Filed on behalf of RTI Surgical, Inc.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

RTI SURGICAL, INC.,
Petitioner

v.

LIFENET HEALTH,
Patent Owner

Case IPR2019-00572
Patent No. 9,579,420

PETITION FOR INTER PARTES REVIEW

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Petitioner's Exhibit List

EX.	DESCRIPTION
1001	Reserved
1002	USPN 9,579,420 ("The 420 patent")
1003	Reserved
1004	USPN 5,336,616 ("Livesey")
1005	WO 9807452 ("Walker")
1006	USPN 4,357,274 ("Werner")
1007	USPN 6,326,019 ("Tseng")
1008	USPN 6,630,001 ("Duran")
1009	USPN 4,776,853 ("Klement")
1010	USPN 4,801,299 ("Brendel")
1011	USPN 5,558,875 ("Wang")
1012	USPN 5,718,012 ("Cavallaro")
1013	A.C.J. de Backere, "Euro Skin Bank: large scale skin-banking in Europe based on glycerol-preservation of donor skin," 20 Burns S4-S9 (1994) ("Backere")
1014	D. Michael Strong, "The US Navy Tissue Bank: 50 years on the cutting edge," Cell and Tissue Banking 1:9-16 (2000) ("Strong")
1015	R.E. Billingham, et al., "The Freezing, Drying and Storage of Mammalian Skin," J. Exp. Biol. 29:454-468 (1952) ("Billingham")
1016	LifeNet Health's Opening Claim Construction Brief, D.I. 65; ("LifeNet Opening Claim Construction Brief")
1017	LifeNet Health's Responsive Claim Construction Brief, D.I. 86; ("LifeNet Responsive Claim Construction Brief")

EX.	DESCRIPTION
1018	Declaration of Dr. David L. Kaplan in Support of LifeNet Health's Responsive Claim Construction Brief, D.I. 88; ("Kaplan Declaration")
1019	Opinion and Order on Claim Construction, D.I. 122; ("Claim Construction Order")
1020	Reserved
1021	A.R.D. Basile, "A Comparative Study of Glycerinized and Lyophilized Porcine Skin in Dressing for Third-Degree Burns," 69 Plastic and Reconstructive Surgery 6, 969 (1982)
1022	M.J. Hoekstra, et al., "History of the Euro Skin Bank: the innovation of preservation technologies," 20 Burns S43-S47 (1994)
1023	M. Ghosh, et al., "A Comparison of Methodologies for the Preparation of Human-Epidermal-Dermal Composites," Annals of Plastic Surgery, Vol. 39, No. 4, 390-404 (1997)
1024	U.S. Pat. Appl. No. 12/701,634, Office Action, Dec. 2, 2015
1025	U.S. Pat. Appl. No. 12/701,634, Amendment, Oct. 5, 2016
1026	U.S. Pat. Appl. No. 12/701,634, Notice of Allowability, Oct. 28, 2016
1027	Reserved
1028	Reserved
1029	Jens O.M. Karlsson and Mehmet Toner, "Long-term storage of tissues by cryopreservation: critical issues," 17 Biomaterials 243-256 (1996)
1030	Ronald L. Levin and Thomas W. Miller, "An Optimum Method for the Introduction or Removal of Permeable Cryoprotectants: Isolated Cells," 18 Cryobiology 32-48 (1981)
1031	J. van Baare et. al., "Virucidal effect of glycerol as used in donor skin preservation," 20 Burns Suppl. 1, S77-S80 (1994)
1032	Reserved

EX.	DESCRIPTION
1033	Reserved
1034	Declaration of David J. McQuillan, Ph.D.

I. Introduction

RTI Surgical, Inc. ("RTI" or "Petitioner") petitions for *inter partes* review of claims 1-18, 20-22, and 24-36 of U.S. Patent No. 9,579,420 ("the 420 patent"; Ex. 1002), which is owned by LifeNet Health ("LifeNet" or "Patent Owner"). The application for the 420 patent was filed on February 8, 2010, and issued as a patent on February 28, 2017.

The 420 patent describes incorporating chemical compounds, identified as "plasticizers," within a cleaned soft tissue graft to replace water at the molecular level with the object of providing a soft tissue graft that "exhibits the materials properties that approximate those properties present in normal hydrated tissue, is not brittle and does not necessitate rehydration prior to implantation." (Ex. 1002, 5:39-46.) The claims are directed to a "plasticized soft tissue graft" wherein the "native orientation of the collagen fibers [of the graft] is maintained." Patent Owner added this limitation to overcome a prior art rejection over U.S. Patent No. 5,336,616 ("Livesey"; Ex. 1004). Patent Owner argued that "Livesey does not disclose, teach, or otherwise render inherent a plasticized soft tissue graft in which the collagen fibers have maintained their native orientation." (Ex. 1025 at 8.) The examiner accepted that explanation, and, in the reasons for allowance, stated "Livesey et al. disclose a related process; however, in this reference there is no

teaching or suggestion that the native orientation of the fibers is maintained." (Ex. 1026 at 2.)

To the contrary, Livesey does disclose a plasticized soft tissue graft in which the native orientation of the collagen fibers is maintained. For example, Livesey expressly states that "analysis of the end product by light and electron microscopy has demonstrated it to be structurally intact with normal collagen banding and the presence of collagen bundles in the matrix of the dermis and with structural preservation of the lamina densa and anchoring fibrils of basement membrane complex." (Ex.1004, 25:12-17.) A person of ordinary skill in the art ("POSITA") at the time of the alleged invention would have understood that the presence of collagen bundles and the preservation of the lamina densa and anchoring fibrils provides evidence that the structural integrity of treated tissue is the same as untreated tissue. (Ex.1034, ¶¶79-81.)

The process of incorporating chemical compounds into a soft tissue graft to produce a graft that maintains the native orientation of the collagen fibers had been widely used in tissue preservation before the filing date of the 420 patent. For example, both Livesey, issued in 1994, and WO 98/07452 (Ex. 1005; "Walker"), published on February 26 1998, disclose methods of incorporating chemical compounds, including glycerol, into the internal matrix of a soft tissue graft to produce a pliable soft tissue graft that maintains the native orientation of the

collagen fibers. (Ex. 1004, 25:12-17; Ex. 1005, 2:14-34.) Similarly, U.S. Patent No. 4,357,274 (Ex. 1006; "Werner"), issued in 1982, discloses a method of incorporating glycerol into the internal matrix of a tissue to produce a pliable soft tissue that does not require rehydration before use. (Ex.1006, 2:12-14, 2:30-36, 2:37-41.)

Each of these prior art references teaches that the "native orientation of the collagen fibers is maintained." The limitation that the "native orientation of the collagen fibers is maintained," does not make the known process of incorporating chemical compounds into a soft tissue graft novel, unexpected, or inventive because maintaining the native orientation of the collagen fibers was an expected and known result of the preservation process itself. Thus, the claims define nothing more than the known benefits of a known process disclosed in the prior art. As such, there is at least a reasonable likelihood that the claims of the 420 patent are unpatentable over Livesey, Walker, and Werner.

II. Mandatory Notices

Real Parties-In-Interest: RTI Surgical, Inc. is the real party-in-interest.

Related Matters: The following judicial or administrative matter would affect or be affected by a decision in the proceedings:

1. *LifeNet Health v. RTI Surgical, Inc.*, Case No. 3:18-CV-817 (M.D. Fla.), filed June 25, 2018 ("the LifeNet-RTI Litigation").

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III. Grounds for Standing

The 420 patent is available for *inter partes* review, and RTI is not barred or estopped from requesting an *inter partes* review challenging claims 1-18, 20-22, and 24-36 on the grounds identified in this Petition.

IV. Identification of Challenge

Petitioner identifies the following five grounds of unpatentability:

Ground 1: Claims 1-3, 5, 8, 10, 13-18, 20-21, 24-28, 30, and 33-35 are anticipated by Walker.

Ground 2: Claims 1-3, 5, 7-8, 10, 13-18, 20-22, 24-28, 30, and 33-35 are obvious over Walker.

Ground 3: Claims 1-3, 6, 8-9, 11-14, 16-18, 24-25, 28-29, 31-32, and 34-36 are anticipated by Livesey.

Ground 4: Claims 1-3, 6, 8-9, 11-14, 16-18, 24-25, 28-29, 31-32, and 34-36 are obvious over Livesey.

Ground 5: Claim 4 is obvious over Walker or Livesey in view of Werner.

V. The 420 Patent

A. The Subject Matter of the 420 Patent

The 420 patent describes a "plasticized soft tissue graft" suitable for transplantation into a human and methods of producing such a graft. The patent discloses that one or more chemical compounds (called "plasticizers") are

incorporated within the internal matrix of the soft tissue graft and act to replace water at the molecular level without increasing the brittleness of the graft. (Ex. 1002, 1:21-26.)

The 420 patent explains that "[s]oft tissue products are typically provided as fresh-frozen or freeze-dried." (*Id*., 3:43-48.) This allegedly "causes [such] grafts to be brittle and typically causes shrinkage where the shrinkage is not uniform, thereby causing graft failure." (*Id.,* 3:54-57.) The patent further states that "solvent preservation using for example, acetone or alcohol, can cause irreversible denaturation of proteins, and solubilization of solvent soluble components, including for example, lipids." (*Id.,* 3:57-60.) The 420 patent states that these methods "necessitate[ ] a rehydration step in preparation of the bone and soft tissue product for implantation." (*Id*., 3:60-63.)

The 420 patent purports to describe a solution to the alleged problems associated with freeze-drying and solvent preservation by incorporating a "plasticizer" within the internal matrix of the tissue graft. (*Id*., 5:39-46.) Examples 9 and 10 (the only soft tissue examples) use glycerol as the plasticizer; however, the specification provides other examples of suitable plasticizers, including sorbitol, ethylene glycol, sucrose, and mannitol. (*Id*., 7:50-61, 8:44-65.) The patent acknowledges that, "[u]nder freeze-drying, the water present in the bone . . . is removed by sublimation, however, *the glycerol will remain and replace the free*

and bound water as the water is removed from the bone tissue." (*Id*., 10:29-34 (emphasis added).)

The claims further recite that the "native orientation of the collagen fibers is maintained." (*Id.*, 24:40-41, 24:47-49, 24:53-54, 25:25-27, 25:32-37.)

B. Prosecution History

The 420 patent issued on February 28, 2017, from U.S. Patent Application No. 12/701,634, filed February 8, 2010, and claims priority as a divisional of application No. 09/107,459, filed on June 30, 1998, which issued as U.S. Patent No. 6,293,970. Therefore, the 420 patent may be entitled to the effective filing date of June 30, 1998.

On September 13, 2002, the Examiner issued a non-final office action rejecting many claims under 35 U.S.C. 102(b) as being anticipated by Livesey. On October 5, 2016, applicants responded to the rejection over Livesey, focusing on, and amending several claims to include, the limitation that states the "native orientation of the collagen fibers is maintained." Quoting the portion of Livesey cited by the Examiner (col. 5, lines 1-6), applicants argued:

> This portion of Livesey plainly states that the structural integrity of the collagen matrix is not damaged. However, it would be understood by one of ordinary skill in the art that the orientation of collagen fibers may be altered without damaging the structural integrity of the collagen matrix . . . . [Livesey] does not rule out the possibility of

> changes to collagen fiber orientation occurring during plasticization after the cell removal process. For at least the above reasons, this portion of *Livesey does not disclose, teach, or otherwise render inherent a plasticized soft tissue graft in which the collagen fibers have maintained their native orientation*.

(Ex. 1025 at 7-9 (emphasis added).)

Quoting another cited portion of Livesey (col. 7, lines 36-51), applicants argued:

> Like the prior portion, this portion of Livesey is directed to minimizing damage to the collagen matrix. As stated above, it would be understood by one of ordinary skill in the art that the orientation of collagen fibers may be altered while minimizing damage to the collagen matrix . . . one of ordinary skill in the art would understand that minimizing or preventing damage to collagen fibers does not necessarily mean that the native orientation of those collagen fibers is maintained . . . .

(Ex. 1025 at 8-9.)

The claims were thereafter allowed. In the reasons for allowance, the examiner stated:

> [In Livesey] there is no teaching or suggestion that the native orientation of the fibers is maintained . . . , No other known prior art references remedy this . . . .

(Ex. 1026 at 2.)

As discussed *infra*,[1] both Walker and Livesey in fact disclose the feature that applicants argued was missing from the prior art – "the native orientation of the collagen fibers is maintained."

C. Person of Ordinary Skill in the Art

As Dr. McQuillan explains, a POSITA relating to the subject matter of the 420 patent would have had at least either (a) a Master of Science degree in biology, biochemistry, biomaterials engineering, biomedical engineering, or a related field and approximately three years of research or work experience related to preparing and/or processing tissue for transplantation into a human, or (b) a Bachelor of Science degree in one of those fields and approximately five years of research or work experience related to preparing and/or processing tissue for transplantation into a human recipient.[2] (Ex.1034, ¶18.)

Such a person would have been familiar with the need for cleaning of soft tissue grafts before transplantation and also with the use of chemical compounds to

[1] Petitioner has provided a summary of 325(d) considerations in Section VIII.

[2] Patent Owner advocated for a slight variation of this level of skill in prior litigation involving the 200 patent in *LifeNet Health v. LifeCell Corp.*, Case No. 13-CV-00486 in the Eastern District of Virginia ("the LifeNet Litigation"). (*See* Ex. 1017 at 4.)

protect and preserve soft tissue grafts as explained in more detail below. (Ex.1034, ¶¶16-17.)

1. Cleaning soft tissue grafts to remove cellular elements

At least as early as 1994, it was known that the "extracellular protein matrix [of a soft tissue graft] is made up of collagen and other proteins and provides a structural template which may be repopulated with new viable cells." (Ex.1034, ¶21; Ex. 1004, 1:26-30.) By February 1998, a POSITA would have known that soft tissue grafts presented a risk of adverse immunogenic response in transplant patients.[3] (Ex.1034, ¶22.) Therefore, a POSITA by February 1998 would have known that soft tissue grafts used for transplantation must be cleaned to remove cellular materials present in the graft from the transplant donor. (Ex.1034, ¶¶23-24; Ex. 1023 at 390-391.) A POSITA in February 1998 would have been familiar with the various methods for cleaning of soft tissue grafts to remove cellular elements such as the cleaning methods disclosed in Livesey, Klement, Wang, Brendel, and Werner. (Ex.1034, ¶¶23-24.)

The only examples of the cleaning procedure for soft tissue are found in Examples 9 and 10 of the 420 patent, which describe soaking the soft tissue graft

[3] In the LifeNet-RTI Litigation, LifeNet has asserted that its invention date was in March 1998. The unpatentability analysis in this Petition is made as of February 1998 (the latest publication date of the primary prior art references in this Petition).

in a 1:100 dilution of Allowash™ Solution for at least 15 minutes. (Ex. 1002, 23:2-5, 23:55-57.) A POSITA would have understood that such a brief soak in Allowash™ Solution would not remove all of the cellular elements from the soft tissue because soft tissues comprise densely organized collagen and therefore would require a more extensive cleaning procedure for complete removal of cellular components. (Ex.1034, ¶¶33-35.) Examples of more extensive methods for cleaning soft tissue can be found in Livesey (Ex.1004, 23:62-65), Klement (Ex.1009, 3:27-66), and Wang (Ex.1011, 3:47-4:35). Such processes include, for example, exposure to detergent solutions for up to one hour while on a rotator at 40 ± 5 RPM. (Ex.1004, 23:62-65.)Therefore, a POSITA would have recognized that the cleaning process described in the 420 patent only partially removes cellular components from a soft tissue graft. (Ex.1034, ¶35.)

2. Use of chemical compositions to preserve soft tissues

By February 1998, preservation and protection of soft tissue grafts using chemical compounds was known in the art. (Ex.1034, ¶¶25-27.) The use of glycerol to preserve and protect tissue was disclosed in patent literature as early as 1981. (Ex.1034, ¶26; Ex. 1006, 2:21-32.) Further, non-patent literature discussed the benefits of glycerol preservation including that "[g]lycerol is . . . a useful plasticizer in biomaterials . . . to make these materials soft, pliable and easy to use." (Ex.1034, ¶28; Ex. 1022 at S44; Ex. 1023 at 396-397; Ex. 1021 at 971.)

By February 1998, it was known that glycerol was non-toxic to humans and exhibited powerful antiseptic action in the body. (Ex.1034, ¶25; Ex. 1021 at 969-971; Ex. 1013 at S6; Ex. 1022 at S44; Ex. 1023 at 394-395.) Further, by February 1998, it was known that glycerol preservation did not affect the fundamental architecture of tissues and that tissues preserved with glycerol have properties approximating those of their natural counterparts. (Ex.1034, ¶30; Ex. 1022 at S4; Ex. 1023 at 396-397; Ex. 1021 at 971.)

D. Claim Construction

The following terms are expressly defined in the 420 patent:

- **"internal matrix"** - "in soft tissue, the intercellular substance of such soft tissue including for example ligaments and tendons, including collagen and elastin fibers and base matrix substances." (Ex. 1002, 7:1-8.)
- **"plasticizer"** - "any biocompatible compounds which are soluble in water and can easily displace/replace water at the molecular level and preferably have a low molecular weight such that the plasticizer fits into the spaces available to water within the hydrated molecular structure of the bone or soft tissue." (*Id.*, 7:40-46.) "Such plasticizers are preferably not toxic to the cellular elements of tissue into which the graft is to be placed, or alternately, the plasticizer is easily removed from the graft

product prior to implantation" and that "[s]uitable plasticizers are preferably compatible with and preferably readily associates [sic] with the molecular elements of the bone tissue and/or soft tissue." (*Id.,* 7:46-52.) Disclosed examples of suitable plasticizers including glycerol, ethylene glycol, propylene glycol, and mannitol. (*Id.,* 7:52-61.)

- **"soft tissue graft" -** "load-bearing and non-load-bearing soft tissue products." (*Id.,* 8:14-16.) Disclosed examples of non-load bearing tissue grafts are cadaveric skin and load-bearing tissue grafts such as pericardium, dura mater, and fascia lata. (*Id.,* 8:16-19.)

The following terms are not expressly defined in the patent, but were construed by the Court in the LifeNet Litigation:

- **"cleaned" –** "a process during which cellular elements and small molecular weight solutes are removed." (Ex. 1019 at 9.)

Petitioner's view is that to fully understand the term "cleaned" as used in the 420 patent, a POSITA in February 1998 would have taken into account the cleaning process disclosed in Examples 9 and 10. (*See* Section V.C.1., *supra*.) A POSITA would have understood that the cleaning process disclosed in the 420 patent only partially removes cellular elements from the soft tissue. (Ex.1034, ¶¶33-35, 48-49.)

- **"plasticized soft tissue graft" -** "a load-bearing and/or non-load-bearing soft tissue product, including skin, pericardium, dura mater, fascia lata, and a variety of ligaments and tendons composed of an internal matrix where free and loosely *bound* waters of hydration in the tissue have been replaced with one or more plasticizers without altering the orientation of the collagen fibers, such that the mechanical properties, including the material, physical and use properties, of the tissue product are similar to those of normal hydrated tissue." (Ex. 1019 at 7-9.)

This definition combines the definitions for "plasticization" and "soft tissue graft." (Ex. 1002, 7:34-39, 8:14-19.) The court in the LifeNet Litigation included the language "such that the mechanical properties, including the material, physical and use properties, of the tissue product are similar to those of normal hydrated tissue," as part of the definition of "plasticized soft tissue graft" stating that it was supported by the specification and that it clarified the claim term. (Ex. 1019 at 7-9.) A POSITA would have agreed with this construction of the claim term "plasticized soft tissue graft" because the term as used in the 420 patent requires that the tissue is being preserved in a way that would both preserve the native orientation of the collagen fibers and preserve the mechanical properties of the tissue so the tissue can function as a natural tissue would when used as a

transplant. (Ex.1034, ¶¶51-52.) LifeNet and its expert advocated for this additional language in the LifeNet Litigation. (Ex. 1016 at 6-8; Ex. 1018 at 8-9.)

The following claim term were not expressly defined in the 420 patent and should be given the plain and ordinary meaning to a POSITA:

- **"mechanical properties approximating mechanical properties of natural soft tissue" -** "mechanical properties, including material properties, physical, and use properties, of tissue are similar to those of normal hydrated tissue."

Petitioner's view is that the "mechanical properties" of natural soft tissue include the material, physical and use properties of the tissue. (Ex.1034, ¶¶54-55.) Similar language was included by the court in the LifeNet Litigation for defining the claim term "plasticized soft tissue graft." (Ex. 1019 at 7-9.) A POSITA would have understood that the plasticization process results in the preservation of the mechanical and structural properties of the tissue. (Ex.1034, ¶¶54-55.)

- **"the native orientation of the collagen fibers is maintained" -** "the orientation of the collagen fibers is not altered."

Petitioner's view is that this construction is supported by the specification which defines "plasticization" as "replacing free and loosely bound waters of hydration in a tissue(s) with one or more plasticizers without altering the

orientation of the collagen fibers." (Ex. 1002, 7:34-39.) Similar language was included by the court in the LifeNet Litigation for defining the claim term "plasticized soft tissue graft." (Ex. 1019 at 7-9.) A POSITA would have understood that the plasticization process results in the native orientation of the collagen fibers being maintained. (Ex.1034, ¶¶56-57.)

VI. Summary of the Asserted Prior Art

A. Livesey

Livesey (USPN 5,336,616, Ex. 1004) is titled "Method for Processing and Preserving Collagen-Based Tissues for Transplantation." As a U.S. patent that issued on August 9, 1994, Livesey is prior art to the 420 patent under 35 U.S.C. 102(b). Livesey was the basis of a rejection of the 420 patent.[4]

Livesey discloses a method for processing and preserving an acellular collagen-based tissue matrix for transplantation into a human. (Ex.1004, Abstract.) The method includes the steps of cleaning the tissue and incorporating a chemical compound, named a "cryoprotectant," within the internal matrix of the tissue. (Ex.1034, ¶¶59-60.)

Livesey discloses that the tissue graft is cleaned to remove viable antigenic cells to prevent adverse immunogenic reactions. (Ex.1034, ¶61; Ex.1004, 5:1-3.) It states that "[t]hese methods produce a tissue product that consists of a selectively

[4] Petitioner has provided a summary of 325(d) considerations in Section VIII.

preserved extracellular protein matrix that is devoid of certain viable cells which normally express major histocompatibility complex antigenic determinants and other antigens which would be recognized as foreign by the recipient." (Ex.1004, 1:21-26; *see also* 1:34-39.) In Example 1, Livesey discloses the use of sodium dodecyl sulfate detergent solution. (Ex.1004, 23:65-67.) A POSITA would have understood that Livesey discloses a "cleaned soft tissue graft." (Ex.1034, ¶61.)

Like the plasticization method disclosed in the 420 patent, Livesey discloses treating soft tissues grafts by incorporating chemical compounds (called "cryoprotectants") within the internal matrix of the graft. (Ex.1034, ¶¶62-64; Ex.1004, 5:15-30, 14:47-54.) Suitable cryoprotectants include many of the same compounds identified in the 420 patent as plasticizers, such as sucrose, glycerol, and propylene glycol. (*Compare* Ex. 1004, 11:49-55 *with* Ex. 1002, 7:52-61.) Livesey discloses that the soft tissue graft is incubated in the cryosolution long enough to allow complete penetration of the cryoprotectants. (Ex.1004, 12:34-37, 15:11-13.) A POSITA would have understood that the cryoprotectants replace free or loosely bound water within the internal matrix to preserve the structural integrity of the tissue. (Ex.1034, ¶62.)

Livesey discloses that "analysis of the end product by light and electron microscopy has demonstrated it to be structurally intact with normal collagen banding and the presence of collagen bundles in the matrix of the dermis and with

structural preservation of the lamina densa and anchoring fibrils of basement membrane complex." (Ex. 1004, 25:12-17.) A POSITA would have understood that those structures, particularly the anchoring fibrils, are difficult to preserve and therefore would recognize that the process described in Livesey maintains the structural and mechanical properties of the soft tissue. (Ex.1034, ¶65.)

B. Walker

Walker (WO 98/07452, Ex. 1005) is titled "Method for Sterilizing Material for Implantation." It is a PCT application published on February 26, 1998. Therefore, Walker is prior art under 35 U.S.C. 102(b). Walker is among the references cited on the face of the 420 patent, but it was neither addressed in any substantive manner nor was it the basis of any rejection.

Walker discloses a method of sterilizing biological materials while preserving the flexibility and structure of the material and preventing it from becoming brittle. (Ex. 1005, cover page.) Walker's process involves cleaning the material, incorporating a chemical compound into the material, and then sterilizing the material. (Ex.1034, ¶83; Ex. 1005, 2:14-21.)

Walker discloses that the material is stored in ethanol before treatment with glycerol. (Ex. 1005, 7:19-20, 15:3-5.) A POSITA in February 1998 would have understood that storage of the tissue in ethanol as described in Walker would at least partially remove cellular components from the tissue by solubilizing the lipid-

containing cell membrane. (Ex.1034, ¶84.) A POSITA would have understood that Walker discloses a "cleaned soft tissue graft." (Ex.1034, ¶84.)

Like the plasticization method disclosed in the 420 patent, Walker discloses the incorporation of glycerol, or another protective chemical compound, into the internal matrix of the material. (Ex.1034, ¶¶85-86; Ex. 1005, 2:14-21, 2:30-34, 3:17-20.) Walker discloses glycerol solutions of various concentrations and states that the material is incubated in the solutions for 16 hours or more. (Ex. 1005, 5:7-8, 5:11-13, 6:27-7:21, 15:13-17, 20:4-8, 25:27-28.) A POSITA would have understood from Walker that the glycerol replaces free and loosely bound water within the internal matrix of the material, thus preserving the physical properties of the material and preventing the material from becoming brittle. (Ex.1034, ¶¶85, 88-89.)

Walker discloses that the glycerol maintains the flexibility and the microstructure of collagen in the material. (Ex. 1005, 2:16-27, 4:20-24.) Referring to tests of suture retention and maximum load (*id.*, Tables 9-14), Walker reports that "[t]he results show that the physical properties of treated bovine arteries are unaffected by the plasticization and sterilization processes." (*Id.*, 8:25-32.) It further discloses that "[s]ince glycerol keeps the dimensions of the graft stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (*Id.*, 19:9-15.) A POSITA

would have understood that the plasticization method disclosed in Walker would maintain the structural and mechanical properties of the biological material. (Ex.1034, ¶¶88-89.)

C. Werner

Werner (USPN 4,357,274, Ex. 1006) is titled "Process for the manufacture of sclera protein transplants with increased biological stability." As a U.S. patent that issued on November 2, 1982, Werner is prior art to the 420 patent under 35 U.S.C. 102(b). Werner was the basis of a rejection of the 420 patent during prosecution.[5]

Werner describes a process for the treatment of sclero protein transplants. (Ex. 1006, Abstract.) The method disclosed in Werner includes cleaning the material and then treating it with glycerin or polyethylene glycol. (Ex.1034, ¶91; Ex. 1006, 2:21-29.) In an example, Werner discloses the cleaning of raw dura mater exposing it to a solution of 2-20% H_2O_2 for 48 hours, then degreasing it in a Soxhlet apparatus in an acetone-diethylether 1:1 mixture for 4 hours, and then rinsing it with water for 12-24 hours. (Ex. 1006, 2:50-57.) A POSITA would have understood that Werner discloses a "cleaned soft tissue graft." (Ex.1034, ¶92.)

As does the 420 patent, Werner discloses treatment of a material with a glycerin solution to increase biological stability. (Ex.1034, ¶93; Ex. 1006, 2:1-4,

[5] Petitioner has provided a summary of 325(d) considerations in Section VIII.

2:8-11.) Specifically, it discloses that the glycerin solution impregnates the tissue via diffusion and remains in the tissue throughout the drying process prior to transplantation. (Ex.1034, ¶93; Ex. 1006, 2:5-8.) Werner discloses several advantages over the prior art including that the resulting product is soft and that no rehydration is necessary prior to transplantation. (Ex.1034, ¶94; Ex. 1006, 2:37-41.)

VII. Grounds for Unpatentability

Petitioner seeks review of claims 1-18, 20-22, and 24-36. Claims 1-3 and 15-16 are independent claims; the rest are dependent.

A. Ground 1: Walker anticipates claims 1-3, 5, 8, 10, 13-18, 20-21, 24-28, 30, and 33-35

Claim 1 can be divided into a preamble and four elements, 1 through 4 (*see* Ex. 1002, 24:35-41), and Walker discloses every element.

Claim 1, preamble: ***A plasticized soft tissue graft suitable for transplantation into a human, comprising:***

To the extent the preamble is limiting, Walker discloses a plasticized soft tissue graft suitable for transplantation into a human. (Ex.1034, ¶188.) Walker discloses a method for plasticization of a biological material such as vascular tissues. (Ex.1034, ¶83; Ex. 1005, 2:14-21, 4:17-18.) The disclosed method involves incubating the biological material in a solution containing a plasticizer, such as glycerol, resulting in the incorporation of the plasticizer within the tissue.

(Ex.1034, ¶¶85-86; Ex. 1005, 3:23-24, 15:16-18.) Walker discloses that the plasticized biological material substantially retains certain physical characteristics of the untreated material, such as flexibility. (Ex.1034, ¶¶88-89; Ex. 1005, 4:20-22.) As evidence that the plasticized material maintains its structural and mechanical properties, Walker reports the results of suture pull-out experiments (Ex. 1005, 7:31-9:31; Tables 9-10) and maximum loading tests. (Ex. 1005, 8:13-23; Tables 11-14.) Those results show that the plasticization method disclosed in Walker does not degrade the physical properties of the tissue as compared to untreated tissue. (Ex.1034, ¶¶88-89; Ex. 1005, 8:25-32.) Walker therefore discloses a plasticized soft tissue graft suitable for transplantation into a human. (Ex.1034, ¶188.)

Claim 1, element 1: ***a cleaned soft tissue graft having an internal matrix;***

In the Walker method, the biological material is stored in ethanol before treatment with glycerol. (Ex.1005, 7:19-20, 15:3-5.) A POSITA would have recognized that storing the biological tissue in ethanol would at least partially remove potentially harmful immunogenic cellular components. (Ex.1034, ¶¶84, 189.) Walker therefore discloses a cleaned soft tissue graft.

Claim 1, element 2: ***and one or more plasticizers contained in said internal matrix,***

Walker discloses treatment of the material with a water-soluble, non-volatile substance for at least 12 hours, reporting examples in which the material is treated with glycerol for 16 hours or more. (Ex. 1005, 2:30-34, 3:23-24, 5:11-13, 15:16-17, 20:7-8.) Incubation for 16 hours or more gives the glycerol sufficient time to impregnate the internal matrix of the material. (Ex.1034, ¶190.) Walker discloses that the glycerol keeps the dimensions of the material stable during processing, evidencing that the glycerol is incorporated within the internal matrix. (Ex.1034, ¶¶88-89; Ex. 1005, 19:9-12.) Walker therefore discloses that one or more plasticizers are contained in the internal matrix of the material.

Claim 1, element 3: ***wherein said cleaned soft tissue graft comprises collagen fibers;***

Walker discloses that the material maintains its physical characteristics including the structure of cells or extracellular material such as collagen and more particularly, the microstructure of collagen. (Ex. 1005, 2:23-27.) Walker therefore discloses that the cleaned soft tissue graft comprises collagen fibers. (Ex.1034, ¶191.)

Claim 1, element 4: ***and the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.***

Walker discloses that the glycerol maintains the flexibility and the microstructure of collagen in the material. (Ex. 1005, 2:16-27, 4:20-24.) Referring

to tests of suture retention and maximum load, (*id.*, Tables 9-14), Walker reports that "[t]he results show that the physical properties of treated bovine arteries are unaffected by the plasticization and sterilization processes." (*Id.*, 8:25-32.) It further discloses that "[s]ince glycerol keeps the dimensions of the graft stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (*Id.*, 19:9-15.) Therefore, a POSITA would have understood Walker's method results in a plasticized soft tissue graft that maintains the native orientation of the collagen fibers. (Ex.1034, ¶¶88-89, 192.)

Element	Claim 1	Walker (Ex.1005)
Preamble	A plasticized soft tissue graft suitable for transplantation into a human, comprising:	"This invention relates to a method of treating a graft for implantation into a body." (Ex. 1005, 1:3-4.) "The pre-sterilizing treatment enables the material substantially to retain certain physical characteristics, such as flexibility, and can suitably replace at least some of the water contained in the material." (Ex. 1005, 4:20-24.) "The results from suture pull out, maximum load and maximum stress are shown below. Each sample is compared to an untreated natural sample, which is the partner of the treated sample. The results show that the physical properties of treated bovine arteries are unaffected by the plasticization and sterilization processes." (Ex. 1005, 8:25-32.) See Suture Retention Results (Ex. 1005, 9-10) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics. See Maximum Load and Stress Results (Ex. 1005 11-14) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics. "Since glycerol keeps the dimensions of the grafts stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (Ex. 1005, 19:9-12.)

Element	Claim 1	Walker (Ex.1005)
1	a cleaned soft tissue graft having an internal matrix;	See Examples 3-4 showing tissue stored in ethanol. (Ex. 1005, 7:19-20, 15:3-5.)
2	and one or more plasticizers contained in said internal matrix,	"Preferably the sterilizing agent and the substance are different. The substance preferably comprises a water-soluble non-volatile substance, and the sterilizing agent can comprise, for example, ethylene oxide. A suitable substance might be glycerol. Other possible substances include sugars such as sorbitol." (Ex. 1005, 4:29-34.) "The material can, after being treated, be drained and/or washed to remove excess glycerol or other substance, prior to implantation." (Ex. 1005, 4:29-31.) "Since glycerol keeps the dimensions of the grafts stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (Ex. 1005, 19:9-12.)
3	wherein said cleaned soft tissue graft comprise collagen fibers	"The physical characteristics of the material which may be maintained by treatment with the substance include flexibility, and/or structure of cells or extracellular material such as collagen, particularly the microstructure of collagen." (Ex. 1005, 2:23-27.)

Element	Claim 1	Walker (Ex.1005)
4	and the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.	"The pre-sterilizing treatment enables the material substantially to retain certain physical characteristics, such as flexibility, and can suitably replace at least some of the water contained in the material." (Ex. 1005, 4:20-24.) "The results from suture pull out, maximum load and maximum stress are shown below. Each sample is compared to an untreated natural sample, which is the partner of the treated sample. The results show that the physical properties of treated bovine arteries are unaffected by the plasticization and sterilization processes." (Ex. 1005, 8:25-32.) See Suture Retention Results (Ex. 1005, Table 9-10) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics. See Maximum Load and Stress Results (Ex. 1005, Table 11-14) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics. "Since glycerol keeps the dimensions of the grafts stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (Ex. 1005, 19:9-12.)

Claim 2 can be divided into a preamble and five elements, 1 through 5 (*see* Ex. 1002, 24:42-48), and Walker discloses every element. (Ex.1034, ¶¶193-199.)

Element	Claim 2	Walker (Ex.1005)
Preamble	A plasticized soft tissue graft, comprising:	See Claim 1 table, Preamble.
1	a cleaned soft tissue graft;	See Claim 1 table, Element 1.
2	and one or more plasticizers,	See Claim 1 table, Element 2.
3	wherein said cleaned soft tissue graft is impregnated with said one or more plasticizers,	See Claim 1 table, Element 2.
4	and wherein said cleaned soft tissue graft comprise collagen fibers	See Claim 1 table, Element 3.
5	and the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.	See Claim 1 table, Element 4.

Claim 3 can be divided into a preamble and four elements, 1 through 4 (*see* Ex. 1002, 24:50-54), and Walker discloses every element. (Ex.1034, ¶¶200-205.)

Element	Claim 3	Walker (Ex.1005)
Preamble	A plasticized soft tissue graft, comprising:	See Claim 1 table, Preamble.
1	a cleaned, soft tissue graft comprising	See Claim 1 table, Element 1.
2	one or more plasticizers,	See Claim 1 table, Element 2.
3	wherein said cleaned soft tissue graft comprise collagen fibers	See Claim 1 table, Element 3.

Element	Claim 3	Walker (Ex.1005)
4	and the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.	See Claim 1 table, Element 4.

Claim 5 recites "The plasticized soft tissue graft of any one of claim 1, 2, or 3, wherein said cleaned soft tissue graft is a load-bearing soft tissue graft." (Ex. 1002, 24:58-60.) Walker discloses the use of its plasticization method on biological materials such as vascular tissues. (Ex.1005, 4:17-18.) Included are examples of the use of its method to treat bovine carotid and thoracic arteries. (*Id.*, 7:19-20.) The 420 patent provides a non-exhaustive listing of such load-bearing soft tissues, including pericardium, dura mater, fascia lata, ligaments, and tendons (Ex. 1002, 8:17-19.) As a POSITA would have known, carotid and thoracic arteries are also examples of load-bearing soft tissues. (Ex.1034, ¶206.)

Claims 8 and 28 add the limitation that the plasticized soft tissue graft is "sterile." (Ex. 1002, 25:1-2, 26:23-24.) Walker discloses a sterilization process using a sterilizing agent such as ethylene oxide. (Ex. 1005, 2:29-32.) Further, Walker discloses a sterilization validation study that showed no sign of bacterial growth in the sterilized materials as compared to the positive controls. (Ex. 1005, 6:13-23, 7:8-15.) A POSITA would understand that Walker's method produces a plasticized soft tissue graft that is "sterile." (Ex.1034, ¶¶207, 231.)

Claims 10, 27, and 30 add the limitation that the plasticizer comprises "glycerol." (Ex. 1002, 25:6-7, 26:22-23, 26:34-36.) Walker discloses that the use of glycerol is extremely advantageous and provides several examples using glycerol as the plasticizer. (Ex.1034, ¶¶208, 230, 232; Ex. 1005, 4:26-27, 7:20-23, 15:13-14.)

Claims 13 and 34 add the limitations that the graft is "essentially free from cellular elements," (Ex. 1002, 25:14-16) or that the graft is "produc[ed]… by removing cellular elements." (*Id.,* 26:36-38.) Walker discloses a method in which the tissue product is stored in ethanol prior to treatment with glycerol. (Ex. 1005, 7:19-20, 15:3-5.) A POSITA would have recognized that storing the biological tissue in ethanol would result in a cleaned, plasticized soft tissue graft that "is essentially free from cellular elements" and that is "produc[ed] by removing cellular elements." (Ex.1034, ¶¶209, 234.)

Claim 14 recites "The plasticized soft tissue graft of any one of claim 1, 2, or 3, wherein the plasticized soft tissue graft has mechanical properties approximating mechanical properties of natural soft tissue." (Ex. 1002, 25:17-20.) Walker discloses that the glycerol maintains the flexibility and the microstructure of collagen in the material. (Ex. 1005, 2:16-27, 4:20-24.) Referring to tests of suture retention and maximum load, (*id.*, Tables 9-14), Walker reports that "[t]he results show that the physical properties of treated bovine arteries are unaffected by the

plasticization and sterilization processes." (*Id.*, 8:25-32.) It further discloses that "[s]ince glycerol keeps the dimensions of the graft stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (*Id.*, 19:9-15.) Therefore, a POSITA would have understood that Walker's method results in a plasticized soft tissue graft that "has mechanical properties approximating mechanical properties of natural soft tissue." (Ex.1034, ¶¶88-89, 210.)

Claim 15 can be divided into a preamble and four elements, 1 through 4 (*see* Ex. 1002, 25:21-27), and Walker discloses every element. (Ex.1034, ¶¶211-217.)

Element	Claim 15	Walker (Ex.1005)
Preamble	A plasticized load-bearing soft tissue graft, comprising:	See Claim 1 table, Preamble.
1	a cleaned load-bearing soft tissue graft comprising	See Claim 1 table, Element 1. "Preferably the material is biological material, such as vascular tissue etc." (Ex. 1005, 4:17-18.) "15 x 15cm samples of Bovine carotid and thoracic arteries were transferred to 50% ethanol." (Ex. 1005, 7:19-20.) "Bovine Carotid and Thoracic arteries (fixed by dye-mediated photo-oxidation) were stored in 20% or 50% ethanol" (Ex. 1005, 15:3-5.)
2	one or more plasticizers,	See Claim 1 table, Element 2.

Element	Claim 15	Walker (Ex.1005)
3	wherein said cleaned soft tissue graft comprises collagen fibers	See Claim 1 table, Element 3.
4	and the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.	See Claim 1 table, Element 4.

Claim 16 can be divided into a preamble and three elements, 1 through 3 (*see* Ex. 1002, 25:28-36), and Walker discloses every element. (Ex.1034, ¶¶218-222.)

Claim 16, preamble: ***A method for producing a plasticized soft tissue graft suitable for transplantation into a human, comprising:***

To the extent the preamble is limiting, Walker discloses a method for producing a plasticized soft tissue graft. (Ex.1034, ¶219.) Walker discloses a method for plasticization of a biological material such as vascular tissues. (Ex.1034, ¶83; Ex. 1005, 2:14-21, 4:17-18.) The disclosed method involves incubating the biological material in a solution containing a plasticizer, such as glycerol, resulting in the incorporation of the plasticizer within the tissue. (Ex.1034, ¶¶85-86; Ex. 1005, 3:23-24, 15:16-18.) Walker discloses that the plasticized biological material substantially retains certain physical characteristics of the untreated material, such as flexibility. (Ex. 1005, 4:20-22.) As evidence that

the plasticized material maintains its structural and mechanical properties, Walker reports the results of suture pull-out experiments (Ex. 1005, 7:31-9:31; Tables 9-10) and maximum loading tests. (Ex. 1005, 8:13-23; Tables 11-14.) Those results show that the plasticization method disclosed in Walker does not degrade the physical properties of the tissue as compared to untreated tissue. (Ex.1034, ¶¶88-89; Ex. 1005, 8:25-32.) Walker therefore discloses a method for producing a plasticized soft tissue graft suitable for transplantation into a human. (Ex.1034, ¶219.)

Claim 16, element 1: ***impregnating a cleaned soft tissue graft with one or more plasticizers to produce a plasticized soft tissue graft,***

In the Walker method, the biological material is stored in ethanol before treatment with glycerol. (Ex.1005, 7:19-20, 15:3-5.) A POSITA would have recognized that storing the biological tissue in ethanol would at least partially remove potentially harmful immunogenic cellular components. (Ex.1034, ¶¶84, 220.) Walker therefore discloses a cleaned soft tissue graft. Further, Walker discloses treatment of the material with a water-soluble, non-volatile substance for at least 12 hours, providing examples in which the material is treated with glycerol for 16 hours or more. (Ex. 1005, 2:30-34, 3:23-24, 5:11-13, 15:16-17, 20:7-8.) Incubation for 16 hours or more gives the glycerol sufficient time to impregnate the internal matrix of the material. (Ex.1034, ¶¶85-86, 220.) Walker discloses that

the glycerol keeps the dimensions of the material stable during processing, evidencing that the glycerol is incorporated within the internal matrix. (*Id.*; Ex. 1005, 19:9-12.) A POSITA would have recognized, therefore, that Walker discloses a clean soft tissue graft impregnated with one or more plasticizers. (Ex.1034, ¶220.)

Claim 16, element 2: ***wherein said cleaned soft tissue graft comprises collagen fibers,***

Walker discloses that the material maintains its physical characteristics including the structure of cells or extracellular material such as collagen and more particularly, the microstructure of collagen. (Ex. 1005, 2:23-27.) Walker therefore discloses that the cleaned soft tissue graft comprises collagen fibers. (Ex.1034, ¶221.)

Claim 16, element 3: ***and the orientation of the collagen fibers is not altered by the step of impregnating, such that the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.***

Walker discloses that the glycerol maintains the flexibility and the microstructure of collagen in the material. (Ex. 1005, 2:16-27, 4:20-24.) Referring to tests of suture retention and maximum load, (*id.*, Tables 9-14), Walker reports that "[t]he results show that the physical properties of treated bovine arteries are unaffected by the plasticization and sterilization processes." (*Id.*, 8:25-32.) It

further discloses that "[s]ince glycerol keeps the dimensions of the graft stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (*Id.*, 19:9-15.) Therefore, a POSITA would have understood that Walker's method results in a plasticized soft tissue graft that maintains the native orientation of the collagen fibers. (Ex.1034, ¶¶88-89, 222.)

Element	Claim 16	Walker (Ex.1005)
Preamble	A method for producing a plasticized soft tissue graft suitable for transplantation into a human, comprising:	See Claim 1 Table, Preamble
1	impregnating a cleaned soft tissue graft with one or more plasticizers to produce a plasticized soft tissue graft,	See Claim 1 Table, Elements 1 and 2
2	wherein said cleaned soft tissue graft comprises collagen fibers	See Claim 1 Table, Element 3
3	and the orientation of the collagen fibers is not altered by the step of impregnating, such that the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft	See Claim 1 Table, Element 4

Claim 17 recites "The method of claim 16, said step of impregnating, comprising: incubating said cleaned soft tissue graft with a plasticizer composition

comprising one or more plasticizers and one or more biocompatible solvents." (Ex. 1002, 25:37-40.) Walker Example 3discloses that the samples were plasticized in a solution of 50% glycerol in 50% ethanol. (Ex.1005, 7:20-22.) Walker therefore discloses a plasticizer composition comprising one or more plasticizers (i.e., glycerol) and one or more biocompatible solvents (i.e., ethanol). (Ex.1034, ¶223.)

Claims 18, 24, and 25 add the additional limitations that "incubating comprises soaking," (Ex. 1002, 25:41-43) "incubated . . . for at least 30 minutes," (*id.*, 26:13-15) and "incubated . . . by soaking." (*Id.*, 26:16-18.) Walker discloses that the material is incubated in the substance solution for at least 12 hours, describing several examples of the material being incubated in glycerol for 16 hours. (Ex.1034, ¶¶224, 227-228; Ex.1005, 3:23-25, 15:16-17.) Walker therefore, discloses the added limitations of claims 18, 24, and 25.

Claim 20 recites "The method of claim 17, wherein said one or more biocompatible solvents comprise one or more alcohols." (Ex. 1002, 26:1-2.) Walker Example 3 discloses that the samples were plasticized in a solution of 50% glycerol in 50% ethanol. (Ex.1005, 7:20-22.) Ethanol is an alcohol and, therefore, Walker discloses the added limitation of Claim 20. (Ex.1034, ¶225.)

Claim 21 recites "The method of claim 20, wherein said one or more plasticizers are present in said plasticizer composition in a weight ratio of from 30 to 90 wt %, and said one or more alcohols are present in said plasticizer

composition in a weight ratio of from 10 to 70 wt %." (Ex. 1002, 26:3-7.) In a Walker example, the samples were plasticized in a solution of 50% glycerol ("plasticizer composition in a weight ratio of from 30 to 90 wt %") in 50% ethanol ("alcohols are present . . . in weight ratio of from 10% to 70 wt %"). Walker therefore discloses the concentration limitation of Claim 21. (Ex.1034, ¶226.)

Claim 26 recites "The method of claim 17, wherein said one or more plasticizers are present in said plasticizer composition in a weight ratio of from 30 to 90 wt %." (Ex. 1002, 26:19-21.) In a Walker example, the samples were plasticized in a solution of 50% glycerol ("plasticizer composition in a weight ratio of from 30 to 90 wt %") in 50% ethanol. Walker therefore discloses the concentration limitation of Claim 26. (Ex.1034, ¶229.)

Claim 33 recites "The method of claim 16, wherein said one or more plasticizers are present in said plasticizer composition in a weight ratio of at least 10 wt %." (Ex. 1002, 26:34-36.) In a Walker example, the samples were plasticized in a solution of 50% glycerol ("plasticizer composition in a weight ratio of from 30 to 90 wt %") in 50% ethanol. Walker therefore discloses the concentration limitation of Claim 33. (Ex.1034, ¶233.)

Claim 35 recites "The method of claim 16, wherein said step of impregnating comprises replacing water in the soft tissue graft with the one or more plasticizers." (Ex. 1002, 26:40-42.) Walker discloses treatment of the

material with a water-soluble, non-volatile substance for at least 12 hours, providing examples of treatment with glycerol for 16 hours or more (Ex. 1005, 2:30-34, 3:23-24, 5:11-13, 15:16-17, 20:7-8.). That incubation gives the glycerol sufficient time to impregnate the internal matrix . (Ex.1034, ¶¶85-86, 235.) Walker discloses that the glycerol keeps the dimensions of the material stable during processing, evidencing that the glycerol is incorporated within the internal matrix. (Ex.1034, ¶88; Ex. 1005, 19:9-12.) A POSITA would have understood from Walker that the glycerol replaces water in the soft tissue graft during the impregnation step . (Ex.1034, ¶¶85-86, 88, 235.) Therefore, a POSITA would have recognized that Walker discloses "replacing water in the soft tissue graft with one or more plasticizers." (*Id*.)

B. Ground 2: Claims 1-3, 5, 7-11, 13-18, 20-22, 24-31, and 33-35 are obvious over Walker

Claims 1-3, 5, 7-11, 13-18, 20-22, 24-31, and 33-35 are obvious over Walker. The explanation of Ground 1 (§VII.A.) details how Walker anticipates many of those claims. To the extent any limitation of those claims is not explicitly disclosed in Walker, the subject matter as a whole of those claims would have been obvious to a POSITA at the time of the alleged invention in view of Walker's disclosure.

To the extent it is determined that Walker does not explicitly disclose that "one or more plasticizers [are] contained in said internal matrix," or that the soft tissue graft is "impregnated with said one or more plasticizers," the subject matter of the claims reciting those elements would have been obvious to a POSITA at the time of the alleged invention for at least the following reasons:

As detailed above in Ground 1, Walker discloses that the plasticizer is contained in the internal matrix and that the graft is impregnated with a plasticizer. (*See* Section VII.A., *supra*.) Walker explicitly discloses that the glycerol keeps the dimensions of the material stable during processing, indicating that the glycerol is contained within the internal matrix and thus that the glycerol impregnates the graft. (Ex. 1005, 19:9-12.) But if it is determined that Walker does not explicitly disclose that the plasticizer is contained in the internal matrix or that the plasticizer impregnates the graft, a POSITA in February 1998 would have understood from Walker that small chemical compounds, such as those disclosed in Walker, act by replacing free and loosely bound water within the tissue thereby incorporating themselves within the internal matrix. (Ex.1034, ¶¶85-86, 88, 236-237.)

Thus, even if Claims 1-2, 5, 7-11, 13-14, 16-18, 20-22, 24-31, and 33-35 are not anticipated by Walker, their subject matter would have been obvious to a POSITA because (1) Walker disclosed a method of incorporating chemical compounds into the internal matrix of a soft tissue graft, (2) if Walker does not

explicitly teach that "one or more plasticizers [are] contained in said internal matrix," or that the soft tissue graft is "impregnated with said one or more plasticizers," a POSITA in February 1998 would have understood from Walker that small chemical compounds such as the ones disclosed in Walker act by penetrating the soft tissue graft and replacing free and loosely bound water within the internal matrix, and (3) a POSITA in February 1998 would have recognized that such penetration of the plasticizer in the soft tissue graft would have yielded the predictable result of a soft tissue graft where the plasticizer is contained in the internal matrix and that the plasticizers impregnate the soft tissue graft. (Ex.1034, ¶¶236-237.)

The additional subject matter of claims 7, 9, 11, 22, 29, and 31 would also have been obvious to a POSITA in view of Walker.

Claim 7 recites "The plasticized soft tissue graft of any one of claim 1, 2, or 3, wherein said cleaned soft tissue graft is selected from the group consisting of: dura, pericardium, fascia lata, tendons, and ligaments." (Ex. 1002, 24:64-67.) A POSITA would have been motivated to apply the teachings of Walker to the recited types of load-bearing soft tissues because of the common use of such types of soft tissue grafts. (Ex.1034, ¶244.) Walker discloses examples of its method using bovine carotid and thoracic arteries, which are other types of load-bearing soft tissue. (*Id.*) A POSITA would therefore have been motivated to apply the

method disclosed in Examples 3 and 4 specifically to the recited "pericardium" because Walker itself discloses that it is possible to plasticize and sterilize bovine pericardium in the same way as bovine arteries and that doing so would not compromise the physical strength of the tissue. (Ex.1005, 25:1-2.) Therefore, Claim 7 would have been obvious to a POSITA in view of Walker. (Ex.1034, ¶244.)

Claims 9 and 29 add the limitation that the plasticized soft tissue graft does not "require refrigeration or freezing" (Ex. 1002, 25:3-5, 26:25-26) and claims 11 and 31 add the limitation that the plasticized soft tissue graft can be "stored at room temperature." (Ex. 1002, 25:8-10, 26:29-30.) A POSITA in February 1998 would have known that soft tissue grafts preserved with glycerol were considered "dried/dehydrated" grafts, and as such, did not require special conditions for storage and that they could be stored at room temperature. A POSITA would have therefore understood that the resulting soft tissue product of Walker would not require special conditions for storage and that it could be stored at room temperature because it was preserved using glycerol. (Ex.1034, ¶¶238-243.) Therefore, the subject matter of claims 9, 11, 29, and 31, including these added limitations, would have been obvious to a POSITA in view of Walker. (*Id.*)

Claim 22 recites "The method of claim 20, wherein said plasticizer comprises glycerol and said alcohol is isopropyl alcohol." (Ex. 1002, 26:8-9.) The

disclosure of Walker would have motivated a POSITA to perform Walker's plasticization process using glycerol as the plasticizer and isopropyl alcohol as the alcohol. (Ex.1034, ¶245.) Walker specifically teaches that using glycerol is advantageous (Ex.1005, 4:26-27) and that glycerol is a suitable pre-sterilizing substance in its examples. (*Id.* at 7:20-23, 15:13-14.) The examples disclosed in Walker also teach the use of ethanol as a solvent. (*Id.*) A POSITA would have known that ethanol is readily interchangeable with other short-chain alcohols such as isopropyl alcohol. (Ex.1034, ¶245.) Further, a POSITA would have known that isopropyl alcohol is less expensive than ethanol and would therefore have been motivated to use isopropyl alcohol to decrease cost. (*Id.*) Therefore, Claim 22 would have been obvious to a POSITA in view of Walker.

C. Ground 3: Livesey anticipates Claims 1-3, 6, 8-9, 11-14, 16-18, 24-25, 28-29, 31-32, and 34-36

Claim 1 can be divided into a preamble and four elements, 1 through 4 (*see* Ex. 1002, 24:35-41), and Livesey discloses every element.

Claim 1, preamble: ***A plasticized soft tissue graft suitable for transplantation into a human, comprising:***

To the extent the preamble is limiting, Livesey discloses a plasticized soft tissue graft. (Ex.1034, ¶247.) Livesey describes a method for processing and preserving collagen-based biological tissues for transplantation. (Ex.1004, 4:39-

42.) Livesey discloses a method wherein the soft tissue is incubated in a cryosolution for a time long enough to obtain complete penetration of the cryoprotectants into the tissue. (Ex.1034, ¶62; Ex.1004, 12:31-39.) Livesey teaches that treatment of the tissue with the processing solution must be done at a concentration and for a duration that avoids degradation of the basement membrane complex and maintains the structural integrity of the matrix, including collagen fibers and elastin. (Ex.1004, 5:1-14.) It discloses that the end product was analyzed using light and electron microscopy, demonstrating that the tissue remained structurally intact with normal collagen banding and that the collagen bundles in the matrix of the dermis were preserved. (Ex.1034, ¶65; Ex.1004, 25:12-17.) Therefore, a POSITA would have recognized that Livesey discloses a plasticized soft tissue graft suitable for transplantation into a human. (Ex.1034, ¶247.)

Claim 1, element 1: ***a cleaned soft tissue graft having an internal matrix;***

Livesey discloses that the soft tissue grafts are decellularized by treatment with a 0.5% sodium dodecyl sulfate solution for 1 hour on a rotator at 40±5 RPM. (Ex.1004, 23:65-67.) A POSITA would have recognized that treatment under those conditions would cause cellular elements to be at least partially, if not substantially, removed, resulting in a cleaned graft with an internal matrix. (Ex.1034, ¶¶61, 248.)

Claim 1, element 2: ***and one or more plasticizers contained in said internal matrix,***

As noted, Livesey discloses a soft tissue graft incubated in a cryosolution containing one or more cryoprotectants (Ex.1004, 11:17-23) and discloses a non-exhaustive list of cryoprotectants that can be used in the invention. (Ex.1004, 11:49-55.) Also disclosed is that the soft tissue graft is exposed to the cryosolution containing the cryoprotectants for a time long enough to obtain complete penetration of the cryoprotectants. (Ex.1004, 12:33-37.) The "cryoprotectants" described in Livesey constitute the "plasticizer" described in the 420 patent. (Ex.1034, ¶¶62-64, 249.) Several examples of plasticizer components given in the 420 patent match the non-exclusive examples of cryoprotectant listed in Livesey. (*Compare* Ex. 1004, 11:49-55 *with* Ex. 1002, 7:52-61.) Therefore, Livesey discloses the recited one or more plasticizers contained in the internal matrix. (Ex.1034, ¶249.)

Claim 1, element 3: ***wherein said cleaned soft tissue graft comprises collagen fibers;***

Livesey discloses that the structural integrity of the matrix is maintained and that degradation of the basement membrane complex is avoided. (Ex. 1004, 5:1-14.) Livesey analyzed samples of the treated tissue by light and electron microscopy and the results showed that the collagen banding of the treated tissue

was normal, therefore, Livesey discloses that the cleaned soft tissue graft comprises collagen fibers. (Ex.1034, ¶250; Ex. 1004, 25:12-17.)

Claim 1, element 4: ***and the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.***

Livesey teaches that treatment of the tissue with the processing solution must be done at a concentration and for a duration that avoids degradation of the basement membrane complex and maintains the structural integrity of the matrix, including collagen fibers and elastin. (Ex.1004, 5:1-14.) It discloses that the end product was analyzed using light and electron microscopy, demonstrating that the tissue remained structurally intact with normal collagen banding and that the collagen bundles in the matrix of the dermis were preserved. (Ex.1004, 25:12-17.) Therefore, a POSITA would have recognized that Livesey discloses that the native orientation of the collagen fibers is maintained. (Ex.1034, ¶¶65, 251.)

Element	Claim 1	Livesey (Ex.1004)
Preamble	A plasticized soft tissue graft suitable for transplantation into a human, comprising:	"This invention relates to methods for procuring[,] decellularizing and further processing and dry preserving collagen-based tissues derived from humans and animals for transplantation into humans or other animals." (Ex. 1004, 1:17-21.) "In the preferred embodiment, the tissue is then incubated in a processing solution to remove viable antigenic cells (including epithelial cells, endothelial cells, smooth muscle cells and fibroblasts) from the structural matrix without damaging the basement membrane complex or the structural integrity of the collagen matrix." (Ex. 1004, 5:1-6.) "Analysis of the end product by light and electron microscopy has demonstrated it to be structurally intact with normal collagen banding and the presence of collagen bundles in the matrix of the dermis and with structural preservation of the lamina densa and anchoring fibrils of basement membrane complex." (Ex. 1004, 25:12-17.)

Element	Claim 1	Livesey (Ex.1004)
1	a cleaned soft tissue graft having an internal matrix;	"These methods produce a tissue product that consists of a selectively preserved extracellular protein matrix that is devoid of certain viable cells which normally express major histocompatibility complex antigenic determinants and other antigens which would be recognized as foreign by the recipient." (Ex. 1004, 1:21-26.) "the tissue is then incubated in a processing solution to remove viable antigenic cells (including epithelial cells, endothelial cells, smooth muscle cells and fibroblasts) from the structural matrix without damaging the basement membrane complex or the structural integrity of the collagen matrix." (Ex. 1004, 5:1-6.) "The dermis is then treated with 50 ml. of De-Cellularizing solution and the petri dish is placed on a rotator at 40+/-5 RPM for 1 hour at room temperature (20-26 C.). The decellularizing solution for human skin consists of 0.5% sodium dodecyl sulfate in Hanks balanced salt solution and for porcine skin contains 1mM disodium ethylenediamine tetraacetic acid (EDTA)." (Ex. 1004, 23:62-67.)
2	and one or more plasticizers contained in said internal matrix,	"In general, cryopreservation is performed as a continuous sequence of events. The tissue is first incubated in the cryosolution for a defined period (0.5 to 2 hours) until complete penetration of the components of the cryosolution is achieved . . . ." (Ex. 1004, 12:33-37.) "After the tissue is decellularized, it is preferably incubated in a cryopreservation

Element	Claim 1	Livesey (Ex.1004)
		solution. In the preferred embodiment, this solution generally contains one or more cryoprotectants to minimize ice crystal damage to the structural matrix that could occur during freezing, and one or more dry-protective components, to minimize structural damage alteration during drying and may include a combination of an organic solvent and water which undergoes neither expansion or contraction during freezing." (Ex. 1004, 5:15-24.) "The initial steps of cryopreserving the decellularized tissue includes incubating the tissue in a cryosolution prior to the freezing step. The cryosolution comprises an appropriate buffer, one or more cryoprotectants and/or dry protectants with or without an organic solvent which in combination with water undergoes neither expansion or contraction." (Ex. 1004, 11:17-23.) "Various cryoprotectants can be used in the present invention. These include: dimethylsulfoxide (DMSO), dextran, sucrose, 1,2 propanediol, glycerol, sorbitol, fructose, trehalose, raffinose, propylene glycol, 2-3 butane diol, hydroxyethyl starch, polyvinylpyrrolidone (PVP), proline, (or other protein stabilizers), human serum albumin and combinations thereof." (Ex. 1004, 11:49-55.) See Example 1 where the plasticizers are dextran and sucrose. (Ex. 1004, 24:10-19.)

Element	Claim 1	Livesey (Ex.1004)
3	wherein said cleaned soft tissue graft comprise collagen fibers	"Treatment of the tissue with this processing solution must be at a concentration for a time duration such that degradation of the basement membrane complex is avoided and the structural integrity of the matrix is maintained including collagen fibers and elastin." (Ex. 1004, 5:10-14.) "Analysis of the end product by light and electron microscopy has demonstrated it to be structurally intact with normal collagen banding and the presence of collagen bundles in the matrix of the dermis and with structural preservation of the lamina densa and anchoring fibrils of basement membrane complex." (Ex. 1004, 25:12-17.)
4	and the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.	"Treatment of the tissue with this processing solution must be at a concentration for a time duration such that degradation of the basement membrane complex is avoided and the structural integrity of the matrix is maintained including collagen fibers and elastin." (Ex. 1004, 5:10-14.) "Analysis of the end product by light and electron microscopy has demonstrated it to be structurally intact with normal collagen banding and the presence of collagen bundles in the matrix of the dermis and with structural preservation of the lamina densa and anchoring fibrils of basement membrane complex." (Ex. 1004, 25:12-17.)

Claim 2 can be divided into a preamble and five elements, 1 through 5 (*see* Ex. 1002, 24:42-48), and Livesey discloses every element. (Ex.1034, ¶¶252-258.)

Element	Claim 2	Livesey (Ex.1004)
Preamble	A plasticized soft tissue graft, comprising:	See Claim 1 table, Preamble.
1	a cleaned soft tissue graft;	See Claim 1 table, Element 1.
2	and one or more plasticizers,	See Claim 1 table, Element 2.
3	wherein said cleaned soft tissue graft is impregnated with said one or more plasticizers,	See Claim 1 table, Element 2.
4	and wherein said cleaned soft tissue graft comprise collagen fibers	See Claim 1 table, Element 3.
5	and the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.	See Claim 1 table, Element 4.

Claim 3 can be divided into a preamble and four elements, 1 through 4 (*see* Ex. 1002, 24:50-54), and Livesey discloses every element. (Ex.1034, ¶¶259-264.)

Element	Claim 3	Livesey (Ex.1004)
Preamble	A plasticized soft tissue graft, comprising:	See Claim 1 table, Preamble.
1	a cleaned, soft tissue graft comprising	See Claim 1 table, Element 1.
2	one or more plasticizers,	See Claim 1 table, Element 2.
3	wherein said cleaned soft tissue graft comprise collagen fibers	See Claim 1 table, Element 3.
4	and the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.	See Claim 1 table, Element 4.

Claim 6 recites "[t]he plasticized soft tissue graft of any one of claim 1, 2, or 3, wherein said cleaned soft tissue graft is a non-load-bearing soft tissue graft." (Ex. 1002, 24:61-63.) Livesey provides an example of its method using cadaveric skin. (Ex. 1004, 23:5-25:42.) The 420 patent discloses that "[n]on-load-bearing soft tissue grafts include cadaveric skin." (Ex. 1002, 8:16-17.) Therefore, Livesey discloses a non-load-bearing soft tissue graft. (Ex.1034, ¶265)

Claims 8 and 28 add the limitation that the plasticized soft tissue graft is sterile. (Ex. 1005, 2:14-21, 26:23-24.) Livesey discloses that following incubation in the cryopreservation solution, the tissue is packaged inside a sterile container or pouch that is impermeable to bacteria (Ex. 1004, 5:27-30) and that prior to use of

the sample in transplantation, all necessary quality assurance is performed including microbiology and structural analysis. (*Id.,* 24:68-25:3.) A POSITA would understand that Livesey's method produces a plasticized soft tissue graft that is "sterile." (Ex.1034, ¶¶266, 282.)

Claims 9 and 29 add the limitation that the plasticized soft tissue graft does not require refrigeration or freezing (Ex. 1002, 25:3-5, 26:25-26) and claims 11 and 31 add the limitation that the plasticized soft tissue graft can be stored at room temperature. (Ex. 1002, 25:8-10, 26:29-30.) Livesey teaches that the packaged dried tissue may be stored for extended time periods under ambient conditions, therefore, a POSITA would have recognized that Livesey discloses a plasticized soft tissue graft that "does not require refrigeration or freezing" and that "can be stored at room temperature." (Ex.1034, ¶¶267, 283; Ex. 1004, 6:6-11.)

Claims 12 and 32 add the limitation that the cleaned soft tissue graft comprises cadaveric skin. (Ex. 1002, 25:11-13, 26:31-32.) Livesey provides an example of its method using cadaveric skin. (Ex.1034, ¶¶269, 285; Ex. 1004, 23:5-25:42.)

Claims 13 and 34 add the limitations that the graft is "essentially free from cellular elements," (Ex. 1002, 25:14-16) or that the graft is "produc[ed]… by removing cellular elements." (*Id.,* 26:36-38.) Livesey discloses a method wherein the tissue is decellularized by treatment with a sodium dodecyl sulfate detergent

solution. (*Id.*, 23:65-67.) A POSITA would have recognized that treatment of the tissue with a detergent as disclosed in Livesey would result in a cleaned, plasticized soft tissue graft that is "essentially free from cellular elements," and that is "produc[ed] by removing cellular elements." (Ex.1034, ¶¶270, 286.)

Claim 14 recites "The plasticized soft tissue graft of any one of claim 1, 2, or 3, wherein the plasticized soft tissue graft has mechanical properties approximating mechanical properties of natural soft tissue." (Ex. 1002, 25:17-20.) Livesey teaches that treatment of the tissue with the processing solution must be done at a concentration and for a duration that avoids degradation of the basement membrane complex and maintains the structural integrity of the matrix, including collagen fibers and elastin. (Ex.1004, 5:1-14.) It discloses that the end product was analyzed using light and electron microscopy, demonstrating that the tissue remained structurally intact with normal collagen banding and that the collagen bundles in the matrix of the dermis were preserved. (Ex.1034, ¶¶65, 271; Ex.1004, 25:12-17.) A POSITA would have recognized that a soft tissue graft with the structural characteristics of natural soft tissue would also maintain the mechanical properties of natural soft tissue because function of a soft tissue is highly dependent on the structure. (*See* Ex.1034, ¶¶74-81.)

Claim 16 can be divided into a preamble and three elements, 1 through 3 (*see* Ex. 1002, 25:28-36), and Livesey discloses every element.

Claim 16, preamble: ***A method for producing a plasticized soft tissue graft suitable for transplantation into a human, comprising:***

To the extent the preamble is limiting, Livesey discloses a method for producing a plasticized soft tissue graft suitable for transplantation into a human. (Ex.1034, ¶273.) Livesey describes a method for processing and preserving collagen-based biological tissues for transplantation. (Ex.1004, 4:39-42.) Livesey discloses a method wherein the soft tissue is incubated in a cryosolution for a time long enough to obtain complete penetration of the cryoprotectants into the tissue. (Ex.1034, ¶62; Ex.1004, 12:31-39.) Livesey teaches that treatment of the tissue with the processing solution must be done at a concentration and for a duration that avoids degradation of the basement membrane complex and maintains the structural integrity of the matrix, including collagen fibers and elastin. (Ex.1004, 5:1-14.) It discloses that the end product was analyzed using light and electron microscopy, demonstrating that the tissue remained structurally intact with normal collagen banding and that the collagen bundles in the matrix of the dermis were preserved. (Ex.1034, ¶65; Ex.1004, 25:12-17.) Therefore, a POSITA would have recognized that Livesey discloses a method for producing a plasticized soft tissue graft suitable for transplantation into a human. (Ex.1034, ¶273.)

Claim 16, element 1: ***impregnating a cleaned soft tissue graft with one or more plasticizers to produce a plasticized soft tissue graft,***

Livesey discloses that the soft tissue grafts are decellularized by treatment with a 0.5% sodium dodecyl sulfate solution for 1 hour on a rotator at 40±5 RPM. (Ex.1004, 23:65-67.) A POSITA would have recognized that treatment under those conditions would cause cellular elements to be at least partially, if not substantially, removed, resulting in a cleaned graft with an internal matrix. (Ex.1034, ¶¶61, 274-275.) As noted, Livesey discloses a soft tissue graft incubated in a cryosolution containing one or more cryoprotectants (Ex.1004, 11:17-23) and discloses a non-exhaustive list of cryoprotectants that can be used in the invention. (Ex.1004, 11:49-55.) Also disclosed is that the soft tissue graft is exposed to the cryosolution containing the cryoprotectants for a time long enough to obtain complete penetration of the cryoprotectants. (Ex.1004, 12:33-37.) The "cryoprotectants" described in Livesey constitute the "plasticizer" described in the 420 patent. (Ex.1034, ¶¶62-64.) Several examples of plasticizer components given in the 420 patent match the non-exclusive examples of cryoprotectant listed in Livesey. (*Compare* Ex. 1004, 11:49-55 *with* Ex. 1002, 7:52-61.) Therefore, Livesey discloses the recited one or more plasticizers contained in the internal matrix. (Ex.1034, ¶¶274-275.)

Claim 16, element 2: ***wherein said cleaned soft tissue graft comprises collagen fibers,***

Livesey discloses that the structural integrity of the matrix is maintained and that degradation of the basement membrane complex is avoided. (Ex. 1004, 5:1-14.) Livesey analyzed samples of the treated tissue by light and electron microscopy and the results showed that the collagen banding of the treated tissue was normal, therefore, Livesey discloses that the cleaned soft tissue graft comprises collagen fibers. (Ex.1034, ¶276; Ex. 1004, 25:12-17.)

Claim 16, element 3: ***and the orientation of the collagen fibers is not altered by the step of impregnating, such that the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft.***

Livesey teaches that treatment of the tissue with the processing solution must be done at a concentration and for a duration that avoids degradation of the basement membrane complex and maintains the structural integrity of the matrix, including collagen fibers and elastin. (Ex.1004, 5:1-14.) It discloses that the end product was analyzed using light and electron microscopy, demonstrating that the tissue remained structurally intact with normal collagen banding and that the collagen bundles in the matrix of the dermis were preserved. (Ex.1004, 25:12-17.) Therefore, a POSITA would have recognized that Livesey's method results in a

soft tissue graft in which the native orientation of the collagen fibers is maintained. (Ex.1034, ¶¶65, 277.)

Element	Claim 16	Livesey (Ex. 1004)
Preamble	A method for producing a plasticized soft tissue graft suitable for transplantation into a human, comprising:	See Claim 1 Table, Preamble
1	impregnating a cleaned soft tissue graft with one or more plasticizers to produce a plasticized soft tissue graft,	See Claim 1 Table, Elements 1 and 2
2	wherein said cleaned soft tissue graft comprises collagen fibers	See Claim 1 Table, Element 3
3	and the orientation of the collagen fibers is not altered by the step of impregnating, such that the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft	See Claim 1 Table, Element 4

Claim 17 recites "The method of claim 16, said step of impregnating, comprising: incubating said cleaned soft tissue graft with a plasticizer composition comprising one or more plasticizers and one or more biocompatible solvents." (Ex. 1002, 25:37-40.) In Example 1, Livesey discloses a cryosolution which contains dextran and sucrose in Hanks balanced salt solution. (Ex.1004, 24:10-19.) A POSITA would have recognized, therefore, that Livesey discloses a plasticizer

composition comprising one or more plasticizers (i.e. dextran and sucrose) and one or more biocompatible solvents (i.e. Hanks balanced salt solution). (Ex.1034, ¶278.)

Claims 18, 24, and 25 add the additional limitations that "incubating comprises soaking," (Ex. 1002, 25:41-43) "incubated . . . for at least 30 minutes," (*id.*, 26:13-15) and "incubated . . . by soaking." (*Id.*, 26:16-18.) Livesey discloses that the soft tissue is first incubated in the cryosolution for a defined period (0.5 to 2 hours) until complete penetration of the components of the cryosolution is achieved . . . ." (Ex. 1004, 12:33-37.) Livesey, therefore, discloses the added limitations of claims 18, 24, and 25. (Ex.1034, ¶¶279-281.)

Claim 35 recites "The method of claim 16, wherein said step of impregnating comprises replacing water in the soft tissue graft with the one or more plasticizers." (Ex. 1002, 26:40-42.) As discussed in relation to Claim 16, element 1, Livesey discloses impregnating a cleaned soft tissue graft with one or more plasticizers to produce a plasticized soft tissue graft. Livesey teaches that the tissue is incubated in the cryosolution for a time long enough to allow complete penetration. (Ex. 1004, 12:33-37.) Incubation of the tissue in the cryosolution for a time long enough to allow complete penetration means that the tissue will be cryoprotectants will impregnate the tissue and replace free and loosely bound water with the internal matrix of the tissue. (Ex.1034, ¶¶62-64, 287.) A POSITA

would have understood from Livesey that the cryoprotectant replaces water in the soft tissue graft during the step of impregnation. (*Id*.) Therefore, a POSITA would have recognized that Livesey discloses "replacing water in the soft tissue graft with one or more plasticizers." (*Id*.)

Claim 36 recites "The method of claim 16, comprising obtaining said cleaned soft tissue graft by using a detergent composition." (Ex. 1002, 26:43-44.) Livesey discloses a method wherein the tissue is decellularized by treatment with a sodium dodecyl sulfate detergent solution, therefore, disclosing the added limitation of Claim 36. (Ex.1034, ¶288; Ex. 1004, 23:65-67.)

D. Ground 4: Claims 1-3, 6, 8-9, 11-14, 16-18, 24-25, 28-29, 31-32, and 34-36 are obvious over Livesey

Claims 1-3, 6, 8-9, 11-14, 16-18, 24-25, 28-29, 31-32, and 34-36 are obvious over Livesey. The explanation of Ground 3 (§VII.C.) shows how Livesey anticipates many of those claims. To the extent any limitation of those claims is not explicitly disclosed in Livesey, the subject matter as a whole of those claims would have been obvious to a POSITA at the time of the alleged invention in view of Livesey's disclosure.

To the extent it is determined that Livesey does not explicitly disclose that "one or more plasticizers [are] contained in said internal matrix," or that the soft tissue graft is "impregnated with said one or more plasticizers," those elements

would have been obvious to a POSITA at the time of the alleged invention for at least the following reasons:

As detailed above in Ground 3, Livesey discloses that the plasticizer is contained in the internal matrix and that the graft is impregnated with a plasticizer. (*See* Section VII.C., *supra*.) Livesey explicitly discloses that the tissue is incubated in a cryosolution for a time long enough to obtain complete penetration of the cryoprotectants into the tissue. (Ex. 1004, 12:31-39). But if it is determined that Livesey does not explicitly disclose that the plasticizer is contained in the internal matrix or that the plasticizer impregnates the graft, a POSITA in February 1998 would have understood from Livesey that small chemical compounds, such as the cryoprotectants disclosed in Livesey, act by replacing free and loosely bound water within the tissue thereby incorporating themselves within the internal matrix. (Ex.1034, ¶¶62-64, 289-290.)

Thus, even if Claims 1-2, 6, 8-9, 11-14, 16-18, 24-25, 28-29, 31-32, and 34-36 are not anticipated by Livesey, their subject matter would have been obvious to a POSITA because (1) Livesey disclosed a method of incorporating chemical compounds into the internal matrix of a soft tissue graft, (2) if Livesey does not explicitly teach that "one or more plasticizers [are] contained in said internal matrix," or that the soft tissue graft is "impregnated with said one or more plasticizers," a POSITA in February 1998 would have understood from Livesey

that small chemical compounds such as the ones disclosed in Livesey act by penetrating the soft tissue graft and replacing free and loosely bound water within the internal matrix, and (3) a POSITA in February 1998 would have recognized that such penetration would have yielded the desirable and predictable result of a soft tissue graft having the plasticizer is contained in the internal matrix and impregnates the soft tissue graft. (Ex.1034, ¶¶62-64, 289-290.)

E. Ground 5: Claim 4 is obvious over Walker or Livesey in view of Werner

Both Walker and Livesey anticipate many claims of the 420 patent. (*See* Grounds 1 and 3 *supra*.) Claim 4 recites "The plasticized soft tissue graft of any one of claim 1, 2, or 3, wherein said plasticized soft tissue graft is suitable for direct transplant into a human without rehydration." (Ex. 1002, 24:55-57.) If neither Walker nor Livesey discloses that the "tissue graft is suitable for direct transplant into a human without rehydration," that limitation is taught by Werner. Werner discloses a process of glycerol treatment of a tissue to increase biological stability. (Ex. 1006, Abstract.) Werner discloses that the resulting tissue product is soft and that no rehydration of the product is necessary before implantation. (Ex. 1006, 2:37-41.) A POSITA would have recognized an advantage to be achieved by adapting Werner's teaching of the use of glycerol for use in the method of either Walker or Livesey; namely, that no rehydration of the tissue product is necessary

before implantation and would have had a reasonable expectation of success in that adaptation. (Ex.1034, ¶¶292-293, 174-175, 295-296.)

A POSITA in February 1998 would have been motivated to simplify the steps for the processing of a soft tissue graft both during preparation and at the time of implantation and would have explored avenues for doing so. (Ex.1034, ¶¶292-293, 176-180, 295-296.) A POSITA by February 1998 would have sought to modify the method of Walker or Livesey by following Werner's teaching in order to simplify the processing of the soft tissue graft during implantation. (*Id.*) Doing so would achieve the known advantage of allowing for direct implantation of the plasticized soft tissue graft instead of requiring rehydration before implantation. (*Id.*) Indeed, Werner teaches the same processing steps as Walker and Livesey, and its further teaching to implant the graft without first rehydrating the graft would have been recognized as desirable by a POSITA. (*Id.*) It would therefore have been evident to a POSITA that Werner's teaching could be advantageously incorporated into the method of Walker or Livesey. (*Id.*) Further, a POSITA would have expected a result similar to that achieved in Werner for the soft tissue grafts referenced in Walker or Livesey utilizing the processing steps of Werner. (Ex.1034, ¶¶293-294, 296-297.)

As explained in Grounds 1 and 3, both Walker and Livesey anticipate claims 1-3 from which claim 4 depends. Therefore, Claim 4 would have been obvious to a POSITA at the time of the invention.

VIII. Consideration under 35 U.S.C. §325(d) Supports Institution

Although Livesey was considered during prosecution, applicants mischaracterized Livesey and the Examiner accepted and relied on applicants' mischaracterization to allow the then-pending claims. Additionally, key portions of Livesey were *not* considered during prosecution and thus, Petitioner's Grounds 3 and 4 do not "present the same or substantially the same prior art or *arguments* previously [] presented to the [Patent] Office." 35 U.S.C. §325(d) (emphasis added).

The Board considers several non-exclusive factors under 35 U.S.C. §325(d) when evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, Case IPR2017-01586, slip op. at 17–28 (PTAB Dec. 15, 2017) (Paper 8) (informative). Relevant here are (i) "the manner in which . . . Patent Owner distinguishes the prior art;" (ii) "how the Examiner erred in its evaluation of the asserted prior art;" and (iii) "additional evidence and facts [that] warrant reconsideration of the prior art or arguments." (*Becton* factors d, e, and f.)

During prosecution of the 420 patent, the claims were rejected over Livesey under 35 U.S.C. §102(b), over Livesey in view of Werner under 35 U.S.C. §103, and over Livesey in view of Klement under 35 U.S.C. §103. (Ex. 1024 at 2.) The Examiner noted that Livesey disclosed all of the elements of many of the claims, and, for those that were not anticipated by Livesey, Werner, and/or Klement, disclosed the additional limitations (certain weight percent limitations and tissue types). (*Id.*)

In response, applicants focused on the following limitation: "the native orientation of the collagen fibers is maintained in said plasticized soft tissue graft." (Ex. 1025 at 8.) Though this limitation was present in some of the then-pending claims, applicants amended then-pending claim 24 (which issued as claim 16) to include this limitation. The applicants' argued that Livesey did not disclose a plasticized soft tissue graft in which the collagen fibers have maintained their native orientation:

> This portion of Livesey plainly states that the structural integrity of the collagen matrix is not damaged. However, it would be understood by one of ordinary skill in the art that the orientation of collagen fibers may be altered without damaging the structural integrity of the collagen matrix. . . . [T]his portion of Livesey does not disclose, teach, or otherwise render inherent a plasticized soft tissue graft in which the collagen fibers have maintained their native orientation.

(Ex. 1025 at 8.) In the reasons for allowance, the Examiner stated that "in [Livesey] there is no teaching or suggestion that the native orientation of the fibers is maintained." (Ex. 1026 at 2.)

Applicants' characterization of Livesey was incorrect and the Examiner erroneously relied on applicants' characterization in allowing the claims. A POSITA would have understood that the cryopreservation method taught by Livesey would not alter "the native orientation of the collagen fibers" of the soft tissue graft as applicants argued. To the contrary, a POSITA would have understood that Livesey's cryoprotectants would function in the same way as the claimed plasticizers (Ex.1034, ¶¶78-79) and that Livesey expressly disclosed that its method of introducing cryoprotectants provided a method for cryopreservation "without causing structural and functional damage" to the soft tissue (Ex.1034, ¶79; Ex.1004, 14:59-63). In direct contrast to applicants' characterization, Livesey states that "analysis of the end product by light and electron microscopy has demonstrated it to be structurally intact with normal collagen banding and the presence of collagen bundles in the matrix of the dermis and with structural preservation of the lamina densa and anchoring fibrils of basement membrane complex." (Ex.1004, 25:12-17.) A POSITA would have understood that the presence of collagen bundles and the preservation of the lamina densa and anchoring fibrils evidences that the treated tissue was structurally the same as

natural tissue. (Ex.1034, ¶80.) Livesey, therefore, does disclose a plasticized soft tissue graft in which the native orientation of the collagen fiber is maintained. (Ex.1034, ¶81.) Notably, neither the Examiner nor the applicants addressed this disclosure in Livesey.

Thus, the considerations under 35 U.S.C. §325(d) support institution of *inter partes* review because, (1) the applicants distinguished Livesey on incorrect grounds during prosecution, (2) the Examiner erred in his evaluation of Livesey, and (3) additional disclosures from Livesey and evidence from Dr. McQuillan (Ex.1034, ¶¶66-73) warrant reconsideration of Livesey. Finally, consideration of Walker and Werner, the other two main references on which this petition relies, supports institution. Although Werner was cited during prosecution in an obviousness rejection, it was not substantially discussed. And, although Walker was cited in an information disclosure statement, it was not discussed at all during prosecution. In view of these additional references, institution is warranted.

IX. Secondary Considerations

Petitioner is not aware of any secondary considerations that would tend to show non-obviousness that have a provable nexus with claims 1-18, 20-22, and 24-36. There is nothing in those claims that is not already taught in the prior art.

X. Conclusion

Petitioner has established a reasonable likelihood of prevailing as to each of claims 1-18, 20-22, and 24-36, and therefore respectfully requests that the Board institute *inter partes* review of those claims.

Respectfully submitted,

McANDREWS, HELD & MALLOY, LTD.

Dated: January 29, 2019

By: /Herbert D. Hart III/
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CERTIFICATE OF WORD COUNT

I hereby certify, pursuant to 37 CFR § 42.24, that this **PETITION FOR INTER PARTES REVIEW** contains fewer than 14,000 words, as determined by Microsoft Word.

Dated: January 29, 2019

By: /Herbert D. Hart III/
Herbert D. Hart III *for Petitioner*
RTI Surgical, Inc.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4) and 42.105, the undersigned certifies on this date, a true and correct copy of this Petition for *Inter Partes* Review and all supporting exhibits were served by Federal Express to the Patent Owner at the following correspondence address of record for U.S. Patent No. 9,579,420:

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