IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IMPAX LABS., INC., ASTRAZENECA AB, and ASTRAZENECA UK LTD.,

Plaintiffs,

v.

LANNETT HOLDINGS INC. and LANNETT CO., INC.,

Defendants.

Nos. 14-cv-984, 14-cv-999 (RGA)

TRIAL OPINION

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March 29, 2017

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs Impax Laboratories, AstraZeneca UK ("AZUK"), and AstraZeneca AB ("AZAB") brought suit against Defendants Lannett Holdings, Inc. and Lannett Company, Inc. for infringement of U.S. Patent Nos. 6,750,237 and 7,220,767 ("the Dearn patents").

The Dearn patents claim invention of a nasal formulation for zolmitriptan. Zolmitriptan is a member of the triptan class of drugs, which treat migraines.

AstraZeneca Pharmaceuticals LP holds New Drug Application No. 21450 for zolmitriptan nasal spray. Zolmitriptan nasal spray, as well as other zolmitriptan products, are marketed as Zomig. The Dearn patents are listed in the Orange Book as covering Zomig.

Plaintiffs brought this infringement suit after Defendants filed Abbreviated New Drug Application No. 206350. Defendants stipulated to infringement.[1] (D.I. 136). Defendants argue, however, that (1) Plaintiffs do not have standing to bring suit, (2) the Dearn patents are invalid as anticipated, and (3) the Dearn patents are invalid as obvious.

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[1] Defendants waited until after trial to offer this stipulation. Yet, they offered no evidence on non-infringement at the trial. Nor have they offered any colorable argument as to why their ANDA, as filed, would not infringe the asserted claims, as construed. This delay required Plaintiffs to put on unnecessary expert testimony on infringement and wasted everyone's time for no apparent reason.

The Court held a three day trial on September 6, 7, and 8, with closing arguments on the 9th. I now address each of Defendants' arguments in turn. My findings of fact and conclusions of law are stated below.

I. STANDING

Defendants challenge Plaintiffs' standing to bring suit. Essentially, Defendants argue that Plaintiffs have failed to establish the exact ownership arrangement of the patents, and, as such, I cannot be sure that all the ownership interests are represented.

Standing to sue is a jurisdictional requirement under Article III of the United States Constitution. *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 560 (1992). In the patent context, standing usually requires the plaintiff to have legal title to the patent. *Abraxis Bioscience, Inc. v. Navinta LLC*, 625 F.3d 1359, 1364 (Fed. Cir. 2010). Further, when ownership is divided, all owners usually must participate as plaintiffs for standing to be proper. *See Textile Prods., Inc. v. Mead Corp.*, 134 F.3d 1481, 1484 (Fed. Cir. 1998).

Following the bench trial, both parties submitted briefing on standing (D.I. 145, 152, 157)[2] and Plaintiffs submitted a declaration by Amy Allen (D.I. 145-1), the Director of Sales Planning and Operations for AstraZeneca, (*Id.* at ¶ 1).

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[2] All docket references are to the docket in No. 14cv984.

A. Admissibility of the Allen Declaration

As a preliminary matter, Defendants move to strike the Allen declaration. (D.I. 152 at 17–19). Defendants argue it is unfair to allow Plaintiffs to submit new evidence this late and without an opportunity for them to cross-examine Ms. Allen.

I do not agree that the admission of the declaration or other evidence of standing is unfair or untimely. While parties are supposed to use the pretrial order process to identify the issues for trial, *see* D. Del. LR 16(c)(5), 16(d)(4), Defendants did not raise standing as an issue to be tried in the pretrial order (*see* D.I. 140), and only brought it up at the pretrial conference (D.I. 121 at 24). That is why, at the conference, I told the parties that I did not consider standing an issue for trial. (*Id.*). It would be unfair to Plaintiffs if, after telling them not to produce evidence of standing at the trial, I then told them they also could not produce evidence of standing outside the trial.

I do not believe cross-examination of Ms. Allen is necessary to rely on her statements to find standing. Defendants argue that Ms. Allen's prior testimony calls her knowledge into question. (D.I. 152 at 18). Specifically, in her deposition, Ms. Allen stated that she did not know how Zomig came to AstraZeneca. (D.I. 152-2 at 3). She also stated that she was unsure if anyone other than Impax approached AstraZeneca about licensing Zomig. (*Id.*). Neither issue is at all relevant to the standing question in the case.

Nevertheless, out of an abundance of caution, if Defendants want to have Ms. Allen testify live, which is not a request they have made, I will schedule such a

hearing at a convenient date. In the meantime, I have made a provisional ruling on standing based on the Allen declaration. Defendants have one week to request a hearing. If that hearing so requires, I will reconsider my standing ruling.

B. Analysis

On the faces of the Dearn patents, AZAB is the assignee. (*See also* DX 111 at 30–37 (USPTO Notice of Recordation of Assignment Document)). The patents issued in 2004 and 2007, and they both ultimately relate back to application 10/129,773, filed on November 28, 2000.

The patents claim priority from a 1999 United Kingdom patent application, No. 9928578.5. On June 27, 2000, AZUK assigned to AZAB all rights related to the UK patent application. (PX 239). Plaintiffs contend this assignment applies to the Dearn patents. (D.I. 145 at pp. 2–3). The agreement stated that AZUK was granting AZAB "all rights in the Inventions [contained in various patent applications including GB 9928578.5] and its rights to apply for prosecute and obtain patent or similar protection in respect of the Inventions in any and all of the countries of the world...." (PX 239 at pp. 1, 4). The agreement does not appear to contemplate any reservation of interest by AZUK.

AstraZeneca also contends that a 2002 Patent Administration Services Arrangement applies to the Dearn patents. (D.I. 145 at pp. 6–7; D.I. 145-1 at ¶ 4). The 2002 administration agreement explicitly reserves to AZUK a "beneficial ownership" interest in "certain patent[s]." (PX 240 at 1–2). This agreement does not appear to describe which patents are the "certain patent[s]" covered. (PX 240 at 1).

Plaintiffs have proffered no addendum or definitional section showing that the Dearn patents are covered by the 2002 Agreement.

While AZAB is the assignee of both patents and the 2000 assignment agreement purports to give AZAB all rights in the patents, the 2012 licensing agreement is between AZUK and Impax. (PX 8). The 2012 licensing agreement purports to bind AZUK and its affiliates. (*Id.* at 60). Affiliates are defined by the agreement as two entities under common control. (*Id.* at 8). Ms. Allen, who represented AztraZeneca in negotiation of the licensing agreement, stated that AZAB consented to the license. (D.I. 145-1 at ¶ 8). Ms. Allen's declaration also confirms that AZAB and AZUK are commonly owned by AstraZeneca PLC and thus would be affiliates. (*Id.* at ¶ 7).

Impax holds an exclusive license. (PX 8 at 61). Ms. Allen also swore in her declaration that the patents have not been further licensed or assigned. (D.I. 145-1 at ¶¶ 9–10).

Defendants hone in on the gap between AZAB and AZUK. They argue that I cannot be sure that all ownership interests are represented without Plaintiffs having filled this gap. There is no reason to believe, however, that all ownership interests are not represented. I credit Ms. Allen's assertion that AZAB consented to an exclusive license to Impax and that no further assignments of the Dearn patents have been made. Her assertion is bolstered by the fact that Impax was satisfied that it had successfully executed an exclusive license to the patents, which it could not have done had a third party had some interest in them.

It is possible, based on the documents before the Court, that AZUK has no ownership interest in the patents, in which case AZUK should not be a plaintiff. On the one hand, the 2012 licensing agreement between AZUK and Impax is consistent with Plaintiffs' argument that the 2002 service arrangement covers the Dearn patents. On the other hand, Plaintiffs have offered no proof that the 2002 agreement does, in fact, extend to the Dearn patents. Defendants, however, have not moved to dismiss AZUK, but only to dismiss the case *in toto* for lack of standing. Because there is a valid assignment of the patents to AZAB, AZAB has consented to an exclusive license to Impax, and there is no evidence that the Dearn patents have been assigned outside of the three plaintiffs, I find that within the plaintiff class there is standing. There is no missing plaintiff. Thus, I have subject matter jurisdiction. As stated earlier, I will reconsider this holding if Defendants request a hearing with Ms. Allen and that hearing necessitates reconsideration.

II. INVALIDITY

Defendants have two invalidity arguments. Defendants argue that two of the asserted claims are anticipated by prior patents. Defendants also argue that all of the asserted claims are obvious in light of the prior art.

First, I describe the inventions in the asserted claims. Second, I make findings on the person of ordinary skill in the art. Third, I make findings on the scope of the prior art that is relied on for Defendants' anticipation and obviousness arguments. Fourth, I address Defendants' anticipation argument and find that Defendants have failed to prove by clear and convincing evidence that the asserted

claims are anticipated. Fifth, I address Defendants' obviousness argument and find that Defendants have failed to prove the patents are obvious by clear and convincing evidence.

A. The Patents in Suit

The '767 patent is a continuation of the '237 patent and both generally relate to pharmaceutical formulations of zolmitriptan. Claims 4, 11, 12, and 14 of the '237 patent and claims 6, 14, 15, and 16 of the '767 patent are asserted in this case. (D.I. 151 at 48–49). Claim 14 of the '237 patent and claim 14 of the '767 patent have four and twelve possible iterations respectively.

Each claim involves zolmitriptan with different combinations of five characteristics: (1) form, (2) pH, (3) buffer, (4) sterility, and (5) packaging.

All but two claims require a pharmaceutical formulation suitable for intranasal administration. Claims 15 and 16 of the '767 patent require an aqueous solution. Defendants have made no unique invalidity arguments as to Claims 15 and 16. Thus, I will treat them in kind with the other claims.

The other characteristics are claimed and asserted in the following combinations:

Claim	pH	Buffer	Sterility	Packaging
'237 Patent				
4	5 (+/- .04)	Buffered	N/A	N/A
11	4.5 to 5.5	Buffered in citric acid and disodium phosphate	N/A	N/A

Claim	pH	Buffer	Sterility	Packaging
12	4.5 to 5.5	Buffered in citric acid and disodium phosphate	Sterile	N/A
14(i)	4.5 to 5.5	N/A	N/A	Intranasal administration device packaged to protect the formulation from light
14(ii)	5 (+/- .04)	N/A	N/A	Intranasal administration device packaged to protect the formulation from light
14(iii)	<7	Buffered in citric acid and disodium phosphate	N/A	Intranasal administration device packaged to protect the formulation from light
14(iv)	4.5 to 5.5	Buffered in citric acid and disodium phosphate	N/A	Intranasal administration device packaged to protect the formulation from light
'767 Patent				
6	3.5 to 5.5	Buffered in citric acid and disodium phosphate	N/A	N/A
14(i)	<6	N/A	N/A	Intranasal administration device packaged to protect the formulation from light
14(ii)	3.5 to 5.5	N/A	N/A	Intranasal administration device packaged to protect the formulation from light
14(iii)	<6	Buffered	N/A	Intranasal administration device packaged to protect the formulation from light
14(iv)	3.5 to 5.5	Buffered	N/A	Intranasal administration device packaged to protect the formulation from light
14(v)	<6	Buffered in citric acid and disodium phosphate	N/A	Intranasal administration device packaged to protect the formulation from light
14(vi)	3.5 to 5.5	Buffered in citric acid and disodium phosphate	N/A	Intranasal administration device packaged to protect the formulation from light

Claim	pH	Buffer	Sterility	Packaging
14(vii)	<6	N/A	Sterile	Intranasal administration device packaged to protect the formulation from light
14(viii)	3.5 to 5.5	N/A	Sterile	Intranasal administration device packaged to protect the formulation from light
14(ix)	<6	Buffered	Sterile	Intranasal administration device packaged to protect the formulation from light
14(x)	3.5 to 5.5	Buffered	Sterile	Intranasal administration device packaged to protect the formulation from light
14(xi)	<6	Buffered in citric acid and disodium phosphate	Sterile	Intranasal administration device packaged to protect the formulation from light
14(xii)	3.5 to 5.5	Buffered in citric acid and disodium phosphate	Sterile	Intranasal administration device packaged to protect the formulation from light
15	<6.0	Buffered	N/A	N/A
16	3.5 to 5.5	Buffered	N/A	N/A

B. Person of Ordinary Skill in the Art

The skilled artisan is an individual with a bachelor's of science or master's degree in pharmacy or chemistry and five years of experience related to pharmaceutical formulations, or a doctorate or medical degree and a lesser degree of experience. The experts did not significantly disagree on the person of ordinary skill in the art. (*See* Tr. at 409, 689–90). The skilled artisan here need not have a specialty in nasal formulations. (Tr. at 690).

C. Prior Art

In assessing Defendants' anticipation and obviousness arguments, first I must make factual findings on the state of the art at the time of invention.[3] Defendants rely on all four references for their obviousness case and the Chauveau and Marquess references for anticipation.

The priority date for both patents is December 3, 1999, the date of the U.K. patent application. (Tr. 689–90; *see* '237 Patent; '767 Patent). All asserted prior art predates December 3, 1999, and their status as prior art is not contested.

i. Sumatriptan Nasal Spray

As of 1997, a sumatriptan nasal spray was being used to treat migraines. (Tr. at 185).[4] The branded name of sumatriptan nasal spray is Imitrex. (Tr. at 90). As formulated, Imitrex is buffered in disodium phosphate and has an approximate pH of 5.5. (DX 63 at 8; D.I. 146 at 14; D.I. 151 at 35). Imitrex has "a very bad taste, a very bitter taste." (Tr. at 195).

Both sumatriptan and zolmitriptan are triptans, a migraine specific family of drugs. (DX 117 at pp. 403–04). Sumatriptan was the first to market; zolmitriptan

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[3] Defendants cited other prior art to show that pH, buffer, sterility, and packaging were previously disclosed. While I have considered those references, because my invalidity opinion hinges on the basic invention at issue, namely putting zolmitriptan into a nasal spray, here I have focused on the prior art relevant to that issue.

[4] The trial transcript ("Tr.") is available at D.I. 164, 165, 166 and 167. It is consecutively paginated.

the second. (*Id.* at p. 403). In 1999, there were seven additional triptans in testing. (Tr. at 213; *see also* DX 117 at pp. 403–04).

As I will discuss, zolmitriptan has a more powerful, active metabolite that is created when zolmitriptan passes through the liver. Sumatriptan, in contrast, does not have an active metabolite. (Tr. at 214). Only two other triptans, eletriptan and almotriptan, have active metabolites, but their metabolites "don't really contribute at all to the efficacy of those drugs." (*Id.*). Zolmitriptan stands alone in the class of triptans as having an active, more potent metabolite. (*Id.*).

ii. Chauveau

U.S. Patent No. 6,326,401 (JX 4) and French Patent Application No. 2,773,489 (DX 3) (collectively "Chauveau") both claim a pharmaceutical formulation containing Labrasol for oromucosal administration. On both the patent and the application, Jacques Chauveau is the first named inventor. The U.S. Patent claims priority from the French application and the two documents are the same in relevant part. The U.S. Patent was filed January 6, 1999. The French Application is dated January 15, 1998.

Chauveau discloses administration through the mouth, nose, or pharynx. Nasal administration, however, is the preferred route.

Chauveau describes the invention as aimed at solving the problem of active substances that degrade in the gastrointestinal tract when taken in pill form. (*See* '401 Patent, col. 1, ll. 15–20 ("However, this administration route, in which the active substance is administered by the buccal route, to be delivered into the

stomach and the small intestine, has its limits, in particular because a large number of active substances are degraded in the gastrointestinal tract."); 29–31 ("For this reason, new pharmaceutical forms are still being sought, in particular for active substances which are degraded particularly in the gastrointestinal tract."); 48–52 ("It would thus be desirable to have available an effective pharmaceutical formulation...in particular suitable for medicaments which have a tendency to be degraded particularly by oral administration."); *see also* DX 3 at 2–3).

Chauveau offers a laundry list of potential active ingredients. In the '401 patent, over twenty-five categories or examples of medications are given. ('401 Patent, col. 2., l. 38–col. 3, l. 14; *see also* DX 3 at 4–5). For example, Chauveau suggests "antibiotics, bacteriostatics, antihistamines, analgesics,...." Importantly for present purposes, included in the list is the following: "The active substance can also be, in particular, an anti-migraine active substance, such as a triptan, such as sumatriptan or zolmitriptan." ('401 Patent, col. 3, ll. 12–14; DX 3 at 5 (disclosing same)). The most preferred embodiment in Chauveau has the peptide IS 159 as the active substance. (Tr. at 720; '401 Patent, col. 2, l. 50– col. 3, l. 11; DX 3 at 4).

The Chauveau specification discusses a broad range of pHs. It describes a preferred embodiment as a "liquid nasal formulation, characterized in that it has a pH of between 4 and 9, in particular between 5 and 8." ('401 Patent, col. 3, ll. 61–63; *see* DX 3 at 6 (disclosing same)). It also describes an embodiment where IS 159 is the active ingredient and is prepared "in a dose which is effective for the pernasal route, and in that it has a pH of 4 to 8, in particular 6 to 7." ('401 Patent, col. 4, ll.

13–16; *see* DX 3 at 6 (disclosing same); *see also* '401 Patent, col. 4, ll. 26–29 (disclosing IS 159 with a pH between 6 and 7); DX 3 at 7 (disclosing same)). In example 3 of the specification, a pH of 2.5 for triethylaminephosphoric acid is disclosed. ('401 Patent, col. 6, l. 28, col. 7, l. 63; DX 3 at 10, 13). Chauveau's claims disclose the same pHs as its specification. ('401 Patent, col. 10; DX 3 at 17). These are the only discussions of pH in Chauveau.

iii. Marquess

Defendants cite to international application No. PCT/US99/12751 with Daniel Marquess listed at the first inventor. (JX 3). Marquess mentions zolmitriptan by name. (*E.g.*, *id.* at 17). The application was filed June 7, 1999 and published December 16, 1999. (*Id.* at 1).

Dr. Alexander Klibanov[5] testified, and I credit the testimony, that zolmitriptan as used in Marquess is different than zolmitriptan as used in the Dearn patents. (*See* Tr. at 729–30 ("[Z]olmitriptan is clearly outside of the scope of [Marquess.]")). Marquess is directed at drugs that are covalently linked to other drugs. (Tr. at 728–29). In my claim construction opinion, I rejected Defendants' argument that zolmitriptan as used in the Dearn patents includes covalently

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[5] Dr. Alexander Klibanov is one of Plaintiffs' expert witnesses. He teaches and researches chemistry and bioengineering at MIT and has done so for nearly forty years. He is a prolific writer (authored 310+ scientific articles), is an inventor in his own right (holds 21 patents), and is an entrepreneur in the pharmaceutical formulation space (founded six pharmaceutical companies). He also has specific experience in pharmaceutical formulations. (D.I. 125-1 at 60–100).

bonded zolmitriptan. (D.I. 60 at 7–9). Marquess, therefore, does not disclose zolmitriptan as used in the asserted claims.

Marquess discusses intranasal administration as one of seven listed methods of drug delivery. (Tr. at 729; JX 3 at 33). It does not refer to the pH of a nasal formulation. Defendants argue that because Marquess incorporates by reference *Remington's Pharmaceutical Sciences* (DX 6) in its entirety (JX 3 at 35), Marquess discloses a pH level. (D.I. 146 at 13). At page 1502, *Remington's* discusses nasal solutions and states that they "usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5." (DX 6 at 1571). I do not find this reference to the entirety of *Remington*'s effectively discloses a single reference to pH on one page of a volume spanning over 1900 pages. *See Advanced Display Sys. Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282–83 (Fed. Cir. 2000). Thus, Marquess also does not disclose a pH for zolmitriptan, even covalently bonded zolmitriptan.

iv. Tepper and Rapoport

In a November 1999 review article entitled *The Triptans: A Summary* (DX 117), Drs. Stewart Tepper and Alan Rapoport state that a "nasal spray form [of zolmitriptan] is under development." (DX 117 at p. 404). The article also indicates that studies had been conducted on zolmitriptan nasal sprays and fast melt tablets. (*Id.* at p. 409). The article, however, only makes passing reference to the nasal spray.

This article, in discussing zolmitriptan, makes reference to the fact that zolmitriptan creates an active metabolite when digested. (*Id.* at p. 408). The article

discusses zolmitriptan encouragingly, explaining that "a large comparative trial" found it more effective than sumatriptan. (*Id.* at p. 409).

The article does not discuss any other elements of the asserted claims such as pH, buffer, sterility, or packaging.

D. Anticipation

Having made findings on the scope of the prior art, I turn to Defendants' first invalidity argument. Defendants argue that the Marquess and Chauveau references anticipate claim 4 of the '237 patent[6] and claim 15 of the '767 patent. (D.I. 146 at 23–26, 28–30).

A patent claim is invalid as anticipated under 35 U.S.C. § 102 if "within the four corners of a single, prior art document . . . every element of the claimed invention [is described], either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009) (alterations in original) (internal quotation marks omitted).

"[T]he hallmark of anticipation is prior invention." *Net MoneyIN Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). Thus, "the prior art reference...

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6 Defendants state in a headline to their brief that claim 14 of the '237 patent is anticipated (D.I. 146 at 27), but direct no argument to it (*see id.* at 27–28). Claim 14 requires specific packaging and Defendants have not even attempted to show that Marquess or Chauveau include a packaging disclosure.

must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Id.*

Both claim 4 and claim 15 require at least (1) zolmitriptan, (2) in a nasal spray (3) at a certain pH. Thus, to anticipate, the prior art must at least disclose zolmitriptan in a nasal spray at the claimed pHs of either 5 (+/-.04) or <6.[7]

Defendants rely on Marquess for anticipation. As I found, *supra* II.C.iii., Marquess does not disclose a pH and does not disclose zolmitriptan as used in the Dearn patents. Thus, Marquess does not anticipate the claimed inventions.

Defendants also rely on Chauveau for anticipation. Chauveau discusses pH at several points. Several of its disclosures, however, relate to the pH of specific substances, in particular, to a pH for IS 159 and for an acid. Zolmitriptan is not the referenced acid, nor is it IS 159, and thus those disclosures are not anticipating.

The only potentially relevant disclosure, then, is the description of an embodiment including a "liquid nasal formulation, characterized in that it has a pH of between 4 and 9, in particular between 5 and 8."

Both 4 to 9 and 5 to 8 are broad ranges and include both acidic and alkaline pHs. (Tr. at 723). All of the asserted claims are under 7 and thus are acidic, not

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[7] The asserted claims also require a buffer. Defendants argue both that a buffer is inherent and that Chauveau's reference to excipients discloses a buffer. First, a buffer is not inherent because a nasal spray does not necessarily function with the use of a buffer. In fact, all nasal examples in Chauveau are unbuffered. (Tr. at 724–25). Second, Chauveau's generic reference to excipients does not disclose a buffer. Chauveau makes no mention of buffers and no other language in Chauveau would lead a skilled artisan to think it means buffer when it says excipients. (*Id.*).

alkaline. *See* "Alkaline," *Merriam-Webster Dictionary* (Online ed.) (accessed Mar. 21, 2017). Chauveau's broad disclosure is not "sufficient[ly] specific to anticipate th[e] limitation[s] of the claim." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). Even if it was sufficiently specific, Chauveau gives no reason to connect this discussion of pH and zolmitriptan. (Tr. at 724). Thus, the reference does not disclose all of the elements as arranged in the claim.

E. Obviousness

Having rejected Defendants' anticipation argument, I turn to Defendants' second invalidity argument. Defendants argue that all of the asserted claims are obvious.

The presumption that all patents are valid is the starting point for any obviousness determination. 35 U.S.C. § 282. A patent claim is invalid as obvious under 35 U.S.C. § 103 if the novel aspect of the claimed invention "would have been obvious... to a person having ordinary skill in the art...." *Id.* § 103(a); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007).

Obviousness is a question of law that depends on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the relevant art; and (4) any objective indicia of nonobviousness. *See KSR*, 550 U.S. at 406; *see also Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1347 (Fed. Cir. 2012).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662–63 (Fed. Cir. 2000); *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 679 (Fed. Cir. 1988).

To prove obviousness, a party must show that a skilled artisan would have been motivated to combine the prior art teachings to create the claimed treatment method with a reasonable expectation of success. *See Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013). The improvement over prior art must be "more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417. Evidence of obviousness, especially when that evidence is proffered in support of an 'obvious-to-try' theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1072 (quoting *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)). Obviousness must be proven by clear and convincing evidence. *Id.* at 1078.

i. First Pass Metabolism

When ingested, a drug travels through the gastrointestinal tract, is absorbed into the bloodstream through the small intestine, and "goes right through the portal system to the liver." (Tr. at 215). In the liver, a portion of the drug is converted to metabolites. (Tr. at 215–16). In the normal case, the metabolites are inactive. (Tr. at 215). The inactive metabolites are then expelled from the body. (*Id.*).

Only after this process—called "first pass metabolism"—does an ingested medication "work on the end[] organ." When nasal formulations are used, first pass metabolism is delayed. (Tr. at 216–17). The drug enters the bloodstream directly through the nasal mucosa and circulates longer before reaching the liver. (*Id.*). None of the active ingredient is lost initially. (Tr. at 217). This is one of the main benefits of putting a drug in a nasal formulation.

Zolmitriptan, however, has a unique attribute that changes the calculus. First pass metabolism results in an active metabolite, 183C91, which is two to eight times more powerful than zolmitriptan itself. (Tr. at 219, 779; *see also* Tr. at 629). 183C91 is only created, though, when zolmitriptan is metabolized by the liver. Thus, bypassing the liver, which is a benefit of nasal sprays for most drugs, would appear to be a detriment for zolmitriptan.

This attribute of zolmitriptan supports nonobviousness in three ways.

First, the state of the art taught away from putting zolmitriptan in a nasal spray because of its active metabolite. A skilled artisan would have been aware of 183C91. The skilled artisan would have been discouraged from using a method that

did not fully utilize the metabolite. Dr. Rapoport testified, Dr. Klibanov echoed, and I agree that it would be "absolutely counterintuitive to make a nasal spray when you have an active metabolite which is more potent... than the drug itself...." (Tr. at 261, *see* Tr. at 780). While resisting the conclusion, Defendants' expert, Dr. Sveinbjörn Gizuarson,[8] acknowledged that a skilled artisan would have been aware of 183C91 and would have considered its greater potency. (Tr. at 629–31).

As all other triptans, including sumatriptan, do not rely on an active metabolite for therapeutic effectiveness, a skilled artisan would look to any of the other triptans before looking to zolmitriptan to develop a pharmaceutical product that would not take advantage of first pass metabolism.

Chauveau specifically teaches away from using zolmitriptan because of its active metabolite. While not using the term "first pass metabolism," Chauveau states it is solving the problem of drugs that degrade when digested.[9] A skilled artisan would read Chauveau and be pointed away from a zolmitriptan nasal spray, because zolmitriptan's "degrading" is what made it a beneficial drug.

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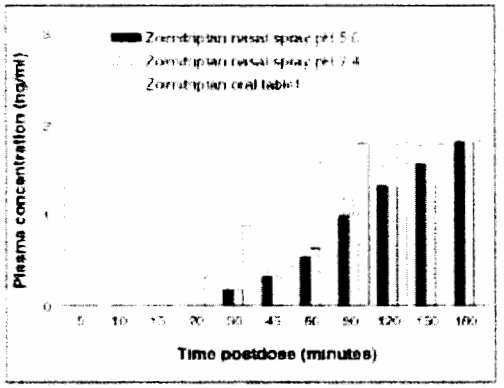
[8] Dr. Sveinbjörn Gizuarson is one of Defendants' expert witnesses. He holds a doctorate in pharmacy and has focused on intranasal drugs. He has taught for 10+ years at the University of Copenhagen and the University of Iceland and founded a research and development company focused on creating intranasal drugs. (D.I. 124-1 at 3).

[9] Marquess also teaches away from placing zolmitriptan in a nasal spray. Marquess says that "drugs that act indiscriminately" have undesirable side effects. (JX 3 at 4). Dr. Klibanov explained that this language would discourage a skilled artisan from using zolmitriptan without covalently attaching it to another drug. (Tr. at 731).

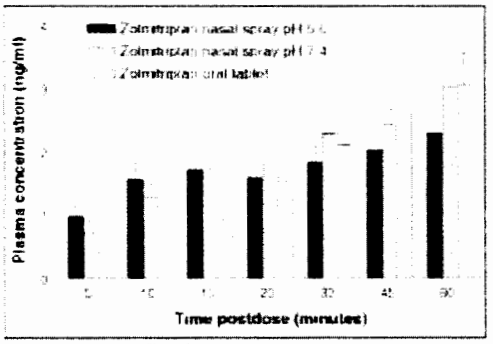
The state of the art at the priority date taught away from using zolmitriptan in a nasal spray. This is strong evidence of nonobviousness.

Second, because of zolmitriptan's reliance on its active metabolite, the prior art failed to teach that zolmitriptan by itself would be effective. When administered nasally, 183C91 takes longer to appear in the bloodstream. (PX 74 at 4–5; Tr. at 219–20; *see also* Tr. at 634). One study compared Zolmitriptan administered by a nasal spray at pH 5.0 to a Zolmitriptan oral tablet and studied the presence of 183C91 in the plasma over time:



(PX 74 at 5). As this graph shows, 183C91 does not show up in the bloodstream until thirty minutes after taking a nasal spray. It is never present in as high a concentration as it is from an oral tablet. The metabolite is not present at an equal level until three hours after administration.

Zolmitriptan itself, in contrast, was present in the bloodstream faster with the nasal spray:



(*Id.*). Thus, any relief from a nasal spray before the thirty minute mark is from zolmitriptan itself, not from 183C91. (Tr. at 219–21).

The state of the art in 1999 did not teach that zolmitriptan itself would have any therapeutic effect. Dr. Alan Rapoport[10] testified he was unaware of any reference that taught as much. (Tr. at 221). When Dr. Gizuarson was asked to point to such a reference, he was unable to do so. (Tr. at 639).

Third, a skilled artisan would not have had a motivation to combine zolmitriptan with a nasal spray. Defendants have not shown the motivation existed, and the prior art did not give a reason to do so. Given what was known about how

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10 Dr. Alan Rapoport was one of Plaintiffs' expert witnesses. He is a medical doctor focused on neurology. He has extensive experience treating migraine patients and participating in medical discourse on the best treatments for migraines. He is a co-author of the prior art reference bearing his name. (D.I. 125-1 at 1–27).

zolmitriptan worked, a skilled artisan would not have had a reasonable expectation of success in combining zolmitriptan in a nasal spray. Thus, there is not a prima facie case of obviousness.

ii. Secondary Considerations of Nonobviousness

Secondary considerations of nonobviousness are important because they "serve as insurance against the insidious attraction of the siren hindsight...." *W.I. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). Defendants' evidence fails to establish a prima facie case that the Dearn patents are obvious. Nonetheless, I will also examine the secondary considerations.

A patentee is not required to present evidence of secondary considerations. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101 (Fed. Cir. 2015). That said, if the patent challenger establishes a prima facie case of obviousness, "the patentee would be well advised to introduce evidence sufficient to rebut that of the challenger." *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007)). There must be enough evidence, however, for me to make a finding that a given secondary consideration exists by a preponderance of the evidence. *See Apple, Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc). If there is, I will then consider the probative value of each secondary consideration in light of the evidence produced. That does not mean, though, that the burden of persuasion on the ultimate question of obviousness transfers to the proponent of the secondary consideration. *Pfizer, Inc.*, 480 F.3d at 1359. That burden stays always with the patent challenger. *Id.* at 1359–60.

Plaintiffs presented evidence of (1) licensing, (2) commercial success, (3) industry praise, (4) long felt need, and (5) unexpected results.[11] I will discuss each in turn.

Licensing

Impax paid AstraZeneca $130 million for an exclusive license to the Zomig franchise and agreed to varying royalty rates, including 40% on the nasal spray.[12] (Tr. at 78–79; PX 8 at 71). That payment included the rights to the nasal spray and oral formulations. (Tr. at 81). The payment of $130 million is an objective indicator that the market valued the licensed technology. The question then is whether there is a nexus between the payment and the Dearn patents specifically.

The license went into effect January 31, 2012. (PX 8 at 7). Mr. Clark testified that the patents protecting the oral formulations expired in April 2013, a little more than one year later. (Tr. at 81). In contrast, the Dearn patents do not expire until 2021. (Tr. at 80–81).

The prior sales data (PX 42) do not suggest that Impax would recoup its entire investment from oral formulations sales in the period where the tablets still

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11 Plaintiffs also argued that copying by Summit is an objective indicia of the nonobviousness of the pH claimed by the Dearn patents. (D.I. 151 at 26). That argument, however, does not speak to the main invention, putting zolmitriptan in a nasal spray and is not strong either way. *See Bristol–Myers Squibb Co. v. Teva Pharma. USA, Inc.*, 923 F. Supp. 2d 602, 676 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014) (stating that copying in the Hatch-Waxman context "is not compelling evidence" of nonobviousness).

12 There can be no serious dispute Zomig nasal spray embodies the claims of the Dearn patents. (*See* Tr. at 137–38).

had patent protection. The net sales from a twelve month period ending September 30, 2011, the year before the licensing agreement took effect, totaled $163 million. (PX 8 at 271). The prior sales data show during that same time the nasal spray made up about twelve percent of Zomig sales and the oral formulations about eighty-eight percent. (PX 42). Without expert testimony or profit data, it is difficult to say how much of the licensing payment Impax could expected to recoup from the oral formulations. I think it is clear, however, Impax could expect to recoup a significant sum from sales of the oral formulation in the fifteen month period the patents would last. If sales remained constant, then Impax could expect net sales of $116.5 million during that period, after the royalty payment to AstraZeneca.[13] Thus, I find there is a nexus between the licensing of the nasal spray and the licensing payment, as I find that a portion of the $130 million had to be based on expected profits from Zomig nasal spray. This conclusion is bolstered by the press release issued following the licensing agreement. In it, Impax emphasized the nasal spray as the focus of the acquisition. (PX 8 at 271) ("[W]e look to build sales of the Zomig® nasal spray dosage form.").

I find that Plaintiffs' licensing evidence is proof of a secondary consideration of nonobviousness.

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[13] To arrive at this number, I multiplied the percent of sales attributable to the oral formulations, eighty-eight percent, by the net sales for the twelve month period, $163 million. I then subtracted the thirty-five percent royalty payment to AstraZeneca and calculated a per month average and multiplied that average by fifteen months.

Commercial Success

Plaintiffs presented evidence of commercial success in the form of revenue growth and market share.

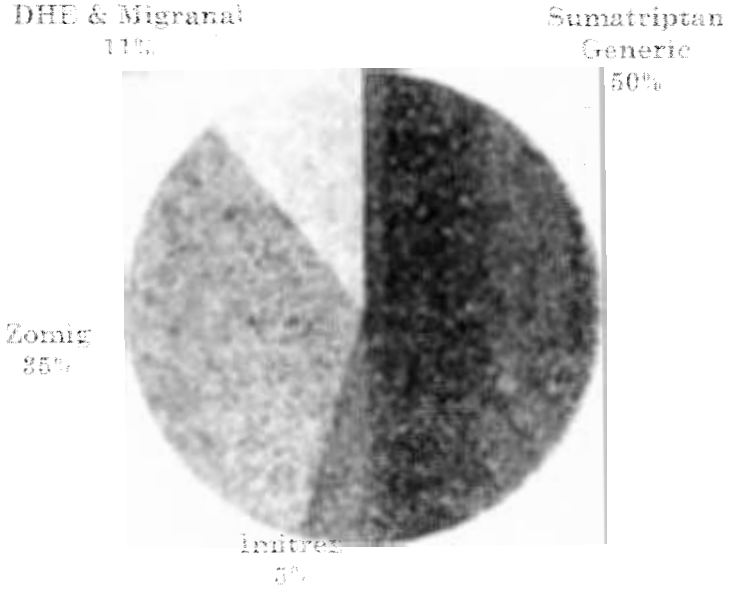
Plaintiffs' evidence of revenue growth is inconclusive. It demonstrates revenue growth but only after Impax took over in 2012. (*See* Tr. at 86). With Impax's stated focus on increasing marketing of the nasal spray (PX 8 at 271), the growth cannot be clearly attributed to the invention in the Dearn patents.

The market share data is also inconclusive. It does not speak for itself and Plaintiffs did not offer sufficient context for it to carry probative force.

Ninety-six percent of the migraine treatment market remains oral formulations. (Tr. at 89; PX 42). Zomig nasal spray represents about one percent of the total market. (*Id.*).

The nasal spray market is as follows:

NASAL MARKET SHARE



(Tr. at 90; PX 42).[14] As a branded drug, zolmitriptan (Zomig) far outpaces sumatriptan (Imitrex). Zomig does not have a close generic. (*See* Tr. at 101, 104). Sumatriptan's generic has half the total nasal market. Compared to sumatriptan's total nasal market share, fifty-five percent, zolmitriptan is behind at thirty-five percent. The problem with this data, ultimately, is that there is no point of reference to understand it. Plaintiffs offered no expert testimony on the significance of zolmitriptan's market share. For the reasons discussed, the market share data does not speak for itself. Thus, it provides no probative evidence of commercial success. I find that commercial success has not been established.

Industry Praise

Plaintiffs offer evidence of industry praise or acclaim in three forms. First, Dr. Rapoport testified Zomig nasal spray was and is his number one migraine treatment. (Tr. at 223). Second, Plaintiffs proffered an industry newsletter touting that the nasal spray "answers pressing need in migraine." (PX 48). Third, Plaintiffs proffered a marketing survey of 197 neurologists and pediatric neurologists. (PX 96). This evidence has little probative force.

First, Dr. Rapoport, while undoubtedly a leading expert in migraine treatment, does not describe industry praise by testifying about his personal

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[14] The market share adds up to 101% because of rounding.

practices and beliefs. His testimony, therefore, is not proof of objective indicia of nonobviousness.

Second, the industry newsletter, dated July 4, 2001, while praising Zomig nasal spray, is unsigned. Without knowing who wrote it, attributing any weight to it would be speculative. It is less than clear that it was written by a person of ordinary skill in the art and it could well be based on AstraZeneca's self-promotion.

Third, while the marketing survey appears to offer support for the proposition that Zomig nasal spray is well regarded by neurologists, it was offered without context. Plaintiffs offered the survey with the testimony of Greg Clark, Impax's Director of Marketing for the Zomig franchise. (Tr. at 73, 98).[15] Mr. Clark was not offered as an expert witness nor was any expert or other witness offered to explain the methodology of the survey and to interpret its meaning. The survey is also largely irrelevant, as it focused on marketing information and not product performance.

Thus, I find inadequate proof to support a finding of industry praise.

Long Felt Need & Failure of Others

Plaintiffs have four arguments that zolmitriptan nasal spray met long felt needs or succeeded where others failed. "In the pharmaceutical industry, the failure

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15 At trial, Defendants objected to admission of PX 96 as hearsay. (Tr. at 94). I provisionally overruled the objection and directed Defendants to renew their objection in the post-trial briefing. (Tr. at 98). In their briefs, Defendants criticized the survey as "highly subjective," but did not renew the objection. (D.I. 158 at 21). Thus, it is waived.

of others to develop a safe and effective drug often supports the nonobviousness of a drug that finally achieves success." *Bristol–Myers Squibb Co. v. Teva Pharma. USA, Inc.*, 923 F. Supp. 2d 602, 680 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014) (citation omitted). The long-felt and unmet need inquiries are judged at the time of the filing date of the patent. *Procter & Gamble Co. v. Teva Pharma. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009).

First, Plaintiffs argue that Zomig nasal spray met a general need for migraine treatment. This argument can be framed in several ways, all of which fail. More generally, Zomig nasal spray provided a much needed effective and quick migraine treatment. More narrowly, the argument runs that zolmitriptan nasal spray met a long felt need for a migraine treatment nasal spray and succeeded where others failed. These arguments are flawed in several ways.

For one, Plaintiffs failed to show that other migraine treatments were true failures. *Contrast ViiV Healthcare UK Ltd. v. Lupin Ltd.*, 6 F. Supp. 3d 461, 496 (D. Del. 2013), *aff'd*, 594 F. App'x 686 (Fed. Cir. 2015) (Claimed combination to treat HIV showed "impressive clinical results" at time when "the art of HIV treatment was littered with failures...."). For two, Plaintiffs failed to show that Zomig nasal spray is clearly considered superior to other migraine treatments. Zomig nasal spray still only constitutes one percent of the migraine treatment market and sumatriptan nasal spray still holds a larger overall share of the market. Further, the marketing survey (PX 96) suggests that many doctors prefer other migraine treatments.

Second, Plaintiffs argue Zomig nasal spray met the long felt need for an effective treatment of cluster headaches. The nasal spray is approved to treat cluster headaches in Europe and is the only nasal spray recommended by the American Headache Association for treatment of cluster headaches. (Tr. at 258–60). Zomig tablets, however, have also proved effective at treating cluster headaches. (PX 63 at 11). Sumatriptan injections have as well. (PX 54 at 2). Plaintiffs do not really dispute the success of either the tablets or the injections. To the extent Plaintiffs are arguing Zomig nasal spray meets a long felt need for a nasal spray to treat cluster headaches, they have not produced evidence of that need.

Third, Plaintiffs argue zolmitriptan nasal spray met the long felt need of treating patients with allodynia. Patients with allodynia experience pain from physical contact and touching. (Tr. at 251). Allodynia can be difficult to treat because it happens inside of the brain while medications work outside of the brain. (Tr. at 252). Zomig nasal spray, however, because it works so quickly, can provide relief to patients that experience allodynia. (Tr. at 254; PX 195). One study tested six triptans and only found "significant pain reduction" in one group, those treated with zolmitriptan nasal spray. (PX 195). Again, while this is an impressive attribute of zolmitriptan nasal spray, Plaintiffs have failed to provide the necessary context to characterize this as satisfying a long felt need. For example, while this one study shows zolmitriptan was the only effective triptan, it does not settle the question of whether other drugs can effectively treat allodynia. Nor have Plaintiffs produced evidence of the failed attempts of others.

Fourth, Plaintiffs argue that zolmitriptan nasal spray satisfies a long felt need because it is approved to treat teenagers. In fact, it is the only nasal spray approved to treat teenagers. (Tr. at 76). Here, Plaintiffs present some evidence of the failure of others. Dr. Rapoport was asked, "did ... the producer of sumatriptan nasal spray... make any effort to get themselves approved to treat adolescents suffering from migraines?" (Tr. at 250). Dr. Rapoport responded "Yes." (*Id.*). No further context, however, was provided. For example, it is unclear whether these attempts were in the past or present or how significant they were. Again, without context, Plaintiffs have failed to offer evidence with any probative force that zolmitriptan nasal spray met a long felt need.

Thus, I find Plaintiffs have not proved long felt need or failure of others.

Unexpected Results

Plaintiffs argue that Zomig nasal spray "is unexpectedly rapid, efficacious, and powerful *despite* delayed formation of its more potent, active metabolite...." (D.I. 151 at 40). This unexpected results argument, however, is just a reframing of the central nonobviousness contention, namely, that zolmitriptan should not have worked in a nasal spray because in tablet form it relies on 183C91, its metabolite, for therapeutic effect.

Thus, I find no proof of unexpected results as a secondary consideration.

iii. Other Claim Elements: pH, Buffer, Sterility, and Packaging

Plaintiffs presented secondary arguments that the asserted claims were not anticipated because of the pH they identified, the inclusion of a buffer generally or of a buffer of citric acid and disodium phosphate specifically, the requirement of sterility, or the added element of packaging for intranasal administration generally or packaging that protects from light specifically. None of these added limitations contribute an element of invention.

A skilled artisan already seeking to put zolmitriptan in a nasal spray would logically consider the proper pH and the most obvious thing to do would be to look at the pH of the closest drug, sumatriptan, which was about 5.5 in Imitrex. About 5.5 overlaps with all of the pH ranges in the asserted claims except for claim 4 of the ′237 patent. Thus, a skilled artisan who was motivated to put zolmitriptan in a nasal spray would have started where those claims ended. The pH of claims 11, 12, and 14 of the '237 patent as well as 6, 14, 15, and 16 of the '767 patent would have been obvious.

Claim 4 requires a pH of 5 +/- .04. Imitrex, therefore, does not literally disclose this pH but still makes the claimed pH obvious. First, it directs a skilled artisan to pHs in the range of 5.5. Second, it debunks the proffered reasons for why a pH of 5 would be counterintuitive. For example, Plaintiffs argued that a skilled artisan would not consider an acidic pH because it would lead to absorbability problems (Tr. at 795), but the success of Imitrex at 5.5 teaches otherwise. Thus,

even for claim 4, the narrowest claim, finding the pH would have been obvious in light of the prior art.

As to the other elements, drugs are frequently buffered and using a taste masking buffer would be obvious given the trouble with the taste of Imitrex. Sterility is a standard practice. Thus, if the basic concept of the claims—putting zolmitriptan in a nasal spray—is obvious, all of the claims fall with it.

iv. The Dearn Patents Are Not Obvious

The question of obviousness is a close one. Clear and convincing evidence, however, requires "evidence that places in the fact finder an abiding conviction that the truth of [the] factual contentions are highly probable." *In re Copaxone Consol. Cases*, 2017 WL 401943, at *11 n. 3 (D. Del. Jan. 30, 2017) (internal quotation marks omitted) (alteration in original).

On the one hand, zolmitriptan was a successful and promising migraine treatment. It had good bioavailability, lower dosage rates, and better "no pain" response than sumatriptan. This would have been encouraging to a skilled artisan motivated to make an anti-migraine nasal spray better than Imitrex.

On the other hand, zolmitriptan had a known, powerful metabolite, the creation of which would be delayed and diminished by nasal administration. This would point a skilled artisan away from including zolmitriptan in a nasal spray. This teaching away demonstrates that the Dearn patents were not obvious. *See Gore*, 721 F.2d at 1550 (faulting the district court for "considering the references in

less than their entireties, i.e., in disregarding disclosures in the references that diverge from and teach away from the invention at hand").

Further, I credit Plaintiffs' experts on obviousness over Defendants' experts. Dr. Rapoport is at the vanguard of migraine treatment and Dr. Klibanov is an expert in formulation. Both articulated their opinions convincingly and with reasoned support. Dr. Gizuarson offered a competing opinion, but in his career he has focused on nasal sprays. As the adage goes, to a hammer everything is a nail.[16]

Because of the active metabolite and its role in making zolmitriptan effective, placing zolmitriptan in a nasal spray was not obvious.

III. CONCLUSION

Defendants have failed to prove the Dearn patents are invalid. If desired, Defendants should request an opportunity to cross-examine Ms. Allen within one week. If Defendants do not make that request, the parties should submit an agreed upon form of final judgment within two weeks.

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[16] Defendants also offered the testimony of Dr. Jinnian Gao. He is employed by Summit Biosciences, a company that has a relationship to Defendants. (Tr. at 929). His testimony focused on pH. (*See* Tr. at 905–24).