UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

OCULAR THERAPEUTIX, INC.
Petitioner

v.

MATI THERAPEUTICS INC.
Patent Owner

US Patent No. 9,849,082

Inter Partes Review No. IPR2019-00448

PETITION FOR INTER PARTES REVIEW OF US PATENT NO. 9,849,082 UNDER 35 USC §§ 311-319 AND CFR § 42.100, *et. seq.*

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Ex. 1001	US Patent No. 9,849,082 (the '082 Patent)
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Ex. 1003	US Provisional Application No. 60/871,864, filed December 26, 2006 (Second '082 Provisional)
Ex. 1004	US Patent Application No. 11/695,454, filed April 2, 2007 (First '082 Non-Provisional)
Ex. 1005	US Patent Application No. 15/405,991, filed January 13, 2017 ('082 Application)
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Ex. 1010	US Application Publication No. 2005/0197614 to Pritchard *et al.*, published September 8, 2005 ("*Pritchard*")
Ex. 1011	US Provisional Application No. 60/550,132, filed March 4, 2004 (the '132 *Pritchard* Provisional)
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Ex. 1015	US Application Publication No. 2002/0169409 to Gillespie ("*Gillespie*")
Ex. 1016	Handbook of Pharmaceutical Excipients (Arthur H. Kibbe ed. 3d ed. 2000) (the "*Handbook*")
Ex. 1017	US Patent No. 6,646,001 to Hellberg et al., issued November 11, 2003 ("*Hellberg*")
Ex. 1018	US Application Publication No. 2006/0020248 to Prescott *et al.*, in the '082 File History
Ex. 1019	US Application Publication No. 2004/0208910 to Ashton *et al.*, in the '082 File History

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Ex. 1020	Baxter *et al*., *Punctal Plugs in the Management of Dry Eyes*, 2 THE OCULAR SURFACE 255-265 (October 2004) ("*Baxter*")
Ex. 1021	Foulds, I*ntra-Canalicular Gelatin Implants in the Treatment of Conjunctivitis Sicca*, 45 BRIT J. OPHTHAL. 625-27 (1961).
Ex. 1022	US Patent No. 3,949,750 to Freeman (*Freeman '750*), in the '082 File History
Ex. 1023	US Patent No. 5,283,063 to Freeman (*Freeman '063*), in the '082 File History
Ex. 1024	US Patent No. 6,196,993 to Cohan *et al*. (*Cohan*), in the '082 File History
Ex. 1025	US Patent No. 5,902,598 to Chen *et al*. (*Chen*)
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Ex. 1028	Scot Morris, O.D., F.A.A.O., *A Lesson in Managing Dry Eye, Plugs, Drugs and Tears: A Dry Eye Update, Part Two*, OPTOMETRIC MANAGEMENT 36-43 (October 2002)
Ex. 1029	U.S. Patent No. 3,826,258 to Abraham ("*Abraham*")
Ex. 1030	U.S. Patent No. 3,993,071 to Higuchi *et al*. ("*Higuchi*")
Ex. 1031	U.S. Patent No. 6,152,943 to Sawhney ("*Sawhney*")
Ex. 1032	M. Balaram *et al., Efficacy and Tolerability Outcomes after Punctal Occlusion with Silicone Plugs in Dry Eye Syndrome*, 131 OPHTHALMOL. 30-36 (2001)
Ex. 1033	U.S. Patent No. 9,309,313, entitled "Therapeutic Compositions for Treatment of Ocular Inflammatory Disorders"
Ex. 1034	US Application Publication No. 2007/0265341, entitled "Compositions and Methods for Treating Eye Disorders and Conditions"
Ex. 1035	Physicians' Desk Reference (57 ed. 2003)
Ex. 1036	Declaration of Reza Dana, M.D., executed December 14, 2018
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I. INTRODUCTION

A. The Parties

Founded in 2006, Ocular Therapeutix, Inc. ("Ocular" or "Petitioner") is an innovative biopharmaceutical company focused on the development and commercialization of therapies for various diseases and conditions of the eye. Ocular is developing the DEXTENZA® drug-eluting intracanalicular insert for treating post-surgical ocular pain and other ophthalmic conditions. On November 30, 2018, after conducting extensive clinical trials, Ocular received FDA approval to market DEXTENZA for treating ocular pain following ophthalmic surgery. Ocular expects to begin marketing DEXTENZA during the first half of 2019.

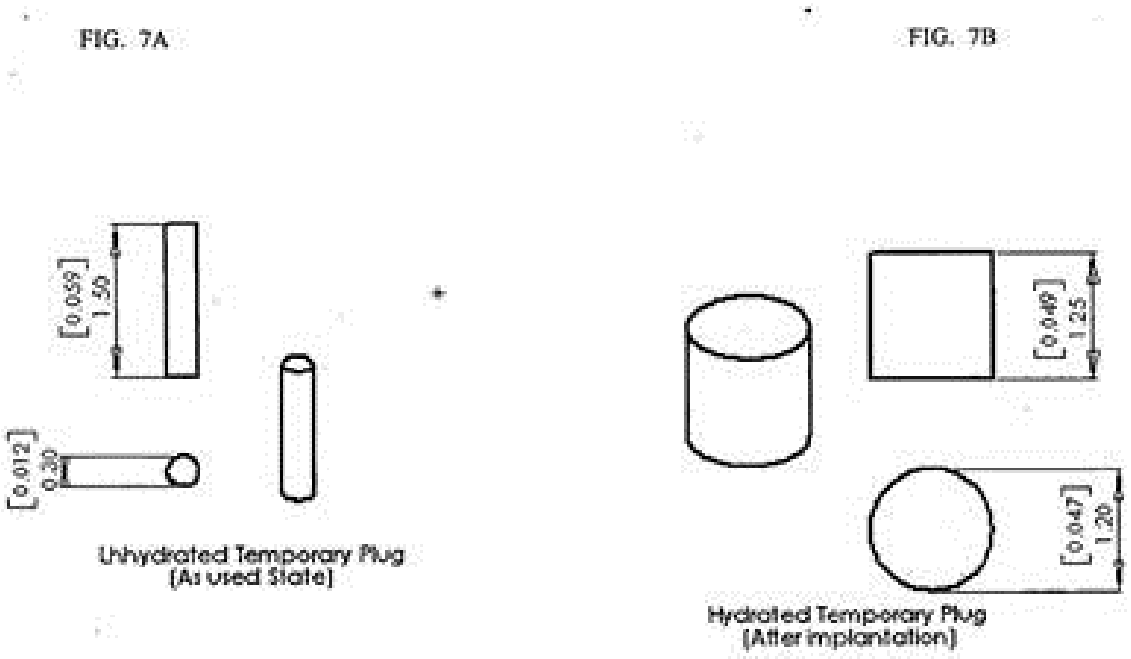
Mati Therapeutics ("Mati" or "Patentee") did not invent the technology claimed in the challenged patent. Instead, years after the alleged invention, Mati acquired from a third party the rights to the series of applications that resulted in U.S. Patent No. 9,849,082 ("the '082 Patent," Ex. 1001). Mati has no products on the market. Nonetheless, aware of the impending FDA approval of the DEXTENZA insert, Mati sent Ocular a letter accusing the DEXTENZA insert of infringing the '082 Patent and two other patents. This review is necessary to remove the cloud of Mati's threats so that Ocular can make this important, FDA-approved medical advancement available to eye surgery patients.

B. The Challenged ‘082 Patent

The ‘082 Patent claims a “drug delivery system for insertion into a lacrimal canaliculus of a patient” that comprise, *inter alia*, a cylindrical rod-shaped body made from hydrogel polymers and a therapeutic agent. *See, e.g.*, Ex. 1001, ‘082 Patent, Claims. To overcome the examiner’s prior art rejections, Patentee amended the claims to add a limitation that these drug delivery systems must also include “a distinguishing color to show placement of the system in the lacrimal canaliculus of the patient.” This limitation appears in all of the independent claims of the ‘082 Patent. Patentee argued that this color limitation—and this limitation alone—distinguished the cited prior art. But, as described in Section IV.C below, the prior art included numerous systems, such as punctal plugs and other canalicular inserts, with a “distinguishing color to show.”

Moreover, the closest prior art was neither discussed nor applied during prosecution of the ‘082 Patent. As detailed in Section V.A and the included claim chart, US Publ. 2005/0197614 to Pritchard *et al*. (“*Pritchard*,” Ex. 1010) discloses lacrimal implants, such as punctal plugs and canalicular inserts, that comprise a cylindrical rod-shaped body made from hydrogel polymers and a therapeutic agent. *Pritchard* further discloses implants that feature color, swell when placed in the canaliculus, include polymers comprising functional groups, and deliver specific therapeutic agents to treat various ophthalmic conditions, such as dry eye,

glaucoma, and post-surgical discomfort. These elements are, in essence, all of the limitations of the challenged claims. For example, in the following figures, *Pritchard* depicts an embodiment of its hydrogel canalicular inserts—both before insertion into the canaliculus and swollen as it would be after insertion:



Ex. 1010, *Pritchard*, FIGS. 7A, 7B. Again, this embodiment is exactly what is contemplated by the challenged claims. As such, *Pritchard* anticipates the claims of the '082 patent and, in combination with other prior art, renders them obvious.

C. Mandatory Notices And Certifications

1. Real Party-in-Interest

The real party in interest for this petition for *inter partes* review is Ocular Therapeutix, Inc., of 15 Crosby Drive, Bedford, MA, 01730.

2. Related Matters

Ocular is not aware of any pending litigation related to the '082 Patent nor of any requested reissue, reexamination, or review of the '082 Patent. Ocular is, however, aware of a co-pending IPR petition regarding U.S. Pat. No. 9,463,114, also filed by Ocular against the same Patentee, Mati. The '114 Patent is not related to the '082 Patent but is directed to similar technology.

Ocular is aware of one pending continuation application, U.S. App. No. 15/852,619, that includes the '082 Patent among its priority claims. A non-final office action issued on August 28, 2018, rejecting the pending claims based on grounds similar to the one that the examiner raised against the '082 Patent.

3. Counsel and Service Information

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4. Standing

Pursuant to 37 CFR § 42.104(a), Ocular certifies that the '082 Patent is available for *inter partes* review and that Ocular is not estopped or barred from requesting *inter partes* review of the '082 Patent on the grounds in this petition.

II. OVERVIEW OF THE '082 PATENT AND ITS PROSECUTION

A. Summary of the '082 Patent and Its Claims

The '082 patent was filed on January 13, 2017, and issued on December 26, 2017. The '082 patent claims priority back through a series of four continuation applications to two provisional applications: US Provisional App. Nos. 60/787,775, dated March 31, 2006 (Ex. 1002), and 60/871,864, dated December 26, 2006 (Ex. 1003). The first non-provisional application was filed on April 2, 2007. Assuming that Patentee is entitled to the priority of the first provisional--while reserving the right to challenge priority if Patentee argues that any of the cited references are too late--then the earliest claimed priority date is March 31, 2006.

The '082 Patent is entitled "Nasolacrimal Drainage System Implants for Drug Delivery." The nasolacrimal system is associated with the eye. Figure 1-1 of

the ‘082 Patent, copied below, illustrates the anatomical tissue structures of a human eye, including the nasolacrimal system:

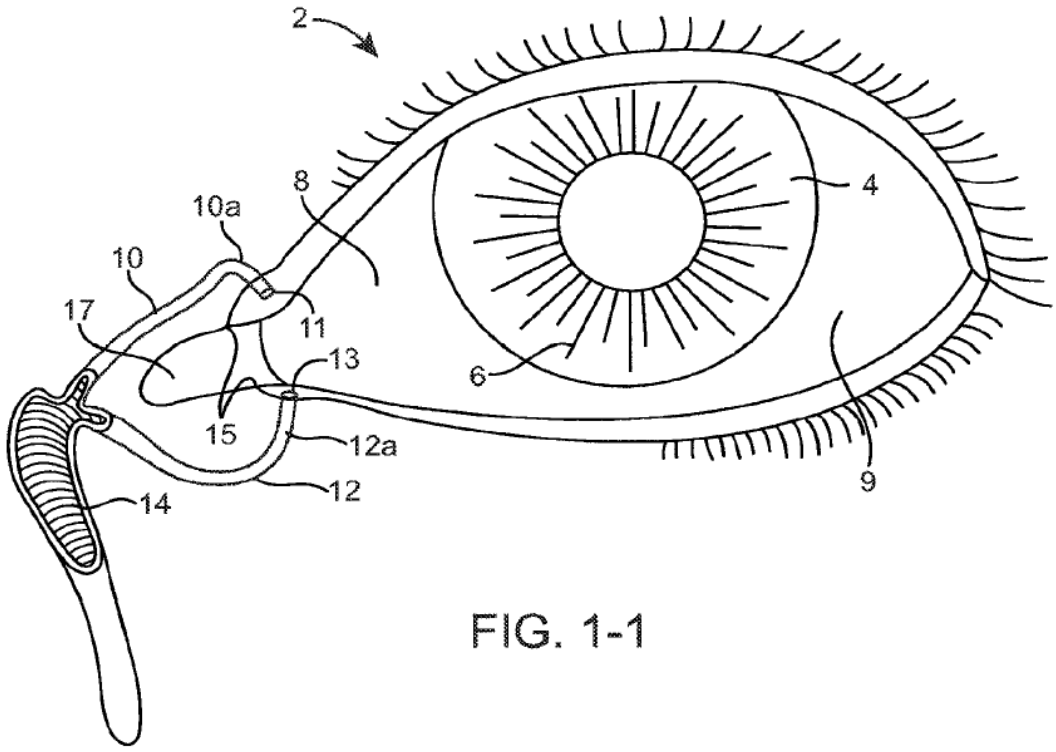

FIG. 1-1

The nasolacrimal system includes upper and lower canaliculi (the two lumens designated as 10 and 12), a lacrimal sac (14), and a punctum (11 and 13) for each canaliculus. Tears drain through the canaliculi, into the lacrimal sac, and then out through the nasal system. *See* Ex. 1001, ‘082 Patent, 7:30-65. *See also* Ex. 1036, Declaration of Reza Dana, M.D., December 14, 2018 (“Dana Decl.”), ¶¶ 28-29.

The ‘082 Patent has 23 claims. Claims 1, 11, and 18 are independent. Each of the independent claims is directed to “[a] drug delivery system for insertion into a lacrimal canaliculus of a patient.” While claiming “systems,” the ‘082 patent generally discloses “implants.” For example, the Abstract discloses “[a]n implant

for insertion through a punctum and into a canalicular lumen of a patient." Ex. 1001, '082 Patent, Abstract. *See also id.*, 1:21-24 ("The present invention is related to implants for use in or near the nasolacrimal drainage system, with embodiments providing canalicular implants . . .and punctal plugs with drug delivery capabilities"). For purposes of this discussion, Petitioner refers to such devices, interchangeably, as "implants" or "inserts."

Each of the independent claims, broadly speaking, requires (1) a therapeutic agent, (2) a cylindrical body of hydrogel polymers to hold the therapeutic agent, and (3) a distinguishing color. For example, Claim 1 recites:

> 1. A drug delivery system for insertion into a lacrimal canaliculus of a patient, comprising:
>
> a therapeutic agent,
>
> a distinguishing color to show placement of the system in the lacrimal canaliculus of the patient and
>
> a body of material to hold the therapeutic agent
>
> wherein the body of material comprises hydrogel polymers and
>
> wherein the body of material is a cylindrical rod.

Independent Claim 11 also requires that the hydrogel body swells when placed in the canaliculus. Independent Claim 18 requires that the therapeutic agent be selected from "an anti-glaucoma agent, a corticosteroid[,] an anti-microbial agent, and anti-allergy agent or a non-steroidal anti-inflammatory agent."

Most of the dependent claims recite specific therapeutic agents or ocular conditions to be treated. Two dependent claims, Claims 9 and 22, recite that the polymers comprise "functional groups."

B. The Prosecution of the '082 Patent

During prosecution, the examiner rejected most of the pending claims as anticipated either by Pub. No. US 2006/0020248, to Prescott *et al*. (Ex. 1018) or by Pub. No. US 2004/0208910, to Ashton *et al*. (Ex. 1019). *See* Ex. 1006, Office Action issued on April 6, 2017, in the '082 File History, 3-4. The examiner did not appreciate, and certainly never applied, the closest prior art, namely, *Pritchard*.

To overcome the examiner's anticipation rejections, Mati amended the pending claims to require that the claimed systems include "a distinguishing color to show placement of the system in the lacrimal canaliculus of the patient." Ex. 1007, Amendment and Response of August 7, 2017, in the '082 File History, 2, 4 (emphasis added). Originally, this "distinguishing color to show" limitation appeared in only prosecution Claim 12 (which issued as Claim 11) and in two dependent claims. Ex. 1005, US Patent App. No. 15/405,991 filed January 13, 2017, in the '082 File History, 56-58 (Claims).[1] In conjunction with these

[1] Although the claimed priority date went back 11 years through four continuations, this was the first time that Patentee included a "distinguishing color"

amendments, Patentee argued that the newly-added "distinguishing color to show" limitation alone distinguished the cited prior art:

> The subject matter of claims 11 and 25, wherein the drug delivery system comprises ". . . a distinguishing color to show placement of the system in the lacrimal canaliculus of the patient" was not included in the instant art rejections and hence is free of the art. The subject matter of those claims was incorporated into claims 1 and 19, respectively. Moreover, claim 12 recites the same language. The references relied upon by the Office Action do not expressly or inherently disclose a drug delivery system for insertion into a lacrimal canaliculus of a patient comprising or consisting essentially of ". . . a distinguishing color to show placement of the system in the lacrimal canaliculus of the patient".

Ex. 1007, Amendment and Response of August 7, 2017, in the '082 File History, 8. Based on this argument, the examiner allowed the claims. *See* Ex. 1008, Notice of Allowance mailed on August 23, 2017, in the '082 File History; Ex. 1009, Notice of Allowance mailed on September 15, 2017, in the '082 File History. *See also* Ex. 1036, Dana Decl., ¶ 42.

As discussed in Section IV.B below, however, a "distinguishing color to show" ocular implants was long known and used in the field. The examiner,

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limitation in any claims. But there is no indication in the '082 application that this was the first presentation of such claims.

apparently, did not appreciate that "distinguishing color to show" was known in the prior art.

III. CLAIM CONSTRUCTION

The claims "shall … be construed using the same claim construction standard that is used to construe the claim in a civil action in district court" because this petition was filed after November 13, 2018. *See* 83 FED. REG. 51340. Thus, claim terms should be given their ordinary meaning to one of ordinary skill in the art. *See* 37 C.F.R. § 42.100; *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). That meaning is always informed by the specification. *Phillips*, 415 F.3d at 1315. Indeed, the specification is "usually dispositive; it is the single best guide to the meaning of a disputed term." *Honeywell Int'l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1318 (Fed. Cir. 2006) (citation omitted). In addition, the tribunal "should also consider the patent's prosecution history, if it is in evidence …." *Phillips*, 415 F.3d at 1317.

A. "Distinguishing Color to Show"

The term "distinguishing color to show" appears in each of the three independent claims of the '082 Patent. But this "distinguishing color to show" limitation did not appear in any of the original claims of the first non-provisional application in the claimed chain of priority. *See generally* Ex. 1004, First '082 Non-Provisional Application, claims. Nor was this concept disclosed in the March

31, 2006 provisional application. *See generally* Ex. 1002.

The only teaching of a "distinguishing color to show" in the specification of the '082 Patent appears is in just one sentence: "In many embodiments, the sheath body and/or retention structure may have a distinguishing feature, for example a distinguishing color, to show placement such that the placement of the sheath body and/or retention structure in the canaliculus or other body tissue structure can be readily detected by the patient." Ex. 1001, '082 Patent, 20:67-21:5 (emphasis added). *See also* Ex. 1036, Dana Decl., ¶ 51.

In the context of claim wording and the specification, a person of ordinary skill in the art would understand that "distinguishing color to show" means a color that improves visibility." Ex. 1036, Dana Decl., ¶ 51.

B. "Sheath Body"

The term "sheath body" is recited in Claim 2 of the '082 Patent. Claim 2, which depends from independent Claim 1, recites that "the [drug delivery] system does not comprise a sheath body." Ex. 1001, '082 Patent, Claim 2.

Here, the specification of the '082 Patent describes "sheath body" throughout the specification (particularly at 20:26-21:9) and make clear what is meant by the term. For example, the specification states that the sheath body "comprises appropriate shapes and materials to control migration of the therapeutic agent from the drug core. The sheath body houses the core and can fit snugly

against the core. The sheath body is made from material that is substantially impermeable to the therapeutic agent so that the rate of migration of the therapeutic agent may be largely controlled by the exposed surface area of the drug core that is not covered by the sheath body." Ex. 1001, '082 Patent, 20:27-34. *See also id.*, Abstract (the disclosed implants include "a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen"). *See also* Ex. 1036, Dana Decl., ¶¶ 68-69.

Thus, in the context of the specification of the '082 patent, a person of ordinary skill in the art would understand "sheath body" to mean a "material or structure that is impermeable to the therapeutic agent and that covers a portion of a drug core to prevent migration of the therapeutic agent from the covered portion of the drug core" Ex. 1036, Dana Decl., ¶ 70.

Summary	
claim term	**proposed construction**
"distinguishing color to show"	"color that improves visibility"
"sheath body"	"material or structure that is impermeable to the therapeutic agent and that covers a portion of a drug core to prevent migration of the therapeutic agent from the covered portion of the drug core"

IV. STATUTORY GROUNDS, CHALLENGED CLAIMS, AND PRIOR ART

Ocular challenges all 23 claims of the '082 Patent. Ocular relies on *Pritchard* (Ex. 1010) as the sole or primary basis for all of its challenges. *Pritchard* anticipates Claims 1-7, 9-16, 18-20, and 22-23. These same claims are also obvious over *Pritchard* in view of either of two alternative secondary references—namely, US Publ. No. 2002/0169409 to Gillespie ("*Gillespie*," Ex. 1015) and the 2000 HANDBOOK OF PHARMACEUTICAL EXCIPIENTS ("*Handbook*," Ex. 1016). Additionally, Claims 8, 17, and 21 are obvious over both of the *Pritchard* combinations in view of US Patent No. 6,646,001 to Hellberg ("*Hellberg*," Ex. 1017).

Grounds	Claims
1-Anticipated by *Pritchard* under §102	Claims 1-7, 9-16, 18-20, and 22-23
2-Obvious over *Pritchard* in view of *Gillespie* under §103	Claims 1-7, 9-16, 18-20, and 22-23
3-Obvious over *Pritchard* in view of *Gillespie* and *Hellberg* under §103	Claims 8, 17, and 21
4-Obvious over *Pritchard* in view of the *Handbook* under §103	Claims 1-7, 9-16, 18-20, and 22-23
5-Obvious over *Pritchard* in view of the *Handbook* and *Hellberg* under §103	Claims 8, 17, and 21

Pritchard was published on September 8, 2005, based on an application filed on March 5, 2005. *See* Ex. 1010. *Pritchard* qualifies as prior art at least because it was filed and published before the earliest priority date claimed in the '082 Patent (*i.e.*, March 31, 2006).

Gillespie was published on November 14, 2002 (*see* Ex. 1015), and is thus prior art at least because it was published more than one year before the earliest priority date claimed in the '082 patent.

The *Handbook* (3rd ed.) published in 2000. *See* Ex. 1016. The *Handbook* is prior art at least because it published more than one year before the earliest priority date claimed in the '082 patent.

Hellberg issued on November 11, 2003. *See* Ex. 1017. *Hellberg* is prior art at least because it issued more than one year before the earliest priority date claimed in the '082 patent.

A. The Legal Standards for Anticipation and Obviousness

Ocular challenges all claims of the '082 patent as anticipated under 35 U.S.C. § 102, obvious under U.S.C. § 103, or both. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). A claim is obvious when the differences between the claim and the prior art are such that the claim as a

whole would have been obvious at the relevant time to a person having ordinary skill in the art to which claim pertains. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

In *KSR*, the Supreme Court confirmed the framework for analyzing obviousness originally stated in *Graham* v. *John Deere Co. of Kansas City*, 383 U.S. 1 (1966). Specifically, "[u]nder §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." *KSR*, 550 U.S. at 406, quoting *Graham*, 383 U.S. at 17-18.

B. The Scope And Content of The Prior Art

The use of implants to temporarily block tear drainage and thus treat dry eye has been known since at least the early 1960s. *See* Ex. 1020, Baxter *et al*., *Punctal Plugs in the Management of Dry Eyes*, 2 THE OCULAR SURFACE at 1(October 2004) ("*Baxter*") (summarizing the history of punctal plugs and state of the art as of 2004); *see also* Ex. 1036, Dana Decl., ¶ 31. For example, as recounted in *Baxter*, in 1961, Dr. Foulds developed and described the first punctal plugs for treating dry eye. Ex. 1020, *Baxter*, 1. As depicted in Figures 1 and 2 from the *Foulds* reference itself (copied below), these punctal plugs were cylindrical gelatin rods inserted through puncta to temporarily block the canaliculi:

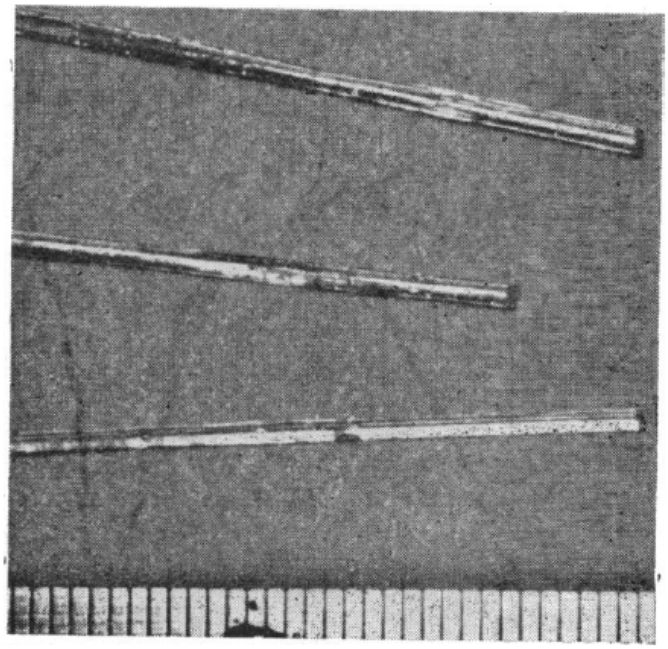


FIG. 1.—Gelatin rods used to occlude the lacrimal puncta. Scale divisions represent 0·5 mm.

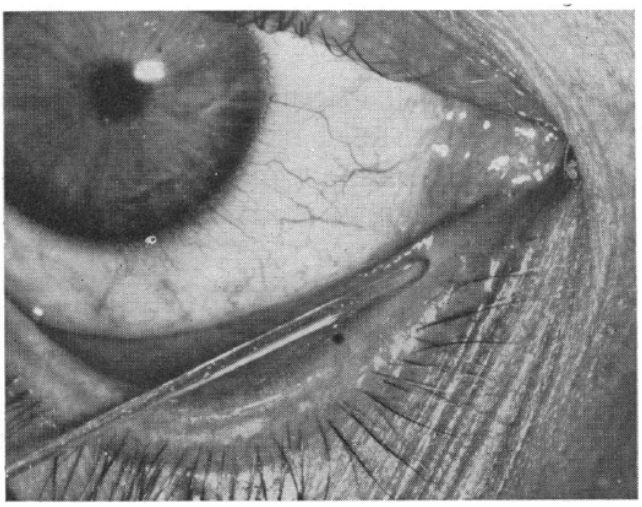


FIG. 2.—Insertion of a gelatin rod into the lower lacrimal punctum.

Ex. 1021, Foulds, *Intra-Canalicular Gelatin Implants in the Treatment of Kerato-Conjunctivitis Sicca*, 45 BRIT J. OPHTHAL. 3,4 (1961).[2]

[2] "[T]he Board may consider a prior art reference to show the state of the art at the time of the invention, regardless of whether that reference was cited in the Board's institution decision." *Genzyme Thera. Prods. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1369 (Fed. Cir. 2016); *see also Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015). Here, Ocular and its expert, Dr. Dana, rely on the prior art discussed in this section to explain and confirm the state of the art and the relevant technology so as to put into context the specific grounds for unpatentability discussed in the next section.

After the introduction of these punctal plugs, it was not long before ophthalmologists realized that they could also be used to deliver medications to the eye. Ex. 1036, Dana Decl., ¶ 32. For example, perhaps the most well-known and commercially successful punctal plugs in the prior art were the Freeman plugs, first patented in 1976. *See* Ex. 1022, U.S. Pat. No. 3,949,750 to Freeman ("*Freeman* '750"). *See also* Ex. 1036, Dana Decl., ¶ 33. *Freeman* '750 discloses a "rod-like plug" that could be made of hydroxyethylmethacrylate (HEMA) hydrophilic polymers (*i.e.*, hydrogel), that can be "impregnated with or otherwise act as a carrier vehicle for an ophthalmic medication," and that can be used to treat dry eye and other ophthalmic ailments. Ex. 1022, *Freeman* '750, Abstract. In particular, *Freeman* '750 teaches that the HEMA hydrophilic polymer material has an "approximate 28% swell rate when moistened" and thus can "improve closure of the punctal aperature more effectively." *Id.*, 4:37-40.[3] Importantly, *Freeman* '750 discloses that these hydrogel punctal plugs could be made to "store and slowly dispense ophthalmic drugs to the eye as they are leached out by the lacrimal fluids." *Id.*, 5:8-14. *See also* Ex. 1036, Dana Decl., ¶33.

[3] As discussed in another Freeman patent, HEMA is a typical hydrogel material. *See* Ex. 1023, U.S. Pat. No. 5,283,063 ("*Freeman* '063"), 6:60-63 ("hydrogel composed of hydroxyethylmethacrylate, which is a hydrophillic polymer, is preferred in the practices of the present invention").

Another known punctal plug, disclosed in U.S. Pat. No. 5,283,063 ("*Freeman* '063"), which issued in 1994, is a canalicular insert that has a "generally cylindrical body member." Ex. 1023, *Freeman* '063, Abstract. *Freeman* '063 further teaches that hydrogel composed of HEMA is the preferred material for making the insert. *Id.*, 6:60-63. This hydrogel swells when hydrated with lacrimal fluid. *Id.*, 10:67-68; 11:40-44; 13:25-46; and 15:18-30. Of note, *Freeman* '063 incorporates by reference *Freeman* '750 (s*ee id.*, 2:6-12) and thus suggests that the canalicular, hydrogel insert could also include therapeutic agents. *See also* Ex. 1036, Dana Decl., ¶34.

In fact, the prior art is full of examples of ocular implants used to deliver therapeutic agents to treat glaucoma, dry eye, and other eye conditions. For example, U.S. Pat. No. 6,196,993 to Cohan *et al*. ("*Cohan*"), issued in 2001, discloses an "ophthalmic insert device" that is inserted through the punctum and into the canaliculus and has a reservoir for dispensing an ophthalmic medication. Ex. 1024, *Cohan*, 2:22-59. *Cohan* discloses preferred therapeutic agents, including anti-glaucoma drugs (*id.*, 7:5-12), as well as antimicrobial agents, antibiotics, both steroidal and non-steroidal anti-inflammatories, antifungal agents, and other medications for treating the eye (*id.*, 13-29). *Cohan* points out that administration of these medications via the insert has many benefits over applying the same agents topically via eye drops, including better patient compliance, more

convenience, and better sustained release of the medication. *Id.* at 6:60-7:4. *See also* Ex. 1036, Dana Decl., ¶36.

Along the same lines, U.S. Pat. No. 5,902,598 to Chen *et al.* ("*Chen*"), issued in 1999, discloses sustained release drug delivery devices, including devices "particularly suitable for treating ocular conditions such as glaucoma . . . and keratitis." Ex. 1025, *Chen*, 5:65-67. These devices are preferably "cylindrical," (*id.*, 5:5) and may be used to administer a wide variety of therapeutic agents, including beta-blockers, dexamethasone, antibiotics, antiallergenics, anti-inflammatories, antibacterials, and other agents later claimed in the '082 Patent. *Also see id.*, 6:5-57 (listing numerous agents suitable for administration to the eye). *See also* Ex. 1036, Dana Decl., ¶37.

Moreover, using swellable hydrogel polymers to construct these cylindrical drug-eluting canalicular inserts for treating ophthalmic conditions was also known before the '082 Patent. For example, US Publ. No. 2005/0095269 to Ainpour *et al.* ("*Ainpour*"), published on May 5, 2005 and based on an application filed on November 4, 2003, discloses a "cylindrical plug for insertion through the punctum and into the canaliculus to block the flow of tears" that comprises "a gelatinous material which when hydrated expands and changes shape, conforming at least to a portion of the canaliculus crosssection ... thus blocking flow." Ex. 1026, *Ainpour*, Abstract. *See also* Ex. 1036, Dana Decl., ¶38.

In particular, *Ainpour* teaches that a "stiff rod shaped" plug is the preferred embodiment and that, once placed in the canaliculus, it expands to conform to the walls of the canaliculus, thus being held in place better. Ex. 1026, *Ainpour*, [0014], [0015]. *Ainpour* explains that "[t]he preferred shape is cylindrical for ease of insertion through the punctal opening." *Id.*, [0041]. This preferred embodiment is illustrated in *Ainpour*'s Figure 5, shown below:

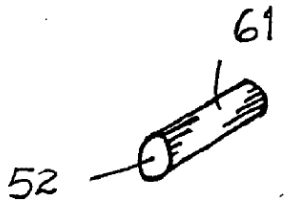


FIG 5

Ainpour then discloses the use of hydrogels that swell when placed in the canaliculus. *See, e.g., id.*, [0034], [0045], Claim 11 ("The device of claim 10, wherein the gel plug is formed from a hydrogel material ..."). *See also* Ex. 1036, Dana Decl., ¶38.

The use of swellable hydrogel polymers to construct ocular implants had been known for years even before *Ainpour*. For instance, U.S. Pat. No. 4,327,725 to Cortese *et al.* ("*Cortese*"), issued in 1982, discloses osmotic drug delivery devices, including an "ocular therapeutic insert" to release an ophthalmic drug to the eye (Ex. 1027, *Cortese*, 5:36-39) and a cylindrical insert for placement in a body passageway or canal (*id.*, 5:21-35). Of particular note, *Cortese* teaches the

preferred use of hydrogel polymers to construct these drug delivery devices. *See, e.g.*, *id.*, 9:18-47 ("The hydrogel suitable for the purpose of this invention are swellable, hydrophilic polymers. The swellable, hydrophilic polymers are in one preferred embodiment lightly cross-linked, such cross-links being formed by covalent or ionic bond, which interact with water and aqueous biological fluids and swell or expand to some equilibrium state. . ."). *Cortese* further discloses a number of therapeutic agents that could be delivered via these devices, including anti-inflammatories, anti-microbials, ophthalmics, corticosteroids, and many other agents. *Id.*, 7:10-8:32; 13:60-68. *See also* Ex. 1036, Dana Decl., ¶ 39.

Baxter discloses several ocular implants that were actually on the market by 2004. For example, the SmartPlug® was approved for use in 2002 and was one of three main designs of non-absorbable punctal plugs available in the United States at the time. Ex. 1020, *Baxter*, 1, 8. *Baxter* describes that plug as follows:

> The SmartPlug (Figures 5 and 6) is rod-shaped, and, before insertion, it has a diameter of 0.4 mm and a length of 9 mm. When it is inserted into the punctum, the increase in temperature produces a change in the shape of the thermodynamic acrylic; the rod's diameter increases up to 1 mm in size and its length decreases to 2 mm. Ultimately, the plug's final resting position is in the canaliculus.

Id., 2. The above-referenced Figures 5 and 6, depicting the rod shape and dimensions of the SmartPlug inserts before and after insertion into the canaliculus are shown below:

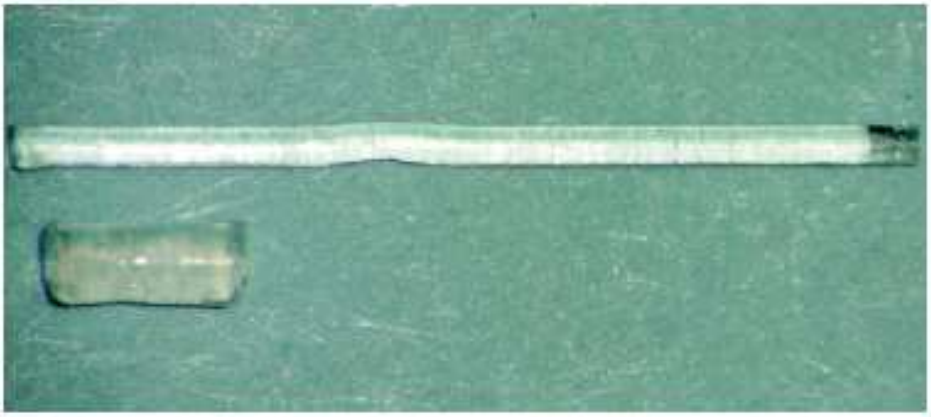


Figure 5. The Smart Plug®, dry (top) and warmed (bottom).

Id., 3.

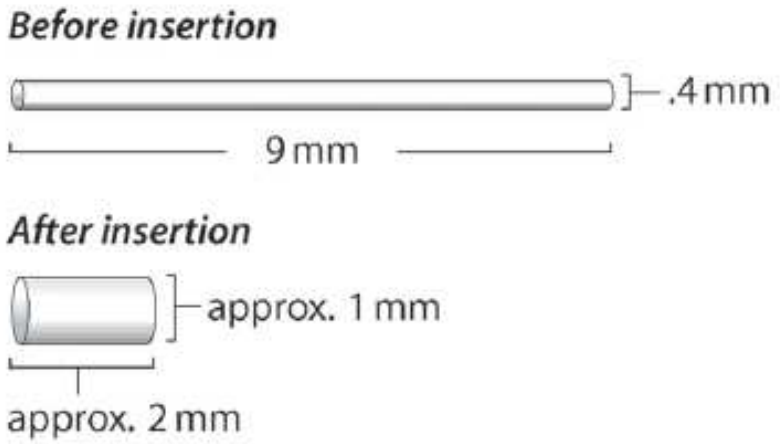


Figure 6. Diagram of the Smart Plug® size before (dry) and after insertion (warmed).

Id., 5.

As such, it is clear that there is nothing particularly new or innovative about the canalicular inserts of the '082 Patent. As seen above, cylindrical, swellable,

hydrogel canalicular inserts used to deliver therapeutic agents to the eye had been known for years before the '082 Patent. Further, the various therapeutic agents recited in the dependent claims of the '082 Patent, such as beta-blockers and dexamethasone, had also been long known for use in treating various ophthalmic conditions for years before the '082 Patent. *See, e.g.*, Ex. 1025, *Chen*, 6:18 (beta-blockers), 6:23 (dexamethasone), 6:32 (antibiotics), 6:38 (antiallergenics), 6:40 (anti-inflammatories). *See also* Ex. 1036, Dana Decl., ¶ 40-4.

That leaves color. As detailed above, Mati distinguished the prior art not on the shape or construction or composition of the canalicular inserts but rather on the "distinguishing color" limitation. But adding color to canalicular inserts to make them more visible was known long before the '082 Patent. Again, there was nothing novel or innovative about that.

Use of a "distinguishing color" in canalicular inserts was already well known in the field years before the filing of the '082 Patent, as seen, for example, in this reference from 2002:

> The standard intracanicular silicone implants still exist but have undergone "cosmetic surgery" and <u>now come in colors to enhance our ability to detect their presence after insertion</u>.

Ex. 1028, Morris, O.D., F.A.A.O., *A Lesson in Managing Dry Eye, Plugs, Drugs and Tears: A Dry Eye Update, Part Two*, OPTOMETRIC MANAGEMENT (October

2002), 10 (emphasis added). This reference is not cited in the '082 Patent, and the examiner did not have the benefit of it. *See also* Ex. 1036, Dana Decl., ¶ 42.

Of particular note, *Gillepsie* is directed to "a punctum plug which is more easily visualized when positioned within a punctal canal of a recipient" (Ex. 1015, [0006]) because it includes "an organic or inorganic phosphor or fluorescent material, reflective beads, quantum dots, a dye or pigment." *Id*., [0007]. The Office did not apply *Gillepsie*, and apparently did not appreciate that it expressly discloses the "distinguishing color to show" element allegedly missing from the prior art.

In 2004, *Baxter* also disclosed the use of color to better visualize placement of a commercially available canalicular insert:

> The Herrick Lacrimal Plug (Figure 4) is shaped like a golf tee and is intended to reside within the canaliculus. This design allows it to be wedged into the canaliculus, preventing its migration into the lacrimal sac. Its blue color helps to identify its position within the canaliculus: when the skin anterior to the plug is transilluminated, the blue plug can be visualized. Similar plugs have been developed that are semi-radiopaque, providing another means by which to verify location.

Ex. 1020, *Baxter*, 2 (emphasis added). These blue Herrick plugs are shown below:

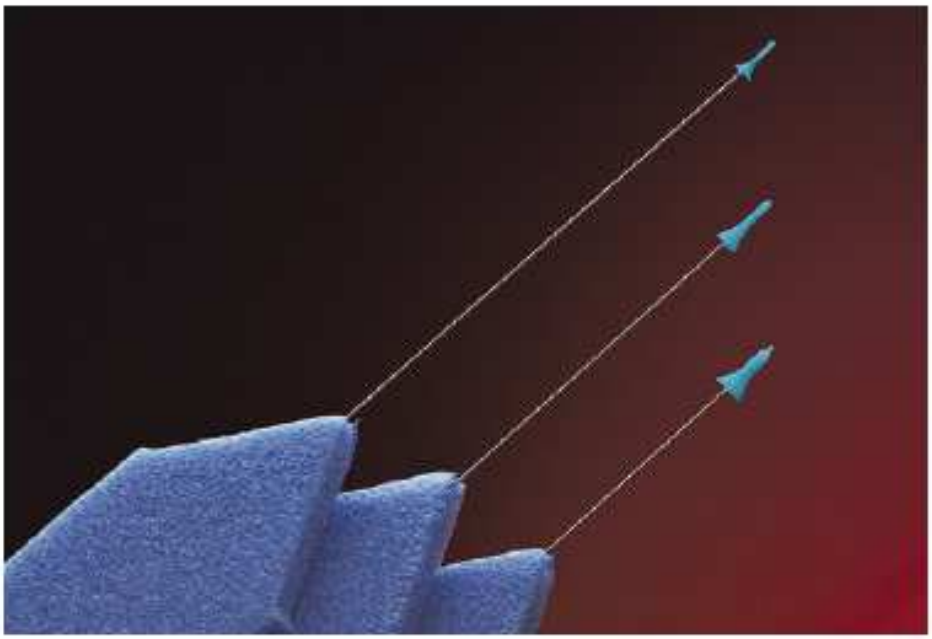


Figure 4. Three sizes of Herrick Lacrimal Plugs® on their inserters.

Id., 3. *See also* Ex. 1036, Dana Decl., ¶ 43.

References to the use of color for ocular inserts dates back decades, to at least the early 1970s, showing how well known it was in the art to add color to inserts so that they could be easily seen for placement or removal. For instance, U.S. Patent No. 3,826,258 to Abraham ("*Abraham*," Ex. 1029), issued in 1974, discloses ocular inserts for drug delivery in the form of capsules placed in the conjunctival sac of the eye. *Abraham* teaches that these capsules "may be colored for ease of visibility." Ex. 1029, *Abraham*, 4:4-5; *see also id.* 2:38-40 ("Coloring facilitates location of the emptied capsule for removal from the conjunctival sac"). Thus, the idea of colored ocular inserts was hardly new in 2006 and, in fact, had been known in the field—in the technical and patent literature and in commercial

applications--for over thirty years before the priority date of the '082 Patent. *See also, e.g.*, Ex. 1030, U.S. Pat. No. 3,993,071 to Higuchi *et al*. ("*Higuchi*") (issued November 23, 1976) 25:50-55 ("The present invention contemplates the use of an indicator dye in the drug or material of the insert, or both, to serve as a visual indication as to the supply or drug within the device or the device itself in the eye. For this purpose, a small amount of methylene blue or any suitable dye material can be used"); Ex. 1031, U.S. Pat. No. 6,152,943 to Sawhney ("*Sawhney*") (issued November 28, 2000) 4:20-23 ("If desired, one or more crosslinkable solutions may contain contrast agents or other means for visualizing the hydrogel implant"). *See also* Ex. 1036, Dana Decl., ¶¶ 43-44.

Accordingly, given the overwhelming disclosure in the prior art of the use of a distinguishing color—the only limitation that distinguished the cited prior art during prosecution—and given that all other limitations of the challenged claims were well-known in the art, each and every claim limitation of the claims of the '082 Patent are either anticipated or obvious, or both as argued below. *See also* Ex. 1036, Dana Decl., ¶¶ 42-46.

C. Level of Ordinary Skill in the Art

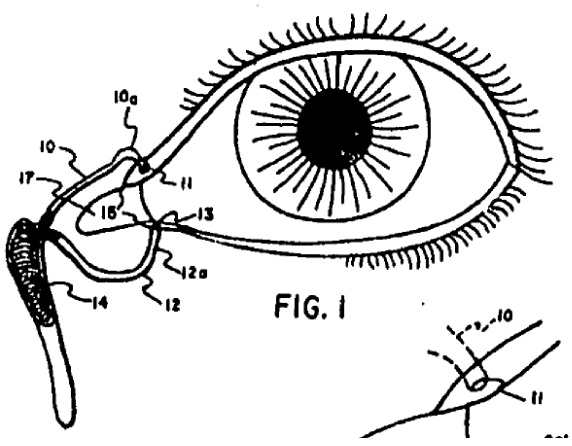
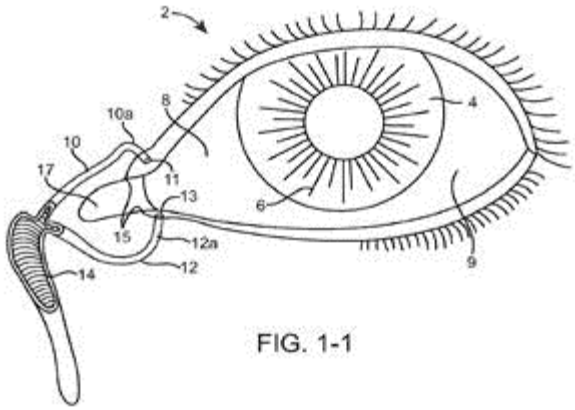
The relevant art is design, development, and/or use of drug delivery systems, such as ocular implants. The person of ordinary skill in the relevant art is an ophthalmologist with several years of experience in the design, development,

and/or study of drug delivery devices and/or ophthalmic inserts. Ex. 1036, Dana Decl., ¶¶ 23-27.

V. THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Ground 1: Anticipation of Claims 1-7, 9-16, 18-20, and 22-23 by *Pritchard* under §102

Pritchard discloses hydrogel canalicular inserts that are cylindrical rods, that are colored, that swell, that comprise functional groups, and that deliver a therapeutic agent to treat various ophthalmic conditions, such as dry eye, glaucoma, and post-surgical discomfort. These elements are, in essence, all of the limitations of the challenged claims. *Pritchard* is so close to the '082 Patent that the '082 Patent appears to have copied some of *Pritchard*'s figures and text. For example, as seen below, the '082 Patent includes the same exact figure of a human eye previously depicted in *Pritchard*. Even the designated component numbers are the same.

Pritchard Fig. 1	**'082 Patent Fig. 1-1**
	

Even the portions of the specifications describing these figures seem to be virtually identical. Compare Ex. 1010, *Pritchard*, [0035] (description of Fig. 1), with Ex. 1001, '082 Patent, 7:49-65 (describing Fig. 1-1).

As explained in the narrative and claim chart below, *Pritchard* expressly discloses all of the limitations recited in Claims 1-7, 9-16, 18-20, and 22-23 of the '082 Patent. *See also* Ex. 1036, Dana Decl. at ¶¶ 46- 48.

1. <u>Limitations Common to All Challenged Claims</u>

(a) "A drug delivery system for insertion into a lacrimal canaliculus of a patient" (Preamble of Claims 1, 11, and 18)

Pritchard's stated field of use "is related to occlusive devices, and includes disclosure of nasolacrimal occlusive devices such as canalicular plugs placed into the punctal opening of the lacrimal duct." Ex. 1010, *Pritchard*, [0002]. *Pritchard* further discloses that the "plug is advanced into the depth of the canaliculus by manipulation of the inserter tool ...." *Id.*, [0041]. Moreover, *Pritchard* discloses that the device can be used to deliver therapeutic agents. *See, e.g., id.*, [0038] ("In certain embodiments of the invention the plugs 20, 20', …, may be of medication-impregnable porous material …, or may be otherwise adapted as with capillaries or the like, to store and slowly dispense ophthalmic drugs to the eye ...."); [0043] ("The device, or a portion thereof, may further comprise a therapeutic agent").

Further detail is provided in the claim chart below. *See also* Ex. 1036, Dana Decl., ¶ 49.

(b) "a therapeutic agent"

As seen above, *Pritchard* expressly discloses that the implants can contain and deliver a therapeutic agent. Ex. 1010, *Pritchard,* [0038], [0043]. *Pritchard* further discloses, under the heading "Drug and Therapeutic Agent Delivery," that the "gels and other devices set forth herein could contain medicaments, therapeutic agents, antimicrobials (e.g., silver), ..., etc." *Id.*, [0131]-[0132]. Further detail is provided in the claim chart below. *See also* Ex. 1036, Dana Decl., ¶ 50.

(c) "a distinguishing color to show placement of the system in the lacrimal canaliculus of the patient"

Pritchard discloses that one may treat the hydrogel polymer material of the insert with ascorbic acid and change the material "from clear and colorless to a light straw color." Ex. 1010, *Pritchard,* [0137]. *See also* Ex. 1036, Dana Decl., ¶ 51.

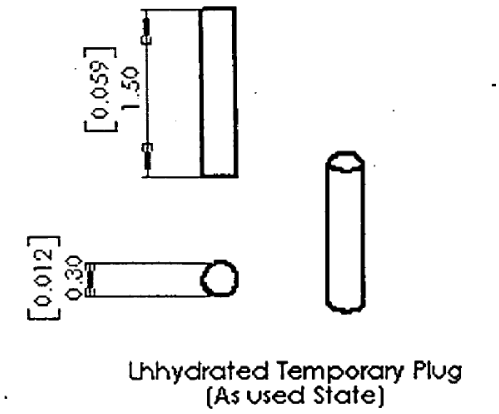
(d) "a body of material to hold the therapeutic agent wherein the body of material comprises hydrogel polymers"

Pritchard discloses numerous hydrogel polymers throughout the specification, teaches how to make them, and further discloses that any embodiment of the disclosed canalicular inserts may be made with hydrogels. Indeed, *Pritchard* touts the benefits of hydrogels in the formulation of the

canalicular inserts. For example, *Pritchard* teaches that "[u]se of anisotropic hydrogels as materials for punctal occlusion solves a problem with many devices. ... Devices made from anisotropic hydrogels, however, require neither measuring punctal size nor keeping of an inventory of many differently sized punctum plugs. ... the device will swell radially until it has expanded sufficiently to occlude the nasolacrimal passage but will otherwise change in other dimensions in a controlled manner." Ex. 1010, [0061]. *Pritchard* further discloses that "[s]ome punctal plug occlusion devices are meant to be inserted below the punctal opening and others possess a rim meant to sit atop the punctal opening. Devices of both categories can be fabricated using hydrogels and other materials as described herein." Ex. 1010, [0029] (emphasis added). The extensive disclosure of the use of hydrogels throughout the specification is further detailed in the claim chart below. *See also* Ex. 1036, Dana Decl., ¶¶ 53-54.

(e) "wherein the body of material is a cylindrical rod"

Pritchard discloses throughout the document that the inserts are, preferably, "cylindrical" in shape. *See*, *e.g.*, Ex. 1010, *Pritchard*, ¶¶ [0030], [0055], [0065], [0066], [0079], [0119], [0140], and [0152]. See also the claim chart below. *Pritchard* depicts implants that are cylindrical in, for example, Figure 7A below:



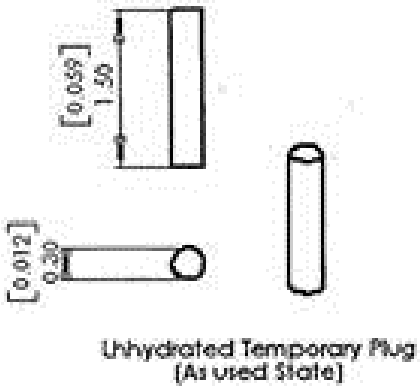
See also Ex. 1036, Dana Decl., ¶ 56-57.

2. <u>Other Limitations</u>

(a) "wherein the hydrogel swells when the system is inserted into the lacrimal canaliculus of the patient"

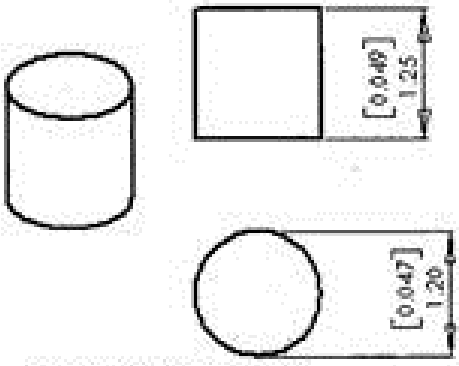
Claim 10, 11, and 23 all provide that the body of the insert swells when inserted or placed into the canaliculus. *Pritchard* extensively discloses this phenomenon. For example, *Pritchard* emphasizes that numerous embodiments of the disclosed canalicular plugs include "swellable devices that expand in volume in response to lacrimal fluid. And other embodiments are anisotropically swellable devices that are swellable in a canaliculus to expand radially, but not longitudinally, whereby the deice fits securely without being dislodged by longitudinal extension." Ex. 1010, [0022]. Such cylindrical, swellable inserts are illustrated in Figures 7A and 7B below.

FIG. 7A



Unhydrated Temporary Plug
(As used State)

FIG. 7B



Hydrated Temporary Plug
(After implantation)

Pritchard describes these figures as follows: "FIGS. 7A and 7B are diagrams showing a nasolacrimal occlusion device that swells after contact with a tear or other physiological fluid." Ex. 1010, *Pritchard*, [0020]; *see also id*., [0057] ("FIGS. 7A-7B depicts an example of a swellable punctum plug, and indicates dimensions before and after swelling. The dimensions in the Figures are based on actual results but are exemplary only, and may be suitably modified in light of the material used and the properties of the lumen or canaliculus that receives it").

Moreover, *Pritchard* makes clear that the swellable materials are hydrogels and can be either hydrogels that swell in all directions or "anisotropic" hydrogels that swell in just one or two directions. *See generally id.*, [0051]-[0061]. For instance, *Pritchard* discloses that a "hydrogel plug that incorporates an

unconstrained hydrogel material will thus be more successful in swelling to achieve a secure fit" (*id.*, [0052]), while "an anistropically swellable hydrogel may swell only in one or two directions while maintaining or diminishing in another direction" (*id.*, [0058]). *Pritchard* emphasizes that the devices can be either swellable in all directions or controllably swellable. *Id.*, [0022]. *See also* Ex. 1036, Dana Decl., ¶¶ 58-60 Further detail of the swellable hydrogels is provided in the claim chart below.

(b) "wherein the polymers comprise functional groups"

Claims 9 and 22 require that the hydrogel polymers comprise "functional groups." *Pritchard* discloses functional group. S*ee, e.g.*, Ex. 1010, *Pritchard*, [0102] ("Either the first or the second polymer has functional groups that are capable of binding a metal ion."). *See also* Ex. 1036, Dana Decl., ¶ 61. Further disclosure of functional groups is provided in the claim chart below.

(c) specific therapeutic agents

Most of the dependent claims, as well as Claim 18, recite a specific therapeutic agent (such as dexamethasone) or category of agent (such as an anti-glaucoma agent. Under the heading "Drug and Therapeutic Agent Delivery" [0131], *Pritchard* discloses that the "gels and other devices set forth herein could contain medicaments, therapeutic agents, antimicrobials (e.g., silver), . . . etc." Ex. 1010, [0132]. *Pritchard* discloses in particular two therapeutic agents, silver

and Triclosan, both of which are common antimicrobials. *See* Ex. 1010, *Pritchard*, [0132], [0135], respectively. But *Pritchard* also expressly incorporates by reference several earlier provisional applications. *See id.*, [0001], [0044]. One of the incorporated provisionals, U.S. Provisional App. 60/557,368 ("the '368 Prov.," Ex. 1012) includes a list of potential therapeutic agents, particularly agents used to treat various ophthalmic conditions, including, for example, anti-glaucoma agents, beta blockers, prostaglandins, corticosteroids, anti-fungal agents, antibiotics, anti-inflammatories, and most of the other agents recited in the dependent claims of the '082 Patent. *See* Ex. 1012, '368 Prov., 5-15.[4] *See also* Ex. 1036, Dana Decl., ¶¶ 62-67 .

(d) "wherein the system does not comprise a sheath body"

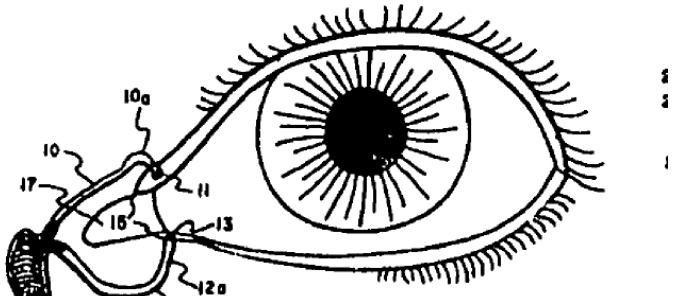
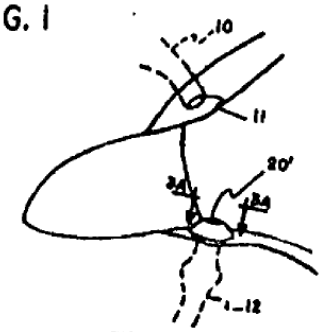
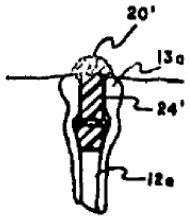
Claim 2 requires that "the system does not comprise a sheath body." As explained in Section III.B above, a sheath body is a "material or structure that is impermeable to the therapeutic agent and that covers a portion of a drug core to

[4] "When a document is 'incorporated by reference' into a host document, such as a patent, the referenced document becomes effectively part of the host document as if it were explicitly contained therein." *Telemac Celluar Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001). Thus, the contents of the incorporated reference become part of the host document even for purposes of an anticipation analysis. *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (2009).

prevent migration of the therapeutic agent from the covered portion of the drug core." *See* Ex. 1036, Dana. Decl., ¶¶ 68-70. *Pritchard* discloses devices that are simply cylindrical pieces of hydrogel material that do not have a structure or material layered over it to prevent release of the therapeutic agent. *Id*., ¶ 71; *see also* Ex. 1010, *Pritchard* at [0030]. *Pritchard* further discloses that hydrogel occlusive devices will achieve a more successful fit without an exterior constraint. Ex. 1010, [0052]. Accordingly, *Pritchard* discloses drug-eluting canalicular inserts that do not have a sheath body. *See* Ex. 1036, Dana Decl., ¶¶ 71-72.

The various claimed therapeutic agents and treatments are more fully detailed in the claim chart below.

GROUND 1: ANTICIPATION BY *PRITCHARD*	
'082 Patent Claims	**US Pub. No. 2005/0197614 ("*Pritchard*")**
1. [1pre] A drug delivery system for insertion into a lacrimal canaliculus of a patient, comprising:	*Pritchard* discloses drug delivery systems for insertion into a lacrimal canaliculus of a patient: *Pritchard* is entitled "Occlusive Biomedical Devices, Punctal Plugs, and Methods of Use." "The field of use is related to occlusive devices, and includes disclosure of nasolacrimal occlusive devices such as canalicular plugs placed into the punctal opening of the lacrimal duct." Ex. 1010, *Pritchard* [0002]. "In certain embodiments of the invention the plugs 20, 20', …', may be of medication-impregnable porous material …, or may be otherwise adapted as with capillaries or the like, to store and slowly dispense ophthalmic drugs to the eye as they are leached out by the lacrimal fluids." *Id.*, [0038]. "An exemplary technique for inserting the plug into the punctal aperture and associated canaliculus will now be set forth . . .." *Id.*, [0039] "The plug is advanced into the depth of the canaliculus by manipulation of the inserter tool . . ." *Id.*, [0041]. "The device, or a portion thereof, may further comprise a therapeutic agent . . ." Ex. 1010, [0043]. *Pritchard* expressly incorporates US Provisional Application No. 60/557,368 ("the '368 Prov.") by reference. *See* Ex. 1010, *Pritchard*, [0001] and [0044]. Via the '368 Prov., *Pritchard* discloses that "[u]ses [of the implants] include occlusion (essentially complete blockage) of an opening, blockage of an opening, and drug delivery. For example, a drug or other therapeutic

	substance may be associated with the implant, which may serve as a delivery vehicle for delivery or release of the drug." Ex. 1012, 3 (emphasis added). "Drug and Therapeutic Agent Delivery. The gels and other devices set forth herein could contain medicaments, therapeutic agents, antimicrobials (e.g., silver), bioactive minerals and glasses, radioactive therapeutic materials, cytotoxic agents (for tissue ablation), etc." Ex. 1010, *Pritchard*, [0131]-[0132]. *Pritchard*'s Figure 1 below illustrates a human eye and its associated upper and lower canaliculae 10 and 12. *See* Ex. 1010, [0035]. *Pritchard*'s Figures 3 and 3A below illustrate a punctal plug embodiment of the invention that is inserted through the punctum and into the lower canaliculus 12. *Id.*, [0013], [0014], [0037].  FIG. 1  FIG. 3  FIG. 3A Figures 7A and 7B, depict an exemplary insert that "may be suitably modified in light of the … caniliculus that receives it." *Id.*, [0057].

[1a] a therapeutic agent,	*Pritchard* discloses devices comprising a therapeutic agent: "The device, or a portion thereof, may further comprise a therapeutic agent …." *Id*., [0043]. "In certain embodiments of the invention[,] the plugs 20, 20', …, may be of medication-impregnable porous material …, or may be otherwise adapted as with capillaries or the like, to store and slowly dispense ophthalmic drugs to the eye as they are leached out by the lacrimal fluids." Ex. 1010, [0038]. Via the '368 Prov., *Pritchard* discloses that implant "[u]ses include occlusion (essentially complete blockage) of an opening, blockage of an opening, and drug delivery. For example, a drug or other therapeutic substance may be associated with the implant, which may serve as a delivery vehicle for delivery or release of the drug." Ex. 1012, '368 Prov., 3. "Drug and Therapeutic Agent Delivery. The gels and other devices set forth herein could contain medicaments, therapeutic agents, antimicrobials (e.g., silver), bioactive minerals and glasses, radioactive therapeutic materials, cytotoxic agents (for tissue ablation), etc." Ex. 1010 ¶¶ [0131]-[0132] (emphasis added). Claims 11, 21, and 70 each recite an ocular punctum plug comprising "a therapeutic agent." Claims 37 and 58 each recite a device for occluding a nasolacrimal passage "comprising a therapeutic agent." *Also see citations for [1pre].*
[1b] a distinguishing color to show placement of the system in the	*Pritchard* discloses devices comprising a distinguishing color to show placement in the lacrimial canaliculus of the patient:

lacrimal canaliculus of the patent and	For example, *Pritchard* discloses processes for making an insert including a therapeutic agent that involve adding ascorbic acid in a solution and allowing the material to develop a distinguishing color: "Anisotropically swellable occlusive devices containing a therapeutic agent, silver, were made from gellan gum. … A silver solution was then made …. One milliliter of this solution was added to the 99 milliliters of gellan gum solution and was subjected to a vacuum to remove air bubbles. This solution was extruded ... into 10% ascorbic acid in water and allowed to incubate for 30 minutes, at which time extrusions changed from clear and colorless to a light straw color...." Ex. 1010, [0137] (emphasis added). The final device featured the light straw color. *Id*., [0138]. "Another set of anisotropically swellable devices were [similarly] made with a therapeutic agent. … After dehydration through a graded ethanol series[, the light straw color] extrusions were stretched to twice their original length and allowed to dry. … After drying, extrusions were placed into a 5% solution of calcium chloride in 70% aqueous ethanol and allowed to incubate for 2 hours. After rinsing … and dehydration …, extrusions were allowed to air dry. Occlusive devices were then fabricated by cutting calcium gellan extrusions into cylindrical pieces. … After 2-3 weeks in the distilled water they retained their original straw color." *Id.*,[0139]-[0140] (emphasis added).
[1c] a body of material to hold the therapeutic agent	*Pritchard* discloses devices comprising a body of material to hold the therapeutic agent: "Some punctal plug occlusion devices are meant to be inserted below the punctal opening and others possess a rim meant to sit atop the punctal opening. Devices of both categories can be fabricated using hydrogels and other materials as described herein." Ex. 1010, [0029].

	"In certain embodiments of the invention the plugs 20, 20', … , may be of medication-impregnable porous material …, or may be otherwise adapted as with capillaries or the like, to store and slowly dispense ophthalmic drugs to the eye as they are leached out by the lacrimal fluids." *Id.*, [0038]. "The device, or a portion thereof, may further comprise a therapeutic agent …." *Id.*, [0043]. Via the '368 Prov., *Pritchard* discloses that "a drug or other therapeutic substance may be associated with the implant, which may serve as a delivery vehicle for delivery or release of the drug." Ex. 1012, '368 Prov., 3. "Drug and Therapeutic Agent Delivery. The gels and other devices set forth herein could contain medicaments, therapeutic agents, antimicrobials (e.g., silver), bioactive minerals and glasses, radioactive therapeutic materials, cytotoxic agents (for tissue ablation), etc." Ex. 1010, *Pritchard*, [0131]-[0132]. *Pritchard* discloses processes whereby a therapeutic agent is dispersed throughout a body of material: "Without being limited to a particular theory of operation, it is believed that this process results in a dispersion of silver particles throughout the hydrogel." *Id.*, [0137]. "Another set of anistropically swellable devices were made with a therapeutic agent ...." *Id.*, [0139]. "The materials described herein may be made into a device with a predetermined structure suitable for its intended purpose. A predetermined structure has a shape that is determined prior to introduction into a patient. For example, a polysaccharide hydrogel formed into a punctum plug shape for use as a punctum plug has a predetermined shape…. Thus, e.g., …, cylinders, and cones are all contemplated as particular predetermined

	shapes." *Id*., [0152]. Claims 11, 21, and 70 each recite an ocular punctum plug comprising "a therapeutic agent." Claims 37 and 58 each recite a device for occluding a nasolacrimal passage "comprising a therapeutic agent." *Also see citations for [1pre] and [1a].*
[1d] wherein the body of material comprises hydrogel polymers and	*Pritchard* discloses devices comprising a body of material comprising hydrogel polymers: "Some punctal plug occlusion devices are meant to be inserted below the punctal opening and others possess a rim meant to sit atop the punctal opening. Devices of both categories can be fabricated using hydrogels and other materials as described herein." Ex. 1010, *Pritchard*, [0029]. "In certain embodiments of the invention the plugs 20, 20', …, may be of medication-impregnable porous material such as HEMA hydrophilic polymer…." *Id.*, [0038]. *Pritchard* discloses "An anisotropically swellable polymer material may be prepared by aligning polymer molecules in one or more preferential directions. … <u>In some embodiments, hydrogels are fabricated by crosslinking of water-soluble polymers so that the crosslinking is only extensive enough to insolublize [sic] the material in water.</u> Upon hydration, the oriented polymer molecules are forced apart, held together only by crosslinks." Ex. 1010, [0058]; *see also*, [0086]; Ex. 1012, '368 Prov., 45 ("Typical hydrogels are fabricated by crosslinking of water-soluble polymers and crosslinking is only extensive enough to insolublize [sic] the material in water."). "As a dry gel material hydrates, it typically swells to fill a space and then takes up no more water. For example, if

	a dry gel material is placed in thin walled flexible silicone tubing and then hydrated, the gel will swell to fill, but only slightly deform, the tubing. A hydrogel plug that incorporates an unconstrained hydrogel material will thus be more successful in swelling to achieve a secure fit." Ex. 1010, *Pritchard*, [0052] (emphasis added). "Use of anisotropic hydrogels as materials for punctal occlusion solves a problem with many devices. The size of the punctal opening varies among patients; therefore the punctum must be measured, and a properly sized plug inserted. Devices made from anisotropic hydrogels, however, require neither measuring punctal size nor keeping of an inventory of many differently sized punctum plugs. Proper dimensions necessary for punctal occlusion are achieved through hydration of the device. For example, the device will swell radially until it has expanded sufficiently to occlude the nasolacrimal passage but will otherwise change in other dimensions in a controlled manner." *Id.*, [0061] (emphasis added). *Pritchard* discloses inserts that include a hydrogel polymer body of material (24, 24') and at least one other element made of "a strong, non-swelling material." *See Id.*, [0052]. "Referring to FIGS. 2A and 2B, for example, plug 20 may be made of an anisotropically swellable material having polymeric alignment parallel to the longitudinal axis, …. Thus, for example, the portion 24, 24' would swell against a wall of a nasolacrimal passage after the device was inserted into the same." *Id.*, [0062].

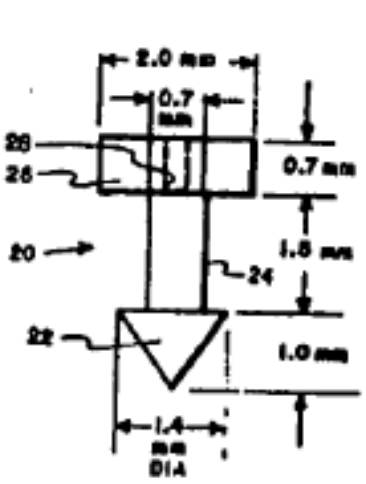


FIG. 2A

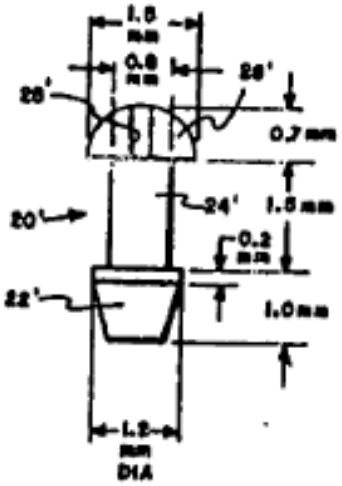
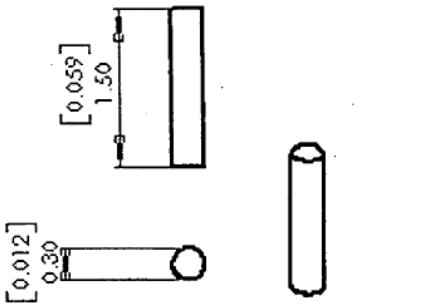


FIG. 2B

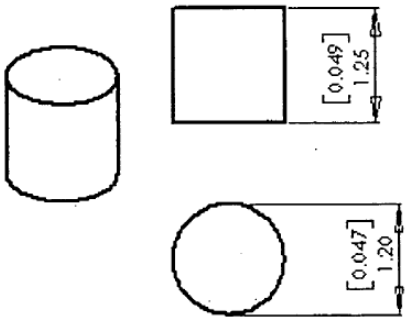
Pritchard discloses inserts wholly comprising an unconstrained hydrogel polymer body of material. *See Id.*, [0057]: Figures 7A and 7B below show cylindrical canalicular inserts comprising hydrogel polymers:

FIG. 7A



Unhydrated Temporary Plug
(As used State)

FIG. 7B



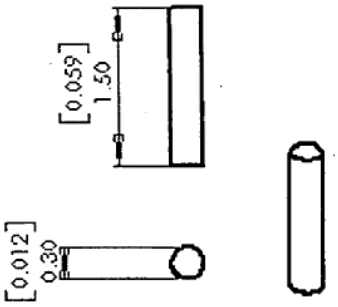
"It is therefore helpful in some situations to use a device which swells only in lateral dimensions, thus effectively blocking, but not protruding from, the opening, e.g., a duct or canal. Further, the device may shrink in at least one dimension, such that a thin, cylindrical device becomes short and fat once hydrated. Punctum plugs, for example, may be made with anisotropically swelling materials. FIGS. 7A-7B depicts an example of a swellable punctum plug, and indicates dimensions before and after swelling." *Id.*, [0057].

"In some embodiments, the crosslinking of a first and a second polymer may create a hydrogel …." *Id.*, [0102].

"The polymers may comprise a polysaccharide, e.g., gellan, Welan, S-88, S-198, a rhamsan gum. The polymers may comprise, e.g., at least one member of the group consisting of alginate, curdlan, carboxymethylcellulose, crosscarmellose, poly(acrylic acid), xanthan, carrageenan, carboxymethyl chitosan, hydroxypropyl carboxymethyl cellulose, pectin, gum Arabic, karaya gum, psyllium seed gum, carboxymethyl guar, and mesquite gum. … The material may be anisotropically swellable, and may comprise polymers processed into an arrangement of polymers that are

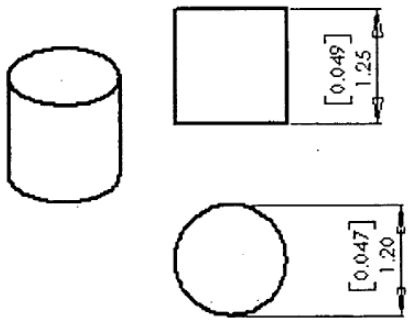
	substantially parallel to each other." *Id.*, [0104]. "Without being limited to a particular theory of operation, it is believed that this process results in a dispersion of silver particles throughout the hydrogel." *Id.*, [0137]. "The materials described herein may be made into a device with a predetermined structure suitable for its intended purpose. A predetermined structure has a shape that is determined prior to introduction into a patient. For example, a polysaccharide hydrogel formed into a punctum plug shape for use as a punctum plug has a predetermined shape …." [0152] (emphasis added). *Also see citations for [1c].*
[1e] wherein the body of material is a cylindrical rod.	*Pritchard* discloses devices comprising a body of material that is a cylindrical rod: *Pritchard* discloses devices comprising only a body of material that is a cylindrical rod: "Devices inserted below the punctal opening are referred to herein as subpunctal devices.... Subpunctal devices are simple in design, being cylindrical pieces of material …." Ex. 1010, *Pritchard*, [0030] (emphasis added). "FIGS. 7A-7B depicts [sic] an example of a swellable punctum plug, and indicates dimensions before and after swelling. The dimensions in the Figures are based on actual results but are exemplary only, and may be suitably modified inlight of the material used and the properties of the lumen or canaliculus that receives it." *Id.*, [0057].

FIG. 7A



Unhydrated Temporary Plug
(As used State)

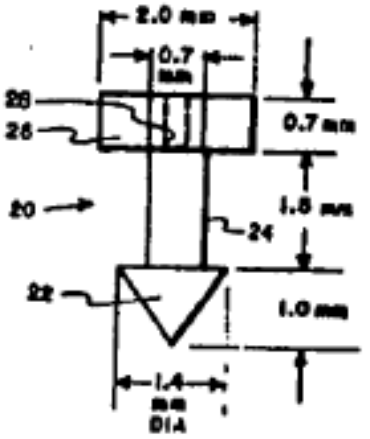
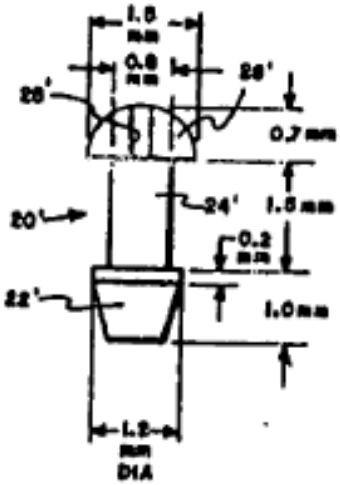
FIG. 7B



Hydrated Temporary Plug
(After implantation)

Pritchard also discloses devices comprising a body of material that is a cylindrical rod and other components:

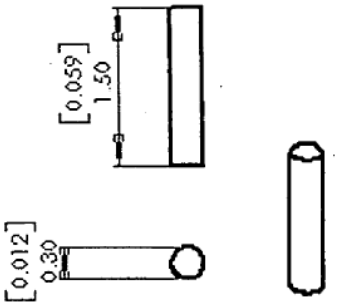
> With respect to FIGS. 2A and 2B, *Pritchard* discloses examplary devices 20, 20' that comprise a body of material that is a cylindrical rod 24, 24' and other components: "Referring initially to the embodiment of FIG. 2A, the punctum plug 20 has an axial length of approximately 3.2 mm and consists of three portions; a projecting tip or barb portion 22, a middle neck or waist portion 24 of somewhat smaller diameter than the tip, and a

	smooth disc-like head portion 26 of relatively larger diameter. The plug embodiment 20' of FIG. 2B is of generally similar dimensions to the first-described embodiment with a somewhat blunted tip or barb portion 22', a cylindrical middle portion 24' of substantially the same dimension, and a dome-shaped head portion 26' of somewhat smaller diameter than its counterpart in the embodiment of FIG. 2A. Ex. 1010, [0036] (emphasis added).  FIG. 2A  FIG. 2B "Prototype occlusive devices were fabricated by cutting neutralized extrusions into cylindrical pieces." *Id.* [0055], [0119]. "In general, an anisotropically swellable nasolacrimal occlusive device may be made from suitable polymers aligned in a predominantly parallel orientation relative to each other. Aligning the polymers may comprise at least one technique chosen from the group consisting of spin coating, spray coating, stretching, unidirectional freezing, extrusion from liquid crystalline solution, ordered convection, and stretching plus drying of an extrusion. A molecularly oriented occlusive device of cylindrical shape can be made in these ways, but the simplest and preferred method is usually by stretching

	and drying of an extrusion." *Id.*, [0065] (emphasis added). "Monofilaments of a hydrogel material may be made, e.g., by extrusion and subsequent stretching to at least 1.5-2 times their original length. Upon drying, they can be cut into small cylinders for easy insertion into a duct or canal." *Id.*, [0066] (emphasis added). "Occlusive devices were then fabricated by cutting neutralized extrusions into cylindrical pieces." *Id.*, [0073]. "Dried calcium alginate solutions were cut into small cylindrical pieces to simulate occlusive devices." *Id.* ¶¶ [0075], [0077]. "Dried, borate-esterified sodium gellan extrusions were cut into small cylindrical pieces to simulate occlusive devices." *Id.*, [0079]. "The anisotropically swellable occlusive devices were then produced by cutting the neutralized extrusions into cylindrical pieces." *Id.*, [0138]. "Occlusive devices were then fabricated by cutting calcium gellan extrusions into cylindrical pieces." *Id.*, [0140]. "The materials described herein may be made into a device with a predetermined structure suitable for its intended purpose. A predetermined structure has a shape that is determined prior to introduction into a patient. For example, a polysaccharide hydrogel formed into a punctum plug shape for use as a punctum plug has a predetermined shape. ... Thus, e.g., … cylinders, … are all contemplated as particular predetermined shapes." *Id.*, [0152] (emphasis added). Similarly, via the '368 Prov., *Pritchard* discloses that: "embodiments provide for materials and devices that are anisotropicly swellable, meaning that the materials or devices are designed to swell more in one direction than in other directions. For example, cylindrical rods may be constructed to have a diameter that increases in response to swelling, and have a length that increases to a lesser

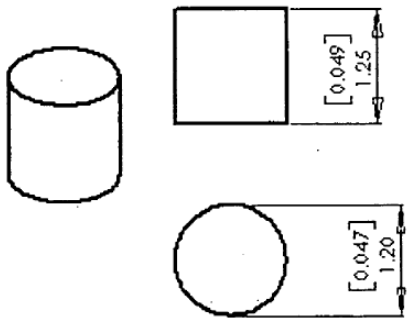
	extent, essentially does not increase, or even shrinks.." Ex. 1012, '368 Prov., 3 (emphasis added). *Also see citations for [1c].*
2. The drug delivery system of claim 1, wherein the system does not comprise a sheath body.	*Pritchard* discloses devices that do not comprise a sheath body: *Pritchard* discloses devices that are simple cylindrical pieces of material: "Devices inserted below the punctal opening are referred to herein as subpunctal devices. … Subpunctal devices are simple in design, being cylindrical pieces of material with dimensions of, e.g., about 1.5 to about 2 mm in length and about 0.3 to about 0.4 mm in diameter." Ex. 1010, *Pritchard*, [0030]. *Pritchard* discloses that hydrogel occlusive devices will achieve a more successful fit without a sheath body: "As a dry gel material hydrates, it typically swells to fill a space and then takes up no more water. For example, if a dry gel material is placed in thin walled flexible silicone tubing and then hydrated, the gel will swell to fill, but only slightly deform, the tubing. A hydrogel plug that incorporates an unconstrained hydrogel material will thus be more successful in swelling to achieve a secure fit." *Id.*, [0052]. *Pritchard* discloses "Anisotropically Swelling Materials and Devices" including exemplary devices illustrated in Figures 7A and 7B (copied below) without a sheath body. *Id.*, [0056]-[0057].

FIG. 7A



Unhydrated Temporary Plug
(As used State)

FIG. 7B



Hydrated Temporary Plug
(After implantation)

"It is … helpful in some situations to use a device which swells only in lateral dimensions, thus effectively blocking, but not protruding from, the opening, e.g., a duct or canal. Further, the device may shrink in at least one dimension, such that a thin, cylindrical device becomes short and fat once hydrated. Punctum plugs, for example, may be made with anisotropically swelling materials. FIGS. 7A-7B depicts an example of a swellable punctum plug, and indicates dimensions before and after swelling. The dimensions in the Figures are based on actual results but are exemplary only, and may

	be suitably modified in light of the material used and the properties of the lumen or canaliculus that receives it." *Id.*, [0057]. *Pritchard* discloses advantages of hydrogel devices that do not comprise a sheath body: "Use of anisotropic hydrogels as materials for punctal occlusion solves a problem with many devices. The size of the punctal opening varies among patients; therefore the punctum must be measured, and a properly sized plug inserted. Devices made from anisotropic hydrogels, however, require neither measuring punctal size nor keeping of an inventory of many differently sized punctum plugs. Proper dimensions necessary for punctal occlusion are achieved through hydration of the device. For example, the device will swell radially until it has expanded sufficiently to occlude the nasolacrimal passage but will otherwise change in other dimensions in a controlled manner." *Id.*[0061].
3. The drug delivery system of claim 1, wherein the therapeutic agent is selected from an anti-glaucoma agent, a corticosteroid, and anti-microbial agent, an anti-allergy agent or a non-steroidal anti-inflammatory agent.	*Pritchard* discloses "the gels and other devices set forth herein could contain … antimicrobials …." Ex. 1010, [0132]; *see also id.*, [0135]. Via the '368 Prov., *Pritchard* discloses that the therapeutic agent may include "anti-glaucoma drugs" (Ex. 1012, 14); "corticosteroids" (*id.*, 10-11); "Antimicrobials" (*id.*, 12; 15; 36; 49; 51); an "antihistamine" (*id.*, 7); "anti-inflammatory agents" (*id.*, 6); and "Non-steroidal anti-inflammatory agents" (*id.*, 9-10.

4. The drug delivery system of claim 1, wherein the system is used to treat glaucoma, pre and post surgical treatments, dry eye or allergy.	*Pritchard* discloses "temporary occlusion may be useful in decreasing contact lens intolerance, to evaluate treatment of ocular dryness secondary to contact lens use, for increasing retention/enhancement of ocular medications or lubricants on the eye, for maintenance of ocular flora, punctal stenosis, and to enhance healing and comfort after surgery." Ex. 1010, *Pritchard,* [0024] (emphasis added). Claim 44 recites a method comprising "using the device to treat at least one eye in a patient having at least one condition chosen from the group consisting of dry eye, seasonal allergy, and trauma caused by surgical correction." *Id*., Claim 44; *see also* Claim 77. Via the '368 Prov., *Pritchard* discloses that the therapeutic agent may include "anti-glaucoma drugs" (Ex. 1012, 14); an "antihistamine" (*Id.,* 7).
5. The drug delivery system of claim 1, wherein the therapeutic agent is dexamethasone.	Via the '368 Prov., *Pritchard* discloses that the "Therapeutic agents, include, for example, …anti-inflammatory agents such as dexamethasone ...." Ex. 1012, 6.
6. The drug delivery system of claim 1, wherein the therapeutic agent is an antibiotic or antifungal agent.	Via the '368 Prov., *Pritchard* discloses that "Therapeutic agents include, for example, … antibiotics" (Ex. 1012, 6; *see also id.*, 7; 12; 13; 14); and that "therapeutic agents include antifungal agents, …." (*id.*, 14; *see also id.*, 12).

7. The drug delivery system of claim 1, wherein the therapeutic agent is a prostaglandin, a prostaglandin precursor, a beta-blocker, or a prostaglandin analog.	Via the '368 Prov., *Pritchard* discloses that the therapeutic agent may include "Prostaglandins" (Ex. 1012, 12) and "a beta blocker" (*id.*, 7).
9. The drug delivery system of claim 1, wherein the polymers comprise functional groups.	*Pritchard* discloses deviced wherein the polymers comprise functional groups: *Pritchard* discloses "chelation-resistant material may … include unmineralized free metal ion-binding functional groups, so that metals may be complexed thereto, and for subsequent metal-catalyzed degradation." Ex. 1010, *Pritchard*,[0086] (emphasis added). *Pritchard* discloses "Triggerable Dissolution of Nasolacrimal Implants," which employs functional groups of polymers to trigger dissolution. *Id*., [0100]. "Metal-catalyzed oxidation may be used to triggerably dissolve a polymeric material. Free metal ions are associated with the polymer before, during, or after the formation of the gel. The metal ions are used as catalysts to catalyze oxidation by a peroxide, e.g., benzoyl peroxide or hydrogen peroxide, or ascorbate (vitamin C). Polymers which effectively bind metals usually have amino, carboxyl, phosphate or sulfate functional groups. Covalent or other crosslinking of such polymers to form hydrogels may therefore be accomplished so as to leave at least some functional groups free to bind metal ions. If polysaccharides are to be used to create gels, therefore, their hydroxyl groups may be utilized in crosslinking reactions instead of other groups such as carboxyls. Some or all of the polymers or materials in a gel or hydrogel may be used to capture the free metal ions."

	Id., ¶¶ [0100]-[0101] (emphasis added). "In some embodiments, the crosslinking of a first and a second polymer may create a hydrogel while degradation of the second polymer causes the gel to degrade. Either the first or the second polymer has functional groups that are capable of binding a metal ion. … To make the gel, the first and second polymer may be mixed together and exposed to heat under acidic conditions to crosslink their functional groups with each other or to a crosslinking agent." *Id.*, [0102] (emphasis added); *see also id*. [0103]-[0104]. "As set forth in detail, herein, and in [the '368 Prov.], devices may be removed using metal-catalyzed oxidation. One method of removing a device for occluding a nasolacrimal passage, comprises exposing the device to metal-catalyzed oxidation to degrade a material in the device to facilitate removal of the device from the nasolacrimal passage. Such a device may have metal ion-binding functional groups to facilitate such catalytic oxidation." *Id*., [0105] (emphasis added).
10. The drug delivery system of claim 1, wherein the hydrogel swells when the system is inserted into the lacrimal canaliculus of a patient.	*Pritchard* discloses device wherein the hydrogel swells when inserted into the lacrimal canaliculus of a patient: "Some embodiments are nasolacrimal occlusive devices made of swellable materials. . . . In some circumstances, the implant must be firmly set into an opening in a patient so that a relatively high degree of swelling is desirable, but the high degree of swelling tends to push the implant out of the opening so that the implant is not stable. Accordingly, controllably swellable materials may be used, as described, below. Ex. 1010, *Pritchard*, [0008]. "Various materials and methods for making improved nasolacrimal occlusive devices are described herein. Certain embodiments are directed to nasolacrimal devices that are swellable, anisotropically swellable ...

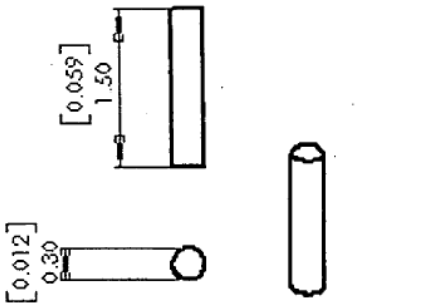
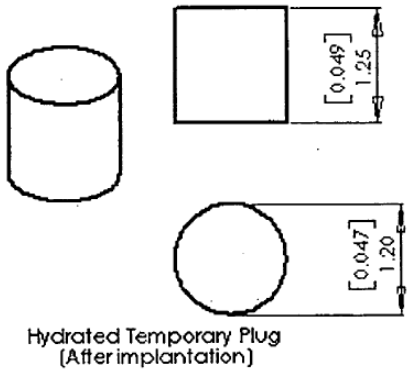
	and gellable by physiological fluids. Embodiments include swellable that are swellable in the a canaliculus to expand radially, but not longitudinally, whereby the device fits securely without be dislodged by longitudinal extension" *Id.*, [0022]. *Pritchard* includes a long "Swellable Materials and Devices" section, which discloses hydrogels throughout. *Id.*,[0051]-[0079]. For example, *Pritchard* discloses that "[s]ome hydrogels are swellable because they are less than fully hydrated when introduced into a patient, so that the hydrogel imbibes fluid from the patient." *Id.*, [0053]. *See also id.*, [0052] ("As a dry gel material hydrates, it typically swells to fill a space and then takes up no more water"); [0058] ("For example, an anisotropically swellable hydrogel may swell only in one or two directions"); [0061] ("Use of anisotropic hydrogels as materials for punctal occlusion solves a problem with many devices"). "FIGS. 7A and 7B are diagrams showing a nasolacrimal occlusion device that swells after contact with a tear or other physiological fluid." *Id.*, [0020]. FIG. 7A  Unhydrated Temporary Plug (As used State)

FIG. 7B



"FIGS. 7A-7B depicts an example of a swellable punctum plug, and indicates dimensions before and after swelling. The dimensions in the Figures are based on actual results but are exemplary only, and may be suitably modified in light of the material used and the properties of the lumen or canaliculus that receives it." *Id.*¶ [0057].

"Use of anisotropic hydrogels as materials for punctal occlusion solves a problem with many devices. The size of the punctal opening varies among patients; therefore the punctum must be measured, and a properly sized plug inserted. Devices made from anisotropic hydrogels, …, require neither measuring punctal size nor keeping of an inventory of many differently sized punctum plugs. Proper dimensions necessary for punctal occlusion are achieved through hydration of the device. For example, the device will swell radially until it has expanded sufficiently to occlude the nasolacrimal passage but will otherwise change in other dimensions in a controlled manner." *Id.*, [0061] (emphasis added).

"Another embodiment is a nasolacrimal occlusive device that comprises gellan and is degradable in a nasolacrimal canaliculus in about 20-40 days, e.g., about 30 days.

	Such a device may be swellable in a physiological fluid, e.g., between 25% and 1000%, 50% and 500%, or between 100% and 400%; persons of ordinary skill in these arts will immediately appreciate that all values and ranges within these explicit ranges are contemplated." *Id.*, [0156]. *Pritchard* discloses "Swellable Temporary Punctum Plugs." Ex. 1010 ¶¶ [0157]-[0158]. According to *Pritchard*, "Swellable temporary punctum plugs have been made that generally take 5-10 minutes to become fully hydrated by the action of tear production, or by the use of saline drops if tear volume is not sufficient (as may be expected from patients suffering from dry eye)." *Id.*, [0158]. *Pritchard* includes a section on "In Vitro Testing of Gellan, Depolymerized to Varying Degrees," which discloses exemplary hydrogel devices and their constrained and unconstrained swelling behavior in response to simulated insertion into the lacrimal system, in the form of exposure to a sterile saline solution. Ex. *Id.*, [0159]-[0161].
11. [11pre] A drug delivery system for insertion into a lacrimal canaliculus of a patient, consisting essential [sic] of:	*See citations for [1pre].* To the extent that the inclusion of the transitional phrase "consisting essential of" in the preamble of claim 11, versus the transitional phrase "comprising" in the preamble of claim 1, is deemed to change the analysis—*Pritchard* discloses devices that consist essentially of the following elements. *See, e.g.*, Ex. 1010, *Pritchard* FIGS. 7A and 7B and related disclosures in the citations.
[11a] a therapeutic agent,	*See citations for [1a].*
[11b] a hydrogel body of material to hold the therapeutic agent	*See citations for [1c] and [1d].*

and	
[11c] a distinguishing color to show placement of the system in the lacrimal canaliculus of the patient,	*See citations for [1b].*
[11d] wherein the body of material is a cylindrical rod and	*See citations for [1e].*
[11e] swells when placed in the lacrimal canaliculus of the patient.	*See citations for Claim 10.*
12. The drug delivery system of claim 11, wherein the therapeutic agent is selected from an anti-glaucoma agent, a corticosteroid, and anti-microbial agent, an anti-allergy agent or a non-steroidal anti-inflammatory agent.	*See citations for Claim 3.*
13. The drug delivery system of claim 11, wherein the system is used to treat glaucoma,	*See citations for Claim 4.*

pre and post surgical treatments, dry eye or allergy	
14. The drug delivery system of claim 11, wherein the therapeutic agent is dexamethasone.	*See citations for Claim 5.*
15. The drug delivery system of claim 11, wherein the therapeutic agent is an antibiotic or antifungal agent.	*See citations for Claim 6.*
16. The drug delivery system of claim 11, wherein the therapeutic agent is a prostaglandin, a prostaglandin precursor, a beta-blocker, or a prostaglandin analog.	*See citations for claim 7.*
18. [18pre] A drug delivery system for insertion into a lacrimal canaliculus of a patient, comprising:	*See citations for [1pre].*
[18a] a therapeutic	*See citations for [1a] and claim 3.*

agent selected from an anti-glaucoma agent, a corticosteroid[, sic] an anti-microbial agent, and anti-allergy agent or a non-steroidal anti-inflammatory agent;	
[18b] a body of material to hold the therapeutic agent	*See citations for [1c].*
[18c] wherein the body of material comprises hydrogel polymers and	*See citations for [1d].*
[18d] wherein the body of material is a cylindrical rod; and	*See citations for [1e].*
[18e] a distinguishing color to show placement of the system in the lacrimal canaliculus of the patent.	*See citations for [1b].*
19. The drug delivery system of claim 18, wherein the system is used to treat glaucoma, pre and post surgical treatments, dry eye or allergy	*See citations for claim 4.*

20. The drug delivery system of claim 18, wherein the therapeutic agent is dexamethasone.	*See citations for claim 5.*
22. The drug delivery system of claim 18, wherein the polymers comprise functional groups.	*See citations for claim 9.*
23. The drug delivery system of claim 18, wherein the hydrogel swells when the system is inserted into the lacrimal canaliculus of a patient.	*See citations for claim 10.*

B. Ground 2: Claims 1-7, 9-16, 18-20, 22-23 Are Obvious Over *Pritchard* in View of *Gillespie* under §103

For the reasons set forth in Ground 1, *Pritchard* anticipates Claims 1-7, 9-16, 18-20, and 22-23. Ocular incorporates by reference the facts and arguments of Ground 1. But to the extent that *Pritchard's* express and inherent disclosure of color is somehow deemed an insufficient disclosure of the "distinguishing color to show" limitation, then Claims 1-7, 9-16, 18-20, and 22-23 are obvious over *Pritchard* in view of *Gillespie*.

Gillespie's "invention relates generally to the punctum plug and in particular, to plugs and apparatus which enable a plug to be more easily visualized following insertion." Ex. 1015, *Gillespie*, [0001]. *Gillespie* discloses that the inserts are "very difficult to see" for various reasons including because they are "extremely small," and may be "translucent." *Id.*, [0005]. Accordingly, an object of *Gillespie* is "to make the punctum plug readably visible or detectable to the recipient or caregiver."[5] *Id.*, [0005]; *see also* [0011]. *Gillespie* is entitled "More Easily Visualized Punctum Plug Configurations," and discloses the desirability of making inserts more easily visible. *See also* Ex. 1036, Dana Decl., ¶¶ 73-75.

Gillespie teaches "the use of [a] substance [that] causes the plug to be more easily visualized than if the substance were not present." Ex. 1015, *Gillespie*, [0006]. *Gillespie* teaches "the rest of the plug body may be composed of any suitable material, including those presently used in the manufacture of such devices." *Id.*, [0006]. "The substance, which may be disposed on the outwardly exposed surface or within the body of the plug, may include a saturated coloration, or may be phosphorescent, fluorescent or otherwise operative to reflect or re-radiate light to assist in visualization." *Id.*, [0007]. *Gillespie* teaches "the substance may include a[] … phosphor or fluorescent material, reflective beads,

[5] The specification of the '082 Patent similarly discloses the use of color to make inserts "more readily detected by the patient." Ex. 1001, 21:1-5.

quantum dots, a dye or pigment." *Id.*, [0007]. *Gillespie* discloses that, "[i[n one preferred embodiment, at least the outwardly exposed surface of the plug, or the entire plug body, is pigmented to contrast with surrounding tissue." *Id.*, [0011] (emphasis added). In other words, *Gillespie* discloses a distinguishing color to show placement of an insert in the lacrimal canaliculus of the patient, and motivations for using such a color. *See also* Ex. 1036, Dana Decl., ¶ 77.

One of ordinary skill would have been motivated to combine the "color" teachings of *Gillespie* with the inserts of *Pritchard* for several reasons. As *Gillespie* explains, "extremely small" inserts, which may be "translucent," are "very difficult to see." Ex. 1015, *Gillespie*, [0005]. One of skill in the art would have understood that a distinguishing color would make the insert easier to see. Ex. 1036, Dana Decl., ¶ 76 (citing Ex. 1015, [0013] ("use of [*Gillespie*'s teachings] preferably permit[] visualization with the unaided eye")). Thus, one of skill in the art would been motivated to combine the "color" teachings of *Gillespie* to make the inserts of *Pritchard* easier to see. Ex. 1036, Dana Decl., ¶ 78. Inserts that are easier see are easier to use and to locate. *Id.*, ¶ 78. Indeed, it has long been known that one of the most common problems of these inserts is that they often become dislodged. *Id.*, ¶ 78. One of skill in the art would have understood that more easily visible inserts would make detection of that problem easier. *Id.*, Also, one of skill in the art would have understood that the addition of a distinguishing color, as

taught by *Gillespie,* to the inserts of *Pritchard* would make the inserts more distinctive, help prevent counterfeiting, and may make the inserts more visually uniform. *Id.*, 84 (citing Ex. 1016, 146). In sum, Claims 1-7, 9-16, 18-20, and 22-23 would have been obvious over *Pritchard* in view of *Gillespie*. Ex. 1036, Dana Decl., ¶ §V.B. (¶¶ 73-78).

C. Ground 3: Claims 8, 17, and 21 Are Obvious Over *Pritchard* in View of *Gillespie* and *Hellberg* under §103

Claims 8, 17, and 21 depend from independent Claims 1, 11, and 18, respectively, and further require that "the therapeutic agent is travoprost." Travoprost is a known agent for treating glaucoma. *See* Ex. 1036, Dana Decl., ¶ 8,); Ex. 1035, PHYSICIANS' DESK REFERENCE (57 ed. 2003) 540-41, 541 ("TRAVATAN® [travoprost] Opthalmic solutions is indicated for reduction of elevated intraocular pressure in patients with open-angle glaucoma ….").

For the reasons set forth in Ground 1, *Pritchard* anticipates Claims 1, 11, and 18 (and other claims) and, for the reasons set forth in Ground 2, *Pritchard* renders those claims obvious in view of *Gillespie*. Ocular incorporates by reference the facts and arguments set forth in Grounds 1 and 2.

Although neither *Pritchard* nor *Gillespie* expressly discloses travoprost, Claims 8, 17, and 21 are obvious over *Pritchard* in view of *Gillespie* and *Hellberg*. *Hellberg* "is directed … to methods of treating glaucoma, comprising …

administration of therapeutically effective amounts of a prostaglandin analog ….” Ex. 1017, *Hellberg*, 5:40-43. *Hellberg* discloses “[t]he preferred methods of the present invention comprise one or more prostaglandin analogs ….” *Id.*, 5:44-46. *Hellberg* identifies travoprost as one of its three “most preferred prostaglandin analogs.” *Id.*, 7:56-58. And *Hellberg* notes that “[t]he prostaglandin analogs of the present invention are known and are either commercially available (Cayman Chemical, Ann Arbor, Mich.) or may be prepared by known methods to those skilled in the art.” *Id.*, 7:59-62. In other words, *Hellberg* teaches the use of travoprost as a preferred therapeutic agent in a drug delivery system to treat glaucoma. Ex. 1036, Dana Decl., ¶ 80.

One of ordinary skill would have been motivated to combine the “travoprost” therapeutic agent for treatment of glaucoma, as taught by *Hellberg*, with the canalicular implants of *Pritchard* and *Gillespie* for several reasons. First, as explained with respect to Ground 1, *Pritchard* discloses systems used to treat glaucoma (*see Pritchard* chart for Claims 4, 13, and 19); wherein the therapeutic agent is an anti-glaucoma agent (*see Pritchard* chart for Claims 3, 12, and 18); and wherein the therapeutic agent is a prostaglandin analog (*see Pritchard* chart for Claims 7 and 16). Thus, *Pritchard* would have motivated a person of oridinary skill to use a prostaglandin analog as a therapeutic agent to treat glaucoma. And one of skill in the art would been motivated to include travoprost, in particular, as

the therapeutic agent in a drug delivery system as one of the three most preferred prostaglandin analogs for treatment of glaucoma. *See* Ex. 1036, Dana Decl., ¶ 81. Second, a person of skill in the art would have understood that travoprost is a similar alternative to other prostaglandin analogs for treatment of glaucoma, including latanaprost and bimatoprost. *Id.,*. Thus, one of skill in the art would been motivated to include travoprost as the therapeutic agent in a drug delivery system to have an available alternative, preferred prostaglandin analogs for treatment of glaucoma. *Id.,* In sum, Claims 8, 17, and 21 would have been obvious over *Pritchard* in view of *Gillespie* and *Hellberg*. *Id.*, §V.C (¶¶ 79-81).

D. Ground 4: Claims 1-7, 9-16, 18-20, 22-23 Are Obvious Over *Pritchard* in View of the *Handbook* under §103

For the reasons set forth in Ground 1, *Pritchard* anticipates Claims 1-7, 9-16, 18-20, and 22-23. Ocular incorporates by reference the facts and arguments of Ground 1. But to the extent that *Pritchard's* express and inherent disclosure of color is somehow deemed an insufficient disclosure of the color recited in the challenged claims, Claims 1-7, 9-16, 18-20, and 22-23 are obvious over *Pritchard* in view of the Handbook (Ex. 1016). .

The *Handbook* includes a section on "Coloring Agents." *See* Ex. 1016, *Handbook*, 21-28. According to the *Handbook,* "[t]he primary purpose of coloring agents is to visually alter the appearance of a medicinal product by imparting a

definite color or shade. This has the advantage to the manufacturer of making otherwise similar products more distinctive. … This commercial distinctiveness also aids in preventing the counterfeiting of products." *Id.*, 21. "Colors … can also serve to introduce a uniformity of appearance to a product, e.g., … where an ingredient in the formulation has itself a variable appearance from batch to batch." *Id.* "Colors for clear liquid preparations are limited to the dyes." *Id.*; *see also id.*, 24-26. In other words, the *Handbook* discloses a distinguishing color to show, and motivations for using such a color in a drug delivery system for insertion into the lacrimal canaliculus of a patient.

A person of ordinary skill would have been motivated to combine the "color" teachings of the *Handbook* with the inserts of *Pritchard* for several reasons. First, a person of skill in the art would have understood that a distinguishing color would make the insert easier to see. Ex. 1036, Dana Decl., ¶ 84. Thus, one of skill in the art would been motivated to combine the "color" teachings of the *Handbook* to make the inserts of *Pritchard* easier to see. *Id.*, ¶ 84. Inserts that are easier see are also easier to use and to locate. *Id.*,. One of skill in the art would have understood that more easily visible inserts would make detection of one of the most common problems, dislodged inserts, easier. *Id.*,. Also, a person of skill in the art would have understood that the addition of a distinguishing color, as taught by the *Handbook*, to the inserts of *Pritchard* would

make the inserts more distinctive, help prevent counterfeiting, and may make the inserts more visually uniform. *Id.*, ¶ 82 (citing Ex. 1016, 21). In sum, Claims 1-7, 9-16, 18-20, and 22-23 would have been obvious over *Pritchard* in view of the *Handbook*. Ex. 1036, Dana Decl., ¶ 82-84.

E. Ground 5: Claims 8, 17, and 21 Are Obvious Over *Pritchard* in View of the *Handbook* and *Hellberg* under §103

Claims 8, 17, and 21 depend from independent Claims 1, 11, and 18, respectively, and further require that "the therapeutic agent is travoprost." As seen above, travoprost is a therapeutic agent used to treat glaucoma. For the reasons set forth in Ground 1, *Pritchard* anticipates Claims 1, 11, and 18 (and other claims) and, for the reasons set forth in Ground 4, *Pritchard* renders those claims obvious when combined with the *Handbook*. Ocular incorporates by reference the facts and arguments set forth in Grounds 1 and 4. Although neither *Pritchard* nor the *Handbook* expressly discloses a drug delivery system wherein the therapeutic agent is travoprost, Claims 8, 17, and 21 are obvious over *Pritchard* in view of the *Handbook* and *Hellberg*.

As explained in Ground 3, *Hellberg* teaches the use of travoprost as one of the three most preferred prostaglandin analog therapeutic agents in a drug delivery system to treat glaucoma. The discussion of *Hellberg* in Ground 3 is incorporated by reference.

One of ordinary skill would have been motivated to combine travoprost, as disclosed in *Hellberg*, with the implants of *Pritchard* and the *Handbook* for several reasons. First, as explained with respect to Ground 1, *Pritchard* discloses systems used to treat glaucoma (*see Pritchard* chart for Claims 4, 13, and 19); wherein the therapeutic agent is an anti-glaucoma agent (*see Pritchard* chart for Claims 3, 12, and 18); and wherein the therapeutic agent is a prostaglandin analog (*see Pritchard* chart for Claims 7 and 16). Thus, *Pritchard* would have motivated one of skill in the art to use a prostaglandin analog as a therapeutic agent to treat glaucoma. And one of skill in the art would been motivated to include travoprost in particular as the therapeutic agent in a drug delivery system because it is one of the three most preferred prostaglandin analogs for treating glaucoma. *See* Ex. 1036, Dana Decl., ¶¶ 86-87.

Second, one of skill in the art would have understood that travoprost is a similar alternative to other prostaglandin analogs for treatment of glaucoma, including latanaprost and bimatoprost. *See* Ex. 1036, Dana Decl., ¶ 87. Thus, one of skill in the art would been motivated to include travoprost as the therapeutic agent in a drug delivery system to have an available alternative, preferred prostaglandin analogs for treatment of glaucoma. *Id.*, ¶¶ 81, 87. In sum, Claims 1-7, 9-16, 18-20, and 22-23 would have been obvious over *Pritchard* in view of the *Handbook* and *Hellberg*. Ex. 1036, Dana Decl., § V.E. (¶¶ 85-87).

VI. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests institution of *inter partes* review of the '082 Patent and cancellation of Claims 1-23 (the "challenged claims").

Respectfully submitted,

Dated: December 14, 2018

By: _____
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CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing petition for *inter partes* review—excluding the Table of Contents, the Table of Authorities, the Table of Exhibits, the Mandatory Notices, this Certificate of Word Count, and the Certificate of Service—includes less than 13,700 wordsbased on a word count using that feature of WORD.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition For *Inter Partes* Review No. IPR2019-00448 (including Exhibits 1001-1037, the Fee Authorization page, the Certificate of Compliance, and the Power of Attorney) was served on December 14, 2018 by transmitting a copy via Priority Mail Express to the patent owner at the correspondence address of record for the subject patent:

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