Buprenorphine was known in the prior art as a potent opioid analgesic. Tr. 91:13–19, 94:23–25; JTX-248 at 1, 9. Prior references, including Cassidy and Bullingham I, taught that buprenorphine had a high first pass effect and thus alternative delivery methods, such as transmucosal delivery, could offer better bioavailability than oral formulations (e.g., a pill or tablet). Tr. 94:21–95:13; DTX-248 at 1; DTX-077 at 1. An artisan of ordinary skill would have been motivated to combine buprenorphine with Tapolsky, because she would have recognized that delivering buprenorphine in the Tapolsky device could reduce first pass effects while also improving bioavailability.

An artisan of ordinary skill also would have had a reasonable likelihood of success in delivering buprenorphine with the Tapolsky device. Tapolsky and Moro teach the use of opioids—including buprenorphine in the case of Moro—in buccal

drug delivery devices. Tr. 111:6–7, 118:8–16; DTX-173 ¶ 53; DTX-178 ¶¶ 35, 64. And the prior work on buprenorphine disclosed in Todd, Weinberg, and Bullingham showed the drug was amenable to delivery through the mouth's mucosal tissue. Tr. 91: 5–19, 170:23–171:2, 173:18–174:6; DTX-077 at 1, 5; DTX-174 at 1; JTX-249 at 6. Formulating a version of the Tapolsky drug delivery device with an effective amount of buprenorphine would have been a matter of routine skill. Tr.134:3–9. Considering this information together, an artisan of ordinary skill would have understood that buprenorphine was suitable for use in the Tapolsky drug-delivery device and would have had a reasonable expectation of successfully using the Tapolsky device to deliver buprenorphine. Tr. 121:9–17, 130:7–20.

6) Buffering the Mucoadhesive Layer to the Claimed pH

In creating a bilayer mucoadhesive film with buprenorphine, an artisan of ordinary skill in the art would have buffered the mucoadhesive layer to the pH range that she expects to maximize bioavailability. To do so, the artisan would considered both the solubility and absorption of buprenorphine.

Because a drug must dissolve in order to be absorbed into the mucosa, an artisian of ordinary skill would have been motivated to use the buprenorphine solubility information reported in Cassidy in formulating a buccal drug delivery device with buprenorphine. Cassidy discloses that the solubility of buprenorphine

is highly pH dependent and is substantially greater below a pH of 5. Tr. 146:6–12, 147:17–23, 150:15–17; JTX-248 at 4, Fig. 1. Even if solubility depends on the specific solution as BDSI argues, *see* D.I. 260 ¶ PFF51 (citing Tr. 624:12–16, 706:5–9), Cassidy would have provided an artisan of ordinary skill reason to expect greater solubility when the pH of the local environment around the buprenorphine is below 5, Tr. 153:2–153:20; JTX-248 at 4. An artisan of ordinary skill, therefore, would have been motivated to formulate the drug delivery environment for buprenorphine, that is the mucoadhesive layer, to have a pH of 4 to 5, which Cassidy identifies as the pH range for maximum buprenorphine solubility. Tr. 150:15–17; JTX-248 at 4, Fig. 1.

And based on the good absorption reported in Todd, an artisan of ordinary skill would have had a reasonable expectation of observing good absorption of buprenorphine in the same pH range using the Tapolsky device. Tr. 175:16–25; 200:22–201:12; Tr. 671:16–672:12. An artisan of ordinary skill would have further expected success in formulating buprenorphine at this pH range because as of 2006 there were no examples in the prior art of buprenorphine formulations with a pH greater than 6.5, but there were several examples of formulations at acidic

pHs. Tr. 176:6–9, 202:1–4; DTX-174 at 3 (using a pH range of 4.5–5.5); DTX-203 at ¶ 71 (using a pH range of 3 to 4.8); JTX-249 at 1 (using a pH of 6.5).[2]

BDSI argues that an artisan would not have been motivated to use the claimed pH range, because an artisan would understand that below a pH of 6 Buprenorphine is nearly 100 percent ionized and that drugs are better absorbed when not ionized. D.I. 261 at 31; Tr. 672:3–7; Tr. 798:6–20 (explaining the pH partition hypothesis). But an artisan of ordinary skill would have readily understood that buprenorphine behaves differently than a generic ionic compound. It is undisputed that the chemical properties of compounds vary based on their unique composition and molecular arrangement. Tr. 254:17–23.[3] And Todd explains that buprenorphine has good uptake in the pH range of 4 to 6—a range in which buprenorphine is ionized. Tr. 672:8–12. Johnson and Bullingham I further teach that buprenorphine is extremely lipophilic. DTX-165 at 5; DTX-077 at 1.

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[2] The parties dispute how to measure the pH of Suboxone® and whether Suboxone® is buffered to a pH of 3.5. D.I. 260 ¶ DFF93. However, there was no suggestion at trial that Suboxone® is buffered to a pH greater than 6.5 or that any prior art before 2006 discloses a pH for suboxone® above 6.5.

[3] In arguing that it would have been nonobvious to use buprenorphine in a bilayer mucoadhesive device, BDSI argues that the "the evidence at trial established that all opioids do not work the same way in solid film devices." D.I. 261 at 27. But in arguing that that an artisan of ordinary skill would not have been motivated to buffer the mucoadhesive layer to the claimed pH ranges, BDSI argues that "all . . . weakly basic compounds such as fentanyl [and buprenorphine] were expected to behave the same." D.I. 261 at 32. BDSI cannot have it both ways.

An artisan of ordinary skill would have known that lipophilic compounds, including buprenorphine, are more easily absorbed into the body. Tr. 783:22–784:4. The artisan would have been motivated to use the claimed pH range because of its solubility properties and would have understood that buprenorphine is sufficiently absorbed at these pH ranges to have a reasonable expectation of success.

I recognize that Dr. Davies, BDSI's chemistry expert, testified that an artisan of ordinary skill "would expect the most efficient uptake [of buprenorphine] to be . . . between [a pH of] about 6 and 10. Between about 8 and 10." Tr. 741:17–18. Dr. Davies further testified that "significant" amounts of unionized buprenorphine exist in the pH range of 8 to 10. Tr. 741:20–21. But crucially this testimony was conditioned on buprenorphine already being solubilized. The question that Dr. Davies provided the quoted answer to was "In your opinion, would a person of ordinary skill in the art have expected, based on the prior art including Todd, that *if any solubility problems of buprenorphine could be overcome*, that buprenorphine uptake would be most efficient at higher pH values?" Tr. 741:12–16 (emphasis added). Yet, "bioavailability depends both on solubility and permeability." Tr. 793:8–9. As of 2006 the prior art taught that buprenorphine needed to be formulated at pHs below 6.5 to dissolve and that buprenorphine's solubility is

maximized in solutions with a pH below 5. Accordingly, I do not find Dr. Davis' testimony on this point probative.

7) Pharmacokinetic Properties

Alvogen's pharmacokinetics expert, Dr. Shafer, explained that pharmacokinetic properties are specific to a particular delivery device, drug, and dose combination. Tr.328:6–12. Thus, the pharmacokinetic properties of a particular delivery device, drug, and dose combination do not necessarily suggest the properties of other combinations.

Alvogen has not identified any dosage that an artisan of ordinary skill would have used when formulating a Tapolsky device with buprenorphine. Although an artisan of ordinary skill might have been motivated to formulate a device for transmucosal delivery of buprenorphine in general, without a specific device, drug, and dose combination there cannot be any inherent pharmacokinetic properties.[4]

Additionally, there would have been no motivation for an artisan of ordinary skill to achieve the claimed pharmacokinetic results. Alvogen itself argues that

[4] Alvogen waived the argument that the pharmacokinetic properties are inherent in Tapolsky alone by not raising that contention before trial. *See* Hr'g, June 8, 2021 (granting motion to strike). Accordingly, I only consider the inherency argument with respect to the obviousness combination of Tapolsky (or Moro), Todd, and Bullingham I, which was disclosed prior to trial. But as explained below, there was also no motivation to combine Bullingham I with other references to obtain the claimed pharmacokinetic properties, and thus the inherency argument is incomplete on that basis as well.

"the parameters of claim 4 and 5 are not meaningful." D.I. 258 at 40; *see also* . And Dr. Shafer, testified that "[t]he FDA does not consider [time of first plasma concentration] a useful or interesting parameter and neither do people skilled in the art of pharmacokinetics . . . ." Tr. 329:25–330:3. Even assuming that the prior art could have taught an artisan of ordinary skill how to achieve the claimed pharmacokinetic properties with buprenorphine in a mucoadhesive device, an artisan of ordinary skill would have been indifferent to these claimed pharmacokinetic properties and would have had no motivation to achieve them.

8) Secondary Considerations

BDSI offered at trial evidence of three secondary considerations: long-felt need, unexpected results, and teaching away. I did not find this evidence to be probative of nonobviousness for the following reasons.

a) Long-Felt, Unmet Need

Long-felt but unresolved need is evidence of nonobviousness, because "it is reasonable to infer that the need would have not persisted had the solution been obvious." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016). In assessing the presence or absence of long-felt need, I consider circumstances as they existed at the filing date of the invention. *Proctor & Gamble v. Teva Pharms. USA Inc.,* 566 F.3d 989, 988 (Fed. Cir. 2009). Whether a need is long felt is based

on considering when the problem was identified and when there is evidence of efforts to solve that problem. *WBIP*, 829 F.3d at 1334.

As of the 2006 effective filing date of the #866 and #843 patents there was at least some need for an opioid for chronic pain with reduced side effects and lower risk of abuse, but the record evidence does not show this need was long felt. Tr. 874:18–23, Tr. 898:17–24. The use of opioids for chronic pain became more accepted in the 1990s and 2000s; opioid sales increased rapidly over the 2000s, peaking in 2010. JTX-3000 at 2; JTX-403 at 1–2, Fig. 1. The evidence presented at trial shows that as of 2006 there was a growing awareness of the need for alternative opioids and that the understanding in the profession was evolving. Tr. 869:9–20, 935:12–22. The fact that there were unmet needs may only be clear thanks to the benefit of hindsight. The only evidence BDSI provided that artisans were aware of limitations with available prescription opioids before 2006 was the testimony of Dr. Rauck, BDSI's pain management medical expert, that artisans of ordinary skill "probably didn't know about [the opioid crises] as much until maybe the early part of the 2000s that I recall, and I think what the documents would show as well." Tr. 936:20–22. But the earliest piece of documentary evidence produced at trial discussing opioid poisonings was published in September 2009. JTX-410. This evidence is not sufficient to show clearly and convincingly that Belbuca® answered a long felt, but unresolved need in medicine.

BDSI identified several possible benefits of Belbuca® over the prior art. *See* Tr. 548:16–549:12, 881:5–19, 922:5–25. But BDSI did not identify any previous unsuccessful attempts to meet the needs satisfied by Belbuca®. No concrete evidence presented at trial established when the problems supposedly addressed by the asserted patents became recognized or when the first efforts to address those problems were. The evidence does not show, at the time of invention, that there was a recognized long-felt, unmet need satisfied by the #866 and #843 patents.

b) Teaching Away

BDSI argues that the prior art taught away from using an acidic pH and instead taught that using a more basic pH would lead to enhanced uptake. D.I. 261 at 49. This argument overlaps with Plaintiff's primary argument for nonobviousness. According to BDSI's argument, because Buprenorphine is a weakly basic compound it is ionized at acidic pHs. Tr. 756:3–5. It was well known that chemical compounds are typically more readily absorbed through the mucosal tissue when unionized. Tr. 630:1–6, 796:21–25. However, as I discussed above, it was also known that buprenorphine was readily absorbed even when ionized and that the challenges from solubility dominated any challenges from absorption in formulating drugs with buprenorphine. *See supra* Part III(C)(2)(e). While concerns about absorption may have favored a higher pH, the more pressing

concern in formulating Belbuca® would have been solubility and the prior art taught that a lower pH is favorable in overcoming this challenge. Tr. 153:12–20, 198:1–7.

Additionally, no prior art taught away from using an acidic pH with buprenorphine.[5] The highest pH used to deliver buprenorphine in the prior art before development of Belbuca® was in Weinberg where buprenorphine was delivered in a pH 6.5 solution. JTX-249 at 1, 3, Fig. 1. But at a pH of 6.5, over 97.87% of buprenorphine is ionized, and Weinberg still reported that buprenorphine was "absorbed to a very high degree." Tr. 170:5–9, 670:12–14; DTX-377; JTX-249 at 6. Rather than suggesting that buprenorphine should be delivered in a basic environment, Weinberg shows that an artisan of ordinary skill would have had a reasonable expectation of success in obtaining good absorption of buprenorphine even in an environment where it is mostly ionized. I conclude

[5] There is one piece of prior art which seems to suggest the use of a higher pH with buprenorphine: Dr. Michniak-Kohn et al.'s book chapter. DTX-355 at 11 ("[S]tudies conducted with sublingual administration of opioids such as buprenorphine, methadone, and fentanyl showed increased absorption with increase in pH, where the drug was predominantly present in the unionized form." (citing Weinberg (DTX-249)). But the relevant language relies on Weinberg and is clearly inconsistent with that reference with respect to Buprenorphine. Weinberg did not observe an increase in absorption for buprenorphine when the drug was predominantly present in the unionized form. In fact, Weinberg only studied buprenorphine at a single pH, which was 6.5 and at which buprenorphine is largely ionized. DTX-249 at 6. Weinberg did not study buprenorphine in the unionized form because the drug was not soluble in more basic solutions. DTX-249 at 6.

therefore that the prior art, when considered as a whole, did not teach away from using a lower pH.

c) Unexpected Results

An unexpected result can support a finding of nonobviousness, because it suggests that an artisan of ordinary skill would not have been motivated to develop an invention or would not have had a reasonable expectation of success. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). To suggest nonobviousness, "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 Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Additionally, "differences in degree" are less probative than "difference in kind." *Id.*

BDSI argues that the enhanced uptake of the claimed inventions was unexpected and that this supports nonobviousness. D.I. 261 at 53. I find, however, that enhanced uptake was not unexpected for the invention claimed in the #866 and #843 patents. Tapolsky teaches a method for drug delivery that improves bioavailability. DTX-173 ¶ 131 ("the pharmaceutical carrier devices of the invention yield . . . excellent bioavailability"). Improved bioavailability is not only a difference in degree rather than kind, but is also the very improvement that would

have motivated an artisan of ordinary skill to combine buprenorphine with the Tapolsky platform in the first place. And it is not surprising that increased bioavailability is observed when the mucoadhesive layer is buffered to the pH range in which buprenorphine is most soluble according to Cassidy. Tr. 183:10–17. Rather than suggesting that the claimed invention was nonobvious, the improved bioavailability merely illustrates why an artisan of ordinary skill would have been motivated to combine the prior art. *Cf. Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014) ("The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success . . . , even if the level of success may have turned out to be somewhat greater than would have been expected.").

BDSI relies on *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265 (Fed. Cir. 2018). In *Orexo*, the Federal Circuit found that the district court improperly discounted the claimed formulation's 66% improvement "in the context of th[at] invention." *Id.* at 1274. The Federal Circuit found that the 66% improvement should be treated as a difference of kind rather than a difference of degree. *Id.* at 1274. However, despite involving the same active ingredient, the facts of that case are quite different. In *Orexo*, the invention used the same route of administration, sublingual tablets, as the prior art. *Id.* at 1268. The novel aspect of the invention was using citric acid as a carrier particle, and no prior art suggested that critic acid

would be an effective carrier particle for buprenorphine. *Id.* at 1272–73. Because the prior art did not suggest that the claimed invention would have improved bioavailability, the significantly improved bioavailability was surprising. *Id.* at 1273. But here the prior art is exactly the opposite. Tapolsky teaches a way to improve bioavailability, and so improved bioavailability when using the Tapolsky platform is expected rather than surprising.

BDSI also cites expert testimony at trial that the bioavailability of the claimed inventions was unexpected. But the cited testimony is not indicative of nonobviousness. Dr. Taft, BDSI's expert in pharmacokinetics, testified that the bioavailability relative to suboxone was "unexpected . . . based on the pH partition theory." Tr. 802:20–24. But, as discussed above, it was known that buprenorphine is very lipophilic and that the general predictions of the pH partition theory do not provide a good description of the specific molecule at issue in this case. Thus, this testimony does not establish that the results were unexpected.

b. Conclusions of Law

1) The Tapolsky Device

The structural elements of the claimed devices are (1) a bioerodable mucoadhesive layer with a pharmaceutical disposed in a polymeric diffusion and (2) a polymeric barrier environment disposed adjacent to the mucoadhesive layer to provide a unidirectional gradient. Claim 9 of the #843 patent further requires

that the polymeric diffusion environment has at least one film-forming water erodible adhesive polymer and at least one bioadhesive polymer.

These elements are taught directly by Tapolsky. Tapolsky teaches the use of a polymeric adhesive layer with a film-forming water erodible polymer and a bioadhesive polymer and also teaches the use of a polymeric non-adhesive backing layer. DTX-173 ¶¶ 31–32, 35. Indeed, Tapolsky teaches that the layers can be made with the very polymers that are used in Belbuca®. Tr. 108:7–10, 19–21; JTX-233 at 23.

2) Use of Buprenorphine in a Tapolsky Device

I have already found as a factual matter that Alvogen has shown by clear and convincing evidence that an artisan of ordinary skill would have been motivated to use buprenorphine in the Tapolsky drug delivery device based on Tapolsky and Todd. I also found as a factual matter that Todd would have given the artisan of ordinary skill a reasonable expectation of success in making this combination. Based on these findings and because the secondary considerations are not probative, I conclude that it was obvious to use buprenorphine in the Tapolsky device.

3) Polymeric Diffusion Environment Buffered to the Claimed pH Ranges

Given that it would have been obvious for an artisan of ordinary skill to use the Tapolsky drug-delivery device with buprenorphine, the next question is

whether it would have also been obvious to buffer the mucoadhesive layer to the claimed pH ranges when using buprenorphine in the Tapolsky device. I find that it would have been.

As I explained above, an artisan of ordinary skill would have been motivated based on Todd in light of the prior art to buffer the local environment in the Tapolsky drug-delivery device to a pH in the claimed ranges, including the narrowest claimed range of about 4.5 to about 5. This is because the artisan of ordinary skill would have understood that buprenorphine is only soluble in solutions that are sufficiently acidic to ionize buprenorphine, but that once dissolved buprenorphine is easily absorbed into the body.

Furthermore, the artisan of ordinary skill would have had a reasonable expectation of success. Buprenorphine is suitable for use in buccal delivery devices and is readily absorbed through the mucosal tissue once dissolved. Tr. 671:16–672:12, 175:16–25. This expectation would have been reinforced because the other buprenorphine drugs in the prior art were also buffered to the same or similar pH ranges. Tr. 176:6–9, 202:1–4; DTX-174 at 3 (using a pH range of 4.5–5.5); DTX-203 ¶ 71 (using a pH range of 3 to 4.8). The use of buffers would have been familiar to someone having skill in the art. Tr. 153:3–9, 200:22–201:5.

Considering this information together, an artisan of ordinary skill would have been motivated to formulate a Tapolsky device with the mucoadhesive layer

buffered to the claimed pH ranges of about 4.5 to about 5, about 4.5 to about 5.5, about 4 to about 6, and about 4 to 7.5. The artisan of ordinary skill also would have had a reasonable expectation of success in doing so. Again the secondary considerations were not probative and do not impact this obviousness analysis.

For these reasons, I find that the combination of a biodegradable mucoadhesive layer containing buprenorphine in a polymeric diffusion environment buffered to the claim pH ranges and a polymeric barrier environment that provides a unidectional gradient was obvious. It also would have been obvious to use this device in a method for delivering buprenorphine and to use the device for delivery in humans. Accordingly, I find that claims 3 and 10 in the #866 patent and claims 8, 9, and 20 in the #843 patent are invalid for obviousness.

4) Pharmacokinetic Properties of Claims 4 and 5 of the #866 Patent

Claim 4 of the #866 patent requires that a first quantifiable plasma concentration of buprenorphine is observed at about 45 minutes, and claim 5 of the patent requires that an effective plasma concentration of buprenorphine is maintained for at least 4 hours. The other limitations of claim 4 and 5 are identical to claim 3, except that the pH range covered by claims 4 and 5 is between about 4 and about 6, which is broader than the pH range in claim 3.

To show that a pharmacokinetic limitation is obvious the party challenging a patent's validity must "demonstrate that a skilled artisan would have been

motivated to create a . . . formulation of [the claimed pharmaceutical] with the[] claimed [pharmacokinetic] characteristics." *Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, 755 F. App'x 983, 991 (Fed. Cir. 2019). Alternatively, the challenging party can show that the claimed pharmacokinetic properties are inherent in an obvious combination. *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) ("[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations, because to hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." (internal quotation marks and alterations omitted)). A patent claim may be found obvious based on inherent properties only in limited circumstances: "inherency renders a claimed limitation obvious only if the limitation is necessarily present or is the natural result of the combination of elements explicitly disclosed by the prior art." *Id.* at 1191 (internal quotation marks omitted).

I already found as a matter of fact that the pharmacokinetic properties are not inherent in the obvious combination of using buprenorphine in the Tapolsky device, because the combination does not include a dosage amount. Additionally, I found there was no motivation to achieve the claimed pharmacokinetic properties

in the prior art. According, Alvogen has failed to establish that claims 4 and 5 of the #866 patent are invalid for nonobviousness.

3. Obviousness of the #539 Patent

a. Findings of Fact

1) Content of the Asserted Claims

The #539 patent discloses the results of a Belbuca® clinical trial and teaches methods for treating chronic pain using a two-layer mucoadhesive bioerodable drug delivery device where the backing layer is buffered to a pH of between 4.0 and 4.8. Plaintiffs assert claims 9 and 20 of the #539 patent. The backing layer pH limitation is required in both asserted claims.

Claim 9 covers a method for treating "moderate to severe chronic low back pain" comprising (1) "administering to the subject twice daily a mucoadhesive bioerodable drug delivery device to an oral mucosal surface of the subject" where the drug delivery device comprises (2) "a bioerodable mucoadhesive layer comprising an effective amount of buprenorphine disposed in a buffered polymeric diffusion environment," (3) "wherein the polymeric diffusion environment is a buffered environment having a pH of between about 4 and about 6," (4) "a backing layer buffered to a pH between about 4.0 and about 4.8 and that does not include an opioid antagonist," (5) wherein the total daily dose of buprenorphine administered to the subject is effective for treating moderate to severe chronic low back pain," (6) "wherein the subject is an opioid-experienced subject," and (7)

"wherein the subject treated experiences mild or moderate common opioid adverse effects, or no common opioid adverse effects."

Claim 20 (which depends from claim 1) requires the same elements as claim 9 except that (1) the method is for treating "chronic pain" generally (as opposed to low back pain), (2) the device can be administered "once or twice" daily, (3) the bioerodable mucoadhesive layer comprises "about 100 g to 0.9 mg of buprenorphine," (4) the device provides a steady-state C_{max} of plasma buprenorphine concentration in a range of about 0.156 to about 0.364 ng/mL, and (5) between 1.5% and 8.5% of subjects experience drug related mild or moderate constipation as a side effect.

2) Content of the Prior Art

The priority date for the #539 patent is December 21, 2011. JTX-0003 at 1. Accordingly, all the prior art considered for the #866 and #843 patents is also prior art for the #539 patent. Additionally, the parent application to the #866 and the #843 patents, Vasisht I, is prior art to the #539 patent, because it was published on January 23, 2008. DTX-17; D.I. 258 at 8. Vasisht I has the same written description as the #866 and #843 patents.

Claims 9 and 20 of the #539 patent require that the backing layer of the claimed device is buffered to a pH range of about 4 to about 4.8. Because the prior art does not explicitly teach that the pH of the backing layer is relevant to delivery

of buprenorphine, Alvogen argues that the pH limitation is inherent in Vasisht I. Alvogen's theory is that the backing layer formula disclosed in Vasisht I is so similar to the backing layer in Belbuca® that they must have the same pH. D.I. 258 at 44–45; *see also* DTX-17 ¶ 99 (providing a backing layer formulation). The pH of the Belbuca® backing layer is between 4.5 and 4.7. Tr. 576:13–25.

Dr. Michniak-Kohn testified that the Vasisht I backing layer and the Belbuca® backing layer have the same weight percentages for all significant ingredients after converting the Vasisht I formula to dry weight. Tr. 206:3–207:23, 209:10–17. In converting to dry weight, Dr. Michniak-Kohn rounded the resulting values to one or two significant figures. Tr. 283:8–15. Based on the observed similarity between the formulations and the undisputed fact that Belbuca® has a backing layer with a pH between 4.0 and 4.8, Dr. Michniak-Kohn testified that Vasisht I necessarily disclosed a backing layer with a pH between 4.0 and 4.8. Tr. 206:23–207:23, 209:10–17. Dr. Michniak-Kohn did not perform any laboratory testing to reach her conclusions. Tr. 257:21–23. Nor did Dr. Michniak-Kohn offer any substantive testimony about whether her rounding could affect her conclusions about the pH of the backing layer taught in Visisht I.

But in a declaration to the Patent Office during prosecution of the #539 patent, Dr. Vasisht, one of the inventors of the asserted patents, said that the backing layer disclosed in Vasisht I had been remade and its pH measured. JTX-

006 at 4101 ¶ 7.[6] Dr. Vasisht represented that the average pH of the Vasisht I formulation was 5.61 and that all the measurements were outside the claimed range of the #539 patent. JTX-006 at 4101 ¶ 7.[7]

Given two incompatible representations in the record, Dr. Michniak-Kohn's testimony is not sufficient to prove by clear and convincing evidence that Vasisht I teaches a backing layer with the same pH as the backing layer of Belbuca®.

3) Secondary Considerations

BDSI offered additional evidence of two secondary considerations for the #539 patent: long-felt need and unexpected results. I find that adjusting the pH of the backing layer produced unexpected results.

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[6] Alvogen brought in JTX-006 during direct examination of their expert Dr. Michniak-Kohn without any limitation on the purpose for which it was admitted. Tr. 210:5–211:22. As a statement made by the opposing party's agent, the declaration of Dr. Vasisht is not hearsay. Fed. R. Evid. 801(d)(2).

[7] Alvogen challenges the veracity of Dr. Vasisht's declaration. D.I. 258 at 46. To the extent that Defendants are suggesting inequitable conduct by Dr. Vasisht, this argument was struck. Hr'g, June 8, 2021. To the extent that Alvogen seeks to challenge the credibility of Dr. Vasisht's declaration, the only relevant evidence is Dr. Michniak-Kohn's testimony that the result reported in Dr. Vasisht's declaration "doesn't make sense" because it reaches a different result than her analysis. Tr. 211:22. But it is also possible that the discrepancy is a result of the fact the data relied on by Dr. Michniak-Kohn did not possess enough significant figures to allow an accurate comparison between the Visisht I and the Belbuca® formulations.

a) Long-Felt, Unmet Need

The #539 patent was filed in 2012. BDSI presented evidence suggesting that as of 2012 there was need for an buprenorphine product that did not cause QT prolongation at higher doses, Tr. 552:14–17, 916:2–11, and that was not a patch, 765:21–766:2, 895:3–5. But there was no evidence presented at trial showing these needs were long felt, because no evidence established when artisans recognized the problems the #539 patent may help solve. Accordingly, I find consideration of long-felt need is not probative in determining the obviousness of the #539 patent.

b) Unexpected Results

I find that the effects on bioavailability from changing the backing layer's pH were unexpected. Lowering the pH of the backing layer resulted in an increase in the bioavailability of buprenorphine. Tr. 804:2–806:19; JTX-353 at 26, PTX-608 at 56, DTX-019 at 30, PTX-325 at 29.[8] At trial Dr. Taft testified that this result were unexpected. Tr. 804:2–806:19. Additionally, no prior art taught that adjusting the pH of the backing layer would affect bioavailability. Dr. Michniak-Kohn testified that an artisan of ordinary skill would expect changing the pH of the backing layer to generally impact the properties of the device but did not testify

[8] These references were admitted only for the purpose of establishing that changing the pH of the backing layer produced unexpected results. Tr. 806:20–7.

that an artisan of ordinary skill would have expected adjusting pH to effect bioavailability. Tr. 225:25–9; *see also* DTX-179 ¶ 134 (teaching that a backing layer's pH could impact drug degradation). The surprising effect of the backing layer's pH on the bioavailability of a drug in the mucoadhesive layer suggests that an artisan of ordinary skill would not have been motivated to buffer the backing layer to the claimed range.

b. Conclusions of Law

I already found that as a matter of fact Alvogen has not shown by clear and convincing evidence that the backing layer pH limitations of the #539 patent are inherent in Vasisht I. Because Alvogen has not argued that any other reference teaches buffering the backing layer to a pH of about 4.0 to about 4.8, Alvogen has not shown that an artisan of ordinary skill would have been motivated to achieve this result. Alvogen, therefore, has not shown that the claims are obvious. This result is supported by the secondary consideration of unexpected results. Thus, Alvogen has not met its burden to prove that either claim 9 or claim 20 of the #539 patent is invalid for obviousness.

B. ANTICPATION

Alvogen argues that claims 3, 4, 5, and 10 of the #866 patent and claims 8 and 20 of the #843 patent are anticipated by a parent application, U.S. patent application 11/B17,915 (the #915 application, DTX-206). Alvogen's position is

that these claims are not entitled to the priority date of the #915 application, because the #915 application does not disclose the specific pH ranges claimed in the #866 and #843 patents, i.e. the pH ranges of about 4–6, about 4.5–5.5, and about 4.5–5. The parties do not dispute that if the #866 and #843 patents cannot claim priority to the #915 application the relevant claims are anticipated.[9]

1. Findings of Fact

The #915 application, discloses the pH of certain embodiments in the following paragraph:

> In one embodiment, e.g., when the medicament is buprenorphine, the pH of the mucoadhesive polymeric diffusion environment in the devices of the present invention is between about 4.0 and about 7.5. In another embodiment, the pH of the mucoadhesive polymeric

[9] Patents are entitled to the priority date of an earlier-filed application, only if the earlier-filed application contains adequate written description to support the subsequent claims. *Hologic, Inc. v. Smith & Nephew, Inc.*, 884 F.3d 1357, 1361 (Fed. Cir. 2018). The "hallmark" of an adequate written description is "disclosure." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). A written description is adequate to support a subsequent filing if the original application "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter" as of the earlier filing date. *Id.* An applicant establishes it was in possession of the invention "by describing the invention[] with all its claimed limitations." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (emphasis omitted). This description can be made using "words, structures, figures, diagrams, formulas, etc." *Id.* A patentee can also "rely on information that is 'well-known in the art' to satisfy written description." *Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1285 (Fed. Cir. 2012) (citation omitted). The adequacy of a written description, including for determining priority, is a question of fact. *Hologic*, 884 F.3d at 1361.

> diffusion environment is about 6.0. In one embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 5.5 to about 6.5, or between about 6.0 and 6.5. In yet another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 7.25. In another embodiment, the pH is between about 7.0 and 7.5, or between about 7.25 and 7.5. In other embodiments, the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5, or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

DTX-206 ¶ 63. It is undisputed that this paragraph discloses at least the following pH values or ranges for the mucoadhesive polymeric diffusion environment: (1) between about 4.0 and about 7.5, (2) about 6.0, (3) between about 5.5 and about 6.5, (4) between about 6.0 and 6.5, (5) about 7.25, (6) between about 7.0 and 7.5, and (7) between about 7.25 and 7.5.

The parties dispute the meaning of "the device" in the sentence "the pH of the *device* may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5 and any incremental value thereof." DTX-206 ¶ 63 (emphasis added). At trial there was competing testimony about how an artisan of ordinary skill would have understood this sentence. Dr. Michniak-Kohn testified that an artisan of ordinary skill would have understood the listed pH values as characterizing the entire device. Tr. 235:17–22. Dr. Williams testified that an artisan of ordinary skill would have understood the listed pH values to refer specifically to the pH of the "polymeric diffusion environment." Tr. 661:1–3. I find Dr. Williams's testimony on this point more

credible. The #915 application only discusses the pH of the mucoadhesive layer, and there is no discussion of the pH of the device as a whole, except for, perhaps, in this one disputed sentence. Tr. 661:13–23. The surrounding paragraphs all concern the mucoadhesive layer and confirm that the quoted paragraph must also pertain to the properties of the mucoadhesive layer. DTX-206 ¶¶ 62, 64–67.

The #915 application would have allowed an artisan of ordinary skill to "immediately discern" that the inventors possessed the pH ranges taught in the asserted claims. *See Gen. Hosp. Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1372 (Fed. Cir. 2018) ("[W]here a specification discloses a broad range of values and a value within that range is claimed, the disclosure must allow one skilled in the art to immediately discern the limitation at issue in the claims." (internal quotation marks and citation omitted)). The #915 application discloses a pH range for the mucoadhesive layer of about 4.0 to about 7.5, which includes the pH ranges in the relevant asserted claims. An artisan of ordinary skill would have understood that the broader range in Vasisht I describes every smaller sub-range as well, because the #915 application explicitly tells the reader "all values and ranges between these values and ranges are meant to be encompassed by the present invention." The plural "values and ranges" cannot only refer to the immediately prior sentence—which does not teach any ranges—but must also refer to the numerous pH ranges listed earlier in the paragraph.

Alternatively, the claimed ranges are also disclosed by the sentence "In other embodiments, the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5 and any incremental value thereof." As I explained, I believe Dr. Williams was credible when he explained that an artisan of ordinary skill would understand this sentence to refer to the pH of the mucoadhesive layer. Because the representation that "all values and ranges between these values and ranges are meant to be encompassed by the present invention" undoubtably covers the immediately preceding sentence, the #915 patent teaches the pH ranges of the relevant claims.

2. Conclusions of Law

Because Alvogen has not shown by clear and convincing evidence that the #915 application's written description is inadequate to support the #866 and #843 patents, those two subsequent patents can claim priority to the #915 application. It follows that the #915 patent cannot anticipate the claims in the #866 and #843 patents. Therefore, the asserted claims of those patents are not anticipated.

V. CONCLUSION

For the foregoing reasons, I find that the asserted claims 4 and 5 of the #866 patent and 9 and 20 of the #529 patent are not invalid and that Alvogen infringes these asserted claims. I further find that asserted claims 3 and 10 of the #866 patent and 8, 9, and 20 of the #843 patent are invalid under § 103.

The parties will be directed to submit a proposed order by which the Court

may enter final judgment consistent with this Opinion.