UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MEDTRONIC, INC., and TYRX, INC.
Petitioner,

v.

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM and TISSUEGEN, INC.
Patent Owner.

Case: IPR2019-00037
U.S. Patent No. 6,596,296

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,596,296

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1028	Jorge Heller, "7.8 Drug Delivery Systems," in Biomaterials Science: An Introduction to Materials in Medicine (1st ed., Buddy D. Ratner, *et al*., eds.), 346–356 (1997)
1029	T. Higuchi, "Mechanism of Sustained Action Medication: Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices," 52 J. Pharmaceutical Sciences, 1145–1149 (1963)
1030	Yolles, *et al*., "Sustained Delivery Of Drugs From Polymer/Drug Mixtures," 4&5 Polymer News, 9–15 (1971)
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1056	U.S. Patent No. 5,688,516

Medtronic, Inc., and Tyrx, Inc. (collectively "Petitioner") petition for *Inter Partes* Review under 35 U.S.C. §§ 311–319 and 37 C.F.R., Part 42 of claims 1–7, 10, 11, 16, 20–23, 25, 26, 31, and 32 of U.S. Patent No. 6,596,296 (the "'296 patent"). As shown herein, Petitioner is reasonably likely to prove these challenged claims unpatentable. Accordingly, Petitioner requests that the Board institute trial and cancel all challenged claims.

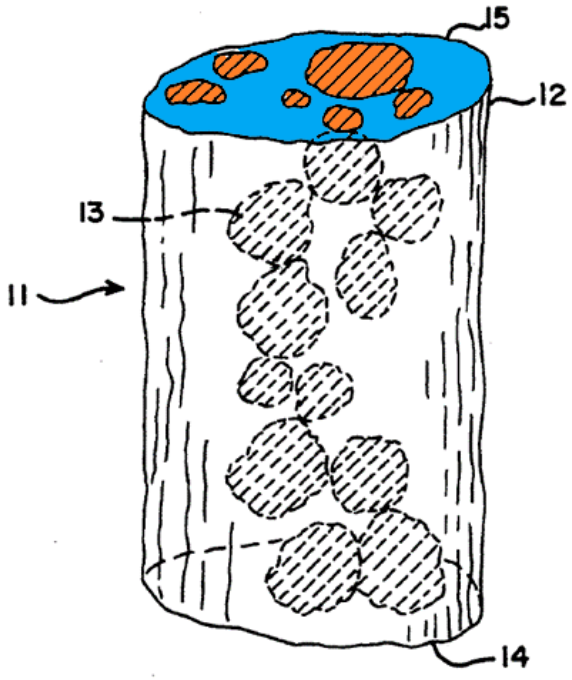
I. INTRODUCTION

Although the '296 patent is entitled, "Drug Releasing Biodegradable Fiber Implant," it does not purport to describe any new biodegradable polymer or therapeutic agent. Rather, the '296 patent specification largely relates to fiber manufacturing processes and various generic medical applications of fibers. *See generally id.*, 17:40–26:20. But the challenged claims recite only compositions, not manufacturing processes or methods of use. Indeed, the examiner reminded the applicant of this fact during prosecution in response to the applicant's attempts to argue patentability based on methods of manufacturing the compositions. *E.g.*, Ex. 1004, 242. Ultimately, the examiner allowed the claims, a decision the examiner would not have made had he been aware of the art cited in this Petition, which discloses all aspects of the challenged claims.

The challenged claims recite a simple composition: a biodegradable polymer fiber composed of two distinct components ("phases") that are immiscible, where

one of the phases includes a drug ("therapeutic agent"). This type of fiber was known well before the claimed effective filing date of the '296 patent.

Drug-delivering biodegradable polymer fibers have a long history. Biodegradable polymers used as medical implants date back to the late 1970s. *Infra* § V. It has long been known that a biodegradable fiber could be loaded with a drug in a number of different ways so that the fiber would release that drug when placed in a person's body. By the time of the '296 patent—in the late 1990s—using different types of biodegradable polymers for delivering different types of drugs was well known to those of skill in art. For example, U.S. Patent No. 5,364,627 to Song ("Song") (Ex. 1007) issued in 1994 and describes a process for making a fiber from a biodegradable polymer (shaded in blue below) with distinct pockets of a drug (shaded in orange below) dispersed throughout that fiber:



Ex. 1007 at Fig. 1 (annotations added). Song explains that the drug and polymer "must be immiscible" (*id.*, 5:5–9), and thereby discloses the simple composition claimed in the '296 patent. Song explains that its drug-loaded biodegradable polymer fibers are beneficial for many applications, including, for example, the controlled release of anti-inflammatory compounds, antibiotics, and anti-coagulation agents. *Id.*, 5:10–12, 4:57–66. As shown in detail herein, the challenged claims of the '296 patent are directed only to what was old and obvious.

Petitioners therefore respectfully request the Board institute *inter partes* review and cancel claims 1–7, 10, 11, 16, 20–23, 25, 26, 31, and 32 of the '296 patent as unpatentable.

II. MANDATORY NOTICES – 37 C.F.R. § 42.8

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Medtronic, Inc., and Tyrx, Inc. are the real-parties-in-interest for the purposes of this proceeding.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Patent Owner is asserting the '296 patent in the following currently pending cases:

- *Board of Regents, the University of Texas Sys. et al. v. Ethicon, Inc. et al.*, No. 1:17-cv-01084 (W.D. Tex.);
- *Board of Regents, the University of Texas Sys. et al. v. Boston Scientific Corp.*,

No. 1:18-cv-00392 (D. Del.); and

- *Board of Regents v. Boston Scientific Corp.*, No. 18-1700 (Fed. Cir.)

Patent Owner also previously asserted the '296 patent against Petitioner in *Board of Regents, the University of Texas System et al. v. Medtronic, Inc. et al.*, No. 1:17-cv-00942 (W.D. Tex.). The complaint in that action was served on October 11, 2017 (Ex. 1005; Ex. 1006), and the suit was dismissed without prejudice on July 19, 2018.

The '296 patent is related to U.S. Patent No. 7,033,603, which is also asserted in each of the above-referenced cases. Petitioner will file a Petition for *Inter Partes* Review regarding the '603 patent concurrently with this Petition. *See* IPR2019-00038.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Lead Counsel: Andrew R. Sommer (Reg. #53,932). **Backup Counsel:** Nimalka R. Wickramasekera, Shilpa A. Coorg, Katherine Hundt, Matthew R. McCullough (*pro hac vice* to be filed).

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Petitioners consent to service by email on the following email addresses: Medtronic-TissueGen-IPRs@winston.com.

III. PETITIONER HAS STANDING TO BRING THIS PROCEEDING

Petitioner certifies (1) the '296 patent is available for IPR, (2) none of the parties constituting Petitioner are the Patent Owner, and (3) it is not barred or

estopped from requesting this IPR. The '296 patent was first asserted in a complaint served on Medtronic, Inc. and Tyrx, Inc. on October 11, 2017, less than one year before this Petition was filed. Ex. 1005; Ex. 1006.

IV. THE '296 PATENT

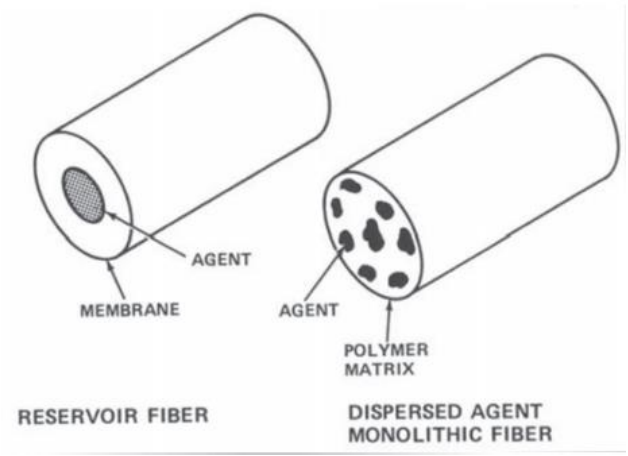
The '296 patent purports to relate to "biodegradable polymer fibers capable of the controlled delivery of therapeutic agents." Ex. 1001, Abstract. The claims at issue here (1–7, 10, 11, 16, 20–23, 25, 26, 31, and 32) generally recite a fiber composed of two phases: (1) a phase comprising a biodegradable polymer, and (2) a phase comprising a therapeutic agent. *See generally* Ex. 1001, Abstract. But the '296 patent does not describe any new type of biodegradable polymer or therapeutic agent. Indeed, the '296 patent admits that using fibers as a "drug delivery platform" was well known. Ex. 1001, 8:37–41 (contrasting known fibers with other known drug delivery devices such as microspheres, porous plugs, or patches).

In Example 1, the '296 patent describes how to manufacture a fiber using a well-known wet-spinning process. *See generally* Ex. 1001, 17:36–19:36; Ex. 1002, ¶¶ 35–39. Generally, the polymer is dissolved in an organic solvent (*id.*, 17:40–50) and the drug is dissolved in water (*id.*, 17:52–54). These solutions are combined to form an emulsion. *Id.*, 18:1–4. Using wet spinning, this mixture is extruded into a coagulation bath, where the organic solvent diffuses out and the polymer precipitates into a fiber. *Id.*, 18:12–28. The fiber is then freeze-dried, frozen, or oven-dried. *Id.*,

18:37–39. The resulting fiber will have two distinct components: (1) polymer, and (2) biomolecule of interest. Ex. 1002, ¶¶ 49–54.

V. PRIOR ART FIBERS FOR DELIVERING DRUGS WERE WELL KNOWN

Uses of polymeric devices for controlled drug delivery are described as early as 1963. Ex. 1002, ¶ 26 (citing Ex. 1029, 1145–49). Real-world devices became known by the 1970s, with disclosures relating to polymer-coated pharmaceutical compositions for the controlled release of drugs over a predetermined time period. *See, e.g.*, Ex. 1030, 9–15; Ex. 1002, ¶ 28. By the mid-1970s, fibers formed of polymers—including biodegradable polymers—for providing the controlled delivery of drugs were disclosed in the art. Ex. 1002, ¶ 31. For example, U.S. Patent No. 3,991,766 issued in 1976 and describes the formation of implantable biodegradable polymer fibers or sutures made of polyglycolic acid "impregnated" with or incorporating therapeutic agents such as antibiotics or other drugs. Ex. 1034, 8:22–50. Later examples include a 1981 article that teaches manufacturing and use of biodegradable polymer fibers for the controlled release of contraceptive drugs. Ex. 1035 ("Dunn"), 125–46. Dunn discloses polymer fibers incorporating a drug dispersed throughout the polymer matrix:



Ex. 1035, 128. Dunn teaches such fibers can be manufactured through "wet-, dry-, and melt-spinning processes." *Id*., 127–29.

By at least 1990, the advantages of using polymeric fibers for controlled drug release were well known. Ex. 1002, ¶ 33. "Major advantages of drug-loaded fibers include ease of fabrication, high surface area for drug release, wide range of physical structures possible, and localized delivery of the bioactive agent to the target." Ex. 1036, 12. Thus, by August 1999, the claimed effective filing date of the '296 patent, use of polymeric devices for controlled drug release had been known for over 27 years and use of polymer fibers had been known for over 22 years. Ex. 1002, ¶ 33.

VI. IDENTIFICATION OF THE CHALLENGES

Claims 1–7, 10, 11, 16, 20–23, 25, 26, 31, and 32 should be canceled in view of the following prior art: U.S. Patent No. 5,364,627 to Song ("Song") (Ex. 1007), PCT International App. Pub. No. WO 98/23167 to Tyrpin *et al*. ("Tyrpin") (Ex. 1008), U.S. Patent No. 5,733,327 to Igaki *et al*. ("Igaki) (Ex. 1009), U.S. Patent No.

6,277,393 to Yrjanheikki *et al*. ("Yrjanheikki") (Ex. 1010), and U.S. Patent No. 5,217,493 to Raad *et al*. ("Raad") (Ex. 1012). All of these references are prior art under pre-AIA § 102. None of these references were considered by the Patent Office during prosecution.

Petitioner presents the following grounds for trial:

- **Ground 1:** Claims 1, 2, 5–7, 11, 16, 23, 25, and 26 are anticipated under 35 U.S.C. § 102(a), (b), and (e) by Song;
- **Ground 2:** Claim 3 is anticipated under 35 U.S.C. § 102(a), (b), and (e) by Song, or, in the alternative, rendered obvious under 35 U.S.C. § 103(a) by Song;
- **Ground 3:** Claims 2, 20–22, 31, and 32 are rendered obvious under 35 U.S.C. § 103(a) by Song in view of Tyrpin;
- **Ground 4:** Claims 3, 4, and 10 are rendered obvious under 35 U.S.C. § 103(a) by Song in view of Igaki;
- **Ground 5:** Claims 1, 4, 11, 16, and 23 are anticipated under 35 U.S.C. § 102(e) by Yrjanheikki;
- **Ground 6:** Claims 20–22 are rendered obvious under 35 U.S.C. § 103(a) by Yrjanheikki in view of Raad.

VII. PROSECUTION HISTORY OF THE '296 PATENT

The '296 patent application was filed on August 4, 2000. As originally filed, none of the claims recited a fiber composed of "phases." *See* Ex. 1004, 113–35.

The first action by the examiner was a restriction requirement on January 29, 2002. Ex. 1004, 174. The examiner identified three distinct sets of claims: (I) claims directed to a "composition"; (II) claims directed to "a method for controlling spatial and temporal concentration of one or more therapeutic agents with a fiber-scaffold implant"; and (III) claims directed to methods of "preparing," "creating," or "fabricating" fibers. *Id.*, 175. The applicant elected to pursue the composition claims (group I). *Id.*, 193–94. At the same time, the applicant canceled all pending claims and proposed nearly 50 new claims, none of which recited a fiber composed of multiple "phases." *See id.*, 195–201.

Thereafter, substantive examination of the claims began. On June 13, 2002, most of the claims were rejected as anticipated by prior art. *Id.*, 221–22. The applicant responded by amending the claims to recite a fiber comprising an emulsion, and introducing the word "phase" into the claims for the first time:

> 199. (Amended) A composition comprising a scaffold matrix which in turn comprises biodegradable polymer fibers [is] selected from a group consisting of a naturally occurring polymer [or] and a synthetic polymer, wherein the fibers or a subset of fibers comprise an emulsion containing one or more therapeutic agents within the aqueous phase of said emulsion.

Id., 233 (original alterations). The applicant further argued that the prior art did not anticipate because "there is no mention in Martin of the manner in which the

therapeutic agents are introduced into the fibers." *Id.*, 231. In response, the examiner made the anticipation rejection final and reminded the applicant it elected to pursue composition claims and, as such, alleged differences in methods of manufacture were immaterial:

> However, a review of the claims shows that ***applicant has claimed a composition, not a method of making*** said composition. ***There is no requirement that the reference teach how the therapeutics are incorporated*** into the claimed fibers. ***Applicant is reminded that a composition is a composition, no matter how it is formulated***. As such, the only requirement of the Martin reference was that it disclose the limitations of the instantly claimed fibers. This requirement is clearly fulfilled.

Id., 242 (emphasis added). The examiner also rejected the claims under section 112 because "there is no support in the original specification for a final product containing" "fibers containing an emulsion." *Id.*, 244.

In response, the applicant cancelled all pending claims and proposed new claims, which ultimately issued as the claims challenged in this Petition. None of the new claims recited a fiber comprising an emulsion. Instead, the new claims recited a fiber composed of two phases:

> 248. (New) A composition comprising at least one biodegradable polymer fiber wherein said fiber is composed of a first phase and a second phase, the first and

> second phases being immiscible, and wherein the second phase comprises one or more therapeutic agents.

Id., 261 (then-claim 248 issued as claim 1 in the ’296 patent). The applicant also argued the claims were not anticipated because the prior art did not show a fiber with two distinct and “separate” phases:

> Martin does not teach or suggest fibers comprising ***a first phase (i.e., the polymer that makes up the fiber)*** and ***a second (inner) phase***, wherein the second phase comprises one or more therapeutic agents.
>
> . . . .
>
> Although Martin teaches that a scaffold comprising fibers may comprise therapeutic agents, Martin does not teach or suggest ***the separation of immiscible phases*** in the formed fibers, or that therapeutic agents can be present in a discontinuous phase ***separate from*** the phase comprising the polymer.

Id., 252–53 (emphasis added). Following an interview, the examiner allowed the claims. *Id.*, 264.

VIII. CLAIM CONSTRUCTION UNDER 37 C.F.R. §§ 42.100(b), 42.104(b)(3)

Pursuant to 37 C.F.R. § 41.100(b), a claim of an unexpired patent is given its broadest reasonable interpretation in light of the specification. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131 (2016); 37 C.F.R. § 42.100(b). For purposes of

this proceeding, Petitioner submits that the following phrase from independent claim 1 should be construed: "***said fiber is composed of a first phase and a second phase, the first and second phases being immiscible***." Based on the intrinsic and extrinsic evidence that Patent Owner is relying on in concurrent litigation, the proper construction of this phrase is "***said fiber is composed of two different components, where the two different components are physically distinct and separable portions of the fiber***."[1] Patent Owner's constructions offered in the pending district court litigation are addressed below. Those proffered constructions, however, are inconsistent with the broadest reasonable interpretation of the claims.

A. The Intrinsic Evidence Supports Petitioner's Proposed Construction.

The intrinsic evidence shows that the phrase "***said fiber is composed of a first phase and a second phase, the first and second phases being immiscible***" has a broadest reasonable interpretation of "***said fiber is composed of two different components, where the two different components are physically distinct and separable portions of the fiber***."

The term "phase" is used in the '296 patent to describe two physically distinct

[1] Petitioner has not performed an analysis under *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*) in this Petition and has only provided the broadest reasonable interpretation of the claim language.

and separable components (polymer solution and therapeutic agent solution) of the mixture used to create a fiber, as described in the '296 patent's Example 1. *See* Ex. 1001, 17:36–19:36. In Example 1, "a biodegradable polymer . . . [is] dissolved in some appropriate solvent" where this solvent "has low miscibility with water." *Id.*, 17:40–50. Then, "an aqueous solution containing both the biomolecules(s) of interest and a surfactant, is added to the polymer solution." *Id.*, 17:52–54. "Using some form of mechanical energy . . . a water-in-oil type emulsion is formed between the aqueous and organic phases." *Id.*, 18:1–4. The "phases" of this emulsion are the aqueous phase (drug and surfactant dissolved in water) and the organic phase (polymer dissolved in organic solvent). Ex. 1002, ¶ 72. The claimed "fiber" is created by extruding the emulsion "into the coagulation bath" where the solvent for the polymer "freely diffuses from the polymer solution stream into the coagulating bath" and the polymer, which is not soluble in the coagulation bath, "begins to precipitate upon itself, forming the outer sheath of a fiber and trapping virtually all of the dispersed aqueous phase of the emulsion within the forming fiber." *Id.*, 18:12–28. The final fiber is made of the polymer with the dispersed biomolecule of interest within it. *Id.*, 18:35–40; Ex. 1002, ¶ 54.

From this description, a person of ordinary skill in the art ("POSA") would have understood that the different "phases" used to create a fiber will result in a fiber—as claimed—that has two separate and distinct components: (1) polymer; and

(2) therapeutic agent. The components are physically distinct and separate because the therapeutic agent and polymer do not dissolve into a single solution during manufacture and, therefore, remain physically distinct and separable in the composition forming the final fiber. Ex. 1002, ¶ 71. The specification therefore supports Petitioner's proposed construction.

The file history supports Petitioner's proposed construction. In the final office action response, the applicant newly proposed what became claim 1 of the '296 patent, distinguishing it over prior art by arguing that the prior art did not show a fiber with two distinct phases:

> Martin does not teach or suggest fibers comprising ***a first phase (i.e., the polymer that makes up the fiber)*** and ***a second (inner) phase***, wherein the second phase comprises one or more therapeutic agents.

Ex. 1004, 252 (emphasis added). The applicant also argued that the prior art did not show separate immiscible phases:

> Although Martin teaches that a scaffold comprising fibers may comprise therapeutic agents, Martin does not teach or suggest ***the separation of immiscible phases in the formed fibers***, or that therapeutic agents can be present in a discontinuous phase ***separate from*** the phase comprising the polymer.

Id., 253 (emphasis added). The applicant thus contended that the fiber of claim 1 is

made of two distinct phases which must be "separate": (1) "the polymer that makes up the fiber" and (2) an "inner" phase comprised of therapeutic agents. *Id.*, 252–53. This argument is consistent with and supports Petitioner's proposed construction that the two immiscible phases refer to two physically distinct and separable components of the fiber. Ex. 1002, ¶ 78.

B. The Extrinsic Evidence Patent Owner Offered in District Court Supports Petitioner's Proposed Construction.

The same extrinsic evidence relied upon by Patent Owner in concurrent litigation supports Petitioner's proposed construction. Patent Owner cited the following definitions in litigation:

- Zbigniew D. Jastrzebski, The Nature and Properties of Engineering Materials, p. 80 (1987) ("A phase can be defined as a homogeneous, ***physically distinct*** part of a system, ***separated*** from other parts of a system by definite bounding surfaces."). (Ex. 1013)
- McGraw-Hill Dictionary of Chemical Terms (3rd ed. 1984) (phase. "Portion of a physical system (liquid, gas, solid) that is homogeneous throughout, ***has definable boundaries, and can be separated physically*** from other phases."). (Ex. 1014)
- Oxford Dictionary of Biochemistry and Molecular Biology (2000) (phase. "the totality of those parts of a heterogeneous material system that are identical in chemical composition and physical state, and that are ***separated***

by an interface from the rest of the system; e.g., solid, liquid, or vapour phases, or the discrete phases into which immiscible liquids separate after mixing."). (Ex. 1015)

- The Random House Dictionary of the English Language (2d ed. Unabridged 1987) (immiscible. "not miscible; ***incapable of being mixed***."). (Ex. 1016)
- Academic Press Dictionary of Science and Technology (1992) (immiscible. "Chemistry. not miscible; ***describing two liquids that do not mix***"). (Ex. 1017)
- Stedman's Medical Dictionary (26th ed. 1995) (immiscible. "***Incapable of mutual solution; e.g., oil and water***."). (Ex. 1018)
- McGraw-Hill Dictionary of Scientific and Technical Terms (5th ed. 1994) (immiscible. "[Chem] Pertaining to ***liquids that will not mix with each other***.") (Ex. 1019); *see also* McGraw-Hill Dictionary of Chemical Terms (1984) (same) (Ex. 1014).

Ex. 1020, A-5 to A-8. Although these definitions differ slightly, each confirms that the phases are different components of the system, and that "immiscible" refers to the concept that the two different components do not mix together, but remain

physically distinct and separable.[2]

C. Patent Owner's District Court Proposed Constructions Are Inconsistent with the Claim Language and File History.

In a pending litigation, Patent Owner proposed the following constructions:

Term	Patent Owner's Proposed Construction
"phase" / "a first phase and a second phase, the first and second phases being immiscible"	"a phase in an emulsion / an emulsion"
"first phase"	"continuous phase comprising the polymer that makes up the fiber"
"second phase"	"dispersed phase containing one or more therapeutic agents"
"immiscible"	Plain and ordinary meaning

Ex. 1021, 10–16.

[2] As noted above, "immiscible" ordinarily describes two liquids that do not mix into a single solution and remain separate even after attempting to mix. Because one cannot "mix" two components of a solid fiber into a single solution, Petitioner's proposed construction is the broadest reasonable interpretation in the context of the claims because it recites the same concept that "immiscible" refers to for liquids, *i.e.*, that the two components of the fiber remain physically distinct and separable.

Patent Owner's proposed construction of "phase" / "a first phase and a second phase, the first and second phases being immiscible" as "a phase in an emulsion / an emulsion" is unsupportable. Although the '296 patent describes creating a fiber where an emulsion is used ***during manufacturing***, there is no discussion of ***a fiber containing an emulsion***. Ex. 1002, ¶ 54. Patent Owner's suggestion to the contrary is inconsistent with the prosecution history. During prosecution, the examiner rejected the applicant's attempt to claim a fiber with an emulsion under § 112 for lack of support: "Applicant has amended the claims to read on fibers containing an emulsion, ***there is no support in the original specification for a final product containing said formulation***." Ex. 1004, 244 (emphasis added). The examiner's statement is consistent with the specification's teaching that the only emulsion present is the one between the polymer solution and drug solution during manufacturing. In the final fiber, the drug solution is dispersed in a solid polymer, the water is either evaporated or frozen, and therefore, there is no emulsion in the final fiber. *Supra* § IV; Ex. 1002, 54. The applicant then removed the concept of an emulsion from the claims and instead inserted the concept of immiscibility.

Patent Owner attempts to evade this language in the file history by arguing in the district court that the examiner "misinterpreted" the patent and "[o]bviously, the examiner corrected his mistake when he allowed claims covering a fiber having two immiscible phases of material in view of the applicants' argument." Ex. 1021, 11–

12 n.6. Not so. To avoid the Section 112 rejection, the applicant not only removed the concept of an emulsion from the claims, but also focused on the requirement that the "fiber comprises a first phase and a second phase." Ex. 1004, 248 (cancelling claims) & 253–54 (arguing Section 112 rejection). The applicant never argued that claim 1 or any other claims added in this response covered an "emulsion." *See id.*, 248–54. Nor could it, given the examiner's rejection of such an argument (*id.*, 244) and the '296 patent's failure to disclose any fiber that contained an "emulsion." The applicant never suggested that an "emulsion" and "immiscible" components were synonymous. And the amendment to the claims made to overcome the Section 112 rejection leads to a different conclusion. The examiner only allowed the claims once the conception of an "emulsion" was removed. Ex. 1004, 248, 266. The file history shows that emulsions are not required by—and should not be read into—the claims.

Thus, Patent Owner's proposed constructions in its concurrent litigation are inconsistent with the claim language and file history, and should not be adopted by the Board. Instead, Petitioner's proposed construction is consistent with the description and claims as they would have been understood by a POSA and should be adopted.

IX. DETAILED EXPLANATION UNDER 37 C.F.R. § 42.104(b)

A. The Grounds for Trial Are Based on Prior Art Patents and Printed Publications Not Considered by the Patent Office

The ’296 patent claims priority to U.S. Provisional Patent Application No. 60/147,827, filed August 6, 1999. For purposes of this IPR, the Board need not evaluate whether the ’296 patent is entitled to claim priority to that date, as all of Petitioner’s prior art qualifies as prior art even under this earliest possible effective filing date. None of Petitioner’s art was considered by the Patent Office during prosecution of the ’296 patent. *Compare* Ex. 1001, cover & page 2 (listing prior art considered) *with* § VI, *supra* (identifying different prior art).

1. *Song is a Prior Art Patent*

Song qualifies as prior art under 35 U.S.C. § 102(a), (b), and (e) because it issued as a U.S. patent on November 15, 1994, more than one year before the claimed effective filing date of the ’296 patent. Ex. 1007, cover.

2. *Tyrpin is a Prior Art Printed Publication*

Tyrpin qualifies as prior art under 35 U.S.C. § 102(a) and (b) because it is a PCT application that was published on June 4, 1998, more than one year before the effective filing date of the ’296 patent. Ex. 1008, cover.

3. *Igaki is a Prior Art Patent*

Igaki qualifies as prior art under 35 U.S.C. § 102(a), (b), and (e) because it issued as a U.S. patent on March 31, 1998, more than one year before the claimed effective filing date of the ’296 patent. Ex. 1009, cover.

4. *Yrjanheikki is a Prior Art Patent*

Yrjanheikki qualifies as prior art under 35 U.S.C. § 102(e) because it is a patent that was granted from an application that was a continuation of U.S. Patent Application No. 09/000,914 (Ex. 1011), which was filed on December 30, 1997, before the claimed effective filing date of the ’296 patent. Ex. 1010, cover.

5. *Raad is a Prior Art Patent*

Raad qualifies as prior art under 35 U.S.C. § 102(a), (b), and (e) because it issued as a U.S. patent on June 8, 1993, more than one year before the claimed effective filing date of the ’296 patent. Ex. 1012, cover.

B. Level of Ordinary Skill in the Art

By the claimed effective filing date of the ’296 patent, a POSA would have a master’s or doctorate degree in one or more of the following: basic chemistry, polymer and materials science, pharmaceutics, and biomedical engineering; or would have a bachelor’s degree and at least five years’ experience in research and development in one or more of the following: basic chemistry, polymer and materials science, pharmaceutics, and biomedical engineering. Ex. 1002, ¶ 13.

In a pending litigation, Patent Owner’s expert has proposed a level of skill

that is similar (Ex. 1039, ¶ 11), and the prior art described below would also invalidate under this proposed level of skill. Ex. 1002, ¶ 17.

C. Ground 1: Claims 1, 2, 5–7, 11, 16, 23, 25, and 26 Are Anticipated by Song

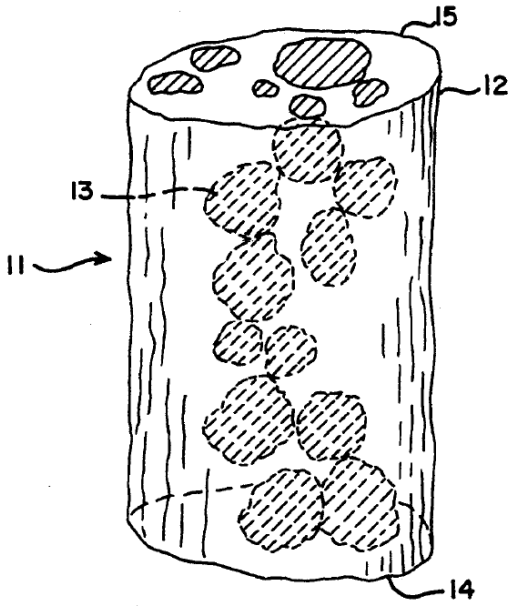
Petitioner requests cancellation of claims 1, 2, 5–7, 11, 16, 23, 25, and 26 because they are anticipated by Song.

1. *Overview of Song*

Song discloses a biodegradable polymer fiber that contains an active agent (*e.g.*, drug) dispersed throughout a wall material (*e.g.*, polymer) such that the active agent is gradually released from the fiber:

> A delivery system and a process for making the system is provided for the gradual release of an active agent. The system comprises an active agent and a wall material. The delivery system is formed by melt spinning a mixture of particles of active agent and wall material into a fiber. . . . The particles of active agent are dispersed throughout the wall material such that the particles of active agent are gradually released from the fiber when the fiber is contacted with a solvent specific to the active agent.

Ex. 1007, Abstract; Ex. 1002, ¶¶ 106–11. Figure 1 of Song illustrates a gradual release fiber with an active agent dispersed in physically distinct pockets (marked 13, diagonally shaded) throughout a support matrix made up of the wall material (marked 12) of the fiber:



Ex. 1007, Fig. 1. Song explains that to form the fiber illustrated above, it is critical that the active agent and wall material "must be immiscible with each other." *Id.*, 5:5–9. As described below, the fiber described in Song discloses each and every limitation of claims 1, 2, 5–7, 11, 16, 23, 25, and 26 of the '296 patent. Song, therefore, anticipates those claims.

2. *Claim 1*

a. "A composition comprising at least one biodegradable polymer fiber"

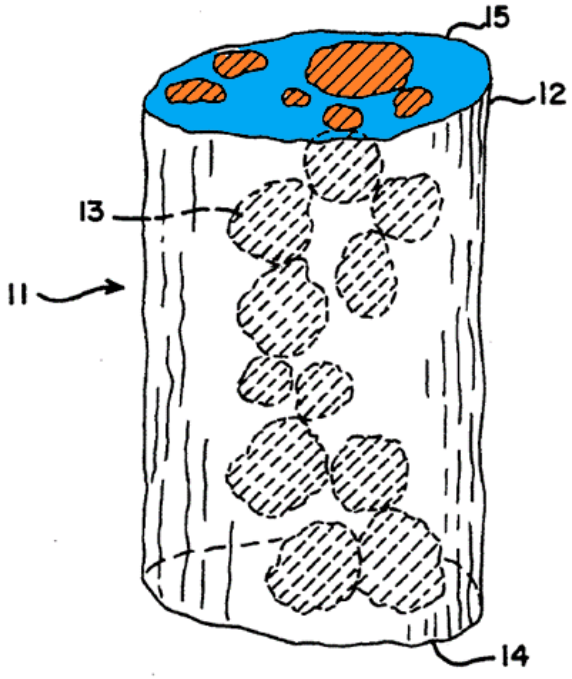
Song discloses the claimed composition that includes "at least one biodegradable polymer fiber." Ex. 1002, ¶¶ 134–37. Song teaches a "delivery system" that can gradually release "an active agent." Ex. 1007, Abst. "The delivery system is formed by melt spinning a mixture of particles of active agent and wall material into a fiber." *Id.*; *see also id.*, 1:52–60. "[P]articles of active agent are

dispersed throughout the wall material such that the particles of active agent are gradually released from the fiber . . . ." *Id.*, Abst.; *see also id.*, 1:61–65, 2:38–40. Song teaches that "the wall material can be any spinnable synthetic or natural polymer," and that for "many applications," "the use of biodegradable polymers is beneficial." *Id.*, 5:1–18. This disclosure of a fiber with wall materials made of "biodegradable polymers" discloses a "biodegradable polymer fiber." Ex. 1002, ¶¶ 134–37.

b. "wherein said fiber is composed of a first phase and a second phase, the first and second phases being immiscible, and"

Song's fiber is "composed of a first phase and a second phase," where the "first and second phases are immiscible." Ex. 1002, ¶¶ 138–141. Song's first phase—the "wall material"—is, for example, a "biodegradable polymer[]" such as "copolymers of lactic and glycolic acid (PLGA)." Ex. 1007, 5:10–18. These polymers are in the same family of polymers disclosed in the '296 patent, further supporting the conclusion that Song discloses the same "first phase" for the resulting fiber as the '296 patent. *See* Ex. 1001, 17:41–46 (disclosing biodegradable polymers such as "poly(L-lactic acid) (PLLA), poly(DL-lactic acid)," "poly(glycolic acid)," "or copolymers or blends of these and other biodegradable polymers"); Ex. 1002, ¶ 139. Thus, the first phase disclosed in Song is a biodegradable polymer.

The second phase disclosed in Song is the "active agent," which may include "drugs" including "anti-hypertensive drugs" and "anti-arrhythmics," Ex. 1007, 4:40–66, which are the same type of therapeutic agents disclosed in the '296 patent, *see* Ex. 1001, 4:1–19 (disclosing "therapeutic agents" including drugs for "high blood pressure" and "anti-arrhythmia" drugs). This shows that the second phase disclosed in Song is the same as the second phase described in the '296 patent. Ex. 1002, ¶ 139. These two phases of material are illustrated in the annotated version of Song's Figure 1 below, in which the top cross section is highlighted in blue shading to indicate the first phase (the biodegradable polymer) and in orange shading for the second phase (Song's "active agent"):



As illustrated above, Song teaches that "[a]n active agent is dispersed throughout the support matrix and may be in contact with itself forming a contiguous phase within

the support matrix. The active agent, however, does not necessarily have to be in a contiguous phase." Ex. 1007, 2:38–42.

Song teaches that the first phase and second phase are immiscible:

> The active agent and all material must meet the solubility requirements discussed above. Additionally, ***they must be immiscible with each other*** and capable of being uniformly dispersed when mixed together during the melt spinning procedure.

Ex. 1007, 5:5–9 (emphasis added). Because the active agent and wall material are immiscible, they will not mix together and the fiber will have two physically distinct and separable components, satisfying Petitioner's proposed construction, as shown above in Figure 1: (1) the polymer and (2) the active agent dispersed throughout that polymer. Ex. 1002, ¶¶ 140–41.

c. "wherein the second phase comprises one or more therapeutic agents."

Song also teaches that the second phase—i.e., Song's "active agent"—comprises one or more therapeutic agents. *See, e.g.*, Ex. 1007, 4:32–60 (listing a host of "pharmaceuticals" that can constitute the "active agent"); Ex. 1002, ¶¶ 142–43. As explained above, some of the disclosed therapeutic agents are the same types of agents disclosed in the '296 patent. *Supra* § IX.C.2.b.

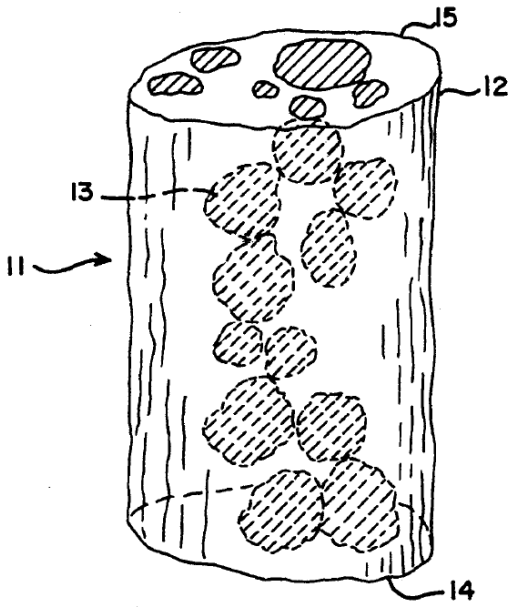
3. *Claim 2: "The composition of claim 1, wherein said second phase is derived from an aqueous solution, a hydrogel or polymer."*

Song discloses the composition of claim 1. *Supra* § IX.C.2. Song further discloses that the second phase—i.e., Song's "active agent"—is derived from a polymer. Ex. 1002, ¶¶ 145–47. Song explains that the active agent "must be solid or in the form of powders, including . . . liquids adsorbed or absorbed into or onto a supporting matrix." Ex. 1007, 4:34–37. Song proceeds to explain that the active agent may be "absorbed into maltodextrin," a well-known polymer. *Id.*, 4:49; Ex. 1002, ¶ 146 (citing Ex. 1054, confirming that maltodextrin is a polymer). In fact, maltodextrin is an example of a polysaccharide, a type of polymer specifically discussed in the '296 patent. Ex. 1001, 10:13–36 (identifying polysaccharides as one of the "Main Polymers Recognized as Biodegradable"); Ex. 1002, ¶ 146. Thus, Song teaches that its second phase, the "active agent," may be derived from a polymer such as maltodextrin.

4. *Claim 5: "The composition of claim 1, wherein the one or more therapeutic agents are distributed within the second phase in a nonhomogeneous pattern."*

Song discloses the composition of claim 1. *Supra* § IX.C.2. Song further discloses that the therapeutic agents are distributed within the second phase in a nonhomogeneous pattern. Ex. 1002, ¶¶ 148–50. Song explains that the "particles of active agent are dispersed throughout the wall material." Ex. 1007, 1:61–65; *see*

also id., 2:38–40, 3:44–51. Song depicts, in the figures, that the active agent is dispersed through the wall material (*i.e.*, the polymer making up the fiber) in a nonhomogeneous (*i.e.*, non-uniform) pattern because it shows that the drug is distributed in pockets of different sizes that are distributed at different locations across the width and length of the fiber:

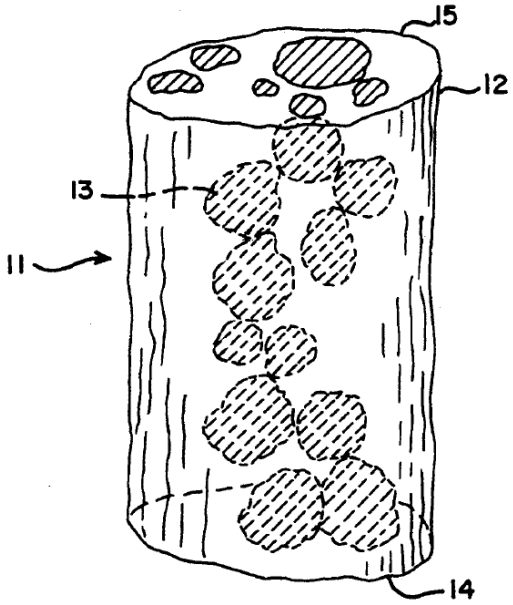


Id., Fig. 1; Ex. 1002, ¶ 149.

5. *Claim 6: "The composition of claim 1, wherein the concentration of said one or more therapeutic agents varies along the longitudinal axis of the fiber."*

Song discloses the composition of claim 1. *Supra* § IX.C.2. Song further discloses wherein the concentration of a therapeutic agent varies along the longitudinal axis of the fiber. Ex. 1002, ¶¶ 151–54. Song discloses that the therapeutic agents within its gradual release fiber are "dispersed throughout the wall material" in a nonhomogeneous pattern. Ex. 1007, 1:61–65; *see also id.*, 2:38–40,

3:44–51. This nonhomogeneous pattern is shown in Figure 1, which shows the active agent (13):



Id., Fig. 1; Ex. 1002, ¶ 152. Because Song's gradual release fiber has drug distributed in pockets of different sizes that are distributed at different locations across the length of the fiber, the concentration of the drug will vary at different points along the length of Song's fiber. Ex. 1002, ¶ 153.

6. *Claim 7: "The composition of claim 6, wherein the concentration of said one or more therapeutic agents varies linearly, exponentially or in any desired fashion, as a function of distance along the longitudinal axis of the fiber."*

Song discloses the composition of claim 6. *Supra* § IX.C.5. Song further discloses that the concentration of said one or more therapeutic agents varies linearly, exponentially or in any desired fashion, as a function of distance within the plurality of layers. Ex. 1002, ¶¶ 155–58. As discussed above, the active agent is

dispersed through the fiber disclosed in Song is distributed in a nonhomogeneous pattern that varies along the length of the fiber. *Supra* § IX.C.5. Because it is dispersed in a nonhomogeneous pattern along the length (both in terms of the size and placement of the pockets of active agent within the wall material), the concentration of active agent varies as a function of distance along the fiber disclosed by Song. Song further teaches that, in creating the fiber, one can choose the amount of active agent, preferably from 10% to 55% of the overall weight but even as low as "a fraction of a percent by weight." Ex. 1007, 2:48–55. Song also explains that the distribution of the drug within the fiber may, but is not required to be contiguous (*i.e.*, the drug may be in contact with itself, or not). *Id.*, 3:1–39. Thus, a POSA would understand that the concentration of Song's active agent varies along the length of the fiber "in any desired fashion" because the concentration of the drug is chosen by the user when forming the fiber. Ex. 1002, ¶¶ 157–58.

7. *Claim 11: "The composition of claim 1, wherein said one or more therapeutic agents are selected from the group consisting of drugs, . . . anti-inflammatory compounds . . . [and] anti-coagulation agents"*

Song discloses the composition of claim 1. *Supra* § IX.C.2. Song further discloses that the active agent may be a "drug," including specifically "anti-inflammatory compounds" and "anti-coagulation agents" as recited by claim 11. Ex. 1002, ¶¶ 159–60. Song expressly states that "[t]he active agent can be any material

such as . . . drugs," including, for example, "anti-inflammatory substances" and "anti-coagulants." *Id.*; Ex. 1007, 4:32–66.

8. *Claim 16: "The composition of claim 1, wherein said biodegradable polymer is a single polymer, a co-polymer, or a mixture of polymers selected from the group consisting of . . . aliphatic polyesters . . ."*

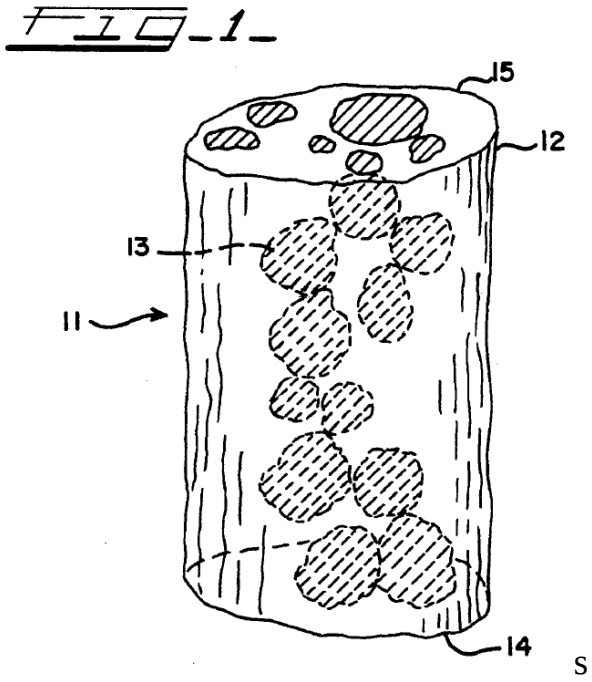
Song discloses the composition of claim 1. *Supra* § IX.C.2. Song further discloses that its "wall material" is, for example, "biodegradable polymers" such as, for example, "copolymers of lactic and glycolic acid (PLGA)" or "polyglycolic acid." Ex. 1002, ¶¶ 161–62; Ex. 1007, 5:10–18. PLGA and polyglycolic acid are examples of the claimed "aliphatic polyesters," as admitted by the '296 patent. Ex. 1001, 10:21–24 (identifying "Poly(glycolic acid) (PGA) and copolymers" and "Poly(lactic acid) (PLA) and copolymer" as "[a]liphatic polyesters").

9. *Claim 23: "The composition of claim 1, wherein the fiber contains more than one therapeutic agent along its length."*

Song discloses the composition of claim 1. *Supra* § IX.C.2. Song further discloses that the fiber may contain more than one therapeutic agent along its length. Ex. 1002, ¶¶ 163–66. For example, Song explains that "[c]ombinations of different active agents in the same structure may also be employed." Ex. 1007, 4:32–40. Song provides specific examples of fibers created with multiple active agents. *Id.*, 9:50–10:6 (discussing three example fibers with two active agents). And, as discussed above, Song explains that its active agents can include drugs of the same type

disclosed in the ’296 patent. *Supra* § IX.C.2.c. Thus, Song teaches that multiple therapeutic agents may be contained within the fiber along its length. Ex. 1002, ¶ 164.

To the extent Patent Owner argues that this claim requires varying the proportion of more than one therapeutic agent along the length of the fiber (although such a requirement is not recited by the claim language), Song discloses that as well. Ex. 1002, ¶ 165. As discussed above, Song discloses that its active agent is distributed in a nonhomogeneous (*i.e.*, non-uniform) pattern in the fiber:



s

Ex. 1007, Fig. 1; *supra* § IX.C.4. Thus, the proportion of the active agents varies along the length of the fiber due to the non-uniform manner in which the active agents are dispersed throughout the fiber. Ex. 1002, ¶ 165.

10. *Claim 25: "The composition of claim 23, wherein said more than one therapeutic agents are released at varying rates over time from said fiber."*

Song discloses the composition of claim 23. *Supra* § IX.C.9. Song further discloses that the therapeutic agents are released at varying rates over time from the fiber. Ex. 1002, ¶¶ 167–70. Song explains that "[g]radual release of the active agent . . . occurs when the fiber is brought in contact with a solvent, or dispersing media, for the active agent." Ex. 1007, 3:57–59. Song teaches that the amount of active agent being released changes over time as more channels open to expose more of the active agent to the solvent:

> As illustrated in FIG. 1A, ***the solvent first dissolves the active agent in the openings at the ends 14 and 15 of the support matrix***. ***As this material is dissolved spaces or channels 13a in the support matrix are opened. The solvent fills these channels and begins to dissolve the newly exposed active agent***, which was in contact with the now dissolved active agent located in the openings at ends of the support matrix. ***Thus, the length of the channels in the support matrix gradually increase as the active agent directly in contact with the solvent is dissolved.***

Id., 3:63–4:5. A POSA would understand that this means the drug would be released at varying rates over time because the distribution of the drug throughout the fiber is non-homogenous (*supra* § IX.C.4) such that as the solvent dissolves the active

agent, more or less drug may be available depending on the concentration of the active agent at that particular point in the fiber. Ex. 1002, ¶ 168.

Additionally, Song teaches that its fiber may be deformed as a person chews (*e.g.*, when Song's fiber is used in a medicated chewing gum), because "the pressure from chewing will flatten, stretch, and deform the fibers exposing new surface areas of active agent to the solvent." Ex. 1007, 3:26–30; *see also id.*, 8:55–9:67 (explaining that exemplary fibers "exhibit a gradual release of the active agent when chewed alone"). A POSA would understand that this would release the active agent at rates that vary over time, as a person chews at different rates. Ex. 1002, ¶ 169.

11. *Claim 26: "The composition of claim 1, wherein said one or more therapeutic agents are released at varying rates over time from said fiber."*

Song discloses the composition of claim 1. *Supra* § IX.C.2. Song further discloses that the active agent is released at varying rates over time, for the reasons (*e.g.*, exposure of more active agent over time, deformation due to chewing) explained above with respect to claim 25. *Supra* § IX.C.10; Ex. 1002, ¶ 171.

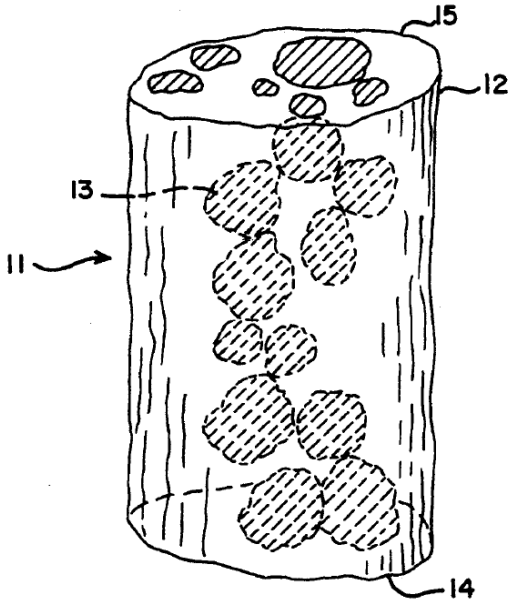
D. Ground 2: Claim 3 is Anticipated, or, in the Alternative, Rendered Obvious by Song

Petitioner requests cancellation of claim 3 because it is anticipated, or, in the alternative, rendered obvious by Song.

1. *Claim 3*

a. "The composition of claim 1, wherein said fiber forms a scaffold,"

As discussed above, Song discloses the composition of claim 1. *Supra* § IX.C.2. Song further discloses that the fiber forms a scaffold. Ex. 1002, ¶¶ 175–77. Song describes its composition as a gradual release matrix in the form of a fiber wherein the fiber is comprised of a support matrix, or wall material, with an active agent dispersed throughout. Ex. 1007, 2:35–40; *see also* Fig. 1 (provided below).



Id., Fig. 1.

Additionally, to the extent Patent Owner contends that Song's fiber does not qualify as a "scaffold," it would have been obvious to a POSA to use multiple of Song's fibers together. For example, Song explains that its fibers release a drug as the user chews on the fiber. Ex. 1007, 3:26–30. From this, a POSA would

understand that one of the uses of Song's fibers is in a chewing gum (*e.g.*, a medicated gum).[3] It would have been obvious to a POSA that a single piece of chewing gum would require more than a single polymer fiber, given the disparity between the size of Song's polymer fibers (cross section "no greater than about 1 mm," Ex. 1007, Abstract) and the size of a piece of chewing gum. Ex. 1002, ¶¶ 176–77. Thus, a POSA would have found it obvious to use multiple of Song's fibers to create, *e.g.*, a single piece of medicated chewing gum. *Id.* Such an arrangement would certainly qualify as a "scaffold" under the '296 patent, which explains that both structured (as in Fig. 1 below) and unstructured (as in Fig. 2 below) arrangements of multiple fibers qualify as a "scaffold":

[3] Additionally, the Song patent issued to the Wm. Wrigley Jr. Company, and from reading Song and other Wrigley patents and publications, such as Tyrpin and Song II, a POSA would understand that the fibers in Song may be used in chewable gum. *Infra* § IX.E.2.

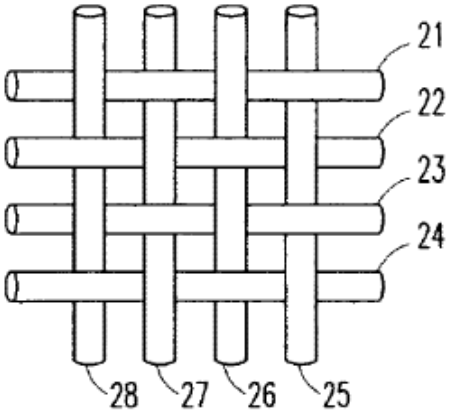


FIG. 1

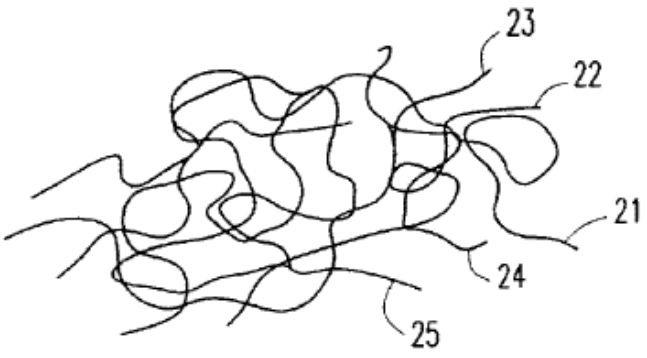
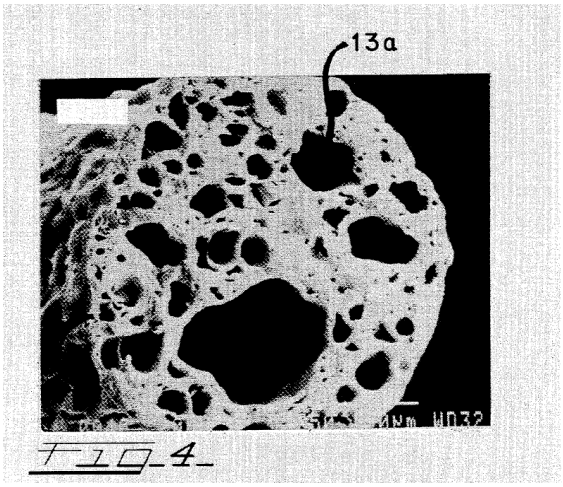


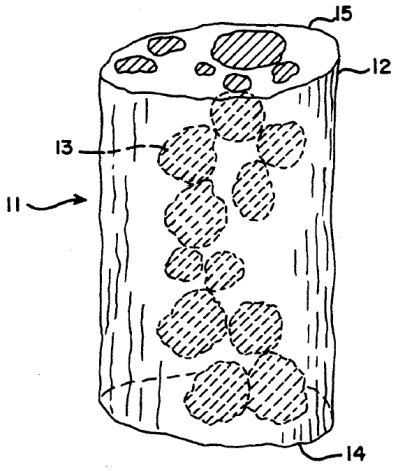
FIG. 2

Ex. 1001, 6:63–7:7 (describing Fig. 1 as "woven scaffolding with patterning" and Fig. 2 as "non-woven scaffolding without patterning").

b. "and further wherein, said second phase is manipulated to form an internal porous structure within the fiber,"

Song's Figures 1 and 4 (provided below) also illustrate that its gradual release fiber has an internal porous structure. Ex. 1002, ¶¶ 178–80; Ex. 1007, Figs. 1 & 4. These figures show the dispersed active agent in physically distinct pockets (marked 13 in both) throughout the fiber. *Id*. These pockets are formed through Song's melt-spinning process which combines the biodegradable polymer that forms the wall material and an immiscible active agent. Ex. 1007, 5:25–45. The combination of the two results in active agent dispersed throughout the support matrix in the manner illustrated below. Ex. 1007, 2:37–40.





As shown in the figures, the drug is dispersed throughout a network of pores in Song's fiber. Indeed, Song explains that as the active agent is dissolved, "spaces or channels in the support matrix are created. The solvent fills these channels and begins to dissolve the newly exposed active agent . . . ." Ex. 1007, 3:3–10. Thus, Song's active agents form an internal porous structure within the fiber. Ex. 1002, ¶¶ 178–80.

E. Ground 3: Claims 2, 20–22, 31, and 32 are Rendered Obvious by Song in View of Tyrpin

Petitioner requests cancellation of claims 2, 20–22, 31, and 32 because they are rendered obvious by Song in view of Tyrpin.

1. *Overview of Tyrpin*

Tyrpin describes "methods for producing chewing gum," including incorporating certain compounds (*e.g.*, bitterness inhibitors) into the gum. Ex. 1008, 1:5–28. Tyrpin explains that fibers making up the gum can be formed using "encapsulation . . . by entrapment of an ingredient by fiber extrusion or fiber

spinning into a polymer," incorporating by reference U.S. Patent No. 4,978,537 ("Song II") (Ex. 1053) and the process disclosed therein. Ex. 1008, 9:19–26 ("A process of encapsulation by fiber extrusion is disclosed in U.S. Patent No. 4,978,537, which is hereby incorporated by reference."); *see Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009) (prior art reference may incorporate by reference by "clearly identifying the subject matter which is incorporated and where it is to be found"). Song II is a prior art patent[4] to the same inventor as Song discussed above and contains substantially similar disclosure, including that a fiber is formed encapsulating a dispersed active agent by extruding and melt-spinning into a fiber, and that the active agent and polymer ("wall material") "must be immiscible with each other." Ex. 1053, 4:41–45; *see also generally id.*, Fig. 1 (depicting fiber) & 1:36–62 (summarizing manufacturing process).

Tyrpin further explains that a method of "modifying the release rate of a bitterness inhibitor is to use it in the coating/panning of a pellet chewing gum." Ex. 1008, 10:33–35. Pellet gum is "prepared as conventional chewing gum" (*e.g.*, according to the fiber extrusion method described in Song II and incorporated into

[4] Song II is a U.S. patent that issued on December 18, 1990, more than one year before the claimed effective filing date of the '296 patent, and therefore qualifies as prior art under 35 U.S.C. § 102(a), (b), and (e).

Tyrpin) and coated with one of a number of compounds. *Id.*, 10:35–12:2. Exemplary coatings in Tyrpin include blends containing "maltodextrins," "cellulose type materials like carboxymethyl cellulose or hydroxymethyl cellulose," or "starch and modified starches." *Id.*, 11:25–32.

2. *Motivation to Combine Song and Tyrpin*

A POSA would be motivated to combine Tyrpin and Song. Ex. 1002, ¶¶ 181–88. Tyrpin, Song, and Song II share the same applicant/assignee: Wm. Wrigley Jr. Company. Exs. 1007, 1008, 1053, cover. A POSA would have been motivated to combine these references to apply a coating to Song's fibers because Tyrpin expressly teaches that one can make fibers to form a chewing gum according to the extrusion process described in Song II—which is incorporated by reference in Tyrpin—before coating them as described in Tyrpin. Ex. 1008, 9:19–26; Ex. 1002, ¶¶ 181–88.

As described above, Song II is substantially similar to the Song reference discussed in Ground 1 of this Petition, and a POSA would therefore have readily considered a combination of Song and Tyrpin due to Tyrpin's explicit incorporation of Song II. Ex. 1002, ¶ 186. Song, like Song II, describes the creation of polymer fibers that can be used in chewing gum. *Supra* § IX.C.10. While Song II describes the use of non-biodegradable polymers for use in chewing gum, Song expressly discloses that "the use of biodegradable polymers is beneficial for many

applications," including in chewing gum. *See generally* Ex. 1053; Ex. 1007, 5:10–12, 3:26–34. Therefore, a POSA would have been motivated to use the fiber manufacturing process in Song (which is also used to create chewing gum), to obtain the benefits of using biodegradable polymers, in combination with the coating process described in Tyrpin. Ex. 1002, ¶ 186. And Tyrpin, like Song, discloses the use of biodegradable polymers (*e.g.*, maltodextrin, cellulose, starch) to coat the chewing gum, further supporting that a POSA would combine it with the biodegradable fibers in Song. *Id.* Such a combination would have rendered obvious claims 2, 20–22, 31, and 32, as explained below.

3. *Claim 2: "The composition of claim 1, wherein said second phase is derived from an aqueous solution, a hydrogel or polymer."*

Song discloses the composition of claim 1. *Supra* § IX.C.2. As also discussed above, Song alone anticipates this claim because it discloses the second phase may be derived from a polymer. *Supra* § IX.C.3.

Tyrpin also discloses this claim limitation and, in combination with Song, also renders claim 2 obvious. Ex. 1002, ¶¶ 189–92. As noted above, Tyrpin discloses that its chewing gum composition may be made by "encapsulation by fiber extrusion" as disclosed in Song II, which is incorporated by reference in Tyrpin and is substantially similar to Song. Ex. 1008, 9:19–26; *supra* § IX.E.2. Tyrpin further explains that an active agent "can be added to chewing gum . . . as an aqueous

dispersion . . . . For aqueous dispersions, an emulsifier can also be mixed in the solution with the bitterness inhibitor and the mixture added to a chewing gum." Ex. 1008, 4:17–24. Although Tyrpin focuses primarily on bitterness inhibitors, other agents can be added to the polymer, for example, the various drugs disclosed in Song. Ex. 1007, 4:31–67; Ex. 1002, ¶ 190.

Tyrpin's disclosure of using an aqueous dispersion to incorporate the active agent is similar to the '296 patent's disclosure that its fiber is created by adding an aqueous solution and a "surfactant," which is a type of emulsifier. Ex. 1001, 17:51–67; Ex. 1002, ¶ 191. Thus, Tyrpin teaches a POSA to produce the fibers in Song using a second phase (containing the active agent) derived from an aqueous solution as recited in claim 2. Ex. 1002, ¶ 192.

4. *Claim 20*

a. "The composition of claim 1, wherein said fiber comprises a plurality of polymer layers,"

As discussed above, Song discloses the composition of claim 1 (*supra* § IX.C.2) and Tyrpin discloses a chewing gum composition made from fibers using the process disclosed in Song II, which is substantially similar to Song (*supra* § IX.E.2).

Song in view of Tyrpin further discloses that the fiber may be comprised of a plurality of polymer layers. Ex. 1002, ¶¶ 193–95. Tyrpin teaches "standard coating techniques [that] generally give varying degrees of coating from partial to full

coating." Ex. 1008, 5:18–22. Specifically, Tyrpin discloses the creation of "pellet chewing gum," which is "prepared as conventional chewing gum," *e.g.*, according to the encapsulation by fiber extrusion method in Song (and incorporated in Tyrpin). *Id.*, 10:35–11:3. The gum is "formed into pellets that are pillow shaped or into balls. The pellets/balls can be sugar coated or panned by conventional panning techniques." *Id.*, 10:35–11:3. Tyrpin teaches that this coating can take the form of a polymer: "recent advances in panning have allowed the use of other carbohydrate materials to be used in the place of sucrose. . . . These materials may be blended with panning modifiers including but not limited to . . . maltodextrin, . . . cellulose type materials like carboxymethyl cellulose or hydroxymethyl cellulose, starch and modified starches." *Id.*, 11:18–32. Each of these examples—maltodextrin, cellulose, and starch—are polysaccharides, which the '296 patent admits are known types of biodegradable polymers. Ex. 1001, 10:13–36 (discussing "[m]odified polysaccharides," including specifically noting "cellulose" and "starch"); Ex. 1002, ¶ 195. Thus, Tyrpin teaches a POSA to coat the fibers in Song with another polymer (*e.g.*, maltodextrin, cellulose, or starch) to create chewable gum, thereby disclosing a fiber comprised of a plurality of polymer layers. Ex. 1002, ¶ 195.

b. "wherein an outer layer circumscribes an adjacent inner layer."

Tyrpin teaches that the encapsulation described above uses "standard coating techniques and generally give[s] varying degrees of coating from partial to ***full***

coating." Ex. 1008, 5:18–22 (emphasis added). A POSA would understand that applying a "full coating" to Song's fiber, as suggested by Tyrpin, discloses that the outer layer circumscribes an inner adjacent layer because it would fully surround the fiber on all sides. *Id.*; Ex. 1002, ¶¶ 196–97.

5. *Claim 21: "The composition of claim 20, wherein said plurality of layers optionally contain one or more therapeutic agents."*

Song in view of Tyrpin renders obvious the composition of claim 20. *Supra* § IX.E.4. Song in view of Tyrpin further discloses that the plurality of layers optionally contains one or more therapeutic agents. Ex. 1002, ¶¶ 198–200. Song discloses that its fiber contains a second phase with a therapeutic agent, such as a drug. *Supra* § IX.C.2.c. Tyrpin discloses that a polymer coating that can surround the therapeutic agent-containing fiber disclosed in Song. *Supra* § IX.E.4.a. Thus, Song in view of Tyrpin discloses that the plurality of polymer layers contains one or more therapeutic agents. Ex. 1002, ¶¶ 198-200.

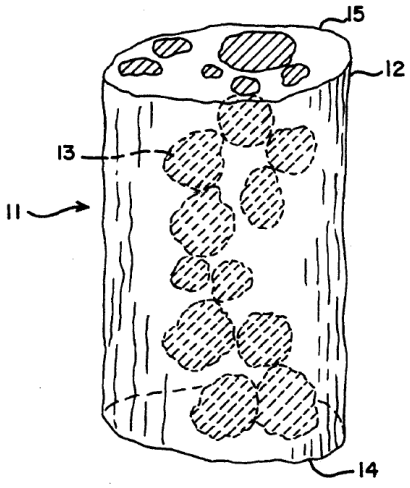
6. *Claim 22: "The composition of claim 21, wherein said one or more therapeutic agents are released over time from said plurality of layers."*

Song in view of Tyrpin renders obvious the composition of claim 21. *Supra* § IX.E.5. Song in view of Tyrpin further discloses that the therapeutic agents are released over time from the plurality of layers. Ex. 1002, ¶¶ 201–04. Song discloses that its active agent is released over time due to exposure of the active agent to a solvent and/or due to deformation as the user chews. *Supra* § IX.C.11. Tyrpin

likewise discloses that the active agent in the coating is released over time: "[t]he amount of coating or encapsulating material on the bitterness inhibitor may also control the length of time for its release from chewing gum." Ex. 1008, 6:10–12. As to the specific materials that may be included in the coating, Tyrpin explains that "compositions that have high organic solubility, good film-forming properties and low water solubility give better delayed release, while compositions that have high water solubility give better fast release." *Id.*, 5:18–26; *see also id.*, 5:35–6:9 (explaining that maltodextrin, cellulose, and starch provide a comparatively "fast release rate"). Thus, Song in view of Tyrpin discloses that the therapeutic agents in both Song's fiber and Tyrpin's coating are released over time. Ex. 1002, ¶¶ 201–04.

7. *Claim 31: "The composition of claim 21, wherein said one or more therapeutic agents are distributed within the plurality of layers in a nonhomogeneous pattern."*

Song in view of Tyrpin renders obvious the composition of claim 21. *Supra* § IX.E.5. Song in view of Tyrpin further discloses that the therapeutic agents are distributed within the plurality of layers in a nonhomogeneous pattern. Ex. 1002, ¶¶ 205–09. Song discloses, through its figures, that its active agent is dispersed through the wall material (*i.e.*, the polymer making up the fiber) in a nonhomogeneous (*i.e.*, non-uniform) pattern. *See, e.g.*, Ex. 1007, Fig. 1 (provided below). Song shows that its drug is distributed in pockets of varying sizes at different locations across the width and length of the fiber:



Id., Fig. 1; Ex. 1002, ¶ 207.

Additionally, as discussed above, Tyrpin teaches a POSA to coat the fibers in Song with another polymer, thereby disclosing a fiber comprised of a plurality of polymer layers. *Supra* § IX.E.4.a. Thus, the combination of Song and Tyrpin teaches a POSA to arrive at a fiber comprised of a plurality of polymer layers and containing a nonhomogeneous pattern of active agent (*i.e.*, a therapeutic agent) dispersed throughout. Ex. 1002, ¶¶ 205–09.

8. *Claim 32: "The composition of claim 31, wherein the concentration of said one or more therapeutic agents varies linearly, exponentially or in any desired fashion, as a function of distance within the plurality of layers."*

Song in view of Tyrpin renders obvious the composition of claim 31. *Supra* § IX.E.7. Song in view of Tyrpin further discloses the concentration of said one or more therapeutic agents [that] varies linearly, exponentially or in any desired fashion, as a function of distance within the plurality of layers. Ex. 1002, ¶¶ 210–12. As discussed above, the active agent dispersed through the fiber disclosed in

Song is distributed in a nonhomogeneous pattern. *Supra* § IX.C.4. Because it is dispersed in a nonhomogeneous pattern (both in terms of the size and placement of the pockets of active agent within the wall material) according to the amount of active agent one chooses to incorporate, the concentration of active agent varies as a function of distance along the fiber in any desired fashion in Song. *Supra* § IX.C.6. When combined with Tyrpin, this variation of concentration occurs within a plurality of layers. Ex. 1001, ¶ 211.

F. Ground 4: Claims 3, 4, and 10 are Rendered Obvious by Song in View of Igaki

Petitioner requests cancellation of claims 3, 4, and 10 because they are rendered obvious by Song in view of Igaki.

1. *Overview of Igaki*

Igaki describes a stent made of multiple biodegradable polymeric fibers woven together. Ex. 1009, Abstract. An example of the woven product is depicted in Figure 1:

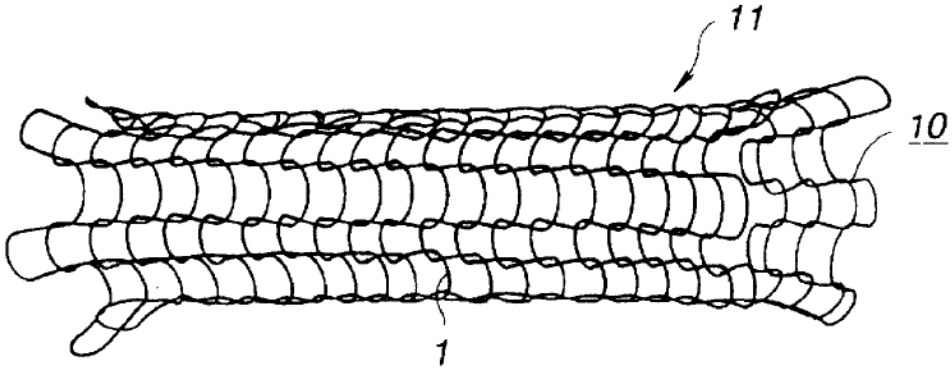


FIG.1

Igaki explains that drugs may be incorporated into the biodegradable polymer. Ex. 1009, 2:65–3:2. But Igaki explains that some biodegradable polymers have a melting point that is sufficiently high that incorporating the drug would cause "undesired chemical conversion, when heated to such elevated temperature." *Id.*, 3:31–36. Thus, Igaki explains that it is desirable to incorporate the drug into a biodegradable polymer with a "low melting point at which the drug added can be present without loss of the pharmacological effects." *Id.*, 3:37–41. Igaki teaches, however, that such polymers "cannot necessarily exhibit sufficient mechanical strength." *Id.*, 3:46–48. Igaki therefore discloses a solution that involves knitting together a low-melting polymer containing a drug (thus preserving the drug's effectiveness) with a high-melting polymer (which adds structural stability):

> In consequence, it is suitable that the fiber composed of the low melting biodegradable polymer containing the drug be woven or knitted together with those made of a high-melting biodegradable polymer to form the tubular stent body.

Id., 3:49–53.

Igaki provides several exemplary stents, of which Example 2 is particularly relevant. In Example 2, the low-melting point biodegradable polymer is made of poly-ε-caprolactone and a "fibrobast hyperplasia-preventing agent[]," *i.e.*, a drug for fighting arthritis. *Id.*, 5:46–52 (describing example 2), 5:12–19 (describing drug).

In Example 2, the high-melting point biodegradable polymer is either poly-lactic acid or poly-glycolic acid. *Id.*, 5:49–62. The low- and high-melting polymers are "formed into a two folded yarn" and "knitted into a stent body." *Id.*, 5:54–58. The low- and high-melting polymers discussed in Igaki are all types of biodegradable polymers mentioned in the '296 patent. Ex. 1001, 9:65–10:4 (identifying "poly(L-lactic acid)," "polycaprolactone," and "poly(glycolic acid)").

2. *Motivation to Combine Song and Igaki*

A POSA would have been motivated to combine Song and Igaki. Ex. 1002, ¶¶ 213–17. Both Song and Igaki relate to drug-releasing biodegradable polymer fibers.

Song discloses "delivery systems using heat sensitive active agents with biodegradable polymers and melt spinning processes for making such systems." Ex. 1007, 1:10–15. As discussed above, Song incorporates drugs into polymers using melt spinning. *Supra* § IX.C.1. Although Song discloses an embodiment relating to chewing gum (as noted above), Song states that its teachings apply more generally to polymers that may be used to release drugs in a number of applications. *See, e.g.*, Ex. 1007, 1:27–37 (describing known drug-releasing fibers and noting usage in female reproductive tract), 4:57–66 (listing wide variety of pharmaceuticals that can be used with invention).

Igaki teaches that one potential challenge with incorporating drugs into polymers using heat, as is done in Song, is that some drugs may lose their "pharmacological effects" if the melting point of a biodegradable polymer is too high. Ex. 1009, 3:31–41. Igaki identifies poly-lactic acid and poly-glycolic acid as example polymers with a higher melting point that may damage certain types of drugs. *Id.* Song discloses the use of polymers in that same family, and thus a POSA familiar with Igaki would understand that Song would benefit from the solution disclosed in Igaki. Ex. 1007, 5:10–18 (Song suggesting use of "copolymers of lactic and glycolic acid (PLGA)" and "polyglycolic acid"). Igaki's solution is to incorporate the drug in a low-melting point polymer (to preserve the drug's effects) and weave that polymer with a high-melting point polymer (to provide strength to the structure). Ex. 1009, 3:49–53. A POSA would have therefore been motivated to modify Song by selecting a lower-melting point polymer to incorporate the drug in and weaving that with a higher-melting point polymer for structural integrity, as explicitly suggested by Igaki. Ex. 1002, ¶¶ 213–17.

3. *Claim 3*

a. <u>"The composition of claim 1, wherein said fiber forms a scaffold,"</u>

As discussed above, Song discloses the composition of claim 1. *Supra* § IX.C.2. Igaki further discloses weaving a drug-releasing fiber with another biodegradable fiber, for example as depicted in Figure 1:

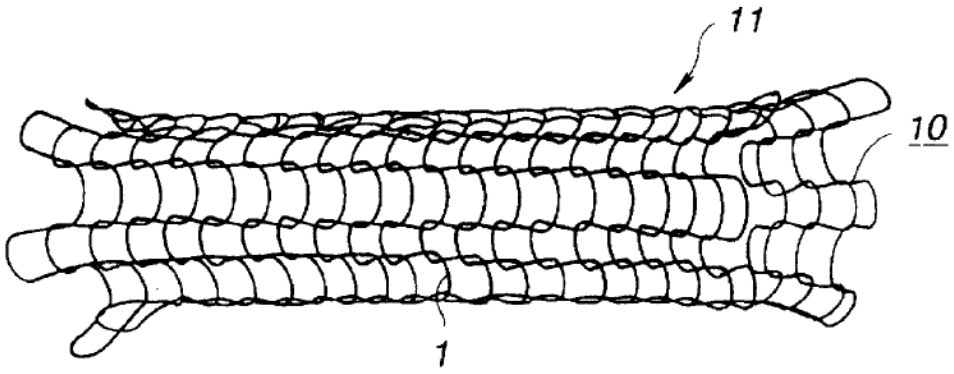


FIG.1

A POSA would be motivated to combine Song and Igaki to blend the drug-releasing fiber of Song with another biodegradable polymer fiber to increase the structural stability of the device. *Supra* § IX.F.2. This combination of Song and Igaki would disclose a three-dimensional network of polymer fibers joined together, *i.e.*, a scaffold. Thus, the combination of Song and Igaki discloses the composition of claim 1 "wherein said fiber forms a scaffold." Ex. ¶¶ 218–21.

b. "and further wherein, said second phase is manipulated to form an internal porous structure within the fiber."

As discussed above, the manufacturing process in Song creates an internal porous structure within the fiber in which Song's active agent is present. *Supra* § IX.D.1.b. Thus, the combination of Song's fibers woven with higher-melting point biodegradable fibers from Igaki would disclose a scaffold with an internal porous structure throughout Song's fibers. Ex. 1002, ¶ 222–23.

4. *Claim 4*

a. "The composition of claim 1, wherein said fiber is woven, braided or knitted in an assembly with other fibers,"

As discussed above, Song discloses the composition of claim 1. *Supra* § IX.C.2. Igaki further discloses weaving a drug-releasing fiber with another biodegradable fiber, for example, as depicted in Figure 1:

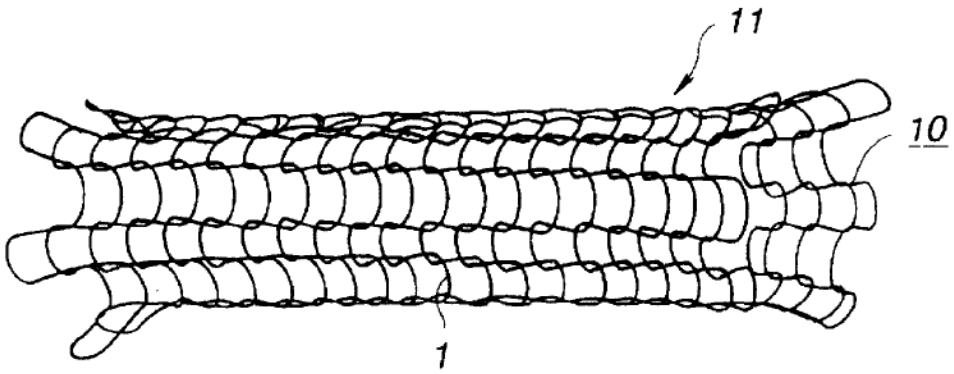


FIG.1

A POSA would be motivated to combine Song and Igaki to blend the drug-releasing fiber of Song with another biodegradable polymer fiber to increase the structural stability of the device. *Supra* § IX.F.2. Thus, the combination of Song and Igaki discloses "wherein said fiber is woven, braided or knitted in an assembly with other fibers." Ex. 1002, ¶ 224–26.

b. "and at least one fiber in the assembly comprises one or more therapeutic agents."

Song discloses a fiber that contains a therapeutic agent, including any one of a number of specifically listed pharmaceuticals such as "anti-hypertensive drugs"

and "anti-arrhythmics." Ex. 1007, 4:40–66; *supra* § IX.C.2.c. Igaki further confirms that one of the fibers in the stent should be loaded with a drug. *Supra* § IX.F.1. As discussed above, a POSA would be motivated to modify Song's fiber to weave it with a second higher-melting temperature fiber as disclosed in Igaki, and therefore the combination of Song and Igaki discloses that at least one fiber in the assembly comprises one or more therapeutic agents. Ex. 1002, ¶¶ 227–28.

5. *Claim 10: "The composition of claim 1, further comprising at least one biodegradable polymer fiber containing no therapeutic agent."*

Song discloses the composition of claim 1. *Supra* § IX.C.2. Song discloses that its fiber contains a therapeutic agent, including any one of a number of specifically listed pharmaceuticals such as "anti-hypertensive drugs" and "anti-arrhythmics." Ex. 1007, 4:40–66; *supra* § IX.C.2.c. Igaki discloses weaving a drug-containing fiber with a higher-melting temperature biodegradable polymer fiber that does not contain a drug to provide a stronger structure for a device. *Supra* § IX.F.1; Ex. 1009, 5:49–62 (Igaki's Example 2 describing that the higher-melting biodegradable polymer fiber does not contain a drug). For the reasons discussed above, a POSA would be motivated to combine Song and Igaki to create a medical structure that both releases a drug (from Song's fiber) and has a stronger structure (from Igaki's higher-melting point biodegradable polymer fiber). *Supra* § IX.F.2. Thus, the combination of Song and Igaki discloses the composition of claim 1

"further comprising at least one biodegradable polymer fiber containing no therapeutic agent." Ex. 1001, cl. 10; Ex. 1002, ¶ 229–30.

G. Ground 5: Claims 1, 4, 11, 16, and 23 are Anticipated by Yrjanheikki

Petitioner requests cancellation of claims 1, 4, 11, 16, and 23 because they are anticipated by Yrjanheikki.

1. *Overview of Yrjanheikki*

Yrjanheikki describes an "active composition" that is a "release system" for "tetracycline and/or tetracycline derivative(s) ('active agent(s)')." Ex. 1010, Abstract. Yrjanheikki teaches that the composition may take many forms, including "short or long fibers or fiber constructions, like threads, cords, fabrics, meshes, non-woven felts, laminates or membranes and polymeric films." *Id.*, 3:29–37. The active agent is released over time using "controlled release formulations, like . . . bioabsorbable fibers, fiber constructions, like threads, cords, bands, knitted or woven fabrics, meshes and films." *Id.*, 6:26–33.

Yrjanheikki also teaches how to make a drug-releasing fiber. First, a bioabsorbable polymer is dissolved into an organic solvent. *Id.*, 10:16–19. Then, the active agent can be "dispersed as a fine powder (particle diameters < 3μm) into the polymer solution" if "the active agent did not dissolve into the organic solvent." *Id.*, 10:19–22. This dispersion is spun into a fiber using a vacuum chamber to evaporate the solvent, leaving only the bioabsorbable fiber and dispersed drug in the

final product. *Id.*, 10:23–29. The fibers can be knitted and/or formed into a mesh for drug delivery. *Id.*, 10:32–37.

2. *Claim 1*

a. "A composition comprising at least one biodegradable polymer fiber"

Yrjanheikki discloses the claimed composition that includes "at least one biodegradable polymer fiber." Ex. 1002, ¶¶ 235–38. Yrjanheikki teaches a "carrier that will protect the active agent(s) against rapid elimination from the body, such as a controlled release matrix." Ex. 1010, 5:39–43. For example, Yrjanheikki describes "active agent(s) releasing meshes" that are configured as "continuous fiber[s]." *Id.*, 10:15–41. The mesh is formed from "[b]ioabsorbable polymer . . ." dissolved into a solvent. *Id.* Yrjanheikki teaches examples in which the active agent does not dissolve into the solvent, leaving a dispersed phase within the polymer solution: "[i]f the active agent did not dissolve into the organic solvent, it was dispersed as a fine powder . . . into the polymer solution." *Id.* The polymer solution with the dispersed active agent is heated and "spun into a continuous fiber by pressing the solution through a conical spinning die . . . into a vacuum chamber. . . . In vacuum, the solvent evaporated and a continuous fiber was formed." *Id.* This disclosure of a fiber made of "bioabsorbable polymers" discloses a composition comprising a "biodegradable polymer fiber." Ex. 1002, ¶ 237.

b. "wherein said fiber is composed of a first phase and a second phase, the first and second phases being immiscible, and"

Yrjanheikki discloses a fiber "composed of a first phase and a second phase," where the "first and second phases are immiscible." Ex. 1002, ¶¶ 239–43. Yrjanheikki's first phase—the "bioabsorbable polymer" is, for example, "polylactides, polyglycolide, and their copolymers." Ex. 1010, 5:43–47. These are the same polymers disclosed in the '296 patent, further supporting the conclusion that Yrjanheikki discloses the same "first phase" for the resulting fiber as the '296 patent. *See* Ex. 1001, 17:41–46 (disclosing biodegradable polymers such as "poly(L-lactic acid) (PLLA), poly(DL-lactic acid)," "poly(glycolic acid)," "or copolymers or blends of these and other biodegradable polymers"); Ex. 1002, ¶ 240. Thus, the first phase disclosed by Yrjanheikki is a biodegradable polymer.

The second phase disclosed in Yrjanheikki is the "active agent," which may include "tetracycline and/or tetracycline derivative." Ex. 1010, 4:52–56. These are examples of the type of therapeutic agents disclosed in the '296 patent, *see* Ex. 1001, 4:1–19 (disclosing "therapeutic agents" including "antibiotics"); *see also* Ex. 1002, ¶ 245 (citing Ex. 1056, which is U.S. Patent No. 5,688,516, a 1997 patent, owned by same assignee, discussing "tetracycline antibiotics"). Thus, the second phase disclosed in Yrjanheikki is the same as the second phase described in the '296 patent, and includes a therapeutic agent. Ex. 1002, ¶¶ 245–47.

Yrjanheikki teaches that these two phases are immiscible: in instances in which the "active agent" does "not dissolve into the" solvent, it is "dispersed as a fine powder . . . into the polymer solution." Ex. 1010, 10:19–22. In such fibers, a POSA would have understood Yrjanheikki's fibers to have two immiscible phases that remain separate and distinct when the final fiber is formed. Ex. 1002, ¶ 242. This is similar to the '296 patent's disclosure in Example 1 that an aqueous drug solution does not dissolve into the polymer solution but instead forms a "water-in-oil type emulsion" before being dried following extrusion. Ex. 1001, 18:1–6; Ex. 1002, ¶ 242. Thus in the '296 patent, the drug is dispersed throughout the polymer solution as a liquid emulsion, similar to the way the drug is dispersed in the polymer solution as a fine powder in Yrjanheikki. Ex. 1002, ¶¶ 241–42. Yrjanheikki further explains that during manufacture of the fiber, the mixture is spun into a vacuum chamber, where the solvent "evaporated," leaving a composition made up of only the polymer and the active agent. Ex. 1010, 10:23–29. Again, this is similar to how the '296 patent obtains a fiber having two immiscible phases. According to the '296 patent, the polymer solvent is also removed during manufacture of the fiber because the mixture is spun into a coagulation bath, where the solvent "freely diffuses from the polymer solution stream, into the coagulating bath." Ex. 1001, 18:22–24. These similarities in the manufacturing process (*e.g.*, dissolving a polymer into a solvent, incorporating a drug that does not mix with the polymer solution, using a spinning

process to manufacture a fiber, and removing the solvent during fiber manufacture) further demonstrate that Yrjanheikki discloses a fiber "composed of a first phase and a second phase," where the "first and second phases are immiscible." Yrjanheikki thus discloses a fiber created from a two-phase mixture (active agent suspended—and dispersed—in the polymer solution) that after manufacture is a fiber composed of two phases (polymer and active agent dispersed throughout). Ex. 1002, ¶ 242.

c. "wherein the second phase comprises one or more therapeutic agents."

Yrjanheikki also teaches that the second phase—i.e., Yrjanheikki's "active agent"—comprises one or more therapeutic agents. *See, e.g.*, Ex. 1010, 4:52–56 (identifying, for example, "tetracycline and/or tetracycline derivative"); Ex. 1002, ¶¶ 245–47. As explained above, some of the disclosed therapeutic agents are the same types of agents (namely, "antibiotics") disclosed in the '296 patent. *Supra* § IX.G.2.b.

3. *Claim 4*

a. "The composition of claim 1, wherein said fiber is woven, braided or knitted in an assembly with other fibers,"

Yrjanheikki discloses the composition of claim 1. *Supra* § IX.G.2. Yrjanheikki also discloses that these fibers can be knit into "bioabsorbable polymer fiber fabrics." Ex. 1010, 10:32–37. Yrjanheikki states that the previously described "fibers were knitted into tricot fabric tube[s]" using a knitting machine, and cut along

their length to create fabric mesh-samples. *Id.* Yrjanheikki thus teaches that multiple "fibers" are used to knit the disclosed fabric, thereby disclosing "woven, braided or knitted" fibers. *Id.*; Ex. 1002, ¶ 250–51.

b. "and at least one fiber in the assembly comprises one or more therapeutic agents."

Yrjanheikki further discloses that "at least one fiber in the [knitted] assembly comprises one or more therapeutic agents." Ex. 1002, ¶¶ 252–53. As discussed above, Yrjanheikki discloses biodegradable polymer fibers containing an "active agent (tetracycline, derivative or tetracycline and/or derivative mixture)." Ex. 1010, 10:16–19. The "tetracycline and/or tetracycline derivative" contained in these fibers are, as stated above, antibiotics and therefore an example of the type of therapeutic agents disclosed in the '296 patent. Ex. 1002, ¶ 252; Ex. 1001, 4:1–5 ("For fibers that contain one or more therapeutic agents, the agent or agents may include . . . an antibiotic").

4. *Claim 11: "The composition of claim 1, wherein said one or more therapeutic agents are selected from the group consisting of drugs, . . . [and] antibiotics . . ."*

Yrjanheikki discloses the composition of claim 1. *Supra* § IX.G.2. Yrjanheikki also discloses that the composition of claim 1 contains therapeutic agent(s), "wherein said one or more therapeutic agents are selected from the group consisting of . . . antibiotics." Ex. 1002, ¶ 254–56. Yrjanheikki discloses a biodegradable polymer fiber containing "tetracycline and/or tetracycline

derivative." Ex. 1010, 10:16–19. As discussed above, tetracycline is an antibiotic. *See* Ex. 1002, ¶ 255 (citing Ex. 1056, which is U.S. Patent No. 5,688,516, a 1997 patent, owned by same assignee, discussing "tetracycline antibiotics").

5. *Claim 16: "The composition of claim 1, wherein said biodegradable polymer is a single polymer, a co-polymer, or a mixture of polymers selected from the group consisting of . . . aliphatic polyesters, . . . poly(ortho ester), . . . [and] polyanhydride . . ."*

Yrjanheikki discloses the composition of claim 1. *Supra* § IX.G.2. Yrjanheikki further discloses that its biodegradable polymer fibers are made from "a single polymer, a co-polymer, or a mixture of polymers selected from the group consisting of . . . aliphatic polyesters, . . . poly(ortho ester), . . . [and] polyanhydride." Ex. 1002, ¶ 257–59. Yrjanheikki teaches that its biodegradable polymer may be made from "poly-α-hydroxy acids (e.g., ***polylactides, polyglycolide and their copolymers***), ***polyanhydrides***, collagen, ***polyorthoesters***, or tyrosine polycarbonates." Ex. 1010, 5:43–47; *see also id.*, col. 11, tbl. II (disclosing same polymers for use in bioabsorbable meshes). Polylactides and polyglycolides are examples of the claimed "aliphatic polyesters," as admitted by the '296 patent. Ex. 1001, 10:21–24 (identifying "Poly(glycolic acid) (PGA) and copolymers" and "Poly(lactic acid) (PLA) and copolymer" as "[a]liphatic polyesters"); Ex. 1002, ¶ 258.

6. *Claim 23: "The composition of claim 1, wherein the fiber contains more than one therapeutic agent along its length."*

Yrjanheikki discloses the composition of claim 1. *Supra* § IX.G.1. Yrjanheikki discloses two-phase biodegradable polymer fibers wherein the fiber contains more than one therapeutic agent along its length. Ex. 1002, ¶¶ 260–63. As explained above, Yrjanheikki teaches an example of manufacturing a biodegradable polymer fiber containing a therapeutic agent or therapeutic agents. *Supra* § IX.G.2.c. Yrjanheikki teaches that the polymer is dissolved into an organic solvent and the active agent is dispersed into the polymer solution, then the polymer solution is spun into a continuous fiber. Ex. 1010, 10:19–29. Because the active agent is mixed into the polymer solution and the combined solution is extruded, the resulting fiber would have the active agent along its length. Thus, Yrjanheikki teaches a method of forming a fiber that has an active agent along its length.

Yrjanheikki also discloses the use of "more than one therapeutic agent." Ex. 1002, ¶ 261. Yrjanheikki's Table II, which includes the biodegradable polymer fiber meshes discussed above, also provides a list of active agents used in these examples, including 1:1 ratios of "Minocycline + Doxycycline" and "Tetracycline + Minocycline." As discussed above, tetracycline and its derivatives, which include minocycline and doxycycline, are forms of antibiotics—a type of therapeutic agent disclosed in the '296 patent. Ex. 1002, ¶ 261 (citing Ex. 1056, which is U.S. Patent No. 5,688,516, a 1997 patent, owned by same assignee, discussing "tetracycline

antibiotics"). Therefore, Yrjanheikki discloses fibers that contain "more than one therapeutic agent along [their] length." Ex. 1002, ¶ 263.

H. Ground 6: Claims 20–22 are Rendered Obvious by Yrjanheikki in View of Raad

Petitioner requests cancellation of claims 20–22 because they are rendered obvious by Yrjanheikki in view of Raad.

1. *Overview of Raad*

Raad discloses a coating combining the antibiotics rifampin and minocycline or rifampin and novobiocin. Ex. 1012, Abstract. When coated on the surface of an implantable medical device, Raad teaches the coating has "long lasting resistance to staphylococcal biofilm colonization." *Id.*, Abstract. Raad discloses a dual-antibiotic coating that is "very effective in killing biofilm-associated staphylococci, particularly *Staphylococcus epidermidis* and *Staphylococcus aureus*, when applied to the surfaces of an indwelling medical device." *Id.*, 2:34–39. Raad teaches "an implantable medical device having a portion of its surfaces coated with an antibiotic combination of (a) rifampin and minocycline or (b) rifampin and novobiocin, the combination of antibiotics in an amount sufficient to inhibit growth of biofilm encased bacteria on the coated surface." *Id.*, 2:47–52. Raad explains that "the antibiotic combination can be applied to the surfaces of the devices in any number of ways, including . . . dispersion within a polymeric base material . . . coated on the device surfaces." *Id.*, 2:52–58. Furthermore, Raad teaches that "[t]he medical

devices which are amenable to coatings of the subject antibiotic combinations generally have surfaces composed of thermoplastic or polymeric materials." *Id.*, 3:26–29.

2. *Motivation to Combine Yrjanheikki and Raad*

A POSA would have been motivated to combine Yrjanheikki with Raad to arrive at claims 20, 21, and 22 of the '296 patent. Ex. 1002, ¶¶ 264–68. Yrjanheikki discloses biodegradable polymer fiber meshes containing "active agents" (or drugs). Ex. 1010, 1:13–21; 3:30–47. It teaches that these meshes can be "administered topically to the brain or spinal cord tissue" to "treat[] and/or prevent[] cerebrovascular diseases, traumas and damages of the nervous system." Ex. 1010, 3:63–4:3; 1:13–21. Yrjanheikki teaches that active agents should be applied "for days and weeks in a controlled manner." *Id.*, 3:44–47.

A POSA looking to use a biodegradable implant, such as the one disclosed in Yrjanheikki, would have been motivated to combine this disclosure with a drug-containing coating that would allow for both a quick release and long term release of drugs. As discussed above, Raad teaches that a drug can be released from its coating. Ex. 1012, 1:24–28. A POSA would understand that multiple layers of antibiotic-releasing polymer would allow for different release profiles. Ex. 1002, 266. Thus, a POSA would have been motivated to apply Raad's coating to Yrjanheikki to obtain both fast-releasing agents (from the Raad coating) and slower-

releasing agents (from the underlying Yrjanheikki meshes). Such a combination would have been readily considered by a POSA and would have been effective at achieving both Yrjanheikki's and Raad's purposes (delivering drugs to affected portion of body and preventing bacterial growth, respectively). Ex. 1002, 266–67.

3. *Claim 20*

a. "The composition of claim 1, wherein said fiber comprises a plurality of polymer layers,"

The teachings of Yrjanheikki and Raad disclose "[t]he composition of claim 1, wherein the fiber comprises a plurality of polymer layers." Ex. 1002, ¶¶ 270–72.

As explained above, Yrjanheikki discloses the composition of claim 1. *Supra* § IX.G.2. Raad discloses "an implantable medical device having a portion of its surfaces coated with an antibiotic combination of (a) rifampin and minocycline or (b) rifampin and novobiocin, the combination of antibiotics in an amount sufficient to inhibit growth of biofilm encased bacteria on the coated surface." Ex. 1012, 2:47–52. Raad further discloses that this "antibiotic combination can be applied to the surfaces of the devices in any number of ways, including . . . dispersion within a polymeric base material . . . coated on the device surfaces." Ex. 1012, 2:52–58. Thus, Raad discloses an antibiotic-containing polymer coating. *Id*. When applied to the teaching in Yrjanheikki, the combination discloses a drug-containing biodegradable polymer fiber (first layer) coated with a drug-containing polymer

coating (second layer), and therefore discloses a "composition of claim 1, wherein the fiber comprises a plurality of polymer layers." Ex. 1002, ¶¶ 271–72.

b. "wherein an outer layer circumscribes an adjacent inner layer."

Raad discloses "an implantable medical device having a portion of its surfaces coated with an antibiotic combination of (a) rifampin and minocycline or (b) rifampin and novobiocin, the combination of antibiotics in an amount sufficient to inhibit growth of biofilm encased bacteria on the coated surface." Ex. 1012, 2:47–52. Raad further discloses that this antibiotic combination can be applied to the implantable device through "dispersion within a polymeric base material [that is] coated on the device surfaces." *Id.*, 2:56–58. Therefore, Raad discloses an antibiotic containing polymer coating. *Id*. When applied to teachings in Yrjanheikki, the combination discloses a drug-containing biodegradable polymer fiber coated and circumscribed by Raad's drug-containing polymer coating. This combination discloses "an outer layer circumscrib[ing] an adjacent inner layer." Ex. 1002, ¶¶ 273–75.

4. *Claim 21: "The composition of claim 20, wherein said plurality of layers optionally contain one or more therapeutic agents."*

The teachings of Yrjanheikki and Raad disclose "[t]he composition of claim 20 wherein said plurality of layers optionally contain one or more therapeutic agents." Ex. 1002, ¶¶ 276–77.

As explained above, when combined, Yrjanheikki and Raad disclose the composition of claim 20. *Supra* § IX.H.3. Yrjanheikki and Raad both further disclose the use of one or more therapeutic agents. First, Yrjanheikki discloses examples of a biodegradable polymer fiber that contains two antibiotics, defined as "therapeutic agents" in the '296 patent. *See* Ex. 1010, col. 11, Table II; Ex. 1002, ¶ 277. Similarly, Raad discloses a polymer coating that contains the antibiotics rifampin and minocycline. *See* Ex. 1012, Abstract, cls. 1, 4. Thus, when the drug-containing biodegradable polymer in Yrjanheikki is combined with the drug-containing polymer coating in Raad, the combination discloses a "plurality of layers optionally contain[ing] one or more therapeutic agents." Ex. 1002, ¶ 277.

5. *Claim 22: "The composition of claim 21, wherein said one or more therapeutic agents are released over time from said plurality of layers."*

The teachings of Yrjanheikki and Raad disclose "[t]he composition of claim 21, wherein said one or more therapeutic agents are released over time from said plurality of layers." Ex. 1002, ¶¶ 278–79.

As explained above, when combined, Yrjanheikki and Raad disclose the composition of claim 21. *Supra* § IX.H.4. Yrjanheikki discloses that the therapeutic agent(s) within its biodegradable fiber meshes can be prepared such that the "implant starts to release the active agent(s) immediately when it has been placed in contact with the surface and/or internal structure of the brain or spinal cord, and continues

the release of the active agent(s) *for days and weeks* in a controlled manner." Ex. 1010, 3:29–46 (emphasis added). Yrjanheikki further teaches that the biodegradable polymer fiber meshes serve as controlled release devices to allow for the release of active agents over time. *Id.*, 6:26–33 ("The active compounds can be prepared with carriers or release matrices that will protect the compound against too rapid release, such as controlled release formulations, like . . . bioabsorbable fibers, fiber constructions, like threads, cords, bands, knitted or woven fabrics, meshes and films.").

When combined with the coating in Raad, the combination teaches "[t]he composition of claim 21, wherein said one or more therapeutic agents are released over time from said plurality of layers." Ex. 1002, ¶ 279.

X. PAYMENT OF FEES – 37 C.F.R. § 42.103

The required fee is being paid through PTABE2E.

XI. CONCLUSION

For the foregoing reasons, Petitioner requests that the Board institute *inter partes* review of claims 1–7, 10, 11, 16, 20–23, 25, 26, 31, and 32 of the '296 patent and cancel those claims as unpatentable.

Dated: October 9, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This petition complies with the word count limits set forth in 37 C.F.R. § 42.24(a)(i), effective May 2, 2016, because this Petition contains 13,993 words, excluding the parts of the petition exempted by 37 C.F.R. § 42.24(a), as corrected in *Amendments to the Rules of Practice for Trials Before the Patent Trial and Appeal Board*, 81 Fed. Reg. 24,702 (Apr. 27, 2016), and determined using the word count provided by Microsoft Word, which was used to prepare this Petition.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that on October 9, 2018, I caused to be served a true and correct copy of the foregoing PETITION FOR *INTER PARTES* REVIEW and Exhibits 1001–1037, 1039–1051, and 1053–1056 by EXPRESS MAIL on Patent Owner the correspondence address of record for U.S. Patent No. 6,596,296, as follows:

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